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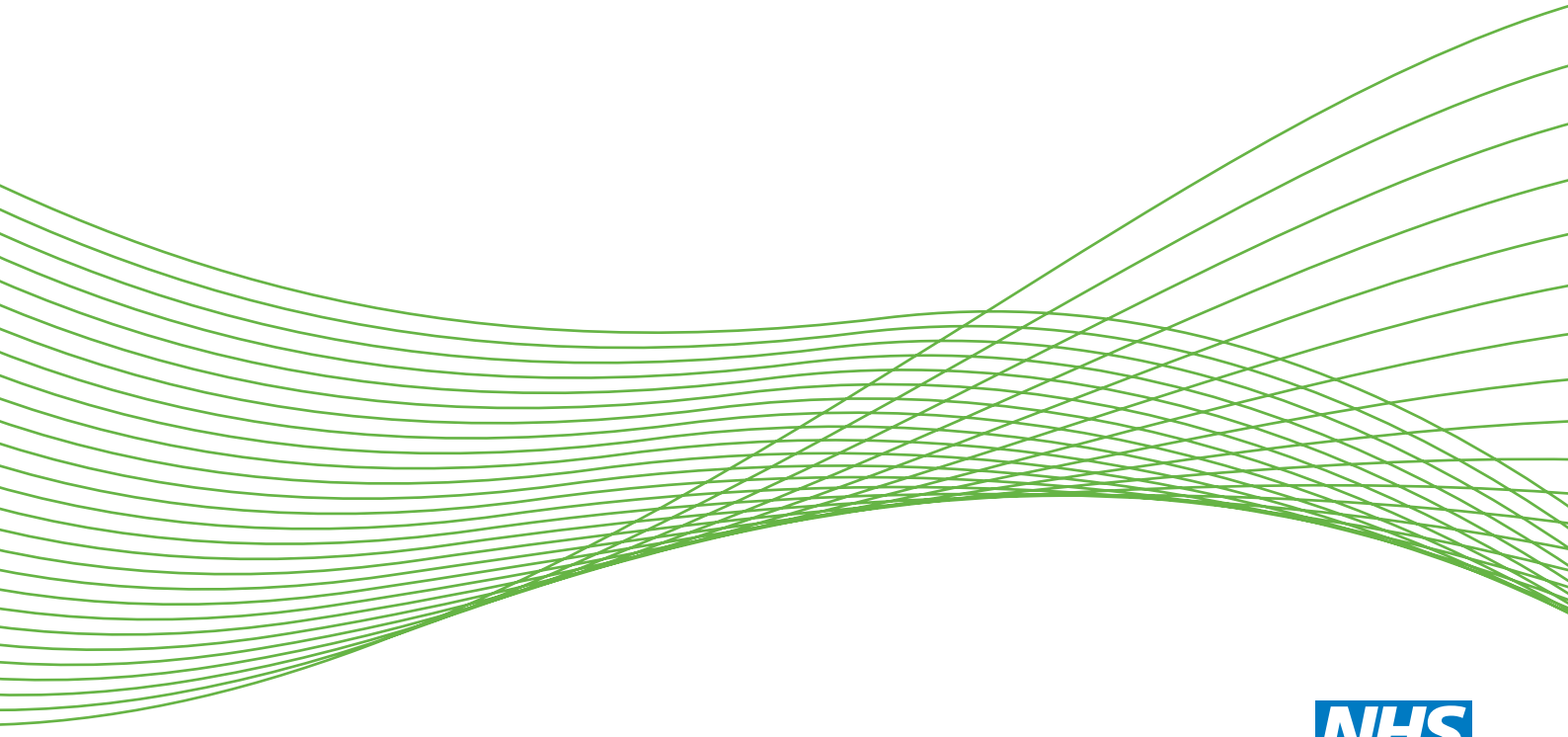

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This report

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Abstract

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

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Background: Prophylactic aspirin has been considered to be beneficial in reducing the risks of heart disease and cancer. However, potential benefits must be balanced against the possible harm from side effects, such as bleeding and gastrointestinal (GI) symptoms. It is particularly important to know the risk of side effects when aspirin is used as primary prevention – that is when used by people as yet free of, but at risk of developing, cardiovascular disease (CVD) or cancer. In this report we aim to identify and re-analyse randomised controlled trials (RCTs), systematic reviews and meta-analyses to summarise the current scientific evidence with a focus on possible harms of prophylactic aspirin in primary prevention of CVD and cancer.

Objectives: To identify RCTs, systematic reviews and meta-analyses of RCTs of the prophylactic use of aspirin in primary prevention of CVD or cancer. To undertake a quality assessment of identified systematic reviews and meta-analyses using meta-analysis to investigate study-level effects on estimates of benefits and risks of adverse events; cumulative meta-analysis; exploratory multivariable meta-regression; and to quantify relative and absolute risks and benefits.

Methods: We identified RCTs, meta-analyses and systematic reviews, and searched electronic bibliographic databases (from 2008 September 2012) including MEDLINE, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, NHS Centre for Reviews and Dissemination, and Science Citation Index. We limited searches to publications since 2008, based on timing of the most recent comprehensive systematic reviews.

Results: In total, 2572 potentially relevant papers were identified and 27 met the inclusion criteria. Benefits of aspirin ranged from 6% reduction in relative risk (RR) for all-cause mortality [RR 0.94, 95% confidence interval (CI) 0.88 to 1.00] and 10% reduction in major cardiovascular events (MCEs) (RR 0.90, 95% CI 0.85 to 0.96) to a reduction in total coronary heart disease (CHD) of 15% (RR 0.85, 95% CI 0.69 to 1.06). Reported pooled odds ratios (ORs) for total cancer mortality ranged between 0.76 (95% CI 0.66 to 0.88) and 0.93 (95% CI 0.84 to 1.03). Inclusion of the Women's Health Study changed the estimated OR to 0.82 (95% CI 0.69 to 0.97). Aspirin reduced reported colorectal cancer (CRC) incidence (OR 0.66, 95% CI 0.90 to 1.02). However, including studies in which aspirin was given every other day raised the OR to 0.91 (95% CI 0.74 to 1.11). Reported cancer benefits appeared approximately 5 years from start of treatment. Calculation of absolute effects per 100,000 patient-years of follow-up showed reductions ranging from 33 to 46 deaths (all-cause mortality), 60–84 MCEs and 47–64 incidents of CHD and a possible avoidance of 34 deaths from CRC. Reported increased RRs of adverse events from aspirin use were 37% for 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. Pooled estimates of increased RR for bleeding remained stable across trials conducted over several decades. Estimates of absolute rates of harm from 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. Meta-analyses aimed at judging risk of bleed according to sex and in individuals with diabetes were insufficiently powered for firm conclusions to be drawn.

Limitations: Searches were date limited to 2008 because of the intense interest that this subject has generated and the cataloguing of all primary research in so many previous systematic reviews. A further limitation was our potential over-reliance on study-level systematic reviews in which the person-years of follow-up were not accurately ascertainable. However, estimates of number of events averted or incurred through aspirin use calculated from data in study-level meta-analyses did not differ substantially from estimates based on individual patient data-level meta-analyses, for which person-years of follow-up were more accurate (although based on less-than-complete assemblies of currently available primary studies).

Conclusions: We have found that there is a fine balance between benefits and risks from regular aspirin use in primary prevention of CVD. Effects on cancer prevention have a long lead time and are at present reliant on post hoc analyses. All absolute effects are relatively small compared with the burden of these diseases. Several potentially relevant ongoing trials will be completed between 2013 and 2019, which may clarify the extent of benefit of aspirin in reducing cancer incidence and mortality. Future research considerations include expanding the use of IPD meta-analysis of RCTs by pooling data from available studies and investigating the impact of different dose regimens on cardiovascular and cancer outcomes.

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Contents

List of abbreviations ix

Scientific summary xi

Chapter 1 Introduction and background 1
Introduction 1
Background 1
Description of technology under assessment 5
Summary 6

Chapter 2 Definition of the decision problem 7
Scoping searches 7
Plan of work 7
Objectives 7

Chapter 3 Methods 9
Search strategies 9
Search restrictions 9
Data extraction strategy 10
Quality assessment strategy 10
Data synthesis 10
Summary 12

Chapter 4 Results 13
Result of searches 13
Description of included studies 13
Summary 26

Chapter 5 Evidence synthesis 29
Meta-analyses of primary outcomes: cardiovascular disease 29
Meta-analyses of primary outcomes: primary prevention of cancer 40
Meta-analyses of primary outcomes: primary prevention of cardiovascular disease in diabetes 46
Systematic review evidence on adverse events: cardiovascular disease studies 47
Systematic review evidence on adverse events: cancer studies 66
Systematic review evidence on adverse events: diabetes studies 68
Summary of evidence synthesis 70

Chapter 6 Discussion 73
Summary of methods and principal findings 73
Limitations in the evidence base 74
Research needs 75
Implications for practice 75
Conclusions 75

Acknowledgements 77

References 79

Appendix 1 Record of searches undertaken 85

Appendix 2 Clinical trials identified from the United Kingdom Clinical Research Network Portfolio and ClinicalTrials.gov databases 89

Appendix 3 Table of reasons for excluding studies at full paper (*n*=121) 93

Appendix 4 Classification of included aspirin publications according to condition and study design (*n*=27) 101

Appendix 5 Quality assessment of included studies (*n*=27) 103

Appendix 6 Data extraction 129

Appendix 7 Summaries of included papers and evidence 227

Appendix 8 Revised protocol: 2 September 2012 239

List of abbreviations

AAA	Aspirin for Asymptomatic Atherosclerosis
ACCEPT-D	Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes
APLASA	antiphospholipid antibody acetylsalicylic acid
ARRIVE	Aspirin to Reduce Risk of Initial Vascular Events
ASA	acetylsalicylic acid
ASCEND	A Study of Cardiovascular Events in Diabetes
ASPREE	Aspirin in Reducing Events in the Elderly
ATT	Antithrombotic Trialists
BDT	British Doctors Trial
BP	blood pressure
CARING	Chronotherapy with Low-dose Aspirin for Primary Prevention
CHD	coronary heart disease
CI	confidence interval
COD	cause of death
COX	cyclo-oxygenase
COX-1	cyclo-oxygenase 1
COX-2	cyclo-oxygenase 2
CRC	colorectal cancer
CRD	Centre for Reviews and Dissemination
CV	cardiovascular
CVD	cardiovascular disease
DoH	Department of Health
ETDRS	Early Treatment Diabetic Retinopathy Study
GI	gastrointestinal
HOT	Hypertension Optimal Treatment
HR	hazard ratio
HTA	Health Technology Assessment
IPD	individual patient data
JPAD	Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes
LCI	lower confidence interval
MACE	major adverse cardiovascular event
MCE	major cardiovascular event
MFU	mean follow-up
MI	myocardial infarction
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNH	number needed to harm
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PHS	Physician's Health Study
POPADAD	Prevention of Progression of Arterial Disease And Diabetes
PPP	Primary Prevention Project
PVD	peripheral vascular disease
RaR	rate ratio
RCT	randomised controlled trial
RR	relative risk
SALT	Swedish Aspirin Low-Dose Trial

SAPAT	Swedish Angina Pectoris Aspirin Trial	UKCRN	United Kingdom Clinical Research Network
TIA	transient ischaemic attack	UK-TIA	Transient Ischaemic Attack trial
TPT	Thrombosis Prevention Trial	USPSTF	US Preventive Services Task Force
UCI	upper confidence interval	WHS	Women's Health Study

Scientific summary

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 ≥ 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.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction and background

Introduction

Taken in appropriate dosage, long-term use of aspirin has for some time been considered to be beneficial in terms of reducing the risks of heart disease and cancer. However, for some individuals, taking aspirin has unwanted side effects such as bleeding and stomach pain. Therefore, the potential benefits of protection must be balanced against the possible harm from side effects. This balance may be different for different people. It is particularly important to know the risk of side effects when aspirin is used as primary prevention – i.e. when used by people as yet free of, but at risk of developing, cardiovascular disease (CVD) or cancer. This report aims to find the current scientific evidence about this and to summarise this literature by looking at the occurrence of side effects from the preventative use of aspirin in people free of CVD and cancer in randomised controlled trials (RCTs), systematic reviews and meta-analyses.

Background

Use of prophylactic aspirin for the primary prevention of CVD has been investigated over the last 25 years. The first RCT on this topic was published in 1988; subsequently, eight further RCTs have been published, the latest in 2010. There are ongoing trials that continue to address this issue. Currently, attention has also focused on the possibility that prophylactic aspirin may have a role in the primary prevention of cancer. In this section we first provide a brief account of the prevalence of CVD and cancer in the UK so as to indicate the potential impact of effective primary prevention measures. Then we describe the possible modes of action by which aspirin may exert its biological effects. Finally, we highlight some of the difficulties encountered by investigators attempting to investigate the benefits of aspirin in primary prevention.

Description of health problem (primary prevention of cardiovascular disease and cancer)

Cancer and CVD exert a heavy burden on the UK population in terms of morbidity, mortality and cost. Primary prevention measures have a large potential impact on these burdens. Some guidelines and investigators have proposed that regular use of aspirin might be effective in this regard. However, some individuals who take aspirin experience unpleasant side effects that occasionally may be life-threatening. This short report aims to review and examine the relevant evidence.

In this report we interpret primary prevention as defined for CVD by the National Institute for Health and Care Excellence (NICE) as follows '. . . interventions that aim to prevent CV [cardiovascular] events in people who have no clinical evidence of CVD'.[1] A similar definition may be used for primary prevention of cancer; we employ a corresponding definition by substituting 'cancer' for 'CVD' in the above statement.

Epidemiology

Cardiovascular disease in England and the UK

Cardiovascular disease [the main form of coronary heart disease (CHD); the main form of coronary CVD and stroke] remains the leading cause of premature death, an increasing cause of morbidity, and a major cause of disability and ill health in the UK.[2–4] Incidence and prevalence of myocardial infarction (MI), stroke and angina increase dramatically with advancing age and are higher in men than in women. It has been estimated that the UK prevalence of CHD is approximately 2.7 million (≈1.6 million men and ≈1 million women).[2–4]

Approximately 1.06 million people with CVD are < 75 years of age. Between 2005 and 2007, the incidence of MI was found to be between 20% and 35% higher in Scotland than in England among both men and women, and the prevalence rate for CHD was comparatively lower in England (3.5%) than in Scotland (4.4%), Wales (4.2%) and Northern Ireland (4.1%).[2–4]

In the UK in 2010, around one-third of all deaths were due to CVD. Approximately 80,000 and 49,000 deaths were caused by CHD and stroke, respectively (*Table 1*).[2] According to British Heart Foundation statistics, there were approximately 80,000 deaths from CHD in the UK, in men and women, and approximately 50,000 from stroke, in 2010.[2]

Cardiovascular disease and diabetes in the UK

In the UK, it is estimated that more than 1 in 20 people have diabetes (either diagnosed or undiagnosed). This translates into approximately 2.9 million people, a figure which is estimated to rise to approximately 5 million by 2025.[5] The risk of CVD is two to three times higher in adults with diabetes.[5–7]

Cancer in the UK

According to Cancer Research UK, more than one in three people in the UK will develop some form of cancer during their lifetime. In 2009, approximately 320,000 people were diagnosed with cancer in the UK. Cancer is predominantly a disease of older people; > 63% of cancer diagnoses are in people aged ≥ 65 years, and 36% in those ≥ 75 years (*Figure 1*). The European age-standardised rate is higher in males than in females (429 per 100,000 vs. 372 per 100,000, respectively).[8] In the UK, around 26% of all deaths are caused by cancer. Lung cancer causes the greatest proportion of deaths in the UK (22%) followed by colorectal cancer (CRC) (10%) and breast cancer (8%).[8]

Current service provision

Management of disease: cardiovascular risk assessment and primary prevention

The assessment of CVD risk is used to identify individuals at increased risk in order to inform about lifestyle advice, preventative measures, and management with drug treatments.[1,9] Risk management programmes typically involve pharmacological treatment (e.g. with statins, antihypertensive drugs), smoking cessation and dietary and other lifestyle advice.[9,10] Factors influencing CVD risk include age, sex, smoking and diabetes status, blood pressure (BP), cholesterol levels and peripheral vascular disease (PVD). Individuals who are asymptomatic and without known CVD are considered at increased risk if their calculated CVD

TABLE 1 Deaths by cause, by age and sex in the UK 2010[a]

COD	Sex	All ages	< 35 years	35–44 years	45–54 years	55–64 years	65–74 years	75+ years
All diseases of circulatory system	Men	87,528	504	1409	3984	8982	16,766	55,883
	Women	91,550	274	566	1523	3382	9004	76,801
	Total	179,078	778	1975	5507	12,364	25,770	132,684
CHD	Men	46,591	102	681	2539	5899	9952	27,418
	Women	33,977	36	166	586	1495	4084	27,610
	Total	80,568	138	847	3125	7394	14,036	55,028
Stroke	Men	19,287	91	224	515	1126	2883	14,448
	Women	30,079	62	131	425	813	2326	26,322
	Total	49,366	153	355	940	1939	5209	40,770

COD, cause of death.
a Courtesy of the British Heart Foundation.[2]

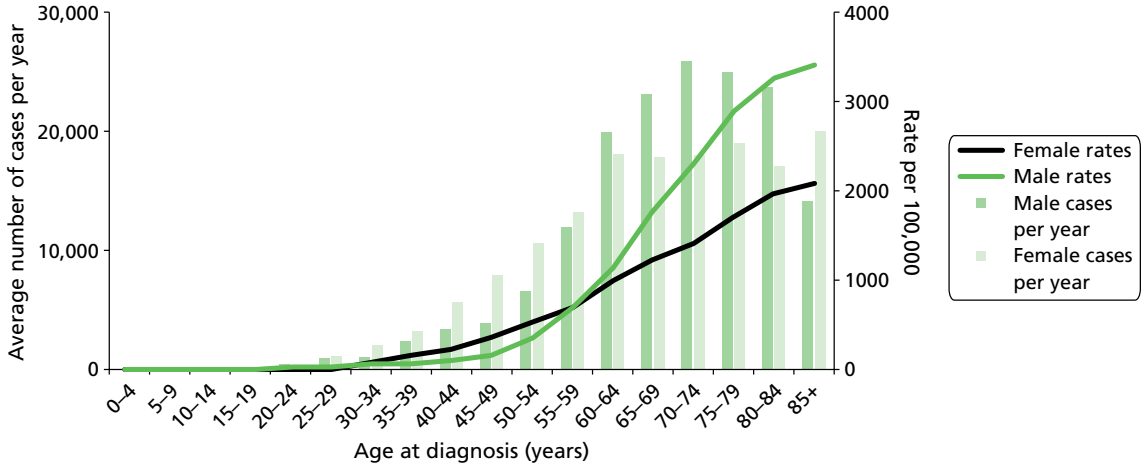


FIGURE 1 Age-specific average incidence of cancers/year (excludes non-melanoma skin cancer). Redrawn from Cancer Research UK.

risk using a recognised scoring tool is at least 20% over 10 years.[1] These individuals might be considered a target population for primary prevention with agents such as aspirin but they represent a small proportion of asymptomatic adults. Currently, patients defined as being at low risk of CVD are asymptomatic, < 75 years old with a calculated risk of < 10% over 10 years, but without known CVD. Their risk management might encompass weight control, dietary advice and lipid modification therapy, if necessary, plus continuing risk assessment.[9,11]

The economic burden of CVD in the UK was estimated to be around £29B in 2004.[12] Similarly, the cost of cancer has been estimated at £18.33B in 2008, and by 2020 the cost is estimated to rise to £24B.[13] The estimated direct cost burden of people with diabetes was approximately £13.8B in 2010.[14] In this context, effective primary prevention has a potentially large medical and economic impact. Should aspirin be found to be effective in primary prevention then its low cost and ease of use offer potential advantages.

Guidelines and recommendations: cardiovascular

According to guidance from NICE, there is currently not enough evidence to recommend prescription of aspirin for primary prevention of CVD. NICE suggests that if a doctor wishes to use it for primary prevention of vascular events in diabetic individuals then the balance of risks and benefits should be assessed for the individual patient.[15] However, international guidelines have adopted differing stances in their recommendations for prophylactic aspirin. These are briefly summarised in *Box 1*.

Guidelines and recommendations: patients with diabetes

The American Diabetic Association/American Heart Association/American College of Cardiology Foundation recently published a scientific statement suggesting that aspirin should not be used for primary prevention of CV events in patients with diabetes who are at low CVD risk (men < 50 years of age; women < 60 years of age with no major additional CVD risk factors; 10-year CVD risk of < 5%).[20]

The European Society of Cardiology does not recommend aspirin for primary prevention in patients with diabetes.[21]

Guidelines and recommendations: primary prevention of cancer

Currently, NICE does not advocate use of aspirin for primary prevention of cancer. Their prescribing guidelines are as follows:

- It is still premature to consider routine administration of daily aspirin to reduce the risk of developing cancer or of dying from it, especially when balancing the benefits against risks of taking aspirin.

BOX 1 Summary of recommendations on prophylactic aspirin use (various organisations)

American Heart Association

Recommends aspirin for patients at 'high risk' of CV events (those with a 10-year risk of 6–10%)[16]

European Stroke Organisation

Not recommended at all for stroke prevention in men, but should considered for MI prevention in men, and should be recommended for stroke prevention for women over the age of 45 years with low risk of intracerebral haemorrhage[17]

US Preventive Services Task Force

Men: not recommended for stroke prevention; recommended for MI prevention in men aged 45–79 years when potential benefits outweigh risks

Women: recommended for women aged 55–79 when benefits outweigh risks of gastrointestinal bleeding; not recommended for stroke prevention in women of < 55 years of age[18]

European Society of Cardiology

Recommended for all patients at 'high risk' and BP controlled (i.e. 10-year risk of CVD markedly increased)[19]

Joint British Societies

Recommended for all patients at 'high risk' of CVD if BP < 150/90 mmHg and aged ≥ 50 years and male or ≥ 65 years and female (high risk = 10-year CVD risk of ≥ 20%)[10]

- It is not yet clear what groups of patients might benefit most and be at the lowest risk from the harms of aspirin.
- Health professionals should be ready to advise those considering taking aspirin to prevent cancer on their risk of vascular events and of extracranial bleeds over time.
- In particular, they should note that aspirin was not found to have any effect on risk of death from cancer until at least 5 years of follow-up.

However, the UK Department of Health (DoH), recently published a document titled 'Improving outcomes, a strategy for cancer', which states 'A recent study has shown that taking low dose aspirin for several years may reduce mortality from cancer by 20%.[22] The DoH will work with Cancer Research UK during 2011 to review these findings and to consider what further work is needed in this area in order to provide appropriate advice to the public'.[23]

The US National Cancer Institute states that research is ongoing to determine the role of aspirin in the prevention of cancer and the US Preventive Services Task Force (USPSTF) recommends against the routine use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) to prevent CRC in individuals at average risk for CRC.[24]

Description of technology under assessment

Aspirin is the generic name for acetylsalicylic acid. Aspirin is administered orally for pain relief, the secondary prevention of CVD and for other purposes. Aspirin is classified in the *British National Formulary* as a 'non-steroidal anti-inflammatory drug', as an 'antiplatelet drug' and as a 'non-opioid analgesic'. Its half-life in the blood is about 20 minutes. The main mode of action is the irreversible inhibition of cyclo-oxygenase 1 (COX-1). This occurs via selective acetylation of the serine hydroxyl group at serine residue 530 in the active site of the enzyme.[25] This effectively blocks the access of arachidonic acid to the enzyme's active binding site, leading to irreversible COX-1 inhibition.[26] This is particularly important for non-nucleated cells, such as platelets, because they are unable to replace the inhibited protein with newly synthesised functional copies of the enzyme. The inhibition is lifelong for the platelet (around 8 days).[27,28] COX-1 inhibition is achieved at relatively low aspirin doses; other isoenzymes of cyclo-oxygenase (COX) require higher doses for effective inhibition.

Aspirin's anti-platelet mechanism is the irreversible inhibition of COX-1, preventing the generation of prostaglandins including thromboxane A2. Thromboxane A2 induces platelet aggregation; consequently, aspirin decreases this and inhibits thrombus formation in the arterial circulation.[29] Endothelial cell COX-1 generates prostacyclin, which inhibits platelet aggregation. However, aspirin is less effective in reducing endothelial prostacyclin production than platelet thromboxane generation because endothelial cells synthesise new functional COX to replace the inhibited enzyme; thus, aspirin delivers a balance between thromboxane A2 and prostacyclin, which favours reduced platelet aggregation and less thrombus formation.

The inhibition of prostaglandin synthesis is also responsible for aspirin's analgesic properties, as prostaglandins are integral to the sensation of pain.

Aspirin and cancer

Studies have suggested that aspirin reduces cancer risk, especially CRC; however, the mechanism is unknown.[30,31] Dovizio *et al.*[32] hypothesised that the role is also likely to involve platelets. It is thought that activated platelets may enhance the metastatic potential of cancer cells. This may occur through a direct interaction and/or the release of soluble mediators, seemingly due to the overexpression of cyclo-oxygenase 2 (COX-2), largely found in inflammatory cells and inducible with mitogens, growth factors and tumour promoters.[33] Therefore, aspirin, as an inhibitor of this enzyme, could consequently reduce metastasis. COX-independent mechanisms of aspirin, such as the inhibition of signalling and the acetylation of extra-COX proteins, have also been suggested to play a role in its putative effect against cancer.

Circulating aspirin is rapidly de-acetylated to release salicylate. Recently, the released salicylate group has been considered to have its own independent anti-inflammatory effects via accelerated polymorphonuclear apoptosis, resulting in an anti-inflammatory effect.[34]

Adverse events

There is a well-documented increased risk of major and minor bleeds and gastric discomfort associated with aspirin use. COX-1 produces prostaglandins that are involved in physiological protection of the gastric mucosa.[35] Aspirin's inhibition of COX-1 suggests a mechanism for unwanted side effects. Efforts to avoid gastric problems have included development of coated or buffered tablets and of NO (nitric oxide)-aspirin, which releases nitric oxide that could counteract the undesired influence of inhibited generation of protective agents. Interestingly, the incidence of gastrointestinal (GI) bleeding from taking low-dose aspirin for a long time appears not to be influenced by the use of enteric-coated compared with buffered aspirin, although these preparations may decrease side effects of gastric irritation and the slow release may be helpful for night pain.[36]

Summary

Although there are guidelines and documented benefits for aspirin in secondary prevention of CVD, and the in vitro mechanisms and potential benefits are clear, 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 as yet free of disease, and as yet at low risk, should be approached with due consideration of aspirin-induced adverse events. No current guidelines 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.

In *Chapter 2* we define the decision problem, plan of work and objectives.

Chapter 2 Definition of the decision problem

Scoping searches

In November 2011, Warwick Evidence carried out a scoping search of current relevant research related to potential harms from aspirin given in low dose (taken as < 300 mg) for any indication [Warwick Evidence. A scoping document for NETSCC: Scoping review on the potential harms from aspirin given in low dose (< 300 mg) for any indication (unpublished). 1–33. 2011]. The aim of the scoping searches was to generate a rapid overview of extent of evidence available on the potential harms from prophylactic aspirin (< 300 mg) for any indication, and to gauge the current status of policy concerning aspirin prophylaxis in primary prevention. We found that aspirin use for secondary prevention of CVD was widely used and recommended but that in recent publications its role in primary prevention had become controversial.

A more recent scoping search in April 2012 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 [Warwick Evidence. Commentary on project NIHR HTA 11/130/02 (unpublished). 1–9. 2012]. Several recent systematic reviews of prophylactic aspirin for the primary prevention of CV events were identified,[37–39] each of which had meta-analysed the same nine RCTs of primary prevention.[40–48]

Similarly, scoping searches indicated the existence of a growing number of reviews and meta-analyses that focus on possible protection by long-term aspirin against cancers and cancer metastasis. Re-analyses of RCTs for primary and secondary prevention of CVD[49] and observational studies have featured in these analyses and, in some, individual patient data (IPD) meta-analyses have been conducted.[22] 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 among the core nine RCTs of long-term aspirin for primary prevention of CVD.

Plan of work

We aimed to undertake four strands in this work to (1) undertake an overview of systematic reviews and meta-analyses of RCTs on the long-term use of aspirin for primary prevention of CVD or cancer with particular reference to adverse events; (2) undertake cumulative meta-analysis of relevant RCTs; (3) investigate the relative influence of individual RCTs on pooled estimates and to undertake study-level meta-analysis of the RCTs; and (4) identify study-level variables that influence occurrence of adverse events and to undertake exploratory multivariable meta-regression of the RCTs.

Objectives

1. To identify RCTs, systematic reviews and meta-analyses of RCTs 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 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.

Chapter 3 Methods

A protocol was produced and approved by the Health Technology Assessment programme before the start of this review (see www.ncchta.org/protocols/). General principles were applied as recommended by the NHS Centre for Reviews and Dissemination (CRD).[50]

Search strategies

The search aimed to identify all references relating to aspirin when taken for the primary prevention of CVD or cancer and adverse events. Searches of electronic bibliographic databases, contact with experts in the field and scrutiny of references of included studies were undertaken. An iterative procedure was used to develop the search strategy, with input from clinical advisors, an experienced information specialist and previous Health Technology Assessment (HTA) and systematic reviews.[22,37,39] The search strategy covered the concepts of aspirin, and prevention and control, and was intentionally kept broad. Copies of the search strategies used in the main electronic databases are provided in *Appendix 1*.

The searches were undertaken in September 2012. Searches were performed 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), HTA databases (NHS CRD); Science Citation Index (SCI) and Conference Proceedings (Web of Science); UK Clinical Research Network Portfolio Database and ClinicalTrials.gov. Citation searches of included studies were undertaken using the Web of Science citation search facility. The reference lists of relevant studies and relevant review articles that were excluded at abstract sift were also checked.

Search restrictions

The searches were restricted to RCTs, meta-analyses and systematic reviews. We limited searches to publications since 2008, based on timing of the most recent comprehensive systematic reviews.

Inclusion of relevant studies

Titles and abstracts of retrieved studies were examined for inclusion by two reviewers independently. Disagreement was resolved by retrieval of the full publication and consensus agreement, with further discussions with a third reviewer if agreement was not obtained. The following inclusion criteria were used:

Study design

Randomised controlled trials, systematic reviews and meta-analyses of RCTs on the use of aspirin in the primary prevention of CVD or cancer.

Studies were defined as primary prevention if participants with previous ischaemic vascular events or relevant cancers had been excluded (or were separately identified and could be excluded) or represented < 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. Systematic reviews needed to report at least one of the following: (1) search strategy; (2) inclusion and exclusion criteria; (3) method of quality assessment; and (4) method of data synthesis.

Population
Adults aged > 18 years without clinical CVD (established or symptomatic), or adults aged > 18 years without cancer (established or symptomatic).

Intervention
Aspirin (any dosage) taken prophylactically for primary prevention of cancer or CVD. Studies reporting on aspirin combination therapy (e.g. aspirin combined with a second antithrombotic agent) were included only if separate placebo and aspirin-only treatment groups were reported separately, in which case data from only these groups were included.

Comparator
Placebo; no aspirin; no other treatment; normal care.

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

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

Exclusion of studies
All designs other than RCTs, systematic reviews or meta-analyses were excluded. Also excluded were systematic reviews or meta-analyses that included only secondary prevention or those in which primary prevention could not be separately identified. Reviews that included only observational studies, and studies not in the English language, were also excluded.

Data extraction strategy

The full data were extracted independently by one reviewer using a data extraction form informed by the NHS CRD and previous systematic reviews.[37,39,49] All included studies were reviewed by a second researcher, and any disagreements were resolved by discussion. Further discrepancies were resolved by discussion, with involvement of a third reviewer when necessary. Summary tables were developed, which list all of the primary outcomes and adverse events reported in the literature. Detailed data extraction was undertaken on the highest quality and most recent systematic reviews/meta-analyses involving patients with CVD and/or cancer and a short-form data extraction process was undertaken for the remaining systematic reviews and any additional RCTs identified.

Quality assessment strategy

Quality criteria were applied independently by two reviewers and an agreed overall quality assessment was determined for each paper. Any disagreements were resolved by independent assessment by a third reviewer. Included systematic reviews were quality assessed using a modified version of the tool developed by the NHS CRD[50] and RCTs were quality assessed using the Cochrane Risk of Bias tool.[51]

Data synthesis

A narrative overview and analysis of included systematic reviews and meta-analyses was undertaken and supplemented with further meta-analysis. Data from included studies were tabulated and summarised. Meta-analyses were undertaken using random-effects models using Stata software version 11 (StataCorp LP, College Station, TX, USA). Particular attention was focused on reporting of adverse events, including overall numbers and proportions, the range of adverse events and definitions used in the primary studies, and methods for synthesis of discrepant event definitions as handled by previous meta-analysts.

Meta-analyses, including cumulative meta-analysis of studies to identify changes through time, and study-level meta-analysis to investigate the relative influence of individual RCTs and exploratory multivariable meta-regression, were undertaken. Because of clinical heterogeneity, a random-effects model was the method of choice, and the tau-squared statistic was recorded. We estimated risk of events in each arm of trials using L'Abbé plots and meta-analysed the risk of events in the comparator arms of trials using fixed-and random-effects meta-analysis. Statistical heterogeneity beyond that expected through chance was investigated using I^2-value.

Quantifying absolute benefits and harms

The number of unwanted events (e.g. all-cause mortality) averted by taking aspirin, and the number of adverse events (e.g. bleeding) incurred from aspirin use, are best calculated using IPD, taking into account the person-years of exposure to aspirin. However, IPD is not available from study-level meta-analyses. There are various ways of calculating the rate of averted or of incurred events from study-level data. We used two methods, described below, and have compared the results across systematic reviews according to outcome.

In the '*aggregated*' method the aggregated number of events (i.e. sum) across all included trials is divided by the aggregated number of persons. This is done separately for each arm (aspirin and control) to calculate 'events/person' (E/p). The weighted average follow-up time across all included trials [mean follow-up (MFU)] (for the intervention arm often equivalent to years of exposure) was calculated as:

$$\text{MFU} = \sum[\text{MTFU} \times \text{PT}]/\sum\text{PT} \quad (1)$$

where MTFU = mean follow-up in each trial and PT = total participants in each trial.

$$\text{Events/person-year (E/py) for each arm} = [\text{E/p}] \times [1/\text{MFU}] \quad (2)$$

The difference between arms then generates the 'events averted/person-year of follow-up or the extra events incurred/person-year of follow-up.

Because these numbers are small, we normalised the results to (1) patients-years' exposure required for one fewer event or for one extra event and (2) number of events averted or extra events incurred should 10,000 patients be followed up for 10 years.

For the '*pooled*' method we used the random-effects pooled risk of event for the control arm (CR). If the systematic review reported pooled odds ratio (ORp) for the outcome then the calculation proceeds as:

$$\text{Odds for an event in control arm (CO)/CR/[1}-\text{CR]} \quad (3)$$

$$\text{Odds for an event in aspirin arm (AO)/CO} \times \text{ORp} \quad (4)$$

$$\text{Risk of an event in the aspirin arm (AR)} = \text{AO}/[\text{AO} + 1] \quad (5)$$

$$\text{Difference in risk between arms (DR)} = \text{AR}-\text{CR} \quad (6)$$

$$\text{Number needed to treat (or harm) (NNT(H))} = 1/\text{DR [i.e. one extra or one fewer event requires NNT(H) persons to be treated with aspirin]} \quad (7)$$

$$\text{As this number requires MFU years of follow-up then MFU} \times \text{NNT(H)} = \text{py follow-up for one less or one extra event} \quad (8)$$

Again, because this number is small, we normalised the results to (1) 'patient-years' follow-up required for one fewer event' or for one extra event and (2) number of events averted or extra events incurred should 10,000 patients be followed up for 10 years.

It has been suggested that the risk observed in the largest available trial may offer a suitable control risk estimate for the number needed to treat (NNT) calculations that are based on study-level meta-analyses; in the face of considerable heterogeneity in control rates, this method was not adopted here because the largest trial for many outcomes was the Women's Health Study (WHS),[46] which was atypical in having an alternate-day dose regimen, a 100% female population and the longest follow-up period.

Summary

Searches aimed to identify RCTs, meta-analyses and systematic reviews relating to adverse events from aspirin when taken by adults for the primary prevention of CVD or cancer.

Searches were performed in MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; CDSR; CENTRAL; DARE, NHS EED, HTA databases (NHS CRD); SCI and Conference Proceedings (Web of Science); United Kingdom Clinical Research Network (UKCRN) Portfolio Database and ClinicalTrials.gov. Searches were limited to publications since 2008. Citation searches and checking of reference lists of included and excluded studies were undertaken. Two reviewers independently applied inclusion and exclusion criteria. Data from included studies were tabulated and summarised. Studies were quality assessed using recognised quality checklists. Meta-analyses, including cumulative meta-analysis, study-level meta-analysis and exploratory multivariable meta-regression, were undertaken. Absolute risks and benefits were calculated.

In *Chapter 4* we describe results, including results of searches and description of included studies.

Chapter 4 Results

The following section provides a summary of the search results, quality assessment and detailed descriptions of included studies.

Result of searches

Number of studies identified

The flow chart outlining the process of identifying relevant literature can be found in *Figure 2*. Following the removal of duplicates, the searches identified 2572 potentially relevant papers. A total of 2425 papers did not meet our inclusion criteria and were removed at title and abstract sift, leaving a total of 147 papers to be further investigated. Of these, 120 were removed at full-paper sift, resulting in 27 papers that met the inclusion criteria.

A search of the UKCRN Portfolio and ClinicalTrials.gov databases retrieved 824 potential trials. The search strategies used can be viewed in *Appendix 1*. After screening by title, 12 trials were identified, two of which had already been identified via the database searches. *Appendix 2* describes these 10 included trials; all have either recently finished or are ongoing.

Number of studies excluded

A list of the 121 papers that were excluded at full-paper sift is provided in *Appendix 3*, with reasons for exclusion. The main reason for excluding a paper at full-paper sift was because it was considered to be a non-systematic review ($n = 52$).

Description of included studies

The following section summarises the main characteristics of the 27 included studies. See *Appendix 4* for a summary of the included papers in relation to study design and disease area.

Quality assessment

The 27 included studies were assessed using standardised or modified quality assessment tools. Systematic reviews of the prophylactic use of aspirin in the primary prevention of CVD ($n = 9$), cancer ($n = 6$) and CVD in patients with diabetes ($n = 7$) were assessed using a modified tool developed by NHS CRD.[50] RCTs concerning CVD ($n = 3$) and CVD in patients with diabetes ($n = 2$) were quality assessed using the Cochrane Risk of Bias tool.[51] The systematic reviews and RCTs were in general very highly rated, representing the high quality of work that has previously been undertaken. Summaries of quality assessment ratings in relation to study design and disease area are provided in *Tables 2–6*. For further details on the quality assessment of included papers, see *Appendix 5*.

The three 'new' RCTs identified in our searches relating to CVD (see *Table 7*) and the two relating to CVD in diabetes added no new evidence to that already included in the systematic reviews identified. The CVD RCTs included (1) a post hoc analysis of the WHS[46] to model treatment effect for individual patients; (2) a core RCT from the nine previously included in systematic reviews; and (3) a pilot RCT. Both RCTs relating to diabetes were from the core nine trials[40–48] previously included in systematic reviews. The searches relating to cancer revealed no new RCTs. Detailed data extraction tables of systematic reviews/meta-analyses involving patients with CVD, cancer and CVD in patients with diabetes are provided in *Appendix 6*.

Cardiovascular disease

Table 7 provides a summary of characteristics of the included systematic reviews and RCTs of aspirin for the primary prevention of CVD. All the papers provided a clear aim. The level of detail in the methods

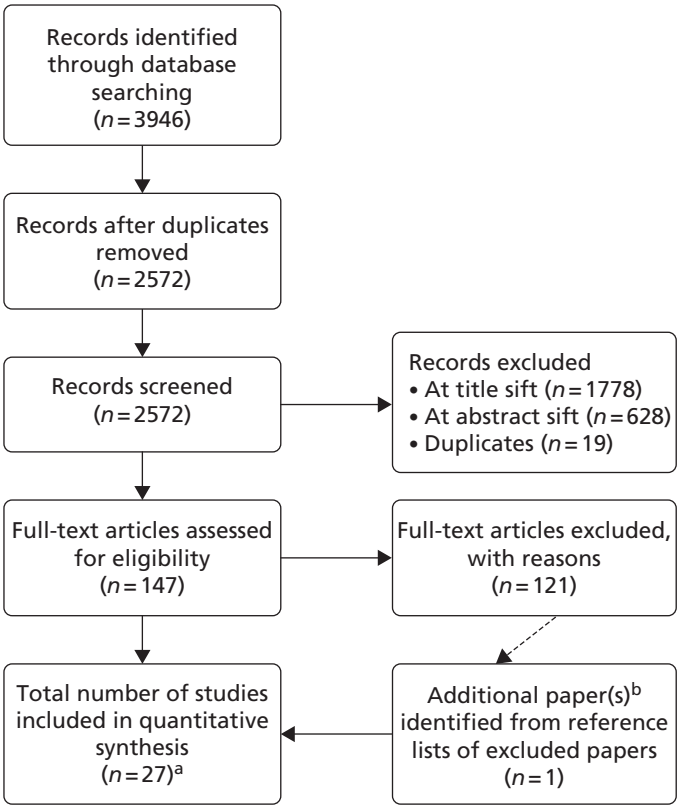


FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. (a) Of the 27 included publications: CVD, systematic reviews = 9, RCTs = 3; cancer, systematic reviews = 6; diabetes, systematic reviews = 7, RCTs = 2; (b) one paper was identified from assessment of reference lists of excluded papers; this had been excluded at abstract sift but was not considered relevant until reading the paper in full.

varied across the papers, with a number of studies not reporting (1) the search strategy ($n = 3$), (2) inclusion criteria ($n = 3$) and (3) quality assessment ($n = 5$). A broad range of outcome measures were reported across the included papers. The majority of the included systematic reviews did not clearly distinguish between primary and secondary outcomes and there was some lack of clarity about what was considered an adverse event (e.g. haemorrhagic stroke, GI bleed, major bleed). See *Appendix 6* for further details.

The nine systematic reviews reported in *Table 7* consistently report on nine (or a subset of the nine) RCTs, depending on the year that their meta-analysis was undertaken. The RCTs are POPADAD (Prevention of Progression of Arterial Disease And Diabetes),[40] BDT (British Doctors Trial),[45] JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes),[44] AAA (Aspirin for Asymptomatic Atherosclerosis),[42] HOT (Hypertension Optimal Treatment),[43] TPT (Thrombosis Prevention Trial),[48] PPP (Primary Prevention Project),[41] PHS (Physician's Health Study)[47] and WHS.[46] These RCTs have been repeatedly subject to meta-analysis of outcomes (*Table 8*).

The majority of these nine RCTs, with the exception of three,[40,42,44] were outside the search dates for the current short report. *Table 9* provides a summary of the aspirin dose and participant characteristics of these nine RCTs.

The latest meta-analysis, published by Seshasai *et al.*,[56] was a study-level meta-analysis that carefully assessed the risk of bleeding (total bleeds and major bleeds). The review team also identified an IPD meta-analysis by Baigent *et al.*[53] examining outcomes and patient subgroups (according to age, sex, diabetes, smoking, mean BP, blood cholesterol, body mass index) in more detail than in a study-level meta-analysis.

TABLE 2 Summary table of quality assessment ratings of systematic reviews of aspirin for the primary prevention of CVD (n=9)[a]

Question	Adelman 2011[52]	ATT 2009[53]	Bartolucci 2011[37]	Berger 2011[39]	Raju 2011[38]	Raju 2012[54]	Selak 2010[55]	Seshasai 2012[56]	Wolff 2009[57]
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of 1 inclusion criterion and 1 exclusion criterion was required to score 'Yes'*	Unclear[a]	Yes	No	Yes	Yes	Yes	Unclear[c]	Yes	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of 1 search terms and 1 bibliographic database identified*	Yes	Unclear[b]	No	Yes	Yes	Yes	No	Yes	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No	No	No	No	Yes	Yes	No	Yes	Yes
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes	Yes	Yes	Yes	Yes	Yes	No[c]	Yes	Yes
Aspirin dose	✓	✓	✓	✓	✓	✓	✗	✓	✓
Aspirin frequency	✓	✓	✓	✓	✓	✓	✗	✓	✓
No. of participants	✓	✓	✓	✓	✓	✓	✗	✓	✓
Age	✓	✓	✓	✓	✓	✓	✗	✓	✓
Sex	✓	✓	✓	✓	✓	✓	✗	✓	✓
Length of follow-up	✓	✓	✓	✓	✓	✓	✗	✓	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*	Yes	Unclear[d]	Unclear[e]	Yes	Yes	Yes	Yes	Yes	Yes[f]
The review primary outcome was presented	✓	Unclear[d]	No[e]	✓	✓	✓	✓	✓	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓	✓	No	✓	✓	✓	✓	✓	✓
6. Was IPD analysed?	No	✓	No	No	No	Yes[g]	Yes[c]	No	No

ATT, Antithrombotic Trialists; CASP, Critical Appraisal Skills Programme.
a No formal listing; criteria more or less implicit.
b The review stated 'Electronic searches established that no similar trials of aspirin had been reported since 2002.'
c The study was based on a previous systematic review, i.e. the IPD meta-analysis reported by the Antithrombotic Trialists in 2009[53] (see above).
d Many outcomes identified and analysed, a primary outcome not specified; review discussed the balance between benefits and harms each represented by various outcomes.
e The review stated 'aspirin may have a differential effect on different aspects of CV disease'; thus many outcomes were identified and analysed, a primary outcome not specified; the review discussed the balance between benefits and harms each represented by various outcomes.
f Analytical framework and key questions were defined.
g This paper was a review of other reviews and considered the IPD meta-analysis reported by the Antithrombotic Trialists in 2009.[53]
Based on NHS CRD.[50]

TABLE 3 Summary table of quality assessment ratings of RCTs of aspirin for the primary prevention of CVD (n=3)[a]

Question	[a]Nelson 2008[58]	[b]Dorresteijin 2011[59]	Fowkes 2010[42]
1. Adequate sequence generation	Yes	Yes	Yes
2. Adequate allocation concealment	Unclear	Yes	Yes
3. Blinding (especially outcome assessment)	Yes ('double-blind')	Yes	Yes
4. Incomplete outcome data addressed	Yes (reported 12-month follow-up attendance)	Yes	Yes
5. Free of selective reporting	Yes	Yes	Yes
6. Free of other potential bias[c]	Yes	Yes	Yes

a This was a pilot study and no primary outcome events occurred (some secondary outcome events were reported).
b This was a post hoc analysis of IPD in the WHS RCT, predicting levels of benefit according to baseline characteristics with regard to MCEs. The above assessment is based on the original study.
c For example, similarity at baseline, power assessment, conflict of interest.
Based on the Cochrane Risk of Bias tool.[51]

In the following section we evaluate the four most recent meta-analyses further,[37,38,53,56] including the systematic reviews by Baigent *et al.*[53] and Seshasai *et al.*[56] We will also refer to the recent high-quality review of reviews by Raju *et al.*,[38] who examined the findings from these meta-analyses.[54] See *Appendix 6* for detailed data extraction of these two studies and a short-form extraction of the remaining studies included.

The paper by Seshasai *et al.*[56] was the most recent and highest-quality study-level meta-analysis concerned with aspirin for the primary prevention of CVD. Seshasai *et al.* reported meta-analyses for nine outcomes based on nine RCTs (see *Table 9*) published between 1988 and 2010 encompassing 102,621 individuals.[40–48] Seshasai *et al.*[56] stated that '. . . primary efficacy endpoints were total CHD and total cancer mortality'. Adverse events were classified as non-trivial bleeds and all bleeds. Haemorrhagic stroke was not selected as an outcome.

Baigent *et al.*[53] used IPD to analyse the effects of aspirin compared with placebo according to baseline risk of CVD. The meta-analyses by Bartolucci *et al.*,[37] Raju *et al.*[38] and Seshasai *et al.*[56] pooled data from the same nine RCTs (see *Table 9*) but included different overall numbers of participants: 100,038,[37] 100,076[38] and 102,621.[56]

Raju *et al.*[54] considered the differences among recent meta-analyses in terms of reported samples. First, it was recognised that Seshasai *et al.*[56] included 2545 warfarin-treated patients, whereas Bartolucci *et al.*[37] and Raju *et al.*[38] excluded these patients. Second, Bartolucci *et al.*[37] excluded 60 patients for reasons that were unclear.

In terms of methods of reporting the pooled data, Seshasai *et al.*[56] and Bartolucci *et al.*[37] both reported pooled treatment effects using the odds ratio (OR). In contrast, Raju *et al.*[38] reported relative risk (RR). Raju *et al.*[54] considered that these differences would not make substantial changes to the interpretation of the findings because the OR approximates the RR when event rates are low. Baigent *et al.*[53] performed IPD analysis using rate ratio (RaR) (events per unit time aspirin/events per unit time control) as the major outcomes statistic.

Adverse events

All of the systematic reviews reported meta-analyses on adverse events except the review by Bartolucci *et al.*,[37] which was supported by an unrestricted research grant from Bayer HealthCare. The balance of incidence between ischaemic stroke (probably reduced by aspirin use) and haemorrhagic stroke (probably

TABLE 4 Summary table of quality assessment ratings of systematic reviews of aspirin for the primary prevention of cancer (n=6)[a]

Question	Mills 2012[60]	Algra 2012[61]	Rothwell 2010[31]	Rothwell 2011[22]	Rothwell 2012[62]	Rothwell 2012[49]
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of 1 inclusion criterion and 1 exclusion criterion was required to score 'Yes'*	Yes	Yes	Yes	Yes	Yes	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of 1 search terms and 1 bibliographic database identified*	Yes	Yes	No[a]	Yes	Yes	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool e.g. CASP, CRD, Cochrane, etc.)*	No	Unclear[b]	No[c]	No[d]	No[d]	No[d]
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes	Yes	Yes	Yes	Yes	Yes
Aspirin dose	✓	✓	✓	✓	✓	✓
Aspirin frequency	✓	✓	✓	✓	✓	✓
Number of participants	✓	✓	✓	✓	✓	✓
Age	✓	✓	✓	✓	✓	✓
Sex	✓	✓	✓	✓	✓	✓
Length of follow-up	✓	✓	✓	✓	✓	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*	Yes	Yes[e]	Yes[f]	Yes[g]	Yes[g]	Yes[g]
the review primary outcome was presented	✓	✓	✓	✓	✓	✓
quantitative results for the primary outcome were presented in sufficient detail	✓	✓	✓	✓	✓	✓
6. Was IPD analysed?	No	Yes	Yes	Yes	Yes	Yes

CASP, Critical Appraisal Skills Programme.
a Trials of aspirin vs. control in the UK or Sweden in the 1980s and early 1990s were studied; however, how these were found or identified was not described.
b No formal assessment was attempted; however, methods used for ascertainment of cancers in each study were described in detail.
c No formal assessment tool was used.
d No formal assessment was undertaken and no assessment tool was used.
e Primary outcome implicit and abstract.
f Primary outcome implicit.
g Primary outcome implicit in title, etc.
Based on NHS CRD.[50]

TABLE 5 Summary table of quality assessment of systematic reviews of aspirin for the primary prevention of CVD in patients with diabetes (n=7)[a]

Question	Butalia 2011[63]	Calvin 2009[64]	De Berardis 2009[65]	Simpson 2011[66]	Stavrakis 2011[67]	Younis 2010[68]	Zhang 2010[69]
1. Are any inclusion/ exclusion criteria reported in the review? *A minimum of 1 inclusion criterion and 1 exclusion criterion was required to score 'Yes'*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of 1 search terms and 1 bibliographic database identified*	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool e.g. CASP, CRD, Cochrane, etc.)*	Yes	Yes	Yes	Yes	Yes	Yes	No
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Aspirin dose	✓	✓	✓	✓	✓	✓	✓
Aspirin frequency	✓	✓	✓	✓	✓	✓	✓
No. of participants	✓	✓	✓	✓	✓	✓	✓
Age	✓	✓	✓	✓	✓	✓	✓
Sex	✓	✓	✓	✓	✓	✓	✓
Length of follow-up	✓	✓	✓	✓	✓	✓	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*	Yes	Yes	Yes	Yes	Yes	Yes	Unclear[a]
The review primary outcome was presented	✓	✓	✓	✓	✓	✓	✗[a]
Quantitative results for the primary outcome were presented in sufficient detail	✓	✓	✓	✓	✓	✓	✗[a]
6. Was IPD analysed?	No	No	No	No	No	No	No

CASP, Critical Appraisal Skills Programme.
a Cardiovascular events appear to be the primary outcome but this was not explicit; the review discussed the balance between benefits and harms each represented by various outcomes.
Based on NHS CRD.[50]

TABLE 6 Summary table of quality assessment ratings of RCTs of aspirin for the primary prevention of CVD in patients with diabetes (n=2)[a]

Question	Belch 2008[40]	Ogawa 2008[44]
1. Adequate sequence generation	Yes	Yes
2. Adequate allocation concealment	Yes	Yes
3. Blinding (especially outcome assessment)	Yes (*'double blind'*)	Open label study for patients; assessors blinded
4. Incomplete outcome data addressed	Yes (*'All analyses were done on an intention-to-treat basis'*)	Yes (*'intention-to-treat principle'*)
5. Free of selective reporting	Yes	Yes
6. Free of other potential bias[a]	Yes	Yes

a For example, similarity at baseline, power assessment, conflict of interest.
Based on the Cochrane Risk of Bias tool.[53]

increased by aspirin use) is the major issue that was addressed in published IPD meta-analysis study by Baigent *et al.*[53] Adverse events will be considered in more detail in the evidence synthesis section of this report.

Cancer

We identified six systematic reviews assessing the effect of aspirin on cancer mortality and cancer incidence with publication dates ranging from 2010 to 2012 (*Table 10*). All these reviews used RCTs in which the primary outcome was not cancer. Instead the reviews considered trials in which the primary outcomes were primary or secondary prevention of CVD, which were retrospectively used to follow-up cancer deaths. Five of the six reviews we identified were analyses by a group led by Rothwell.[22,31,49,61,62] The most recent highest-quality systematic review from these six publications was fully data extracted and summarised (see *Appendix 6*).

Using the NHS CRD[50] assessment criteria, the quality of the papers by Rothwell and colleagues was generally rated as high,[22,31,49,62] (see *Quality assessment*, above).

Rothwell and colleagues[49] suggest that some trials had reported deaths due to cancer which was diagnosed prior to randomisation. In this case conclusions on the *primary* prevention of cancer should be drawn with caution.

Adverse events

Adverse events were reported in only one of the systematic reviews related to cancer.

Cardiovascular events in patients with diabetes

Table 11 provides details and publication dates of the seven identified systematic reviews meta-analysing the effect of aspirin in the primary prevention of CVD events in patients with diabetes.

Adverse events

Adverse events will be considered in detail in the evidence synthesis section of report.

TABLE 7 Summary characteristics of included CVD systematic reviews and RCTs

Study type	Aims	Methods	Outcomes	Adverse events[a]
Systematic reviews (first author, year)				
Adelman 2011[52]	To examine sex differences in the primary prevention of stroke with aspirin	*Search*: MEDLINE, guidelines from US, British and European organisations and citations from articles *Inclusion criteria*: Not reported *Analysis*: Study-level meta-analysis *Quality assessment*: None	Combination of MI, stroke or vascular death; risk of haemorrhage was reported	Not clearly distinguished – haemorrhagic stroke
Baigent 2009[53]	To undertake an IPD analysis to compare primary with secondary intervention	*Search*: Electronic searches, not specified *Inclusion criteria*: Trials on randomised comparison of aspirin vs. no aspirin *Analysis*: Collaborative meta-analysis of individual participant data *Quality assessment*: None	Serious vascular event, defined as MI, stroke, or death from a vascular cause; major coronary event; any stroke; death from any cause; and major extracranial bleed; MI and strokes (fatal or non-fatal)	Not clearly distinguished – major extracranial bleed and haemorrhagic stroke
Bartolucci, 2011[37]	To update previous six-trial meta-analysis with three most recent trials	Search: No systematic review methods, meta-analysis only *Inclusion criteria*: Not reported *Analysis*: Study-level meta-analysis *Quality assessment*: None	(1) Total CHD as non-fatal and fatal MI and death due to CHD; (2) non-fatal MI as confirmed MI that did not result in death; (3) total CV events as a composite of CV death, MI or stroke; (4) stroke as ischaemic or haemorrhagic stroke that may or may not have resulted in death; (5) CV mortality as death related to CHD or stroke; and (6) all-cause mortality as death related to any cause	None
Berger, 2011[39]	To update a previous meta-analysis that included six trials to test null hypothesis that there is no net benefit relative to risk for aspirin for patients without clinical CVD	*Search*: MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE *Inclusion criteria*: Aspirin alone was used for the primary prevention of CVD; comparisons of	Risk ratio of aspirin therapy compared with placebo or control on the composite end point, which includes non-fatal MI, non-fatal stroke or CV death. All MI, all stroke, all-cause mortality, and	Not clearly distinguished – Major bleeding and haemorrhagic stroke

TABLE 7 Summary characteristics of included CVD systematic reviews and RCTs (*continued*)

Study type	Aims	Methods	Outcomes	Adverse events[a]
		outcomes were made between aspirin and placebo or open control groups; data were available on MI, stroke and CV deaths *Analysis*: Meta-regression *Quality assessment*: None	CV mortality. Occurrence of major bleeding	
Raju, 2011[38]	To perform a meta-analysis of all RCTs on aspirin for the primary prevention of CVD	*Search*: MEDLINE, EMBASE, CINAHL, The Cochrane Library, ClinicalTrials.gov, references of articles, related items search in PubMed, contacted experts *Inclusion criteria*: RCT; adults without a history of symptomatic CVD (> 95% of enrolled participants); compare aspirin (any dose) with placebo or no aspirin treatment for the prevention of CVD; report at least one of the following outcomes: all-cause mortality, CV mortality, MI, stroke, and bleeding *Analysis*: Pooling individual trial data with the DerSimonian and Laird random-effects model *Quality assessment*: Cochrane Risk of Bias tool	All-cause mortality, CV mortality, MCEs, MI, all-cause stroke, ischaemic stroke, haemorrhagic stroke, GI bleed, major bleed	Not clearly distinguished – haemorrhagic stroke, GI bleed and major bleeds
Raj 2012[54]	To critically examine recent meta-analyses comparing aspirin with placebo or no aspirin for the primary prevention of CVD	*Search*: MEDLINE (2007–12) *Inclusion criteria*: Not reported *Analysis*: Review of reviews *Quality assessment*: Strength of recommendation/level of evidence rating	All-cause and CV mortality, MI, stroke, MCEs, bleeding	No new data

continued

TABLE 7 Summary characteristics of included CVD systematic reviews and RCTs (*continued*)

Study type	Aims	Methods	Outcomes	Adverse events[a]
Selak 2010[55]	To model benefit vs. harm of aspirin for primary prevention of CVD for age group, sex and risk categories using data from ATT Collaboration meta-analysis	*Search*: No search reported *Inclusion criteria*: Trials on randomised comparison of aspirin vs. no aspirin *Analysis*: Rates of benefit (avoided vascular events) and harm (additional major extracranial bleeds) for each sex and age group were calculated from data from the six RCTs included in the ATT Collaboration meta-analysis[55] *Quality assessment*: None	CV events and serious side effects (extracranial bleeding) Vascular events: MI, stroke (haemorrhagic or other) or death from a vascular cause (CHD death, stroke death or other vascular death, including sudden death, death from pulmonary embolism and death from any haemorrhage)	Not clearly distinguished – as Baigent *et al.*[55]
Seshasai 2012[56]	To provide an updated synthesis of evidence regarding the wider role of aspirin in primary prevention of CVD and cancer	*Search*: Pubmed and The Cochrane Library until June 2011 *Inclusion criteria*: Randomised placebo-controlled trials (primary prevention studies) with at least 1000 participants (without previous CHD or stroke), and had at least 1 year of follow-up during which CHD and/or CVD outcomes (CHD, stroke, cerebrovascular disease, heart failure and PAD) were recorded as the main end points, and details were provided of bleeding events *Analysis*: Study-level meta-analysis *Quality assessment*: Delphi scoring system	Total CHD and total cancer mortality. Subtypes of vascular disease, total CVD events, cause specific death and all-cause mortality. Non-trivial bleeding (fatal bleeding from any site; cerebrovascular or retinal bleeding; bleeding from hollow viscus; bleeding requiring hospitalisation and/or transfusion; or study-defined major bleeding regardless of source)	Not clearly distinguished – total bleeds, non-trivial bleeds
Wolff 2009[57]	To update previous review (2002 USPSTF review) and focuses on new evidence on the benefits and harms of aspirin for the primary prevention of CVD	*Search*: PubMed and CENTRAL 2001–8 *Inclusion criteria*: Studies that evaluated aspirin vs. control for the primary prevention of CVD events in adults *Analysis*: No meta-analysis; synthesised qualitatively *Quality assessment*: USPSTF criteria	Not clearly reported; some discussion about bleeds	No new data

TABLE 7 Summary characteristics of included CVD systematic reviews and RCTs (*continued*)

Study type	Aims	Methods	Outcomes	Adverse events[a]
RCTs				
Dorresteijin 2011[59]	To identify women who benefit from aspirin 100 mg on alternate days for primary prevention of vascular events by using treatment effect prediction based on individual patient characteristics	*Study design*: RCT data from the WHS	Occurrence of MCEs (i.e. non-fatal MI, non-fatal stroke, or death from CV causes)	Major and minor bleeds, treatment-induced GI bleeds/ peptic ulcers, haematuria, epistaxis and easy bruising
Fowkes 2010[42]	To determine the effectiveness of aspirin in preventing events in people with a low ABI identified on screening the general population. To determine whether screening the general population for a low ABI could identify a higher-risk group who might derive substantial benefit from aspirin therapy	*Study design*: A pragmatic intention-to-treat, double-blind, RCT	Composite of initial fatal or non-fatal coronary event or stroke or revascularisation. All initial vascular events defined as a composite of a primary end point event or angina, intermittent claudication, or TIA. All-cause mortality	Major haemorrhage, fatal SAHs or SDHs, haemorrhagic stroke, fatal and non-fatal subarachnoid/ subdural, fatal and non-fatal GI, GI ulcer retinal haemorrhage, severe anaemia
Nelson 2008[58]	To determine the feasibility of performing a large clinical trial of the use of aspirin for the primary prevention of CVD in older participants: the ASPirin in Reducing Events in the Elderly (ASPREE) trial	*Study design*: Randomised double-blind, placebo-controlled pilot trial	The level of response to participation by GPs; the level of response from potential trial participants; the screening-to-randomisation rate to ensure the recruitment target could be achieved; and the retention of participants in the trial after 12 months Fatal and non-fatal stroke and coronary events Dementia and clinically significant bleeding (haemorrhagic stroke or GI bleeding requiring transfusion or hospitalisation)	GI and intracranial bleeding – adverse events were determined by patient and investigator report, a search of the medical record held by the practice, and further tracing of data to source documents in specialist and hospital records

ABI, ankle–brachial index; ATT, Antithrombotic Trialists; MCE, major cardiovascular event; PAD, peripheral arterial disease; SAH, subarachnoid haemorrhage; SDH, subdural haemorrhage; TIA, transient ischaemic attack.

a We considered adverse events attributable only to aspirin. If the outcomes were thought to indicate aspirin benefit but have been called 'adverse events' we have written 'not clearly distinguished'.

TABLE 8 Cardiovascular systematic reviews and their included RCTs

RCTs included: systematic review (first author, year, country)	BDT 1988[45]	PHS 1989[47]	HOT 1998[43]	TPT 1998[48]	PPP 2001[41]	WHS 2005[46]	POPADAD 2008[40]	JPAD 2008[44]	AAA 2010[42]
Adelman 2011,[52] USA	✓	✓	✓	✓	✓	✓			✓
ATT 2009,[53] UK	✓	✓	✓	✓	✓	✓			
Bartolucci, 2011,[37] USA	✓	✓	✓	✓	✓	✓	✓	✓	✓
Berger 2011,[39] USA	✓	✓	✓	✓	✓	✓	✓	✓	✓
Raju 2011,[38] Australia	✓	✓	✓	✓	✓	✓	✓	✓	✓
Raju 2012,[54] Australia	✓	✓	✓	✓	✓	✓	✓	✓	✓
Selak 2010,[55] New Zealand	As ATT	As ATT	As ATT	As ATT	As ATT	As ATT			
Seshasai 2012,[56] UK	✓	✓	✓	✓	✓	✓	✓	✓	✓
Wolff 2009,[57] USA	✓	✓	✓	✓	✓	✓	✓	✓	✓

ATT, Antithrombotic Trialists.
AAA (*JAMA* **303**: 841); BDT (*BMJ* **296**: 313); HOT (*Lancet* **351**: 1755); JPAD (*JAMA* **300**: 2134); PHS (*NEJM* **321**: 129); PPP (*Lancet* **357**: 89); POPADAD (*BMJ* **337**: a1840); TPT (*Lancet* **351**: 233); WHS (*NEJM* **352**: 1293).

TABLE 9 Aspirin dose and participant characteristics in the nine RCTs of primary prevention using aspirin

Study	Aspirin dose	Sex	Participants (*n*)
BDT[45]	500 mg/day	All male	5139
PHS[47]	325 mg every other day	All male	22,071
HOT[43]	75 mg/day	47% female	18,790
TPT[48]	75 mg/day	All male	5058
PPP[41]	100 mg/day	58% female	4495
WHS[46]	100 mg every other day	All female	39,876
POPADAD[40]	100 mg/day	56% female	1276
JPAD[44]	81 or 100 mg/day	45% female	2539
AAA[42]	100 mg/day	72% female	3350

AAA (*JAMA* **303**: 841); BDT (*BMJ* **296**: 313); HOT (*Lancet* **351**: 1755); JPAD (*JAMA* **300**: 2134); PHS (*NEJM* **321**: 129); PPP (*Lancet* **357**: 89); POPADAD (*BMJ* **337**: a1840); TPT (*Lancet* **351**: 233); WHS (*NEJM* **352**: 1293).

TABLE 10 Summary characteristics of included systematic reviews investigating aspirin in the primary prevention cancer

Systematic reviews (first author, year)	Aims	Methods	Outcomes[a]	Adverse events
Algra 2012[61]	To compare effects of aspirin on risk and outcome of cancer in observational studies vs. randomised trials	*Search*: PubMed (only for case control and cohort studies), trials from Rothwell *et al.*[22] *Inclusion criteria*: for RCTs: RCT of aspirin vs. no aspirin, mean treatment duration of > 4 years *Analysis*: Study-level meta-analysis *Quality assessment*: No formal quality assessment	Death, incidence of CRC, death due to cancer, cancers with distant metastasis	Not reported
Mills 2012[60]	To determine whether cancer mortality is also reduced in the shorter term	*Search*: extensive database search *Inclusion criteria*: RCTs evaluating low-dose, daily aspirin *Analysis*: Study-level meta-analysis *Quality assessment*: Quality assessment without validated tool	Non-CV death and cancer death	Not reported
Rothwell 2010[31]	To establish the effects of aspirin on incidence and mortality due to CRC in relation to dose of aspirin and duration of trial	*Search*: No formal search *Inclusion criteria*: RCTs on daily aspirin vs. control, minimum of 1000 participants Median scheduled treatment period of 2.5 years	Death due to CRC and incidence of CRC	Not reported
Rothwell 2011[22]	To determine the effect of aspirin on risk of fatal cancer by analysis of IPD for deaths due to cancer during randomised trials of daily aspirin vs. control	*Search*: Trials from the ATT Collaboration review, PubMed, EMBASE and Cochrane database *Inclusion criteria*: Randomised trials of aspirin (any dose) vs. control with a mean duration of trial treatment of at least 4 years *Analysis*: IPD meta-analysis *Quality assessment*: No formal quality assessment	Total cancer mortality, all-cause mortality, death by site of primary cancer	Not reported
Rothwell 2012[49]	To establish the effect of aspirin on cancer incidence and the time course of effects on cancer incidence	*Search*: trials from ATT review, PubMed, Cochrane database and EMBASE	Non-vascular death, cancer incidence and cancer death	Major extracranial bleeds

continued

TABLE 10 Summary characteristics of included systematic reviews investigating aspirin in the primary prevention cancer (*continued*)

Systematic reviews (first author, year)	Aims	Methods	Outcomes[a]	Adverse events
		Inclusion criteria: RCTs on daily aspirin, Exclusion of short-term trials (≤ 90 days) and trials in the treatment or prevention of secondary cancer or colonic polyps *Analysis*: IPD meta-analysis *Quality assessment*: no formal quality assessment		
Rothwell 2012[62]	To study metastasis at initial diagnosis and during subsequent follow-up in all participants with a new diagnosis of cancer	*Search*: refers to Rothwell *et al.*[22,49] *Inclusion criteria*: UK trials of daily aspirin vs. control, exclusion of trials with < 10 incident cancers, trials of short-term (≤ 90 days) treatment and trials in the treatment or prevention of secondary cancer or colonic polyps *Analysis*: IPD meta-analysis *Quality assessment*: No formal quality assessment	Incidence and mortality due to cancer, cancer metastasis	Not reported

ATT, Antithrombotic Trialists.
a Primary outcome was generally not reported.

Summary

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. The 27 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 use of aspirin for primary prevention of CVD ($n = 3$) and CVD in patients with diabetes ($n = 2$). Quality ratings were, in general, high.

Systematic reviews consistently reported on nine (or a subset of the nine) RCTs, depending on the year in which their meta-analysis was undertaken. No completed RCTs providing new information were identified.

In the next chapter we report evidence syntheses. First, meta-analyses of primary outcomes are reported and subsequently meta-analyses of adverse events.

TABLE 11 Summary characteristics of included systematic reviews and RCTs investigating aspirin in the primary prevention CV events in patients with diabetes

Study type	Aims	Methods	Outcomes	Adverse events
Systematic reviews (first author, year)				
Butalia 2011[63]	To quantify treatment effects in absolute terms of the risk–benefit trade-off of aspirin therapy in patients with diabetes	*Search*: MEDLINE, PubMed, EMBASE, The Cochrane Library and BIOSIS *Inclusion criteria*: RCTs of aspirin vs. placebo or vitamins; adults ≥ 18 years with diabetes without previous historical or clinical evidence of CVD *Analysis*: Study-level meta-analysis *Quality assessment*: Jadad	*Primary*: MACE (composite of non-fatal MI, non-fatal ischaemic stroke, CV death due to MI and ischaemic stroke) and all-cause mortality *Secondary*: Total MI, total stroke, CV death	Haemorrhage, GI bleeding and other GI events
Calvin, 2009[64]	To determine whether the effect of aspirin in the primary prevention of CV events differs between patients with and without diabetes	*Search*: Comprehensive search *Inclusion criteria*: RCTs of aspirin vs. placebo, patients with diabetes without previous historical evidence of MI *Analysis*: Study-level meta-analysis *Quality assessment*: Quality assessment without validated tool	Ischaemic stroke, MI and all-cause mortality	Not reported
De Berardis 2009[65]	To evaluate the benefits and harms of low dose aspirin in people with diabetes and no CVD	*Search*: MEDLINE, CENTRAL *Inclusion criteria*: RCTs with > 500 participants of aspirin vs. placebo or no treatment, patients with diabetes mellitus and no CVD *Analysis*: Study-level meta-analysis *Quality assessment*: Quality assessment without validated tool	*Primary*: MCE *Secondary*: All-cause mortality, death from CV causes, non-fatal MI and non-fatal stroke	Any bleeding, GI bleeding, GI symptoms, incidence of cancer
Simpson 2011[66]	To explore the relationship between aspirin dose and prevention of CV events	*Search*: Comprehensive search *Inclusion criteria*: RCTs, patients with diabetes with or without prior CV event, aspirin (any dose) vs. placebo *Analysis*: Study-level meta-analysis *Quality assessment*: 27-item checklist	*Primary*: All-cause mortality *Secondary*: CV-related mortality, MI, stroke	Not reported
Stavrakis 2011[67]	To evaluate the effect of low-dose aspirin for the primary prevention of CV event in patients with diabetes mellitus	*Search*: MEDLINE, EMBASE *Inclusion criteria*: RCTs on aspirin vs. placebo or no treatment, patients with diabetes and no history of CV events *Analysis*: Study-level meta-analysis *Quality assessment*: Jadad	Total mortality, CV mortality (deaths from MI or stroke), major adverse CV events (death from CV causes, non-fatal MI, non-fatal stroke), MI (fatal and non-fatal), stroke (fatal and non-fatal)	Major bleeding events including GI bleeding

continued

TABLE 11 Summary characteristics of included systematic reviews and RCTs investigating aspirin in the primary prevention CV events in patients with diabetes (*continued*)

Study type	Aims	Methods	Outcomes	Adverse events
Younis 2010[68]	To evaluate the benefits of aspirin in people with diabetes mellitus for the primary prevention of CVD	*Search*: MEDLINE and Cochrane database *Inclusion criteria*: RCTs, diabetic patients, aspirin as a primary prevention of CVD vs. placebo or no aspirin *Analysis*: Study-level meta-analysis *Quality assessment*: No formal quality assessment	MCE (composite of CV death, non-fatal MI and stroke), total mortality, MI, ischaemic stroke	Bleeding
Zhang 2010[69]	To determine the effect of aspirin therapy in the prevention of CV events in patients with diabetes	*Search*: MEDLINE, EMBASE and CENTRAL *Inclusion criteria*: RCTs on aspirin vs. control, participants with diabetes, at least 12 months' follow-up *Analysis*: Study-level meta-analysis *Quality assessment*: No formal quality assessment	MCEs, all-cause mortality, CV mortality, MI and stroke	Major bleeding
RCTs				
Belch 2008[40]	To assess whether aspirin and antioxidant therapy, combined or alone, are more effective than placebo in reducing the development of CV events in patients with diabetes mellitus and asymptomatic PAD	*Inclusion criteria*: Adults aged ≥ 40 years with type 1 or 2 diabetes and an ankle–brachial pressure index of 0.99 or less, no symptomatic CVD *Intervention*: Daily aspirin vs. placebo	*Primary*: death from CHD or stroke, non-fatal MI or stroke, or amputation above ankle or critical limb ischaemia, death from CHD or stroke	Malignancy, GI bleeding, GI symptoms, arrhythmia, allergy including skin rash
Ogawa 2008[44]	To investigate the efficacy of low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes	*Inclusion criteria*: People with type 2 diabetes mellitus, aged 30–85 years, able to give informed consent *Intervention*: Daily aspirin vs. no aspirin	*Primary*: Any atherosclerotic event (composite of sudden death; death from coronary, cerebrovascular and aortic causes; non-fatal acute MI; unstable angina; newly developed exertional angina; non-fatal ischaemic and haemorrhagic stroke; TIA; non-fatal aortic and PVD)	GI events, haemorrhagic events other than haemorrhagic stroke

MACE, major adverse cardiovascular event; MCE, major cardiovascular event; PAD, peripheral arterial disease; TIA, transient ischaemic attack.

Chapter 5 Evidence synthesis

Meta-analyses of primary outcomes: cardiovascular disease

Nine systematic reviews and three RCTs were found to meet the inclusion criteria for aspirin for the primary prevention of CVD. As explained in *Chapter 2*, we selected the four most recent systematic reviews and meta-analyses to investigate in more detail. Details of the other reviews are included in *Chapter 2* and *Appendices 6* and *7*, and referred to in the text where appropriate.

In this section we report on the four selected most recent study-level reviews,[37–39,56] the Antithrombotic Trialists (ATT) IPD-level meta-analysis[53] and we discuss two further relevant reviews.[52,70]

Seshasai et al. 2012

Primary prevention of cardiovascular disease

The authors stated that the '. . . primary efficacy endpoints were total CHD, and total cancer mortality'.[56] Total CHD comprised major cardiovascular events (MCEs) defined as the composite of non-fatal MI, non-fatal stroke or CV death. The reported pooled random-effects OR was 0.86 [95% confidence interval (CI) 0.74 to 1.01] (*Figure 3*).

Only one trial (PHS)[47] reached statistical significance at $p = 0.05$. This trial was the most influential for the pooled estimate (*Figure 4*); when omitted from the analysis the effect size diminishes considerably and the pooled upper confidence interval (UCI) encompasses a worse result for aspirin than for the comparator.

The event rate across studies varied considerably (see *Figure 4a*). The risk in control groups ranged from 1% (WHS)[46] to 12.8% (POPADAD)[40] (*Figure 5*).

Repeated test meta-analysis according to recruitment year indicated that statistical significance in the pooled RR was reached with the inclusion of the PHS study,[47] after which with addition of further studies the pooled estimate tended to diminish (*Figure 6*).

The NNT based on a control group risk of 3.249% (random-effects pooled estimate) and OR of 0.86 calculates to 226. Taking the mean follow-up as 6.9 years, this indicates about 64 fewer events among 10,000 persons followed for 10 years. Seshasai *et al.*[56] reported a reduced event rate of 100/100,000 person-years.

Primary prevention of cancer

Seshasai *et al.*[56] also identified total cancer mortality as a primary outcome (*Figure 7*). The pooled OR from eight RCTs was 0.93 (95% CI 0.84 to 1.03) in favour of aspirin.

No study alone reached statistical significance and no single study was greatly influential for the pooled estimate (*Figure 8a*). The event rate varied across an approximate sixfold range across studies (see *Figure 8b*) in a manner partly explained by differing length of follow-up as indicated for the control group in *Figure 9*.

Based on pooled estimates (OR 0.93 and control risk of 2.155%) and the mean follow-up of 7.1 years, the calculated NNT of 677 suggests that very large numbers of people would need to be treated to prevent one event, equivalent to 21 cancer deaths averted among 10,000 persons followed up for 10 years.

Repeated test meta-analysis according to recruitment year (*Figure 10*) indicated that after the early BDT[45] RCT, the inclusion of subsequent studies pulls the pooled OR towards a null effect for aspirin. The pooled OR failed to reach statistical significance ($p < 0.05$) at any time.

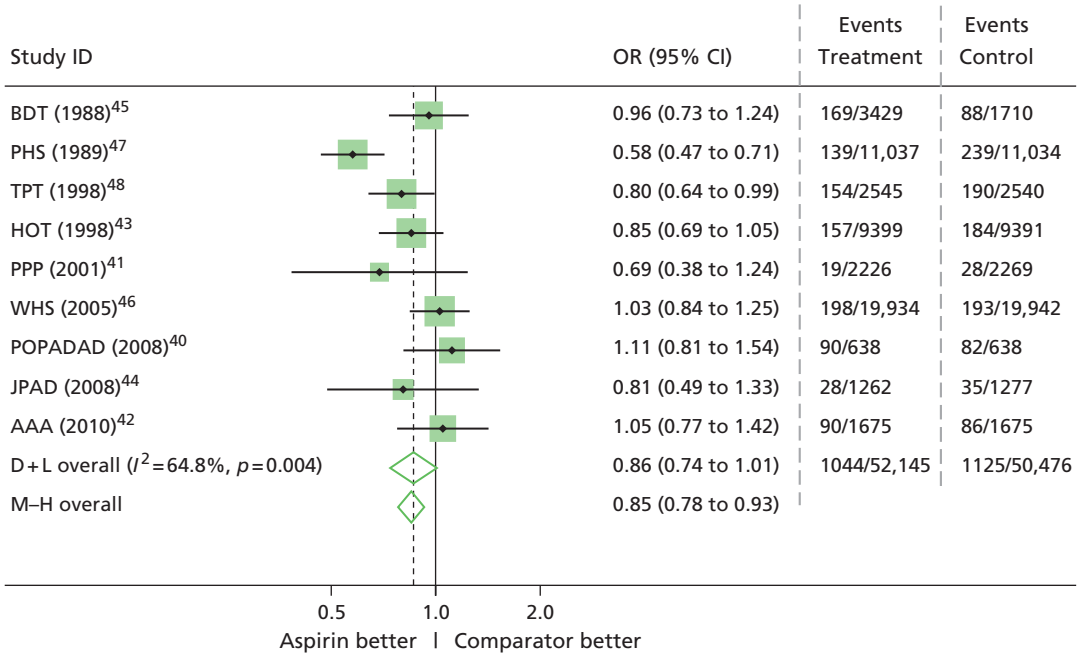


FIGURE 3 Meta-analysis of total CHD.[56]

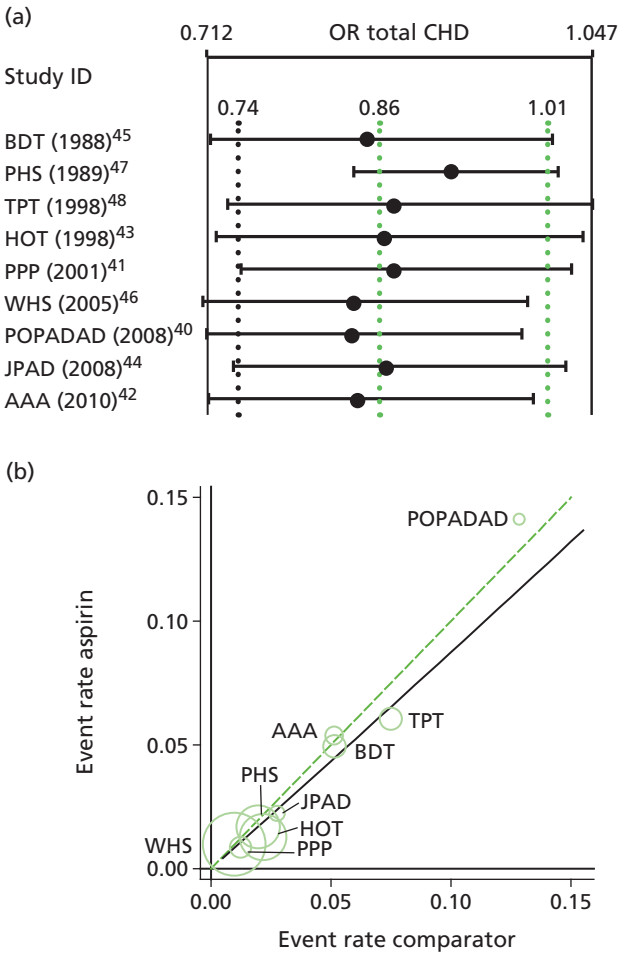


FIGURE 4 (a) Influence of individual studies on pooled OR for total CHD. (b) L'Abbé plot showing total CHD event rates [dashed line = OR of 1; solid line = pooled OR (random effects)].

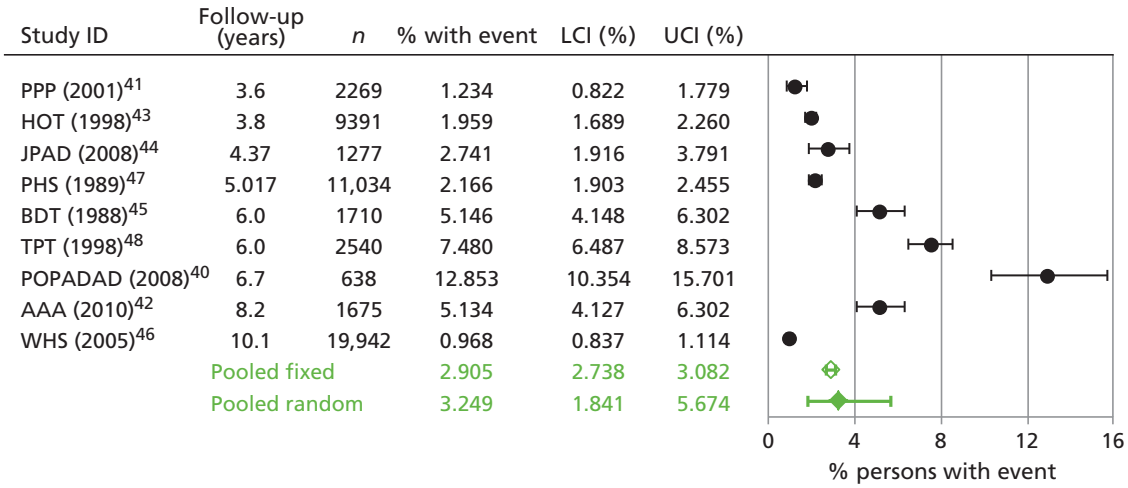


FIGURE 5 Total CHD in control arm; trials arranged according to follow-up (years). LCI, lower confidence interval.

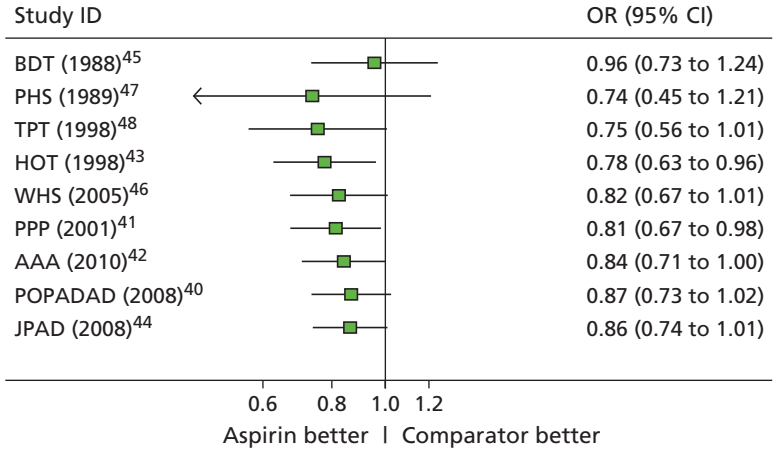


FIGURE 6 Cumulative meta-analysis: OR for total CVD (data from Seshasai *et al.*[56]); studies arranged according to recruitment period.

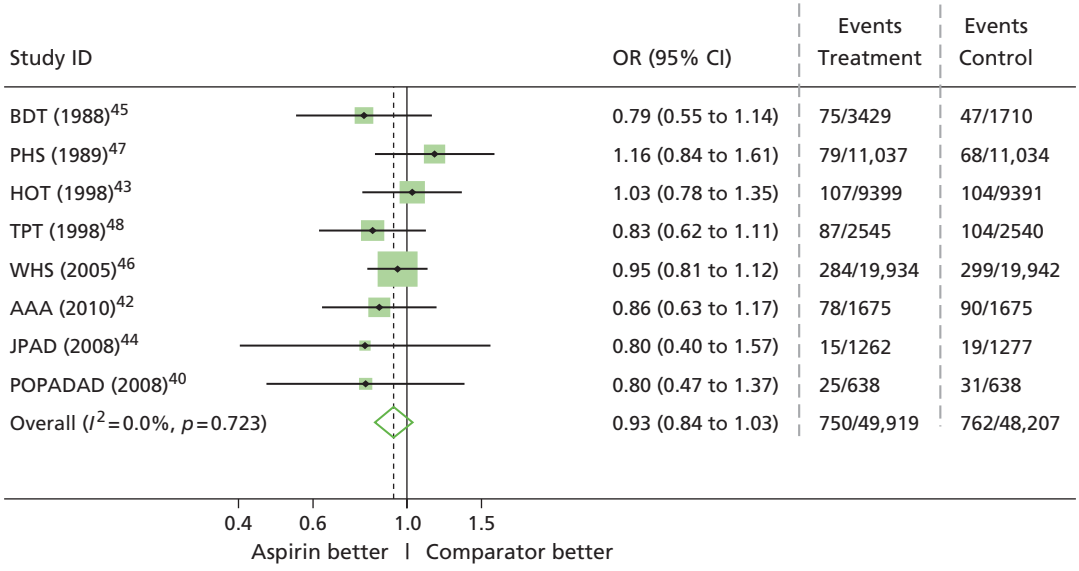


FIGURE 7 Odds ratio for cancer mortality (Seshasai *et al.*[56]).

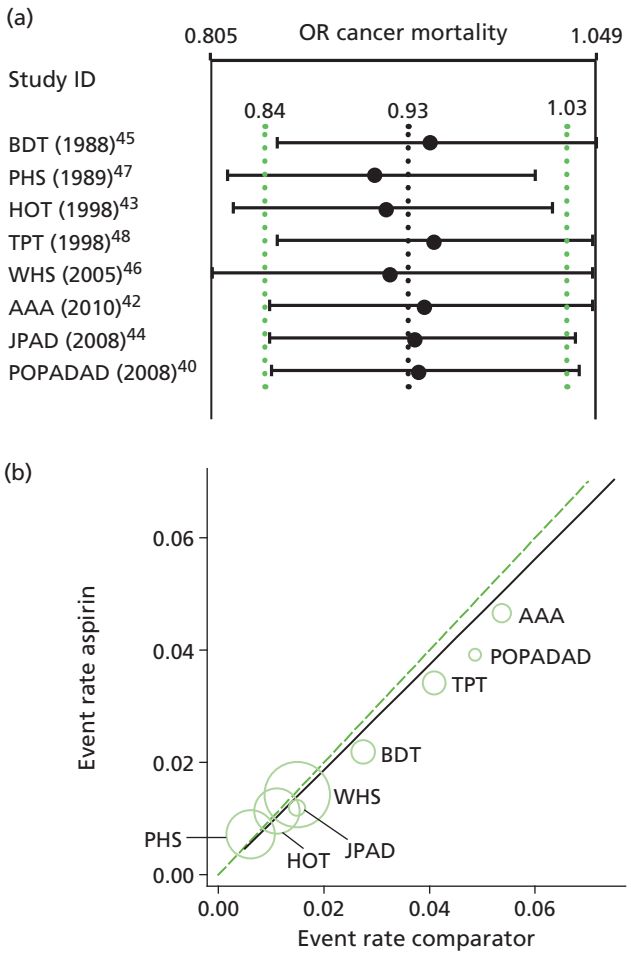


FIGURE 8 (a) Influence of individual studies on pooled OR for cancer mortality. (b) L'Abbé plot showing total cancer mortality event rates [dashed line = OR of 1; solid line = pooled OR (random effects)].

Study ID	Follow-up (years)	*n*	% with event	LCI (%)	UCI (%)
HOT (1998)[43]	3.8	9391	1.107	0.906	1.340
JPAD (2008)[44]	4.37	1277	1.488	0.898	2.314
PHS (1989)[47]	5.017	11,034	0.616	0.479	0.781
BDT (1988)[45]	6.0	1710	2.749	2.026	3.638
TPT (1998)[48]	6.0	2540	4.094	3.358	4.939
POPADAD (2008)[40]	6.7	638	4.859	3.325	6.826
AAA (2010)[42]	8.2	1675	5.373	4.342	6.563
WHS (2005)[46]	10.1	19,942	1.499	1.335	1.678
	Pooled fixed		1.912	1.779	2.056
	Pooled random		2.155	1.283	3.598

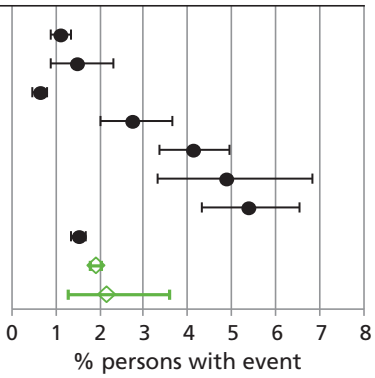


FIGURE 9 Cancer mortality in control arm; trials arranged by length of follow-up (years). LCI, lower confidence interval.

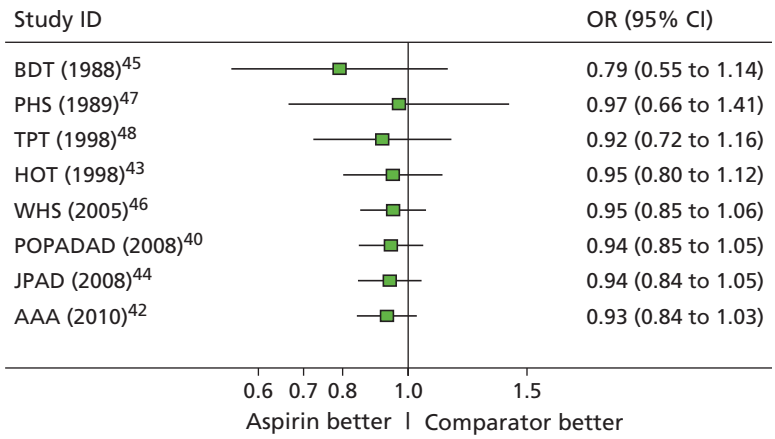


FIGURE 10 Repeated test with accumulating studies arranged by recruitment year (cancer mortality).

Berger et al. (2011)

The primary outcome in this meta-analysis was a composite major cardiovascular event (MCE) end point, which included non-fatal MI, non-fatal stroke or CV death. The reported pooled RR was 0.90 (95% CI 0.85 to 0.96) (*Figure 11*), indicating a 10% risk reduction from aspirin.

Only the PHS[47] reached statistical significance ($p < 0.05$), and this was the single most influential study for the pooled estimate (*Figure 12b*). The event rates varied considerably across trials (see *Figure 12a*). In the control arms the risk of MCE varied between 2.6% and 10.2% (*Figure 13*).

Repeated test meta-analysis according to recruitment year, indicated that statistical significance in the pooled RR was reached with the inclusion of the PHS[47] study, after which with addition of further studies the pooled estimate tended to slightly decrease but remained statistically significant at $p < 0.05$ level (*Figure 14*).

Berger *et al.*[39] reported an NNT of 253 and a mean follow-up of 6.9 years; this yields 57 fewer events for 10,000 persons followed for 10 years. Using a pooled estimate of risk for the control group of 5.84%, the pooled RR of 0.9 and mean follow-up of 6.9 years, a higher value of 84 events avoided is estimated for 10,000 persons followed for 10 years.

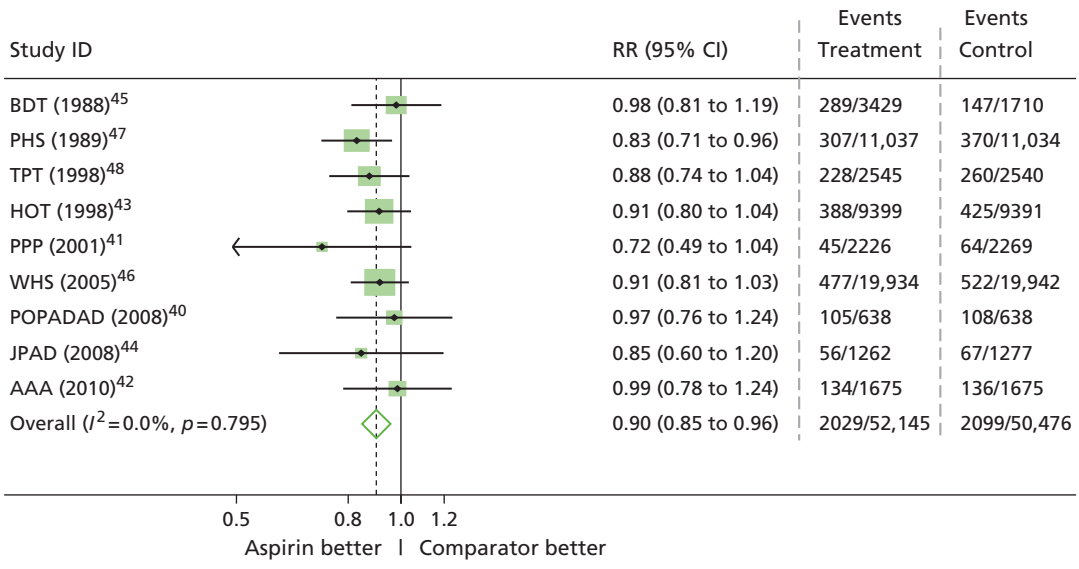


FIGURE 11 Meta-analysis of MCEs (Berger *et al.*).[39]

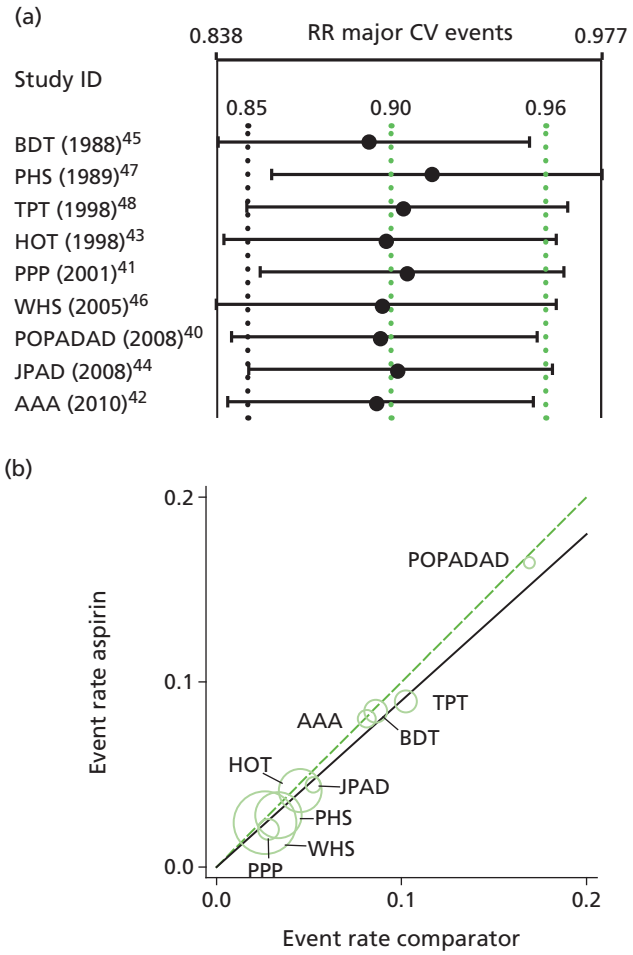


FIGURE 12 (a) Influence of individual studies on pooled RR for total bleed events. (b) L'Abbé plot showing bleed event rates [dashed line = RR of 1; solid line = pooled OR (random effects)].

Study ID	Follow-up (years)	*n*	% with event	LCI (%)	UCI (%)
PPP (2001)[41]	3.6	2269	2.821	2.179	3.588
HOT (1998)[43]	3.8	9391	4.526	4.114	4.966
JPAD (2008)[44]	4.37	1277	5.247	4.089	6.616
PHS (1989)[47]	5.017	11,034	3.353	3.025	3.706
BDT (1988)[45]	6.0	1710	8.596	7.311	10.026
TPT (1998)[48]	6.0	2540	10.236	9.084	11.481
POPADAD (2008)[40]	6.7	638	16.928	14.098	20.067
AAA (2010)[42]	8.2	1675	8.119	6.856	9.532
WHS (2005)[46]	10.1	19,942	2.618	2.400	2.849
	Pooled fixed		4.697	4.501	4.901
	Pooled random		5.840	3.899	8.661

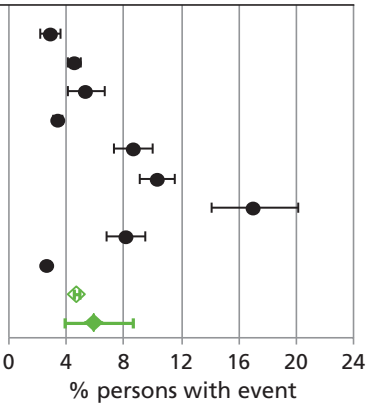


FIGURE 13 Major CV events in control arm [studies arranged according to follow-up (years)]. LCI, lower confidence interval.

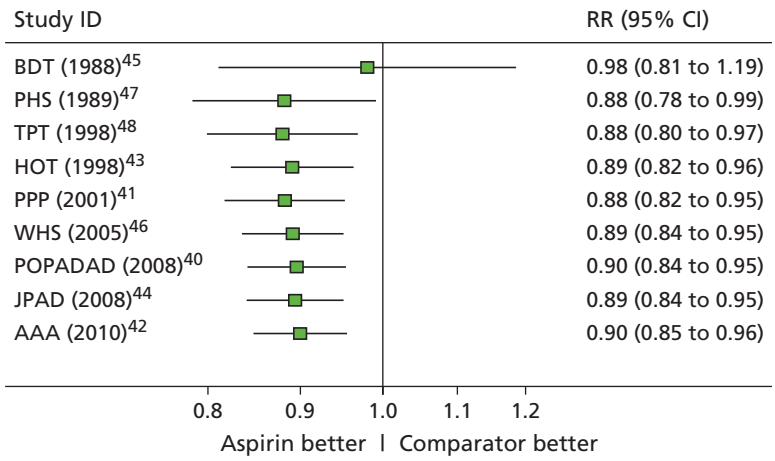


FIGURE 14 Repeated test with accumulating studies arranged by recruitment year (MCE).

Raju et al. (2011)

In this meta-analysis, the primary outcome was specified as part of the objective of the study which was stated as: 'to obtain best estimates of the effect of aspirin on mortality in primary prevention'. The pooled RR of death was 0.94 (95% CI 0.88 to 1.00) indicating a modest 6% reduced risk with aspirin use (*Figure 15*).

No study alone reached statistical significance. The 95% UCI for the pooled RR encompassed no effect. The range in event rate varied considerably across both arms of the trials (*Figure 16a*). No single study was particularly influential for the pooled estimate; however, omitting any one of BDT,[45] PPP,[41] HOT[43] or WHS[46] from the analysis moved the 95% UCI beyond RR of 1.0 (see *Figure 16b*). The risk of death in the control arms varied from 2% in PHS[47] to 16% in the POPADAD[40] study (*Figure 17*). Cleland[71] commented on the Raju meta-analysis,[38] stating that, despite 100,000 years of follow-up, aspirin prevented only 21 deaths. In fact, in aggregating across studies, 21 more deaths are recorded in the aspirin group (1859/50,868 vs. 1838/49,208). However, aggregation by group breaks randomisation and, in this instance, underestimates the contribution of the influential BDT[45] study, in which participants were randomised 2 : 1 aspirin–comparator.

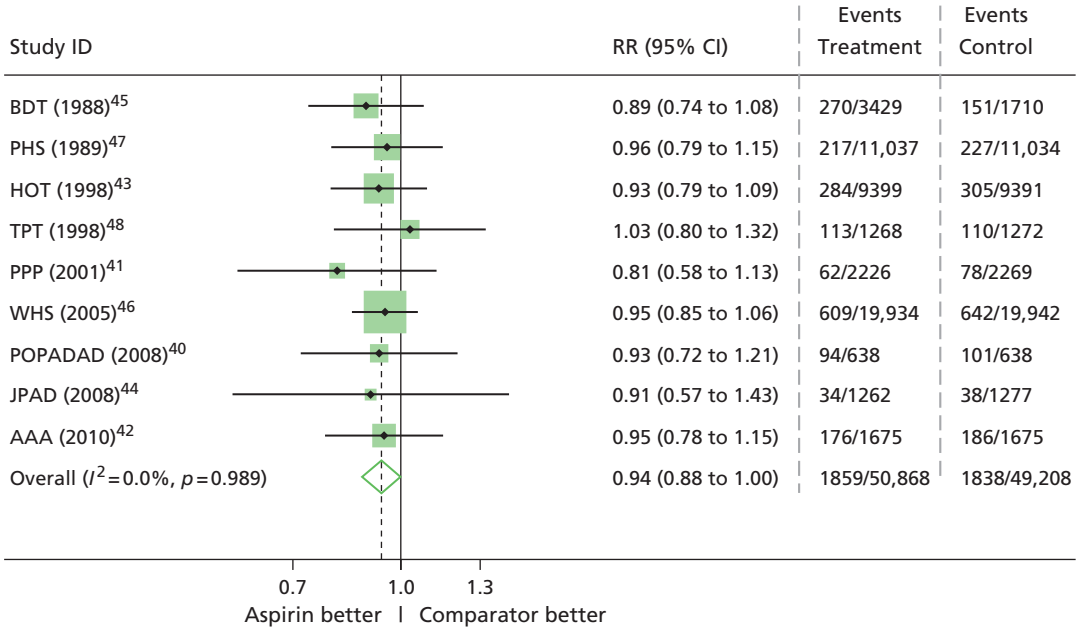


FIGURE 15 Relative risk for all-cause mortality (data from Raju *et al.*[38]).

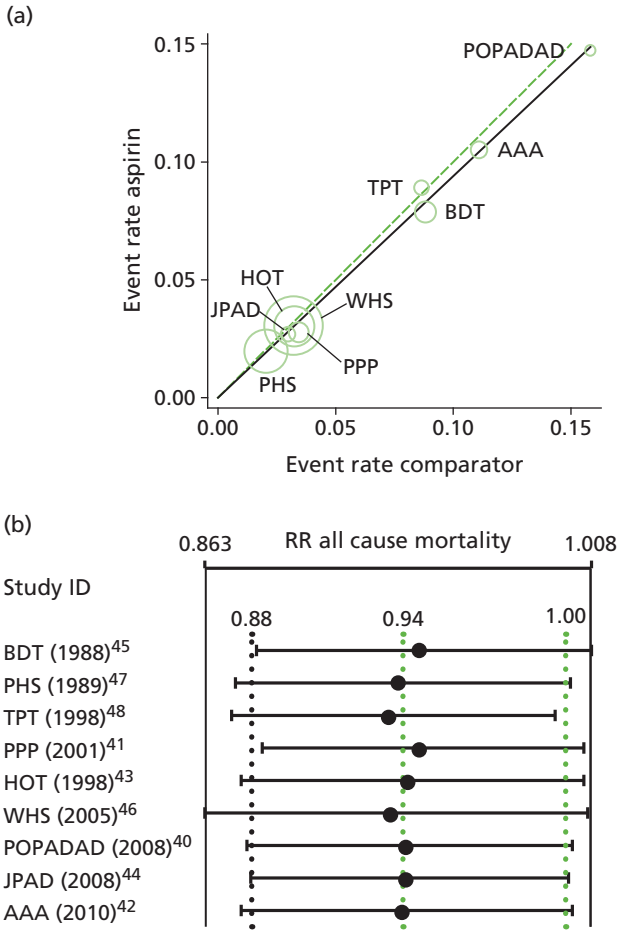


FIGURE 16 (a) L'Abbé plot showing all-cause mortality event rates [dashed line = RR of 1; solid line = pooled RR (random effects)]; (b) Influence of individual studies on pooled RR for all-cause mortality.

Study ID	Follow-up (years)	*n*	% with event	LCI (%)	UCI (%)
PPP (2001)[41]	3.6	2269	3.438	2.727	4.272
HOT (1998)[43]	3.8	9391	3.248	2.898	3.626
JPAD (2008)[44]	4.37	1277	2.976	2.114	4.062
PHS (1989)[47]	5.017	11,034	2.057	1.801	2.340
BDT (1988)[45]	6.0	1710	8.830	7.528	10.276
TPT (1998)[48]	6.0	1272	8.648	7.161	10.329
POPADAD (2008)[40]	6.7	638	15.831	13.083	18.899
AAA (2010)[42]	8.2	1675	11.104	9.639	12.708
WHS (2005)[46]	10.1	19,942	3.219	2.979	3.474
	Pooled fixed		4.277	4.086	4.477
	Pooled random		5.315	3.409	8.196

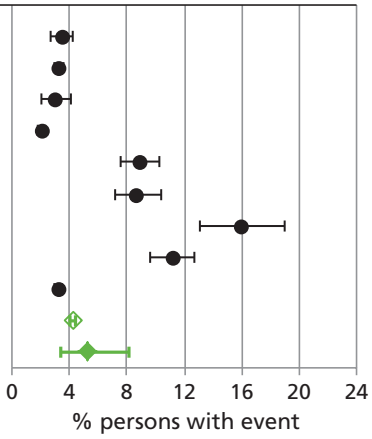


FIGURE 17 All-cause mortality event rate in control arms (data from Raju *et al.*).[38] LCI, lower confidence interval.

Using the 'aggregated' and 'pooled' methods for calculating absolute benefit yielded estimates of 36 and 46 events avoided for 10,000 persons followed up for 10 years. Estimates of 33 and 46 events can be calculated using data from Berger *et al.*,[39] who also meta-analysed all-cause mortality from the same set of nine trials.

Repeated test meta-analysis according to recruitment year indicated that statistical significance in the pooled RR was not convincingly reached at any time; the pooled point estimate remained stable with the addition of further studies (*Figure 18*).

Bartolucci et al. *(2011)*

The primary outcome was not explicitly defined but 'total coronary heart disease' was categorised as prespecified 'outcome 1' and was defined as 'non fatal and fatal MI and death due to CHD'; it was not clear if non-fatal stroke was omitted from this outcome because event and patients numbers were not included in the publication.[37] Pooled OR for this outcome was 0.854 (95% CI 0.688 to 1.061) (*Figure 19*).

Repeated test meta-analysis according to recruitment year indicated that statistical significance in the pooled OR was achieved with inclusion of the four earliest studies; the pooled estimate tended to lower effect size with the addition of subsequent later studies and statistical significance was lost (*Figure 20*).

Because of the lack of event numbers and patient numbers reported, further exploration of this meta-analysis has not been undertaken.

Antithrombic Trialists' Collaboration (individual patient data)

The implicit primary outcome in the ATT Collaboration[53] (IPD) meta-analysis was the risk of any serious vascular event (a composite of MI, stroke or CV death). The pooled RaR (yearly event rate) for the six included RCTs was 0.88 (95% CI 0.82 to 0.94). Data for individual trials for this outcome were not reported. The absolute difference in rates (aspirin minus control) was reported as 0.07%/person-year (70 events avoided for 10,000 persons followed up for 10 years). The RaR for 'any major coronary event' (non-fatal MI or CHD death) was 0.82 (95% CI 0.75 to 0.90) (*Figure 21*) and the corresponding absolute rate difference 0.055% (55 events avoided for 10,000 persons followed up for 10 years). The RaRs for any vascular death and for CHD death were 0.97 (95% CI 0.87 to 1.09) and 0.95 (95% CI 0.82 to 1.10), respectively, indicating a lack of statistically significant benefit from aspirin for these outcomes; the absolute rate difference for CHD death was 0.01%/person-year, equivalent to only 10 events averted among 10,000 persons followed up over 10 years. Overall stroke mortality (including both haemorrhagic and ischaemic stroke) was worse in the aspirin than the comparator group (RaR 1.23, 95% CI 0.84 to 1.74). The event rates for all-cause mortality (any death) were reported as 0.5% (aspirin) and 0.53%/person-year (control); a difference of 0.03% represents 30 deaths avoided should 10,000 persons be followed up for 10 years.

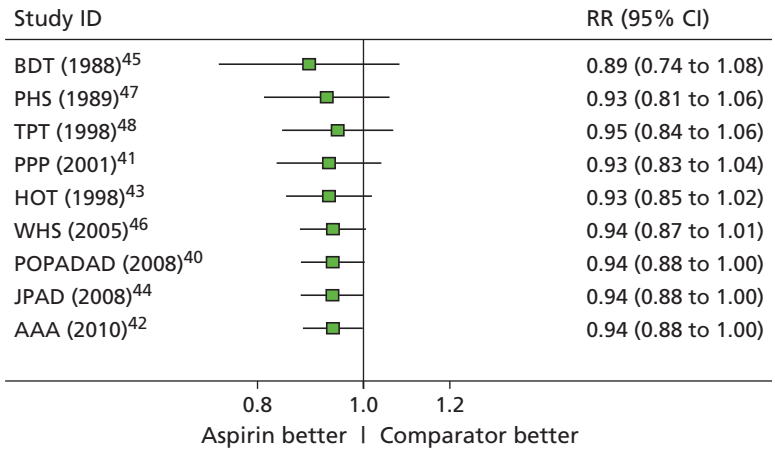


FIGURE 18 Cumulative meta-analysis of RR for all-cause mortality; studies arranged according to recruitment period. [NB-PPP (2001)[41] and HOT (1998)[43] had comparable estimated mid-point recruitment periods (i.e. 1993).]

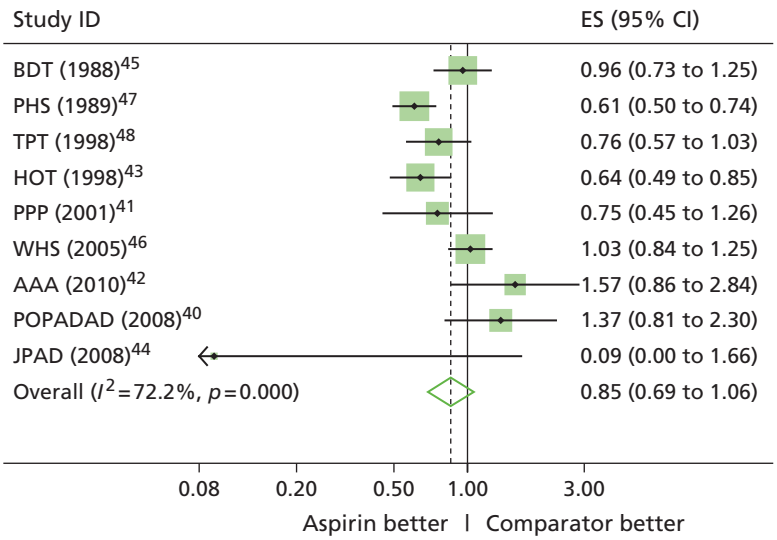


FIGURE 19 Odds ratio for total CHD (data from Bartolucci *et al.*[37]).

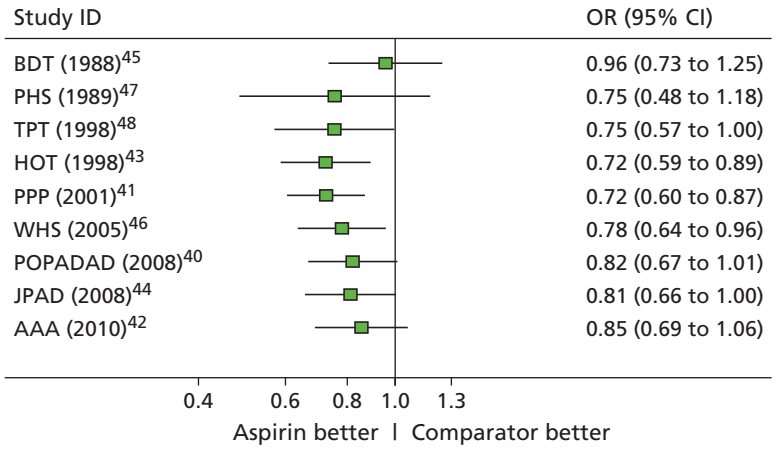


FIGURE 20 Cumulative meta-analysis of OR for total CHD; studies arranged according to recruitment period.

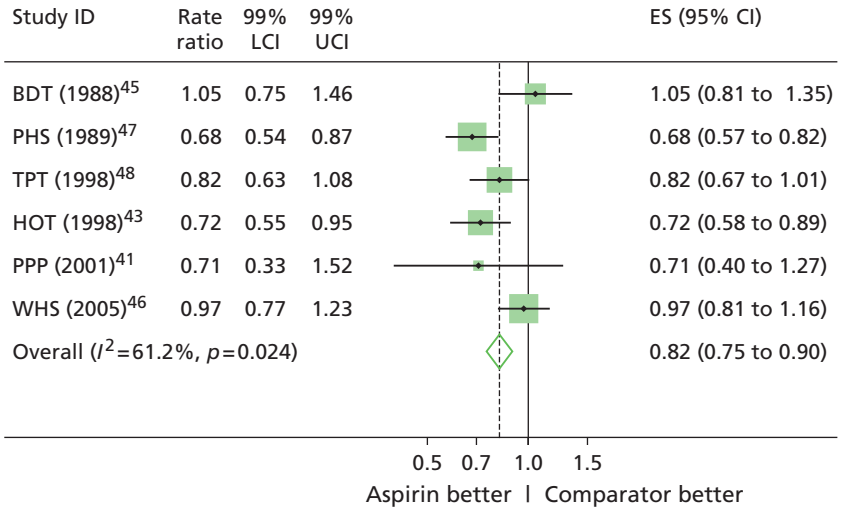


FIGURE 21 Meta-analysis of IPD for any major coronary event reported by the ATT Collaboration. LCI, lower confidence interval.

Selak et al. *(2010)*

Selak *et al.*[55] undertook a modelling study using ATT[53] IPD data so as to assess the balance of harm and benefit in primary prevention of CVD. The expressed aim was to 'interpret results in the light of current New Zealand CVD risk assessment and management guidelines'. The ATT outcome chosen to represent benefit was 'any serious vascular event' (a composite of MI or stroke or CV death) for which the Trialists' IPD analysis estimated an annual RaR of 0.88 (95% CI 0.82 to 0.94) assumed by Selak *et al.*[55] to equate to a 12% reduction in events over 5 years (table 1 in Selak *et al.*,[55] reproduced below in *Table 12*). Selak *et al.*[55] applied this 12% reduction across 5 years to hypothetical populations of 1000 men or women in different 10-year age bands (50–59 years to 80–89 years) for whom the number of expected events per 5 years without aspirin was based on the 5-year risk of a serious CV event predicted using the Framingham equation. For example, for 1000 individuals (any age group or sex) whose 5-year risk of a CV

TABLE 12 Table 1 from Selak *et al.*[55]

Five-year risk of CVD event (%)	CVD events expected[a] (*n*)	Estimated vascular events avoided[b] in 5 years (*n*)							
		Men aged (years)				Women aged (years)			
		50–59	60–69	70–79	80–89	50–59	60–69	70–79	80–89
1	10	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
2	20	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
3	30	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
4	40	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
5	50	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
6	60	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
7	70	8.4	8.4	8.4	8.4	8.4	8.4	8.4	8.4
8	80	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6
9	90	10.8	10.8	10.8	10.8	10.8	10.8	10.8	10.8
10	100	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
11	110	13.2	13.2	13.2	13.2	13.2	13.2	13.2	13.2
12	120	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4
13	130	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6
14	140	16.8	16.8	16.8	16.8	16.8	16.8	16.8	16.8
15	150	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
16	160	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2
17	170	20.4	20.4	20.4	20.4	20.4	20.4	20.4	20.4
18	180	21.6	21.6	21.6	21.6	21.6	21.6	21.6	21.6
19	190	22.8	22.8	22.8	22.8	22.8	22.8	22.8	22.8
20	200	24.0	24.0	24.0	24.0	24.0	24.0	24.0	24.0
***Estimated additional non-fatal extracranial bleeds in 5 years* (n)**									
		2.0	4.3	9.2	19.9	1.0	2.2	4.6	9.9

a Based on the Framingham equation, i.e. including MI, angina, stroke, transient ischaemia, congestive heart failure, PVD- and CVD-related deaths.

b Vascular events avoided defined as MI, stroke (ischaemic, haemorrhagic or other) or vascular death [CHD death, stroke death, or other vascular death (which includes sudden death, death from pulmonary embolism, and death from any haemorrhage)].

Shaded areas indicate combinations of 5-year CVD risk, sex and age for which the estimated number of additional extracranial bleeds are greater than or equal to the estimated number of vascular events avoided.

event is 10%, the expected number of events is 100 in 5 years; applying the assumed 12% reduction delivers 12 events avoided in 5 years (i.e. over 5000 person-years; table 1 in Selak *et al.*[55]). This absolute reduction in events of 12/5000 person-years is considerably larger than the absolute reduction reported by the ATT (0.07%/person-year, or 3.5 events averted over 5000 person-years). The only cohorts of 1000 persons for whom the predicted number of events averted was not greater than the overall rate reported in the ATT meta-analysis were those with the lowest 5-year risks of 1% or 2%.

It is worth noting that most individuals included in the ATT analysis had an estimated 5-year risk of < 2.5%.

Selak *et al.*[55] selected the ATT outcome 'non-fatal extracranial bleeds' to represent harm. For this outcome, the ATT IPD analysis reported 554 events over 660,000 person-years (0.08%/person-year or 4.2 events per 5000 person-years), a risk ratio of 1.54 (95% CI 1.30 to 1.82) and a relative rate of 1.98 greater for men than women, and 2.15 greater for each decade beyond 50–59 years. The absolute rates (rounded to two decimals) for aspirin and control groups were 0.10%/person-year and 0.07%/person-year, respectively (equivalent to 0.03 extra events per 100 person-years or 1.5 events per 5000 person-years). Selak *et al.*[55] allocated one additional (aspirin dependent) event for 1000 women (age band 50–59 years) over 5 years (see *Table 12*). This was multiplied by 1.98 for men and by 2.15 for each sex according to ATT data (see *Table 12*, bottom row).

Assuming equivalence of desirability for beneficial and harmful events the balance between benefit and harm favoured benefit for most risk groups under the age of 80 years (represented by the unshaded cells in *Table 12*).

After considering additional factors, including the availability and effectiveness of other primary prevention measures (especially lipid-lowering with statins), the authors concluded that, in New Zealand, aspirin should be considered for primary prevention of CVD in those persons with five-year CVD risk of ≥ 15%, up to the age of 80 years. This represents only 13% of the New Zealand primary prevention population.[72] A recent UK study of a primary prevention population from England and Wales (encompassing 750,232 individuals, and 2,969,311 person-years of observation, mean age 48 years) estimated that about 10% had a 10-year risk of CVD of ≥ 20%.[3] This similarly implies that aspirin use for those with a 5-year risk of ≥ 15% and up to 80 years of age (suggested by Selak *et al.*[55]) would in practice involve only a small proportion of the primary prevention population in England and Wales.

The crude incidence rate of CVD events [a diagnosis of CVD including angina, MI, stroke or transient ischaemic attacks (TIAs), but not PVD] in the Hippisley-Cox *et al.* study[3] was reported to be 0.73%/person-year for men and 1.05%/person-year for women; remarkably, this is about 10 times greater than that observed in the ATT study.[53]

Further relevant systematic reviews

Adelman *et al.*[52] undertook a study-level subgroup analysis by sex. The primary outcome for this meta-analysis was stroke. The reported OR was 0.83 (95% CI 0.70 to 0.97) for women (based on the HOT,[43] PPP[41] and WHS[46] trials) and 1.13 (95% CI 0.96 to 1.33) for men based on BDT,[45] HOT,[43] PHS,[47] PPP[41] and TPT[48] studies. These results were reproduced from Berger's 2006 meta-analysis.[70]

Meta-analyses of primary outcomes: primary prevention of cancer

We identified six systematic reviews assessing the effect of aspirin on cancer mortality and cancer incidence.

Rothwell et al. *(2010)*

Rothwell *et al.*[31] used IPD to look at the incidence and mortality of CRC over 20 years of follow-up in RCTs that were aimed at investigating effectiveness of aspirin in CVD prevention. Eligible trials needed to have recruited at least 1000 participants and a median scheduled treatment period of at least 2.5 years. Two CVD primary prevention trials were included: TPT[48] and BDT,[45] and two CVD secondary prevention trials (SALT, Swedish Aspirin Low Dose Trial;[73] UK-TIA, Transient Ischaemic Attack trial[74]) in which patients had experienced a TIA or mild stroke before recruitment. Those patients in these trials who were free of cancer at the start of treatment could be construed as suitable individuals in whom to test a hypothetical benefit of aspirin in the primary prevention of CRC. However, it should be borne in mind that post hoc investigation of a post hoc outcome for a subgroup selected post hoc may compromise the continuing integrity of the randomisation. The study's design relies on correct ascertainment, and recording, of cause of death (COD) in the post-trial period.

The pooled OR for death from CRC was 0.66 (95% CI 0.52 to 0.85) (*Figure 22*), indicating a one-third reduction in risk from aspirin use. However, the large WHS[46] and PHS[47] trials were not included in these analyses because alternate-day dose regimens were excluded (WHS[46] and PHS[47] 100 mg and 325 mg aspirin, respectively, on alternate days). Subgroup analysis according to aspirin dose hinted at greater effectiveness for aspirin at lower dosages (75–300 mg daily compared with 500–1200 mg daily). Further subgroup analysis indicated that aspirin was most effective in preventing deaths from colorectal tumours in the proximal colon, and was relatively less effective for rectal tumours. Taking the reported event rates as 119/8282 aspirin users and 121/5751 non-users and a follow-up of 20 years the number of colorectal deaths avoided should 10,000 persons be followed for 10 years is 34. Using the pooled OR of 0.66, taking follow-up as 20 years and the random-effects pooled control risk of 0.0217, the estimated number of deaths avoided, should 10,000 persons be followed for 10 years, is 36.

The hazard ratio (HR) for CRC incidence (irrespective of scheduled duration of aspirin use) was reported as 0.76 (95% CI 0.63 to 0.94) (397 events). For low-dose aspirin (196 events out of 8073 participants) the HR was reported to be 0.75 (95% CI 0.56 to 0.97). It is worth noting that the OR for CRC incidence reported over considerable follow-up in the WHS[46] and PHS[47] trials was 1.07 (95% CI 0.75 to 1.53) and 0.97 (95% CI 0.77 to 1.24), respectively. If HR is equated to OR then inclusion of these trials generates an overall pooled estimate (OR) of 0.91 (95% CI 0.74 to 1.11) (*Figure 23*).

Rothwell et al. *(2011)*

Rothwell *et al.*[22] analysed cancer deaths in eight trials[40,42,44,45,48,74–76] of aspirin for primary or secondary prevention of CVD; these were BDT,[45] UK-TIA,[74] ETDRS (Early Treatment Diabetic Retinopathy Study),[75] SAPAT (Swedish Angina Pectoralis Aspirin Trial),[76] TPT,[48] JPAD,[44] POPADAD[40] and AAA[42] trials. Seven of these were available for IPD analysis.[40,42,44,48,74–76] Eligible trials had a median or mean treatment period of

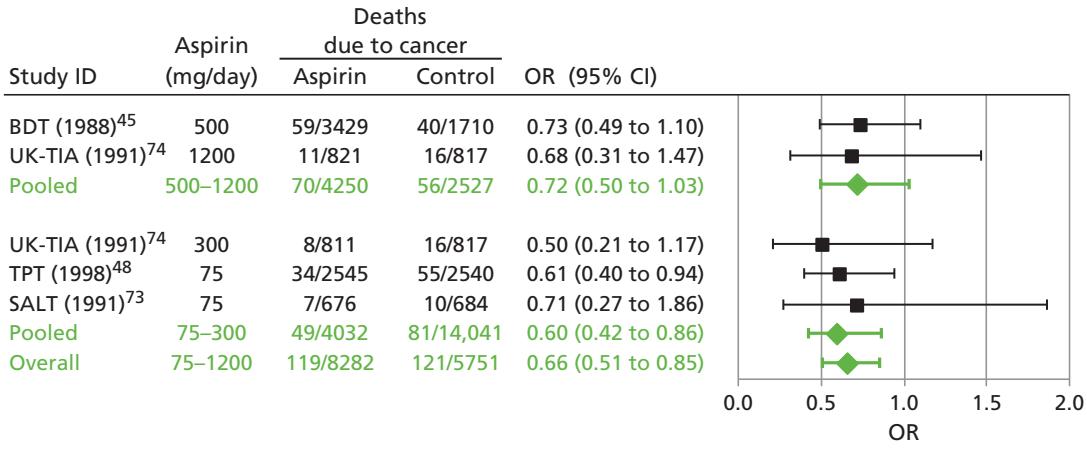


FIGURE 22 Representation of results as reported by Rothwell *et al.*,[31] stratified by dose regimen. Note: The authors applied a correction to allow for the fact that the control group from UK-TIA[74] was used twice in the analysis.

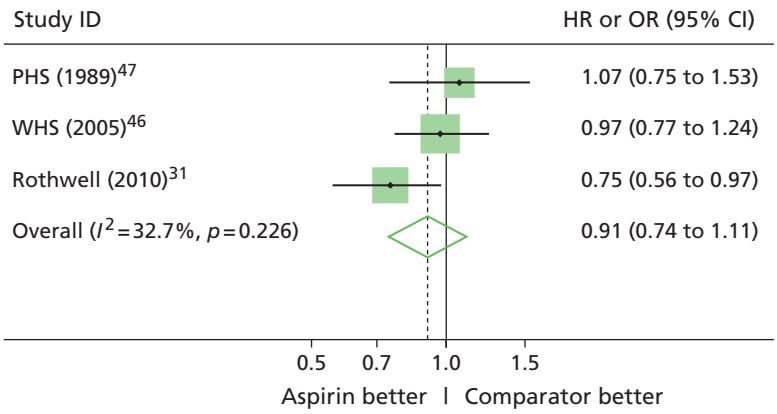


FIGURE 23 Odds ratio/hazard ratio for incidence of CRC including WHS[46] and PHS[47] trials.

at least 4 years and a range extending beyond 5 years. For inclusion, aspirin had to be given without a second agent or, if given with another agent, both needed to be used in the same way in both trial arms; trials of aspirin at any dose for primary or secondary CVD prevention could be included.

The within-trial pooled OR for death from cancer (eight trials[40,42,44,45,48,74–76]) was 0.79, 95% CI 0.68 to 0.92 (main paper, slightly different in supplementary appendix because of reclassification of some deaths). All of the trials but one[75] had reduced risk for the aspirin group; however, only the UK-TIA study[74] reached statistical significance (*Figure 24*).

There was little statistical heterogeneity among the studies. Using the aggregated data from the eight studies[40,42,44,45,48,74–76] to estimate the number of cancer deaths avoided requires a value for mean follow-up; taking 10 years as mean follow-up then 66 cancer deaths would be averted for every 10,000 persons receiving aspirin. If the pooled random-effects control rate (*Figure 25*) is used for the calculation then 54 deaths are averted.

The OR for all-cause mortality for the eight trials[40,42,44,45,48,74–76] was 0.92 (95% CI 0.85 to 1.00) (*Figure 26*).

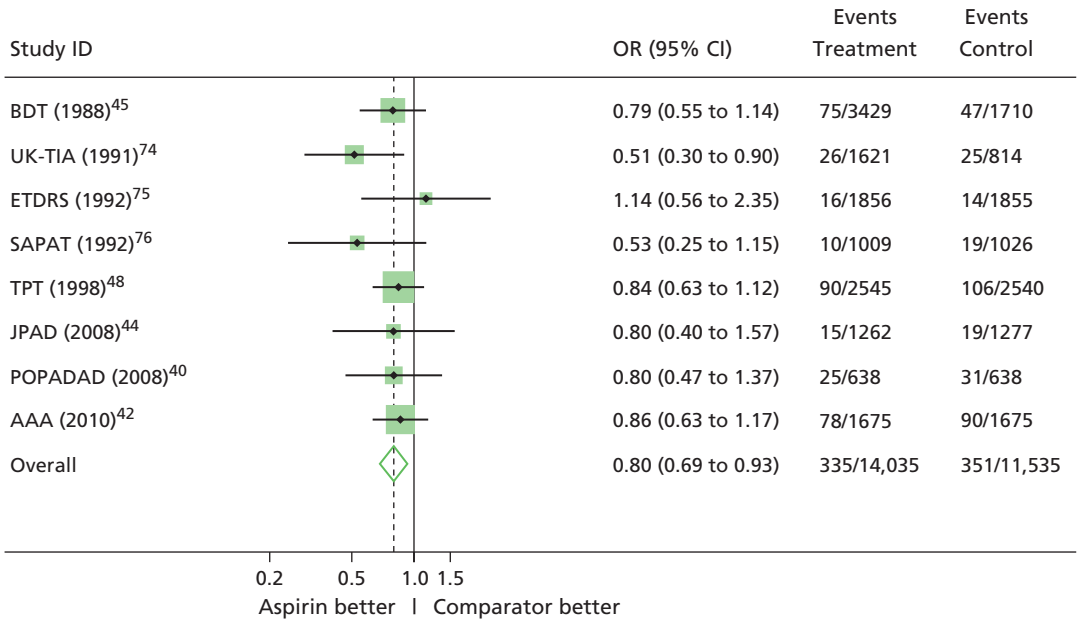


FIGURE 24 Odds ratio of death from cancer in eight RCTs[40,42,44,45,48,74–76] of primary or secondary prevention of CVD. Note: Based on data provided in the supplementary web appendix.

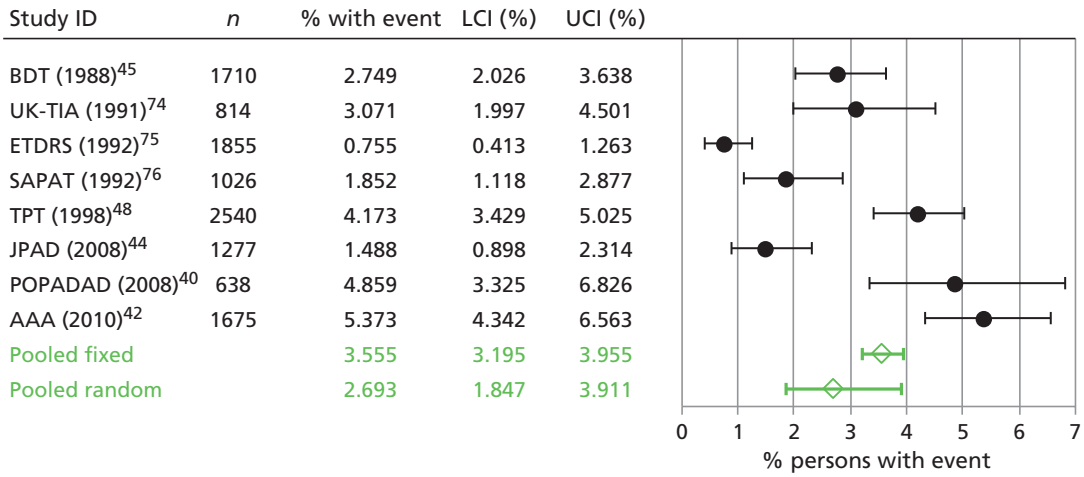


FIGURE 25 Risk of cancer death in the control arm in eight RCTs[40,42,44,45,48,74–76] CVD primary or secondary prevention. LCI, lower confidence interval.

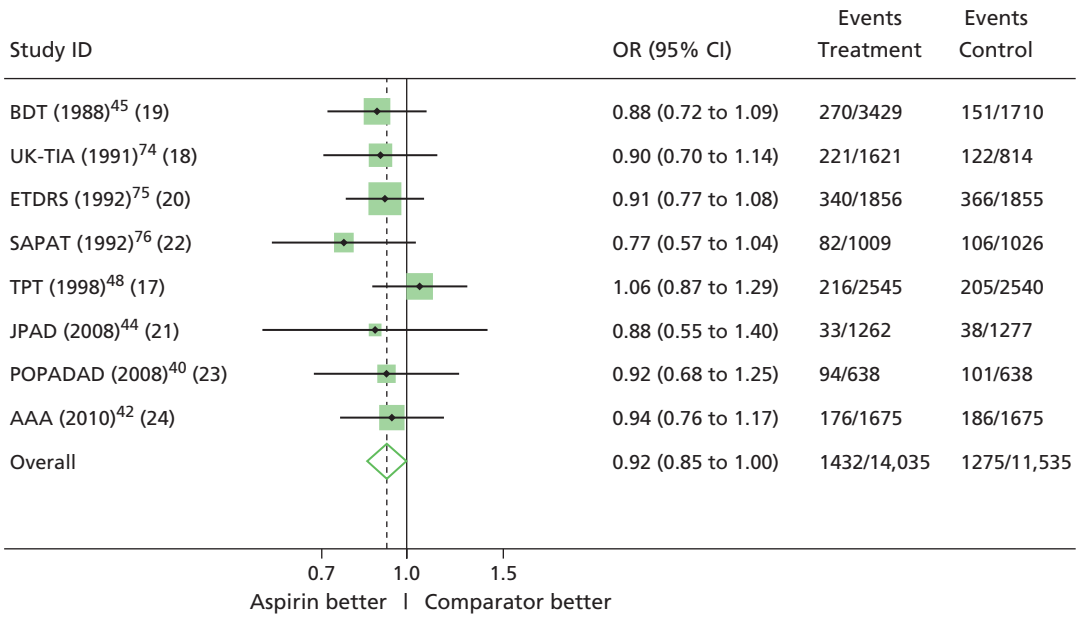


FIGURE 26 Odds ratio of death (any cause) in eight RCTs[40,42,44,45,48,74–76] of primary or secondary prevention of CVD.

Using the aggregated data, assuming 10 years' mean follow-up, the number of deaths (any cause) averted is estimated to be 85 among 10,000 persons who received aspirin; using the pooled control risk of 10.4% (*Figure 27*) the averted deaths amount to 75. According to these estimates, approximately three-quarters of all of the deaths averted because of aspirin use are attributable to avoidance of cancer.

In IPD analysis of seven trials,[40,42,44,45,48,74,75] the risk of death from cancer during trial treatment was reduced in the aspirin group (HR 0.82, 95% CI 0.70 to 0.95; $p = 0.01$); benefit became apparent after about 5 years, after which the percentage risk in the control group increased more rapidly than for the aspirin group. These results are represented in *Figure 28*.

Further analyses were stratified according to type/site of tumour (for details see *Appendix 6*). Three trials[45,48,74] provided IPD for analysis up to 20 years; HRs (aspirin vs. control) indicated reduced risk for small-cell lung cancer, adenocarcinoma of the lung and of the oesophagus but not for squamous cell lung cancer (for details, see *Appendix 6*). In three trials[45,48,74] with prolonged follow-up the HR for all-cause mortality over 20 years was 0.96 (95% CI 0.90 to 1.02; $p = 0.37$).

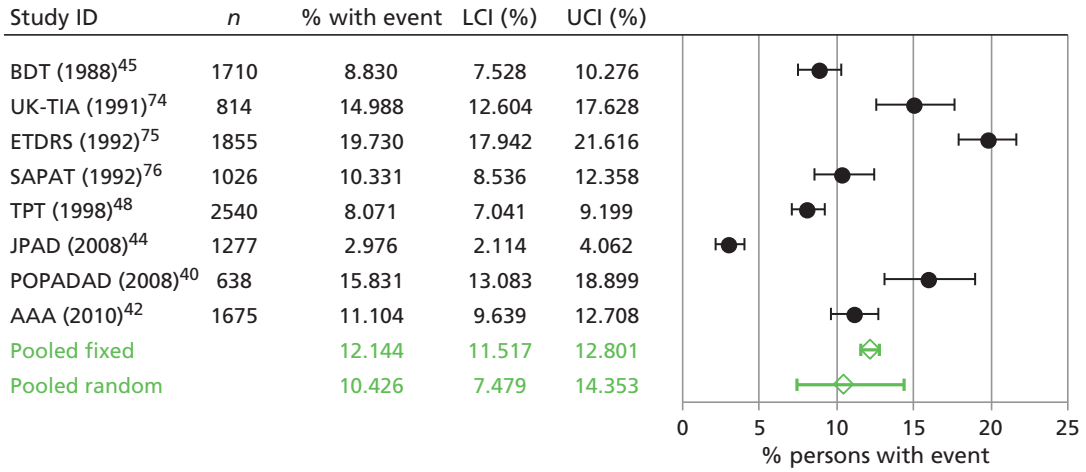
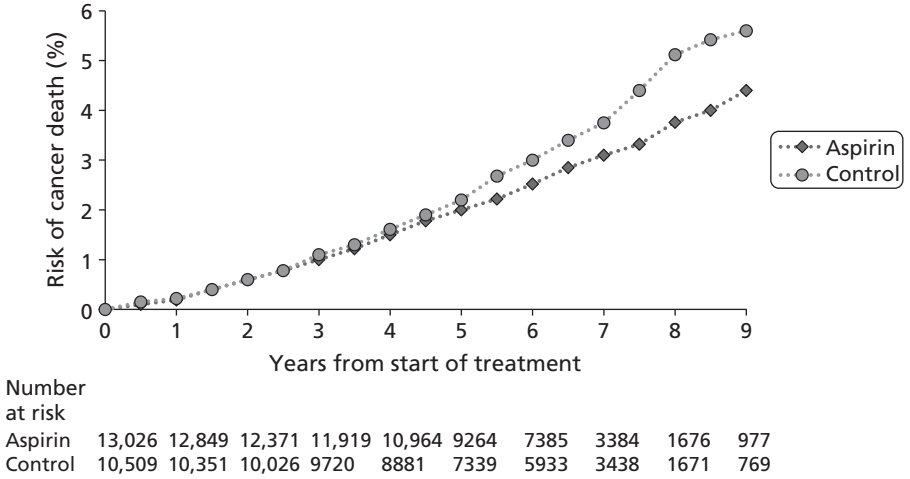


FIGURE 27 Risk of death (all-cause) in the control arm in eight RCTs of CVD primary or secondary prevention. LCI, lower confidence interval.



Number at risk

Aspirin	13,026	12,849	12,371	11,919	10,964	9264	7385	3384	1676	977
Control	10,509	10,351	10,026	9720	8881	7339	5933	3438	1671	769

FIGURE 28 Risk of cancer death during treatment period (IPD analysis) (data taken from Rothwell *et al.*[22]).

Rothwell et al. *(2012)*

In this IPD study,[49] the risk of cancer death and cancer incidence, and their time courses, were examined in 51 RCTs in which daily aspirin was investigated for the prevention of CVD (vascular events). Eligible trials randomised participants to daily aspirin (any dose) compared with no aspirin (studies of aspirin in association with anticoagulation were also eligible). Secondary cancer prevention trials and studies of duration < 90 days were excluded. Twelve of the included trials were classified as primary prevention studies and 39 as secondary prevention. A primary outcome was not specified.

The risk of cancer death in the 51 RCTs is shown in *Figure 29*. The pooled OR for cancer death was 0.84 (95% CI 0.74 to 0.94; $p = 0.002$). *Figure 30* shows the risk of cancer death in the control arms.

The two large primary prevention studies PHS[47] and WHS[46] in which aspirin was administered on alternate days and where outcomes were likely less favourable for aspirin did not satisfy the inclusion criteria.

The number of cancer deaths averted should 10,000 persons be followed for 10 years is estimated to be 25 (assuming mean follow-up for the 51 RCTs was 10 years) and 36 (assuming mean follow-up was 7 years) according to the 'aggregated' method, and 31 and 44 (follow-up assumed to be 10 and 7 years) according to the 'pooled' method.

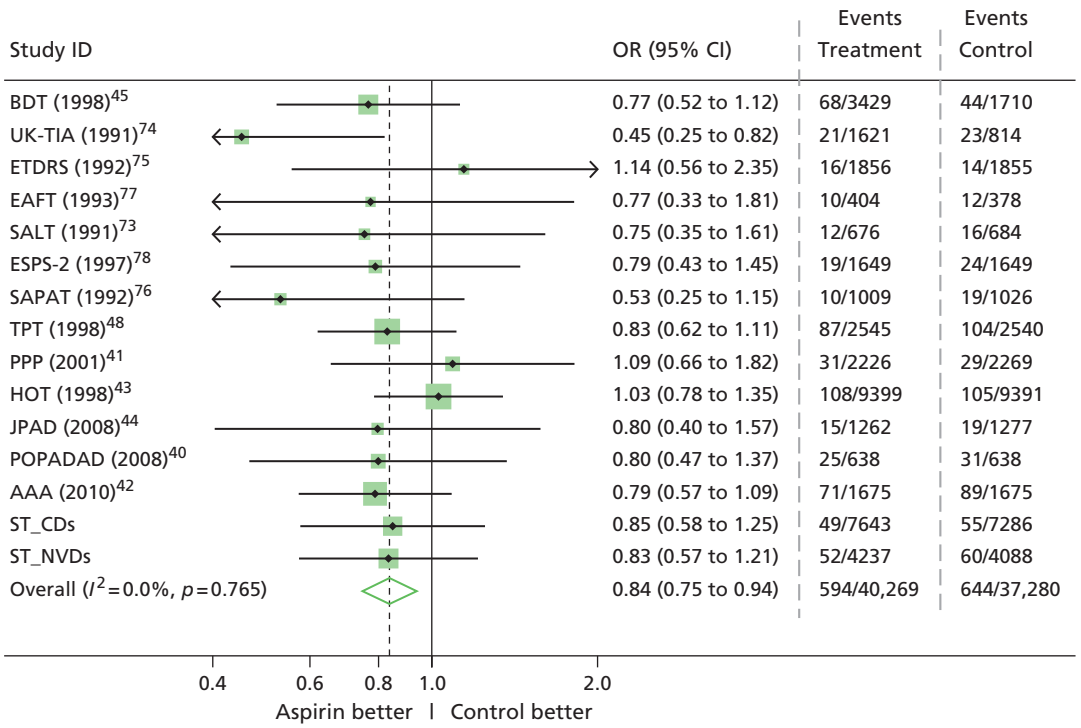


FIGURE 29 Risk of cancer death in 51 RCTs of CVD prevention. ST_CDs, cancer deaths in 21 small studies; ST_NVDs, non-vascular deaths in 17 small studies. Meta-analysis adjusted for 2 : 1 randomisation ratio used in some trials.[49] EAFT, European Atrial Fibrillation Trial.

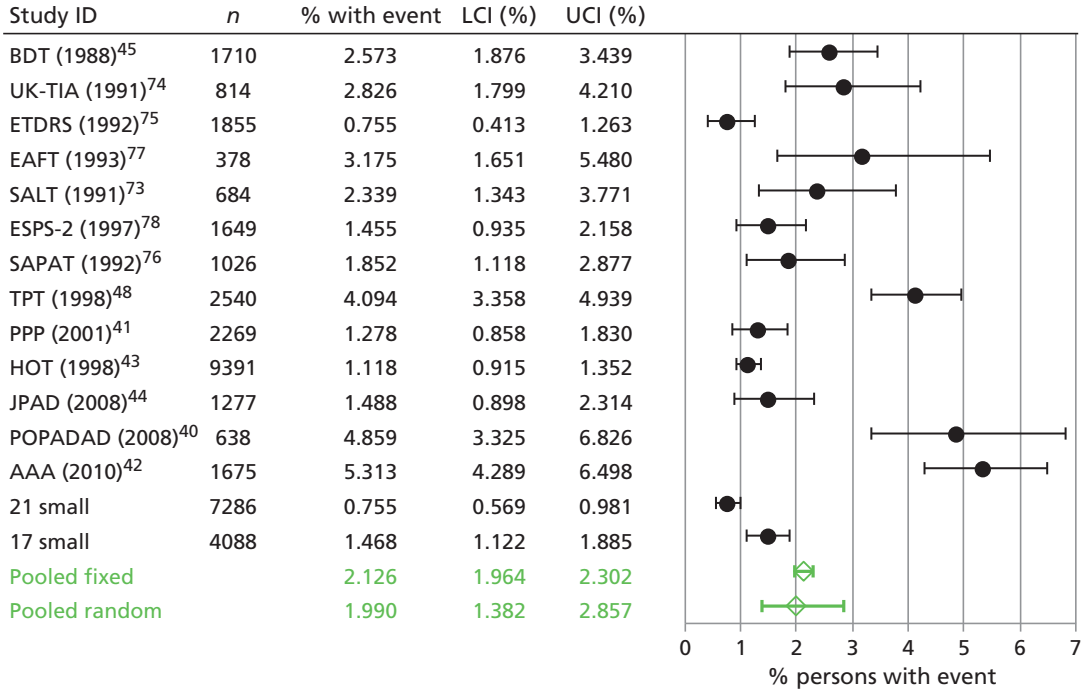


FIGURE 30 Risk of cancer death in control arms (based on Rothwell *et al.*[49]). LCI, lower confidence interval. EAFT, European Atrial Fibrillation Trial.

Cancer incidence

Rothwell *et al.*[49] also reported the OR for cancer incidence beyond 3 years in six CVD primary prevention trials;[40–44,48] this was found to be 0.76 (95% CI 0.66 to 0.88). However, if data from the WHS trial[46] are included then the effectiveness of aspirin appears to be reduced and the OR is increased to 0.819 (95% CI 0.690 to 0.970; *Figure 31*). Data for incidence of all cancer types from the PHS trial[47] beyond 3 years are not available. It should be noted that Seshasai *et al.*[56] reported greater cancer mortality in the aspirin group for the PHS trial.[47]

Rothwell et al. *(2012)*

This study by Rothwell *et al.*[62] generally repeated previous analyses on cancer incidence and mortality apart from analysis of the impact of aspirin on cancer metastasis. This element is excluded from this report, which has primary (metastasis is secondary prevention) prevention as its focus.

Algra et al. *(2012)*

The primary outcome in this systematic review[61] derived from observational studies that provided evidence about the effect of aspirin or NSAIDs on the incidence and outcome of cancer. The authors included the meta-analysis of RCTs, which was also presented in other systematic reviews published by these authors (details in *Appendix 7*). The conclusion from the review was that data from observational studies support the results derived from analysis of RCTs.

Mills et al. *(2012)*

The authors[60] undertook a study-level meta-analysis of RCTs that investigated the effect of low-dose aspirin on cancer mortality or non-CV death. Trials were included if daily aspirin was administered alone (75–325 mg aspirin and no other anticoagulants) in any population and if the required outcomes were reported. Of 24 included trials, 11 reported cancer mortality. The pooled RR of death from cancer was 0.77 (95% CI 0.63 to 0.95). The numbers of events and participants in each study were not provided. The forest plot listed 11 studies but RR was reported for only eight. The reason why three trials were excluded was unclear.

Meta-analyses of primary outcomes: primary prevention of cardiovascular disease in diabetes

Seven systematic reviews[63–69] and two RCTs were found to meet the inclusion criteria for aspirin for the primary prevention of CVD in diabetes. We report here on the systematic reviews.[63–69]

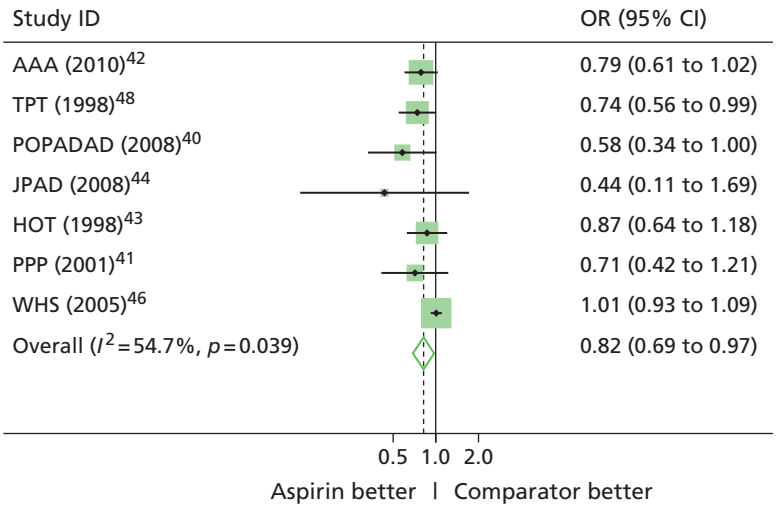


FIGURE 31 Odds ratio for cancer incidence when data from WHS[46] is included.

The implicitly or explicitly stated primary outcome in all of these studies, other than those by Calvin *et al.*[64] and Simpson *et al.*,[66] was a composite of CVD events made up from CV death plus non-fatal stroke or MI. Various primary studies were included in these analyses and the pooled estimates of RR or HR for this composite outcome indicated a modest ≈10% reduction in risk from aspirin use. However, all of the upper 95% CIs included the possibility of no improvement, and, for some,[67–69] CIs implied the possibility of greater risk from aspirin. *Table 13* summarises these results.

For Calvin *et al.*,[64] the primary outcome was taken to be RR for all-cause mortality. Data from six studies[40,41,43,44,46,47] were pooled to generate a RR of 0.81 (0.55 to 1.19) using Bayesian meta-analytic techniques. Simpson *et al.*[68] implicitly defined all-cause mortality and CV mortality as primary outcomes. Random-effects meta-analysis yielded RRs of 1.01 (95% CI 0.85 to 1.19) for all-cause death and 0.98 (95% CI 0.63 to 1.53) for CV death. Seven of the nine core primary prevention RCTs were included in the analyses.[40–42,44–47] The HOT[43] study was omitted and categorised as a mixed primary/secondary prevention study. Subgroup analyses by aspirin dose were undertaken; as in the main analysis, no benefit from aspirin was found. The numbers of events and of participants by trial arm were not provided.

Systematic review evidence on adverse events: cardiovascular disease studies

We included nine systematic reviews[37–39,52–57] of RCTs which investigated use of aspirin for primary prevention of CVD. These reviews were of good quality. However, they identified differing primary outcomes and used different outcome definitions in the meta-analyses of adverse event rates. For binary outcomes, the statistic chosen was OR or RR and both random- and fixed-effects models were variously deployed. In this section we report on the four most recent study-level reviews on primary prevention of CVD, the ATT[53] IPD analysis, and refer to other reviews in the text where appropriate. The systematic reviews synthesised evidence from either all, or a subgroup of, the same core of nine primary studies of aspirin for the primary prevention of CVD. (See *Table 8* for further explanation of this.)

Adverse events

Table 14 summarises the adverse events reported in the four selected study-level systematic reviews[37–39,56] and the ATT IPD review of CVD prevention and *Table 9* summarises the RCTs from which the systematic reviews were drawn.

Bartolucci *et al.*[37] did not meta-analyse adverse events but produced a table of percentage of participants with GI bleed in the nine primary studies; the remainder of this section concentrates on the other three recent meta-analyses.[38,39,56]

TABLE 13 Summary of results from systematic reviews of studies of patients with diabetes

Study	Studies (*n*)	ETDRS[75]	HOT[45]	PPP[43]	POPADAD[42]	WHS[48]	JPAD[46]	RR or HR	95% CI
Zhang 2010[69]	6	Yes	Yes	Yes	Yes	Yes	Yes	0.92 (re)	0.83 to 1.02
Younis 2010[68]	5	No	Yes	Yes	Yes	Yes	Yes	0.90 (re)	0.78 to 1.05
Stavrakis 2011[67]	3	No	Yes	Yes	No	Yes	No	0.89 (re)	0.70 to 1.13
De Berardis 2009[65]	5	Yes	No	Yes	Yes	Yes	Yes	0.90	0.81 to 1.00
Butalia 2011[63]	6	Yes	Yes	Yes	Yes	Yes	Yes	0.91	0.82 to 1.00

re, random-effects model.

TABLE 14 Adverse events in systematic reviews of primary prevention of CVD

	Adverse event			
Systematic review	Non-trivial/major bleeds	GI bleeds	Total bleeds	Haemorrhagic stroke
Berger 2011[39]	Yes			Yes
Raju 2011[38]	Yes	Yes		Yes
Bartolucci 2011[37]		Yes		
Seshasai 2012[56]	Yes		Yes	
ATT (Baigent 2009[53])	Yes			Yes

Non-trivial bleeds and major bleeds; study-level meta-analyses

A difficulty faced by systematic reviewers was that the primary studies spanned three decades of investigation, during which classification and reporting of clinically important bleeding evolved. Seshasai *et al.*[56] meta-analysed 'non-trivial bleeds' using ORs, whereas Berger *et al.*[39] and Raju *et al.*[38] meta-analysed 'major bleeds' using RRs. Definitions provided in the systematic reviews for these outcomes are summarised in *Table 15*, whereas *Table 16* is based on the systematic review by Seshasai *et al.*,[56] which provided the definitions of bleeds given in the nine studies[40–48] of aspirin for primary prevention of CVD.

All of the three reviews used a random-effects model. The random-effects pooled OR for non-trivial bleeds was 1.31 (95% CI 1.14 to 1.50);[56] the pooled RRs for major bleeds were, respectively, 1.62 (95% CI 1.31 to 2.00)[39] and 1.66 (95% CI 1.41 to 1.95)[38] (*Figure 32*). All three analyses therefore found that aspirin was associated with a statistically significant increase in non-trivial or major bleeds, considered clinically important by the reviewers.

Berger *et al.*[39] and Seshasai *et al.*[56] included data on important bleeds from all nine core studies; Raju *et al.*[38] excluded both the JPAD[44] and POPADAD[40] studies from the analysis. In the Seshasai *et al.*[56] analysis, those studies with the largest number of participants (HOT,[43] PHS[47] and WHS[46]) were the most influential in determining the non-trivial bleed pooled OR, whereas in the Berger *et al.*[39] analysis WHS,[46] PPP[41] and POPADAD[40] studies were most influential for the RR of major bleeds. In the Raju *et al.* review,[38] the most influential studies were WHS[46] and PPP[41] (since Raju *et al.*[41] excluded POPADAD[40] from the meta-analysis).

Figure 33 shows our re-analysis for the OR for non-trivial bleeds (*see Figure 33a*) and the RR for major bleeds (*see Figure 33b*). Each line indicates the effect on the outcome measure of excluding the listed study. As can be seen in *Figure 33a*, removal of the HOT trial[43] reduces the OR considerably, and removal of the PHS trial[47] increases the OR. In *Figure 33b* the RR is reduced by exclusion of the PPP trial[41] and increased by exclusion of the WHS.[46]

TABLE 15 Definitions of bleeding used in systematic reviews of aspirin for primary prevention of CVD

Systematic review	Stated definition
Bartolucci 2011[37]	No meta-analysis of adverse events discussed
Berger 2011[39]	Major bleeding as defined by each study (because the definition of major bleeding differed by trial, GI haemorrhage and cerebral haemorrhage were reported separately)
Raju 2011[38]	Raju accepted the primary study investigators' definitions of major bleeding; however, these were not itemised

TABLE 16 Definitions of bleeding events used in RCTs of primary prevention of CVD (based on systematic review by Seshasai *et al.*[56])

Events/ trials	BDT 1988[45]	PHS 1989[47]	HOT 1998[43]	PPP 2001[41]	TPT 1998[48]	WHS 2005[46]	POPADAD 2008[42]	JPAD 2008[44]	AAA 2010[42]
Major bleeds	Fatal GI haemorrhages, haemorrhagic peptic ulcers, haemorrhagic stroke and non-fatal probable haemorrhagic stroke	Haemorrhagic stroke, haematemesis, melaena, other non-specified GI bleeds, epistaxis, haematuria	All GI, cerebral and nasal bleeds	GI bleeds, intracranial bleeds, ocular bleeds, epistaxis	Haemorrhagic stroke, SAH, GI bleed, GU bleed, nasal/ throat bleed, ocular bleed, haematuria	Haemorrhagic stroke, GI bleeding, epistaxis, haematuria	GI bleeding (including haemorrhagic gastric ulcer, bleeding from oesophageal varices, colonic diverticula, haemorrhoids, GI cancer (and unknown GI bleeding), retinal bleeding, haematuria, epistaxis, haemorrhagic stroke	GI bleeding (including haemorrhagic gastric ulcer, bleeding from oesophageal varices, colonic diverticula, haemorrhoids, GI cancer and unknown GI bleeding) retinal bleeding, haematuria, epistaxis, haemorrhagic stroke	Diagnosis of SAH or SDH recorded by a doctor, SAH ICD10 code – I60; SDH ICD10 code – I62 Criteria: Extracranial haemorrhage from site other than GI tract requiring hospitalisation (e.g. haematuria, epistaxis etc.) to control bleeding Diagnosis of haemorrhage from GI tract recorded by a doctor *and* requiring hospitalisation to control bleeding
Fatal major bleeds	GI haemorrhages, haemorrhagic peptic ulcers and haemorrhagic stroke	Fatal GI bleeds Cerebral bleeds unspecified	All fatal bleeds including cerebral and GI	All fatal GI bleeds Cerebral bleeds unspecified	Fatal non-cerebral bleeds Cerebral bleeds unspecified	GI haemorrhages Cerebral bleeds unspecified	Fatal haemorrhagic stroke	Fatal haemorrhagic stroke	Post-mortem: cerebral haemorrhage and no other disease processor event, such as brain tumour, subdural haematoma, SAH, metabolic disorder or peripheral lesion that could cause localising neurological deficit or coma according to hospital records *or* definite stroke within 6 weeks of death and no other disease processor event such as brain tumour, subdural

continued

TABLE 16 Definitions of bleeding events used in RCTs of primary prevention of CVD (based on systematic review by Seshasai *et al.*[56]) (*continued*)

Events/ trials	BDT 1988[45]	PHS 1989[47]	HOT 1998[43]	PPP 2001[41]	TPT 1998[48]	WHS 2005[46]	POPADAD 2008[42]	JPAD 2008[44]	AAA 2010[42]
									haematoma, SAH, metabolic disorder, or peripheral lesion that could cause localising neurological deficit or coma according to hospital records *or* COD on death certificate, verified by OEC, consistent with haemorrhage from any site within GI tract. GI bleeds unspecified in data
Non-fatal major bleeds	Non-fatal probable haemorrhagic stroke	GI bleeds requiring transfusion Cerebral bleeds unspecified	All non-fatal bleeds including GI, cerebral and nasal bleeds	Non-fatal bleeds were major (life-threatening non-cerebral haemorrhage requiring surgery or transfusion) and intermediate bleeds (macroscopic haematuria and prolonged nose bleeds) Cerebral bleeds unspecified	Non-fatal severe and unexpected bleeding (GI plus intracranial plus ocular plus epistaxis)	GI bleeding, epistaxis, haematuria Cerebral bleeds unspecified	GI bleeding only	Non-fatal haemorrhagic strokes, GI bleeding, retinal bleeding, haematuria, epistaxis, haemorrhagic stroke	Non-fatal subarachnoid bleeds and haemorrhagic stroke as defined above. GI bleeds unspecified in data

Events/ trials	BDT 1988[45]	PHS 1989[47]	HOT 1998[43]	PPP 2001[41]	TPT 1998[48]	WHS 2005[46]	POPADAD 2008[42]	JPAD 2008[44]	AAA 2010[42]
Non-major bleeds	–	Easy bruising, GI bleeding not requiring transfusion, epistaxis or other bleeding Cerebral bleeds unspecified	Minor bleeds including GI, nasal bleeds and purpura	Bruising, nose bleeds, rectal bleeds and pink or red urine	–	Easy bruising	–	Minor GI bleeds, bruising, epistaxis, haematuria, bleeding after tooth extraction and chronic SDH	Retinal haemorrhages
Total non-fatal bleeds	Non-fatal probable haemorrhagic stroke and non-cerebral bleed	Easy bruising, all non-fatal GI bleeding, epistaxis or other bleeding Cerebral bleeds unspecified	All GI, cerebral, nasal bleeds and purpura	Non-fatal major bleeds and minor bleeds Cerebral bleeds unspecified	Non-fatal severe and unexpected bleeding (GI plus intracranial plus ocular plus epistaxis)	GI bleeds, haematuria, epistaxis and easy bruising Cerebral bleed unspecified	GI bleeding only	GI, bruising, epistaxis, haematuria, bleeding after tooth extraction and chronic SDH	Non-fatal subarachnoid bleeds, haemorrhagic stroke and retinal haemorrhages GI bleeds non-specified in data

GU, genitourinary; ICD, *International Classification of Diseases*; OEC, Organisational Ethics Committee; SAH, subarachnoid haemorrhage; SDH, subdural haemorrhage.

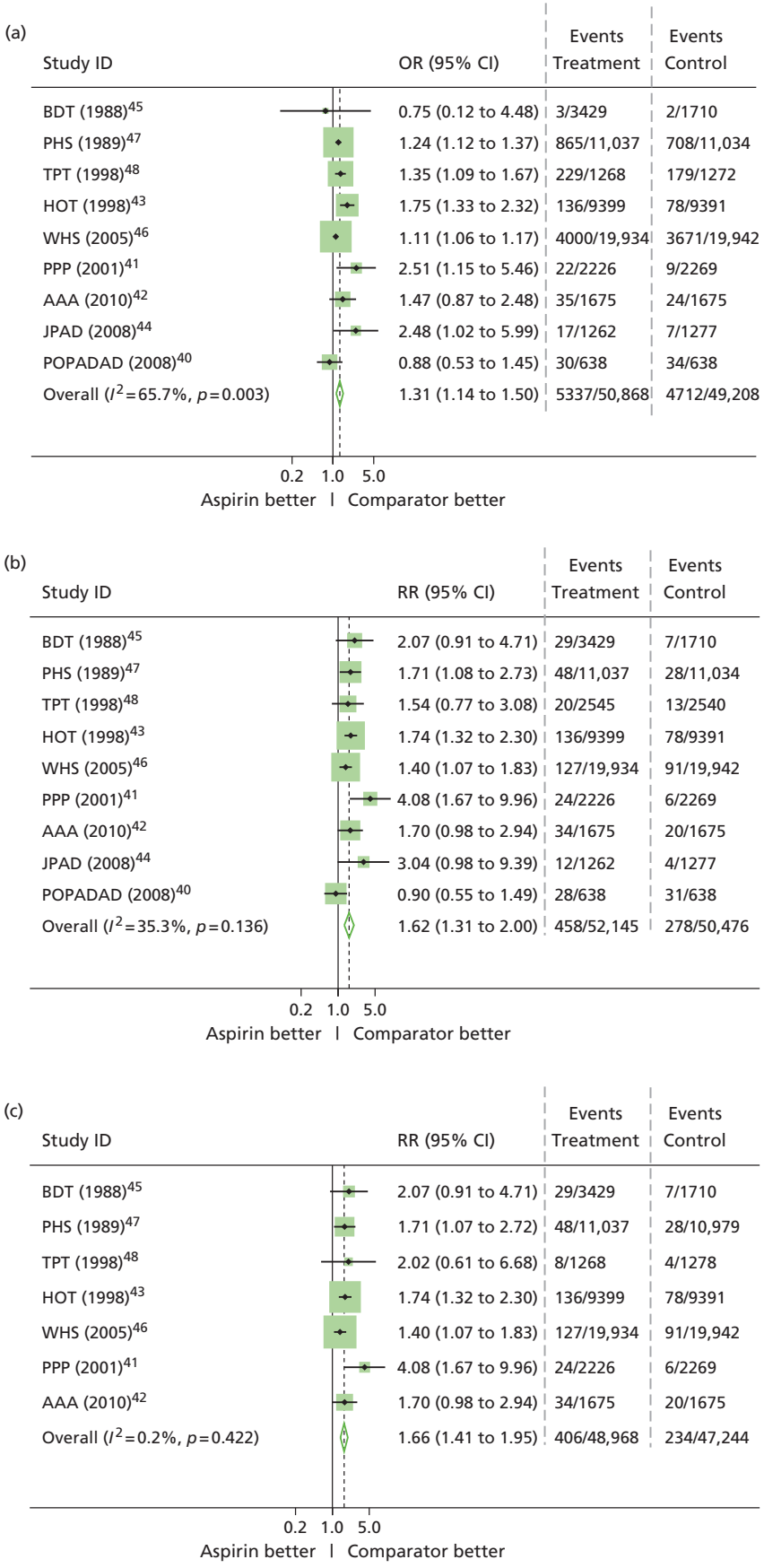


FIGURE 32 Odds ratio of non-trivial and RR of major bleeds in study-level meta-analyses. (a) Seshasai *et al.*;[56] (b) Berger *et al.*;[39] (c) Raju *et al.*[38] Note that the apparent precision for the WHS[48] study is greater in the Seshasai *et al.*[56] analysis.

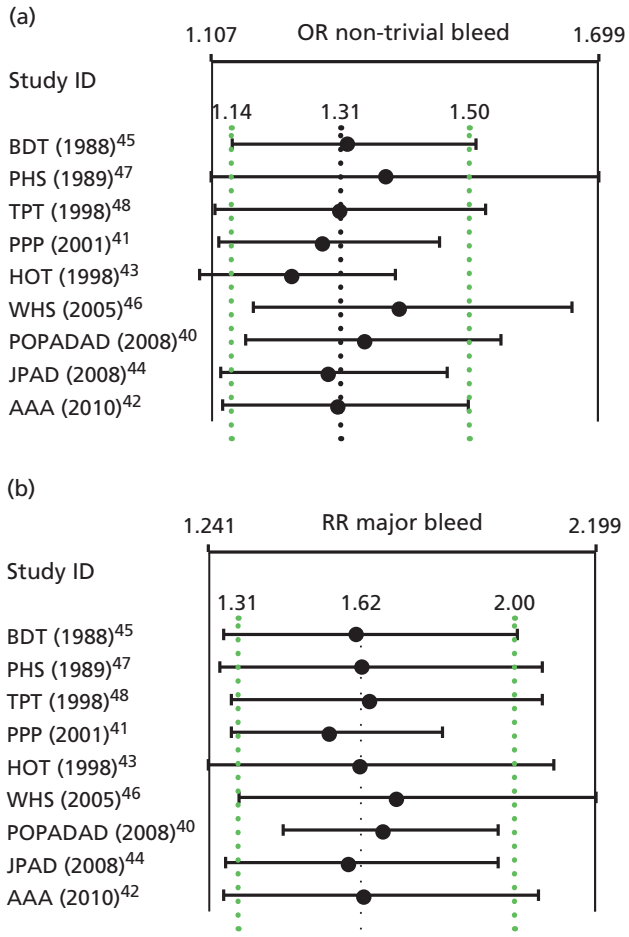


FIGURE 33 Influence of individual studies on pooled estimates of (a) odds ratio for non-trivial bleeds and (b) risk ratio for major bleeds.

Non-trivial bleeds and major bleeds: study-level meta-analyses concerns

As might be expected, the event rates in aspirin and control groups for non-trivial bleeds[56] varied over a much wider range than those for major bleeds[39] (*Figure 34*). In Berger *et al.*,[39] the POPADAD study[40] appears to be an outlier, although this study was not included in the Raju *et al.* review.[38,39]

The event rates in the Seshasai *et al.*[56] meta-analysis for several studies are so much larger than for the other meta-analyses that it is suspected that double-counting of individuals may have occurred so that 'count data' (see Cochrane Handbook for Systematic Reviews of Interventions, section 9.2.5[79]) from these trials has been treated as dichotomous data. The Cochrane handbook[79] terms this 'a unit-of-analysis' error (p. 261, section 9.3.5).

Figure 35 illustrates the control group risk for non-trivial bleeds and major bleeds with studies arranged according to length of follow-up; the risks for non-trivial bleeds can be seen to be more variable and the pooled effect is much higher.

The assessment of risk by Berger *et al.*[39] and Raju *et al.*[38] for the PHS,[47] TPT[48] and WHS[46] studies was clearly different from the Seshasai *et al.*[56] assessment of risk. For example, in Berger *et al.*,[39] the control group risk of a *major* bleed in the WHS[46] trial was ≈0.5%, but in Seshasai *et al.*[56] the risk of a *non-trivial* bleed in WHS[46] was considered to be 18.4%. In Seshasai *et al.*, 'non-trivial bleeds' was a composite end point defined as "clinically 'nontrivial' bleeding (fatal bleeding from any site; cerebrovascular or retinal bleeding; bleeding from hollow viscus; bleeding requiring hospitalisation and/or transfusion; or study-defined major bleeding regardless of source)."[56] In the report of WHS,[46] we consider that it is likely that this definition identifies events rather than individuals and may have been meta-analysed as

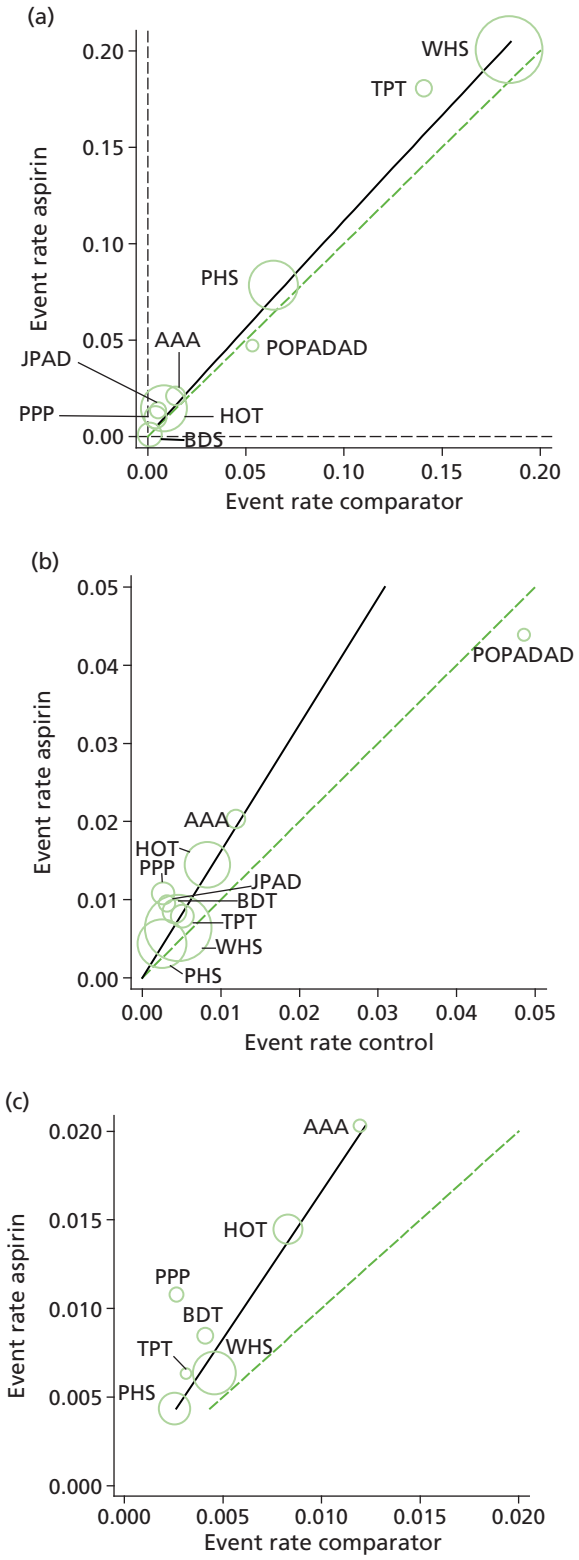
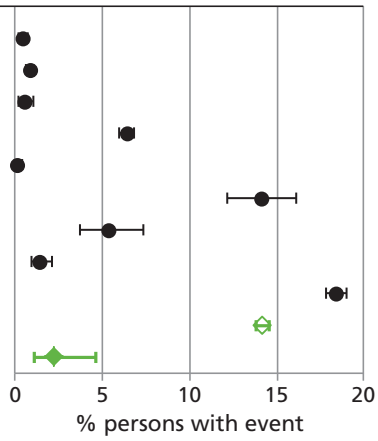


FIGURE 34 L'Abbé plot of event rates. (a) Non-trivial bleeds (Seshasai *et al.*[56]); (b) and (c) major bleeds (Berger *et al.*,[39] Raju *et al.*,[38] respectively). The dashed line represents null effect and the solid line the pooled effect size. Note the difference in axis scales.

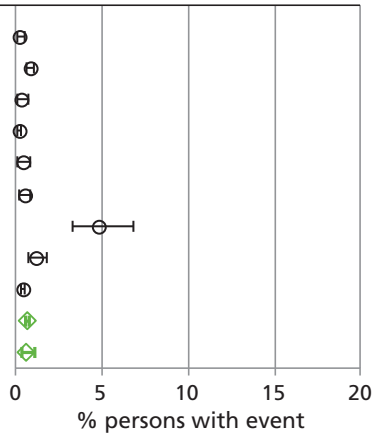
(a)

Study ID	Follow-up (years)	*n*	% with event	LCI (%)	UCI (%)
PPP (2001)[41]	3.6	2226	0.397	0.182	0.752
HOT (1998)[43]	3.8	9399	0.831	0.657	1.036
JPAD (2008)[44]	4.37	1262	0.548	0.221	1.126
PHS (1989)[47]	5.017	11,037	6.417	5.966	6.890
BDT (1988)[45]	6.0	1710	0.117	0.014	0.422
TPT (1998)[48]	6.0	1268	14.072	12.207	16.106
POPADAD (2008)[40]	6.7	638	5.329	3.718	7.368
AAA (2010)[42]	8.2	1675	1.433	0.920	2.124
WHS (2005)[46]	10.1	19,934	18.408	17.873	18.953
	Pooled fixed		14.168	13.791	14.554
	Pooled random		2.281	1.105	4.650



(b)

Study ID	Follow-up (years)	*n*	% with event	LCI (%)	UCI (%)
PPP (2001)[41]	3.6	2269	0.264	0.097	0.575
HOT (1998)[43]	3.8	9391	0.831	0.657	1.036
JPAD (2008)[44]	4.37	1277	0.313	0.085	0.800
PHS (1989)[47]	5.017	11,034	0.254	0.169	0.367
BDT (1988)[45]	6.0	1710	0.409	0.165	0.842
TPT (1998)[48]	6.0	2540	0.512	0.273	0.874
POPADAD (2008)[40]	6.7	638	4.859	3.325	6.826
AAA (2010)[42]	8.2	1675	1.194	0.731	1.838
WHS (2005)[46]	10.1	19,942	0.456	0.368	0.560
	Pooled fixed		0.696	0.616	0.787
	Pooled random		0.626	0.339	1.154



(c)

Study ID	Follow-up (years)	*n*	% with event	LCI (%)	UCI (%)
PPP (2001)[41]	3.6	2269	0.264	0.097	0.575
HOT (1998)[43]	3.8	9391	0.831	0.657	1.036
PHS (1989)[47]	5.017	10,979	0.255	0.170	0.368
BDT (1988)[45]	6.0	1710	0.409	0.165	0.842
TPT (1998)[48]	6.0	1278	0.313	0.085	0.799
AAA (2010)[42]	8.2	1675	1.194	0.731	1.838
WHS (2005)[46]	10.1	19,942	0.456	0.368	0.560
	Pooled fixed		0.554	0.485	0.632
	Pooled random		0.485	0.314	0.751

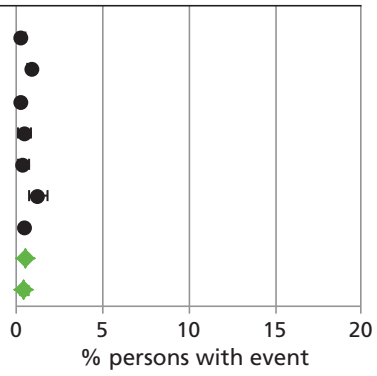


FIGURE 35 Baseline risk. (a) Non-trivial bleeds (Seshasai *et al.*[56]); (b) and (c) major bleeds (Berger *et al.*,[39] Raju *et al.*,[38] respectively). LCI, lower confidence interval.

'counts'. However, mixing count data with dichotomous data in the meta-analysis is unlikely to be a sound procedure.[79]

Number needed to harm and number of extra events incurred through aspirin

Seshasai *et al.*[56] pooled baseline risk using a random-effects model and then applied the pooled OR to obtain a number needed to harm (NNH); this was calculated for a mean period of aspirin treatment estimated to be 6 years. The resulting NNH for a non-trivial bleed was 73. Using a pooled baseline risk of

0.02281 (for random effects, see *Figure 27*) and pooled OR of 1.31 (for random effects, see *Figure 32*) we calculate the NNH (non-trivial bleed) as 146 (for method, see p. 376 of the Cochrane handbook[79]). We estimate the number of extra events incurred to be 178 ('aggregated' method) and 99 using the 'pooled' method; the large difference in estimates is due to heterogeneity in the control risk between studies (see *Figure 35a*) so that there is a considerable difference in the aggregate control risk and the random-effects pooled control risk.

For major bleeds, Berger *et al.*[39] estimated the NNH as 261 (95% CI 182 to 476). Control risk of 278 events/50,421 individuals over mean follow-up of 6.9 years was reported as 0.55% compared with 0.88% (458/52,145) for the aspirin group. The RR (aspirin vs. control) was 1.62, equating to a 62% increased risk relative to control; Berger *et al.*[39] reported that 'in aggregate the absolute risk' (presumably the absolute risk increase) was 0.38%, corresponding to a NNH of 261 (1/0.0038) over 6.9 years. Using the method described in the Cochrane handbook,[79] with a baseline risk of 0.55% and RR of 1.62, the NNH calculates to 293. If the pooled random-effects baseline risk of 0.626% and RR of 1.62 (95% CI 1.31 to 2.00) is used, the NNH becomes 258 (95% CI 160 to 515).

Raju *et al.*[38] reported a NNH of 300. The control group risk was 0.00495 (234 events among 47,244 individuals), the aspirin rate was given by RR (1.66) × control rate = (0.00829) (406 events among 48,968 individuals), giving an absolute increase of 0.00334 and a NNH of 300 (1/0.00334).

We estimated the number of extra events incurred should 10,000 persons be followed up for 10 years to be 48 (both Berger *et al.*[39] and Raju *et al.*,[38] 'aggregated' method), and 49 and 46 (Berger *et al.*[39] and Raju *et al.*,[38] respectively, using the 'pooled' method).

Cumulative meta-analyses

We undertook cumulative meta-analysis to examine how the pooled estimate for risk of important bleeds changed with time; studies were arranged according to estimated mid-period of recruitment. The pooled estimates became statistically significant after the accumulation of only the first two studies[45,47] and remained fairly constant thereafter (*Figure 36*).

All major bleeds; individual patient data-level meta-analyses

The ATT[53] Collaboration performed an IPD meta-analysis using data from six[41,43,45–48] of the core nine RCTs[40–48] of aspirin for the primary prevention of CVD. The three RCTs not included were JPAD,[44] POPADAD[40] and AAA,[42] which were published in 2008–10. Major bleeds were defined as major GI and extracranial bleeds that were fatal or required blood transfusion. Trials with fewer than 1000 non-diabetic patients (e.g. JPAD[44] and POPADAD[40]) were excluded. Major bleeds were meta-analysed as RaRs (ratio of events/person-years at risk) determined using log-rank statistics from analysis of IPD. The report quoted a 99% CI for RaRs for individual studies and a 95% CI for the pooled estimate. The pooled RaR was 1.54 (95% CI 1.30 to 1.82) (*Figure 37*), representing a 54% increase in event rate from aspirin use. The reported rate of events (rounded) across six studies was 0.1% per year for the aspirin group and 0.07% per year for the comparator group; this generated a reported yearly absolute difference of 0.03%/year (i.e. three events per 100 patient-years of exposure). The numbers of major bleed events were 335 and 219 for aspirin and control groups, respectively and the total person-years 330,000. This generates an absolute rate difference (not rounded) of 0.03515%/person-year, equivalent to 35 extra events incurred should 10,000 persons be followed up for 10 years.

Gastrointestinal and other extracranial bleeds that were fatal or required blood transfusion

In *Table 17* these results are compared with those from the Raju *et al.*[38] and Berger *et al.*[39] study-level meta-analyses. Although across studies the absolute increase in the rate of major bleeds were of the same order, the estimated increase in rate from IPD meta-analysis was lower (0.035%/patient year) than for study-level analyses. This could be attributed to more precise methodology with IPD analysis, as a crude weighted mean for follow-up time is required for the study-level calculations; however, the use of different

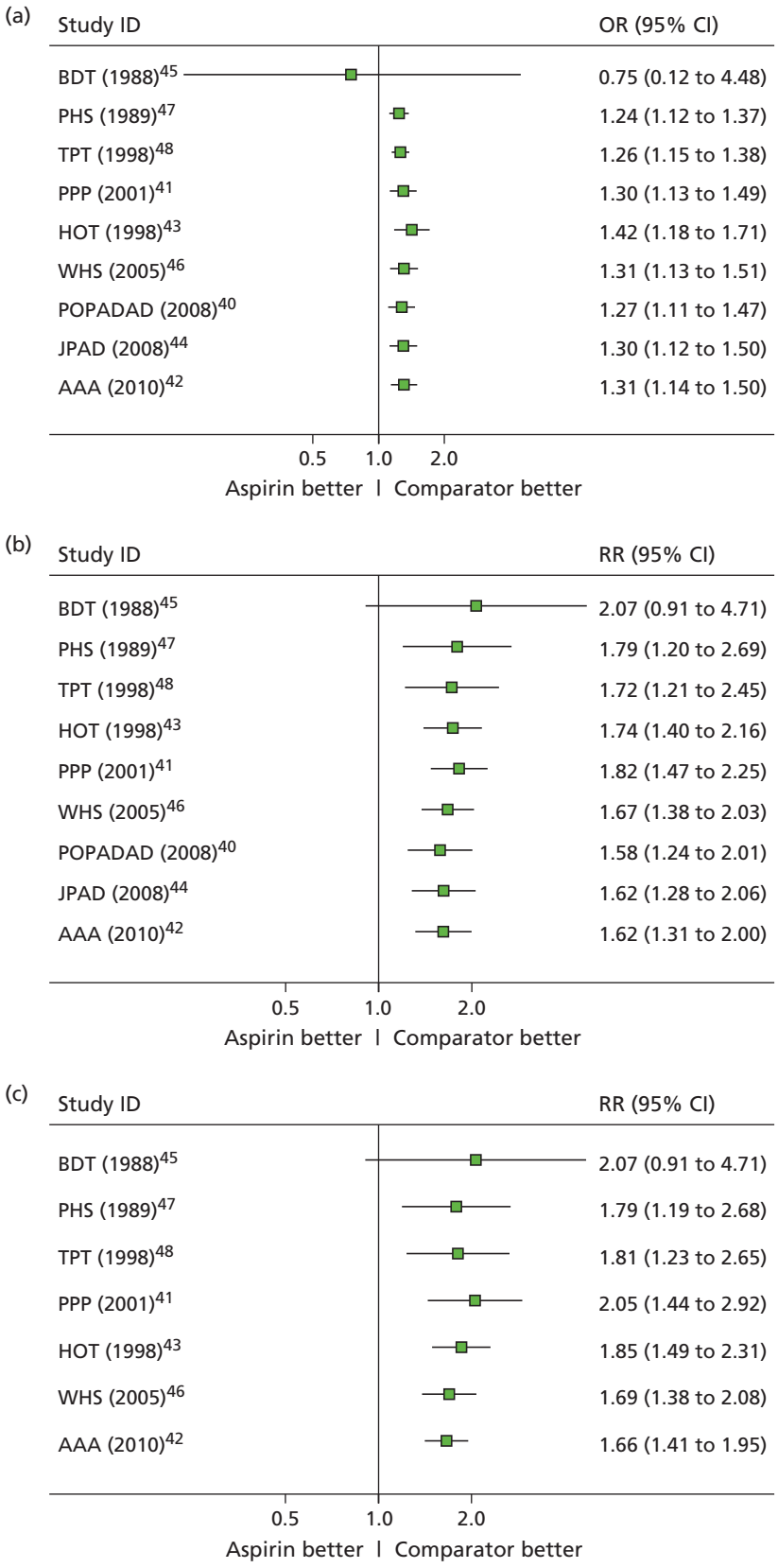


FIGURE 36 Repeated test with accumulating studies arranged by recruitment year: non-trivial bleeds. (a) Major bleed; (b) Berger *et al.*;[39] and (c) Raju *et al.*[38] [NB-PPP (2001)[41] and HOT (1998)[43] had comparable estimated mid-point recruitment periods (i.e. 1993).]

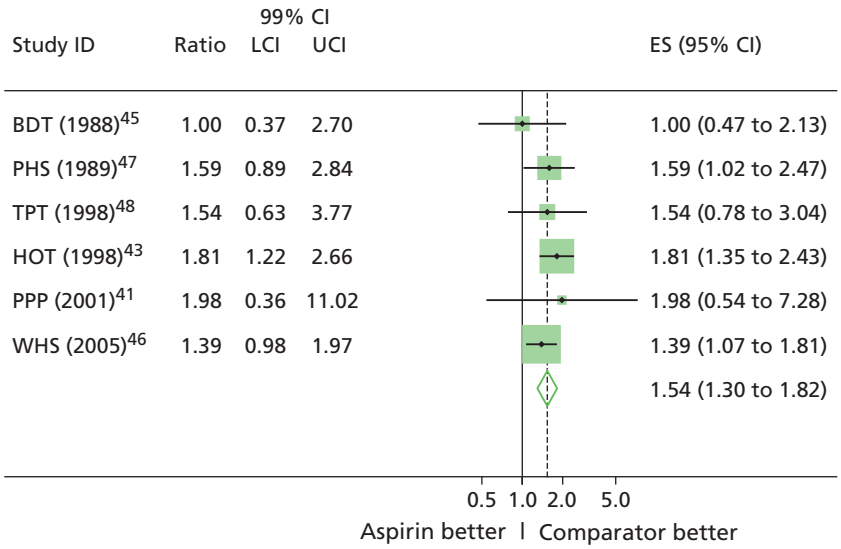


FIGURE 37 Meta-analysis of IPD for major bleeds reported by ATT.[53] LCI, lower confidence interval.

major bleed definitions and the inclusion of differing groups of RCTs may be contributory factors. In the six RCTs common to all three meta-analyses, the total number of major bleeds reported for aspirin and comparator groups, respectively, were 335 compared with 219, 372 compared with 214, and 384 compared with 223 for the ATT, Raju *et al.*[38] and Berger *et al.*,[39] respectively.

The ATT IPD meta-analysis allowed estimates of RaR of major bleeds according to patient level variables;[53] these results are summarised in *Table 18*. Age and male sex appear to be risk factors associated with major bleed from aspirin use.

In the next sections we discuss details of different types of major bleeding.

Gastrointestinal bleeds

Raju *et al.*[38] presented a random-effects meta-analysis for the RR of a GI bleed (RR 1.37, 95% CI 1.15 to 1.62) (*Figure 38*).

The risk of a GI bleed was higher in the aspirin group in all studies except POPADAD.[40] The two largest studies (WHS[46] and PHS[47]) were highly influential in determining the pooled estimate (*Figure 39*) and had high risk in both arms of the trials. Bartolucci *et al.*[37] presented a table with percentage of patients with GI bleeds in the nine core RCTs.[40–48] These are shown in *Table 19*, together with percentages calculated from the data in Raju *et al.*[38]

Across the eight RCTs[40–44,46–48] the risk of a GI bleed in the control arms was heterogeneous, varying between 0.22% and 6.30% (*Figure 40*); the highest risk was exhibited by the two largest studies (PHS[47] and WHS[46]) and the POPADAD study.[40]

Raju *et al.*[54] reported an NNH of 109 for a GI bleed based on the Raju *et al.*[38] meta-analysis. It is unclear what control risk was used in this calculation. Using number of events and total number of patients aggregated across the control arms (1560/47,498) and a RR of 1.37 the absolute risk difference (aspirin minus control) becomes 0.012 and the NNH 83. If the pooled risk for the control group is used (random effects 0.01281) with the random-effects pooled RR (1.37), the NNH becomes 211. The number of extra GI bleeds if 10,000 persons were followed for 10 years was estimated to be 117 according to the 'aggregated' method and 68 according to the 'pooled' method.

TABLE 17 Major bleeds; comparison of reported IPD and study-level results

Meta-analysis	RCTs	Aspirin events	Aspirin total	Control events	Control total	Mean follow-up (year)	Aspirin rate (%)	Aspirin rate (%/year)	Control rate (%)	Control rate (%/year)	Absolute difference (%/year)	NNH	RR[a]
Berger 2011[39]	9	458	52145	278	50421	6.9	0.87832	0.1273	0.55136	0.0799	+0.0474	261[b]	1.31
Raju 2011[38]	7	406	48968	234	47244	6.157	0.82911	0.1347	0.4953	0.0804	+0.0542	300[b]	1.66
ATT Collaboration 2009[53]	6	335	[c]	219	[c]	[d]		0.1000	[d]	0.0700	+0.0350		1.54

a RR, relative risk for Berger *et al.*[39] and Raju *et al*;[38] RR, rate ratio for ATT Collaboration.[53]
b Calculated from risk difference.
c The total number of individuals (both groups) was reported, to the nearest 1000, as 95,000. Total person-years = 330,000 for each group.
d The total person-years of observation was reported as 660,000.

TABLE 18 Rate ratios for major bleed according demographic characteristics

Variable	Major GI or other extracranial bleed: rate ratio (95% CI)	Non-fatal major GI or other extracranial bleed: rate ratio (95% CI)
Age, per decade	2.15 (1.93 to 2.39)	2.10 (1.88 to 2.34)
Male sex	1.99 (1.45 to 2.73)	1.98 (1.42 to 2.75)
Diabetes mellitus	1.55 (1.13 to 2.14)	1.55 (1.11 to 2.16)
Current smoker	1.56 (1.25 to 1.94)	1.50 (1.20 to 1.88)
Mean BP (per 20 mmHg)	1.32 (1.09 to 1.58)	1.32 (1.09 to 1.60)
Cholesterol (per 1 mmol/l)	0.99 (0.90 to 1.08)	0.98 (0.89 to 1.08)
Body mass index (per 5 kg/m²)	1.24 (1.13 to 1.35)	1.22 (1.11 to 1.34)

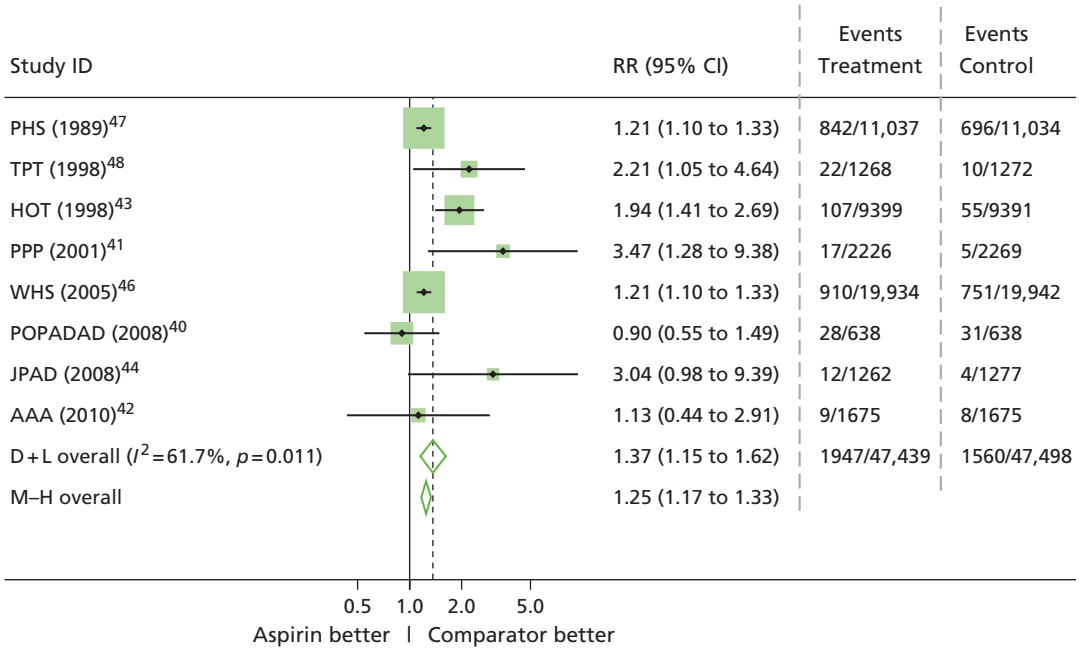


FIGURE 38 Relative risk of GI bleed (Raju *et al.*[38]).

Haemorrhagic stroke

Both Raju *et al.*[38] and Berger *et al.*[39] reported study-level meta-analyses of the RR of haemorrhagic stroke; data came from eight[40–42,44–48] of the nine[40–48] core CVD RCTs. Data input and results for each trial were similar (small differences existed for TPT and JPAD); no data were available from HOT.[43] No study alone reached statistical significance; the pooled estimates [random-effects model RR 1.36 (95% CI 1.01 to 1.82) in Raju *et al.*,[38] and 1.35 (95% CI 1.01 to1.81) in Berger *et al.*[39]] indicated a statistically significant increased risk of 35% or 36% with use of aspirin (*Figure 41*). As pooled outputs were almost identical, only the results from Raju *et al.*[38] are illustrated in *Figure 41*.

The most influential studies were PPP,[41] PHS[47] and WHS;[46] if any one of these were omitted from the analysis (*Figure 42*) the pooled estimate lost statistical significance (at $p < 0.05$). Repeated test meta-analysis (*Figure 43*) according to recruitment year indicated that statistical significance in the pooled RR was reached with the inclusion of the PPP[41] study, after which, with addition of further studies, the pooled estimate tended to decrease but remained statistically significant at the $p < 0.05$ level.

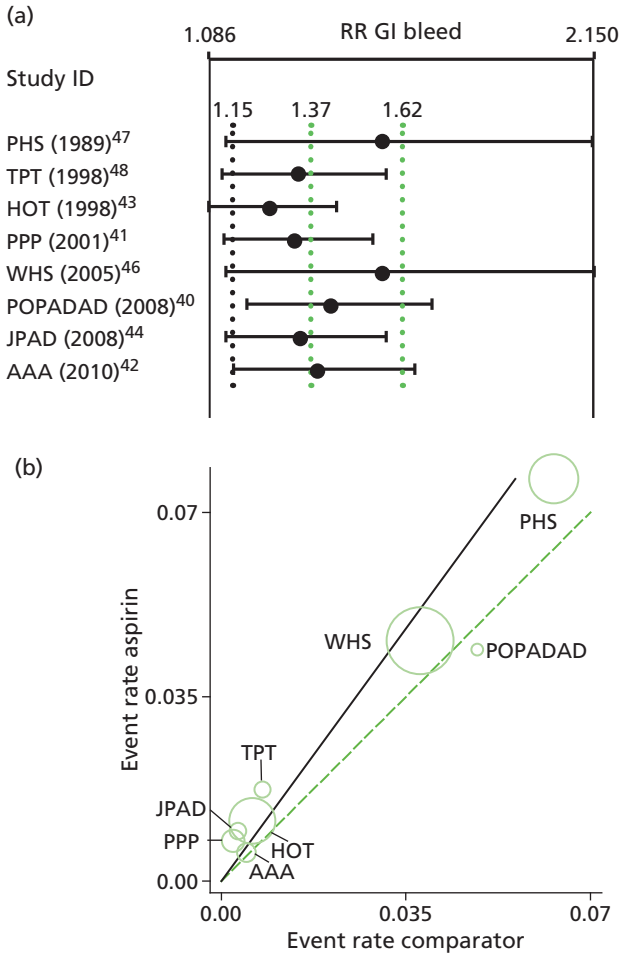


FIGURE 39 (a) Influence of individual studies on pooled estimate of RR of GI bleeds; (b) L'Abbé plot showing GI bleed event rates (the dashed line corresponds to RR of 1; the solid line represents the pooled RR (random effects).

TABLE 19 Percentage of patients with GI bleeding

	Data from Bartolucci *et al.*[37]		Data from Raju *et al.*[38]	
Trials	Aspirin	Control	Aspirin	Control
WHS[46]	4.50	3.80	4.57	3.77
BDT[45]	0.30	0.40		
PHS[47]	4.00	3.80	7.63	6.31
HOT[43]	0.80	0.40	1.14	0.59
PPP[41]	0.80	0.20	0.76	0.22
TPT[48]	1.40	0.90	1.74	0.79
AAA[42]	0.50	0.50	0.54	0.48
JPAD[44]	0.80	0.30	0.95	0.31
POPADAD[40]	4.40	4.90	4.39	4.86

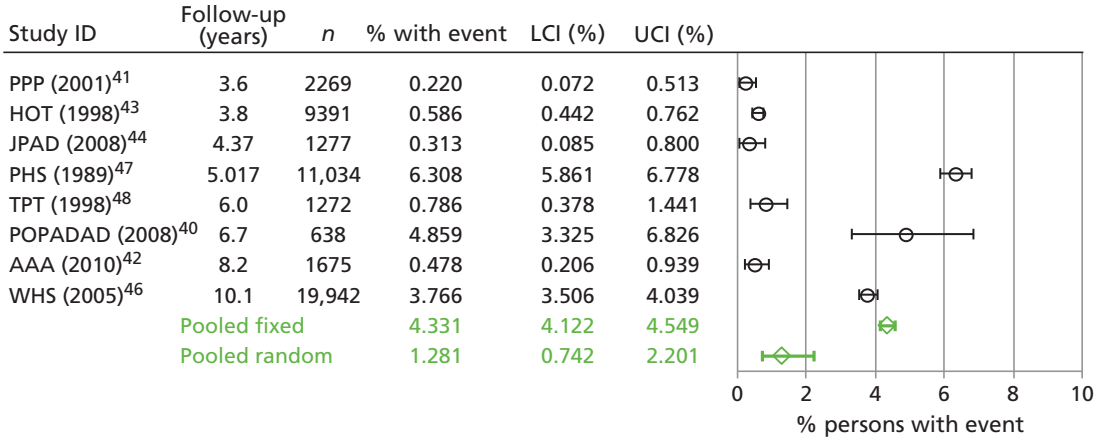


FIGURE 40 Risk of GI bleed in control groups; studies arranged according to follow-up. LCI, lower confidence interval.

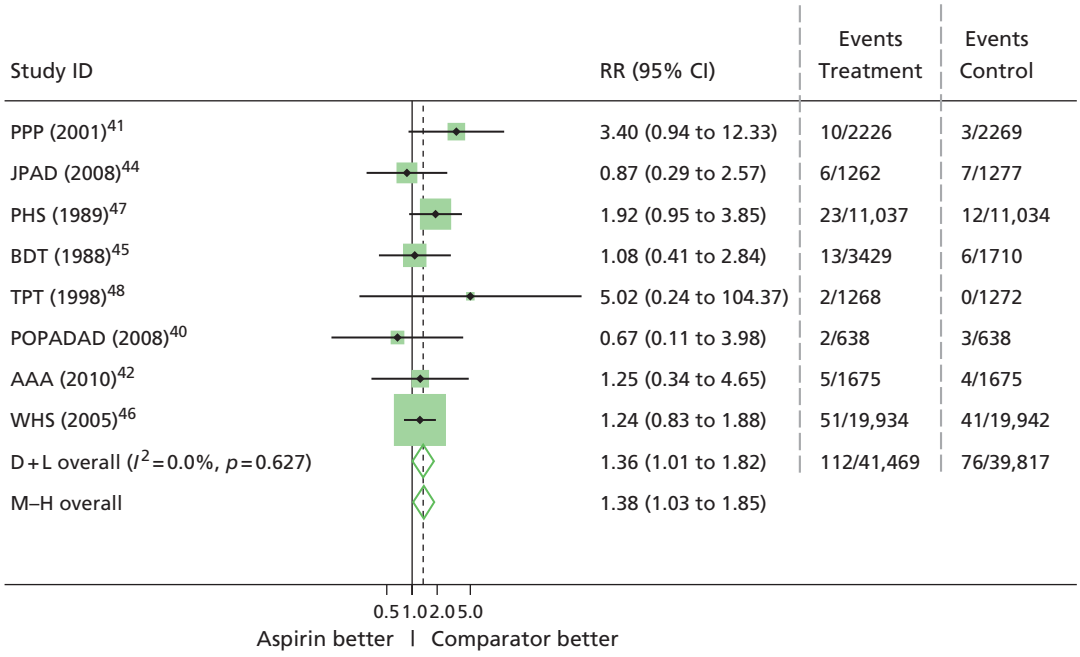


FIGURE 41 Relative risk of haemorrhagic stroke (Raju *et al.*[38]).

Raju *et al.*[38] did not compute a NNH for this outcome. Using the pooled random-effects risk (1.36) and random-effects pooled estimate for risk in the control group (0.219%) (*Figure 44*), the absolute risk difference is 0.00079 and NNH 1270. With a mean (weighted) follow-up across the eight studies[40–42,44–48] of 7.64 years both 'aggregated' and 'pooled' methods estimate 10 extra haemorrhagic strokes should 10,000 persons be followed up for 10 years. Using the corresponding data from the Berger *et al.* review[39] generates nine extra haemorrhagic strokes (by both 'aggregated' and 'pooled' methods).

Haemorrhagic stroke: individual patient data-level meta-analyses

The ATT Collaboration[53] reported a statistically significant increased risk of first haemorrhagic stroke for individuals receiving aspirin (pooled RaR of 1.32, 95% CI 1.00 to 1.75; *Figure 45*).[53] The estimates of absolute rates (rounded) were 0.04%/patient-year and 0.03%/patient-year for aspirin and comparator group, respectively, providing an absolute difference of 0.01%/patient-year (10 extra first haemorrhagic strokes if 10,000 persons are followed up for 10 years; this corresponds well with Raju *et al.*'s[38] study-level analysis of haemorrhagic stroke[38]). The numbers of haemorrhagic stroke events were reported as 116 and 89 for aspirin and control groups, respectively, and the total person-years 330,000. This generates an absolute rate (not rounded) of 0.03515%/person-year (aspirin) and 0.02697%/person-year (control)

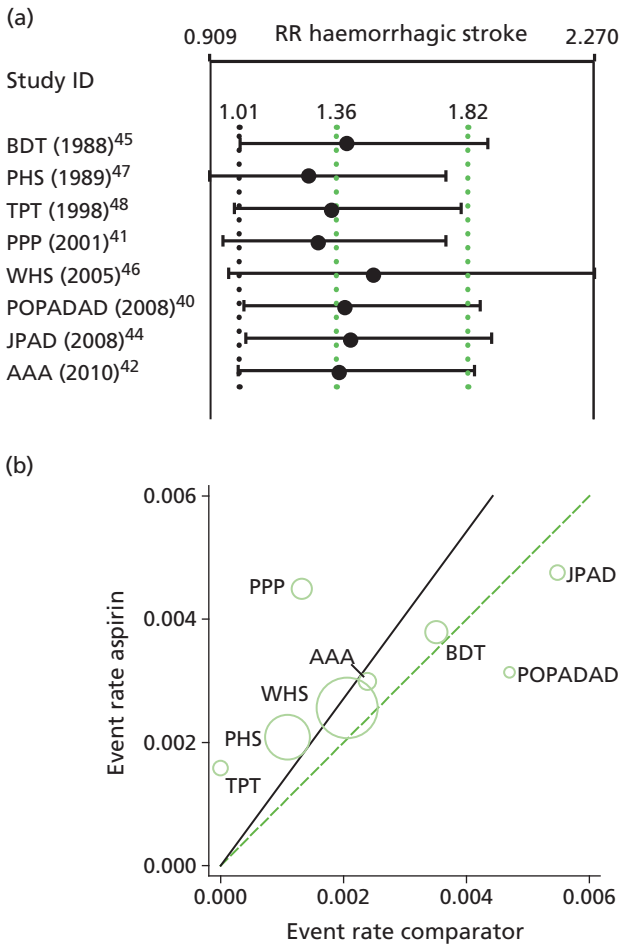


FIGURE 42 (a) Influence of individual studies on pooled estimate of RR of haemorrhagic stroke; (b) L'Abbé plot showing haemorrhagic stroke event rates [the dashed line corresponds to RR of 1; the solid line represents the pooled RR (random effects)].

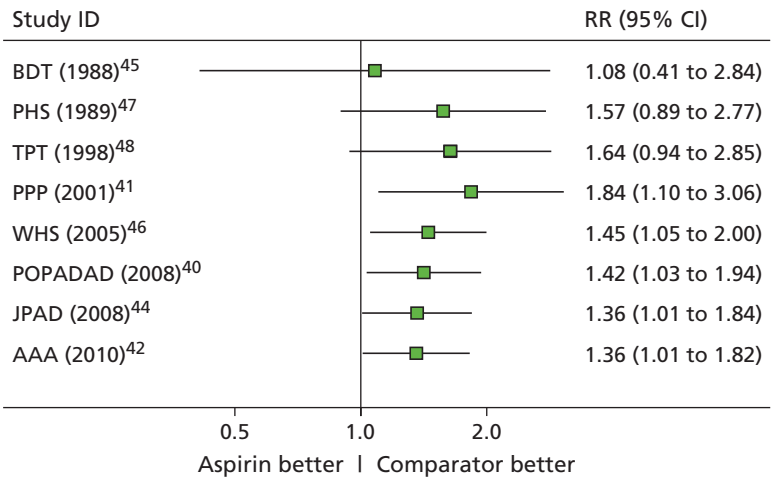


FIGURE 43 Haemorrhagic stroke: repeated test with accumulating studies arranged by recruitment year.

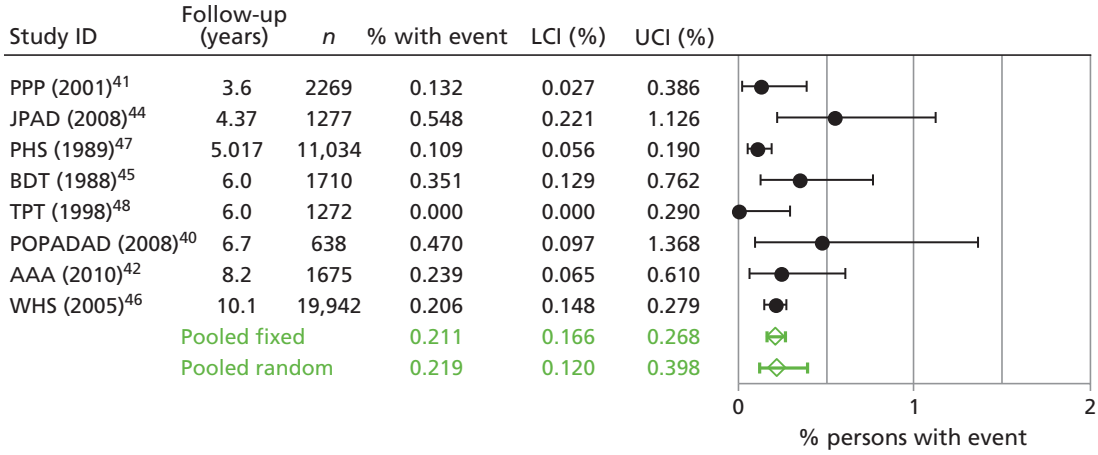


FIGURE 44 Risk of haemorrhagic event in comparator groups. LCI, lower confidence interval.

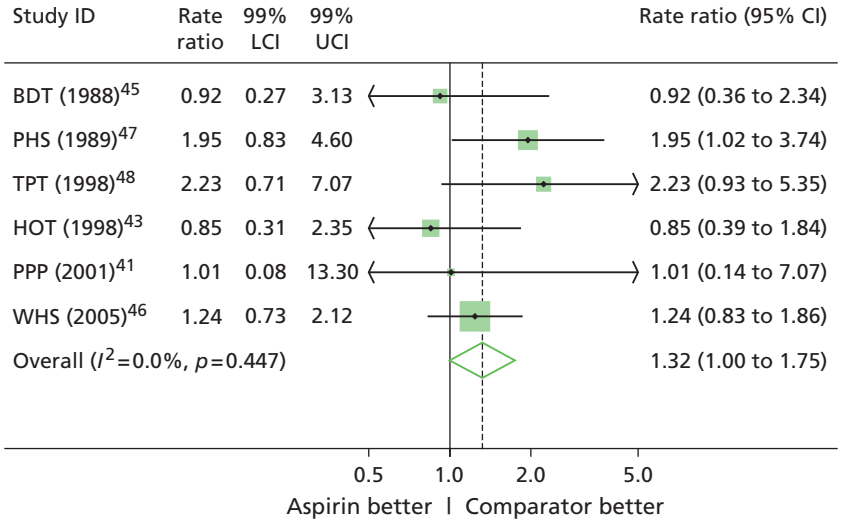


FIGURE 45 Meta-analysis of IPD for first haemorrhagic stroke reported by ATT.[53] LCI, lower confidence interval.

equivalent and a rate difference equivalent to eight extra events incurred should 10,000 persons be followed up for 10 years.

The number of haemorrhagic stroke events used in meta-analyses differs somewhat between the different meta-analyses (*Table 20*); the reason for this is not clear. Only ATT specified 'first haemorrhagic stroke';[53] if second strokes were counted in the other meta-analyses then it is possible that double-counting occurred. Equally, if a first stroke occurred before randomisation then such patients should not have been included in a primary prevention trial. Transcription errors or variation in interpretation of the primary study data represent other potential reasons for discrepancies.

Haemorrhagic stroke: study-level subgroup analysis by sex

Adelman *et al.*[52] reviewed meta-analyses of RCTs for primary prevention of CVD so as to investigate a possible difference in outcome between men and women. The particular focus was total stroke and subcategories of stroke (ischaemic and haemorrhagic). For these outcomes, the authors reproduced the study-level sex-specific subgroup meta-analysis published by Berger *et al.*[70] For this meta-analysis, six[41,43,45–48] of the core nine[40–48] primary studies, which were also analysed in Berger *et al.*,[39] Raju *et al.*[38] and Seshasai *et al.*,[56] were included.

TABLE 20 Number of RCT haemorrhagic stroke events used in systematic review meta-analyses

	ATT 2011[53]		Berger 2011[39]		Raju 2011[38]	
Trial	Aspirin events	Control events	Aspirin events	Control events	Aspirin events	Control events
BDT[45]	13	14[a]	13	6	13	6
PHS[47]	24	12	23	12	23	12
TPT[48]	14	6	12	6	2	0
HOT[43]	12	14				
PPP[41]	2	2	2	3	10	3
WHS[46]	51	41	51	41	51	41

a The ATT Collaboration doubled the events because of the 2 : 1 randomisation ratio.

Three of the six primary studies[45,47,48] enrolled only male patients, one enrolled only women[46] and two[41,43] enrolled men and women. These last two studies[41,43] were subdivided by sex and contributed data to the separate analyses of men and women. In the PPP study,[41] randomisation was stratified by physician but not by sex; the HOT trial[43] stratified randomisation by baseline variables including sex. HOT[43] did not provide usable outcome data for haemorrhagic stroke, so for haemorrhagic stroke only PPP[41] and WHS[46] provided data for women, whereas BDT,[45] PHS,[47] PPP[41] and TPT[48] provided data for men.

The reported pooled ORs for haemorrhagic stroke (aspirin compared with comparator) were 1.07 (95% CI 0.42 to 2.69) for women and 1.69 (95% CI 1.04 to 2.73) for men. This apparent difference between sexes led to a discussion of possible reasons for different response to aspirin. The meta-analysis figure in Adelman *et al.*[52] was taken from the original Berger *et al.*[72] paper; however, using the data therein does not generate the reported results. A published erratum corrected the data and these have been used in *Figure 46*.

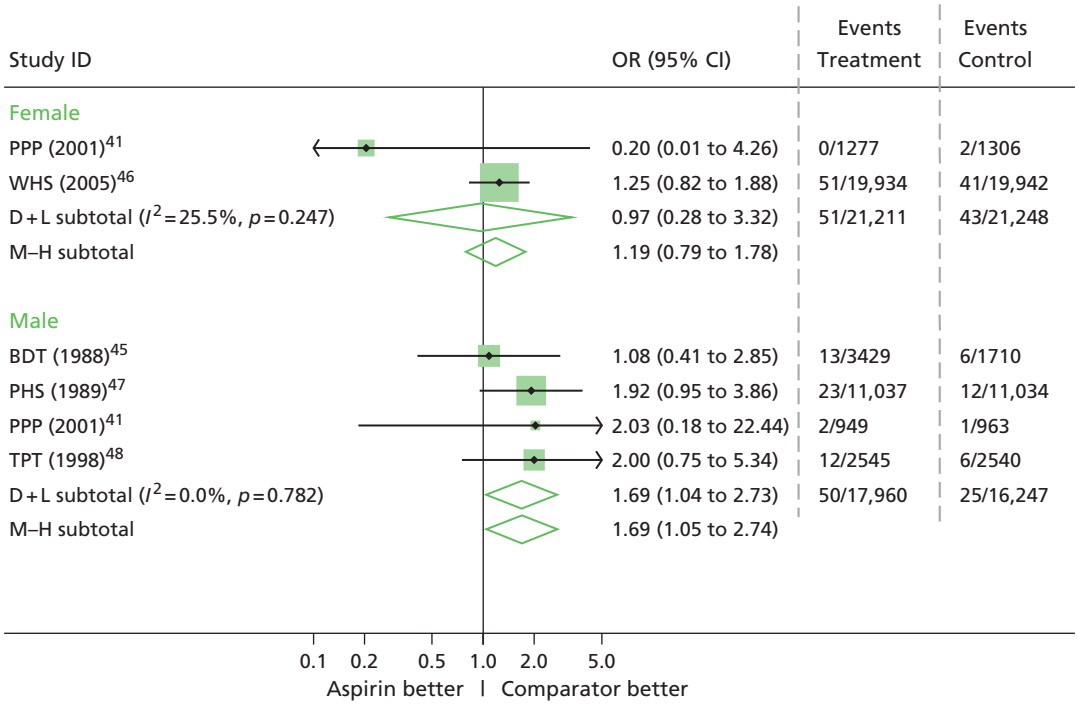


FIGURE 46 Meta-analysis of haemorrhagic stroke by sex using erratum data from Berger *et al.*[80]

Aspirin increases the risk of haemorrhagic stroke in men, but for women, although data indicate a 20% increased risk with aspirin, this does not reach statistical significance. The pooled random-effects OR is about 1 and depends on the continuity correction applied for the PPP study.[41] With the continuity correction set at 0.1 the pooled random-effects estimate becomes 1.180 (95% CI 0.518 to 2.686). In the PPP study[41] aspirin appeared protective but there were only two events (none in the aspirin arm) and using random-effects weighting to the studies may provide an underestimate of the haemorrhagic stroke risk for women.

Total bleeds

Seshasai *et al.*[56] reported the pooled random-effects OR for total bleeds (1.70, 95% CI 1.17 to 2.46). For ease of comparison with Berger *et al.*[39] and Raju *et al.*[38] meta-analyses of bleeds, *Figure 47* shows RR for total bleeds (1.33, 95% CI 1.19 to 1.49). In all studies other than POPADAD[40] there were more bleeds in the aspirin group than the comparator group.

In this analysis the WHS[46] was the most influential trial (*Figure 48a*); in the WHS[46] a very high proportion of participants experienced bleeds in both aspirin and comparator groups (see *Figure 48b*).

As shown in *Figure 49*, the proportion with events in the control arm of the trials varied from < 1% to nearly 80%. From the number of events (15,542) attributed to the control group in the WHS trial,[46] it appears that the numbers of any bleed were combined from multiple categories of event (haematuria, easy bruising and epistaxis) to provide a grand total. As many of these events are likely to have occurred in the same individuals, the results for the WHS[46] are almost certainly counts of events rather than proportion of individuals with a bleed event. Combining these data as dichotomous measures represents a 'unit-of-analysis' error (as discussed in the Cochrane handbook, section 9.2.5.1[79]).

Systematic review evidence on adverse events: cancer studies

Of included systematic reviews, only one included results for adverse events attributable to aspirin use.[49] Data came from IPD analysis of six of the core nine RCTs[40–48] of primary prevention of CVD with aspirin; these were the AAA,[42] TPT,[48] POPADAD,[40] JPAD,[44] HOT,[43] and PPP[41] trials. In some respects the data used were similar to that used by the Antithrombic Trialists Collaboration (ATT IPD systematic review);[53] however, in the ATT[53] analysis of GI and major extracranial bleeds, the included studies were BDT,[45] PHS,[47] TPT,[48] HOT,[43] PPP[41] and WHS.[46] A required inclusion criterion for the Rothwell *et al.* analysis[49] of aspirin for primary prevention of cancer was that aspirin be administered each day,[49] this led to the exclusion of the large WHS[46] and PHS[47] trials in which aspirin was taken on alternate days. Rothwell *et al.*[49] meta-analysed

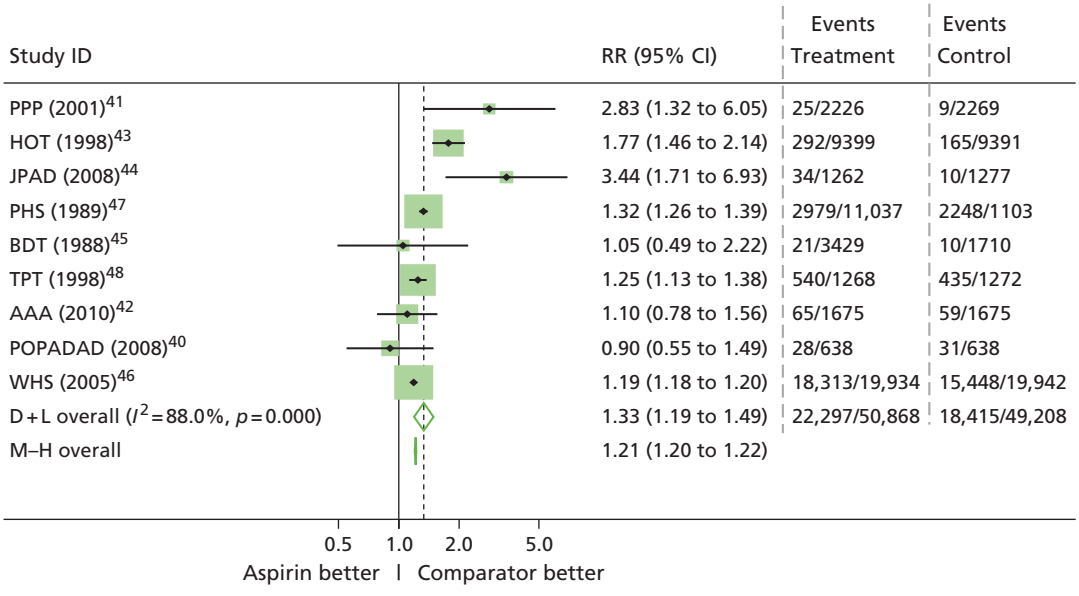


FIGURE 47 Meta-analysis of total bleeds (Seshasai *et al.*[56]).

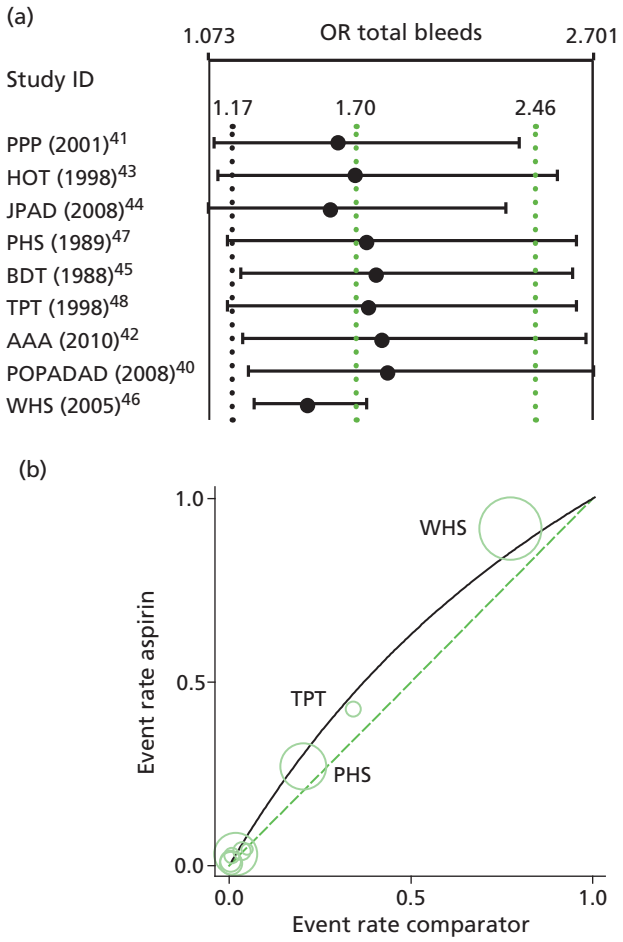


FIGURE 48 (a) Influence of individual studies on pooled OR for all bleeds; (b) L'Abbé plot showing bleed event rates [dashed line = OR of 1; solid line = pooled OR (random effects)].

Study ID	Follow-up (years)	*n*	% with event	LCI (%)	UCI (%)
PPP (2001)[41]	3.6	2269	0.397	0.182	0.752
HOT (1998)[43]	3.8	9391	1.757	1.501	2.044
JPAD (2008)[44]	4.37	1277	0.783	0.376	1.435
PHS (1989)[47]	5.017	11,034	20.373	19.625	21.137
BDT (1988)[45]	6.0	1710	0.585	0.281	1.073
TPT (1998)[48]	6.0	1272	34.198	31.591	36.879
POPADAD (2008)[40]	6.7	1675	4.859	3.325	6.826
AAA (2010)[42]	8.2	638	3.522	2.692	4.520
WHS (2005)[46]	10.1	19,942	77.465	76.878	78.043
	Pooled fixed		52.863	52.219	53.506
	Pooled random		5.057	1.406	16.594

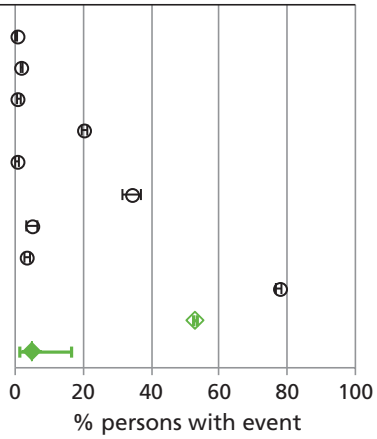


FIGURE 49 Percentage with bleed event in comparator arm; trials arranged by length of follow-up (years). LCI, lower confidence level.

extracranial bleeds for aspirin exposure for 0–2.9 years and for > 3 years. This analysis yielded pooled ORs of 1.95 (95% CI 1.47 to 2.59) and 1.04 (95% CI 0.73 to 1.49), respectively (*Figure 50*), and led the authors to conclude that there was an early risk of bleeding that reduced after 3 years of exposure.

Systematic review evidence on adverse events: diabetes studies

Of six included systematic reviews investigating the effectiveness of aspirin in the primary prevention of CVD in diabetic patients four provided information about adverse events attributable to aspirin. Stavrakis *et al.*[67] reported a pooled RR of 2.12 (95% CI 0.63 to 7.08) for a GI bleed based on PPP,[41] POPADAD[40] and JPAD[44] studies and of 3.02 (95% CI 0.48 to 18.86) for a major bleed based on data from PPP and JPAD trials (*Figure 51*). Event and participant numbers for trial arms were not presented.

The Butalia *et al.*[63] systematic review included the ETDRS[75] in their analysis, together with six[40,41,43,44,46,47] of the nine RCTs analysed by Berger *et al.*,[39] Raju *et al.*[38] and Seshasai *et al.*[56] There is some concern about whether ETDRS[75] qualifies as a primary prevention trial, as it was excluded by other reviewers. In ETDRS,[75] PPP,[41] JPAD,[44] POPADAD[40] all participants were classified as diabetic, whereas < 10% of the participants in PHS,[47] WHS[46] and HOT[43] trials were classified as having diabetes at entry.

Butalia *et al.*[63] reported a pooled RR of 2.5 (95% CI 0.77 to 8.1) for 'all bleeds' based on data from ETDRS,[75] PPP[41] and JPAD[44] studies, a pooled RR of 2.13 (95% CI 0.63 to 7.25) for GI bleeds based on PPP,[41] POPADAD[40] and JPAD[44] studies, and a RR of 2.92 (95% CI 0.17 to 50.23) for a GI non-bleed event. The individual trial RR and number of participants for each arm in each trial were not provided and so it is not possible to reproduce these results. There was insufficient detail in Butalia *et al.*[63] to determine why the RR for GI bleeding should differ slightly from that reported by Stavrakis *et al.*[67]

Younis *et al.*[68] reported a RR of bleeding that was non-significantly higher for aspirin compared with the control group of 2.49 (95% CI 0.70 to 8.84). The contributory trials and definition of bleeding was not clear.

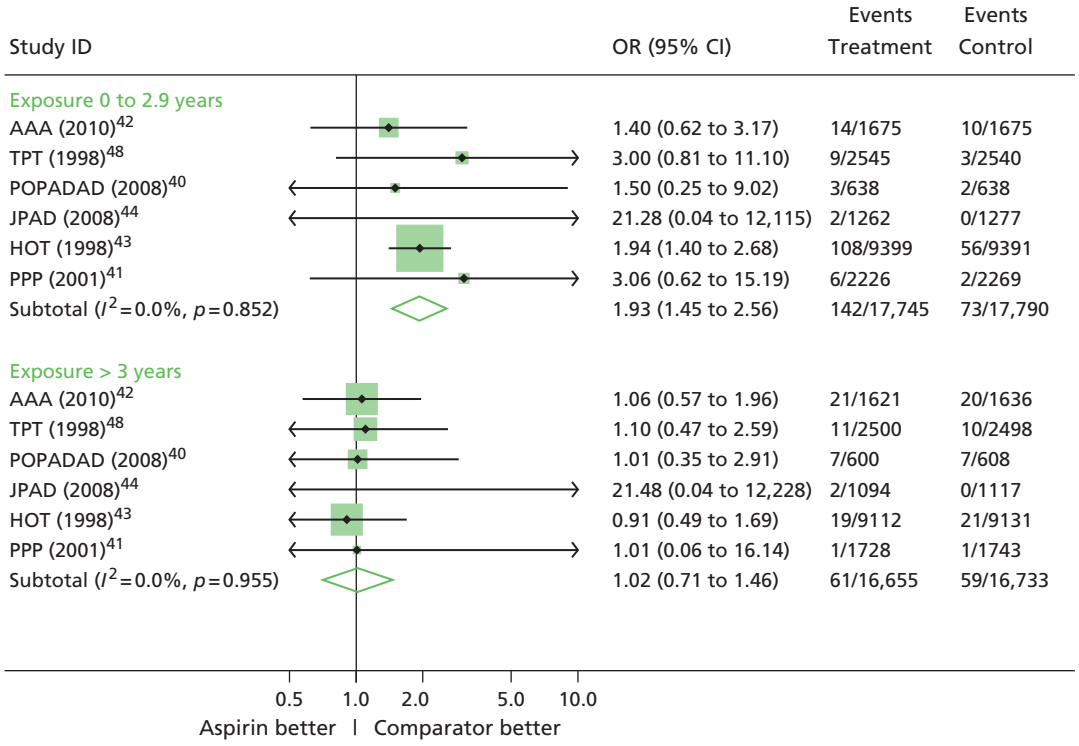


FIGURE 50 Meta-analysis of extracranial bleeds using data from Rothwell *et al.*[49] Note: Results differ slightly from Rothwell *et al.*[49] because of differing outcome statistic and continuity correction for zero events in JPAD.[44]

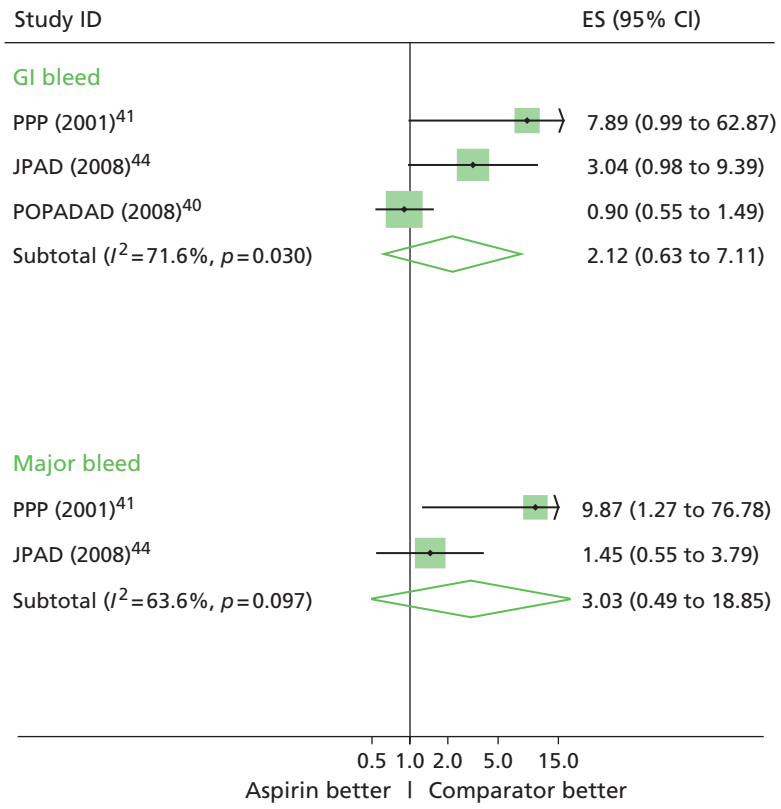


FIGURE 51 Relative risk of major bleeds and GI bleeds in participants with diabetes (Stavrakis *et al.*[67]). Note: Stavrakis provided trial results only as RR with 95% CI rounded to two decimal places; consequently pooled estimate and CIs above do not exactly correspond with those reported.

Zhang *et al.*[69] pooled major bleed events from three studies (JPAD,[44] POPADAD[40] and PPP[41]); the RR (random effects) was 2.46 (95% CI 0.70 to 8.61).

In each systematic review, the pooled point estimates for these outcomes were strongly in favour of the comparator but were associated with considerable uncertainty so that effect sizes were statistically insignificant (at $p < 0.05$) and the 95% lower confidence interval (LCI) encompassed protection by aspirin. The pooled estimates for various categorisations of bleed are summarised in *Table 21*.

TABLE 21 Relative risk of bleed reported in meta-analysis studies including patients with diabetes

Type of bleed/study	No. of trials pooled	RR	95% CI
Major/all bleeds			
[a]Butalia 2011[63]	3	2.50	0.77 to 8.10
[b]Stavrakis 2011[67]	2	3.02	0.48 to 18.86
[b]Zhang 2011[69]	3	2.46	0.70 to 8.61
[c]Younis 2010[68]	Unclear	2.49	0.70 to 8.84
GI bleed			
Stavrakis 2011[67]	3	2.12	0.63 to 7.08
Butalia 2011[63]	3	2.13	0.63 to 7.25

a All bleeds.
b Major bleeds.
c Bleeds ill defined.

Summary of evidence synthesis

Relative effects; benefits

In CVD primary prevention meta-analyses, the potential relative benefits of aspirin appear modest: reduced risk ranges from 6% for all-cause mortality, RR 0.94 [95% CI 0.88 to 1.00 (Raju *et al.*)][38] to 10% for MCEs RR 0.90 [95% CI 0.85 to 0.96 (Berger *et al.*)],[39] whereas the OR 95% CI for total CHD included a null effect or harm from aspirin (Bartolucci *et al.*[37] 95% CI 0.69 to 1.06, and Seshasai *et al.*[56] 95% CI 0.74 to 1.01). In cumulative meta-analysis the effect sizes appear to have diminished in recent years with the accumulation of later studies. Early studies tended to be more favourable and this may be ascribed to improving treatments for CVD over the years or changes in underlying risk and lifestyle factors as suggested by Seshasai *et al.*[56] and others.

Apparent cancer benefits appear after about 5 years from start of treatment. The reported pooled ORs for total cancer mortality was 0.93 (95% CI 0.84 to 1.03) when mean follow-up was only about 6 or 7 years.[56] With longer follow-up, a HR of 0.76 (95% CI 0.66 to 0.88) has been reported.[20] The within-trial OR for cancer death in eight trials (25,570 persons) was 0.80 (95% CI 0.69 to 0.93); the large WHS[46] and PHS[47] (together representing nearly 62,000 individuals) were omitted. The analyses may be considered at risk of selective inclusion of relevant studies (the very large alternate-day dosing studies were excluded and these provide little or no evidence of cancer benefit from aspirin).[81,82] Relative beneficial effects have been found to be most striking for CRC mortality, where an OR of 0.66 (95% CI 0.9 to 1.02) has been reported. However, again, this study omitted the two largest studies where aspirin was given every other day. Including these studies in the estimate of CRC incidence produced 95% CIs suggesting the possibility that aspirin might increase as well as reduce risk. In the longest follow-up analysis of cancer benefit[22] at 20 years, the HR for all-cause mortality for three long-term studies was 0.96 (95% CI 0.90 to 1.02); authors hypothesised that the small magnitude of long-term mortality benefit might be due to a rebound effect subsequent to withdrawal from continuous aspirin use.

Relative effects: harms

Study-level meta-analyses of nine trials indicated a 62% and 66% increased risk of a major bleed from aspirin usage. IPD meta-analysis of six trials[41,43,45–48] suggested a similarly increased event rate of 54%. Increased risk of a GI bleed was estimated to be 37% (study-level analysis of eight RCTs[40–44,46–48]). The estimated increased risk of a haemorrhagic stroke ranged from 32% (IPD analysis of six trials[41,43,45–48]) to 36% (study-level analysis of eight trials[40–42,44,45–48]).

Absolute number of events averted or incurred through use of aspirin

The number of unwanted events (e.g. all-cause mortality) averted by taking aspirin, and the number of adverse events (e.g. bleeding) incurred from aspirin use, are best calculated using IPD taking into account the person-years of exposure to aspirin or length of follow-up. This was done in the ATT meta-analysis of CVD primary prevention trials.[53] The ATT publication reported the rate of averted and of incurred events as %/person-year; thus an absolute difference (aspirin minus control) of –0.06% is equivalent to 0.06 events being avoided per 100 patient-years of exposure. However, the ATT analysis included only six of the core nine trials[40–48] currently available, which have been used in recent study-level meta-analyses.[37–39,56] The inclusion of these trials might modify the results coming from the ATT analysis. We therefore estimated the aspirin dependent number of events avoided or incurred using study-level data reported in the four recent meta-analyses, and, where possible, we compared these estimates with those of the ATT analysis. There are various ways of calculating the rate of averted or of incurred events from study-level data; here we have used two methods, an 'aggregated' and an 'alternative' procedure (see *Chapter 3*).

The numbers of averted events should 10,000 persons be followed up for 10 years, estimated from data presented in various meta-analyses, were as follows: 33–46 deaths (any cause), 60–84 MCEs (MI or stroke or CV death), 47–64 total CHD events, 34–36 CRC deaths, and 17–85 cancer deaths. The number of incurred events should 10,000 persons be followed for 10 years were 46–48 major bleeds, 117–182 GI bleeds, and 8 or 10 haemorrhagic strokes. Overall the estimated event rates conform to a few tens of events per 100,000 person-years' follow-up, other than GI bleeds, which appear to occur at somewhat

higher rates of 68–117 per 100,000 person-years. It should be borne in mind that these values represent 'best point' estimates and although based on the most complete available systematic review evidence they are associated with appreciable uncertainties. *Table 22* summarises these findings.

Composite primary outcomes in the primary prevention of CVD in diabetes show that for all seven of the included systematic reviews and meta-analyses, all of the upper 95% CIs included the possibility of no improvement, and for some[67–69] CIs implied the possibility of greater risk from aspirin.

TABLE 22 Results from CVD and cancer systematic reviews: all comparisons aspirin vs. control

Event	Author (*n* studies)	Pooled estimate (95% CI)	NNT or NNH	Absolute difference (%/patient-year)	Person-years' exposure for one less or one extra event	Events averted or events incurred for 10,000 persons followed up for 10 years
All-cause mortality	Raju 2011[38] (9)	RR 0.94 (0.88 to 1.00)	314[a]		2752,[b] 2172[a]	36,[b] 46[a]
All-cause mortality	Berger 2011[39] (9)	RR 0.94 (0.89 to 1.00)	318[a]		2996,[b] 2198[a]	33,[b] 46[a]
All-cause mortality	[c]Rothwell 2011[22] (8)	OR 0.92 (0.85 to 1.00)				85,[b] 75[a]
All-cause mortality	[d]Rothwell 2011[22] (3)	HR 0.96 (0.90 to 1.02)				
Cancer mortality[e]	Seshasai 2012[56] (8)	OR 0.93 (0.84 to 1.03)	677[a]		5974[b] 4779[a]	17,[b] 21[a]
Cancer mortality	[c]Rothwell 2011[22] (8)	OR 0.80 (0.69 to 0.93)				85,[b] 54[a]
Cancer mortality	[c]Rothwell 2012[49] (51)	OR 0.84 (0.75 to 0.94)	319[a]			25[b] (36[f]), 31[a] (44[f])
CRC death[g]	Rothwell 2010[31] (4)	OR 0.66 (0.51 to 0.85)		0.034,[h] 0.036		34,[b] 36
MI/stroke/CV death	ATT 2009[53] IPD (6)	RaR 0.88 (0.82 to 0.94)		–0.06	1667	60
MI/stroke/CV death	Berger 2011[39] (9)	RR 0.90 (0.85 to 0.96)	171[a]		1676,[b] 1184[a]	60,[b] 84[a]
Total CHD	Seshasai 2012[56] (9)	OR 0.86 (0.74 to 1.01)	226[a]		2146,[b] 1564[a]	47,[b] 64[a]
Non-trivial bleed	Seshasai 2012[56] (9)	OR 1.31 (1.14 to 1.50)	146[a]		562, 1010[a]	178,[b] 99[a]
Major bleed	Berger 2011[39] (9)	RR 1.62 (1.31 to 2.00)	293[a]		2082, 2208	48,[b] 49[a]

continued

TABLE 22 Results from CVD and cancer systematic reviews: all comparisons aspirin vs. control (*continued*)

Event	Author (*n* studies)	Pooled estimate (95% CI)	NNT or NNH	Absolute difference (%/patient-year)	Person-years' exposure for one less or one extra event	Events averted or events incurred for 10,000 persons followed up for 10 years
Major bleed	Raju 2011[38] (7)	RR 1.66 (1.41 to 1.95)	312[a]		2078,[b] 2186[a]	48,[a] 46[a]
Major bleed	ATT 2009[53] IPD (6)	RaR 1.54 (1.30 to 1.82)		0.030	3333	30
GI bleed	Raju 2011[38] (8)	RR 1.37 (1.15 to 1.62)	211[b]		853,[a] 1476[b]	117,[a] 68[b]
Haemorrhagic stroke	Raju 2011[38] (8)	RR 1.36 (1.01 to 1.82)	534[b]		10,516,[b] 4080[a]	10,[b] 25[a]
Haemorrhagic stroke	Berger 2011[39] (8)	RR 1.35 (1.01 to 1.82)	1421[b]		11,165,[a] 10,798[b]	9,[a] 9[b]
Haemorrhagic stroke	ATT 2009[53] IPD (6)	RaR 1.32 (1.00 to 1.74)		0.01,[i] 0.00818[j]		10,[i] 8[j]

a Alternative method.
b Aggregate method.
c Assumes mean follow-up of 10 years.
d Follow-up 20 years.
e Approximately 7 years of follow-up.
f Assumes mean follow-up is 7 years.
g Approximately 20 years of follow-up.
h Aggregate data from figure 1 of Rothwell 2010[31] [119 colorectal deaths/8282 aspirin users and 121 colorectal deaths/5751 aspirin 'non-users', over 20 years of follow-up (including approximately 5 years of scheduled aspirin use)].
i Based on rounded data.
j Based on unrounded aggregate data.

Chapter 6 Discussion

Summary of methods and principal findings

Although there are clearly identified benefits in secondary prevention of CVD, and although the in vitro mechanisms and potential benefits are clear, the overall benefits of use of aspirin in the primary prevention of either cancer or CVD are not yet clear. In this study we aimed to investigate these issues in more depth.

Evidence was retrieved through searches during June 2012 in 13 electronic bibliographic databases, contact with experts in the field, scrutiny of references of included studies, and checking various health services research-related resources. The search strategy covered the concepts of aspirin and primary prevention. 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. Overall quality of the included systematic reviews was good.

The reported CV benefits of aspirin ranged from a 6% reduction in all-cause mortality (RR 0.94, 95% CI 0.88 to 1.00), and a 10% reduced risk of MCEs (RR 0.90, 95% CI 0.85 to 0.96) to a 15% reduced risk for total CHD (RR 0.85, 95% CI 0.69 to 1.06); the last 95% CI just mentioned included a null effect for aspirin. Larger relative effects were reported for reduced risk of death from cancer [pooled ORs ranged between 0.76 (95% CI 0.66 to 0.88) and 0.93 (95% CI 0.84 to 1.03)], depending on length of follow-up. Reported benefits appear to develop after about 5 years from start of treatment. A considerable number of analyses have been conducted implying benefit, but currently these should be viewed with some caution because two very large studies with essentially null effect were omitted from analysis because in these RCTs aspirin was used on alternate days rather than as a daily dose.

The OR for death from CRC was 0.66 (95% CI 0.90 to 1.02) in favour of aspirin. However, including studies in which aspirin was given on alternate days gave an OR of 0.91 (95% CI 0.74 to 1.11) for incidence of CRC, a value which includes the possibility that aspirin might increase, as well as reduce risk of incidence of CRC. These studies of the primary prevention of cancer are interesting post hoc analyses that generate valuable hypotheses; however, they required accurate retrospective ascertainment of cause death and categorisation of individuals free of cancer at inception. New RCTs that have cancer prevention as their primary aim are now under way.

The risk of bleeding events was statistically significantly greater in aspirin users than in control subjects. Study-level meta-analyses of nine trials[40–48] indicated a 62% and 66% increased risk of a major bleed from aspirin usage. IPD meta-analysis of six trials[41,43,45–48] suggested a similarly increased event rate of 54%. Increased risk of a GI bleed was estimated to be 37% (study-level analysis of eight RCTs[40–44,46–48]). The estimated increased risk of a haemorrhagic stroke ranged from 32% (IPD analysis of six trials[41,43,45–48]) to 36% (study-level analysis of eight trials[40–42,44–48]). The pooled estimates of increased RR for bleeding remained stable across trials conducted over several decades. Study-level meta-analyses aimed at judging RR of bleeding according to sex and in individuals with diabetes were insufficiently powered for firm conclusions to be drawn.

Point estimates of the number of extra events incurred due to aspirin or the number of events averted from aspirin use depended on the method of estimation; however, it is clear that the absolute rates of events were low, so that a large number of individuals would need to take aspirin and be followed up for many years for a few events (either beneficial or adverse) to occur. For most outcomes, event rates ranged between about 10 and 60 for 10,000 persons followed up for 10 years; however, the rate of GI bleeds was estimated as likely to be slightly higher – in the range 68 to 117 for 10,000 persons followed up for 10 years.

Limitations in the evidence base

The RCT evidence base to address the objectives of the current short report does not appear to have grown since the publication of the AAA[42] trial in 2011 (several unreported ongoing trials have been identified). This evidence has been subject to intense systematic review and meta-analysis including many study-level meta-analytic investigations, a landmark IPD meta-analysis published in 2009[53] for CVD and multiple publications by Rothwell *et al.* for cancer.[22,31,49,62] In general, the published meta-analyses appear to be well conducted and up to date according to the time at which they were undertaken; however, inferences and conclusions appear to differ from study to study.

New evidence on aspirin for the primary prevention of CVD appears to be limited, with no new completed RCTs identified. The dose of aspirin used in the included RCTs varied; this limits the current conclusions and estimation of the most appropriate dose for primary prevention. It has also been noted in previous reviews that several of the core nine RCTs[40–48] were conducted within populations of health professionals, which potentially limits generalisability of the findings.

Strengths and limitations of this review

We undertook comprehensive searches and thorough systematic review methods following recognised guidelines. We evaluated all studies and re-analysed meta-analytic findings to ensure our own interpretations were in agreement with those of the authors.

A limitation was that we date-limited searches to 2008; nevertheless, because of the intense interest that this subject has generated and the cataloguing of all primary research in so many systematic reviews, we are confident that we have not omitted any major relevant RCTs or systematic reviews.

A further limitation is our potential over-reliance on study-level systematic reviews in which the person-years of follow-up are not accurately ascertainable. However, estimates of number of events averted or incurred through aspirin use calculated from data in study-level meta-analyses did not differ substantially from estimates based on IPD-level meta-analyses for which person-years of follow-up were more accurate (although based on less-than-complete assemblies of currently available primary studies). Seshasai *et al.*[56] calculated similar estimates of averted and incurred events to us. Despite identifying several weaknesses in terms of double-counting, we found the analyses of previous RCTs and listing of outcome definitions across studies in this paper extremely helpful.

Overall assessment of evidence

Benefits of aspirin for primary prevention of cancer or CVD are relatively modest, remain statistically uncertain, and are an order of magnitude less than that observed in secondary prevention for CVD. In contrast, harms (especially bleeding) occur at relatively higher frequency (apparently very high frequency in some populations) and are statistically based on strong evidence. Second, 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, and also protection against cancer metastasis. However, these studies should be viewed with caution because data from the two largest primary prevention trials (WHS[46] and PHS[47]) were excluded but show no evidence of cancer protection by aspirin after $\geq$ 10 years' follow-up,[81,82] and because these are post hoc analyses of studies aimed at a different primary outcome, for which rigorous case ascertainment cannot be verified. In practice, people who suffer GI problems may self-select to discontinue aspirin use and this effect may introduce selection bias.

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 estimated values represent 'best point' estimates and 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 meanwhile, 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 [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); CARING (Chronotherapy with Low-dose Aspirin for Primary Prevention), June 2019; see *Appendix 2*], including large RCTs of the potential benefits of aspirin in the prevention of cancer. According to our latest search these remain unpublished and we do not think the published evidence base has expanded since Seshasai *et al.*[56] 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.

The inclusion of observational studies and registry data into primary prevention analyses of CVD and cancer might enormously expand the available data on rare events such as haemorrhagic stroke (e.g. the UK NHS general practice registry that holds data on several million patients). However, ascertaining accurate aspirin consumption may be problematic, whereas RCT data are likely to be more secure and already about 100,000 participants have accumulated in such studies. Cost-effectiveness assessment of primary prevention with aspirin and modelling of the net benefit of aspirin are potential extensions of the clinical effectiveness research already completed.

Implications for practice

There are several guidelines that propose the widespread employment of aspirin for individuals at increased risk for CVD, based on an assessment of the balance between CV benefits (e.g. reduced MI and stroke) and various harms (especially bleeding). Definitions of 'high' risk vary according to country and guideline.[18,10,20,83]

However, as we have indicated in this short report, opinion and evidence have shifted over time. At a population level, aspirin for primary prevention of CVD is associated with net harm due to increased potential for bleeding, while the results for benefits are not persuasive. For the primary prevention of cancer we consider that more information is desirable.

Conclusions

We have found that the benefit from regular aspirin use in primary prevention of CVD is modest, whereas its use increases risk of haemorrhagic stroke and major/minor bleeding. Effects on cancer prevention have a long lead time and are at present reliant on post hoc analyses. New RCTs are under way which may clarify the extent of benefit of aspirin in reducing cancer incidence and mortality.

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Contributions of authors

Paul Sutcliffe (Associate Professor) and **Martin Connock** (Senior Research Fellow) undertook the review.

Samantha Johnson (Information Specialist) developed the search strategy and undertook searches.

Paul Sutcliffe and **Martin Connock** screened the search results.

Binu Gurung (Research Assistant) retrieved the papers.

Paul Sutcliffe, **Karoline Freeman** (Research Fellow), **Tara Gurung** (Research Fellow) and **Martin Connock** screened the retrieved papers against the inclusion criteria, appraised the quality of papers and abstracted data from papers.

Martin Connock and **Ngianga-Bakwin Kandala** (Principal Research Fellow) analysed the data.

Paul Sutcliffe, **Karoline Freeman**, **Tara Gurung** and **Amy Grove** (Project Manager) wrote sections of the report.

Sarah Morrow (Postgraduate Student) assisted with writing the background section.

Aileen Clarke (Professor of Public Health and Health Services Research) provided advice on design and analysis, coordinated the review, and wrote sections of the report and the summary.

About Warwick Evidence

Warwick Evidence is a Health Technology Assessment Group, located in Warwick Medical School, working in close collaboration with the NHS to support the further development of knowledge-based health services. Warwick Evidence brings together experts in clinical effectiveness and cost-effectiveness reviewing, health economics and modelling.

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Appendix 1 Record of searches undertaken

Medline via Ovid interface

Searched on 19 September 2012.

Results	Search type	Actions
1	exp *Aspirin/	19,106
2	(aspirin or acetylsalicyl* or "acetyl-salicyl*" or "acetyl salicyl*").tw.	38,918
3	1 or 2	41,948
4	(prevent* or prophyla*).tw.	885,027
5	exp Primary Prevention/	105,281
6	4 or 5	969,687
7	randomized controlled trial.pt.	336,449
8	(random* or controlled trial* or clinical trial* or rct).tw.	709,686
9	meta-analysis.pt.	36,189
10	("meta-analysis" or "meta analysis" or metaanalysis or "systematic review*").tw.	60,362
11	7 or 8 or 9 or 10	833,781
12	3 and 6 and 11	2773
13	limit 12 to (english language and humans)	2397
14	limit 13 to yr = "2008 -Current"	614

Medline In-Process & Other Non-Indexed Citations via Ovid interface

Searched on 19 September 2012.

Results	Search type	Actions
1	exp *Aspirin/	2
2	(aspirin or acetylsalicyl* or "acetyl-salicyl*" or "acetyl salicyl*").tw.	1732
3	1 or 2	1733
4	(prevent* or prophyla*).tw.	46,556
5	"primary prevent*".tw.	606
6	4 or 5	46,556
7	randomized controlled trial.pt.	449
8	meta-analysis.pt.	43
9	(random* or "controlled trial*" or "clinical trial*" or rct).tw.	49,519
10	(metaanalysis or "meta analy*" or "meta-analy*").tw.	4026
11	7 or 8 or 9 or 10	51,642
12	3 and 6 and 11	125
13	limit 12 to english language	116
14	limit 13 to yr = "2008 -Current"	82

EMBASE 1980–2011, week 38 via OVID interface

Searched on 19 September 2012.

Results	Search type	Action
1	exp acetylsalicylic acid/	137,449
2	(aspirin or acetylsalicyl* or "acetyl-salicyl*" or "acetyl salicyl*").tw.	87,233
3	1 or 2	144,909
4	exp primary prevention/	22,741
5	(prevent* or prophyla*).tw.	1,117,343
6	4 or 5	1,124,596
7	randomized controlled trial/	329,063
8	("random*or controlled trial*" or "clinical trial" or rct).tw.	94,960
9	meta analysis/	65,756
10	(metaanalysis or "meta-analysis" or "meta analysis" or "systematic review*").tw.	83,512
11	7 or 8 or 9 or 10	490,269
12	3 and 6 and 11	3852
13	limit 12 to (human and english language)	3338
14	limit 13 to yr = "2008 -Current"	955

Science Citation Index and Conference Proceedings via the Web of Science interface

Searched on 19 September 2012.

(aspirin or acetylsalicyl* or "acetyl-salicyl*" or "acetyl salicyl*") AND (prevent* or prophyla* or "primary prevent*") AND ("randomi?ed controll* trial*" or random* or "controlled trial*" or "clinical trial*" or rct or "systematic review*" or metaanalysis or "meta-analysis" or "meta analysis")

Refined by: Languages = (ENGLISH)

Time span = 1 January 2008 to 19 September 2012

Databases = Science Citation Index Expanded (SCIE), Conference Proceedings Citation Index-Science (CPCI-S)

Total retrieved: 1748

Database of Systematic Reviews and CENTRAL

Searched via The Cochrane Library on 20 September 2012.

1. aspirin or acetylsalicyl* or "acetyl salicyl*" or "acetyl-salicyl*":ti,ab,kw (Word variations have been searched)
2. prevent* or prophyla*
3. MeSH descriptor: [Aspirin] explode all trees
4. MeSH descriptor: [Primary Prevention] explode all trees

5. (#1 or #3) and (#2 or #4)
6. 2944 (not limited by date)

Reviews limited to 2008 onwards: 53

CENTRAL limited to 2008 onwards: 321

Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database and Health Technology Assessment databases

Searched via the Centre for Reviews and Dissemination at www.crd.york.ac.uk/crdweb/SearchPage.asp on 20 September 2012.

(aspirin or acetylsalicyl* or "acetyl salicyl*" or "acetyl-salicyl*") and (prevent* or prophyla*)

Limited to 2008 onwards

Results:

- DARE: 128
- HTA: 11
- NHS EED: 34

ClinicalTrials.gov (http://clinicaltrials.gov/)

Clinical trials database searched on 20 September 2012 with no date restriction.

(Aspirin AND primary): 797

UK Clinical Research Network's Portfolio Database (http://public.ukcrn.org.uk/search/)

UKCRN searched using Title/Acronym field on 20 September 2012 with no date restriction.

Aspirin: 27

Appendix 2 Clinical trials identified from the United Kingdom Clinical Research Network Portfolio and ClinicalTrials.gov databases

Title	Condition	Intervention	Date	Summary	Outcome measures
Chronotherapy With Low-dose Aspirin for Primary Prevention (Recruiting) NCT00725127	Type 2 diabetes	Aspirin	October 2008 to June 2017 (update: March 2012)	This prospective, randomised, parallel-arm study will investigate the potential influence of ASA on the primary prevention of CV, cerebrovascular and renal events in subjects with either impaired fasting glucose (≥ 100 mg/dl) or previous diagnosis of type 2 diabetes mellitus, who will receive low-dose ASA (100 mg/day) at different circadian times (upon awakening or at bedtime) in relation to their rest–activity cycle	To evaluate the effects of awakening vs. bedtime 100 mg/day ASA administration on primary prevention of CV, cerebrovascular and renal fatal, and non-fatal events
Japanese Primary Prevention Project With Aspirin (Recruiting) NCT00225849	Hypertension Hyperlipidaemia Diabetes mellitus	Aspirin	March 2005 to September 2010 (update: September 2005)	A multicentre, open-label, centrally randomised, controlled trial. 10,000 elderly patients with one or more CV risk factors (age 60–85 years, combined with hypertension, hyperlipidaemia, and/or diabetes) will be assigned to enteric-coated aspirin (100 mg/day) or control	The primary end point is composite event of CV death, non-fatal stroke (of any cause) and non-fatal MI
A Study to Assess the Efficacy and Safety of Enteric-Coated Acetylsalicylic Acid in Patients at Moderate Risk of Cardiovascular Disease (Active, not recruiting) NCT00501059	Moderate risk of CVD	Aspirin and placebo	July 2007 to May 2015 (update: July 2012)	The current study is designed to prove the efficacy and tolerability of 100 mg enteric-coated aspirin vs. placebo in the prevention of CVD events, which include fatal and non-fatal MI, stroke and CV death, in a population with no history of known CVD at moderate risk of major CHD events	Time to first occurrence of composite outcome or individual components of fatal or non-fatal MI, stroke or CV incident. Time to incidence of all-cause mortality. Time to first occurrence of incidence of all cancers, excluding non-melanoma skin cancer Incidence of treatment-emergent adverse events and changes in the physical examination findings, weight, and vital signs

Title	Condition	Intervention	Date	Summary	Outcome measures
ASCEND: A Study of Cardiovascular Events iN Diabetes (Active, not recruiting) NCT00135226	Diabetes mellitus	Aspirin and omega-3-acid ethyl esters	March 2005 to August 2010 (update: August 2011)	The purpose of this study is to determine whether 100 mg daily aspirin vs. placebo and/or supplementation with 1 g daily omega-3 fatty acids or placebo prevents 'serious vascular events') in patients with diabetes who are not known to have occlusive arterial disease and to assess the effects on serious bleeding or other adverse events	The combination of non-fatal MI, non-fatal stroke or vascular death, excluding confirmed cerebral haemorrhage, serious vascular event in various prognostic subgroups, cerebral haemorrhage
Aspirin in Reducing Events in the Elderly (Recruiting) NCT01038583	Functional disability, dementia, heart disease, stroke, cancer, bleeding	100 mg enteric-coated aspirin and placebo	January 2010 to August 2016 (update: February 2012)	Do the potential benefits of low dose aspirin outweigh the risks in people aged > 70 years? Does taking a daily low-dose aspirin extend the length of a disability-free life in healthy participants aged ≥ 70 years?	The primary end point is death from any cause or incident, dementia or persistent physical disability
Aspirin in Preventing Colorectal Cancer in Patients at Increased Risk of Colorectal Cancer (Active, not recruiting) NCT00468910	CRC, precancerous/ non-malignant condition	Aspirin and placebo Procedure: biopsy	May 2007 to April 2014 (update: April 2011)	This randomised Phase II trial is studying how well aspirin works in preventing CRC in patients at increased risk of CRC	Observed change in spectral slope and fractal dimension from baseline. Colonic epithelial apoptosis and cell proliferation Rectal prostaglandin levels Platelet COX activity Correlation of spectral marker alterations with UGT1A6 genotype
Improving Aspirin Use Among Adults at Risk for Cardiovascular Disease (CVD) (Completed)	CVD	Pre-visit summary and clinical decision sharing tool	October 2009 to July 2010 (update: February 2011)	The specific aims of the proposed work are to compare the reliability and overall effectiveness of two different methods (patient or physician initiated) for motivating patients to take aspirin to prevent	Aspirin use at 2-week follow-up (measures taken at baseline and follow-up) patient knowledge of risks/benefits of aspirin

Title	Condition	Intervention	Date	Summary	Outcome measures
NCT00981032				stroke and heart attacks as well as to develop a plan for translating the intervention into a process that is suitable for a paper-based clinic	
A Healthy Female and Male Volunteers Aspirin Study (Completed) NCT01448031	Healthy	Capsule ASA 81 mg/ esomeprazole 20 mg and acetylsalicylzuur Apotex cardio	November 2011 to April 2012 (update: May 2012)	A Phase I, open-label, randomised, two-way crossover pharmacokinetic study comparing the bioavailability of ASA after 5 days' repeated once-daily administration of a fixed-dose combination capsule of ASA 81 mg/esomeprazole 20 mg and ASA 80 mg (European aspirin reference product)	Pharmacokinetic profile of ASA and salicylic acid in terms of AUC, maximum concentration at steady state (CSS,max), time to reach maximum concentration (*T*max) and terminal half-time Description of the safety profile in terms of adverse events, BP, pulse, ECG, physical examination, safety laboratories
Observational Aspirin Use and CVD in the Physicians' Health Study (Completed) NCT00005493	CVDs Coronary disease Heart diseases MI Stroke		April 1998 to March 2001 (update: June 2005)	To analyse existing data from the PHS,[47] a randomised primary prevention trial of low-dose aspirin and beta-carotene conducted among 22,071 US male physicians to address questions concerning aspirin and CVD that could not adequately be addressed during the randomised aspirin period	
Aspirin Effectiveness Study (Recruiting)	Coronary artery disease		April 2010 to April 2011 (Update: May 10)	This study is being done to identify the percentage of patients in Ireland whose aspirin is not working effectively and to help identify factors that could be used to target interventions to increase aspirin's effectiveness in Irish patients	Percentage of patients with non-response to aspirin

ASA, acetylsalicylic acid; AUC, area under curve; CSS, concentration at steady state; ECG, electrocardiography.

Appendix 3 Table of reasons for excluding studies at full paper (*n* = 121)

Selected for review	Reason for exclusion
Acelajado MC, Oparil S. Antiplatelet therapy for transient ischemic attack. *J Clin Hypertens* 2012;**14**:103–11	Non-systematic review
Agrawal A, Fentiman IS. NSAIDs and breast cancer: a possible prevention and treatment strategy. *Int J Clin Pract* 2008;**62**:444–9	Non-systematic review – difficult to distinguish NSAIDs from aspirin
Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischaemic stroke. *Chest* 2008;**133**:S630–69	Non-systematic review
Anoop B, Janusz J, Keith RA. Nonsteroidal anti-inflammatories (NSAIDs) and aspirin for intestinal metaplasia of the stomach. *Cochrane Database Syst Rev* **10**: 2010	Non-systematic review
Ansara AJ, Nisly SA, Arif SA, Koehler JM, Nordmeyer ST. Aspirin dosing for the prevention and treatment of ischaemic stroke: an indication-specific review of the literature. *Ann Pharmacother* 2010;**44**:851–62	Non-systematic review
Apostolakis S, Marin F, Lip GY. Antiplatelet therapy in stroke prevention. *Adv Cardiol* 2012;**47**:141–54	Non-systematic review
Anon. Aspirin and primary cardiovascular prevention. Uncertain balance between benefits and risks. *PrescrireInt* 2010;**19**:258–61	Non-systematic review
Anon. Aspirin for primary prevention of cardiovascular disease? *Drug Therapeut Bull* 2009;**47**:122–5	Non-systematic review
Bailey AL, Smyth SS, Campbell CL. The case against routine aspirin use for primary prevention in low-risk adults. *Am Fam Physician* 2011;**83**: 1387–90	Non-systematic review
Barbhaiya M, Erkan D. Primary thrombosis prophylaxis in antiphospholipidantibody-positive patients: where do we stand? *Curr Rheumatol Rep* 2011;**13**:59–69	Non-systematic review
Barnett H, Burrill P, Iheanacho I. Do not use aspirin for primary prevention of cardiovascular disease, *BMJ* 2010;**340**:c1805	Non-systematic review
Baron JA. Aspirin and NSAIDs for the prevention of colorectal cancer. *Rec Res Cancer* 2009;**181**:223–9	Non-systematic review
Barry EL, Sansbury LB, Grau MV, Ali IU, Tsang S, Munroe DJ, *et al.* Cyclooxygenase-2 polymorphisms, aspirin treatment, and risk for colorectal adenoma recurrence: data from a randomized clinical trial. *Cancer Epidem Biomar* 2009;**18**:2726–33	Secondary prevention
Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, *et al.*, WARFASA I. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med* 2012;**366**:1959–67	Secondary prevention
Becker RC, Meade TW, Berger PB, Ezekowitz M, O'Connor CM, Vorchheimer DA, *et al.* The primary and secondary prevention of coronary artery disease. *Chest* 2008;**133**:S776–814	Non-systematic review
Benamouzig R, Uzzan B. Aspirin to prevent colorectal cancer: time to act? *Lancet* 2010;**376**:1713–14	Comment
Berger JS. Aspirin as preventive therapy in patients with asymptomatic vascular disease. *JAMA* 2010;**303**:880–2	Editorial

Selected for review	Reason for exclusion
Bjorklund L, Wallander MA, Johansson S, Lesen E. Aspirin in cardiology: benefits and risks. *Int J Clin Pract* 2009;**63**:468–77	Non-systematic review
Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. Aspirin and cancer risk: a quantitative review to 2011. *Ann Oncol* 2012;**23**:1403–15	Systematic review – focus on observational studies
Bowry AD, Brookhart MA, Choudhry NK. Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events. *Am J Cardiol* 2008;**101**:960–6	Effectiveness of clopidogrel
Burn J. Chemoprevention. *Viszeralmedizin* 2011;**27**:322–8	Non-systematic review
Burness CB, Scott LJ. Acetylsalicylic acid/esomeprazole fixed-dose combination. *Drugs Aging* 2012;**29**:233–42	Combined drugs
Burt RW. Chemoprevention for colorectal cancer. In: Lieberman DA, Malfertheiner P, Riemann JF, Spechler SJ, editors. *Strategies of Cancer Prevention in Gastroenterology*. Falk Symposium, Vol. 165A. London: Springer 2009; pp. 74–81	Non-systematic review
Casado-Arroyo R, Bayrak F, Sarkozy A, Chierchia GB, de Asmundis C, Brugada P. Role of ASA in the primary and secondary prevention of cardiovascular events. *Best Pract Res Cl Ga* 2012;**26**:113–23	Non-systematic review
Casado-Arroyo R, Gargallo C, Arbeloa AL. Balancing the risk and benefits of low-dose aspirin in clinical practice. *Best Pract Res Cl Ga* 2012;**26**: 173–84	Non-systematic review
Caso V, Santalucia P, Acciarresi M, Pezzella FR, Paciaroni M. Antiplatelet treatment in primary and secondary stroke prevention in women. *Eur J Int Med* 2012;**23**:580–5	Non-systematic review
Chan AT, Cook, NR. Are we ready to recommend Aspirin for cancer prevention? *Lancet* 2012; **379**:1569–71	Comment
Chan AT, Arber N, Burn J, Chia WK, Elwood P, Hull MA, *et al.* Aspirin in the chemoprevention of colorectal neoplasia: an overview. *Cancer Prev Res* 2012;**5**:164–78	Non-systematic review
Chasman DI, Shiffman D, Zee RYL, Louie JZ, Luke MM, Rowland CM, *et al.* Polymorphism in the apolipoprotein(a) gene, plasma lipoprotein(a), cardiovascular disease, and low-dose aspirin therapy. *Atherosclerosis* 2009;**203**:371–6	Genetic study
Cho E, Curhan G, Hankinson SE, Kantoff P, Atkins MB, Stampfer M, *et al.* Prospective evaluation of analgesic use and risk of renal cell cancer. *Arch Int Med* 2011;**171**:1487–93	Non-RCT
Coccheri S. Antiplatelet drugs: do we need new options? With a reappraisal of direct thromboxane inhibitors. *Drugs* 2010;**70**: 887–908	Non-systematic review
Coccheri S. Antiplatelet therapy: controversial aspects. *Thromb Res* 2012;**129**:225–9	Non-systematic review
Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, *et al.* Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. *J Nat Cancer Inst* 2009;**101**:2009	Secondary prevention
Coleman CI, Sobieraj DM, Winkler S, Cutting P, Mediouni M, Alikhanov S, *et al.* Effect of pharmacological therapies for stroke prevention on major gastrointestinal bleeding in patients with atrial fibrillation. *Int J Clin Pract* 2012;**66**:53–63	Population
Cook NR, Cole SR, Buring JE. Aspirin in the primary prevention of cardiovascular disease in the Women's Health Study: effect of noncompliance. *Eur J Epidemiol* 2012;**27**:431–8	Subgroup analysis of WHS trial[46] randomisation of original trial not preserved
Cooper K, Squires H, Carroll C, Papaioannou D, Booth A, Logan RF, *et al.* Chemoprevention of colorectal cancer: systematic review and economic evaluation. *Health Technol Assess* 2010;**14**(32):1–206	Population

Selected for review	Reason for exclusion
Dalen JE. Aspirin for prevention of myocardial infarction and stroke. Is the right dose 81 or 160 mg/day? *J Am Coll Cardiol* 2009;**53**:2010	Editorial
Dalen JE. Aspirin for the primary prevention of stroke and myocardial infarction: ineffective or wrong dose? *Am J Med* 2010;**123**:101–2	Commentary
De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, *et al.* Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. *BMJ* 2009;**339**:b4531	Duplication of the study by De Berardis *et al.*[65]
De Schryver EL, Algra A, Kappelle LJ, van GJ, Koudstaal PJ. Vitamin K antagonists versus antiplatelet therapy after transient ischaemic attack or minor ischaemic stroke of presumed arterial origin. *Cochrane Database Syst Rev* 2012;**9**:CD001342	Secondary prevention
Diehl AK. Individual-patient meta-analysis: Daily aspirin reduces risk for incident cancer with distant metastasis. *Ann Int Med* 2012;**157**: JC2–2,2–3	Non-systematic review
Diehl AK. Review: Daily aspirin reduces short-term risk for cancer and cancer mortality. *Ann Int Med* 2012;**157**:JC2–2, 2–3	Non-systematic review
Fowkes G. AAA: Randomized controlled trial of low-dose aspirin in the prevention of cardiovascular events and death in subjects with asymptomatic atherosclerosis. *Eur J Heart Fail* 2009;**11**:1214–19	Conference abstract
Galloway CF, Stevenson JC. Aspirin in the primary prevention of cardiovascular disease. *Maturitas* 2011;**68**:3–4	Editorial
Garcia-Albeniz X, Chan AT. Aspirin for the prevention of colorectal cancer. *Best Pract Res Cl Ga* 2011;**25**:461–72	Non-systematic review
Goldstein LB, Bushnell CCD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, *et al.* Guidelines for the Primary Prevention of Stroke A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 2011;**42**:517–84	Non-systematic review
Haynes R, Bowman L, Armitage J. Aspirin for primary prevention of vascular disease in people with diabetes. *BMJ* 2009;**339**	Editorial
Hebert PR, Schneider WR, Hennekens CH. Use of aspirin among diabetics in the primary prevention of cardiovascular disease: need for reliable randomized evidence and astute clinical judgment. *J Gen Int Med* 2009;**24**:1248–50	Non-systematic review
Hennekens CH, Baigent C. Prevention. Aspirin in primary prevention: good news and bad news. *Nature Rev Cardiol* 2012;**9**:262–3	Commentary
Herrmann N, Chau SA, Kircanski I, Lanctot KL. Current and emerging drug treatment options for Alzheimer's disease: a systematic review. *Drugs* 2011;**71**:2031–65	Non-systematic review
Ikeda T, Taniguchi R, Watanabe S, Kawato M Kondo H, Shirakawa R, *et al.* Characterization of the antiplatelet effect of aspirin at enrolment and after 2 year follow up in a real clinical setting in Japan. *Circulation* 2010;**74**:1227–35	Non-RCT
Kappagoda T, Amsterdam E. Aspirin for primary prevention of myocardial infarction: what is the evidence? *J Cardiopulm Rehabil Prev* 2012;**32**:1–8	Non-systematic review
Karthikeyan G, Eikelboom JW, Turpie AG, Hirsh J. Does acetyl salicylic acid (ASA) have a role in the prevention of venous thromboembolism? *Br J Haematol* 2009;**146**:142–9	Non-systematic review
Kral M, Herzig R, Sanak D, Skoloudik D, Vlachova I, Bartkova A, *et al.* Oral Antiplatelet Therapy in Stroke Prevention. Mini review. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2010;**154**:203–10	Non-systematic review
Kurth T. Aspirin and cancer prevention. *BMJ* 2012;**344**:e2480	Editorial

Selected for review	Reason for exclusion
Kurth T, Diener HC, Buring JE. Migraine and cardiovascular disease in women and the role of aspirin: subgroup analyses in the Women's Health Study. *Cephalalgia* 2011;**31**:1106–15	Subgroup analysis of WHS trial[46] randomisation of original trial not preserved
Lanas A, Wu P, Medin J, Mills EJ. Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding in a meta-analysis. *Clin Gastroenterol Hepatol* 2011;**9**:762–8	Systematic review; secondary prevention trials > 50%
Law EH, Simpson SH. Aspirin use rates in diabetes: a systematic review and cross-sectional study. *Can J Diabetes* **34**:211–17	Outcomes
Leaberry BA. Aspirin for the prevention of cardiovascular disease: systematic review. *J Nurs Care Qual* 2010;**25**:17–21	Non-systematic review
Leshno M, Moshkowitz M, Arber N. Aspirin is clinically effective in chemoprevention of colorectal neoplasia: point. *Cancer Epidem Biomar* 2008;**17**:1558–61	Non-systematic review
Li L. Aspirin in the primary prevention of vascular disease: meta-analysis from randomised trials. *Cardiology* 2009;**114**:141–2	Conference abstract
Lischke S, Schneider DJ. Recent developments in the use of antiplatelet agents to prevent cardiovascular events. *Future Cardiol* 2011;**7**:403–13	Non-systematic review
Macchia A, Laffaye N, Comignani PD, Cornejo PE, Igarzabal C, Scazziota AS, *et al.* Statins but not aspirin reduce thrombotic risk assessed by thrombin generation in diabetic patients without cardiovascular events: the RATIONAL trial. *PLoS ONE* 2012;**7**:e32894	Outcomes
Martin-Carrillo P, Anino A, Pinar O, Fernandez I, Saenz A, Ausejo M. Aspirin for people with diabetes: a misleading inference in a recent meta-analysis? *Diabetes Res Clin Pract* 2010;**90**:e1	Letter
McGrath E, O'Conghaile A, Eikelboom JW, Dinneen SF, Oczkowski C, O'Donnell MJ. Validity of composite outcomes in meta-analyses of stroke prevention trials: the case of aspirin. *Cerebrovasc Dis* 2011;**32**:22–7	Population
McNeil J, Tonkin A. The MAGIC Study and the gastrointestinal effects of low-dose aspirin. *Cardiovasc Drugs Ther* 2011;**25**:503–4	Editorial
McTiernan A, Wang CY, Sorensen B, Xiao L, Buist DSM, Bowles EJA, *et al.* No Effect of aspirin on mammographic density in a randomized controlled clinical trial. *Cancer Epidemiol Biomar* 2009;**18**:1524–30	Outcomes
Meade T. Primary prevention of ischaemic cardiovascular disorders with antiplatelet agents. *Handb Exp Pharmacol* 2012;**210**:565–605	Non-systematic review
Meade T. The effect of aspirin on cancer mortality. Thrombosis Research Conference: 6th International Conference on Thrombosis and Hemostasis Issues in Cancer, Bergamo, Italy, 2012;**129**, various pagings	Conference
Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, *et al.* Representation of women in randomized clinical trials of cardiovascular disease prevention. *Circ Cardiovasc Qual Outcomes* 2010;**3**:134–42	Outcomes
Miser WF. Appropriate aspirin use for primary prevention of cardiovascular disease. *Am Fam Physician* 2011;**83**:1380–90	Editorial
Moayyedi P, Jankowski JA. Does long term aspirin prevent cancer? *BMJ* 2011;**342**:1	Editorial
Moon KT. Aspirin after peptic ulcer bleeding: is it worth the risk? *Am Fam Physician* 2010;**82**:1395–6	Abstract
Mora S. Aspirin therapy in primary prevention: to use or not to use? *Arch Int Med* 2012;**172**:217–18	Commentary
Morgan G. Cost-effectiveness comparison of breast cancer screening and vascular event primary prevention with aspirin in Wales. *Health Educ J* 2011;**70**:296–300	Outcomes

Selected for review	Reason for exclusion
Mourad JJ, Le Jeune S. Blood pressure control, risk factors and cardiovascular prognosis in patients with diabetes: 30 years of progress. *J Hypertens* 2008;**26**:S7–13	Non-systematic review
Mulders TA, Sivapalaratnam S, Stroes ES, Kastelein JJ, Guerci AD, Pinto-Sietsma SJ. Asymptomatic individuals with a positive family history for premature coronary artery disease and elevated coronary calcium scores benefit from statin treatment: a post hoc analysis from the St. Francis Heart Study. *JACC* 2012;**5**:252–60	Intervention not appropriate
Nonsteroidal anti-inflammatory drugs: add an anti-ulcer drug for patients at high risk only. Always limit the dose and duration of treatment with NSAIDs. *Prescrire Int* 2011;**20**:216–19	Non-systematic review
Ogawa H. Series, clinical study from Japan and its reflections: Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) Trial. *Nippon Naika Gakkai Zasshi* 2011;**100**:218–23	In Japanese
Ogawa H, Kojima S. Clinical evidence for Japanese population based on prospective studies: linking clinical trials and clinical practice. *J Cardiol* 2009;**54**:171–82	Non-systematic review
Okada K, Inamori M, Imajo K, Chiba H, Nonaka T, Shiba T, *et al.* Clinical study of upper gastrointestinal bleeding associated with low-dose aspirin in Japanese patients. *Hepato-Gastroenterology* 2009;**56**:1665–9	Non-RCT
Okada S, Morimoto T, Ogawa H, Kanauchi M, Nakayama M, Uemura S, *et al.*, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial Investigators. Differential effect of low-dose aspirin for primary prevention of atherosclerotic events in diabetes management: a subanalysis of the JPAD trial. *Diabetes Care* 2011;**34**:1277–83	Subgroup analysis of WHS trial[46] randomisation of original trial not preserved
Okada S, Morimoto T, Ogawa H, Sakuma M, Soejima H, Nakayama M. Is aspirin beneficial for primary prevention of cardiovascular events in high-risk diabetic patients? Insights from the JPAD Trial. Circulation Conference: American Heart Association's Scientific Sessions, Orlando, FL, USA, 2011;**124**:22, various pagings	Conference
Paikin JS, Eikelboom JW. Aspirin. *Circulation* 2012;**125**:E439–42	Non-systematic review
Paikin JS, Wright DS, Eikelboom JW. Effectiveness and safety of combined antiplatelet and anticoagulant therapy: a critical review of the evidence from randomized controlled trials. *Blood Rev* 2011;**25**:123–9	Non-systematic review
Patel A, Joshi R, de Galan B. Trials of cardiovascular risk factor management in type 2 diabetes. *Curr Opin Cardiol* 2009;**24**:288–94	Non-systematic review
Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet JP, *et al.* Antiplatelet agents for the treatment and prevention of atherothrombosis. *Eur Heart J* 2011;**32**:2922–33B	Non-systematic review
Peace, A, McCall M, Tedesco T, Kenny D, Conroy RM, Foley D, *et al.* The role of weight and enteric coating on aspirin response in cardiovascular patients. *J Thromb Haemost* 2010;**8**:2323–5	Non-RCT
Pignone M. Aspirin for cardiovascular prevention in patients with diabetes. *Clin Diabetes* 2009;**27**:70–1	Non-systematic review
Pignone M, Williams CD. Aspirin for primary prevention of cardiovascular disease in diabetes mellitus. *Nat Rev Endocrinol* 2010;**6**:619–28	Non-systematic review
Pignone M, Alberts MJ, Colwell JA, Cushman M, Inzucchi SE, Mukherjee D, *et al.* Aspirin for primary prevention of cardiovascular events in people with diabetes a position statement of the American Diabetes Association, a Scientific Statement of the American Heart Association, and an Expert Consensus Document of the American College of Cardiology Foundation. *Circulation* 2010;**121**:2694–701	Non-systematic review

Selected for review	Reason for exclusion
Pradhan AD, Cook NR, Manson JE, Ridker PM, Buring JE. A randomized trial of low-dose aspirin in the prevention of clinical type 2 diabetes in women. *Diabetes Care* 2009;**32**:3–8	Subgroup analysis of WHS trial[46] randomisation of original trial not preserved
Price HC, Holman RR. Primary prevention of cardiovascular events in diabetes: is there a role for aspirin? *Nat Clin Pract Cardiovasc Med* 2009;**6**:168–9	Comment
Qayyum R, Becker DM, Yanek LR, Moy TF, Becker LC, Faraday N, *et al.* Platelet inhibition by aspirin 81 and 325 mg/day in men versus women without clinically apparent cardiovascular disease. *Am J Cardiol* 2008;**101**:1359–63	Non-RCT
Raju NC, Sobieraj-Teague M, Eikelboom JW. A meta-analysis of randomised controlled trials of aspirin in primary prevention of cardiovascular disease. *Blood* 2009;**114**:77–8	Conference abstract
Rees M, Stevenson J, British Menopause Society. Primary prevention of coronary heart disease in women. *Menopause Int* 2008;**14**:40–5	Non-systematic review
Rembold CM. ACP Journal Club. Review: aspirin does not reduce CHD or cancer mortality but increases bleeding. *Ann Int Med* 2012;**156**:JC6–3	Commentary
Rose PW, Watson EK, Jenkins LSC. Aspirin for prevention of cancer and cardiovascular disease. *Br J Gen Pract* 2011;**61**:412–15	Non-systematic review
Rothwell PM. Aspirin in prevention of sporadic colorectal cancer: current clinical evidence and overall balance of risks and benefits. *Recent Results Canc Res* 2012;**191**:121–42	Non-systematic review
Saito Y, Morimoto T, Ogawa H, Nakayama M, Uemura S, Doi N, *et al.*, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial Investigators. Low-dose aspirin therapy in patients with type 2 diabetes and reduced glomerular filtration rate: subanalysis from the JPAD trial. *Diabetes Care* 2011;**34**:280–5	Subgroup analysis of JPAD[44] trial randomisation of original trial not preserved
Shakib S. Aspirin for primary prevention: do potential benefits outweigh the risks? *Int Med J* 2009;**39**:401–7	Non-systematic review
Sirois C, Poirier P, Moisan J, Gregoire JP. The benefit of aspirin therapy in type 2 diabetes: what is the evidence? *Int J Cardiol* 2008;**129**:172–9	Systematic review, but only one in four included studies is relevant
Soejima H, Ogawa H. Investigation of the effects of low dose aspirin therapy on primary and secondary prevention of cardiovascular disease. *Jpn J Clin Med* 2010;**68**:882–6	In Japanese
Soejima H, Morimoto T, Saito Y, Ogawa H. Aspirin for the primary prevention of cardiovascular events in patients with peripheral artery disease or diabetes mellitus Analyses from the JPAD, POPADAD and AAA trials. *Thromb Haemostasis* 2010;**104**:1085–8	Non-systematic review
Soejima H, Ogawa H, Morimoto T, Nakayama M, Okada S, Uemura S, *et al.* Aspirin reduces cerebrovascular events in type 2 diabetic patients with poorly controlled blood pressure: subanalysis from the JPAD trial. *Circulation J* 2012;**76**:1526–32	Subgroup analysis of JPAD[44] trial randomisation of original trial not preserved
Song Y, Klevak A, Manson JE, Buring JE, Liu S. Asthma, chronic obstructive pulmonary disease, and type 2 diabetes in the Women's Health Study. *Diabetes Res Clin Prac* 2010;**90**:365–71	Outcomes
Sugano K. A Phase 3 multinational, multicenter, randomised, double blind, parallel group, comparative efficacy and safety study of D961H (20 mg once daily) versus placebo for prevention of gastric and/or duodenal ulcers associated with continuous low dose aspirin (LDA) Use. JAPIC Clinical Trials Information/JapicCTI. 2010	Intervention

Selected for review	Reason for exclusion
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. *Am Heart J* 2010;**159**:361–9	Outcomes
The Norwegian Knowledge Centre for the Health Services. *Primary prevention of cardiovascular disease, with emphasis on pharmacological interventions.* Oslo: Norwegian Knowledge Centre for the Health Services (NOKC). Report number 20; 2008	Full text in Norwegian
Thun MJ, Jacobs EJ, Patrono C. The role of aspirin in cancer prevention. *Nature Rev Clin Oncol* 2012;**9**:259–67	Non-systematic review
Tsoi KK, Ng SC, Hirai HW, Chan FK, Sung JJ. Low-dose aspirin cannot prevent colorectal cancer: a meta-analysis of randomized controlled trials. *J Gastroenterol Hepatol* 2010;**25**:A16–7	Conference
Vial A, Mathelier-Fusade P, Gaouar H, Leynadier F, Chosidow O, Aractingi S, *et al.* Safety of reintroducing platelet inhibitory doses of aspirin in patients with urticaria or angioedema induced by anti-inflammatory doses. *Annales Dermatol Venereol* 2009;**136**:15–20	In French
Warkentin AE, Donadini MP, Spencer FA, Lim W, Crowther M. Bleeding risk in randomized controlled trials comparing warfarin and aspirin: a systematic review and meta-analysis. *J Thromb Haemostasis* 2012; **10**:512–20	Secondary prevention
Wilson R, Gazzala J, House J. Aspirin in primary and secondary prevention in elderly adults revisited. *Southern Med J* 2012;**105**:82–6	Non-systematic review
Woods RL, Tonkin AM, Nelson MR, Britt HC, Reid CM. Should aspirin be used for the primary prevention of cardiovascular disease in people with diabetes? *Med J Australia* 2009;**190**:614–15	Editorial
Xenos ES, O'Keeffe S, Minion D, Sorial E, Endean E. Aspirin versus aspirin and plavix in the prevention of stroke: a meta-analysis. arteriosclerosis thrombosis and vascular biology **30**:E257, 2010	Conference abstract
Xu JL, Yin ZQ, Gao W, Liu LX, Wang RS, Huang PW, *et al.* Meta-analysis on the association between nonsteroidal anti-inflammatory drug use and lung cancer risk. *Clin Lung Cancer* 2012;**13**:44–51	Limited RCT evidence in systematic review
Yang P, Zhou Y, Chen B, Wan HW, Jia GQ, Bai HL, *et al.* Aspirin use and the risk of gastric cancer: a meta-analysis. *Dig Dis Sci* 2010;**55**:1533–9	Limited RCT evidence in systematic review
Zhang SM, Cook NR, Manson JE, Lee IM, Buring JE. Low-dose aspirin and breast cancer risk: results by tumour characteristics from a randomised trial. *Br J Cancer* 2008;**98**:989–91	Non-RCT (retrospective analysis)
Zhao YS, Zhu S, Li XW, Wang F, Hu FL, Li DD, *et al.* Association between NSAIDs use and breast cancer risk: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2009;**117**:141–50	Limited RCT evidence in systematic review
Zheng JS, Wang QY, Wang QZ. Effects of intervention with simvastatin and aspirin on carotid artery atherosclerosis. *J Clin Neurol* 2009;**22**:219–21	In Chinese

Appendix 4 Classification of included aspirin publications according to condition and study design ($n = 27$)

CVD		Cancer		CVD in patients with diabetes	
Systematic reviews	RCTs	Systematic reviews	RCTs	Systematic reviews	RCTs
Adelman 2011[52]	[a]Dorresteijin 2011[59]	Algra 2012[61]	None	Butalia 2011[63]	[b]Belch 2008[40]
ATT 2009[53]	[b]Fowkes 2010[42]	Mills 2012[60]		Calvin 2009[64]	[b]Ogawa 2008[44]
Bartolucci 2011[37]	[c]Nelson 2008[58]	Rothwell 2011[22]		De Berardis 2009[65]	
Berger 2011[39]		Rothwell 2012[49]		Simpson 2011[66]	
Raju 2011[38]		Rothwell 2010[31]		Stavrakis 2011[67]	
Raju 2012[54]		Rothwell 2012[62]		Younis 2010[68]	
Selak 2010[55]					
Seshasai 2012[56]					
Wolff 2009[57]					
Zhang 2010[69]					

a Post hoc analysis to predict treatment effect for individual patients.
b Three of the core nine RCTs concerned with the risk of adverse events from aspirin, taken for prophylactic use for the primary prevention of CVD.
c Pilot RCT.

Appendix 5 Quality assessment of included studies ($n = 27$)

Quality assessment criteria for systematic reviews: cardiovascular disease

Based on NHS CRD.[50]

Author date reference: Adelman 2011[52]

Title: Gender differences in the primary prevention of stroke with aspirin.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Unclear[a]
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.
a No formal listing; criteria more or less implicit.

Quality assessment criteria for systematic reviews: cardiovascular

Based on NHS CRD.[50]

Author date reference: ATT (2009)[53]

Title: Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Unclear[a]
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Unclear[b]
The review primary outcome was presented	Unclear[b]
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	✓

CASP, Critical Appraisal Skills Programme.

a The review stated 'Electronic searches established that no similar trials of aspirin had been reported since 2002.'

b Many outcomes identified and analysed, a primary outcome not specified; review discussed the balance between benefits and harms, each represented by various outcomes.

Quality assessment criteria for systematic reviews: cardiovascular disease

Based on NHS CRD.[50]

Author date reference: Bartolucci et al. *(2011)*[37]

Title: Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	No
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	No
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Unclear[a]
The review primary outcome was presented	No[a]
Quantitative results for the primary outcome were presented in sufficient detail	No
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

a The review stated: 'aspirin may have a differential effect on different aspects of cardiovascular (CV) disease;' thus many outcomes were identified and analysed, a primary outcome not specified, the review discussed the balance between benefits and harms each represented by various outcomes.

Quality assessment criteria for systematic reviews: cardiovascular disease

Based on NHS CRD.[50]

Author date reference: Berger et al. *(2011)*[39]

Title: Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease – a meta-analysis of randomised trials.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

Quality assessment criteria for systematic reviews: cardiovascular disease

Based on NHS CRD.[50]

Author date reference: Raju et al. *(2011)*[38]

Title: Effect of aspirin on mortality in the primary prevention of cardiovascular disease.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	Yes
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

Quality assessment criteria for systematic reviews: cardiovascular disease

Based on NHS CRD.[50]

Author date reference: Raju et al. *(2012)*[54]

Title: The aspirin controversy in primary prevention

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	Yes
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	Yes[a]

CASP, Critical Appraisal Skills Programme.
a This paper was a review of other reviews and considered the IPD meta-analysis reported by the ATT[53] in 2009.

Quality assessment criteria for systematic reviews: cardiovascular disease

Based on NHS CRD.[50]

Author date reference: Selak et al. *(2010)*[55]

Title: Aspirin for primary prevention – yes or no?

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Unclear[a]
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	No
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	No[a]
Aspirin dose	✗
Aspirin frequency	✗
No. of participants	✗
Age	✗
Sex	✗
Length of follow-up	✗
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	Yes[a]

CASP, Critical Appraisal Skills Programme.

a The study was based on a previous systematic review, i.e. the IPD meta-analysis reported by the ATT[53] in 2009 (see above).

Quality assessment criteria for systematic reviews: cardiovascular disease

Based on NHS CRD.[50]

Author date reference: Seshasai et al. *(2012)*[56]

Title: Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	Yes
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

Quality assessment criteria for systematic reviews: cardiovascular disease

Based on NHS CRD.[50]

Author date reference: Wolff et al. *(2009)*[57]

Title: Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the US Preventive Services Task Force

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	Yes
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes[a]
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.
a Analytical framework and key questions were defined.

Quality assessment criteria for randomised controlled trials: cardiovascular disease

Based on the Cochrane Risk of Bias tool.[28]

Author date reference: Nelson et al. *(2008)*[58]

Title: Feasibility of conducting a primary prevention trial of low-dose aspirin for major adverse cardiovascular events in older people in Australia: results from the ASPirin in Reducing Events in the Elderly (ASPREE) pilot study.

Question	Rating[a]
1. Adequate sequence generation	Yes
2. Adequate allocation concealment	Unclear
3. Blinding (especially outcome assessment)	Yes ('*double blind*')
4. Incomplete outcome data addressed	Yes (*reported 12-month follow-up attendance*)
5. Free of selective reporting	Yes
6. Free of other potential bias[b]	Yes

a This was a pilot study and no primary outcome events occurred (some secondary outcome events were reported).
b For example, similarity at baseline, power assessment, conflict of interest.

Quality assessment criteria for randomised controlled trials: cardiovascular disease

Based on the Cochrane Risk of Bias tool.[28]

Author date reference: Dorresteijn et al. *(2011)*[59]

Title: Aspirin for primary prevention of vascular events in women: individualized prediction of treatment effects.

Question	Rating[a]
1. Adequate sequence generation	Yes
2. Adequate allocation concealment	Yes
3. Blinding (especially outcome assessment)	Yes
4. Incomplete outcome data addressed	Yes
5. Free of selective reporting	Yes
6. Free of other potential bias[b]	Yes

a This was a post hoc analysis of IPD in the WHS RCT,[46] predicting levels of benefit according to baseline characteristics with regard to MCEs. The above assessment is based on the original study.
b For example, similarity at baseline, power assessment, conflict of interest.

Quality assessment criteria for randomised controlled trials: cardiovascular disease

Based on the Cochrane Risk of Bias tool.[28]

Author date reference: Fowkes et al. *(2010)*[42]

Title: Aspirin for prevention of cardiovascular events in a general population screened for a low ankle–brachial index: a randomized controlled trial.

Question	Rating
1. Adequate sequence generation	Yes
2. Adequate allocation concealment	Yes
3. Blinding (especially outcome assessment)	Yes
4. Incomplete outcome data addressed	Yes
5. Free of selective reporting	Yes
6. Free of other potential bias[a]	Yes

a For example, similarity at baseline, power assessment, conflict of interest.

Quality assessment criteria for systematic reviews: cancer

Based on NHS CRD.[50]

Author date reference: Mills et al. *(2012)*[60]

Title: Low-dose aspirin and cancer mortality – a meta-analysis of randomised trials.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

Quality assessment criteria for systematic reviews: cancer

Based on NHS CRD.[50]

Author date reference: Algra et al. *(2012)*[61]

Title: Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	Unclear[a]
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes[b]
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	Yes

CASP, Critical Appraisal Skills Programme.

a No formal assessment was attempted; however, methods used for ascertainment of cancers in each study were described in detail.

b Primary outcome implicit and abstract.

Quality assessment criteria for systematic reviews: cancer

Based on NHS CRD.[50]

Author date reference: Rothwell et al. *(2010)*[31]

Title: Long-term effect of aspirin on colorectal cancer incidence and mortality – 20-year follow-up of five randomised trials.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	No[a]
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No[b]
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes[c]
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	Yes

CASP, Critical Appraisal Skills Programme.

a Trials of aspirin vs. control in the UK or Sweden in the 1980s and early 1990s were studied; however, how these found/identified was not described.

b No formal assessment tool was used.

c Primary outcome implicit.

Quality assessment criteria for systematic reviews: cancer

Based on NHS CRD.[50]

Author date reference: Rothwell et al. *(2011)*[22]

Title: Effect of daily aspirin on long-term risk of death due to cancer – analysis of individual patient data from randomised trials.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No[a]
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes[b]
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	Yes

CASP, Critical Appraisal Skills Programme.
a No formal assessment was undertaken and no assessment tool was used.
b Primary outcome implicit in title etc.

Quality assessment criteria for systematic reviews: cancer

Based on NHS CRD.[50]

Author date reference: Rothwell et al. *(2012)*[62]

Title: Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No[a]
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes[b]
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	Yes

CASP, Critical Appraisal Skills Programme.
a No formal assessment was undertaken and no assessment tool was used.
b Primary outcome implicit in title, etc.

Quality assessment criteria for systematic reviews: cancer

Based on NHS CRD.[50]

Author date reference: Rothwell et al. *(2012)*[49]

Title: Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No[a]
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes[b]
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	Yes

CASP, Critical Appraisal Skills Programme.
a No formal assessment was undertaken and no assessment tool was used.
b Primary outcome implicit in title etc.

Quality assessment criteria for randomised controlled trials: cancer

Based on the Cochrane Risk of Bias tool.[28]

Author date reference: Burn et al. *(2012)*[84]

Title: Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial

Question	Rating
1. Adequate sequence generation	Yes[a]
2. Adequate allocation concealment	Unclear but likely
3. Blinding (especially outcome assessment)	Yes (*'double blind'*)
4. Incomplete outcome data addressed	Yes
5. Free of selective reporting	Yes
6. Free of other potential bias[b]	Yes

a Some patients refused randomisation to aspirin and were secondarily assigned comparators; although small in number this could compromise randomisation to some extent.
b For example, similarity at baseline, power assessment, conflict of interest.

Quality assessment criteria for systematic reviews: cardiovascular disease in patients with diabetes

Based on NHS CRD.[50]

Author date reference: Butalia et al. *(2011)*[63]

Title: Aspirin effect on the incidence of major adverse cardiovascular events in patients with diabetes mellitus: a systematic review and meta-analysis

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*:	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	Yes
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	Yes
Quantitative results for the primary outcome were presented in sufficient detail	Yes
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

Quality assessment criteria for systematic reviews: cardiovascular disease in patients with diabetes

Based on NHS CRD.[50]

Author date reference: Calvin et al. *(2009)*[64]

Title: Aspirin for the primary prevention of cardiovascular events – a systematic review and meta-analysis comparing patients with and without diabetes.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	Yes
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

Quality assessment criteria for systematic reviews: cardiovascular disease in patients with diabetes

Based on NHS CRD.[50]

Author date reference: De Berardis et al. *(2009)*[65]

Title: Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	Yes
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

Quality assessment criteria for systematic reviews: cardiovascular disease in patients with diabetes

Based on NHS CRD.[50]

Author date reference: Simpson et al. *(2011)*[66]

Title: effect of aspirin dose on mortality and cardiovascular events in people with diabetes: a meta-analysis

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*:	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	Yes
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

Quality assessment criteria for systematic reviews: cardiovascular disease in patients with diabetes

Based on NHS CRD.[50]

Author date reference: Stavrakis et al. *(2011)*[67]

Title: Low-dose aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*:	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	Yes
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

Quality assessment criteria for systematic reviews: cardiovascular disease in patients with diabetes

Based on NHS CRD.[50]

Author date reference: Younis et al. *(2010)*[68]

Title: Role of aspirin in the primary prevention of cardiovascular disease in diabetes mellitus: a meta-analysis.

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*:	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	Yes
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Yes
The review primary outcome was presented	✓
Quantitative results for the primary outcome were presented in sufficient detail	✓
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

Author date reference: Zhang 2010[69]

Title: Aspirin for primary prevention of cardiovascular events in patients with diabetes: a meta-analysis

Question	Score: yes, no, unclear
1. Are any inclusion/exclusion criteria reported in the review? *A minimum of one or more inclusion criteria and one or more exclusion criteria were required to score 'Yes'*	Yes
2. Is there evidence of a substantial effort to search for all relevant research? *A minimum of one or more search terms and one or more bibliographic databases identified*	Yes
3. Is the quality of included studies adequately assessed? *Quality assessment tool was used (this could have been adapted from a standardised tool, e.g. CASP, CRD, Cochrane, etc.)*	No
4. Is sufficient detail of the individual studies presented? *All six listed baseline characteristics should be provided to score 'Yes'*:	Yes
Aspirin dose	✓
Aspirin frequency	✓
No. of participants	✓
Age	✓
Sex	✓
Length of follow-up	✓
5. Are the primary studies summarised appropriately? *The two listed items should be provided to score 'Yes'*:	Unclear[a]
The review primary outcome was presented	✗[a]
Quantitative results for the primary outcome were presented in sufficient detail	✗[a]
6. Were IPD analysed?	No

CASP, Critical Appraisal Skills Programme.

a Cardiovascular events appear to be the primary outcome but this was not explicit; the review discussed the balance between benefits and harms each represented by various outcomes.

Quality assessment criteria for randomised controlled trials: cardiovascular disease in patients with diabetes

Based on the Cochrane Risk of Bias tool.[28]

Author date reference: Belch 2008[40]

Title: The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease.

Question	Rating
1. Adequate sequence generation	Yes
2. Adequate allocation concealment	Yes
3. Blinding (especially outcome assessment)	Yes (*'double blind'*)
4. Incomplete outcome data addressed	Yes (*'all analyses were done on an intention-to-treat basis'*)
5. Free of selective reporting	Yes
6. Free of other potential bias[a]	Yes

a For example, similarity at baseline, power assessment, conflict of interest.

Quality assessment criteria for randomised controlled trials: cardiovascular disease in patients with diabetes

Based on the Cochrane Risk of Bias tool.[28]

Author date reference: Ogawa 2008[44]

Title: Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomised controlled trial.

Question	Rating
1. Adequate sequence generation	Yes
2. Adequate allocation concealment	Yes
3. Blinding (especially outcome assessment)	Open-label study for patients; assessors blinded
4. Incomplete outcome data addressed	Yes (*'intention-to-treat principle'*)
5. Free of selective reporting	Yes
6. Free of other potential bias[a]	Yes

a For example, similarity at baseline, power assessment, conflict of interest.

Appendix 6 Data extraction

A. Systematic reviews about the prophylactic use of aspirin in the primary prevention of cardiovascular disease

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[52]

First author surname: Adelman

Year of publication: 2011

Country: USA

Funding: None

Title: Gender differences in the primary prevention of stroke with aspirin

Aim of the study

To examine sex difference observed in the primary prevention of stroke with aspirin

Methods

Databases searched: MEDLINE search of primary prevention trials that studied aspirin with stroke as an outcome. Guidelines from US, British and European organisations. The citations from the articles to find additional references

Last date of search: Not reported

Inclusion criteria: Not reported

Participants: Not reported

Interventions: Aspirin

Comparators: Control/placebo

Outcome measures:
Primary outcome: Combination of MI, stroke or vascular death
Secondary outcome: Stroke
Primary safety outcome: Not reported

Types of studies included: Seven primary prevention trials

Methods of analysis: Not reported

Meta-analysis: Yes

Results

Adverse events: Not reported
MCEs: Not reported
Myocardial events: MI in men by 32% (95% CI 0.54 to 0.86; $p = 0.001$); no statistically significant effect in women (OR 1.01, 95% CI 0.84 to1.21; $p = 0.95$)

Stroke: Yes
Women

HOT (1996)	54/4437	67/4446	0.81 (0.56 to 1.16)
PPP (2001)	6/1277	11/1306	0.56 (0.21 to 1.51)
WHS (2005)	221/19,934	255/19,942	0.84 (0.70 to 1.01)
Total	281/25,648	344/25,694	0.83 (0.70 to 0.97)

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe			
Men			
BDT (1988)	61/3429	27/1710	1.13 (0.72 to 1.78)
HOT (1998)	94/4962	80/4945	1.17 (0.87 to 1.57)
PHS (1989)	119/11,037	95/11,034	1.22 (0.93 to 1.59)
PPP (2001)	10/949	13/963	0.78 (0.34 to 1.78)
TPT (1998)	47/2545	48/2540	0.98 (0.65 to 1.47)
Total	331/22,922	266/21192	1.13 (0.96 to 1.33)
Ischaemic stroke: Yes			
Women			
PPP (2001)	6/1277	9/1306	0.68 (0.24 to 1.92)
WHS (2005)	179/19,934	221/19,942	0.77 (0.63 to 0.94)
Total	179/21,211	230/21,248	0.76 (0.63 to 0.93)
Men			
BDT (1988)	61/3429	27/1710	1.50 (0.64 to 3.53)
PHS (1989)	119/11,037	95/11034	1.11 (0.82 to 1.50)
PPP (2001)	10/949	13/963	1.16 (0.42 to 3.22)
TPT (1998)	47/2545	48/2540	0.64 (0.37 to 1.11)
Total	331/17,960	266/16,247	1.00 (0.72 to 1.41)
Haemorrhagic stroke: Yes			
Women			
PPP (2001)	8/1277	2/1306	0.20 (0.01 to 4.23)
WHS (2005)	51/19,934	41/19,942	1.25 (0.83 to 1.88)
Total	51/21,211	43/21,248	0.07 (0.42 to 2.69)
Men			
BDT (1988)	13/3429	5/1710	1.08 (0.41 to 2.85)
PHS (1989)	23/11,037	12/11,034	1.92 (0.95 to 3.86)
PPP (2001)	2/949	1/963	2.03 (0.18 to 22.44)
TPT (1998)	12/2545	6/2540	2.00 (0.75 to 5.34)
Total	50/17,960	25/16,247	1.69 (1.04 to 2.73)
Mortality: Not reported			
All-cause death: Not reported			
CV death: Not reported			
Major bleeding: Not reported			

Author's conclusion

Aspirin prevents MI in men and stroke in women, although the findings in women were driven by the results of a single large study and a subsequent meta-analysis did not find a sex difference

Reviewer's conclusion

Lack of comprehensive searches, inclusion and exclusion criteria, data extraction and quality assessment of the studies. However, the paper summarised the results of seven primary prevention trials of aspirin in CVD

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Study details

Study ID (Ref man):[53]

First author surname: Baigent

Year of publication: 2012

Country: UK

Funding: UK Medical Research Council, British Heart Foundation, Cancer Research UK, and the European Community Biomed Programme

Title: Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials

Aim of the study

To undertake a collaborative meta-analysis of individual participant data, established involving the principal investigators of all large trials of primary prevention with aspirin. Meta-analyses of previously obtained individual participant data from 16 secondary prevention trials of aspirin were also undertaken to compare the proportional and absolute effects of aspirin in these two treatment settings

Study designs of included studies

(a) RCT (*n*) = nine randomised placebo-controlled trials
(b) Observational studies (*n*) = none
(c) Primary prevention (*n*) = nine trials
(d) Secondary prevention (*n*) = none

Inclusion criteria for systematic review:

- Primary or secondary prevention trials were eligible only if they involved a randomised comparison of aspirin vs. no aspirin (with no other antiplatelet drug in either group)
- Primary prevention trials excluded individuals with any history of occlusive disease at entry
- Primary prevention trials were sought only if they recruited at least 1000 non-diabetic participants with at least two years of scheduled treatment

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Characteristics of individual trials:
Baseline characteristics of the primary and secondary prevention trials

Trial	Dates of recruitment	Participating countries	Year of main publication	No. of participants	Mean duration of follow-up (years)	Target population	Eligible age range (years) at entry	Aspirin regimen	Randomised factorial comparison	Placebo control
BDT	November 1978 to November 1979	UK	1988	5139	5.6	Male doctors	19–90	500 mg daily	None	No
PHS	August 1981 to April 1984	USA	1988	22,071	5.0	Male doctors	45–73	325 mg alternate days	Beta-carotene vs. placebo	Yes
TPT	February 1989 to May 1994	UK	1998	5085	6.7	Men with risk factors for CHD	45–69	75 mg daily	Warfarin vs. placebo	Yes
HOT	October 1992 to May 1994	Europe, North and South America, Asia	1998	18,790	3.8	Men and women with DBP 100–115 mmHg	50–80	75 mg daily	Three blood pressure regimens	Yes
PPP	June 1993 to April 1998	Italy	2001	4495	3.7	Men and women with one or more risk factors for CHD	45–94	100 mg daily	Vitamin E vs. open control	No
WHS	September 1992 to May 1995	USA	2005	39,876	10.0	Female health professionals	≥ 45	100 mg alternate days	Vitamin E vs. placebo	Yes

DBP, diastolic blood pressure.

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Additional baseline characteristics

Trial	No. of participants	Male (%)	Age: years	Blood pressure (SBP/DBP) (mmHg)	Total cholesterol (mmol/l)	Current smokers (%)	Body mass index (kg/m²)	Diabetes mellitus (%)	Hypertension (%)	Any vascular disease (%)
Primary prevention trials										
BDT	5139	100	61 (7)	136 (17)/83 (10)	–	31	24.4 (2.5)	2	10	8
PHS	22,071	100	53 (10)	126 (12)/79 (8)	5.5 (1.2)	11	24.9 (3.0)	2	24	1
TPT	5085	100	57 (7)	139 (18)/83 (10)	6.4 (1.0)	41	27.4 (3.6)	2	16	< 1
HOT	18,790	53	61 (7)	170 (14)/105 (3)	6.0 (1.1)	16	28.4 (4.7)	8	100	3
PPP	4495	43	64 (8)	145 (16)/85 (8)	6.1 (1.2)	15	27.6 (4.7)	17	68	4
WHS	39,876	0	54 (7)	124 (13)/77 (8)[a]	5.2 (1.0)[a]	13	26.0 (5.1)	3	26	< 1
Subtotal: Six trials	95,456	46	56 (9)	136 (22)/84 (13)	5.6 (1.1)	16	26.3 (4.6)	4	41	2
Secondary prevention post-MI trials										
Cardiff-I	1239	100	55 (8)	–	–	–	–	–	–	100
Cardiff-II	1725	85	56 (10)	143 (29)/90 (18)	–	–	–	5	–	100
PARIS-I	1216	87	56 (8)	132 (18)/83 (9)	–	–	–	10	–	100
AMIS	4524	89	55 (8)	128 (16)/80 (9)	–	–	–	11	–	100
CDP-A	1529	100	56 (7)	132 (18)/81 (10)	–	–	–	14	–	100
Gamis	626	78	59 (7)	–	–	–	–	20	19	100
Subtotal: six trials	**10,859**	**90**	**56 (8)**	**132 (21)/82 (12)**	**–**	**–**	**–**	**11**	**19**	**100**

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Trial	No. of participants	Male (%)	Age: years	Blood pressure (SBP/DBP) (mmHg)	Total cholesterol (mmol/l)	Current smokers (%)	Body mass index (kg/m²)	Diabetes mellitus (%)	Hypertension (%)	Any vascular disease (%)
Secondary prevention post-TIA/stroke trials										
AITIA	319	70	58 (14)	–	–	–	–	–	–	100
UK-TIA	2435	73	60 (9)	151 (25)/88 (12)	–	–	–	4	27	100
Reuther	60	65	58 (10)	–	–	–	–	17	50	100
CA Co-op	283	67	61 (9)	146 (23)/85 (11)	–	–	–	8	37	100
Toulouse TIA	303	86	63 (9)	–	–	–	–	–	–	100
AICLA	402	68	64 (10)	150 (21)/90 (12)	–	–	–	23	64	100
Danish Co-op	203	73	59 (9)	138 (22)/84 (12)	–	–	–	6	–	100
Britton	505	62	68 (10)	–	–	–	–	17	46	100
Danish Low Dose	301	65	59 (8)	149 (23)/85 (12)	–	–	–	7	–	100
SALT	1359	66	67 (7)	–	–	–	–	13	47	100
Subtotal: 10 trials	**6170**	**70**	**62 (10)**	**149 (24)/87 (12)**	**–**	**–**	**–**	**9**	**38**	**100**

–, Not available; CA, critical appraisal; DBP, diastolic blood pressure; SBP, systolic blood pressure.

a In the WHS, individual blood pressure and cholesterol levels were imputed based on categories provided by the investigators [in 10-mmHg ranges for SBP, 5 mmHg ranges for DBP and 10 mg/dl (≈ 0.25 mmol/l) ranges for cholesterol]. Continuous data are presented as mean [standard deviation (SD)]. Percentages are based on the proportions among those participants with data available. Some patients in the primary prevention trials were found, after randomisation, to have had vascular disease (i.e. prior history of MI, cerebrovascular disease, angina pectoris, peripheral arterial disease or heart failure).

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Outcome measures: The main outcomes were 'serious vascular event, defined as MI, stroke, or death from a vascular cause (including sudden death, pulmonary embolism, haemorrhage, and, for secondary prevention trials only, death from an unknown cause); major coronary event (MI, coronary death or sudden death); any stroke [haemorrhagic or probably ischaemic (definitely ischaemic or of unknown type)]; death from any cause; and major extracranial bleed (mainly GI and usually defined as a bleed requiring transfusion or resulting in death). In the primary prevention trials, MIs and strokes were classified as fatal or non-fatal in accordance with each trial's definitions

Methods

Search strategy: Not specified
Study selection: Not specified – the authors undertook a collaborative meta-analysis of individual participant data was established involving the principal investigators of all large trials of primary prevention with aspirin
What quality assessment tool was used: No
Data extraction: Yes
Meta-analysis: Yes
Inclusion criteria described: Yes
No. of excluded studies described: No
Reasons for excluding studies described: Yes
Details of literature search given: No
Study selection described: Yes – but method of sifting is not described
Data extraction described: Yes
Study quality assessment described: No
Definitions of outcome measures provided: Not clear
Study flow shown: No
Study characteristics of individual studies given: Yes
Quality of individual studies given: No
Results of individual studies shown: Yes
Data analysis: (a) Random-/fixed-effect model = Yes; (b) Meta-regression = Yes; (c) Cumulative meta-analysis = No; (d) L'Abbé plot = No; (e) Funnel plot = No
Subgroup/sensitivity analysis: No
Statistical analysis appropriate: Yes – although authors do not state that the data satisfy the assumptions of the statistical tests

Results

Primary outcome: Did not specify – see outcomes listed above
Primary efficacy end point: Did not specify – see outcomes listed above
Secondary efficacy end point: Did not specify – see outcomes listed above
MCEs:

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

No. of events in the primary and secondary prevention trials

Trial	Serious vascular event	Major coronary events	Non-fatal MI	Any stroke	Stroke of unknown cause	Mortality							Major extracranial bleed	Fatal bleed
						CHD	Stroke	Other vascular	Any known vascular	Non-vascular	Unknown cause	All Causes		
Primary prevention trials														
BDT (2 : 1[a])	434	267	149	133	87	136	42	46	224	194	3	421	30	4
PHS	686	459	342	219	10	127	22	28	177	205	62	444	78	2
TPT	468	353	233	100	22	141	25	28	194	197	48	439	33	5
HOT	712	345	182	317	291	170[b]	51	63	284	305	0	589	176	10
PPP	112	46	36	39	6	10	7	35	52	76	12	140	9	4
WHS	999	493	365	487	4	134	58	55	247	850	154	1251	218	1
Subtotal: six trials	**3411**	**1963**	**1307**	**1295**	**420**	**718**	**205**	**255**	**1178**	**1827**	**279**	**3284**	**544**	**26**
Secondary prevention post-MI trials														
Cardiff-I	133	129	25	1	0	104	1	2	107	6	1	114	0	0
Cardiff-II	316	306	96	10	7	206	10	4	220	10	0	230	0	0
PARIS-I (2 : 1[a])	212	195	84	20	18	110	5	3	118	19	0	137	0	0
AMIS	795	707	317	101	97	388	10	10	408	52	5	465	0	0
CDP-A	178	146	59	25	24	85	5	14	104	6	0	110	0	0
Gamis	78	61	26	2	0	35	2	7	44	7	8	59	0	0
Subtotal: six trials	**1712**	**1544**	**607**	**159**	**146**	**928**	**33**	**40**	**1001**	**100**	**14**	**1115**	**0**	**0**

Trial	Serious vascular event	Major coronary events	Non-fatal MI	Any stroke	Stroke of unknown cause	Mortality							Major extracranial bleed	Fatal bleed
						CHD	Stroke	Other vascular	Any known vascular	Non-vascular	Unknown cause	All Causes		
Secondary prevention post-TIA/stroke trials														
AITIA	61	17	6	40	39	7	6	10	23	3	0	26	3	0
UK-TIA (2 : 1[a])	558	245	77	320	224	163	55	35	253	77	13	343	15	2
Reuther	7	1	0	6	4	1	2	0	3	0	0	3	1	0
CA Co-op	63	16	4	43	43	12	9	5	26	5	0	31	0	0
Toulouse TIA	27	7	2	16	16	5	5	4	14	11	0	25	0	0
AICLA	79	15	11	53	49	4	6	5	15	12	10	37	0	0
Danish Co-op	50	20	10	32	29	10	4	1	15	5	1	21	0	0
Britton	114	42	21	63	15	15	20	22	57	14	0	71	5	0
Danish Low Dose	42	16	2	21	20	14	1	3	18	4	2	24	0	0
SALT	307	119	53	180	11	54	32	34	120	35	5	160	4	0
Subtotal: 10 trials	**1308**	**498**	**186**	**774**	**450**	**285**	**140**	**119**	**544**	**166**	**31**	**741**	**28**	**2**

CA, critical appraisal.
a Allocation ratio 2 : 1; in tables or figures where adjusted numbers of controls are given, the number of events in the control group of this study is doubled.
b Includes 149 sudden deaths.

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Rate ratios associated with risk factors for selected outcomes among people with no known vascular disease in primary prevention trials

Variable	Serious vascular event, rate ratios (95% CI)	Non-fatal MI, rate ratios (95% CI)	CHD death, rate ratios (95% CI)	Major coronary event, rate ratios (95% CI)	Probably ischaemic stroke, rate ratios (95% CI)	Haemorrhagic stroke, rate ratios (95% CI)	Any stroke, rate ratios (95% CI)	Non-fatal MI or probably ischaemic stroke, rate ratios (95% CI)	Major GI or other extracranial bleed, rate ratios (95% CI)	Non-fatal major GI or other extracranial bleed, rate ratios (95% CI)
Age, per decade	2.08 (1.99 to 2.17)	1.63 (1.52 to 1.75)	2.37 (2.15 to 2.62)	1.84 (1.74 to 1.95)	2.46 (2.27 to 2.65)	1.59 (1.33 to 1.90)	2.29 (2.13 to 2.46)	1.91 (1.81 to 2.02)	2.15 (1.93 to 2.39)	2.10 (1.88 to 2.34)
Male sex[a]	1.86 (1.60 to 2.16)	2.58 (1.91 to 3.49)	2.21 (1.58 to 3.07)	2.43 (1.94 to 3.04)	1.44 (1.14 to 1.82)	1.11 (0.52 to 2.34)	1.39 (1.12 to 1.74)	1.85 (1.52 to 2.24)	1.99 (1.45 to 2.73)	1.98 (1.42 to 2.75)
Diabetes	2.43 (2.16 to 2.74)	2.80 (2.31 to 3.40)	2.42 (1.86 to 3.15)	2.66 (2.28 to 3.12)	2.06 (1.67 to 2.54)	1.74 (0.95 to 3.17)	2.02 (1.66 to 2.46)	2.39 (2.06 to 2.78)	1.55 (1.13 to 2.14)	1.55 (1.11 to 2.16)
Current smoker	2.03 (1.87 to 2.20)	1.96 (1.72 to 2.23)	2.17 (1.83 to 2.58)	2.05 (1.85 to 2.28)	2.00 (1.72 to 2.31)	2.18 (1.57 to 3.02)	2.02 (1.77 to 2.31)	1.97 (1.78 to 2.17)	1.56 (1.25 to 1.94)	1.50 (1.20 to 1.88)
Mean blood pressure (mmHg)	1.79 (1.67 to 1.92)	1.59 (1.42 to 1.77)	2.10 (1.83 to 2.42)	1.73 (1.59 to 1.89)	2.00 (1.77 to 2.26)	2.18 (1.65 to 2.87)	2.02 (1.81 to 2.26)	1.76 (1.62 to 1.92)	1.32 (1.09 to 1.58)	1.32 (1.09 to 1.60)
Cholesterol	1.10 (1.06 to 1.14)	1.23 (1.16 to 1.31)	1.09 (1.00 to 1.18)	1.18 (1.12 to 1.24)	1.02 (0.95 to 1.09)	0.90 (0.77 to 1.07)	1.00 (0.94 to 1.06)	1.13 (1.08 to 1.19)	0.99 (0.90 to 1.08)	0.98 (0.89 to 1.08)
BMI (per 5 kg/m^2)	1.07 (1.02 to 1.11)	1.10 (1.03 to 1.18)	1.07 (0.97 to 1.18)	1.09 (1.03 to 1.15)	1.06 (0.98 to 1.14)	0.85 (0.71 to 1.02)	1.02 (0.96 to 1.09)	1.08 (1.03 to 1.14)	1.24 (1.13 to 1.35)	1.22 (1.11 to 1.34)

a The relevance of male sex can be assessed only in the two trials that included both men and women, so the CIs for its relevance are wide, particularly for stroke.

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Total cholesterol was not available in the British Doctors Trial
Excluding the 2% of participants with known history of vascular disease.
Rate ratios for cholesterol are per 1 mmol/l and for mean blood pressure per 20 mmHg.
Study details of losses to follow-up:
Comparison of proportional and absolute effects of aspirin in primary and secondary prevention trials

Event	No. of events (aspirin vs. control)		Rate ratio (95% CI) (aspirin vs. control)			Yearly absolute difference (% per year)	
	Primary prevention (660,000 person-years)	Secondary prevention (43,000 person-years)	Primary prevention	Secondary prevention	*p*-value for heterogeneity	Primary prevention	Secondary prevention
Major coronary event	934 vs. 1115	995 vs 12140	0.82 (0.75 to 0.90)	0.80 (0.73 to 0.88)	0.7	–0.06	–1.00[a]
Non-fatal MI	596 vs. 756	357 vs. 505	0.77 (0.69 to 0.86)	0.69 (0.60 to 0.80)	0.5	–0.05	–0.66
CHD mortality	372 vs. 393	614 vs. 696	0.95 (0.82 to 1.10)	0.87 (0.78 to 0.98)	0.4	–0.01	–0.34
Stroke	655 vs. 682	480 vs 580	0.95 (0.85 to 1.06)	0.81 (0.71 to 0.92)	0.1	–0.01	–0.46[a]
Haemorrhagic	116 vs. 89	36 vs. 19	1.32 (1.00 to 1.75)	1.67 (0.97 to 2.90)	0.4	0.01	[b]
Ischaemic	317 vs. 367	140 vs. 176	0.86 (0.74 to 1.00)	0.78 (0.61 to 0.99)	0.5	–0.02	[b]
Unknown cause[c]	222 vs. 226	304 vs. 385	0.97 (0.80 to 1.18)	0.77 (0.66 to 0.91)	0.1	–0.001	[b]
Vascular death	619 vs. 637	825 vs. 896	0.97 (0.87 to 1.09)	0.91 (0.82 to 1.00)	0.4	–0.01	–0.29
Any serious vascular event	1671 vs. 1883 (0.51% vs. 0.57% per year)	1505 vs. 1801 (6.69% vs. 8.19% per year)	0.88 (0.82 to 0.94)	0.81 (0.75 to 0.87)	0.1	–0.07	–1.49[a]

a Major coronary event rates (per cent per year, aspirin vs. control).
b Stroke causes, and extracranial bleeds, very incompletely reported.
c Refers to stroke.

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Rate ratios (95% CI) associated with risk factors for selected outcomes in people with no known vascular disease in primary prevention trials

Risk	Major coronary event	Probably ischaemic stroke	Haemorrhagic stroke	Major extracranial bleed
Age (per decade)	1.84 (1.74 to 1.95)	2.46 (2.27 to 2.65)	1.59 (1.33 to 1.90)	2.15 (1.93 to 2.39)
Male sex[a]	2.43 (1.94 to 3.04)	1.44 (1.14 to 1.82)	1.11 (0.52 to 2.34)	1.99 (1.45 to 2.73)
Diabetes mellitus	2.66 (2.28 to 3.12)	2.06 (1.67 to 2.54)	1.74 (0.95 to 3.17)	1.55 (1.13 to 2.14)
Current smoker	2.05 (1.85 to 2.28)	2.00 (1.72 to 2.31)	2.18 (1.57 to 3.02)	1.56 (1.25 to 1.94)
Mean blood pressure (per 20 mmHg)[b]	1.73 (1.59 to 1.89)	2.00 (1.77 to 2.26)	2.18 (1.65 to 2.87)	1.32 (1.09 to 1.58)
Cholesterol (per 1 mmol/l)	1.18 (1.12 to 1.24)	1.02 (0.95 to 1.09)	0.90 (0.77 to 1.07)	0.99 (0.90 to 1.08)
Body mass index (per 5 kg/m^2)	1.09 (1.03 to 1.15)	1.06 (0.98 to 1.14)	0.85 (0.71 to 1.02)	1.24 (1.13 to 1.35)

a Analyses are stratified by trial. The relevance of male sex can therefore be assessed in only the two trials that included both men and women, so the 95% CIs for it are wide, particularly for stroke.
b Stroke causes, and extracranial bleeds, very incompletely reported.

Author's conclusion

'In primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds. Further trials are in progress'

Reviewer's conclusion

A comprehensive IPD analysis, but lacks sufficient methodological detail to enable replication

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[132]

First author surname: Bartolucci

Year of publication: 2011

Country: Germany

Funding: This study was supported by an unrestricted research grant from Bayer HealthCare AG (Leverkusen, Germany)

Title: Meta-analysis of multiple primary prevention trials of CV events using aspirin

Aim of the study

To examine the more recent trials those have been published since Bartolucci and Howard and add data from those studies to enlarge the sample and thus the power and precision

Methods

Databases searched: Not reported

Last date of search: Not reported

Inclusion criteria: Not reported

Participants: Not reported

Interventions: Aspirin

Comparators: Placebo or control

Outcome measures: Were not reported as primary or secondary outcomes
Outcomes were classified as follows: (1) total CHD as non-fatal and fatal MI and death due to CHD; (2) non-fatal MI as confirmed MI that did not result in death; (3) total CV events as a composite of CV death, MI or stroke; (4) stroke as ischaemic or haemorrhagic stroke that may or may not have resulted in death; (5) CV mortality as death related to CHD or stroke; and (6) all-cause mortality as death related to any cause
Primary outcome: Not defined
Secondary outcome: Not defined
Primary safety outcome: Not reported

Types of studies included:

Methods of analysis:
A summary OR with 95% CI was calculated
Calculation of the overall effect combining the nine studies used the Mantel–Haenszel chi-squared statistic with 1 df
Heterogeneity was calculated using the chi-squared test with $n - 1$ df, where n represents the number of studies contributing to the meta-analysis
Forest plots were used to assess if there was significant heterogeneity (defined as $p < 0.01$) and allowed assessment by considering the direction of the results
The random-effects model also helps further account for the heterogeneity across the studies, between-study variation and within-study variation or patient selection
The assessment of the small study effects (i.e. a trend for relatively smaller studies to show larger treatment effects) has been the use of funnel plots using Egger's test

Meta-analysis: Yes

df, degree of freedom.

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Results

Adverse events

MCEs

Total CHD

Trial	Lower limit	Upper limit
BMD	0.733	1.245
PHS	0.498	0.739
TPT	0.566	1.027
HOT	0.486	0.849
PPP	0.453	1.257
WHS	0.841	1.253
AAA	0.862	2.840
POPADAD	0.812	2.298
JPAD	0.005	1.659

Non-fatal CHD events

Trial	Lower limit	Upper limit
BMD	0.664	1.423
PHS	0.482	0.749
TPT	0.434	0.920
HOT	0.442	0.809
PPP	0.359	1.339
WHS	0.828	1.250
AAA	0.701	1.644
POPADAD	0.666	1.452
JPAD	0.568	3.221

Stroke

Trial	Lower limit	Upper limit
BMD	0.799	1.708
PHS	0.930	1.591
TPT	0.376	1.265
HOT	0.783	1.241
PPP	0.359	1.278
WHS	0.693	0.992
AAA	0.551	1.267
POPADAD	0.466	1.124
JPAD	0.508	1.407

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Mortality
All-cause death

Trial	Lower limit	Upper limit
BMD	0.717	1.087
PHS	0.791	1.152
TPT	0.785	1.360
HOT	0.788	1.094
PPP	0.574	1.129
WHS	0.846	1.060
AAA	0.715	1.915
POPADAD	0.786	1.973
JPAD	0.565	1.443

CV death

Trial	Lower limit	Upper limit
BMD	0.659	1.349
PHS	0.416	0.986
TPT	0.661	1.711
HOT	0.476	2.097
PPP	0.385	1.928
WHS	0.540	2.524
AAA	0.705	2.055
POPADAD	0.786	1.973
JPAD	0.013	0.777

CV death, MI and stroke

Trial	Lower limit	Upper limit
BMD	0.820	1.275
PHS	0.656	0.900
TPT	0.565	0.972
HOT	0.690	0.985
PPP	0.483	1.075
WHS	0.804	1.034
AAA	0.735	1.244
POPADAD	0.720	1.298
JPAD	0.562	1.332

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Major bleeding
GI bleeding for the nine-study meta-analysis

Trial	Aspirin (%)	Control (%)
WHS	4.50	3.80
BMD	0.30	0.40
PHS	4.00	3.80
HOT	0.80	0.40
PPP	0.80	0.20
TPT	1.40	0.90
AAA	0.50	0.50
JPAD	0.80	0.30
POPADAD	4.40	4.90

Author's conclusion

Aspirin decreased the risk for CV events and non-fatal MI in this large sample. Thus, primary prevention with aspirin decreased the risk for total CV events and non-fatal MI, but there were no significant differences in the incidences of stroke, CV mortality, all-cause mortality and total CHD

Reviewer's conclusion

This study is an update of a previous systematic review in which meta-analysis of nine primary prevention trials with aspirin, including the AAA, POPADAD, and JPAD trials, added to the six trials included in the previous meta-analyses (the ATT Collaboration) and Bartolucci and Howard. There was a lack of a clear methods section

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Study details

Study ID (Ref man):[39]

First author surname: Berger 2011

Year of publication: 2011

Country: USA

Funding: AstraZeneca

Title: Aspirin for the prevention of CV events in patients without clinical CV disease: a meta-analysis of randomized trials

Aim of the study

To assess the effect of aspirin on MCEs (non-fatal MI, non-fatal stroke or CV death), individual components of the MCE, stroke subtype, all-cause mortality and major bleeding

Methods

Databases searched: MEDLINE, CENTRAL and EMBASE

Last date of search: From 1966 to 2005

Inclusion criteria:

1. Aspirin alone was used for the primary prevention of CVD
2. Comparisons of outcomes were made between aspirin and placebo or open control groups
3. Data were available on MI, stroke and CV deaths. Studies published in English

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Participants: Patients without clinical CVD, which was defined as the absence of a CV event, or clinical symptoms of CVD including angina or TIA. Among the three new trials, two included only diabetic patients and two required a low ABI measurement as a marker of subclinical atherosclerosis for inclusion. Of the nine trials, three included only men and one included only women

Interventions: Aspirin (dosage ranged from 100 mg every other day to 500 mg daily)

Comparators: Placebo

Outcome measures:
Primary outcomes: Risk ratio of aspirin therapy compared with placebo or control on the composite MCE end point, which includes non-fatal MI, non-fatal stroke or CV death.
Secondary outcomes: Included all MI, all stroke, all-cause mortality and CV mortality
Primary safety outcome: Occurrence of major bleeding

Types of studies included: Prospective randomised trials

Methods of analysis: Sensitivity analysis of the primary analysis was performed, linear meta-regression analysis

Meta-analysis: Yes

Results

Adverse events
MCEs: defined as the composite of non-fatal MI, non-fatal stroke or CV death

	Aspirin		Placebo	
Trials	Events	Total	Events	Total
BDT	289	3429	147	1710
PHS	307	11,037	370	11,034
TPT	228	2545	260	2540
HOT	388	9399	425	9391
PPP	45	2226	64	2269
WHS	477	19,934	522	19,942
POPADAD	105	638	108	638
JPAD	56	1262	67	1277
AAA	134	1675	136	1675

Myocardial events
Fatal and non-fatal

	Aspirin		Placebo	
Trials	Events	Total	Events	Total
BDT	170	3429	88	1710
PHS	139	11,037	239	11,034
TPT	154	2545	190	2540
HOT	157	9399	184	9391
PPP	19	2226	28	2269
WHS	198	19,934	193	19,942
POPADAD	12	638	14	638
JPAD	76	1262	69	1277
AAA	68	1675	1675	1675

ABI, ankle–brachial index.

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Stroke
Fatal and non-fatal

	Aspirin		Placebo	
Trials	Events	Total	Events	Total
BDT	91	3429	39	1710
PHS	119	11,037	98	11,034
TPT	47	2545	48	2540
HOT	146	9399	148	9391
PPP	16	2226	24	2269
WHS	221	19,934	266	19,942
POPADAD	29	638	41	638
JPAD	28	1262	32	1277
AAA	44	1675	50	1675

Stroke (subtypes): data available from eight studies
Ischaemic stroke

Trials	Events	Total	Events	Total
BDT	21	3429	7	1710
PHS	91	11,037	82	11,034
TPT	21	2545	33	2540
HOT	0	0	0	0
PPP	14	2226	21	2269
WHS	170	19,934	221	19,942
POPADAD	5	638	3	638
JPAD	22	1262	24	1277
AAA	30	1675	37	1675

Haemorrhagic stroke

Trials	Events	Total	Events	Total
BDT	13	3429	6	1710
PHS	23	11,037	12	11,034
TPT	12	2545	6	2540
HOT	0	0	0	0
PPP	2	2226	3	2269
WHS	51	19,934	41	19,942
POPADAD	2	638	3	638
JPAD	5	1262	3	1277
AAA	5	1675	4	1675

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Mortality

All-cause death

	Aspirin		Placebo	
Trials	Events	Total	Events	Total
BDT	270	3429	151	1710
PHS	217	11,037	227	11,034
TPT	216	2545	205	2540
HOT	284	9399	305	9391
PPP	62	2226	78	2269
WHS	609	19,934	642	19,942
POPADAD	94	638	101	638
JPAD	34	1262	38	1277
AAA	176	1675	186	1675

CV death

	Aspirin		Placebo	
Trials	Events	Total	Events	Total
BDT	148	3429	79	1710
PHS	81	11,037	83	11,034
TPT	101	2545	81	2540
HOT	133	9399	140	9391
PPP	17	2226	31	2269
WHS	120	19,934	126	19,942
POPADAD	43	638	35	638
JPAD	1	1262	10	1277
AAA	35	1675	30	1675

Major bleeding

	Aspirin		Placebo	
Trials	Events	Total	Events	Total
BDT	29	3429	7	1710
PHS	48	11,037	28	11,034
TPT	20	2545	13	2540
HOT	136	9399	78	9391
PPP	24	2226	6	2269
WHS	127	19,934	91	19,942
POPADAD	28	638	31	638
JPAD	12	1262	4	1277
AAA	34	1675	20	1675

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Author's conclusion

Aspirin decreased MCE by approximately 10% among patients without clinical CVD. Major bleeding occurred more frequently with aspirin therapy. The decision to use aspirin for the prevention of a first MI or stroke remains a complex issue. Weighing the overall benefit and risk requires careful consideration by the physician and patient before initiating aspirin for preventative therapy in patients without clinical CVD

Reviewer's conclusion

Aspirin showed a beneficial effect over placebo, with additional major bleeding

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[38]

First author surname: Raju

Year of publication: 2011

Country: Australia

Funding: None

Title: Effect of aspirin on mortality in the primary prevention of cardiovascular disease

Aim of the study

An updated meta-analysis of RCTs of aspirin to obtain best estimates of the effect of aspirin on mortality in primary prevention

Methods

Databases searched:

- MEDLINE (1966 to May 2010), EMBASE (1980 to May 2010), CINAHL (1982 to May 2010) and The Cochrane Library (to May 2010) using the terms aspirin, acetylsalicylic acid, CVD, MI, stroke, cerebrovascular disease, mortality, death, survival, randomised trial, controlled trial, random, prevent and primary prevention.
- Bibliographies of journal articles were hand-searched, and a 'related article' PubMed search was performed to identify additional relevant articles
- The National Institutes of Health Clinical Trials Registry (http://clinicaltrials.gov) and contacted experts to identify unpublished studies

Last date of search: May 2010

Inclusion criteria:

(a) RCT
(b) Include adults without a history of symptomatic CVD (> 95% of enrolled participants)
(c) Compare aspirin (any dose) with placebo or no aspirin treatment for the prevention of CVD
(d) Report at least one of the following outcomes: all-cause mortality, CV mortality, MI, stroke and bleeding
(e) RCTs in which aspirin was combined with a second antithrombotic agent were not included, unless there were separate placebo and aspirin-only treatment groups, in which case only the data from these groups were included

Participants: 100,076 participants were included (see table below)

Interventions: Aspirin

Comparators: Placebo or no aspirin

Outcome measures:

All-cause mortality, CV mortality, MCEs, MI, all-cause stroke, ischaemic stroke, haemorrhagic stroke, GI bleed, major bleed
Primary outcome: Not clear – see above
Secondary outcome: Not clear – see above
Primary safety outcome: Not clear – see above

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Types of studies included: RCTs comparing aspirin with placebo or no aspirin treatment in individuals without a history of symptomatic CVD

Methods of analysis:

- Interobserver agreement for full text study selection was measured using Cohen's unweighted kappa statistic
- Results are presented using RR, and all effect estimates are presented with 95% CIs
- RRs for the prespecified primary and secondary outcomes were calculated by pooling individual trial data with the DerSimonian and Laird random-effects model
- Results from the random-effects model were compared with those obtained using a fixed-effects model

Meta-analysis: Yes

Results

Adverse events

MCEs

	Aspirin		Placebo/no treatment	
Trials	Events	Total	Events	Total
BDT	289	3429	147	1710
PHS	320	11,037	388	11,034
HOT	315	9399	368	9391
TPT	112	1268	147	1272
PPP	47	2226	71	2269
WHS	477	19,934	522	19,942
POPADAD	127	638	132	638
JPAD	40	1262	46	1277
AAA	134	1675	136	1675

MI

	Aspirin		Placebo/no treatment	
Trials	Events	Total	Events	Total
BDT	169	3429	88	1710
PHS	139	11,037	239	11,034
HOT	82	9399	127	9391
TPT	69	1268	98	1272
PPP	19	2226	28	2269
WHS	198	19,934	193	19,942
JPAD	12	1262	14	1277
POPADAD	76	638	69	638
AAA	90	1675	86	1675

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Stroke

	Aspirin		Placebo/no treatment	
Trials	Events	Total	Events	Total
BDT	91	3429	39	1710
PHS	119	11,037	98	11,034
HOT	146	9399	148	9391
TPT	18	1268	26	1272
PPP	16	2226	24	2269
WHS	221	19,934	266	19,942
JPAD	28	1262	32	1277
POPADAD	37	638	50	638
AAA	44	1675	50	1675

Ischaemic stroke

	Aspirin		Placebo/no treatment	
Trials	Events	Total	Events	Total
BDT	61	3429	29	1710
PHS	91	11,037	82	11,034
TPT	10	1268	18	1272
PPP	16	2226	22	2269
WHS	170	19,934	221	19,942
POPADAD	3	638	5	638
JPAD	22	1262	25	1277
AAA	30	1675	37	1675

Haemorrhagic stroke

	Aspirin		Placebo/no treatment	
Trials	Events	Total	Events	Total
BDT	13	3429	6	1710
PHS	23	11,037	12	11,034
TPT	2	1268	0	1272
PPP	10	2226	3	2269
WHS	51	19,934	41	19,942
JPAD	6	1262	7	1277
POPADAD	2	638	3	638
AAA	5	1675	4	1675

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

The HOT study did not report haemorrhagic stroke. The JPAD and POPADAD studies did not report major bleeding and BDT did not report GI bleeding

Mortality

All-cause mortality

	Aspirin		Placebo/no treatment	
Trials	Events	Total	Events	Total
BDT	270	3429	151	1710
PHS	217	11,037	227	11,034
HOT	284	9399	305	9391
TPT	113	1268	110	1272
PPP	62	2226	78	2269
WHS	609	19,934	642	19,942
POPADAD	94	638	101	638
JPAD	34	1262	38	1277
AAA	176	1675	186	1675

CV mortality

	Aspirin		Placebo/no treatment	
Trials	Events	Total	Events	Total
BDT	148	3429	79	1710
PHS	81	11,037	83	11,034
HOT	133	9399	140	9391
TPT	49	1268	49	1272
PPP	17	2226	31	2269
WHS	120	19,934	126	19,942
JPAD	1	1262	10	1277
POPADAD	43	638	35	638
AAA	35	1675	30	1675

All-cause death: *Not reported*
CV death: *MI*

Bleeding

GI bleeding

	Aspirin		Placebo/no treatment	
Trials	Events	Total	Events	Total
PHS	842	11,037	696	11,034
TPT	22	1268	10	1272
HOT	107	9399	55	9391
PPP	17	2226	5	2269
WHS	910	19,934	751	19,942
POPADAD	28	638	31	638
JPAD	12	1262	4	1277
AAA	9	1675	8	1675

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Major bleeding

	Aspirin		Placebo/no treatment	
Trials	Events	Total	Events	Total
BDT	29	3429	7	1710
PHS	48	11,037	28	10,979
HOT	136	9399	78	9391
TPT	8	1268	4	1278
PPP	24	2226	6	2269
WHS	127	19,934	91	19,942
AAA	34	1675	20	1675

Author's conclusion

Aspirin prevents deaths, MI, and ischaemic stroke, and increases haemorrhagic stroke and major bleeding when used in the primary prevention of CVD

Reviewer's conclusion

The authors provide a comprehensive coverage of the available evidence. Greater clarity of the primary and secondary outcomes along with appropriate definitions should have been provided

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[54]

First author surname: Raju

Year of publication: 2012

Country: Australia

Funding: Not reported

Title: The aspirin controversy in primary prevention

Aim of the study

To critically examine the results of the recent meta-analyses comparing aspirin with placebo or no aspirin for the primary prevention of CVD and evaluate whether aspirin provides a net benefit when used for this indication

Methods

Databases searched: MEDLINE database for the past 5 years (January 2007 to March 2012)

Last date of search: March 2012

Inclusion criteria: Not reported

Participants: Not reported

Interventions: Aspirin

Comparators: Placebo

Outcome measures:
All-cause and CV mortality
MI
Stroke
MCEs
Bleeding
Primary outcome: Not defined
Secondary outcome: Not defined
Primary safety outcome: Not defined

Types of studies included: RCTs and meta-analyses of RCTs of aspirin in the primary prevention of CVD

Methods of analysis:

Meta-analysis: Not reported

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Results

Results of the recent meta-analyses of aspirin for the primary prevention of CVD: mortality and thrombotic outcomes
Mortality and thrombotic outcomes: aspirin vs. placebo

Author (year of publication)	No. of participants[a] (no. of studies)	Overall mortality	CV mortality	Major CV events[b]	All CHD	Non-fatal MI	Stroke	Ischaemic stroke	NNT major CV events
ATTC (2009)	95,000 (6)	0.95 (0.88 to 1.02)	0.97 (0.87 to 1.09)	0.88 (0.82 to 0.94)	0.82 (0.75 to 0.90)	0.77 (0.67 to 0.89)	0.95 (0.85 to 1.06)	0.86 (0.74 to 1.00)	–
Raju (2011)	100,076 (9)	0.94 (0.88 to 1.00)	0.96 (0.84 to 1.09)	0.88 (0.83 to 0.94)	0.83 (0.69 to 1.00)	Not available[c]	0.93 (0.82 to 1.05)	0.86 (0.75 to 0.98)	314
Bartolucci (2011)	100,038 (9)	0.95 (0.88 to 1.01)	0.96 (0.80 to 1.14)	0.87 (0.80 to 0.93)	0.85 (0.69 to 1.06)	0.81 (0.67 to 0.99)	0.92 (0.83 to 1.02)	Not available	–
Seshasai (2012)	102,621 (9)	0.94 (0.88 to 1.00)	0.99 (0.85 to 1.15)	0.90 (0.85 to 0.96)	0.86 (0.74 to 1.01)	0.80 (0.67 to 0.96)	0.94 (0.84 to 1.06)	Not available	384
Berger (2011)[d]	710,053 (9)	0.94 (0.89 to 1.00) All-cause death	0.99 (0.85 to 1.14) CV death	0.90 (0.85 to 0.96)	Not available	0.86 (0.74 to 1.00) (fatal and non-fatal)	0.94 (0.84 to 1.06)	0.87 (0.73 to 1.02)	–

a Refers to total number of participants; some of the analyses were limited to fewer participants according to data availability (data separating ischaemic and haemorrhagic stroke were not available from HOT).
b MCEs includes a composite of cardiovascular death, MI and stroke.
c Reported separately in publication.
d RR with 95% CI.

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Bleeding outcomes

Author (year of publication)	No. of participants[a] (no. of studies)	Haemorrhagic stroke	Major bleeding	NNH major bleeding
ATTC (2009)	95,000 (6)	1.32 (0.91 to 1.91)	1.54 (1.30 to 1.82)	–
Raju (2011)	100,076 (9)	1.36 (1.01 to 1.82)	1.66 (1.41 to 1.95)	300 (109 GI)[b]
Bartolucci (2011)	100,038 (9)	Not available	Not available	–
Seshasai (2012)	102,621 (9)	Not available	1.31 (1.14 to 1.50)	109
Berger (2011)[c]	710,053 (9)	1.35 (1.01 to 1.81)	1.62 (1.31 to 2.00)	–

a Some of the analyses were limited to fewer participants according to data availability, for example BDT did not report GI bleeding, and HOT did not provide separate data on ischaemic and haemorrhagic stroke.
b Raju *et al.* reported major and GI bleeding separately; Seshasai *et al.* reported all nontrivial bleeding combined.
c RR with 95% CI.

Author's conclusion

The absolute benefit of aspirin is expected to be higher for those at higher levels of CV risk

Reviewer's conclusion

This study reported the finding of four recent meta-analyses, thus suggesting that aspirin for primary prevention should be individualised, taking into account the balance between benefits and risk and patient's choice

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[55]

First author surname: Selak

Year of publication: 2010

Country: New Zealand

Funding: Vanessa Selak is the recipient of a National Heart Foundation Research Fellowship

Title: Aspirin for primary prevention: yes or no?

Aim of the study

To model benefit vs. harm of aspirin for CVD primary prevention for age group, sex and risk categories using data from the ATT Collaboration meta-analysis and to interpret these results in light of current NZ CVD risk assessment and management guidelines

Methods

Databases searched: Refer to ATT study

Last date of search: Refer to ATT study

Inclusion criteria: Refer to ATT study

Participants: 95,456 individuals without prior CVD who had been randomised to aspirin or no aspirin in six RCTs of at least 1000 non-diabetic participants each with at least 2 years of scheduled treatment

Interventions: Aspirin

Comparators: Placebo

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Outcome measures: CV events and serious side effects (extracranial bleeding). Vascular events in the meta-analysis were defined as MI, stroke (haemorrhagic or other), or death from a vascular cause (CHD death, stroke death, or other vascular death, including sudden death, death from pulmonary embolism and death from any haemorrhage)
Primary outcome: Not clear
Secondary outcome: Not clear
Primary safety outcome: Not clear

Types of studies included: The ATT IPD meta-analysis that included six primary prevention RCTs

Methods of analysis: Using the proportional reduction in serious vascular events observed in the ATT the MA population was subdivided into categories according to 5-year risk of a CVD event (1% to 20% risk in 1% steps) according to 10-year age bands (50–89 years) and sex (men and women); the CV event rate and serious adverse event rate within each category was estimated (from ATT data); using these results an assessment was made of which categories of individuals might gain more benefit than harm from the use of aspirin

Meta-analysis: Not reported

Results

Adverse events: Not reported
MCEs: Not reported
Myocardial events: Not reported
Stroke: Not reported
Ischaemic stroke: Not reported
Haemorrhagic stroke: Not reported
Mortality: Not reported
All-cause death: Not reported
CV death: Not reported
Major bleeding: Not reported

		Estimated vascular events avoided[b] in 5 years, [c]*n*							
		Men				Women			
Five-year risk of CVD event (%)	CVD events expected, [a]*n*	Age (50–59 years)	Age (60–69 years)	Age (70–79 years)	Age (80–89 years)	Age (50–59 years)	Age (60–69 years)	Age (70–79 years)	Age (80–89 years)
1	10	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
2	20	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
3	30	3.6	3.6	3.6	3.6	3.6	3.6	3.6	3.6
4	40	4.8	4.8	4.8	4.8	4.8	4.8	4.8	4.8
5	50	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
6	60	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2
7	70	8.4	8.4	8.4	8.4	8.4	8.4	8.4	8.4
8	80	9.6	9.6	9.6	9.6	9.6	9.6	9.6	9.6
9	90	10.8	10.8	10.8	10.8	10.8	10.8	10.8	10.8
10	100	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
11	110	13.2	13.2	13.2	13.2	13.2	13.2	13.2	13.2
12	120	14.4	14.4	14.4	14.4	14.4	14.4	14.4	14.4
13	130	15.6	15.6	15.6	15.6	15.6	15.6	15.6	15.6
14	140	16.8	16.8	16.8	16.8	16.8	16.8	16.8	16.8
15	150	18.0	18.0	18.0	18.0	18.0	18.0	18.0	18.0
16	160	19.2	19.2	19.2	19.2	19.2	19.2	19.2	19.2
17	170	20.4	20.4	20.4	20.4	20.4	20.4	20.4	20.4
18	180	21.6	21.6	21.6	21.6	21.6	21.6	21.6	21.6

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Five-year risk of CVD event (%)	CVD events expected, [a]*n*	Estimated vascular events avoided[b] in 5 years, [c]*n*							
		Men				Women			
		Age (50–59 years)	Age (60–69 years)	Age (70–79 years)	Age (80–89 years)	Age (50–59 years)	Age (60–69 years)	Age (70–79 years)	Age (80–89 years)
19	190	22.8	22.8	22.8	22.8	22.8	22.8	22.8	22.8
20	200	24.0	24.0	24.0	24.0	24.0	24.0	24.0	24.0
		Estimated additional non-fatal extracranial bleeds[d] in 5 years (*n*)							
		2.0	4.3	9.2	19.9	1.0	2.2	4.6	9.9

a Based on Framingham equation, i.e. including MI-, angina-, stroke-, transient ischaemia-, congestive heart failure-, PVD- and CVD-related deaths.

b Vascular events avoided defined as MI, stroke (ischaemic, haemorrhagic or other) or vascular death [CHD death, stroke death, or other vascular death (which includes sudden death, death from pulmonary embolism, and death from any haemorrhage)].

c Assuming 12% proportional net reduction in vascular events.

d Calculated from number of excess non-fatal GI or other extracranial bleeds (usually defined as a bleed requiring a transfusion) among those aged 50–59 years and allocated to aspirin. Extrapolated to older age groups using rate ratio associated with age (2.15 per decade). Haemorrhagic stroke and fatal extracranial haemorrhage counted in vascular events (see above).

The shaded areas indicate combinations of 5-year CVD risk, sex and age for which the estimated number of additional extracranial bleeds are greater than or equal to the estimated number of vascular events avoided.

Author's conclusion

The findings of this analysis reinforce the importance of basing preventative management decisions on CVD risk. Aspirin should still be considered for primary prevention of CVD in those with 5-year CVD risk > 15%, up to the age of 80 years, although in men aged 70–79 years consider lipid and blood pressure-lowering therapies first and then reassess whether aspirin adds additional net benefit

Reviewer's conclusion

This study is the evidence-based modelling of benefit and harm of aspirin for primary prevention of CVD. ATT results were used for the analysis

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Study ID (Ref man):[56]

First author surname: Seshasai

Year of publication: 2012

Country: England

Funding: Not reported

Title: Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials

Aim of the study

To provide an updated synthesis of evidence regarding the wider role of aspirin in primary prevention, including its effect on outcomes such as non-vascular disorders (e.g. cancer), and to investigate the risks and benefits of aspirin treatment in relation to demographic or participant characteristics

Study designs of included studies

(a) RCT (*n*) = 9 randomised placebo-controlled trials; (b) observational studies (*n*) = none; (c) primary prevention (*n*) = 9 trials; (d) secondary prevention (*n*) = none
Inclusion criteria for systematic review: Randomised placebo-controlled trials (primary prevention studies) with at least 1000 participants (without previous CHD or stroke), and had at least 1 year of follow-up during which CHD and/or CVD outcomes (CHD, stroke, cerebrovascular disease, heart failure, and PAD) were recorded as the main end points, and details were provided of bleeding events

Characteristics of individual trials

Source	Location	Year	No. of participants	Age (years): mean (SD)	Male: %	Diabetes: %	Smokers: %	Mean (SD): mmHg
BDT or BDS	England	1988	5139	63.6	100	2	31	135.8
PHS	USA	1989	22,071	53.8	100	2	11	128.5
HOT	Multiple	1998	18,790	61.5	53	8	6	170.0
TPT	UK	1998	5085	57.5	100	NS	41	139.0
PPP	Italy	2001	4495	64.4	42	17	15	145.1
WHS	USA	2005	39,876	54.6	0	3	13	127.3
POPADAD	Scotland	2008	1276	60.3	44	100	31	145.0
JPAD	Japan	2008	2539	64.5	55	100	21	135.0
AAA	Scotland	2010	3350	61.6	28	3	32	147.5
Total or mean (SD)	NA	NA	**102,621**	**57.3[a] (4.1)**	**46**	**8**	**16**	**138.0[a] (17)**

NA, not applicable; NS, not specified; PAD, peripheral arterial disease; SD, standard deviation.
a Represents weighted mean (SD).

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Source	Total cholesterol (mmol/l), mean (SD)	Aspirin dose (mg) and schedule	Aspirin formulation	Concomitant treatment[a]	All participants, duration of follow-up[b]	Aspirin arm, duration of follow-up: person-years[c]	Placebo arm, duration of follow-up: person-years[c]
BDT or BDS	NS	500 or 300 daily	Ordinary, soluble or effervescent (500 mg) or enteric coated (300 mg)	No	6.0	18,820	9470
PHS	5.46	325 alternate day	Regular (most)	No	5.02	54,560	54,356
HOT	6.1	75 daily	NS	Yes	3.8	35,716	35,686
TPT	6.4	75 daily	Controlled release	Yes	6.4	8105	8071
PPP	6.1	100 daily	Enteric coated	Yes	3.6	8014	8168
WHS	5.2	100 alternate day	NS	Yes	10.1	201,333	201,414
POPADAD	5.52	100 daily	NS	Yes	6.7	4,275	4275
JPAD	5.21	81 or 100 daily	NS	No	4.37	5515	5580
AAA	6.2[a]	100 daily		No	8.2	13,735	13,735
Total or mean (SD)	**5.5 (0.5)**	**NA**	**NA**	**NA**	**6.0 (2.1)**	**350,073**	**340,755**

NA, not applicable; NS, not specified; SD, standard deviation.

a Concomitant treatments include agents other than anti-platelet drugs (e.g. blood pressure-lowering medication), as in factorial trials.

b Follow-up duration shown for POPADAD and JPAD represents median follow-up, not mean. Also, total cholesterol values for POPADAD are median, not mean. Data on cholesterol measurements at baseline were missing in approximately 0.6% of all participants in the AAA study.

c Follow-up duration shown in person-years according to treatment arm was obtained directly from study reports for BDS and TPT, and was calculated based on numbers per group multiplied by mean (or median) follow-up time for other studies. In PHS, the reported duration of follow-up differed for various outcomes, and the numbers shown correspond to those for MI (including non-fatal and fatal MI).

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Outcome measures

Events	Trials								
	BDT 1988	PHS 1989	HOT 1998	TPT 1998	PPP 2001	WHS 2005	POPADAD 2008	JPAD 2008	AAA 2010
MCEs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total CVD events	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CV events	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Myocardial events (fatal and non-fatal)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
MI (fatal and non-fatal)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Stroke (fatal and non-fatal)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Haemorrhagic stroke	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CHD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
All-cause mortality	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CV death	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Non-CVD death	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Cancer mortality	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Non cancer, non vascular mortality	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Major bleeding	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
GI bleed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Non-trivial bleed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Haemorrhagic stroke	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Methods

Search strategy: Yes
Study selection: Yes
What quality assessment tool was used: Delphi scoring system, which is based on the following: adequacy of randomisation; allocation concealment; balance between randomised groups at baseline; a priori identification of inclusion criteria; presence or absence of blinding; use of intention-to-treat analyses; and reporting of point estimates and measures of variability for main outcomes
Data extraction: Yes
Meta-analysis: Yes
Inclusion criteria described: Yes – (1) Randomised placebo-controlled trials that included > 1000 participants (without previous CHD or stroke, i.e. primary prevention studies) and had at least 1 year of follow-up during which CHD and/or CVD outcomes (CHD, stroke, cerebrovascular disease, heart failure and PAD) were recorded as the main end points, and details were provided of bleeding events, and (2) trials that enrolled subjects with pre-existing PAD were eligible for inclusion if they had been asymptomatic for this condition and had no history of CVD
No. of excluded studies described: Yes
Reasons for excluding studies described: Yes
Details of literature search given: Yes
Study selection described: Yes
Data extraction described: Yes

PAD, peripheral arterial disease.

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Study quality assessment described: Yes (see quality ratings using Delphi score below)

Events	Trials								
	BDT 1988	PHS 1989	HOT 1998	PPP 2001	TPT 1998	WHS 2005	POPADAD 2008	JPAD 2008	AAA 2010
Was a method of randomisation performed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the treatment allocation concealed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the groups similar at baseline with regards to the most important prognostic indicators?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the eligibility criteria specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the outcome assessor blinded?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the care provider blinded?	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Was the patient blinded?	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Were point estimates and measures of variability presented for the primary outcome measures?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the analysis include an intention-to-treat analysis?	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Total score	**16**	**18**	**17**	**18**	**16**	**18**	**17**	**18**	**18**

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Definitions of outcome measures provided: Yes (see table below)
Defined a category of clinically 'non-trivial' bleeding (fatal bleeding from any site; cerebrovascular or retinal bleeding; bleeding from hollow viscus; bleeding requiring hospitalisation and/or transfusion; or study-defined major bleeding regardless of source) as our composite primary safety end point. This roughly corresponds to type 2 or above of the Bleeding Academic Research Consortium definition for bleeding

	Trials								
Events	BDT 1988	PHS 1989	HOT 1998	PPP 2001	TPT 1998	WHS 2005	POPADAD 2008	JPAD 2008	AAA 2010
Major bleeds	Fatal GI haemorrhages, haemorrhagic peptic ulcers, haemorrhagic stroke and non-fatal probable haemorrhagic stroke	Haemorrhagic stroke, haematemesis, melaena, other non-specified GI bleeds, epistaxis, haematuria	All GI, cerebral and nasal bleeds	GI bleeds, intracranial bleeds, ocular bleeds, epistaxis	Haemorrhagic stroke, SAH, GI bleed, GU bleed, nasal/ throat bleed, ocular bleed, haematuria	Haemorrhagic stroke, GI bleeding, epistaxis, haematuria	GI bleeding (including haemorrhagic gastric ulcer, bleeding from: oesophageal varices, colonic diverticula, haemorrhoids, GI cancer and unknown GI bleeding) retinal bleeding, haematuria, epistaxis, haemorrhagic stroke	GI bleeding (including haemorrhagic gastric ulcer, bleeding from: oesophageal varices, colonic diverticula, haemorrhoids, GI cancer and unknown GI bleeding) retinal bleeding, haematuria, epistaxis, haemorrhagic stroke	Diagnosis of SAH or SDH recorded by a doctor, SAH ICD10 code – I60, SDH ICD10 code – I62 Criteria: Extracranial haemorrhage from site other than GI tract, requiring hospitalisation (e.g. haematuria, epistaxis etc.) to control bleeding Diagnosis of haemorrhage from GI tract recorded by a doctor *and* requiring hospitalisation to control bleeding
Fatal major bleeds	GI haemorrhages, haemorrhagic peptic ulcers and haemorrhagic stroke	Fatal GI bleeds. Cerebral bleeds unspecified	All fatal bleeds including cerebral and GI	All fatal GI bleeds Cerebral bleeds unspecified	Fatal non-cerebral bleeds Cerebral bleeds unspecified	GI haemorrhages Cerebral bleeds unspecified	Fatal haemorrhagic stroke	Fatal haemorrhagic stroke	Post mortem: cerebral haemorrhage and no other disease process or event, such as brain tumour, subdural

Events	Trials									
	BDT 1988	PHS 1989	HOT 1998	PPP 2001	TPT 1998	WHS 2005	POPADAD 2008	JPAD 2008	AAA 2010
haematoma, SAH, metabolic disorder, or peripheral lesion that could cause localising neurological deficit or coma according to hospital records *or* definite stroke within 6 weeks of death and no other disease process or event such as brain tumour, subdural haematoma, subarachnoid haemorrhage, metabolic disorder, or peripheral lesion that could cause localising neurological deficit or coma according to hospital records *or* COD on death certificate, verified by OEC, consistent with haemorrhage from any site within GI tract. GI bleeds unspecified in data									

	Trials								
Events	BDT 1988	PHS 1989	HOT 1998	PPP 2001	TPT 1998	WHS 2005	POPADAD 2008	JPAD 2008	AAA 2010
Non-fatal major bleeds	Non-fatal probable haemorrhagic stroke	GI bleeds requiring transfusion Cerebral bleeds unspecified	All non-fatal bleeds including GI, cerebral and nasal bleeds	Non-fatal bleeds were major (life-threatening non-cerebral haemorrhage requiring surgery or transfusion), and intermediate bleeds (macroscopic haematuria, and prolonged nose bleeds) Cerebral bleeds unspecified	Non-fatal severe and unexpected bleeding (GI+ intracranial+ ocular+ epistaxis)	GI bleeding, epistaxis, haematuria. Cerebral bleeds unspecified	GI bleeding only	Non-fatal haemorrhagic strokes, GI bleeding, retinal bleeding, haematuria, epistaxis, haemorrhagic stroke	Non-fatal subarachnoid bleeds and haemorrhagic stroke as defined above. GI bleeds unspecified in data
Non-major bleeds	–	Easy bruising, GI bleeding not requiring transfusion, epistaxis or other bleeding Cerebral bleeds unspecified	Minor bleeds including GI, nasal bleeds and purpura	Bruising, nose bleeds, rectal bleeds and pink or red urine	–	Easy bruising	–	Minor GI bleeds, bruising, epistaxis, haematuria, bleeding after tooth extraction and chronic SDH	Retinal haemorrhages
Total non-fatal bleeds	Non-fatal probable haemorrhagic stroke and non-cerebral bleed	Easy bruising, all non-fatal GI bleeding, epistaxis or other bleeding Cerebral bleeds unspecified	All GI, cerebral, nasal bleeds and purpura	Non-fatal major bleeds and minor bleeds Cerebral bleeds unspecified	Non-fatal severe and unexpected bleeding (GI+ intracranial+ ocular+ epistaxis)	GI bleeds, haematuria, epistaxis and easy bruising Cerebral bleed unspecified.	GI bleeding only	GI, bruising, epistaxis, haematuria, bleeding after tooth extraction and chronic SDH	Non-fatal subarachnoid bleeds, haemorrhagic stroke and retinal haemorrhages. GI bleeds non-specified in data

GU, genitourinary; ICD, *International Classification of Diseases*; OEC, Organisational Ethics Committee; SAH, subarachnoid haemorrhage, SDH; subdural haemorrage.

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Study flow shown: Yes
Study characteristics of individual studies given: Yes
Quality of individual studies given: Yes (see above)
Results of individual studies shown: Yes
Data analysis

(a) Random/fixed effect model – Yes
(b) Meta-regression – Yes
(c) Cumulative meta-analysis – No
(d) L'Abbé plot – No
(e) Funnel plot – Yes

Subgroup/sensitivity analysis: Yes
Statistical analysis appropriate: Yes

Results

Primary outcome
Primary efficacy end point: Total CHD and total cancer mortality.
Secondary efficacy end point: Subtypes of vascular disease, total CVD events, cause specific death and all-cause mortality
Primary safety end point: Non-trivial bleeding (fatal bleeding from any site; cerebrovascular or retinal bleeding; bleeding from hollow viscus; bleeding requiring hospitalisation and/or transfusion; or study-defined major bleeding regardless of source)
MCEs
Total CVD events

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	284	3429	143	1710
PHS	320	11,037	388	11,034
TPT	228	2545	250	2540
HOT	388	9399	425	9391
PPP	45	2226	64	2269
WHS	477	19,934	522	19,942
POPADAD	116	638	117	638
JPAD	68	1262	86	1277
AAA	181	1675	176	1675

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Fatal

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	89	3429	47	1710
PHS	10	11,037	26	11,034
TPT	60	2545	53	2540
HOT	89	9399	70	9391
PPP	4	2226	6	2269
WHS	14	19,934	12	19,942
POPADAD	35	638	26	638
JPAD	0	1262	5	1277
AAA	28	1675	18	1675

Non-fatal

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	80	3429	41	1710
PHS	129	11,037	213	11,034
TPT	94	2545	137	2540
HOT	68	9399	114	9391
PPP	15	2226	22	2269
WHS	184	19,934	181	19,942
POPADAD	55	638	56	638
JPAD	12	1262	9	1277
AAA	62	1675	68	1675

Stroke

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	91	3429	39	1710
PHS	119	11,037	98	11,034
TPT	47	2545	48	2540
HOT	146	9399	148	9391
PPP	16	2226	24	2269
WHS	221	19,934	266	19,942
POPADAD	37	638	50	638
JPAD	28	1262	32	1277
AAA	44	1675	50	1675

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Total CHD

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	169	3429	88	1710
PHS	139	11,037	239	11,034
TPT	154	2545	190	2540
HOT	157	9399	184	9391
PPP	19	2226	28	2269
WHS	198	19,934	193	19,942
POPADAD	90	638	82	638
JPAD	28	1262	35	1277
AAA	90	1675	86	1675

All-cause mortality

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	270	3429	151	1710
PHS	217	11,037	227	11,034
TPT	216	2545	205	2540
HOT	284	9399	305	9391
PPP	62	2226	62	2269
WHS	609	19,934	642	19,942
POPADAD	94	638	101	638
JPAD	34	1262	38	1277
AAA	176	1675	186	1675

CV mortality

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	143	3429	75	1710
PHS	81	11,037	83	11,034
TPT	101	2545	81	2540
HOT	133	9399	140	9391
PPP	17	2226	31	2269
WHS	120	19,934	126	19,942
POPADAD	43	638	35	638
JPAD	1	1262	10	1277
AAA	35	1675	30	1675

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Study details of losses to follow-up

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	127	3429	76	1710
PHS	124	11,037	133	11,034
TPT	115	2545	124	2540
HOT	151	9399	165	9391
PPP	45	2226	47	2269
WHS	489	19,934	516	19,942
POPADAD	51	638	66	638
JPAD	33	1262	28	1277
AAA	141	1675	156	1675

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	75	3429	47	1710
PHS	79	11,037	68	11,034
TPT	87	2545	104	2540
HOT	107	9399	104	9391
WHS	284	19,934	299	19,942
POPADAD	25	638	31	638
JPAD	15	1262	19	1277
AAA	78	1675	90	1675

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	52	3429	29	1710
PHS	45	11,037	65	11,034
TPT	28	2545	20	2540
HOT	44	9399	61	9391
WHS	205	19,934	217	19,942
POPADAD	26	638	35	638
JPAD	18	1262	9	1277
AAA	63	1675	66	1675

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	21	3429	10	1710
PHS	2979	11,037	2248	11,034
TPT	540	1268	435	1272
HOT	292	9399	165	9391
PPP	25	2226	9	2269
WHS	18,313	19,934	15,448	19,942
POPADAD	28	638	31	638
JPAD	34	1262	10	1277
AAA	65	1675	59	1675

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT	3	3429	2	1710
PHS	865	11,037	708	11,034
TPT	229	1268	179	1272
HOT	136	9399	78	9391
PPP	22	2226	9	2269
WHS	4000	19,934	3671	19,942
POPADAD	30	638	34	638
JPAD	17	1262	7	1277
AAA	35	1675	24	1675

	Trials								
Events	BDT 1988	PHS 1989	HOT 1998	PPP 2001	TPT 1998	WHS 2005	POPADAD 2008	JPAD 2008	AAA 2010
Details of losses to follow-up	'Data on mortality were thought to be complete and data on morbidity virtually complete'	A reported event could not be confirmed if written consent or relevant records were not available for verification Approximately 5% of cases of MI, stroke, or death could not be confirmed	491 subjects (2.6% of all participants) were lost to follow-up	At end of study 4150 (92.3%) patients had clinical follow-up	A total of 187 (3.4%) men moved away from their general practitioner during follow-up In total, 2969 (58%) reportedly withdrew from study during follow-up	'Rates of follow-up with respect to morbidity and mortality were 97.2% complete and 99.4% complete, respectively'	In total, 6 of 1276 participants enrolled were lost to follow-up, and one withdrew consent	A total of 193 participants (7.6%) were lost to follow-up	A total of 193 participants (7.6%) were lost to follow-up

Name of the reviewer: Paul Sutcliffe and checked by Tara Gurung

Author's conclusion

Aspirin reduced total CVD events by 10%. No significant reduction in CVD death or cancer mortality. Reduction in non-fatal MI. Increased risk of non-trivial bleeding events. There was significant heterogeneity for CVD and bleeding outcomes. Despite important reductions in non-fatal MI, aspirin prophylaxis in people without prior CVD did not lead to reductions in either CV death or cancer mortality. The benefits were further offset by clinically important bleeding events; routine use of aspirin for primary prevention was not warranted and treatment decisions should be considered on a case-by-case basis

Reviewer's conclusion

Comprehensive systematic review, which provides excellent coverage of the nine core RCTs. Further information is provided in the online appendices

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Study details

Study ID (Ref man): [431]

First author surname: Wolff

Year of publication: 2009

Country: USA

Funding: The general work of the USPSTF is supported by the Agency for Healthcare Research and Quality. This specific review did not receive separate funding

Title: Aspirin for the Primary Prevention of Cardiovascular Events: An Update of the Evidence for the U.S. Preventive Services Task Force

Aim of the study

To determine the benefits and harms of taking aspirin for the primary prevention of MIs, strokes, and death

Methods

Databases searched:

- MEDLINE and The Cochrane Library (search dates 1 January 2001 to 28 August 2008)
- Recent systematic reviews, reference lists of retrieved articles, and suggestions from experts
- PubMed

Last date of search: 28 August 2008

Inclusion criteria:

- Studies that evaluated aspirin vs. control for the primary prevention of CVD events in adults, had a study population of patients without a history of CVD or who were not at very high risk for CVD (such as patients with atrial fibrillation) and was generalisable to the US primary care population, and calculated risk estimates for one of the following out-comes: MI, stroke, death from MI or stroke, or all-cause mortality for benefits and GI bleeding, serious bleeding episodes, haemorrhagic stroke, or cerebral haemorrhage for harms
- Studies that included patients with a history of CVD or patients who were at very high risk for CVD only if those studies reported separate results for patients without a history of CVD or who were not at very high risk for CVD.

Participants: Not reported

Interventions: Aspirin

Comparators: Control

Outcome measures: Not reported

(a) Primary outcome: Not reported
(b) Secondary outcome: Not reported
(c) Primary safety outcome: Not reported

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Types of studies included: RCTs, randomised open-label trial, meta-analysis

Methods of analysis: Synthesised qualitatively

Meta-analysis: Not reported

Results

Adverse events: Not reported
MCEs: Not reported
Myocardial events: Not reported
Stroke: Not reported
Ischaemic stroke: Not reported
Haemorrhagic stroke: Not reported
Mortality: Not reported
All-cause death: Not reported
CV death: Not reported
Major bleeding: Not reported

Author's conclusion

Aspirin reduces the risk for MI in men and strokes in women. Aspirin use increases the risk for serious bleeding events

Reviewer's conclusion

In this study the author discussed only the results of the Berger study. The author synthesised the studies qualitatively and organised them by key question

B. Randomised controlled trials about the prophylactic use of aspirin in the primary prevention of cardiovascular disease

Name of the reviewer: Paul Sutcliffe and checked by Karoline Freeman

Study details

Study ID (Ref man): [61]

First author surname: Dorresteijin

Year of publication: 2011

Country: The Netherlands

Funding: The WHS was supported by grants (HL-43851 and CA-47988) from the NIH and the National Cancer Institute, Bethesda, MD, USA. Aspirin and aspirin placebo were provided by Bayer HealthCare who had no role in study design, data collection, data analysis, data interpretation, or writing of the report

Title: Aspirin for primary prevention of vascular events in women: individualised prediction of treatment effects

Aim of the study

To identify women who benefit from aspirin 100 mg on alternate days for primary prevention of vascular events by using treatment effect prediction based on individual patient characteristics. To show how predicted reduction in vascular events can be weighed against treatment harm and calculate the net benefit of the following treatment strategies: (1) treat no one, (2) treat everyone, (3) treatment according to the current guidelines (i.e. selective treatment of women of $\geq$ 65 years of age or having a $\geq$ 10% 10-year risk for CHD), and (4) prediction-based treatment (i.e. selective treatment of patients whose predicted treatment effect exceeds a decision threshold)

Methods

Design: RCT

Setting: Unclear from the current paper; details provided elsewhere

Participants: From 39,876 initially healthy women of 45 years of age or older, women eligible for the current analysis were those who provided an adequate baseline plasma sample ($n = 27,939$)
Inclusions: Unclear from the current paper; details provided elsewhere. The 'optimal fit' model was developed based on data from the 27,939 WHS participants for whom one or more baseline laboratory values were available
Exclusions: Unclear from the current paper; details provided elsewhere

Intervention:
100 mg aspirin on alternate days during 10 years

Comparator:
Placebo; no further information provided

Outcome measures:
Occurrence of MCEs (i.e. non-fatal MI, non-fatal stroke or death from CV causes)

(a) Primary outcome: Unclear – see above
(b) Secondary outcome: Unclear – see above
(c) Adverse events: Unclear – see above

Results

Baseline characteristics:
Women were at lower baseline risk for CVD, because the mean 10-year risk for CV events was 2.9%. High-risk groups such as women of $\geq$ 65 years of age ($n = 2968$), women with diabetes mellitus ($n = 687$), and women having a $\geq$ 10% 10-year risk for CHD ($n = 1068$). In the aspirin-treated group (13,976 women), 312 MCEs were found, whereas in the placebo-treated group (13,963 women) 340 MCEs were found

Name of the reviewer: Paul Sutcliffe and checked by Karoline Freeman

Baseline characteristics of the total study population and of women having a <2% vs ≥2% predicted absolute treatment effect based on the 'optimal fit' model

Characteristic	Parameter	Total study population (*N* = 27,939)	<2% predicted ARR (*n* = 26,712)	≥2% predicted ARR (*n* = 1227)
Age (years)	Mean (SD)	54.7 (7)	54.7 (7)	69.4 (4)
	% >65	10.6	7.2	84.4
Ethnicity	% Caucasian	95.3	95.3	96.1
Current smoking	%	11.7	12.1	2.7
Family history of premature CHD	%	14.4	14.4	13.3
HDL cholesterol (mmol/l)	Mean (SD)	1.40 (0.39)	1.40 (0.39)	1.22 (0.34)
Total cholesterol (mmol/l)	Mean (SD)	5.5 (1.0)	5.5 (1.0)	5.9 (1.0)
Hs-C-reactive protein (mg/l)	Median (IQ range)	2.0 (0.8–4.4)	2.0 (0.8–4.4)	1.9 (0.9–3.6)
SBP (mmHg)	Mean (SD)	124.0 (14)	123.0 (13)	141.0 (14)
Blood pressure-lowering medication use	%	13.4	11.9	45.1
Lipid-lowering medication use	%	3.2	2.9	10.8
Diabetes mellitus	%	2.5	1.9	15.6
Body mass index (kg/m^2)	Mean (SD)	25.9 (5)	25.8 (5)	28.0 (5)
Menopausal status	% post-menopausal	54.4	52.3	98.8
Hormone replacement therapy use	%	48.6	48.2	55.3
10-year risk for CV events (%)[a]	≤5.0%	84.8	88.3	8.7
	5.0–9.9%	10.0	8.6	41.3
	5.0–9.9%	5.2	3.1	50.0

HDL, high-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.
a Based on the Reynolds Risk Score.

Subgroup analysis:
After a mean follow-up of 10.1 years (range 8.2–10.9), the HR for occurrence of the primary end point was 0.91 (95% CI 0.80 to 1.03), favouring aspirin treatment. Aspirin treatment was associated with increased risk for GI bleeding (RR 1.22, 95% CI 1.10 to 1.34), peptic ulcer (RR 1.32, 95% CI 1.16 to 1.50), haematuria (RR 1.06, 95% CI 1.01 to 1.12), easy bruising (RR 1.40, 95% CI 1.37 to 1.45) and epistaxis (RR 1.16, 95% CI 1.11 to 1.22)
Age was the strongest determinant of treatment effect ,as women having a ≥2% predicted absolute treatment effect were much older on average (mean 69.4 years vs. 54.7 years in the total study population) and almost all women who were <65 years of age (99.2%) had a ≤2% predicted absolute treatment effect

Author's conclusion

'Individual patient characteristics predict absolute treatment effect of aspirin in primary prevention of vascular events in women. Absolute treatment effect from aspirin is most importantly determined by age and not by baseline risk for MCEs. Aspirin was ineffective or even harmful in the majority of study participants. When the number willing to treat to prevent one MCE in 10 years is 50 or lower, the aspirin treatment strategy that is associated with optimal net benefit in primary prevention of vascular events in women is to treat none'

Reviewer's conclusion

Incomplete reporting and reliance on previous publications for more detailed information about baseline characteristics of sample

Name of the reviewer: Paul Sutcliffe and checked by Karoline Freeman

Study details

Study ID (Ref man):[42]

First author surname: Fowkes

Year of publication: 2010

Country: Scotland

Funding: The trial was funded by the British Heart Foundation and Chief Scientist's Office, Scotland
Bayer HealthCare provided the aspirin and placebo tablets and funds for packaging, dispensing and some statistical analysis. Drs Fowkes and Price reported that they have received research support from Bayer HealthCare. Drs Fowkes and Sandercock reported that they have received lecture fees and expenses from Bayer HealthCare. Dr Fowkes reported that he has received research support and honoraria from Sanofi-aventis and Bristol-Myers Squibb

Title: Aspirin for prevention of cardiovascular events in a general population screened for a low ankle–brachial index: a randomized controlled trial

Aim of the study

To determine the effectiveness of aspirin in preventing events in people with a low ABI identified on screening the general population. To determine whether screening the general population for a low ABI could identify a higher-risk group who might derive substantial benefit from aspirin therapy

Methods

Design: A pragmatic intention-to-treat, double-blind, RCT

Setting: Recruited from Lanarkshire, Glasgow, and Edinburgh, central Scotland

Participants:
Inclusions: Those with an ABI of ≤ 0.95 were entered into the trial; men and women aged 50–75 years
Exclusions: History of MI, stroke, angina, or peripheral artery disease; currently using aspirin, other antiplatelet or anticoagulant agents; had severe indigestion; had chronic liver or kidney disease; were receiving chemotherapy; had contraindications to aspirin; and had an abnormally high or low haematocrit value (measured after the screening)

Intervention:

- Participants free of clinical CVD and with a low ABI were randomised to receive 100 mg of enteric-coated aspirin daily or placebo
- Consecutive participant study numbers were assigned to aspirin or placebo with permuted blocks of size 8, which varied randomly
- Participants were followed up after 3 months, 1 year and 5 years at special clinics, and annually by telephone

Comparator: Placebo

Outcome measures:

(a) Primary outcome:

The primary end point was a composite of initial fatal or non-fatal coronary event or stroke or revascularisation

(b) Secondary outcome:
- All initial vascular events defined as a composite of a primary end point event or angina, intermittent claudication or TIA
- All-cause mortality

(c) Adverse events:
- For example: Major haemorrhage, fatal SAHs or SDHs (see tables below)

ABI, ankle–brachial index; SAH, subarachnoid haemorrhage; SDH, subdural haemorrhage.

Name of the reviewer: Paul Sutcliffe and checked by Karoline Freeman

Results

Baseline characteristics:
Characteristics of participants in aspirin and placebo groups at randomisation

Characteristic[a]	Aspirin group (*n* = 1675)	Placebo group (*n* = 1675)
Age, mean (SD), years	62.2 (6.7)	61.7 (6.6)
Men, no. (%)	481 (29)	473 (28)
Socioeconomic status, no. (%)[b]		
1 (most deprived)	438 (26)	450 (27)
2	380 (230)	371 (22)
3	255 (15)	250 (15)
4	236 (14)	247 (15)
5 (least deprived)	366 (22)	357 (21)
ABI, mean (SD)	0.86 (0.09)	0.86 (0.09)
Blood pressure: mean (SD), mmHg		
Systolic	148 (22)	147 (22)
Diastolic	84 (11)	84 (11)
Serum total cholesterol: mg/dl	239 (41.3)	238 (42.4)
Smoking status, no. (%) current	547 (33)	538 (32)
Previous[c]	542 (32)	564 (34)
Never	586 (35)	573 (34)
Diabetes mellitus, no. (%)[d]	45 (3)	43 (3)
Medication, no. (%) diuretic	260 (15.5)	251 (15.0)
3-Blocker	168 (10)	161 (9.6)
Nitrate/calcium channel blocker	110 (6.6)	106 (6.3)
ACE inhibitor/angiotensin II antagonist	105 (6.3)	102 (6.1)
Lipid-lowering agents	69 (4.1)	73 (4.4)

ABI, ankle–brachial index; ACE, angiotensin-converting enzyme; SD, standard deviation.

a Data complete except cholesterol (1664 in aspirin group and 1666 in placebo group).

b Based on Scottish Index of Multiple Deprivation, which assigns each postcode of residence to deprivation score derived from levels of income, employment, health, education, access to services, housing and crime.

c Smokers who had stopped smoking for at least 6 months before randomisation.

d Self-reported.

SI conversion factor: To convert total serum cholesterol from mg/dl to mmol/l, multiply by 0.0259.

Name of the reviewer: Paul Sutcliffe and checked by Karoline Freeman

Subgroup analysis:
Vascular end point events in participants randomised to aspirin or placebo

No. (%) of participants with event (95% CI)						
	Aspirin group ($n = 1675$): No.	%	95% CI	Placebo group ($n = 1675$): No.	%	95% CI
Primary end point event[a]	181	10.8	9.4 to 12.4	176	10.5	9.1 to 12.1
Fatal						
Coronary event	28	1.7	1.2 to 2.4	18	1.1	0.7 to 1.7
Stroke[b]	7	0.4	0.2 to 0.9	12	0.7	0.4 to 1.2
Non-fatal						
MI	62	3.7	2.9 to 4.7	68	4.1	3.2 to 5.1
Stroke[b]	37	2.2	1.6 to 3	38	2.3	1.7 to 3.1
Coronary revascularisation[c]	24	1.4	1.0 to 2.1	20	1.2	0.8 to 1.8
Peripheral revascularisation[d]	23	1.4	0.9 to 2.1	20	1.2	0.8 to 1.8
Secondary end point event[e]	288	17.2	15.5 to 19.1	290	17.3	15.6 to 19.2
Angina	72	4.3	3.4 to 5.4	64	3.8	3.0 to 4.8
Intermittent claudication	53	3.2	2.4 to 4.1	53	3.2	2.4 to 4.1
TIA	38	2.3	1.7 to 3.1	41	2.4	1.8 to 3.3

a Initial primary event only.
b Fatal strokes include two ischaemic, three haemorrhagic, two unknown in aspirin group; seven ischaemic, three haemorrhagic, two unknown in placebo group. Non-fatal strokes include 28 ischaemic, two haemorrhagic, seven unknown in aspirin group; 30 ischaemic, one haemorrhagic, seven unknown in placebo group.
c Includes coronary artery bypass surgery, angioplasty or stent.
d Includes carotid and lower limb surgery, angioplasty or stent.
e Initial event only, which includes events as in primary end point, plus angina, intermittent claudication and TIA.

Primary end point events by age, sex and ankle–brachial index

	Participants with event				
	Aspirin group ($n = 1675$)		Placebo group ($n = 1675$)		
Subgroup	*n*	Per 1000 person-years (95% CI)	*n*	Per 1000 person-years (95% CI)	HR (95% CI)
Age (years)					
< 62	57	8.6 (6.5 to 11.2)	70	10 (8 to 12.9)	0.85 (0.6 to 1.2)
≥ 62	124	18.8 (15.6 to 22.4)	106	17 (14 to 20.1)	1.13 (0.9 to 1.47)
Sex					
Men	96	27.4 (22.2 to 33.5)	83	24 (19 to 29.6)	1.15 (0.86 to 1.54)
Women	85	8.8 (7 to 10.8)	93	9.6 (7.7 to 11.7)	0.92 (0.68 to 1.23)
ABI					
≤ 0.95	181	13.7 (11.8 to 15.9)	176	13 (11 to 15.4)	1.03 (0.84 to 1.27)
≤ 0.90	134	15.7 (13.2 to 18.6)	134	16 (13 to 18.3)	1.02 (0.8 to 1.29)
≤ 0.85	78	18.6 (14.7 to 23.2)	82	19 (15 to 23.3)	0.99 (0.73 to 1.35)
≤ 0.80	53	24.3 (18.2 to 31.8)	57	23 (17 to 29.8)	1.06 (0.73 to 1.54)

ABI, ankle–brachial index.

Name of the reviewer: Paul Sutcliffe and checked by Karoline Freeman

Adverse events in participants randomised to aspirin or placebo

	No. (%) of participants with adverse event (95% CI)[a]		Total adverse events[b]	
	Aspirin group (*n* = 1675)	Placebo group (*n* = 1675)	Aspirin group (*n* = 65)	Placebo group (*n* = 59)
Major haemorrhage	34 (2.0) (1.5 to 2.8)	20 (1.2) (0.8 to 1.8)	39	32
Haemorrhagic stroke (*n*)[c]				
Fatal	3	3	3	4
Non-fatal	2	1	2	1
Subarachnoid/subdural (*n*)[c]				
Fatal	3	0	3	
Non-fatal	3	3	3	4
GI (*n*)[d]	9	8	13	14
Other (*n*)[d]	14	5	15	9
GI ulcer	14 (0.8) (0.5 to 1.4)	8 (0.5) (0.2 to 0.9)	15	11
Retinal haemorrhage	1 (0.1) (0.0 to 0.3)	4 (0.2) (0.1 to 0.6)	1	5
Severe anaemia	6 (0.4) (0.2 to 0.8)	10 (0.6) (0.3 to 1.1)	10	11

a Initial primary, secondary, or adverse event.
b Includes all adverse events, except repeat of same event in any given participant.
c Diagnosis based on brain scan.
d Required admission to hospital to control bleeding. Admission only to investigate bleeding was not included as major haemorrhage.

'34 participants (2.0%) in the aspirin group had an initial event of a major haemorrhage compared with 20 (1.2%) in the placebo group [aspirin 2.5 (95% CI 1.7 to 3.5) vs. placebo 1.5 (95% CI, 0.9 to 2.3) per 1000 person-years; HR 1.71 (95% CI) 0.99 to 2.97]. Of these events, 11 in the aspirin group and seven in the placebo group were intracranial, including three fatal SAHs or SDHs in the aspirin group compared with none in the placebo group. Differences in total number of adverse events between groups were similar but less marked than for initial events.'

Additional information is provided in a supplementary appendices online

Author's conclusion

This trial was the first to report on the effectiveness of aspirin in reducing major CV and cerebrovascular events in individuals from the general population who were free of clinical CVD but at higher risk as identified by ABI screening. No reductions were observed in major vascular events. Among participants without clinical CVD, identified with a low ABI based on screening a general population, the administration of aspirin compared with placebo did not result in a significant reduction in vascular events or in the secondary vascular end point, which also included angina, intermittent claudication and TIA

Reviewer's conclusion

Good-quality study with clear methodology

ABI, ankle–brachial index.

Name of the reviewer: Paul Sutcliffe and checked by Karoline Freeman

Study details

Study ID (Ref man):[58]

First author surname: Nelson

Year of publication: 2008

Country: Australia

Funding: Unclear

Title: Feasibility of conducting a primary prevention trial of low-dose aspirin for major adverse CV events in older people in Australia: results from the ASPirin in Reducing Events in the Elderly (ASPREE) pilot study

Aim of the study

To determine the feasibility of performing a large clinical trial of the use of aspirin for the primary prevention of CVD in older participants: the ASPirin in Reducing Events in the Elderly (ASPREE) trial

Methods

Design: Randomised, double-blind, placebo-controlled pilot trial

Setting: The Melbourne metropolitan area between March 2003 and June 2005

Participants: Letters were sent to 2614 patients, of whom 243 were screened and 209 (86%) were randomly allocated to receive aspirin or placebo. Participants were identified from the computer databases of general practitioners who were co-investigators in a previous trial
Inclusions: See below
Exclusions: See below

Intervention:

- Pilot trial of 100 mg of enteric-coated aspirin tablets daily
- Men and women aged ≥ 70 years and over who did not have overt CVD
- Followed for 12 months

Comparator: Placebo

Outcome measures:
The level of response to participation by GPs; the level of response from potential trial participants; the screening-to-randomisation rate to ensure that the recruitment target could be achieved; and the retention of participants in the trial after 12 months. The primary end points of the pilot study were fatal and non-fatal stroke and coronary events. Secondary end points included dementia and clinically significant bleeding (haemorrhagic stroke or GI bleeding requiring transfusion or hospitalisation)

(a) Primary outcome:
– Fatal and non-fatal stroke and coronary events

(b) Secondary outcome:
– Dementia and clinically significant bleeding (haemorrhagic stroke or GI bleeding requiring transfusion or hospitalisation)

(c) Adverse events:
– See above

Results

Forty-two GPs (23% of 180 mailed) expressed interest in participating in the pilot trial. Nineteen became co-investigators, of whom six were not required to meet recruitment targets. At 12 months, 192 (92%) returned for follow-up, and 153 of these (80%) were still taking trial medication. There was a significant reduction in mean haemoglobin level in those taking aspirin
Baseline characteristics: See below
Baseline measurements were obtained: demographic data, family and medical history, concomitant medications, and lifestyle risk factors such as smoking history, alcohol use and physical activity. BP, height and weight were recorded. Standardised questionnaires were administered: the Geriatric Depression Scale, the MOS SF-36, the IADL scale, the Modified Mini-Mental State examination, and the Colour Trails Test. A biochemical screen at GPs' routine pathology service providers included measurement of fasting lipid, haemoglobin, glucose and serum creatinine levels

IADL, Instrumental Activities of Daily Living; MOS SF-36, Modified Outcomes Study 36-item Short Form survey.

Name of the reviewer: Paul Sutcliffe and checked by Karoline Freeman

Pre-screening for exclusion criteria on general practice computer databases

	No. of patients
Total patient records reviewed	13,258
Patients excluded at pre-screening on exclusion criteria (below)	5487
Patients excluded at pre-screening because they were taking aspirin or anticoagulants	3607
Exclusion criterion	**No. of reports**
Abdominal aortic aneurysm	91
MI	264
Angina	632
Angioplasty (coronary)	50
Aspirin or anticoagulants:	
Anticoagulant	837
Aspirin	538
Astrix	1298
Cardiprin	229
Cartia	176
Disprin	1
Solprin	738
Coronary artery bypass graft	247
Coronary artery disease	567
Cerebral aneurysm	6
Coronary angiography	18
Dementia	37
Diabetes	1121
Gastric ulcer	107
Heart failure	246
Ischaemic heart disease	42
Peptic ulcer	253
PAD	209
Stroke	231
TIA	195

PAD, peripheral arterial disease.

Name of the reviewer: Paul Sutcliffe and checked by Karoline Freeman

Baseline characteristics of the 209 study participants

Characteristic	Value
Mean age in years (SD)	76.2 (4.6)
Age (%)	
70–74 years	49.8
75–80 years	31.6
≥ 80 years	18.7
Sex (%)	
Male	40.7
Family medical history (%)	
None	52.2
Heart attack	25.4
Stroke	13.9
Dementia	4.8
Heart attack and stroke	2.9
Heart attack and stroke and dementia	1.0
First language English	93.3
Years lived in Australia	
0–14	2.8
15–29	2.8
30–44	25.0
45–59	50.0
60–74	8.3
≥ 75	11.1
Education (years)	
< 9	31.6
9–11	33.5
12	9.1
13–15	13.4
16	6.2
17–21	6.2

SD, standard deviation.

Name of the reviewer: Paul Sutcliffe and checked by Karoline Freeman

Subgroup analysis:
No primary end points in the 192 participants during the 12 months. Nineteen secondary end points consisted of three cases of Alzheimer's disease, four cancers and 12 hospitalisations unrelated to the study drug. There was no major bleeding
Clinical measurements, neuropsychological and quality-of-life test scores[a] *at baseline and 12 months, overall and by treatment group for the 192 participants who returned for 12-month follow-up*

	Baseline			12-month follow-up		
Parameter	Overall	Aspirin	Placebo	Overall	Aspirin	Placebo
Height (m)	1.64 (0.09)					
Weight (kg)	71.6 (13.4)	71.8 (12.9)	71.7 (13.9)	71.0 (13.6)	71.3 (13.4)	70.8[b] (13.8)
Waist circumference (cm)	89.3 (12.1)	89.9 (11.5)	89.2 (11.5)	87.9 (12.1)	87.9[b] (11.8)	87.9[b] (12.5)
SBP (mmHg)	142.3 (17.3)	141.3 (18.5)	142.2 (16.0)	145.9 (20.7)	147.5[b] (23.1)	144.3 (17.8)
DBP (mmHg)	78.0 (9.4)	77.2 (9.4)	78.3 (9.2)	79.5 (10.9)	80.0[b] (11.1)	79.0 (10.8)
Total cholesterol (mmol/l)	5.6 (1.0)	5.6 (1.0)	5.6 (0.9)	5.5 (0.9)	5.5 (1.0)	5.4[b] (0.9)
LDL cholesterol (mmol/l)	3.2 (0.8)	3.3 (0.9)	3.3 (0.8)	3.2 (0.9)	3.2 (0.9)	3.1 (0.9)
HDL cholesterol (mmol/l)	1.7 (0.4)	1.7 (0.4)	1.7 (0.4)	1.6 (0.4)	1.6 (0.4)	1.6 (0.4)
Triglycerides (mmol/l)	1.4 (0.7)	1.4 (0.6)	1.4 (0.7)	1.4 (0.6)	1.4 (0.5)	1.4 (0.6)
Haemoglobin (g/l)	139.7 (12.7)	138.9 (12.6)	140.8 (12.4)	139.0 (14.1)	136.5[b] (14.4)	141.5 (13.4)
Glucose (mmol/l)	5.1 (0.6)	5.1 (0.8)	5.1 (0.5)	5.0 (0.5)	4.9[b] (0.6)	5.0 (0.5)
Creatinine (mmol/l)	0.08 (0.02)	0.1 (0.02)	0.1 (0.02)	0.09 (0.02)	0.1 (0.02)	0.1 (0.02)
Median C-reactive protein (IQR) (mg/l)	3.0 (2.9–5.3)	3.0 (2.9–5.6)	3.0 (2.9–5.1)	3.0 (3.0 – 5.0)	3.8 (3.0 – 5.0)	3.8 (3.0–5.0)
Scores on:						
Geriatric Depression Scale	1.6 (1.7)	1.7 (1.7)	1.5 (1.6)	2.0 (2.2)	2.1[b] (2.2)	1.8 (1.9)
IADL Scale	7.9 (0.4)	7.8 (0.5)	8.0 (0.2)	7.79 (0.60)	7.8 (0.7)	7.8 (0.5)
MOS SF-36						
Physical component summary	48.7 (8.2)	47.9 (7.7)	49.7 (8.4)	48.3 (8.6)	47.8 (8.2)	48.8 (8.9)
Mental component summary	56.1 (7.0)	55.8 (7.7)	56.3 (6.1)	54.9 (8.4)	54.7 (7.9)	55.1 (9.0)
Colour Trails Interference Index (*z*-score)[c]	–0.054 (1.20)	–0.057 (1.36)	–0.051 (1.03)	–0.280 (0.99)	–0.269 (1.01)	–0.290 (0.98)
Modified Mini-Mental State examination	93.1 (6.2)	92.7 (6.3)	93.9 (5.4)	93.3 (6.4)	93.0 (6.0)	93.7 (6.8)

DBP, diastolic blood pressure; HDL, high-density lipoprotein; IADL, instrumental activities of daily living; IQR, interquartile range. LDL, low-density lipoprotein; SBP, systolic blood pressure; MOS SF-36, Medical Outcomes Study 36-item short form survey.
a All values are mean (standard deviation) unless otherwise specified.
b Indicates a statistically significant difference between baseline and 12 months within group ($p < 0.05$).
c Colour Trails Test, Psychology Assessment Resources, 1999.

Name of the reviewer: Paul Sutcliffe and checked by Karoline Freeman

Author's conclusion

The recruitment strategy for ASPREE, based on methods developed for the conduct of a previous large-scale trial conducted in general practice, was successfully redeployed in this pilot study, with improved efficiency resulting from computerised database searching, telephone pre-screening, a simpler run-in phase and participant familiarity with the trial drug. The authors conclude that conducting ASPREE in Australian general practice with 18,000 participants is feasible

Reviewer's conclusion

Difficult to draw firm conclusions from this pilot study. This was a pilot study and no primary outcome events occurred (some secondary outcome events were reported)

C. Systematic reviews about the prophylactic use of aspirin in the primary prevention of cancer

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[61]

First author surname: Algra

Year of publication: 2012

Country: UK

Funding: None

Title: Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies vs randomised trials

Aim of the study

To compare effects of aspirin on risk and outcome of cancer in observational studies vs. randomised trials

Methods

Databases searched: PubMed (only for case control and cohort studies)

Last date of search: January 2011

Inclusion criteria: for RCTs: RCT of aspirin vs. no aspirin and a mean treatment duration of ≥ 4 years

Participants: Not reported

Interventions: Daily aspirin (any dose)

Comparators: No aspirin

Outcome measures: Death, incidence of CRC, *death due to cancer*, cancer with distant metastasis

(a) Primary outcome for primary prevention of cancer: Death due to cancer
(b) Primary safety outcome: Not reported

Types of studies included: Case–control and cohort studies and RCTs

Methods of analysis:

- Meta-analysis of ORs from each trial
- Rothwell, 2012[62] and Rothwell 2011[22]

Meta-analysis: see Rothwell 2012[62] and Rothwell 2011[22]

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Results

Adverse events: Not reported

Death due to cancer

	Aspirin		Control			
Type of cancer	Deaths	Total	Deaths	Total	OR	95% CI
CRC	91	9833	154	9859	0.58	044 to 0.78
Other cancers						
Biliary	7	9833	13	9859	0.55	0.23 to 1.34
Oesophageal	27	9833	52	9859	0.51	0.31 to 0.83
Gastric	40	9833	52	9859	0.77	0.49 to 1.22
Breast	12	4197	11	4220	1.17	0.50 to 2.71
Lung	209	9833	248	9859	0.84	0.69 to 1.03
Prostate	116	9833	149	9859	0.77	0.59 to 1.01
Haematological	85	9833	90	9859	0.92	0.66 to 1.29
Pancreatic	48	9833	52	9859	0.91	0.59 to 1.40
Bladder	31	9833	39	9859	0.91	0.54 to 1.51
Gynaecological	8	4197	7	4220	1.04	0.40 to 2.73
Renal	23	9833	25	9859	0.88	0.48 to 1.61

Results from six trials (BDT, UK-TIA, TPT, JPAD, POPADAD, AAA)

Daily aspirin		Control				
Death	Total	Death	Total	OR	95% CI	*p*-value
91	9833	154	9859	0.58	0.44–0.78	0.0002
Daily aspirin ≥ 5 years		Control				
74	8034	134	8012	0.55	0.41–0.76	0.0002

Author's conclusion

Results of methodologically rigorous studies are consistent with those obtained from RCTs

Reviewer's conclusion

This study concentrates on the results reported in observational studies; it therefore does not add any new evidence in terms of effect of aspirin on prevention of cancer based on RCTs alone

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[60]

First author surname: Mills

Year of publication: 2012

Country: Canada

Funding: Mills is supported through a Canada Research Chair

Title: Low-dose aspirin and cancer mortality – a meta-analysis of randomized trials

Aim of the study

To determine whether cancer mortality is also reduced in the shorter term

Methods

Databases searched: MEDLINE, EMBASE, AMED, CINAHL, TOXNET, CENTRAL, PsycINFO and Web of Science

Last date of search: December 2011

Inclusion criteria: RCTs evaluating low-dose, daily aspirin

Participants: Any population

Interventions: Daily, low-dose aspirin (75–325 mg)

Comparators: No aspirin

Outcome measures: non-CV and *cancer death*

(a) Primary outcome: Not reported
(b) Primary safety outcome: Not reported

Types of studies included: RCTs

Methods of analysis:

- Random-effects model of RRs
- Univariate random-effects meta-regression assessing the impact of duration and dose on effect size
- Cumulative meta-analysis based on shortest to longest-duration trials
- Trial sequential analysis to determine the strength of information

Meta-analysis: Random-effects model (DerSimonian and Laird)

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Results

Adverse events: Not reported
Non-vascular mortality

Trial			RR	95% CI	*p*-value
Laffort			2.20	0.48 to 10.15	
Cote			0.16	0.03 to 1.02	
UK-TIA			0.62	0.37 to 1.03	
Richard			0.45	0.06 to 3.33	
Ogawa			0.93	0.54 to 1.62	
Giannarini			Excluded		
PHS			0.93	0.73 to 1.19	
ECLAP			0.63	0.24 to 1.64	
TPT			0.93	0.72 to 1.19	
SPAF			0.66	0.28 to 1.57	
CLIPS			4.89	0.51 to infinity	
HOT			0.91	0.73 to 1.14	
PEP			0.88	0.76 to 1.03	
PEP			0.43	0.12 to 1.51	
Turpie			0.79	0.23 to 2.68	
FFAACS			1.07	0.11 to 10.10	
SALT			0.88	0.53 to 1.45	
Lewis			Excluded		
Casais			Excluded		
PPP			0.98	0.64 to 1.46	
POPADAD			0.75	0.52 to 1.09	
AFASAK			0.63	0.22 to 1.80	
SAPAT			0.88	0.55 to 1.40	
EAFT			0.96	0.61 to 1.53	
Total	**Non-vascular deaths**	**Non-vascular deaths**	**0.88**	**0.81 to 0.96**	**0.003**
	Aspirin: 944	**Control: 1074**			

CLIPS, Critical Leg Ischaemia Prevention Study; EAFT, European Atrial Fibrillation Trial; FFAACS, Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontané.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Cancer mortality

Trial			RR	95% CI	*p*-value
Laffort			1.10	0.12 to 10.47	
UK-TIA			0.58	0.29 to 1.15	
Ogawa			0.80	0.41 to 1.55	
Giannarini			Excluded		
TPT			0.83	0.63 to 1.10	
CLIPS			4.89	0.51 to infinity	
FFAACS			Excluded		
SALT			0.67	0.31 to 1.46	
Lewis			Excluded		
PAPADAD			0.81	0.48 to 1.34	
SAPAT			0.54	0.25 to 1.13	
Total	**Cancer deaths aspirin: 162**	**Cancer deaths control: 210**	**0.77**	**0.63 to 0.95**	**0.019**

CLIPS, Critical Leg Ischaemia Prevention Study; FFAACS, Fluindione, Fibrillation Auriculaire, Aspirin et Contraste Spontané.

Excluded trials were excluded without reason
Longer trial vs. shorter trials: coefficient –0.16 (95% CI –0.67 to 0.34); $p = 0.52$
dosage of aspirin (75–325 mg): coefficient –0.12 (95% CI –0.51 to 0.25); $p = 0.51$
Follow-up period that starts to show significant effect: 4 years of follow-up

Author's conclusion

Low-dose aspirin reduces non-CV deaths including cancer deaths

Reviewer's conclusion

The results are similar to those reported by Rothwell *et al.* However, no formal quality appraisal was carried out and no reason was provided for the exclusion of three trials from the pooled meta-analysis investigating cancer mortality

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study ID (Ref man):[22]

First author surname: Rothwell

Year of publication: 2011

Country: UK

Funding: None

Title: Effect of daily aspirin on long-term risk of death due to cancer – analysis of individual patient data from randomised trials

Aim of the study

To determine the effect of aspirin on risk of fatal cancer by analysis of individual patient data for deaths due to cancer during randomised trials of daily aspirin vs. control

Study designs of included studies

(a) RCT (*n*) = 8; (b) observational studies (*n*) = none; (c) primary cancer prevention (*n*) = 8 trials; (d) secondary cancer prevention (*n*) = none
Inclusion criteria for systematic review: Randomised trials of aspirin (any dose) vs. control (no aspirin) in the presence or absence of another anti-platelet agent or antithrombotic agent, if the other agent was used in the same way in both groups with a trial period of at least 4 years. Trials of aspirin in primary and secondary prevention of vascular disease were included

Characteristics of individual trials

Source	Location	Year	Aspirin comparison	No. of participants	Placebo controlled/ double blind	Age (years): mean (SD)	Male (%)	Smokers (%)
BDT or BDS	England	1988	500 mg daily vs. control	5139	No	61.6 (7.0)	100.0	31.0
UK-TIA	UK and Ireland	1991	300 mg vs. 1200 mg daily vs. placebo	2435	Yes	60.3 (9.0)	73.0	53.0
ETDRS	USA	1992	650 mg vs. placebo	3711	Yes	51.0 (20–70) (range)	56.5	44.2
SAPAT	Sweden	1992	75 mg vs. placebo	2035	Yes	67.0 (8.0)	52.0	16.0
TPT	UK	1998	75 mg daily vs. placebo	5085	Yes	57.5 (6.7)	100.0	41.2
POPADAD	Scotland	2008	100 mg vs. placebo	1276	Yes	60.3 (10.0)	44.1	31.7
JPAD	Japan	2008	81 or 100 mg vs. placebo	2539	Yes	64.5 (10.0)	54.6	21.2
AAA	Scotland	2010	100 mg vs. placebo	3350	Yes	62.0 (6.6)	28.5	32.4

SD, standard deviation.

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Outcome measures

Events	Trials							
	BDT (1988)	TPT (1998)	POPADAD (2008)	JPAD (2008)	AAA (2010)	UK-TIA	ETDRS	SAPAT
MCEs	Yes	Yes	Yes	Yes	Yes			
Total CVD events	Yes	Yes	Yes	Yes	Yes			
CV events	Yes	Yes	Yes	Yes	Yes			
Myocardial events (fatal and non-fatal	Yes	Yes	Yes	Yes	Yes			
MI (fatal and non-fatal)	Yes	Yes	Yes	Yes	Yes			
Stroke (fatal and non-fatal)	Yes	Yes	Yes	Yes	Yes			
Haemorrhagic stroke	Yes	Yes	Yes	Yes	Yes			
CHD	Yes	Yes	Yes	Yes	Yes			
All-cause mortality	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
CV death	Yes	Yes	Yes	Yes	Yes			
Non-CVD death	Yes	Yes	Yes	Yes	Yes			
Cancer incidence	*Yes*	*Yes*				*Yes*		
Cancer mortality	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*	*Yes*
Non-cancer, non-vascular mortality	Yes	Yes	Yes	Yes	Yes			
Major bleeding	Yes	Yes	Yes	Yes	Yes			
GI bleed	Yes	Yes	Yes	Yes	Yes			
Non-trivial bleed	Yes	Yes	Yes	Yes	Yes			
Haemorrhagic stroke	Yes	Yes	Yes	Yes	Yes			

Note: Only data in italics taken from Rothwell paper.

Methods

Search strategy:

- Trials from ATT collaboration review
- Searched PubMed, EMBASE and Cochrane Database after last ATT search (2002) until March 2012
- 'aspirin' or 'salicyl*' or 'antiplatelet' with the term 'randomised controlled trial'
- search restricted to humans, no language restriction

Study selection:

- Randomised trials of aspirin (any dose) vs. control (no aspirin) in the presence or absence of another antiplatelet agent or antithrombotic agent, if the other agent was used in the same way in both groups with a trial period of at least 4 years. Trials of aspirin in primary and secondary prevention of vascular disease were included

What quality assessment tool was used:

- None reported

Data extraction:

Not reported
- (Used death certificate and cancer registration data of three UK trials with long-term follow-up)

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Meta-analysis:
Fixed-effects meta-analysis of ORs of risk of death due to cancer by trial

- Pooling of IPD

Inclusion criteria described:

- Yes, see study selection above

No. of excluded studies described:

- No

Reasons for excluding studies described:

- No

Details of literature search given:

- Yes – see search strategy above

Study selection described:

- Eight eligible trials, data for number of deaths due to cancer available for all trials, IPD data available for seven trials

Data extraction described:

- No

Study quality assessment described:

- No

Study flow shown:

- No

Study characteristics of individual studies given:

- Aspirin comparison
- Patients (*n*)
- Placebo-controlled/double-blind
- Recruitment period
- Year of completion of original trial
- Median (range) duration of scheduled treatment in trial (years)
- Mean (SD) age at randomisation
- % male
- Current smokers at randomisation
- Additional short summary of 3/7 trials with long-term follow-up

Quality of individual studies given:

- No

Results of individual studies shown:

- In forest plots only

SD, standard deviation.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Data analysis:

- (a) Random/fixed effect model: yes; (b) meta-regression; (c) cumulative meta-analysis; (d) L'Abbé plot; (e) funnel plot; (f) IPD analysis: yes
- Stratified analyses for cancers of the GI tract vs. other solid cancers vs. haematological cancers
- For the first 5 years after randomisation vs. thereafter
- For common specific cancers

Subgroup/sensitivity analysis:

- Risk of death due to solid cancers stratified by dose of aspirin and cancer histology
- Age
- Smokers (no data shown)

Statistical analysis appropriate:

- Yes
- Fixed-effects meta-analysis for risk of death to cancer and all-cause mortality
- Pooling of IPD following assessment of heterogeneity in effect of aspirin
- Very little heterogeneity between trials in the effect of allocation to aspirin (heterogeneity $p = 0.84$) on risk of death due to cancer
- Kaplan–Meyer curves and log-rank test and HRs to estimate cumulative effect of aspirin on risk of cancer death
- Analyses were by intention to treat on the basis of treatment allocation in the original trial

Results

Primary outcome:
death due to cancer
Primary efficacy end point: Total cancer mortality
Secondary efficacy end point: All-cause mortality, death by site of primary cancer
Primary safety end point: None

Total cancer deaths

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT or BDS	75	3429	47	1710
UK-TIA	21	1621	23	814
ETDRS	16	1856	14	1855
SAPAT	10	1009	19	1026
TPT	87	2545	104	2540
POPADAD	25	638	31	638
JPAD	15	1262	19	1277
AAA	78	1635	90	1675
Total	**327**	**14,035**	**347**	**11,535**

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Pooled OR: 0.79 (95% CI 0.68 to 0.92); $p_{sig} = 0.003$, $p_{het} = 0.84$
All-cause mortality

	Aspirin		Placebo	
Trials	No. of cases	No. of participants	No. of cases	No. of participants
BDT or BDS	270	3429	151	1710
UK-TIA	221	1621	122	814
ETDRS	340	1856	366	1855
SAPAT	82	1009	106	1026
TPT	216	2545	205	2540
POPADAD	94	638	101	638
JPAD	33	1262	38	1277
AAA	176	1635	186	1675
Total	**1432**	**14,035**	**1275**	**11,535**

Pooled OR: 0.92 (95% CI 0.85 to 1.00); $p = 0.047$
IPD (time to death) analyses:
Risk of death due to cancer during trial treatment (pooled analysis of 23,535 patients in seven trials)

Years to death	0	1	2	3	4	5	6	7	8	9
No. at risk: aspirin	13,026	12,849	12,371	11,919	10,964	9264	7385	3384	1676	977
No. at risk: control	10,509	10,351	10,026	9720	8881	7339	5933	3438	1671	969

HR 0.82 (95% CI 0.70 to 0.95); $p = 0.01$
Death due to cancer for IP data stratified by type of primary tumour and period of follow-up

		0–5 years' follow-up		≥ 5 years' follow-up	
Site of primary cancer	*n*	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
GI					
Oesophagus	23	0.78 (0.27 to 2.23)	0.64	0.43 (0.11 to 1.72)	0.230
Pancreas	45	0.88 (0.44 to 1.77)	0.73	0.25 (0.07 to 0.92)	0.040
Colorectal	54	0.78 (0.39 to 1.56)	0.48	0.41 (0.17 to 1.00)	0.050
Stomach	36	1.85 (0.81 to 4.23)	0.14	3.09 (0.64 to 14.91)	0.160
Other	24	0.67 (0.23 to 1.99)	0.47	0.20 (0.04 to 0.91)	0.040
All	182	0.96 (0.67 to 1.38)	0.81	0.46 (0.27 to 0.77)	0.003
Non-GI					
Lung	198	0.92 (0.65 to 1.30)	0.65	0.68 (0.42 to 1.10)	0.110
Prostate	37	0.70 (0.29 to 1.73)	0.44	0.52 (0.20 to 1.34)	0.170
Bladder and kidney	31	1.04 (0.44 to 2.47)	0.93	1.28 (0.36 to 4.54)	0.700
Other solid	93	0.86 (0.52 to 1.44)	0.57	1.01 (0.51 to 1.98)	0.980
All	359	0.90 (0.69 to 1.16)	0.41	0.76 (0.54 to 1.08)	0.120
Unknown primary	36	0.56 (0.28 to 1.15)	0.12	0.56 (0.09 to 3.38)	0.530
All solid cancers	577	0.88 (0.72 to 1.08)	0.22	0.64 (0.49 to 0.85)	0.002

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe					
Histological type					
Adenocarcinoma	247	0.86 (0.62 to 1.18)	0.34	0.53 (0.35 to 0.81)	0.003
Non-adenocarcinoma	224	0.89 (0.65 to 1.23)	0.48	0.79 (0.50 to 1.24)	0.300
Unknown	106	0.91 (0.58 to 1.44)	0.70	0.69 (0.34 to 1.43)	0.320
Haematological	50	0.82 (0.44 to 1.54)	0.53	0.34 (0.09 to 1.28)	0.110
All cancers	627	0.88 (0.72 to 1.06)	0.17	0.62 (0.47 to 0.82)	0.001
All cancers including ETDRS	657	0.86 (0.71 to 1.04)	0.11	0.66 (0.50 to 0.87)	0.003

Post-trial follow-up:
Risk of death due to any solid cancer stratified by duration of trial in trials with long-term follow-up: 1–4.9 years

Years to death	0	5	10	15	20
No. at risk: aspirin	1337	1151	942	732	347
No. at risk: control	820	733	622	497	199

HR 1.06 (95% CI 0.82 to 1.39); $p = 0.62$
Risk of death due to any solid cancer stratified by duration of trial in trials with long-term follow-up: 5–7.4 years

Years to death	0	5	10	15	20
No. at risk: aspirin	5426	5028	4528	3871	2274
No. at risk: control	3383	3135	2814	2390	1134

HR 0.79 (95% CI 0.70–0.90); $p = 0.0003$
Risk of death due to any solid cancer stratified by duration of trial in trials with long-term follow-up: ≥ 7.5 years

Years to death	0	5	10	15	20
No. at risk: aspirin	832	788	715	614	360
No. at risk: control	861	813	731	616	359

HR 0.69 (95% CI 0.54 to 0.88); $p = 0.003$
Risk of death due to cancer during and after trial periods in 10,502 patients with scheduled treatment of > 5 years

		0–10 years' follow-up		10–20 years' follow-up		0–20 years' follow-up	
Type of cancer	*n*	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Solid cancers							
GI							
Oesophagus	62	0.53 (0.24 to 1.18)	0.12	0.36 (0.18 to 0.71)	0.003	0.42 (0.25 to 0.71)	0.001
Pancreas	77	0.82 (0.41 to 1.67)	0.59	0.79 (0.44 to 1.42)	0.43	0.81 (0.51 to 1.26)	0.34
Colorectal	179	0.79 (0.49 to 1.26)	0.32	0.51 (0.35 to 0.74)	0.0005	0.60 (0.45 to 0.81)	0.0007
Stomach	71	1.36 (0.64 to 2.90)	0.43	0.42 (0.23 to 0.79)	0.007	0.69 (0.43 to 1.10)	0.11
Other	18	0.68 (0.14 to 3.36)	0.64	1.97 (0.53 to 7.27)	0.31	1.33 (0.50 to 3.54)	0.57
All	409	0.80 (0.59 to 1.08)	0.14	0.56 (0.44 to 0.72)	< 0.0001	0.65 (0.53 to 0.78)	< 0.0001

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Non-GI							
Lung	326	0.68 (0.50 to 0.92)	0.01	0.75 (0.55 to 1.02)	0.07	0.71 (0.58 to 0.89)	0.002
Prostate	210	0.83 (0.47 to 1.46)	0.52	0.80 (0.58 to 1.09)	0.15	0.81 (0.61 to 1.06)	0.12
Bladder and kidney	94	0.75 (0.41 to 1.37)	0.35	0.90 (0.52 to 1.57)	0.72	0.83 (0.55 to 1.25)	0.37
Other solid	128	0.68 (0.39 to 1.17)	0.16	1.28 (0.80 to 2.05)	0.31	0.98 (0.69 to 1.39)	0.91
All	757	0.71 (0.56 to 0.88)	0.002	0.85 (0.71 to 1.03)	0.10	0.79 (0.69 to 0.91)	0.001
Unknown primary	89	1.19 (0.58 to 2.42)	0.63	0.95 (0.56 to 1.61)	0.84	1.03 (0.67 to 1.57)	0.90
All solid cancers	1251	0.76 (0.63 to 0.90)	0.002	0.75 (0.65 to 0.87)	0.0001	0.75 (0.67 to 0.84)	< 0.0001
Histological type[a]							
Adenocarcinoma	648	0.70 (0.54 to 0.91)	0.008	0.64 (0.53 to 0.77)	< 0.0001	0.66 (0.56 to 0.77)	< 0.0001
Non-adenocarcinoma	302	1.04 (0.72 to 1.52)	0.83	0.74 (0.55 to 0.98)	0.04	0.87 (0.70 to 1.08)	0.21
Unknown	331	0.66 (0.49 to 0.90)	0.01	1.12 (0.83 to 1.52)	0.46	0.84 (0.67 to 1.05)	0.13
Haematological cancers	126	1.31 (0.69 to 2.50)	0.41	1.00 (0.65 to 1.54)	0.99	1.09 (0.76 to 1.56)	0.65
All cancers	1378	0.79 (0.66 to 0.93)	0.005	0.77 (0.67 to 0.89)	0.0002	0.78 (0.70 to 0.87)	< 0.0001

a Analysis confined to solid (non-haematological) cancers.

Risk of death due to GI cancer with increasing age:
Interaction: Relative effect $p = 0.44$; absolute effect $p = 0.96$
Risk of death due to non-GI cancer with increasing age: Relative effect $p = 0.056$; absolute effect, $p = 0.001$
Relative and absolute effects for smokers and non-smokers were similar (data not shown)
20-year risk of death by histological type:

- Small-cell lung cancer: HR 0.85 (95% CI 0.52 to 1.39), $p = 0.56$
- Squamous-cell lung cancer: HR 1.26 (95% CI 0.73 to 2.18), $p = 0.49$
- Adenocarcinoma of the lung: HR 0.55 (95% CI 0.33 to 0.94), $p = 0.04$
- Adenocarcinoma of the oesophagus: HR 0.36 (95% CI 0.21 to 0.63), $p = 0.0001$

The effect on adenocarcinomas was consistent across the three trials and for different doses
All-cause mortality after long-term follow-up in patients with scheduled treatment of ≥5 years:

- 15 years: HR 0.92 (95% CI 0.86 to 0.99), $p = 0.03$
- 20 years: HR 0.96 (95% CI 0.90 to 1.02), $p = 0.37$

Author's conclusion

Aspirin reduces deaths due to several cancers (mainly adenocarcinomas) shown by a reduction in deaths after 5 years of treatment, which is maintained over a 20-year period and increases with the duration of the treatment. This effect was consistent across trials with different trial populations and is therefore likely to be generalisable

Reviewer's conclusion

This review seems to provide good evidence of an effect of aspirin on cancer deaths mainly because the analyses were very thorough. However, it needs to be considered that the trials for the primary or secondary prevention of CVD might not have vigorously recorded cancer incidence/death as a primary outcome. Furthermore, the quality of the trials was not considered

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[49]

First author surname: Rothwell

Year of publication: 2012

Country: UK

Funding: None

Title: Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials

Aim of the study

To increase the reliability of estimates on the short-term effect of aspirin in the prevention of cancer, to establish the effect on cancer incidence and to establish the time course of effects on cancer incidence

Methods

Databases searched:

- PubMed and EMBASE
- Cochrane Collaboration databases

Identified trials from systematic reviews of RCTs of aspirin vs. control in the ATT collaboration

Last date of search: May 2011

Inclusion criteria:

- Random assignment to daily aspirin (any dose) vs. no aspirin in the absence of another platelet agent in either group
- Trials done on a background of anticoagulation were eligible
- Daily aspirin only

Exclusion of short-term trials ($\leq$ 90 days) and trials in the treatment or prevention of secondary cancer or colonic polyps

Participants: Not reported

Interventions: Daily aspirin (any dose)

Comparators: No aspirin

Outcome measures: Risk of non-vascular death, cancer incidence and *cancer mortality*

(a) Primary outcome of primary cancer prevention: Not reported
(b) Primary safety outcome: Major extracranial bleeds

Types of studies included: RCTs of aspirin for primary and secondary prevention of CVD

Methods of analysis:

- ORs of aspirin vs. control for each outcome were obtained pooled estimates were obtained by fixed-effects meta-analysis
- IPD analysis of cancer deaths stratified by years from randomisation, dose of aspirin and site of primary cancer
- IPD data pooled and Kaplan–Meier curves generated for time to diagnosis

Meta-analysis: Fixed-effects meta-analysis (Mantel–Haenszel–Peto method)

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Results

Adverse events:
Major extracranial bleeds: *0–2.9 years*

	Aspirin		Control				
Trial	Events	Participants	Events	Participants	OR	95% CI	*p*-value
AAA	14	1675	10	1675	1.40	0.62 to 3.17	
TPT	9	2545	3	2540	3.00	0.81 to 11.10	
POPADAD	3	638	2	638	1.50	0.25 to 9.02	
JPAD	2	1262	0	1277	21.28	NA	
HOT	108	9399	56	9391	1.94	1.40 to 2.68	
PPP	6	2226	2	2269	3.06	0.62 to 15.19	
Total	**142**	**17,745**	**73**	**17,790**	**1.95**	**1.47 to 2.59**	**< 0.0001**

NA, not applicable.

Major extracranial bleeds: ≥ 3 years

	Aspirin		Control				
Trial	Events	Participants	Events	Participants	OR	95% CI	*p*-value
AAA	21	1621	20	1636	1.06	0.57 to 1.96	
TPT	11	2500	10	2498	1.10	0.47 to 2.59	
POPADAD	7	600	7	608	1.01	0.35 to 2.91	
JPAD	2	1094	0	1117	21.48	NA	
HOT	19	9112	21	9131	0.91	0.49 to 1.69	
PPP	1	1728	1	1743	1.01	0.06 to 16.14	
Total	**61**	**16,655**	**59**	**16,733**	**1.04**	**0.73 to 1.49**	**0.9**

NA, not applicable.

Non-vascular death

	Aspirin		Control				
Trial	Events	Participants	Events	Participants	OR	95% CI	*p*-value
BDT	122	3429	72	1710	0.84	0.62 to 1.13	
TPT	115	2545	124	2540	0.92	0.71 to 1.20	
POPADAD	42	638	57	638	0.72	0.47 to 1.09	
HOT	151	9399	165	9391	0.91	0.73 to 1.14	
PPP	45	2226	47	2269	0.98	0.65 to 1.47	
JPAD	23	1262	25	1277	0.93	0.52 to 1.65	
AAA	1115	1675	130	1675	0.88	0.68 to 1.14	
5 small trials	10	843	18	839	0.55	0.25 to 1.19	
Total	**623**	**22,017**	**638**	**20,339**	**0.88**	**0.78 to 0.98**	**0.02**

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

All deaths due to cancers

	Aspirin		Control				
Trial	Events	Participants	Events	Participants	OR	95% CI	*p*-value
BDT	75	3429	47	1710	0.79	0.55 to 1.14	
UK-TIA	24	1621	25	814	0.47	0.27 to 0.84	
ETDRS	16	1856	14	1855	1.14	0.56 to 2.35	
EAFT	10	404	12	378	0.77	0.33 to 1.81	
SALT	12	676	16	684	0.75	0.35 to 1.61	
ESPS-2	19	1649	24	1649	0.79	0.43 to 1.45	
SAPAT	10	1009	19	1026	0.53	0.25 to 1.15	
TPT	90	2545	106	2540	0.84	0.63 to 1.12	
PPP	31	2226	29	2269	1.09	0.66 to 1.82	
HOT	108	9399	105	9391	1.03	0.78 to 1.35	
JPAD	15	1262	19	1277	0.80	0.40 to 1.57	
POPADAD	25	638	31	638	0.80	0.47 to 1.37	
AAA	78	1675	90	1675	0.86	0.63 to 1.17	
21 small trials (cancer deaths)	49	7643	55	7286	0.85	0.58 to 1.25	
17 small trials (non-vascular deaths)	52	4237	60	4088	0.83	0.57 to 1.21	
Subtotal	**614**	**40,269**	**652**	**37,280**	**0.85**	**0.76 to 0.95**	**0.005**

EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study.

Deaths due to cancers excluding deaths due to cancers diagnosed prior to randomisation

	Aspirin		Control				
Trial	Events	Participants	Events	Participants	OR	95% CI	*p*-value
BDT	68	3429	44	1710	0.77	0.52 to 1.12	
UK-TIA	21	1621	23	814	0.45	0.25 to 0.82	
ETDRS	16	1856	14	1855	1.14	0.56 to 2.35	
EAFT	10	404	12	378	0.77	0.33 to 1.81	
SALT	12	676	16	684	0.75	0.35 to 1.61	
ESPS-2	19	1649	24	1649	0.79	0.43 to 1.45	
SAPAT	10	1009	19	1026	0.53	0.25 to 1.15	
TPT	87	2545	104	2540	0.83	0.62 to 1.11	
PPP	31	2226	29	2269	1.09	0.66 to 1.82	
HOT	108	9399	105	9391	1.03	0.78 to 1.35	
JPAD	15	1262	19	1277	0.80	0.40 to 1.57	
POPADAD	25	638	31	638	0.80	0.47 to 1.37	
AAA	71	1675	89	1675	0.79	0.57 to 1.09	
21 small trials (cancer deaths)	49	7643	55	7286	0.85	0.58 to 1.25	
17 small trials (non-vascular deaths)	52	4237	60	4088	0.83	0.57 to 1.21	
Subtotal	**594**	**40,269**	**644**	**644**	**0.84**	**0.75 to 0.94**	**0.002**

EAFT, European Atrial Fibrillation Trial; ESPS, European Stroke Prevention Study.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Cancer incidence: *0–2.9 years*

	Aspirin		Control				
Trial	Events	Participants	Events	Participants	OR	95% CI	*p*-value
AAA	50	1675	49	1675	1.02	0.68 to 1.52	
TPT	72	2545	78	2540	0.92	0.66 to 1.27	
POPADAD	23	638	23	638	1.00	0.56 to 1.80	
JPAD	12	1262	12	1277	1.01	0.45 to 2.26	
HOT	219	9399	225	9391	0.97	0.81 to 1.17	
PPP	69	2226	55	2269	1.29	0.90 to 1.84	
Total	**445**	**17,745**	**442**	**17790**	**1.01**	**0.88 to 1.15**	**0.92**

Cancer incidence: ≥ 3 years

	Aspirin		Control				
Trial	Events	Participants	Events	Participants	OR	95% CI	*p*-value
AAA	116	1593	145	1599	0.79	0.61 to 1.02	
TPT	84	2431	112	2433	0.74	0.56 to 0.99	
POPADAD	22	592	37	593	0.58	0.34 to 1.00	
JPAD	3	1095	7	1117	0.44	0.11 to 1.69	
HOT	75	9063	86	9029	0.87	0.64 to 1.18	
PPP	24	1689	34	1713	0.71	0.42 to 1.21	
Total	**324**	**16,463**	**421**	**16,484**	**0.76**	**0.66 to 0.88**	**0.0003**

Author's conclusion

Short-term aspirin reduces cancer incidence and mortality, while extended use decreases risk of major bleeding

Reviewer's conclusion

A thorough analysis of the short term effect of aspirin on cancer incidence and mortality. However, the analysis groups smaller trials together and considers only the six large trials in the analysis of major bleeding. A formal quality appraisal was not carried out

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[31]

First author surname: Rothwell

Year of publication: 2010

Country: UK

Funding: None

Title: Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials

Aim of the study

To establish the effects of aspirin on incidence and mortality due to CRC in relation to dose of aspirin and duration of trial

Methods

Databases searched: Not reported

Last date of search: Not reported

Inclusion criteria:

- Trials of aspirin vs. control in the UK or Sweden in the 1980s and early 1990s
- Minimum of 1000 participants
- Median scheduled treatment period of 2.5 years

Participants: Not reported

Interventions: Aspirin any dose

Comparators: No aspirin

Outcome measures: Death due to CRC and incidence of CRC

(a) Primary outcome of primary cancer prevention: Not reported
(b) Primary safety outcome: None

Types of studies included: RCTs of aspirin for primary and secondary prevention of CVD

Methods of analysis:
Meta-analysis of ORs of deaths due to CRC and incidence of CRC by trial and aspirin dose

- Analysis of pooled IPD:
- Kaplan–Meier analysis for survival curves
- Log-rank tests for assessment of significance
- Cox regression to establish HRs for incidence of CRC and risk of death
- Analysis stratified by high dose/low dose of aspirin, duration of treatment and by site of cancer

Meta-analysis: Fixed-effects meta-analysis (Peto method)

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Results

Adverse events: Not reported
Death due to CRC

	Aspirin		Control			
Dose/trial	**Cancer death**	**No cancer death**	**Cancer death**	**No cancer death**	**OR**	**95% CI**
500–1200 mg daily						
BDT (500 mg)	59	3429	40	1710	0.73	0.49 to 1.10
UK-TIA (1200 mg)	11	821	16	817	0.68	0.31 to 1.47
Subtotal	**70**	**4250**	**56**	**2527**	**0.72**	**0.50 to 1.03**
75–300 mg daily						
UK-TIA (300 mg)	8	811	16	817	0.50	0.21 to 1.17
TPT (75 mg)	34	2545	55	2540	0.61	0.40 to 0.94
SALT (75 mg)	7	676	10	684	0.71	0.27 to 1.86
Subtotal	**49**	**4032**	**81**	**4041**	**0.60**	**0.42 to 0.86**
Total	**119**	**8282**	**121**	**5751**	**0.66**	**0.51 to 0.85**

OR 0.66 (95% CI 0.51 to 0.85); $p = 0.002$
Results HR (95% CI)
Low-dose aspirin:

- Death due to CRC: 0.75 (0.56 to 0.97) $p = 0.02$
- Incidence of CRC: 0.61 (0.43 to 0.87) $p = 0.005$

Site of cancer and duration of treatment:

- Proximal colon: 0.45 (0.28 to 0.74); $p = 0.001$ treatment ≥5 years: 0.35 (0.20 to 0.63); $p = 0.0001$
- Distal colon: 1.10 (0.73 to 1.64); $p = 0.66$ treatment ≥5 years: 1.14 (0.69 to 1.86); $p = 0.61$

Author's conclusion

Aspirin at doses of at least 75 mg daily reduced long-term incidence and mortality due to CRC. Reduction in risk was greater for proximal than distal colon

Reviewer's conclusion

A thorough analysis providing good evidence on the effect of aspirin on the incidence and mortality due to CRC. However, no search strategy and quality assessment were reported. The methodology is short and lacks detail. Daily aspirin compared with alternate-day aspirin. Aspirin may reduce the development of tumours by inhibition of COX-2. CVD events are probably affected by irreversible inhibition of COX-1 on platelets. COX-2 needs higher doses and might not be irreversibly inhibited, providing a potential reason why alternate and low-dose aspirin for the prevention of cancer might not be effective (see Rothwell 2010 and other Rothwell reviews). Low-dose aspirin for cancer seems to involve 75–325 mg aspirin. Dutch-TIA showed that 30 mg daily dose of aspirin is no less effective than 283 mg for prevention of CVD. Dutch-TIA (included in Rothwell 2010) reports adverse events

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[62]

First author surname: Rothwell

Year of publication: 2012

Country: UK

Funding: None

Title: Effect of daily aspirin on risk of cancer metastasis – a study of incident cancers during randomised controlled trials

Aim of the study

To study metastasis at initial diagnosis and during subsequent follow-up in all participants with a new diagnosis of cancer

Methods

Databases searched: Refers to Rothwell 2011 and 2012

Last date of search: Not reported

Inclusion criteria:

- Randomised trials of aspirin (any dose) vs. no aspirin in the presence or absence of another anti-platelet agent or antithrombotic agent, if the other agent was used in the same way in both groups in prevention of vascular deaths
- Trials done in UK (availability of death certification and cancer registration)
- Exclusion of trials with < 10 incident cancers recorded during follow-up, trials of short-term (≤ 90 days) treatment and trials in the treatment or prevention of secondary cancer or colonic polyps

Participants: Not reported

Interventions: Daily aspirin (any dose)

Comparators: No aspirin

Outcome measures: Incidence and mortality due to cancer

(a) Primary outcome of primary prevention: Not reported
(b) Primary safety outcome: Not reported

Types of studies included: RCTs of aspirin for primary and secondary prevention of CVD

Methods of analysis:

Meta-analysis: Fixed-effects meta-analysis

Results

Adverse events: Not reported
Cancer incidence

	Aspirin		Control			
Trial	Cancer	No cancer	Cancer	No cancer	OR	95% CI
BDT	137	3429	62	1710	1.11	0.81 to 1.50
UK-TIA	51	1621	31	814	0.82	0.52 to 1.29
TPT	154	2545	188	2540	0.81	0.65 to 1.00
POPADAD	45	638	60	638	0.73	0.49 to 1.09
AAA	178	1675	195	1675	0.90	0.73 to 1.12
Subtotal	**565**	**9908**	**536**	**7377**	**0.88**	**0.78 to 0.99**

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Cancer mortality

	Aspirin		Control			
Trial	Cancer death	No cancer death	Cancer death	No cancer death	OR	95% CI
BDT	68	3429	44	1710	0.77	0.52 to 1.12
UK-TIA	21	1621	23	814	0.45	0.25 to 0.82
TPT	87	2545	104	2540	0.83	0.62 to 1.11
POPADAD	25	638	31	638	0.80	0.47 to 1.37
AAA	71	1675	89	1675	0.79	0.57 to 1.09
Subtotal	**272**	**9908**	**291**	**7377**	**0.77**	**0.65 to 0.91**

Author's conclusion

The reduction in cancer death in trials of daily aspirin might be due to the effect of aspirin on the prevention of distant metastasis

Reviewer's conclusion

A thorough analysis of the prevention of metastasis of trial incident cancers providing good evidence on the effect of aspirin on the incidence and mortality due to cancer. However, no quality assessment was reported and the methodology is short and lacks detail

D. Systematic reviews on the prophylactic use of aspirin in the primary prevention of cardiovascular disease in patients with diabetes

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[63]

First author surname: Butalia

Year of publication: 2011

Country: Canada

Funding: Funders had no role in the design, data collection, analysis, decision to publish or preparation of the manuscript

Title: Aspirin effect on the incidence of major adverse cardiovascular events in patients with diabetes mellitus: a systematic review and meta-analysis

Aim of the study

To quantify treatment effects in absolute terms of the risk–benefit trade-off of aspirin therapy in patients with diabetes

Methods

Databases searched: MEDLINE, PubMed, EMBASE, The Cochrane Library and BIOSIS

Last date of search: February 2011

Inclusion criteria:

- RCTs of aspirin vs. placebo or vitamins

Adults ≥ 18 years with diabetes without previous historical or clinical evidence of CVD

Participants: Adults ≥ 18 years with diabetes without previous historical or clinical evidence of CVD

Interventions: Aspirin

Comparators: Placebo or vitamins

Outcome measures:

(a) Primary outcome MACE (composite of non-fatal MI, non-fatal ischaemic stroke, CV death due to MI and ischaemic stroke) and all-cause mortality
(b) Secondary outcome Total MI, total stroke, CV death
(c) Primary safety outcome Haemorrhage, GI bleeding and other GI events

Types of studies included: RCTs

Methods of analysis: Risk ratios and 95% CI and absolute risk reduction, NNT for all outcomes
Likelihood of being helped vs. harmed
Meta-regression analysis using maximum likelihood estimation
Assessment of publication bias for main outcome using Egger's linear regression test

Meta-analysis: Fixed-effects model (Mantel–Haenszel) for primary outcome. Random-effects model (DerSimonian and Laird) for other outcomes

MACE, major adverse cardiovascular event.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Results

Adverse events

Study and year	Total patients with diabetes	All bleeding (ASA)	All bleeding (control)	All GI bleeding (ASA)	All GI bleeding (control)	Non-bleeding GI symptoms (ASA)	Non-bleeding GI symptoms (control)
PHS, 1989	533						
ETDRS, 1992	3711	37	37				
HOT, 1998	1501						
PPP, 2003	1031	10	1	8	1		
WHS, 2005	1027						
POPADAD, 2008	1276	–	–	28	31	73	94
JPAD, 2008	2539	34	10	12	4	47	4
No. of events/ no. of participants		81/3637	48/3644	48/2419	36/2427	120/1900	98/1915
Pooled RR (95% CI)	**–**	**2.5**	**(0.77 to 8.10)**	**2.13**	**(0.63 to 7.25)**	**2.92**	**(0.17 to 50.23)**

MACE

	Aspirin		Control			
Trial	Events	Participants	Events	Participants	RR	95% CI
JPAD	40	1262	46	1277	0.88	0.58 to 1.33
POPADAD	127	638	132	638	0.96	0.77 to 1.20
WHS	51	538	55	489	0.84	0.59 to 1.21
PPP	14	519	20	512	0.69	0.35 to 1.35
ETDRS	333	1856	361	1855	0.92	0.81 to 1.05
HOT	47	752	54	749	0.87	0.59 to 1.26
Total	**612**	**5565**	**668**	**5520**	**0.91**	**0.82 to 1.00**

All-cause mortality

	Aspirin		Control			
Trial	Events	Participants	Events	Participants	RR	95% CI
JPAD	34	1262	38	1277	0.91	0.57 to 1.43
POPADAD	94	638	101	638	0.93	0.72 to 1.21
PPP	25	519	20	512	1.23	0.69 to 2.19
ETDRS	340	1856	2661	1855	0.93	0.81 to 1.06
HOT	40	752	36	749	1.11	0.71 to 1.72
Total	**533**	**5027**	**561**	**5031**	**0.95**	**0.85 to 1.06**

ASA, acetylsalicylic acid; MACE, major adverse cardiovascular event.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Author's conclusion

There is an indication that aspirin reduces MACE in patients with diabetes but with a trend towards higher rates of bleeding and GI complications. Diabetes patients lie somewhere between primary and secondary prevention on the spectrum of risk and benefit

Reviewer's conclusion

This is a thorough analysis of the data for diabetes patients without prior CVD event. The quality assessment concluded that all trials were of reasonably high quality, with the PPP and JPAD scoring the lowest. Adverse events were reported inconsistently in trials and the analysis based on relatively small numbers

MACE, major adverse cardiovascular event.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[64]

First author surname: Calvin

Year of publication: 2009

Country: USA

Funding: No potential conflicts of interest were reported relevant to this article

Title: Aspirin for the primary prevention of cardiovascular events – a systematic review and meta-analysis comparing patients with and without diabetes

Aim of the study

To determine whether the effect of aspirin in the primary prevention of cardiovascular events differs between patients with and without diabetes

Methods

Databases searched: MEDLINE, PubMed, EMBASE, The Cochrane Library, Web of Science and Scopus

Last date of search: November 2008

Inclusion criteria: See below

Participants: Patients with diabetes without previous historical evidence of MI or stroke

Interventions: Aspirin

Comparators: Placebo

Outcome measures:

(a) Primary outcome: Ischaemic stroke, MI and all-cause mortality
(b) Primary safety outcome: Not reported

Types of studies included: RCTs

Methods of analysis:

- RRs and 95% CI for all outcomes
- Ratio of RRs and its 95% CI using the method of Altman and Bland to determine the difference in aspirin effect in patients with and without diabetes
- Bayesian random effects logistic regression with aspirin use and diabetes status

Meta-analysis: Random-effects model of RRs

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Results

Adverse events: Not reported

Mortality

		Aspirin		Control				
Diabetes/no diabetes	Trial	Events	Participants	Events	Participants	Risk ratio	95% CI	*p*-value
Diabetes	HOT	11	752	18	749	0.61	0.29 to 1.28	0.19
	JPAD	12	1262	14	1277	0.87	0.40 to 1.87	0.72
	PHS	11	275	26	258	0.40	0.20 to 0.79	0.01
	POPADAD	90	638	82	638	1.10	0.83 to 1.45	0.51
	PPP	5	519	10	512	0.49	0.17 to 1.43	0.19
	WHS	36	538	24	499	1.39	0.84 to 2.30	0.20
	Subtotal					0.81	0.55 to 0.94	0.29
No diabetes	HOT	71	8647	109	8642	0.65	0.48 to 0.88	0.00
	PHS	128	10,750	213	10,763	0.60	0.48 to 0.75	0.00
	PPP	15	1849	22	1904	0.70	0.37 to 1.35	0.29
	WHS	162	19,396	169	19,443	0.96	0.78 to 1.19	0.72
	Subtotal					0.72	0.55 to 0.94	0.02
	Total					**0.75**	**0.60 to 0.93**	**0.01**

MI

		Aspirin		Control				
Diabetes/no diabetes	Trial	Events	Participants	Events	Participants	Risk ratio	95% CI	*p*-value
Diabetes	JPAD	22	1262	25	1277	0.89	0.50 to 1.57	0.69
	WHS	1	538	29	499	0.42	0.22 to 0.79	0.01
	Subtotal					0.62	0.29 to 1.30	0.21
No diabetes	APLASA	1	44	0	48	3.27	0.14 to 78.15	0.46
	WHS	157	19,396	192	19,443	0.82	0.66 to 1.01	0.06
	Subtotal					0.89	0.41 to 1.94	0.07
	Total					**0.73**	**0.43 to 1.22**	**0.04**

APLASA, antiphospholipid antibody acetylsalicylic acid.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Ischaemic stroke

		Aspirin		Control				
Diabetes/no diabetes	Trial	Events	Participants	Events	Participants	Risk ratio	95% CI	*p*-value
Diabetes	HOT	40	752	36	749	1.11	0.71 to 1.72	0.65
	JPAD	34	1262	38	1277	0.91	0.57 to 1.43	0.67
	POPADAD	116	638	117	638	0.99	0.79 to 1.25	0.94
	PPP	25	519	20	512	1.23	0.69 to 2.19	0.48
	Subtotal					1.02	0.85 to 1.21	0.86
No diabetes	APLASA	1	44	1	48	1.09	0.07 to 16.92	0.95
	HOT	244	8647	269	8642	0.91	0.76 to 1.08	0.26
	PPP	42	1849	61	1904	0.71	0.48 to 1.04	0.08
	Subtotal					0.87	0.75 to 1.02	0.08
	Total					**0.93**	**0.83 to 1.05**	**0.24**

Author's conclusion

Benefits of aspirin for patients with diabetes remain imprecise. The relative benefit of aspirin in patients with and without diabetes is similar

Reviewer's conclusion

Inclusion of APLASA trial (a small trial) does not result in the formulation of any new conclusions. Although the rest of the trials are reasonably big, the proportion of diabetes patients is relatively small. Possibility of publication bias cannot be adequately assessed and corrected because of the small number of RCTs. Adverse events were not investigated because these events are usually rare in the small population of diabetes patients and would lead to imprecise results

APLASA, antiphospholipid antibody acetylsalicylic acid.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[65]

First author surname: De Berardis

Year of publication: 2009

Country: Italy

Funding: None

Title: Aspirin for primary prevention of cardiovascular events in people with diabetes – meta-analysis of randomised controlled trials

Aim of the study

To evaluate the benefits and harms of low-dose aspirin in people with diabetes and no CVD

Methods

Databases searched: MEDLINE and CENTRAL

Last date of search: November 2008

Inclusion criteria: Trials with > 500 participants

Participants: Patients with diabetes mellitus and no CVD

Interventions: Aspirin

Comparators: Placebo or no treatment

Outcome measures:

(a) Primary outcome: MCE
(b) Secondary outcome: All-cause mortality, death from CV causes, non-fatal MI and non-fatal stroke
(c) Primary safety outcome: any bleeding, GI bleeding, GI symptoms, incidence of cancer

Types of studies included: RCTs

Methods of analysis:

- Comparison of treatment using RRs (95% CI)
- Estimation of overall RR by random effects meta-analysis
- Subgroup analysis to investigate potential sources of heterogeneity

Meta-analysis: Random-effects meta-analysis

Results

Adverse events:

Side effect	No. of trials reporting	No. of patients	RR (95% CI)
Any bleeding	3	7281	2.50 (0.76 to 8.21)
GI bleeding	3	4846	2.11 (0.64 to 6.95)
GI symptoms	2	3815	5.09 (0.08 to 314.39)
Cancer	2	2307	0.84 (0.62 to 1.14)

MCEs:

	Aspirin		Control or placebo			
Trial	Events	Participants	Events	Participants	RR	95% CI
JPAD	68	1262	86	1277	0.80	(0.59 to 1.09)
POPADAD	105	638	108	638	0.97	(0.76 to 1.24)
WHS	58	514	62	513	0.90	(0.63 to 1.29)
PPP	20	519	22	512	0.90	(0.50 to 1.62)
ETDRS	350	1856	379/	1855	0.90	(0.78 to 1.04)
Total	**601**	**4789**	**657**	**4795**	**0.90**	**(0.81 to 1.00)**

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

	Aspirin		Control or placebo			
Trial	Events	Participants	Events	Participants	RR	95% CI
JPAD	28	1262	14	1277	0.87	(0.40 to 1.87)
POPADAD	90	638	82	638	1.10	(0.83 to 1.45)
WHS	36	514	24	513	1.48	(0.88 to 2.49)
PPP	5	519	10	512	0.49	(0.17 to 1.43)
ETDRS	241	1856	283	1855	0.82	(0.69 to 0.98)
PHS	11	275	26	258	0.40	(0.20 to 0.79)
Total	**395**	**5064**	**439**	**5053**	**0.86**	**(0.61 to 1.21)**

Stroke:

	Aspirin		Control or placebo			
Trial	Events	Participants	Events	Participants	RR	95% CI
JPAD	12	12	32	1277	0.89	(0.54 to 1.46)
POPADAD	37	37	50	638	0.74	(0.49 to 1.12)
WHS	15	15	31	513	0.46	(0.25 to 0.85)
PPP	9	9	10	512	0.89	(0.36 to 2.17)
ETDRS	92	92	78	1855	1.17	(0.87 to 1.58)
Total	**181**	**4789**	**201**	**4795**	**0.83**	**(0.60 to 1.14)**

Death from CV causes:

	Aspirin		Control or placebo			
Trial	Events	Participants	Events	Participants	RR	95% CI
JPAD	1	1262	10	1277	0.10	(0.01 to 0.79)
POPADAD	43	638	35	638	1.23	(0.80 to 1.89)
PPP	10	519	8	512	1.23	(0.49 to 3.10)
ETDRS	244	1856	275	1855	0.87	(0.73 to 1.04)
Total	**298**	**4275**	**328**	**4282**	**0.94**	**(0.72 to 1.23)**

All-cause mortality:

	Aspirin		Control or placebo			
Trial	Events	Participants	Events	Participants	RR	95% CI
JPAD	34	1262	38	1277	0.90	(0.57 to 1.14)
POPADAD	94	638	101	638	0.93	(0.72 to 1.21)
PPP	25	519	20	512	1.23	(0.69 to 2.19)
ETDRS	340	1856	366	1855	0.91	(0.78 to 1.06)
Total	**493**	**4275**	**525**	**4282**	**0.93**	**(0.82 to 1.05)**

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Author's conclusion

A clear benefit of aspirin in people with diabetes remains unproven. An important effect modifier may be sex. Adverse events need be explored further

Reviewer's conclusion

A critical and thorough analysis with results that appear to be consistent with other meta-analyses. Authors have concerns about quality of papers in terms of concealment of randomisation and the fact that some trials were relatively outdated in terms of management of CV risk factors in diabetic patients. Decision on the use of aspirin should be taken on an individual basis and should include weighing up benefits and harm as no subgroup could be identified for which aspirin is clearly beneficial. Results seem to indicate that benefits may not exceed risks of major bleeding, particularly in patients at low risk of CV events and in people of > 70 years who are at high risk of bleeding

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[66]

First author surname: Simpson

Year of publication: 2011

Country: Canada

Funding: No conflict of interest disclosed
Canadian Institutes of Health Research

Title: Effect of aspirin dose on mortality and cardiovascular events in people with diabetes – a meta-analysis

Aim of the study

To explore the relationship between aspirin dose and prevention of cardiovascular events

Methods

Databases searched: MEDLINE, EMBASE, The Cochrane Library, Web of Science, International Pharmaceutical Abstracts and Scopus

Last date of search: February 2010

Inclusion criteria: See below

Participants: Patients with diabetes with or without prior CV event

Interventions: Aspirin with dose specified

Comparators: Placebo

Outcome measures:

(a) Primary outcome: All-cause mortality
(b) Secondary outcome: CV-related mortality, MI, stroke
(c) Primary safety outcome: Not reported

Types of studies included: RCTs, cohort studies, meta-analyses

Methods of analysis:

- Pooling of risk ratios (95% CI) using random-effects meta-analysis

Studies grouped by daily aspirin dose
Stratified according to primary/secondary prevention and RCT/observational study

Meta-analysis: Random-effects model

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Results

Adverse events: Not reported
All-cause mortality: ≤ 100 mg

	Aspirin		Control			
Trial	Events	Participants	Events	Participants	Risk ratio	95% CI
HOT	40	752	36	749	1.11	0.71 to 1.72
JPAD	34	1262	38	1277	0.91	0.57 to 1.43
PPP (2003 subgroup)	25	519	20	512	1.23	0.69 to 2.19
POPADAD	94	638	101	638	0.93	0.72 to 1.21
AAA	10	45	13	43	0.74	0.36 to 1.50

Author's conclusion

An aspirin dose response effect is not supported for the prevention of CV events in diabetic patients. There is a gap in evidence from RCTs for using 101–325 mg of aspirin daily in diabetes

Reviewer's conclusion

Because of this evidence gap in the form of higher-dose RCTs this conclusion does not hold when looking at evidence from RCTs of the primary prevention of CVD in diabetic patients only. All-cause mortality was chosen as primary outcome because it provides a balanced assessment of overall safety and effectiveness for any treatment option and it provides a homogenous outcome across decades and countries of publication. Included PHS and WHS, even although they report on daily aspirin. Dose effect cannot be concluded from RCT trials of aspirin for primary prevention, as all 5fiv trials included in the analysis of all-cause mortality fall in the ≤ 100-mg category

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[67]

First author surname: Stavrakis

Year of publication: 2011

Country: USA

Funding: Not reported

Title: Low-dose aspirin for primary prevention of cardiovascular events in patients with diabetes – a meta-analysis

Aim of the study

To undertake a meta-analysis of published trials to evaluate the effect of low-dose aspirin for the primary prevention of cardiovascular event in patients with diabetes mellitus

Methods

Databases searched: MEDLINE and EMBASE

Last date of search: November 2009

Inclusion criteria: See below

Participants: Patients with diabetes and no history of CV events

Interventions: low-dose aspirin

Comparators: Placebo or no treatment

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Outcome measures:

(a) Primary outcome: Total mortality, CV mortality (deaths from MI or stroke), major adverse CV events (death from CV causes, non-fatal MI, non-fatal stroke)
(b) Secondary outcome: MI (fatal and non-fatal), stroke (fatal and non-fatal)
(c) Primary safety outcome: Major bleeding events including GI bleeding

Types of studies included: RCTs

Methods of analysis:
Rates of events per 1000 person-years were estimated for each outcome
Log HR was pooled using inverse variance method. Fixed-effects model and random effects model used; random-effects model (DerSimonian and Laird) reported due to identified heterogeneity. Number of events or number of subjects experiencing an adverse event was reported. Pooled RRs of each study was calculated using Mantel–Haenszel fixed-effects model and a random-effects model (DerSimonian and Laird)

Meta-analysis: Random- and fixed-effect models

Results

Adverse events:
Major bleeding:

Trial	RR	95% CI
PPP	9.87	1.27 to 76.78
JPAD	1.45	0.55 to 3.79
Total	**3.02**	**0.48 to 18.86**

GI bleeding:

Trial	RR	95% CI
PPP	7.89	0.99 to 62.87
JPAD	3.04	0.98 to 9.39
POPADAD	0.90	0.55 to 1.49
Total	**2.12**	**0.63 to 7.08**

All-cause mortality:

Trial	HR	95% CI
HOT	1.12	0.72 to 1.76
PPP	1.23	0.69 to 2.19
JPAD	0.90	0.57 to 1.14
POPADAD	0.93	0.71 to 1.24
Total	**0.99**	**0.82 to 1.24**

CV death:

Trial	HR	95% CI
HOT	0.89	0.51 to 1.57
PPP	1.23	0.49 to 3.10
JPAD	0.10	0.01 to 0.79
POPADAD	1.23	0.79 to 1.93
Total	**0.99**	**0.79 to 1.93**

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

MCE:

Trial	HR	95% CI
PPP	0.90	0.50 to 1.62
HOT	0.87	0.59 to 1.28
WHS	0.90	0.63 to 1.29
Total	**0.89**	**0.70 to 1.13**

Author's conclusion

Effect of low-dose aspirin for primary prevention of CVD in diabetes patients remains unproven and its routine use cannot be justified at present

Reviewer's conclusion

The results of the meta-analysis are consistent with other analyses. Only a small number of trials were included in each analysis. JPAD included retinal haemorrhage in major bleeding. Fixed and random effect models results for major bleeding did not agree therefore the results should be interpreted with caution

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[68]

First author surname: Younis

Year of publication: 2010

Country: UK

Funding: No conflict of interest stated and no payment received for preparation of the manuscript

Title: Role of aspirin in the primary prevention of cardiovascular disease in diabetes mellitus – a meta-analysis

Aim of the study

To evaluate the benefits of aspirin in people with diabetes mellitus for the primary prevention of CVD

Methods

Databases searched: MEDLINE and the Cochrane database

Last date of search: December 2009

Inclusion criteria:

Participants: Diabetic patients

Interventions: Aspirin as a primary prevention of CVD

Comparators: Placebo or no aspirin

Outcome measures:

(a) Primary outcome: MCE (composite of CV death, non-fatal MI and stroke), total mortality
(b) Secondary outcome: MI, Ischaemic stroke
(c) Primary safety outcome: bleeding

Types of studies included: RCTs

Methods of analysis: RR and 95% CI were calculated using the Mantel–Haenszel method

Meta-analysis: Fixed-effects model (Mantel–Haenszel) and random-effects model

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Results

Adverse events:
Risk of bleeding: RR 0.90 (5% CI 0.53 to 1.51); $p = 0.17$
MCEs:

	Aspirin		Control			
Trial	Events	Participants	Events	Participants	RR	95% CI
PHS						
HOT (2001)					0.87	0.60 to 1.27
PPP (2003)					0.90	0.50 to 1.62
WHS					0.93	0.67 to 1.30
JPAD					0.80	0.59 to 1.24
POPADAD					0.97	0.76 to 1.24
Total	**298**	**3685**	**332**	**3689**	**0.90**	**0.78 to 1.05; $p = 0.17$**

MI:

	Aspirin		Control			
Trial	Events	Participants	Events	Participants	RR	95% CI
PHS					0.40	0.20 to 0.79
HOT					0.61	0.29 to 1.28
PPP					0.49	0.17 to 1.43
WHS					1.50	0.90 to 2.47
JPAD					0.87	0.40 to 1.87
POPADAD					1.10	0.83 to 1.45
Total	**165**	**3960**	**174**	**3947**	**0.95**	**0.76 to 1.18; $p = 0.63$**

Ischaemic stroke

	Aspirin		Control			
Trial	Events	Participants	Events	Participants	RR	95% CI
PHS						
HOT					0.91	0.50 to 1.64
PPP					0.89	0.36 to 2.17
WHS					0.42	0.22 to 0.82
JPAD						
POPADAD						
Total	**64**	**3047**	**93**	**3038**	**0.75**	**0.55 to 1.02; $p = 0.07$**

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

All-cause mortality

	Aspirin		Control			
Trial	Events	Participants	Events	Participants	RR	95% CI
PHS						
HOT						
PPP					1.23	0.69 to 2.19
WHS						
JPAD					0.91	0.57 to 1.43
POPADAD					0.93	0.72 to 1.21
Total	**153**	**2419**	**159**	**2427**	**0.96**	**0.78 to 1.18; $p = 0.71$**

Author's conclusion

The results do not support the wide-spread use of aspirin for the primary prevention of CVD in diabetes patients

Reviewer's conclusion

The results are consistent with other meta-analyses. No formal quality assessment of trials was reported. The overall number of bleeding events reported in DM patients was small and too imprecise to make any valid conclusions. Evidence about harm is better obtained from larger trials that included patients without diabetes. The lack of significance probably represents a lack of power, as three of the trials were subgroup analyses from lager patient population studies, three of the trials had under-recruited participants and two reported significantly low annual CV event rates at < 2%, rendering the precision of these trials inadequate. WHS, PHS and PPP are old trials with higher event rates. More current trials have lower event rates very likely due to greater usage of statin therapy. Includes summary of guidelines for primary prevention of CVD in patients with diabetes mellitus. Aspirin-resistance and Non-compliance are factors that can influence the effect of aspirin in the prevention of CVD events. Large adequately powered trials are needed. Studies are needed on the mechanisms of aspirin resistance in DM patients, optimal dose and frequency of aspirin. Subgroup analyses of elderly people, women and patients with poor glycaemic control need to be carried out

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[69]

First author surname: Zhang

Year of publication: 2010

Country: China

Funding: This study was funded by National Basic Research Program of China (2006CB503803 and 2005CB523302), 863 Program of Science and Technology Ministry (2006AA0ZA406), Outstanding Youth Grant from National Natural Science Foundation of China (30725036), and Key Projects in the National Science & Technology Pillar Program in the Eleventh Five-year Plan Period (2006BAI01A04)

Title: Aspirin for primary prevention of CV events in patients with diabetes – a meta-analysis

Aim of the study

To determine the effect of aspirin therapy in the prevention of cardiovascular events in patients with diabetes

Methods

Databases searched:

- MEDLINE, EMBASE and CENTRAL, without language restriction, between 1950 and June 2009
- The bibliographies of retrieved articles and previous meta-analysis were searched for other relevant studies

Last date of search: June 2009

Inclusion criteria:
Prospective RCTs
Participants with diabetes mellitus
Assignment of participants to aspirin therapy or control group for primary prevention of CV events
Follow-up duration at least 12 months; (5) any of the data about MCEs (a composite of CV mortality, non-fatal MI or non-fatal stroke), MI, stroke, all-cause mortality, CV mortality or major bleeding

Participants: Participants with diabetes mellitus

Interventions: Aspirin

Comparators: Placebo

Outcome measures: The efficacy outcomes were MCEs, all-cause mortality, CV mortality, MI, and stroke

(a) Primary outcome: Not defined
(b) Secondary outcome: Not defined
(c) Primary safety outcome: Major bleeding

Types of studies included: Prospective RCTs

Methods of analysis:
- Meta-analysis was done in line with recommendation from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines with Review Manager 5.0
- Intension-to-treat principle
- Random-effect model was used due to the difference of patient characteristics and aspirin dosage
- RR and 95% CIs with the use of Mantel–Haenszel method
- Meta-regression conducted to identify the heterogeneity
- Publication bias was assessed by the funnel plot and the Bag's and Egger's tests.
- Sensitivity analysis

Meta-analysis: Done

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

Results

Adverse events:
MCEs:

	Aspirin		Control	
Study of subgroups	Total	Events	Total	Events
ETDRS	1856	350	1855	379
HOT	752	47	749	54
JPAD	1262	40	1277	46
POPADAD	638	105	638	108
PPP	519	20	512	22
WHS	524	58	503	62

MI:

	Aspirin		Control	
Study of subgroups	Total	Events	Total	Events
ETDRS	1856	244	1855	275
HOT	752	23	749	26
JPAD	1262	1	1277	10
POPADAD	638	43	638	35
PPP	519	10	512	8

Stroke:

	Aspirin		Control	
Study of subgroups	Total	Events	Total	Events
ETDRS	1856	92	1855	78
HOT	752	20	749	22
JPAD	1262	23	1277	29
POPADAD	638	37	638	50
PPP	519	9	512	10
WHS	524	15	503	31

Ischaemic stroke: Not reported
Haemorrhagic stroke: Not reported
Mortality
All-cause mortality:

	Aspirin		Control	
Study of subgroups	Total	Events	Total	Events
ETDRS	1856	340	1855	366
HOT	752	40	749	36
JPAD	1262	34	1277	38
POPADAD	638	94	638	101
PPP	519	25	512	20

Name of the reviewer: Tara Gurung and checked by Paul Sutcliffe

CV mortality:

	Aspirin		Control	
Study of subgroups	Total	Events	Total	Events
ETDRS	1856	241	1855	283
HOT	752	11	749	18
JPAD	1262	12	1277	14
PHS	275	11	258	26
POPADAD	638	76	638	69
PPP	519	5	512	10
WHS	524	36	503	24

Major bleeding:

	Aspirin		Control	
Study of subgroups	Total	Events	Total	Events
JPAD	1262	34	1277	10
POPADAD	638	28	638	31
PPP	519	10	512	1

Author's conclusion

In patients with diabetes, aspirin therapy did not significantly reduce the risk of CV events without an increased risk of major bleeding, and showed sex-specific effects on MI and stroke

Reviewer's conclusion

This study conducted a pooled meta-analysis of RCTs

E. Randomised controlled trials on the prophylactic use of aspirin in the primary prevention of cardiovascular disease in patients with diabetes

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[40]

First author surname: Belch

Year of publication: 2008

Country: Scotland

Funding: Medical Research Council (investigators were independent of the funder)

Title: The prevention of progression of arterial disease and diabetes (POPADAD) trial – factorial randomised placebo-controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease

Aim of the study

To assess whether aspirin and antioxidant therapy combined or alone, are more effective than placebo in reducing the development of cardiovascular events in patients with diabetes mellitus and asymptomatic peripheral arterial disease

Methods

Design: multicentre, randomised, double-blind 2 × 2 factorial, placebo-controlled trial

Setting: 16 hospital centres in Scotland

Enrolment period: November 1997 to July 2001

Follow-up: Until 2006 (range: 4.5 to 8.6 years)

Participants:
Inclusions: A total of 1276 adults aged ≥ 40 years with type 1 or 2 diabetes and an ABI of 0.99 or less, no symptomatic CVD
Exclusions: People with symptomatic CVD, using aspirin or antioxidants, with peptic ulceration, severe dyspepsia, bleeding disorder, intolerance to aspirin, with suspected serious illness (including cancer), with psychiatric illness, congenital heart disease, unable to give informed consent

Intervention:
- Daily aspirin (100 mg) plus antioxidant
- Daily aspirin (100 mg) only

Comparator: Placebo

Outcome measures:

(a) Primary outcome:
- Death from CHD or stroke, non-fatal MI or stroke, or amputation above ankle or critical limb ischaemia
- Death from CHD or stroke

(b) Secondary outcome:
- Death (any cause)
- CHD death
- Stroke death
- Non-fatal MI
- Non-fatal stroke
- Above-ankle amputation for critical ischaemia
- TIA
- Coronary bypass surgery
- Coronary artery angioplasty
- Development of angina
- Peripheral arterial bypass surgery
- Peripheral arterial angioplasty
- Development of critical limb ischaemia
- Development of claudication

ABI, ankle–brachial index.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

(c) Adverse events:
- Malignancy
- GI bleeding
- GI symptoms
- Arrhythmia
- Allergy including skin rash

Results

Baseline characteristics:
Values are medians (interquartile ranges) unless stated otherwise

Characteristics	Aspirin plus antioxidant (*n* = 320)	Aspirin plus placebo (*n* = 318)	Placebo plus antioxidant (*n* = 320)	Placebo plus placebo (*n* = 318)
Mean (SD) age (years)	61.0 (10.0)	60.0 (10.1)	60.0 (10.3)	60.1 (9.7)
No. (%) women	169 (53)	183 (58)	181 (57)	180 (57)
Time since diagnosis of diabetes (years)	6.7 (2.9 to 12.9)	6.0 (2.7 to 13.0)	5.7 (2.4 to 11.7)	6.4 (2.6 to 11.6)
No. (%) treated with insulin	107 (33)	112 (35)	96 (30)	91 (29)
Smoking status				
No. (%) current smokers	105 (33)	99 (31)	106 (33)	87 (27)
No. (%) former smokers	113 (35)	107 (34)	111 (35)	116 (36)
No. (%) never smokers	102 (32)	112 (35)	103 (32)	115 (36)
Body mass index (kg/m^2)	29.7 (26.2 to 33.3)	28.7 (25.2 to 33.0)	29.4 (26.1 to 33.5)	29.2 (25.8 to 33.2)
Mean (SD) SBP (mmHg)	146 (22)	143 (21)	144 (20)	147 (21)
Mean (SD) DBP (mmHg)	79 (10)	78 (10)	79 (10)	80 (11)
ABI	0.90 (0.82 to 0.95)	0.91 (0.84 to 0.95)	0.89 (0.81 to 0.94)	0.90 (0.83 to 0.96)
Mean (SD) HbA_{1c} level (%)	8.0 (1.8)	8.0 (1.7)	7.9 (1.8)	7.9 (1.7)
Total cholesterol level (mmol/l)	5.5 (4.8 to 6.2)	5.6 (4.9 to 6.2)	5.5 (4.9 to 6.3)	5.5 (4.9 to 6.2)
Triglyceride level (mmol/l)	2.2 (1.5 to 3.2)	2.2 (1.5 to 3.3)	2.3 (1.4 to 3.4)	2.1 (1.5 to 3.3)
High-density lipoprotein level (mmol/l)	1.2 (1.0 to 1.5)	1.3 (1.0 to 1.5)	1.2 (1.0 to 1.5)	1.2 (1.0 to 1.5)
Low-density lipoprotein level (mmol/l)	3.1 (2.5 to 3.7)	3.1 (2.5 to 3.7)	3.2 (2.6 to 3.9)	3.1 (2.6 to 3.7)

ABI, ankle–brachial index; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Aspirin vs. no aspirin groups in number (%)

Variables	Aspirin ($n = 638$)		No aspirin ($n = 638$)		Effect estimate[a] (95% CI)			*p*-value
Primary end points								
Composite end point[b]	116	18.2	117	18.3	0.98	0.76	1.26	0.86
Death from CHD or stroke	43	6.7	35	5.5	1.23	0.79	1.93	0.36
Secondary end points								
Death (any cause)	94	14.7	101	15.8	0.93	0.71	1.24	0.63
CHD death	35	5.5	26	4.1	1.35	0.81	2.25	0.24
Stroke death	8	1.3	9	1.4	0.89	0.34	2.3	0.80
Non-fatal MI	55	8.6	56	8.8	0.98	0.68	1.43	0.93
Non-fatal stroke	29	4.6	41	6.4	0.71	0.44	1.14	0.15
Above ankle amputation for critical limb ischaemia	11	1.7	9	1.4	1.23	0.51	2.97	0.64
TIA	14	2.2	20	3.1	0.70	0.36	1.39	0.31
Coronary artery bypass surgery	10	1.6	16	2.5	0.62	0.28	1.38	0.24
Coronary artery angioplasty	7	1.1	8	1.3	0.88	0.32	2.43	0.81
Development of angina	70	11.0	78	12.2	0.90	0.66	1.25	0.54
Peripheral arterial bypass surgery	7	1.1	5	0.8	1.41	0.45	4.43	0.56
Peripheral arterial angioplasty	11	1.7	13	2.0	0.85	0.38	1.89	0.68
Development of critical limb ischaemia	21	3.3	19	3.0	1.11	0.60	2.06	0.75
Development of claudication	97	15.2	107	16.8	0.89	0.68	1.18	0.42
Adverse events								
Malignancy	53	8.3	68	10.7	0.76	0.52	1.11	0.15
GI bleeding	28	4.4	31	4.9	0.90	0.53	1.52	0.69
GI symptoms, including dyspepsia	73	11.4	94	14.7	0.77	0.55	1.08	0.081
Arrhythmia	55	8.6	47	7.4	1.19	0.79	1.78	0.41
Allergy including skin rash	72	11.3	64	10.0	1.14	0.80	1.63	0.47

a HRs (aspirin vs. no aspirin) for primary and secondary end points and ORs (aspirin vs. no aspirin) for adverse events.
b Death from CHD or stroke, non-fatal MI or stroke, or above ankle amputation for critical limb ischaemia.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Subgroup analysis:

Primary end point[a]	Aspirin			No aspirin			HR (95% CI)			*p*-value[b]
	No. of patients	No (%) with event		No. of patients	No (%) with event					
Composite end point										
Age (years)										
< 60	297	38	12.8	315	36	11.4	1.1	0.7	1.75	0.44
≥ 60	341	78	22.9	323	81	25.1	0.9	0.65	1.21	
Sex										
Women	352	48	13.6	361	55	15.2	0.9	0.6	1.31	0.54
Men	286	68	23.8	277	62	22.4	10	0.74	1.47	
ABI										
≤ 0.90	314	59	18.8	332	75	22.6	0.8	0.58	1.14	0.089
0.91–0.99	324	57	17.6	306	42	13.7	1.3	0.86	1.91	
Death from CHD or stroke										
Age (years)										
< 60	297	10	3.4	315	10	3.2	1.1	0.44	2.56	0.77
≥ 60	341	33	9.7	323	25	7.7	1.2	0.74	2.09	
Sex										
Women	352	17	4.8	361	16	4.4	1.1	0.55	2.16	0.68
Men	286	26	9.1	277	19	6.9	1.3	0.73	2.4	
Ankle–brachial pressure index										
≤ 0.90	314	22	7	332	24	7.2	10	0.54	1.71	0.17
0.91–0.99	324	21	6.5	306	11	3.6	1.8	0.89	3.82	

ABI, ankle–brachial index.
a Death from CHD or stroke, non-fatal MI or stroke, or above-ankle amputation for critical limb ischaemia.
b Test for heterogeneity of treatment effect in subgroups.

Author's conclusion

The trial does not provide evidence for the use of aspirin in the primary prevention of CVD in patients with diabetes mellitus

Reviewer's conclusion

This is a well-designed trial looking at aspirin compared with no aspirin. The no aspirin group includes patients randomised to placebo plus antioxidants and placebo plus placebo

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Study details

Study ID (Ref man):[44]

First author surname: Ogawa

Year of publication: 2008

Country: Japan

Funding: Ministry of Health, Labour and Welfare of Japan, funder had no role in the design, conduct or preparation of the manuscript

Title: Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes – a randomized controlled trial

Aim of the study

To investigate the efficacy of low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes

Methods

Design: Prospective, randomised, open-label, controlled trial with blinded end-point assessment

Setting: 163 institutions in Japan

Enrolment period: December 2002 to May 2005

Follow-up: Until April 2008

Participants:
Inclusions: 2539 people with type 2 diabetes mellitus, age 30–85 years, able to give informed consent
Exclusions: Suggested ischaemic ST segment depression, ST-segment elevation, pathologic Q-waves, history of CHD, history of cerebrovascular disease, history of arteriosclerotic disease, atrial fibrillation, pregnancy, use of anti-platelet or antithrombotic therapy, history of severe gastric or duodenal ulcer, severe liver dysfunction, severe renal dysfunction, allergy to aspirin

Intervention: Daily aspirin (81 or 100 mg)

Comparator: No aspirin

Outcome measures:

(a) Primary outcome: Any atherosclerotic event (composite of: sudden death, death from coronary, cerebrovascular, and aortic causes, non-fatal acute MI, unstable angina, newly developed exertional angina, non-fatal ischaemic and haemorrhagic stroke, TIA, non-fatal aortic and PVD)
(b) Secondary outcome: Each primary end point, combinations of primary end points, death from any cause
(c) Adverse events: GI events, haemorrhagic events other than haemorrhagic stroke

Results

Baseline characteristics:

Characteristic	No. (%)			
	Aspirin group ($n = 1262$)		Non-aspirin group ($n = 1277$)	
Age, mean (SD), years	65	10	64	10
Male	706	56	681	53
Current smoker	289	23	248	19
Past smoker	545	43	482	38
Body mass index, mean (SD)	24	4	24	4
Hypertension	742	59	731	57
Dyslipidaemia	680	54	665	52
SBP, mean (SD), mmHg	136	15	134	15
DBP, mean (SD), mmHg	77	9	76	9
Duration of diabetes, median (IQR), years	7.3	2.8–12.3	6.7	3.0–12.5

DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Characteristic	No. (%) Aspirin group ($n = 1262$)		Non-aspirin group ($n = 1277$)	
Diabetic microvascular complication:				
Diabetic retinopathy	187	15	178	14
Diabetic nephropathy	169	13	153	12
Proteinuria, ≥ 15 mg/dl	222	18	224	18
Diabetic neuropathy	163	13	137	11
Dermal ulcer	6	0.5	6	0.5
Treatment for diabetes				
Sulfonylureas	737	58	710	56
Alpha-glucosidase inhibitors	422	33	414	32
Biguanides	168	13	186	15
Insulin	166	13	160	13
Thiazolidines	63	5	65	5
Treatment for hypertension and dyslipidaemia				
Calcium channel blockers	436	35	440	34
Angiotensin-II receptor antagonists	269	21	266	21
Angiotensin-converting enzyme inhibitors	178	14	195	15
Beta blockers	75	6	87	7
Alpha blockers	53	4	38	3
Statins	322	26	328	26
Family history type 2 diabetes mellitus	526	42	513	40
Ischaemic heart disease	147	12	143	11
Stroke	275	22	251	20
Patient medical history				
Peptic ulcer	83	7	96	8
Clinical laboratory measurements				
Mean (SD) glycosylated haemoglobin level, %	7.1	1.4	7	1.2
Fasting plasma glucose level, mg/dl	148	50	146	48
Total cholesterol level, mg/dl	202	34	200	34
Fasting triglyceride level, mg/dl	135	88	134	89
HDL cholesterol level, mg/dl	55	15	55	15
Blood urea nitrogen level, mg/dl	16	5	16	5
Serum creatinine level, mg/dl	0.8	0.3	0.8	0.2
Red blood cells, $\times 10^5$/ml	45	4.7	45	4.8
White blood cells, $\times 10^3$/ml	6.2	1.6	6.1	1.7
Haemoglobin level, g/dl	14	1.5	14	1.5

HDL, high-density lipoprotein; IQR, interquartile range; SD, standard deviation.

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Adverse events:

	No.	
	Aspirin group	Non-aspirin group
Bleeding, GI[a]		
Haemorrhagic gastric ulcer	5	3
Bleeding from oesophageal varices	1	0
Bleeding from colon diverticula	2	0
GI bleeding due to cancer	2	0
Haemorrhoid bleeding	1	0
GI bleeding (cause unknown)	1	1
Other bleeding		
Retinal bleeding	8	5
Bleeding after tooth extraction	1	0
Subcutaneous haemorrhage	3	1
Haematuria	2	1
Nose bleeding	6	1
Chronic subdural haematoma	2	0
Non-bleeding GI event		
Non-haemorrhagic gastritis	3	0
Non-haemorrhagic gastric ulcer	17	3
Non-haemorrhagic duodenal ulcer	1	1
Only GI symptom	26	0
Other		
Anaemia	4	0
Asthma	1	0

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe

Atherosclerotic events:

	Aspirin group			Non-aspirin group						
	No.	%	No. per 1000 person-year	No.	%	No. per 1000 person-year	HR (95% CI)			*p*-value
Primary end point: all atherosclerotic events	68	5.4	13.6	86	6.7	17	0.8	0.58	1.1	0.16
Coronary and cerebrovascular mortality	1	0.08	0.2	10	0.8	2	0.1	0.01	0.79	0.0037
CHD events (fatal + non-fatal)	28	2.2	5.6	35	2.7	6.9	0.8	0.49	1.33	0.4
Fatal MI	0		0	5	0.4	1				
Non-fatal MI	12	1	2.4	9	0.7	1.8	1.3	0.57	3.19	0.5
Unstable angina	4	0.3	0.8	10	0.8	2	0.4	0.13	1.29	0.13
Stable angina	12	1	2.4	11	0.9	2.2	1.1	0.49	2.5	0.82
Cerebrovascular disease (fatal + non-fatal)	28	2.2	5.6	32	2.5	6.3	0.8	0.53	1.32	0.44
Fatal stroke	1	0.08	0.2	5	0.4	1	0.2	0.02	1.74	0.15
Non-fatal stroke										
Ischaemic	22	1.7	4.4	24	1.9	4.6	0.9	0.52	1.66	0.8
Haemorrhagic	5	0.4	1	3	0.2	0.6	1.7	0.4	7.04	0.48
TIA	5	0.4	1	8	0.6	1.6	0.6	0.21	1.93	0.42
Peripheral artery disease[a]	7	0.6	1.4	11	0.9	2.2	0.6	0.25	1.65	0.35

a Arteriosclerosis obliterans (five in aspirin group and eight in non-aspirin group); aortic dissection (two fatal in the aspirin group and one non-fatal in the non-aspirin group); mesenteric artery thrombosis (one in the non-aspirin group), and retinal artery thrombosis (one in the non-aspirin group).

Subgroup analysis:

	Events						
	Aspirin group		Non-aspirin group		HR (95% CI)		
	No.	Total no.	No.	Total no.			
Age (years)							
≥ 65	45	719	59	644	0.7	0.46	0.99
< 65	23	543	27	633	10	0.57	1.70
Sex							
Male	40	706	51	681	0.7	0.49	1.12
Female	28	556	35	596	0.9	0.53	1.44
Hypertensive status							
Hypertensive	49	742	55	731	0.9	0.60	1.30
Normotensive	19	520	31	546	0.6	0.36	1.13
Lipid status							
Dyslipidaemia	38	680	43	665	0.9	0.57	1.37
Normolipidaemia	30	582	43	612	0.7	0.45	1.14
Smoking							
Current or past	36	565	42	494	0.7	0.47	1.14
Non-smoker	32	697	44	783	0.8	0.53	1.31

Name of the reviewer: Karoline Freeman and checked by Paul Sutcliffe
Author's conclusion
Aspirin did not reduce the risk of CV events in patients with type 2 diabetes. Owing to the low event rate, the study was underpowered to demonstrate a significant effect of aspirin
Reviewer's conclusion
The design of the trial is of average quality because it was not placebo controlled, was not double blind, and allocation concealment was not reported. The results are consistent with the POPADAD trial results

Appendix 7 Summaries of included papers and evidence

Overall survey of additional cardiovascular disease outcomes examined in primary prevention studies

In terms of the outcomes reported, the most recent meta-analyses pooled data for all-cause and CV mortality, (including MI and stroke); although as noted in *Table 8*, the review team were often unclear as to which outcomes were considered as primary and which as secondary by the authors. The following section is a brief review of the reported results of the included reviews. These results are also examined in the evidence synthesis section.

Baigent et al. *(2009)*

Baigent *et al.*[53] included 95,000 individuals, followed for 660,000 person-years, during which 3435 total deaths and 1256 vascular deaths occurred. Aspirin compared with placebo or control did not reduce all-cause mortality, CV mortality, non-vascular mortality or deaths of unknown cause.[54] The meta-analyses by Seshasai *et al.*,[56] Bartolucci *et al.*[37] and Raju *et al.*[38] did suggest a nominally significant reduction in total mortality; this is consistent with the findings from eight[40–47] of the nine[40–48] included studies that had a point estimate in favour of aspirin for total mortality.

Baigent *et al.*[53] assessed the benefits and risks of aspirin in primary prevention by undertaking a pivotal IPD meta-analyses of major bleeds and serious vascular events (i.e. vascular death, MI, stroke) in six primary prevention trials (95,000 individuals at low average risk) and 16 secondary prevention trials (17,000 individuals at high average risk) that compared long-term aspirin and control subjects. The IPD meta-analysis by Baigent *et al.*[53] did not include three RCTs in this landmark analysis: these were the JPAD,[44] POPADAD[40] and AAA[42] studies.

Individual patient data allowed the authors to examine outcomes and patient subgroups (according to age, sex, diabetes, smoking, mean BP value, blood cholesterol level, body mass index score) in more detail than in a study-level meta-analysis. Aspirin resulted in a 12% proportional reduction in serious vascular events (0.51% aspirin vs. 0.57% control per year; $p = 0.0001$), this was mainly due to the reduction in non-fatal MI (0.18% vs. 0.23% per year; $p < 0.0001$). No significant net effect on stroke was found (0.20% vs. 0.21% per year; $p = 0.4$; haemorrhagic stroke 0.04% vs. 0.03%; $p = 0.05$; other stroke 0.16% vs. 0.18% per year; $p = 0.08$) and no differences between aspirin and control subjects on vascular mortality (0.19% vs. 0.19% per year; $p = 0.7$). Aspirin allocation increased major GI and extracranial bleeds (0.10% vs. 0.07% per year; $p < 0.0001$), and the main risk factors for coronary disease were also risk factors for bleeding. The major findings of this IPD meta-analysis, relevant to adverse events, were that over 660,000 patient-years aspirin was associated with (1) 50 fewer ischaemic strokes (0.02%/year reduction); (2) 27 more haemorrhagic strokes (0.01%/year increase); and (3) 116 more major extracranial bleeds (0.03%/year increase). Also, fatal strokes occurred at a yearly event rate that was 1.21 times greater with aspirin than without aspirin (implying greater hazard from haemorrhagic strokes than ischaemic strokes), and absolute CVD benefits observed with aspirin in primary prevention RCTs were an order of magnitude less than those found in IPD analysis of 16 secondary prevention RCTs.

Raju et al. *(2011) and Seshasai* et al. *(2012)*

Raju *et al.*[38] and Seshasai *et al.*[56] documented the GI, major and non-trivial bleeding. Furthermore, only the meta-analysis by Seshasai *et al.*[56] considered the effect of aspirin on cancer mortality.

Considerable heterogeneity was observed for efficacy and safety outcomes. Seshasai *et al.*[56] assessed the OR risk of bleeding (aspirin compared with control), the absolute increase in risk, and the NNH having taken into account person-years of exposure. The analyses did not subdivide strokes according to type (haemorrhagic or ischaemic). The main findings were:

Odds ratios comparing aspirin use with no aspirin use:

Outcome	OR	95% CI
Fatal stroke	0.94	0.84 to 1.06
Fatal MI	1.06	0.83 to 1.37
All-cause death	0.94	0.88 to 1.00
Total bleeds	1.70	1.17 to 2.46
Non-trivial bleeds	1.31	1.14 to 1.50

Number needed to treat to observe one event over 6 years of aspirin use compared with no use:

Outcome	NNT
Non-fatal MI	162
CVD event	120
Non-vascular death	297
At least one non-trivial bleed	73

Seshasai *et al.*[56] performed outcome sensitivity analyses looking at the influence of daily compared with every-other-day dosage, age, and baseline rates. The authors concluded that benefits of aspirin in primary prevention were modest but risk of adverse events appreciable and that guideline should be re-examined. In their assessment of the impact (and safety) of aspirin on vascular and non-vascular outcomes in primary prevention, Seshasai *et al.*,[56] during a mean follow-up of 6.0 years of over 100,000 participants, found that aspirin treatment reduced total CVD events by 10% (OR 0.90, 95% CI 0.85 to 0.96; NNT = 120); the authors claim that this was mainly due to the reduction found in non-fatal MI (OR 0.80; 95% CI 0.67 to 0.96; NNT = 162). No significant reduction was reported in CVD death (OR 0.99, 95% CI 0.85 to 1.15) or cancer mortality (OR 0.93; 95% CI 0.84 to 1.03) and increased risk of non-trivial bleeding events (OR 1.31, 95% CI 1.14 to 1.50; NNH = 73).

Raju *et al.*[38] published another study-level meta-analysis of the same core of nine primary prevention RCTs[40–48] (unfunded study). The following RR statistics (random-effects model) were reported (aspirin compared with no aspirin):

Outcome	RR (95% CI?)
Haemorrhagic stroke	1.36 (1.01 to 1.82)
Ischaemic stroke	0.86 (0.75 to 0.98)
Major bleeding	1.66 (1.41 to 1.95)
GI bleeding	1.37 (1.15 to 1.62)
Stroke (fatal and non-fatal)	0.93 (0.82 to 1.05)

Overall, aspirin for the primary prevention of CVD was reported to produce a significant 6% reduction in all-cause mortality without reducing CV mortality; this conclusion by Raju *et al.*[54] was based on four

meta-analyses between 2009 and 2012, involving between 95,000 and 102,621 individuals at low-risk of CVD. These findings reported by Raju *et al.*[54] were in agreement with the results of the 2002 ATT Collaboration meta-analysis,[53] which found that aspirin reduces CV events through mainly reducing non-fatal MI.

Berger et al. *(2011)*

The other study-level meta-analysis included in the current short report was published by Berger *et al.*[39] This study involved the nine core primary prevention RCTs.[40–48] The following RR statistics (Mantel–Haenszel random effects) were reported (aspirin compared with no aspirin):

Outcome	RR (95% CI)
Haemorrhagic stroke	1.35 (1.01 to 1.81)
Ischaemic stroke	0.87 (0.73 to 1.02)
Major bleeding	1.62 (1.31 to 2.00)
Stroke (fatal and non-fatal)	0.94 (0.84 to 1.06)

Berger *et al.*[39] reported NNT and NNH values calculated for a period of 6.9 years. These were 253 for one major CV event avoided (CV event = non-fatal MI, non-fatal stroke or CV death) and 261 for one extra major bleed to be experienced.

Berger *et al.*[39] conducted meta-regression indicating that benefits and bleeding were independent of study-level baseline CVD risk, background therapy, age, sex and aspirin dose.

Bartolucci et al.

A further meta-analysis of the nine core RCTs[40–48] by Bartolucci *et al.*[37] generated pooled estimates for outcomes that were essentially indistinguishable from the pooled estimates of the Seshasai *et al.*[56] and Bartolucci *et al.*;[37] however, the meta-analysis did not report on bleeding or other adverse events.

Myocardial infarction

Baigent *et al.*,[53] Seshasai *et al.*[56] and Bartolucci *et al.*[37] reported that aspirin reduced non-fatal MI by 19–23%. Raju *et al.*[54] also reported that aspirin compared with placebo or no aspirin was associated with a reduced total MI in all meta-analyses,[37,38,53,56] although this was significant only in the meta-analysis by Baigent *et al.*[53] Wolff *et al.*[57] reported that men have a reduced risk for MIs.

Major cardiovascular events

All four meta-analyses reported that aspirin reduced MCEs when used for primary prevention.[37,38,53,56] Baigent *et al.*[53] reported a 12% reduction in vascular death, stroke and MI.

Bleeding

Aspirin was reported to increase major bleeding, GI bleeding and haemorrhagic stroke.[38,53,56] Although it is important to note that that has been despite different definitions of bleeding across the included studies. Seshasai *et al.*[8] found that aspirin increased total bleeding by 70% and non-trivial bleeding by 31%. Baigent *et al.*[53] reported that aspirin increased major GI and additional extracranial bleeds by approximately 54%; fatal haemorrhagic strokes were more common than fatal ischaemic strokes (82 vs. 53). Raju *et al.*[38] found that aspirin increased major bleeding by 66%, GI bleeding by 37% and haemorrhagic stroke by 36%. However, it should be considered whether an individual is receiving proton-pump inhibitors, as this may modify the risk for GI bleeding.[57]

Stroke

There was no overall reported benefit of aspirin in terms of stroke reduction. Raju *et al.*[38] did report that aspirin reduced ischaemic stroke, but, as was proposed by Raju *et al.*,[54] the accompanying increase in

haemorrhagic stroke is likely to have negated this benefit. Wolff *et al.*[57] reported that women have a reduced risk for ischaemic strokes.

Estimates of clinical benefit in relation to sex and age

Selak *et al.*[55] calculated the rates of benefit (i.e. avoided vascular events) with aspirin by applying the proportional reduction in serious vascular events observed in the Baigent *et al.*,[53] meta-analysis (12%, 99% CI 6% to 18%) to the expected number of CVD events avoided in 5 years.

Seshasai *et al.*[54] did not report any material differences in aspirin treatment effect by sex, although it was stated that the meta-analysis findings may be prone to ecological and other biases; despite this they are in agreement with large-scale IPD meta-analyses that showed lack of any important interaction by sex (Baigent *et al.*[53]) for major CVD outcomes. Rates of harm (i.e. the difference between rates of non-fatal major extracranial bleeds in the aspirin and control groups) were provided by the Baigent *et al.*[53] meta-analysis for men and women aged 50–59 years (0.2% and 0.1%, respectively). Selak *et al.*[55] proposed that the overall benefits of aspirin appear to outweigh the risks in primary prevention of CVD in individuals with 5-year CVD risk of > 15%, up to the age of 80 years; however, harm could possibly outweigh the benefit for primary prevention for those over 80 years, especially in men.

Wolff *et al.*[57] also evaluated the benefits and harms of taking aspirin for the primary prevention of strokes, MIs and death. Although the authors concluded that aspirin appears to reduce the risk for MI in men and strokes in women, it was also reported that aspirin appears to increases the risk for serious bleeding events. The overall benefit in the reducing CVD events with aspirin appears to depend on individual's baseline CVD risk and risk for GI bleeding.

Dose

The dosages used in the included primary prevention trials ranged from 75 to 500 mg/day. It is difficult to draw conclusions on the impact dose has on outcomes. It has also been questioned whether low doses may impact on some of the findings seen, for example, in the WHS (which used 100 mg every other day) – no effect in the reduction of heart attacks or in the reduction of the combined outcome of CVD events.[57]

Summary of cardiovascular disease

Nine systematic reviews[37–39,52–57] and three RCTs were found to meet the current inclusion criteria concerning aspirin for the primary prevention of CVD. In the most recent highest-quality systematic review by Seshasai *et al.*,[56] which included the nine core RCTs,[40–48] repeatedly evaluated in many of the other included systematic reviews, aspirin did not have a protective role against cancer in individuals with low to moderate CVD but was more effective in the primary prevention of non-fatal MI, with limited benefit on fatal MI, stroke and CVD; these benefits are offset against elevated risk bleeds. Modest non-significant reductions in non-vascular death and all-cause mortality were also observed. Seshasai *et al.*,[56] despite having several weaknesses (see evidence synthesis section of the current short report: double-counting, definitions of outcome measures and adverse events), concluded that although finding important reductions in non-fatal MI, aspirin prophylaxis in individuals without prior CVD did not result in reductions in cancer mortality or CVD death; aspirin for primary prevention does not appear to be warranted and treatment decisions need to be considered on a case-by-case basis. Similarly, the earlier pivotal IPD meta-analysis by Baigent *et al.*[53] concluded that the net value of aspirin is uncertain as the reduction in occlusive events needs to be considered relative to increases in major bleeds.

Overall survey of cancer outcomes examined in primary prevention studies

Algra *et al.*[61] compared effects of aspirin on risk and outcome of cancer in observational studies compared with randomised trials. A total of 150 case–control and 45 cohort studies were included and results compared with previously identified trials[22] for which IPD was available, and excluding the ETDRS trial,[75] leaving six eligible trials.[40,42,44,45,48,74] Meta-analysis was carried out on study level rather than IPD to increase comparability with observational studies. Reduction in 20-year risk of death due to CRC and

oesophageal cancer was statistically significant in the aspirin group. Non-significant reductions could also be demonstrated for biliary, gastric, prostate and lung cancer. An association between aspirin and reduction in cancer risk could also be seen in good-quality observational studies. The authors concluded that outcomes from observational studies and RCTs are generally in good agreement, but that outcomes from observational studies are dependent on an adequate definition of aspirin dose and frequency, assessment of aspirin exposure during follow-up, and adjustments in baseline characteristics of participants. This study concentrated on the results reported in observational studies, it therefore does not add any new evidence in terms of effect of aspirin on prevention of cancer based on RCTs alone.

Mills *et al.*[60] aimed to determine whether cancer mortality is also reduced in the shorter term by aspirin therapy as opposed to long-term effects of aspirin shown by Rothwell *et al.*[22] Twenty-three studies matched the inclusion criteria of investigating low-dose aspirin. Studies of any trial length were considered. There were 41,398 patients in the aspirin group and 41,470 in the control group. The average trial duration was 2.5 years. Outcomes measured were non-CVD mortality and cancer mortality. Adverse events such as bleeding were not considered. The 23 trials reporting on non-vascular death revealed a statistically significant reduction in non-vascular death in favour of aspirin therapy. Out of the 23 trials, 11 reported on cancer mortality. The effect of aspirin in reducing cancer mortality was also statistically significant, with a RR of 0.77 (95% CI 0.63 to 0.94; $p = 0.019$). The effect size was not influenced by trial duration or aspirin dose. A statistical significant effect was reported after an average follow-up period of 4 years. Owing to the short time of the trials, the observed effect might underestimate the effect of long-term treatment. Furthermore, cancer mortality might be under-reported in the trials, as they were designed to investigate CVD events. This is suggestive of a conservative treatment effect. However, Mills *et al.*[60] excluded three trials from the meta-analysis of non-CV death and cancer mortality without providing a rational for this decision.

Across the four Rothwell reviews,[22,31,49,62] methodology was consistent but included number of studies varied as did the study focus, which ranged from aspirin effect on CRC only,[31] aspirin effect on all cancers,[22] short-term effects of aspirin[51] to the effect of aspirin on risk of metastasis.[62] Although the analyses were generally thorough, it needs to be considered that the trials for the primary or secondary prevention of CVD might not have vigorously recorded cancer incidence or death due to cancer as a primary outcome. Furthermore, the quality of the trials and the subsequent impact of quality on the outcome and conclusions were not considered in any of the analyses.

In 2010, Rothwell *et al.*[31] aimed to establish the effects of aspirin on incidence and mortality due to CRC by investigating a total of only four trials[45,48,73,74] of daily aspirin (any dose) compared with control in primary or secondary prevention of CVD and considering one additional trial that investigated different doses of aspirin (Dutch-TIA). Effects were assessed in relation to dose, duration of treatment and site of cancer by analysing pooled IPD. In the four trials[45,48,73,74] of aspirin compared with control with a mean duration of treatment of 6 years, 2.8% (391/14,933) patients had CRC. The reported outcomes of the analysis were incidence and death due to CRC with reported HRs of 0.75 (95% CI 0.56 to 0.97; $p = 0.02$) and 0.61 (95% CI 0.43 to 0.87; $p = 0.005$) and absolute reduction in 20-year risk of 1.21% (95% CI 0.19% to 2.22%) and 1.36% (95% CI 0.44% to 2.28%), respectively, for low-dose aspirin (75–300 mg). The reduction in risk of cancer increased with duration of treatment for both, incidence and mortality due to CRC. However, reduction in risk was greater for cancers of the proximal than the distal colon.

In 2011, one study[22] investigated the long-term risk of death due to cancer using IPD from randomised trials of daily aspirin compared with no aspirin. The study included eight trials,[40,42,44,45,48,74–76] of which seven[40,42,44,45,48,74,75] provided IPD for analysis. The mean duration of scheduled treatment was 4 years or more. The primary outcome was death due to cancer. Adverse events in terms of bleeding were not considered. Long-term follow-up to estimate the 20-year risk of cancer death was only based on three trials.[45,48,74] Time to death analysis using IPD was based on 657 cancer deaths in 23,535 patients and demonstrated a reduction in cancer deaths in the aspirin group (HR 0.82, 95% CI 0.70 to 0.95; $p = 0.01$). The study concluded that aspirin reduces deaths due to several cancers (mainly adenocarcinomas) shown

by a reduction in deaths after 5 years of treatment, which is maintained over a 20-year period and increases with the duration of the treatment (data extraction table). The effect, however, did not increase with increasing aspirin dose of > 75 mg but the absolute reduction in death increased with age. This effect on cancer death resulted in a small reduction in all-cause mortality. The observed effect of aspirin on cancer mortality was consistent across trials with different trial populations and is therefore likely to be generalisable.

In 2012, Rothwell *et al.*[49] analysed 51 randomised trials of aspirin compared with control to establish the short-term effect of aspirin on cancer incidence and to establish the time course of effects on cancer incidence. Studies were included if they were designed for the primary or secondary prevention of CVD and if they reported death due to cancer or non-vascular death. The primary outcome was death due to cancer. The outcome considered for adverse events of aspirin treatment were major extracranial bleeds. Considering all trials, death due to cancer was reduced in the aspirin group (OR 0.85, 95% CI 0.76 to 0.95). However, 17 small trials did not report death due to cancer and were included as non-vascular deaths contributing 52/614 death in the aspirin group and 60/652 deaths in the control group. The effect was still statistically significant when deaths were excluded that were due to cancers diagnosed prior to randomisation. Comparison of the effect of aspirin on CV death and non-CV death in trials of daily aspirin in the primary prevention of CV events ($n = 12$), a statistically significant reduction in deaths was demonstrated only in non-vascular death (OR 0.88, 95% CI 0.78 to 0.98; $p = 0.02$).

Effect of aspirin on cancer incidence and major extracranial bleeds were investigated in six trials.[40–44,48] Reduction in risk of cancer incidence was statistically significant in patients with ≥ 3 years' follow-up (OR 0.76, 95% CI 0.66 to 0.88; $p = 0.0003$). In contrast, the statistical significance of a detrimental effect of allocation to aspirin in terms of extracranial bleeds disappeared when comparing patients with < 3 years' trial follow-up (OR 1.95, 95% CI 1.47 to 2.59; $p < 0.0001$) with patients receiving ≥ 3 years' trial follow-up (OR 1.04, 95% CI 0.73 to 1.49; $p = 0.90$). A composite outcome of MCEs, cancer or fatal extracranial bleeds appears to suggest an overall positive balance of risk and benefit (HR 0.88, 95% CI 0.82 to 0.98; $p = 0.01$); however, the number of extracranial bleeds that were fatal were very small in the two groups (8/203 aspirin vs. 15/132 control).

In a second study in 2012, Rothwell *et al.*[62] studied metastasis at initial diagnosis and during subsequent follow-up in participants with a new diagnosis of cancer to assess the effect of aspirin on risk of metastasis. This study was restricted to trials done in the UK because of the availability of reliable death certification and cancer registers for data collection. A total of five trials[40,42,45,48,74] were included in the analysis. The primary outcome of the study was metastasis of cancers. However, effect of aspirin on metastasis is considered to be secondary prevention of cancer, this review considered only data on cancer incidence and cancer death. The study did not investigate adverse events of aspirin therapy. Incidence of cancers was reduced in the aspirin group (OR 0.88, 95% CI 0.78 to 0.99; $p = 0.04$) with a more pronounced effect on cancer mortality (OR 0.77, 95% CI 0.65 to 0.91; $p = 0.002$). The study concluded that early effects of aspirin on cancer death in the RCTs under investigation were likely due to a reduction in distant metastasis.

In general, the systematic reviews provide evidence of a benefit of aspirin in the prevention and treatment of cancer. However, the studies by Rothwell *et al.*[22,31,49,62] lack detail in the methodology and consequently some lack of transparency, which hindered data extraction and assessment of reported outcomes. The rational of only including trials investigating daily aspirin was that (1) less frequent use is thought to be less effective in the prevention of cancer and (2) daily use is common in clinical practice. By considering only daily aspirin, two large trials, namely the PHS[47] and WHS,[46] investigating aspirin given every other day, were excluded from the analysis. No analysis was planned or carried out to investigate the claims that daily aspirin is better than less frequent aspirin, nor what impact the two large trials[46,47] would have had on the reported outcome and conclusions. However, a 10-year follow-up of WHS[46] indicated possible reduction in lung cancer incidence but no other cancers.[85]

The observed effect on cancer mortality and incidence is believed to be a true effect and studies argue that the potential benefit of aspirin to prevent different cancers might be underestimated in the analyses. The effect of aspirin appears to increase with treatment duration. Hence, it is likely that the relatively short trials underestimate the potential benefit of aspirin. Long-term effects might also be underestimated when looking at post-trial data for long term effects, since many patients went onto aspirin after the trial finished.

Rothwell *et al.*[22] argue that bias would be minimal by using data on cancer incidence and cancer mortality from the CVD trials. First, long-term follow-up is reliable because cancer death can be ascertained reliably due to UK cancer registers. Second, cancer deaths were recorded during trials and attribution of COD was from death certificates and, third, trial investigators were unaware that data might later be used for the investigation of the effect of aspirin therapy on cancer deaths. Furthermore, early diagnosis of cancer due to bleeding was regarded as unlikely to have been a source of bias.

Summary of cancer

The searches identified six systematic reviews[22,31,49,60–62] assessing the effect of aspirin on cancer mortality and cancer incidence. The overall conclusion is that further trials are urgently needed, as despite benefits of aspirin in the prevention and treatment of cancer being reported, the studies by Rothwell *et al.*[22,31,49,62] lack detail in methodology and consequently some lack of transparency. Furthermore, trials studying follow-up beyond 20 years are needed to identify any late rebound in cancer deaths. Continued long-term treatment with aspirin requires investigation and, although two trials have been started, more randomised trials of aspirin in treatment of cancer are needed.

Overall survey of cardiovascular disease outcomes for patients with diabetes examined in primary prevention studies

Butalia *et al.*[63] aimed to quantify treatment effects in absolute terms of the risk-benefit trade-off of aspirin therapy in patients with diabetes by investigating seven RCTs,[40,41,43,44,46,47,75] six of which studied aspirin for the primary prevention of CV events only[40,41,43,44,46,47] and one, the ETDRS trial,[75] that included a proportion of patients taking aspirin for secondary prevention of CVD. Three trials[40,44,75] were designed to investigate the effect of aspirin in diabetic patients, whereas the other trials provided information on subgroups of patients with diabetes. Aspirin dosage varied between < 100 mg and 650 mg daily or ≥ 100 mg every other day across trials and follow-up ranged from 3.6 to 10.1 years. The primary outcomes were a composite of non-fatal MI, non-fatal ischaemic stroke, CV death due to MI and ischaemic stroke [MACE (major adverse cardiovascular event)], and all-cause mortality. Adverse events considered were haemorrhage, GI bleeding and other GI events. MACE events occurred in 612/5565 participants in the aspirin arm and in 668/5520 participants in the control group. The pooled estimate using the fixed-effects model by Mantel–Haenszel was nearly significant with a RR of 0.91 (95% CI 0.82 to 1.00). All-cause mortality and all secondary outcomes revealed no significant effect between the two groups. Adverse events were reported inconsistently across trials and occurred with relatively low frequency, which is why statistical power was limited. Analysis of all three adverse events considered showed no statistically significant difference between the aspiring and the placebo group, even although total numbers were higher for the aspirin group in all three events, suggesting a trend towards increased risk of bleeding and adverse GI events among patients receiving aspirin. The reported NNT was 92 to prevent one MCE. This thorough analysis concluded that patients with diabetes are positioned somewhere in the middle of the spectrum of primary and secondary prevention of CV events, and that the results no more than indicate an effect of aspirin in diabetic patients but that this comes at an expense of increased risk of bleeding and GI events.

Calvin *et al.*[64] aimed to determine whether the effect of aspirin in the primary prevention of CV events differs between patients with and without diabetes. The study included eight RCTs. In addition to the seven trials included by Butalia *et al.*,[63] Calvin *et al.*[64] also included the APLASA (antiphospholipid antibody acetylsalicylic acid) trial, a small aspirin trial in the primary prevention of CVD of about 100 participants, which contributed only six diabetes patients to the analysis. Outcomes were ischaemic stroke, MI

and all-cause mortality. Adverse events were not investigated because these events are usually rare in the small population of diabetes patients and would lead to imprecise results. The study found no significant benefit of aspirin for patients with diabetes, even although the overall effect for patients with and without diabetes was statistically significant in the risk reduction of MI. On the other hand, a between-studies approach, within-studies approach and Bayesian analysis revealed no significant difference in treatment effect between patients with and without diabetes. This analysis demonstrated that there are no sufficient data to reliably show a benefit of aspirin for the primary prevention of CV events in patients with diabetes but suggests that the relative benefit in patients with and without diabetes is similar.

De Berardis *et al.*[65] attempted to evaluate the benefits and harms of low-dose aspirin in people with diabetes in the primary prevention of CVD. Six RCTs[40,41,44,46,47,75] were included in the analysis; these consisted of the same trials as considered by Butalia *et al.* minus the HOT trial. The assumed primary outcome reported was MCEs. Other outcomes were all-cause mortality, death from CV causes, non-fatal MI and non-fatal stroke. Adverse events were grouped under any bleeding, GI bleeding, GI symptoms and cancer.

The analysis by De Berardis *et al.*[65] did not show a clear benefit of aspirin in the prevention of MCEs or mortality in patients with diabetes, RRs 0.90 (95% CI 0.81 to 1.00) and 0.93 (95% CI 0.82 to 1.05), respectively. They argued that there might be an effect similar to that in other high-risk people, but trials were underpowered to detect this potential effect. Alternatively, aspirin could have lower efficacy in patients with diabetes then participants without and an explanation is given that point in the direction that diabetes people are not a subgroup of patients with high risk of CVD but that they should be viewed entirely independent due to their altered metabolism rendering diabetes an effect modifier. Furthermore, the data may be suggestive of a sex interaction with the effect of aspirin on some outcomes. Authors voiced concerns about the quality of papers in terms of concealment of randomisation and the fact that some trials were relatively outdated in terms of management of CV risk factors in diabetic patients. The study showed no statistically significant increase in the risk of any of the adverse events considered because studies were underpowered to detect this relatively rare event. Adverse events were reported by type rather than by study, and the RR reported for any bleeding and GI bleeding were 2.50 (95% CI 0.76 to 8.21) and 2.11 (95% CI 0.64 to 6.95), respectively.

Simpson *et al.*[66] explored the relationship between aspirin dose and prevention of CV events by studying RCTs and cohort studies in the primary and secondary prevention of CVD. They included 17 RCTs and four cohort studies in the final analysis. All-cause mortality was chosen as primary outcome because it is less sensitive to differences in definition, to the overall safety and effectiveness outcome for any treatment option and outcome across decades and countries of publication. Simpson *et al.*[66] concluded that an aspirin dose response effect is not supported for the prevention of CV events in diabetic patients. This conclusion is based on RCTs as well as cohort studies and considers primary and secondary prevention of CVD. They identified a gap in the evidence from RCTs for using 101–325 mg aspirin daily in diabetes and a dose effect cannot be concluded from RCT trials of aspirin for primary prevention, as all five trials[40–44] included in the analysis of all-cause mortality fall into the $\leq$ 100-mg category. The study conclusions, therefore, do not hold when looking at evidence from RCTs for the primary prevention of CVD in diabetic patients only. Concentrating on results from these RCTs only, this systematic review has limited value in adding additional evidence. Adverse events were not reported or meta-analysed in this review.

Stavrakis *et al.*[67] evaluated the effect of low-dose aspirin for the primary prevention of CV event in patients with diabetes mellitus. The study included seven trials.[40,41,43,44,46–48] However, the PHS[47] and the TPT[48] were not considered in the analysis because they either did not report any diabetes specific data[48] or restricted the reporting to HR without CI of diabetic patients.[47] The remaining five RCTs were HOT,[43] PPP,[41] WHS,[46] JPAD[44] and POPADAD.[40] The study did not clearly define a primary outcome. The outcomes measured were total mortality, CV mortality (deaths from MI or stroke), major adverse CV events (death from CV causes, non-fatal MI, non-fatal stroke), MI (fatal and non-fatal) and stroke (fatal and non-fatal). Adverse events considered were major bleeding events including GI bleeding. The study revealed no significant

effect of aspirin in the protection against any CV event measured. However, a small benefit was not disregarded since statistical power was small. In terms of adverse events, the study concluded that there is a possibility of harm due to aspirin therapy. However, no firm conclusion could be made because the statistically significant increase in major bleeding using a fixed-effect model could not be confirmed when basing the analysis on a random-effect model. The major problem in the analysis of bleeding events was pointed out to be the varying definitions of bleeding complications among trials. The results of this meta-analysis are consistent with other systematic reviews in that the effect of low-dose aspirin for primary prevention of CVD in diabetes patients remains unproven.

Younis *et al.*[68] evaluated the benefits of aspirin in people with diabetes mellitus for the primary prevention of CVD considering six trials[40,41,43,44,46,47] in the analysis. The study did not clearly define a primary outcome. Outcomes that were reported were MCE (composite of CV death, non-fatal MI and stroke), total mortality, MI and ischaemic stroke. Adverse events were expressed as risk of bleeding. The pooled estimate for any of the outcomes did not reveal any statistically significant benefit for aspirin, which was consistent for a fixed-effects and a random-effects meta-analysis. The precision of the included trials was questioned because three of the trials[43,46,47] were subgroup analyses from larger trials, three trials[40,41,44] had under-recruited participants and two[40,44] reported very low annual CV event rates at < 2%. The risk of bleeding was non-significantly higher in the aspirin group compared with the non-aspirin group (RR 2.49, 95% CI 0.70 to 8.84; $p = 0.16$). This number is based on a small number of bleeding events and was considered to imprecise on which to base any valid conclusions.

Zhang *et al.*[69] determined the effect of aspirin therapy in the prevention of CV events in patients with diabetes. The study included seven trials.[40,41,43,44,46,47,75] The efficacy outcomes were MCEs, all-cause mortality, CV mortality, MI and stroke. Major bleeding was reported as adverse event. Risk of CVD was not significantly reduced by aspirin for any of the outcomes measured in patients with diabetes. Furthermore, the increased risk in major bleeding in the patients with aspirin was not statistically significant. Associations between male percentage and incidence of MI or stroke were significant. The authors suggest that aspirin may reduce MI in men with diabetes, and stroke in women with diabetes. The analysis of major bleeding was underpowered because only three out of the seven trials reported major bleeding. The study pointed out differences on trial level, including variation in participant characteristic, follow-up and aspirin dosage, which is why any reported outcomes should be interpreted with caution.

Overall, studies are consistent in their conclusion that the effect of aspirin in the primary prevention of CVD in the more general population of patients without CVD could not be reliably reproduced in the subgroup of patients with diabetes. Two explanations were discussed in the papers, both of which might be contributing to the lack of a clear benefit. First, the low numbers of diabetes patients included in the trials combined with improved diabetes care and the subsequent low number of events, which led to underpowered trials. The improvement in treating CV risk factors in diabetes patients since the 1990s, which has led to better control of glucose, BP and lipid levels, is mainly due to the availability of statins discussed in several papers because reported events were markedly lower in later trials than in the early WHS and PHS trials.[44,65,67,68] Second, aspirin could be less effective in patients with diabetes then people without diabetes because 'resistance' to aspirin seems to have greater prevalence in diabetes patients with diabetes,[63] meaning that diabetes patients are not simply patients with increased risk of CVD. However, the pooled estimates move closer to being statistically significant than the estimates of the individual trials, which points in the direction that more participants are needed until a statistically significant effect of aspirin will be seen in this subgroup of patients with diabetes.

Subsequently, the analysis of adverse events was hindered by the low incidence in this small subgroup and evidence of harm would be more reliably obtained from larger trials that included patients without diabetes.

The meta-analyses of the seven systematic reviews included slightly different trials but nonetheless showed similar results. Systematic reviews pooled estimates on the grounds of homogeneity of reported trial

outcomes; however, Butalia *et al.*[63] reported great variations in study population, geographic location, years of study and design of trials, inconsistency in reporting and variability in definitions.

None of the systematic reviews considered the quality of the trial in the analysis, even if a quality appraisal had been carried out, and only one considered the quality assessment results in the discussion, which reported the quality of the trials to be suboptimal.[65]

Two RCTs[40,44] were identified that investigated the effect of aspirin in the primary prevention of CVD in patients with diabetes.

The POPADAD trial[40] was a multicentre, randomised, double-blind 2 × 2 factorial, placebo-controlled trial, which assessed the effect of aspirin or antioxidants in the prevention of progression of arterial disease and diabetes in patients with type 1 and type 2 diabetes. The trial[40] could not demonstrate any statistically significant effect of aspirin on the composite primary outcomes of CV events and CV mortality or in any of the secondary outcomes. The authors concluded that these results are probably indicative of a lack of any clinically important benefit for patients with diabetes and the question was raised whether aspirin provides an additional benefit to statins in the risk management of CVD. Adverse events were reported as malignancy, GI bleeding, GI symptoms including dyspepsia, arrhythmia and allergy. Adverse event rates between the aspirin and non-aspirin group were not statistically different. Taking GI bleeding as an example, 4.4% (28/638) of patients in the aspirin group and 4.9% (31/638) in the control group experienced GI bleeding (HR 0.90, 95% CI 0.53 to 1.52; $p = 0.69$). Generally, this was a well-designed trial[40] looking at aspirin and antioxidants to prevent CV events. The non-aspirin group, therefore, included patients randomised to placebo plus antioxidants and placebo plus placebo.

The JPAD trial[44] was a prospective, randomised, open-label, controlled trial with blinded end point assessment, which investigated the effect of aspirin in the primary prevention of atherosclerotic events in patients with type 2 diabetes. Owing to an unanticipated low event rate, the trial[44] could not demonstrate any significant reduction in risk of the composite primary outcome, namely any atherosclerotic event, in patients with type 2 diabetes studied nor in the majority of secondary outcomes. However, coronary and cerebrovascular mortality was reduced significantly with a HR of 0.10 (95% CI 0.01 to 0.79; $p = 0.0037$). Furthermore, the subgroup analysis identified those of > 65 years of age as potentially benefitting from aspirin treatment (HR 0.68, 95% CI 0.46 to 0.99; $p = 0.047$). The reported results are not easily generalisable to the European context, as atherosclerotic disease has a generally low incidence in Japan. Considering adverse events that were broadly grouped into GI bleeding, other bleeding, non-bleeding GI event and other, the study concluded that aspirin therapy was well tolerated in the participants, as there was no death due to haemorrhagic stroke and only a small increase in serious GI bleeding events, of which four required transfusion. However, considering all reported adverse events, the aspirin group had 12 GI bleeding events compared with four in the non-aspirin group; 32 patients experienced other bleeding events compared with six events in the non-aspirin group; and 47 non-bleeding GI events were noted in the aspirin group compared with six in the control group. Anaemia and asthma were reported four times and once in the aspirin group, respectively, but no event was reported in the control group. The design of the trial was of average quality because it was not placebo controlled, was not double blind, and allocation concealment was not reported. However, the reported results were consistent with the POPADAD trial[40] results.

Recommendations to use aspirin in the primary prevention of CVD in patients with diabetes could not be strongly supported by any findings of the studies. Studies therefore concluded that decision on the use of aspirin should be taken on an individual basis and should include weighing up benefits and harm, as no subgroup could be identified for which aspirin is clearly beneficial. Results seem to indicate that benefits may not exceed risks of major bleeding, particularly in patients who are at low risk of CV events and in people of > 70 years who are at high risk of bleeding.[65] Aspirin resistance and non-compliance are factors that need to be taken into consideration, as these can influence the effect of aspirin in the prevention of CVD events, particularly in patients with diabetes.

Summary of cardiovascular events in patients with diabetes

The searches identified seven systematic reviews meta-analysing the effect of aspirin in the primary prevention of CVD events in patient with diabetes. The majority of papers claimed that large and adequately powered trials are needed. Furthermore, studies are needed on the mechanisms of aspirin resistance in diabetes patients, optimal dose and frequency of aspirin. Subgroup analyses of elderly people, women and patients with poor glycaemic control need to be carried out. More specifically, factors that need to be further investigated include whether poor metabolic control, degree of insulin resistance and duration of diabetes could modulate the response to aspirin and could therefore influence the effect in patients with diabetes.

Appendix 8 Revised protocol: 2 September 2012

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.

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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:

1. 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.
2. With particular reference to adverse events, undertake an overview and quality assessment of the identified systematic reviews and meta-analyses.

3. 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.
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 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.)
6. 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 from 75 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 with 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 < 300 mg) for any indication. The aim of the scoping searches was to generate a rapid overview of evidence on the potential harms from prophylactic aspirin (< 300 mg) for any indication, and to gauge the current status of policy concerning aspirin prophylaxis in primary prevention. Details are provided in *Appendix 1.*

A more 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 September 2012.

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,* and selected publication types (systematic reviews, meta-analyses and randomised controlled trials).

(*MeSH floating sub-heading pc.fs which will be used in MEDLINE and EMBASE. An alternative will be considered for other databases.)

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

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 with 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, TX, 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

9. Team members' contributions

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9.1 Methodological advisors

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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.

9.2 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.

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11. 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 (< 300 mg) 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 (< 300 mg) 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:

Author's 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 gender:

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**

Author's 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

EME
HS&DR
HTA
PGfAR
PHR

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