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SYSTEMATIC REVIEW

A Systematic Review of Aspirin in Primary Prevention: Is It Time for a New Approach?

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Abstract

Background and Objectives While evidence in support of aspirin use in secondary prevention is well documented, the role of aspirin in primary prevention remains unclear. We conducted a systematic literature review to evaluate aspirin use in cardiovascular disease (CVD) and cancer primary prevention, and consider whether aspirin's role is set to become more clearly defined based on past and prospective studies.

Data Sources Utilizing PubMed, the reviewers identified appropriate Medical Subject Headings (MeSH) terms to establish CVD-based studies, cancer-based studies, and studies on adherence.

Study Eligibility Criteria Date restrictions of May 31, 2008 to May 31, 2013 were applied to capture the most robust meta-analyses and randomized controlled trials. Websites of relevant EU and US scientific societies were used to identify the key guidelines for aspirin use in primary prevention of CVD, and ClinicalTrials.gov was used to establish future or ongoing trials.

Results Evidence in support of aspirin prophylaxis is conflicting, though some meta-analyses have underlined potential benefit in reducing cardiovascular events. Despite this apparent benefit, bleeding risk with aspirin is consistently higher versus control, and remains a concern. A reduction of cancer incidence and mortality after a least 3 and 5 years treatment, respectively, is also apparent with aspirin.

Conclusion Available data on aspirin in primary prevention suggest a modest benefit for patients at high risk of CVD, and a promising benefit for those at risk of cancer. Future studies should help to elucidate whether the benefit of aspirin outweighs risk in appropriate patient groups.

Key Points

Aspirin appears to provide a somewhat modest benefit in primary prevention of cardiovascular disease; more well-defined patient groups to establish those who would benefit most from regular aspirin are required.

Data from post hoc analyses of aspirin use in primary prevention of cancer are promising, especially in colorectal cancer; however, the extent of aspirin benefit in a high-burden disease requires further investigation in randomized controlled trials.

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1 Introduction

Both cardiovascular disease (CVD) and cancer are leading causes of mortality worldwide. In 2008, of the 57 million deaths that occurred globally, 36 million of these—almost two-thirds—were due to non-communicable diseases (NCDs), of which CVD and cancer were responsible for 17 million (47 % of all NCD deaths) and 7.6 million (21 % of all NCD deaths), respectively [1].

Low-dose aspirin has been used for many years in the treatment and prevention of CVD. While the clinical benefits of aspirin for secondary prevention are well established, evidence on the role of aspirin for primary prevention is less clear. Current guidelines on the prophylactic use of aspirin vary widely, sometimes with conflicting recommendations. This may be due to varying interpretations of data from clinical trials of aspirin in primary prevention, which lead to differences in the perceived risk–benefit profile for aspirin.

Perception of the benefit versus risk ratio of aspirin for primary prevention may be influenced by the increasing body of evidence that aspirin reduces the risk of colorectal cancer (CRC) and other cancers [2, 3]. Recently revised guidelines on the management of Lynch syndrome (LS), which is the major, hereditary form of CRC, recommend the use of aspirin on the basis of long-term (i.e., 10 years) follow-up data from the CAPP2 trial, where aspirin significantly reduced the incidence of CRC in LS carriers [4].

As the overall benefit versus risk ratio is not yet clear, this paper systematically reviews the clinical evidence on the use of aspirin in primary prevention for CVD (with or without diabetes) and cancer. Moreover, it explores current use of aspirin in clinical practice and the clinical implications should subjects not adhere to their prophylactic regimen. Subsequent to these findings, we explore whether it is time for a new approach to the prophylactic use of aspirin by the most appropriate patient groups and make recommendations of our own while we await further outcome data from ongoing trials.

2 Methods

We conducted a systematic literature review, utilizing the PubMed database, to identify randomized controlled trials (RCTs) and meta-analyses of aspirin in the primary prevention of CVD (in subjects with and without diabetes) and cancer. We also investigated the impact of non-adherence and discontinuation of aspirin use once prescribed for primary prevention, and searched the websites of relevant EU and US scientific societies to identify the key guidelines for aspirin use in primary prevention of CVD.

2.1 Literature Searches and Data Extraction

The systematic review was conducted following the PRISMA guidelines. The search criteria can be observed in Table 1. The following search criteria to establish CVD-based studies on patients with or without diabetes were included: (clinical trial or meta-analysis), aspirin, primary prevention, and CVD. For the cancer search criteria, the following search terms were used: aspirin, cancer, and (meta-analysis or clinical trial). For all searches, the search was limited to human studies, English language was used, and date restrictions May 31, 2008 to May 31, 2013 were applied to allow for a 5-year assessment of the evidence base.

In order to be included, the meta-analyses had to (1) provide information on prophylactic aspirin use in relation to CVD or cancer incidence; and/or (2) have cancer in general or CRC incidence or mortality as an endpoint; (3) report original data and include hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs) and their 95 % confidence intervals (CIs); and (4) synthesize data from RCTs that compared aspirin therapy with placebo/vitamins in adults >18 years old with no history of CVD, or adults >18 years without cancer, though meta-analyses of observational and cohort studies were considered if they addressed point 1 of the criteria. Indeed, cancer is often studied observationally. Exclusion criteria for the meta-analyses included studies that were considered to be short term (less than 1 year of follow-up), and studies that were not published as full reports, such as conference abstracts and letters to editors. In addition, individual articles that were not of RCTs were excluded from this systematic review as cohort and case–control studies have limitations in the study design, which reduced the quality of the data obtained. Full text review was performed, and all authors determined the quality of articles. Risk of bias was considered and minimized by our chosen selection criteria.

For the search relating adherence to aspirin, the following search criteria were used: aspirin, primary prevention, CVD, and (prevalence or patient medication knowledge or patient adherence or medication adherence/persistence). Because of the low number of relevant publications retrieved, we analyzed all relevant studies that provided information on aspirin use in primary prevention, and therefore included cohort studies and cross-sectional studies. Additional publications identified in pertinent review articles were also reviewed. We understand the merit and limitations of these studies, and provide a narrative summation to help form our future hypotheses in the conclusions.

2.2 Data Synthesis

A narrative review of all extracted articles was undertaken; data reported from retrieved articles were either

Table 1 Search criteria for systematic review

Search strategy	Number of articles retrieved	Included	Excluded
Clinical trial[Publication Type] OR meta-analysis[Publication Type] AND "aspirin"[MeSH Terms] AND "primary prevention"[MeSH Terms] AND "cardiovascular diseases"[MeSH Terms] AND "humans"[MeSH Terms] AND English[Language] AND "2008/05/31"[PDAT]: "2013/05/31"[PDAT]	31	13	18
(("aspirin"[MeSH Terms] AND "neoplasms"[MeSH Terms]) AND (("meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]) OR clinical trial[Publication Type])) AND ("2008/05/31"[PDAT]: "2013/05/31"[PDAT]) AND (("2008/05/31"[PDAT]: "2013/05/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])	80	6	74
(((Aspirin[MeSH] AND primary prevention[MeSH] AND cardiovascular disease[MeSH] AND (Prevalence[MeSH] OR Patient Medication Knowledge[MeSH] OR Patient Adherence[MESH] OR Medication Adherence[MeSH] OR Medication Persistence[MeSH]))) AND ("2008/05/31"[Date—Publication]: "2013/05/31"[Date—Publication])	13	3	10

summarized or tabulated. The limitations for each study were considered and documented accordingly (e.g., publications bias and heterogeneity).

3 Results

3.1 Aspirin Use in the Prevention of Cardiovascular Disease

3.1.1 Cardiovascular (CV) Events

The search terms yielded 31 publications, of which nine were appropriate meta-analyses [5–13]. Ten primary studies are included in the meta-analyses, though only one of these was identified in our own search because of the publication date restrictions. The Early Treatment Diabetic Retinopathy Study (ETDRS) was included in three of the meta-analyses, though prevention of CVD was not the purpose of the study [14]. The nine trials that investigated aspirin for the primary prevention of cardiovascular (CV) events are listed in Table 2 [15–23]. Four additional subgroup or post hoc analyses for these trials were identified in our literature search, and are analyzed in the context of their original studies [24–27]. The meta-analyses and trials focused on patients with diabetes are described in a later section [9–13, 15, 19, 27].

The reasons for exclusion of the other 18 articles were varied; however, the most common reasons were review article ($n = 4$ articles), use of aspirin as a polypill ($n = 2$), use of aspirin in other indications ($n = 3$), and study of determinants of aspirin use ($n = 2$). The primary analysis of one retrieved meta-analysis [28] pooled data from primary and secondary prevention trials and was therefore excluded. No meta-analyses of observational studies of aspirin for primary CVD prevention were retrieved by the search terms. Inspection of one of the review articles obtained in the search [29] identified an additional relevant meta-analysis [30].

Details of the meta-analyses included are shown in Table 3 [5–13, 30]. The meta-analyses report reductions in CV events with aspirin treatment compared with non-aspirin treatment; however, the differences are significant in only a small number of cases (Table 4) [5–13, 30]. For example, a 12 % proportional reduction in serious vascular events [myocardial infarction (MI), stroke, or vascular death] was reported in Baigent et al. [5] (aspirin 0.51 % vs. control 0.57 % per year; $p = 0.0001$), which was largely due to a 23 % RR reduction for non-fatal MI (aspirin 0.18 % vs. control 0.23 % per year; $p < 0.0001$) (Table 2). The meta-analysis by de Berardis et al. [10] also explored sex-specific differences; aspirin significantly reduced the risk of MI among men by 43 % [three trials: Primary Prevention Project (PPP), ETDRS, and Physicians' Health Study (PHS); 3,126 participants; 265 events; RR 0.57 (95 % CI 0.34–0.94); $p = 0.03$]. Conversely, no effect of aspirin was observed among women [three studies: Women's Health Study (WHS), PPP, ETDRS; 3,176 participants; 245 events; RR 1.08 (95 % CI 0.71–1.65); $p = 0.71$]. In men, aspirin use was not associated with a reduced risk of stroke compared with placebo or no treatment [two trials: PPP and WHS; 2,593 participants; 93 events; RR 1.11 (95 % CI 0.75–1.64); $p = 0.61$], while in women, a risk reduction was observed [three studies: WHS, PPP, ETDRS; 3,176 participants; 127 events; RR 0.75 (95 % CI 0.37–1.53); $p = 0.43$], albeit deemed not significant. Of note, Berger et al. [31] investigated the sex-specific differences in these outcomes in a previous meta-analysis; these findings influenced guideline development and are discussed later in the review.

There was no evidence that aspirin significantly reduces CV mortality in the five meta-analyses that did not focus on patients with diabetes (Table 4). A similar effect was seen for all-cause mortality, although in one meta-analysis, the

Table 2 Summary of the key trials of aspirin in primary prevention

Study	Trial design	Treatment regimen	Primary endpoint(s)
British Doctors' Study (BDS) [20]	Randomized, non-blinded; apparently healthy male doctors aged 19−90 years ($N = 5,139$); 47 % aged <60 years); mean follow-up 6 years	Aspirin 500 mg/day (ordinary, soluble, or effervescent as desired) or enteric-coated aspirin 300 mg/day or no aspirin	Reduction in incidence of, and mortality from, stroke, MI, or other vascular conditions
Physicians' Health Study (PHS) [22]	Randomized, double-blind, placebo-controlled; healthy male physicians aged 40−84 years ($N = 22,071$); mean follow-up 5.2 years (terminated early)	Aspirin 325 mg every other day or no aspirin	Incidence of first MI (fatal, non-fatal, total), stroke (fatal, non-fatal, total), and combined events (non-fatal MI, non-fatal stroke, CV death)
Thrombosis Prevention Trial (TPT) [23]	Randomized, factorial, double-blind; men aged 45–69 years, at high risk of ischemic heart disease ($N = 5,499$); mean follow-up 6.8 years	Aspirin 75 mg/day and placebo warfarin, placebo aspirin and placebo warfarin, active aspirin and active warfarin, or placebo aspirin and active warfarin	All ischemic heart disease, defined as the sum of coronary death and fatal and non-fatal MI
Hypertension Optimal Treatment study (HOT) [18]	Randomized, double-blind; men and women with hypertension aged 50−80 years ($N = 18,790$); mean follow-up 3.8 years (range 3.3−4.9 years)	Aspirin 75 mg/day randomly added to antihypertensive treatment (felodipine and if necessary stepwise ACE inhibitors, beta-blockers, diuretics)	Incidence of CV complications
Primary Prevention Project (PPP) [16]	Randomized, open-label, factorial; patients (mean age 64.4 years) with one or more of the following: hypertension, hypercholesterolemia, diabetes, obesity, family history of premature MI, or individuals who are elderly ($N = 4,495$); mean follow-up 3.6 years (terminated early)	Aspirin 100 mg/day or no aspirin	Cumulative rate of CV death, non-fatal MI, and non-fatal stroke
Women's Health Study (WHS) [21]	Randomized, double-blind, placebo-controlled, 2 × 2 factorial; apparently healthy women aged ≥45 years ($N = 39,876$); mean follow-up 10.1 years (range 8.2−10.9 years)	Aspirin 100 mg every other day or placebo	Combination of non-fatal MI, non-fatal stroke, CV-related death Incidence of total malignant neoplasms of epithelial cell origin
Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial (JPAD) [19]	Multicenter, prospective, randomized, open-label, blinded study in Japan; patients ($N = 2,539$) aged 30–85 years with type 2 diabetes without a history of atherosclerotic disease; median follow-up 4.37 years	Aspirin 81 or 100 mg daily or no aspirin	Atherosclerotic events, including fatal or non-fatal ischemic heart disease, fatal or non-fatal stroke, and peripheral arterial disease
Prevention of Progression of Arterial Disease and Diabetes trial (POPADAD) [15]	Multicenter, randomized, double-blind, 2 × 2 factorial, placebo-controlled; adults ($N = 1,276$) aged ≥40 years with type 1 or 2 diabetes and an ankle brachial pressure index ≤0.99 but no symptomatic CVD; median follow-up for randomized participants 6.7 years	Daily aspirin 100-mg tablet plus antioxidant capsule ($n = 320$), aspirin tablet plus placebo capsule ($n = 318$), placebo tablet plus antioxidant capsule ($n = 320$), or placebo tablet plus placebo capsule ($n = 318$)	Two hierarchical composite primary endpoints: death from CHD or stroke, non-fatal MI or stroke, or amputation above the ankle for critical limb ischemia; and death from CHD or stroke
Aspirin for Asymptomatic Atherosclerosis Trial (AAAT) [17]	Randomized, double-blind, controlled; men and women ($N = 3,350$) aged 50–75 years who were free from CVD and had a low ankle brachial pressure index (≤0.95); mean (SD) follow-up 8.2 (1.6) years	Daily aspirin 100-mg aspirin (enteric coated) or placebo	Composite of initial fatal or non-fatal coronary event or stroke or revascularization

ACE angiotensin-converting enzyme, *CHD* coronary heart disease, *CV* cardiovascular, *CVD* cardiovascular disease, *MI* myocardial infarction, *SD* standard deviation

Table 3 Meta-analyses reporting use of aspirin for the prevention of CV events: main features

Meta-analysis	Publication year	Duration of follow-up (years)	Primary prevention studies included	Trial eligibility criteria	Aspirin doses included	Number of patients
Baigent et al. [5]	1988–2005	3.6–10.1	6 (BDS, PHS, TPT, HOT, PPP, WHS)	Includes randomized comparison of aspirin versus no aspirin Recruited ≥1,000 non-DM patients with ≥2 years of scheduled treatment	75–500 mg; daily and alternate days	95,000
Bartolucci et al. [6]	1988–2010	3.6–10.1	9 (WHS, BDS, PHS, HOT, PPP, TPT, AAAT, JPAD, POPADAD)	Not specified	75–325 mg/dl	>100,000
Berger et al. [30]	1988–2010	3.7–10	9 (WHS, BDS, PHS, HOT, PPP, TPT, AAAT, JPAD, POPADAD)	Randomized comparison of aspirin versus placebo or control Aspirin alone used for the primary prevention of CVD Data available on MI, stroke, and CV deaths	75–500 mg; daily and alternate days	>100,000
Raju et al. [7]	1988–2010	3.6–10.1	9 (WHS, BDS, PHS, HOT, PPP, TPT, AAAT, JPAD, POPADAD)	RCT Includes patients without a history of symptomatic CVD (>95 % of enrolled participants) Comparison of aspirin with placebo or no aspirin for prevention of CVD Reports at least one of the following outcomes: all-cause mortality, CV mortality, MI, stroke, and bleeding	75–500 mg; daily and alternate days	>100,000
Seshasai et al. [8]	1988–2010	3.6–10.1	9 (WHS, BDS, PHS, HOT, PPP, TPT, AAAT, JPAD, POPADAD)	Randomized placebo-controlled trials that had included ≥1,000 participants Primary prevention studies with ≥1 year of follow-up during which CHD and/or CVD outcomes (CHD, stroke, cerebrovascular disease, HF, and PAD) were recorded as the main endpoints, and details were provided of bleeding events	75–500 mg; daily and alternate days	>100,000
Butalia et al. [9]	1989–2008	3.6–10.1	7 (PHS, ETDRS, HOT, PPP, WHS, POPADAD, JPAD)	RCTs comparing aspirin versus cardiac-neutral comparator Included adults with DM without previous history or clinical evidence of CVD	75–650 mg: daily and alternate days	11,618
De Berardis et al. [10]	1989–2008	3.6–10.1	6 (PHS, ETDRS, PPP, WHS, POPADAD, JPAD)	Prospective, RCTs Open or blinded trials of participants with DM who were allocated to aspirin treatment or a control group (placebo or no treatment) for the primary prevention of CV disease	81–650 mg: daily and alternate days	10,117
Stavrakis et al. [11]	1989–2008	3.6–10.1	5 (POPADAD, JPAD, PPP, HOT, WHS)	Prospective, randomized, controlled, open or blinded trials Comparison of low-dose aspirin versus placebo or no treatment Inclusion of patients with no previous history of CVD, including MI, stroke, angina, TIA or symptomatic peripheral vascular disease (<10 % of patients with history of CVD allowed) Inclusion of patients with DM, either exclusively or as a subgroup Data on outcome measures of total and CV mortality, MI or stroke	75–100 mg: daily and alternate days	7,384 (with DM)
Younis et al. [12]	1989–2008	3.7–10.1	6 (PHS, HOT, PPP, WHS, JPAD, POPADAD)	RCTs that assigned patients with DM to either aspirin as a primary prevention strategy or placebo/no aspirin	75–325 mg; daily and alternate days	7,374

Table 3 continued

Meta-analysis	Publication year	Duration of follow-up (years)	Primary prevention studies included	Trial eligibility criteria	Aspirin doses included	Number of patients
Zhang et al. [13]	1989–2008	3.7–10.1	7 (PHS, ETDRS, HOT, PPP, WHS, POPADAD, JPAD)	Prospective RCTs Participants with DM Assignment of participants to aspirin therapy or control group for primary prevention of CV events Follow-up duration at least 12 months Any of the data about major CV events (a composite of CV mortality, non-fatal MI or non-fatal stroke), MI, stroke, all-cause mortality, CV mortality or major bleeding	75–325 mg; daily and alternate days	11,618

AAAT Aspirin for Asymptomatic Atherosclerosis Trial, *BDS* British Doctors' Study, *CHD* coronary heart disease, *CV* cardiovascular, *CVD* cardiovascular disease, *DM* diabetes mellitus, *ETDRS* Early Treatment Diabetic Retinopathy Study, *HF* heart failure, *HOT* Hypertension Optimal Treatment study, *JPAD* Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial, *MI* myocardial infarction, *PAD* peripheral arterial disease, *PHS* Physicians' Health Study, *POPADAD* Prevention of Progression of Arterial Disease and Diabetes trial, *PPP* Primary Prevention Project, *RCT* randomized controlled trial, *TIA* transient ischemic attack, *TPT* Thrombosis Prevention Trial, *WHS* Women's Health Study

reduction in patients receiving aspirin was of borderline significance [RR 0.94 (95 % CI 0.88–1.00); $p = 0.05$] [7].

In the WHS, the primary endpoint (major CV events) was not reduced significantly with aspirin use [RR 0.91 (95 % CI 0.80–1.03); $p = 0.13$], though risk of all-cause stroke and ischemic stroke were significantly reduced [RR 0.83 (95 % CI 0.69–0.99), $p = 0.04$, and RR 0.76 (95 % CI 0.63–0.93), $p = 0.009$, respectively] [21]. A post hoc analysis of this study, utilizing existing risk scores and an 'optimal fit' model to predict treatment effects for individual women in terms of absolute risk reduction for major CV events with aspirin concluded that aspirin appeared to be ineffective in the majority of females, but that selective treatment of women ≥65 years of age was of positive net benefit if the 10-year number-willing-to-treat (NWT) individuals was >50, but not if the NWT was ≤50 [24]. Since almost all women <65 years of age (99.2 %) had ≤2 % predicted absolute treatment effect, the authors of this study concluded that the place for aspirin in primary prevention in women is limited, with age being the strongest determinant of treatment effect. A separate subanalysis of the WHS aimed to explore the role of aspirin in CVD prevention in subjects with migraine; aspirin had similar protective effects on ischemic stroke for women with or without migraine [26]. By contrast, women with migraine with aura on aspirin had increased risk of MI. Authors acknowledge that this result should be cautiously interpreted.

In the primary RCT focusing on patients with hypertension [Hypertension Optimal Treatment study (HOT)], aspirin significantly reduced major CV events [RR 0.85 (95 % CI 0.73–0.99); $p = 0.03$], particularly MI [RR 0.64 (95 % CI 0.49–0.85); $p = 0.002$], though did not affect the overall incidence of stroke [RR 0.98 (95 % CI 0.78–1.24); $p = 0.88$] [18]. In a post hoc subgroup analysis of this study, it was concluded that the benefit of aspirin is amplified in patients with hypertension and chronic kidney disease, with progressive (but non-linear) increases in aspirin benefit for major CV events, MI, all-cause stroke, CV mortality, and total mortality with decreasing renal function [25]. Aspirin was associated with pronounced, statistically significant reductions in the endpoints of CV mortality, all-cause stroke, and all-cause mortality in patients with an estimated glomerular filtration rate (GFR) of ≤ 45 ml/min/1.73 m^2. These findings indicate a greater benefit of aspirin in patients with reduced GFR, which is likely attributable to these patients being at higher CV risk.

3.1.2 Bleeding Events

Of the six meta-analyses focusing on data from non-diabetes patients (Table 4), bleeding events were analyzed in five. Baigent et al. [5] reported a significantly increased

Table 4 Meta-analyses reporting use of aspirin for the prevention of CV events: main outcomes

Meta-analysis	Main CV outcomes (aspirin versus control)	Bleeding outcomes (aspirin versus control)	Heterogeneity in outcomes	Risk of publication bias
Baigent et al. [5]	Serious vascular events: 1,671 versus 1,883 [rate ratio 0.88 (95 % CI 0.82–0.94); $p = 0.0001$] Major coronary events: 934 versus 1,155 [rate ratio 0.82 (95 % CI 0.75–0.90); $p = 0.00002$] Stroke: 655 versus 682 [rate ratio 0.95 (95 % CI 0.85–1.06); $p = 0.4$] Vascular death: 619 versus 637 [rate ratio 0.97 (95 % CI 0.87–1.09); $p = 0.7$] Death from any cause: 1,669 versus 1,766 [rate ratio 0.95 (95 % CI 0.88–1.02); $p = 0.1$]	Major extracranial bleeding: 335 versus 219 [rate ratio 1.54 (95 % CI 1.30–1.82); $p < 0.0001$]	Serious vascular events: global test for heterogeneity based on predefined subgroups from baseline characteristics; $p = 0.7$ Major coronary events: men versus women heterogeneity $p = 0.03$ (not significant if considered in multiple comparisons)	N/A
Bartolucci et al. [6]	Total CHD: OR 0.854 (95 % CI 0.688–1.016); $p = 0.154$ Non-fatal MI: OR 0.813 (95 % CI 0.667–0.992); $p = 0.042$ Total CV events: OR 0.865 (95 % CI 0.804–0.930); $p = 0.001$ Stroke: OR 0.919 (95 % CI 0.828–1.021); $p = 0.116$ CV mortality: OR 0.956 (95 % CI 0.799–1.143); $p = 0.233$ All-cause mortality: OR 0.945 (95 % CI 0.881–1.014); $p = 0.115$	Listed only for each individual RCT study	Total CHD: $p = 0.001$ Nonfatal MI: $p = 0.042$ Total CV events: $p = 0.001$	No bias: $p > 0.05$
Berger et al. [30]	All-cause mortality: RR 0.94 (95 % CI 0.89–1.00); $p = 0.07$ CV mortality: RR 0.99 (95 % CI 0.85–1.14); $p = 0.86$ Major CV events: RR 0.90 (95 % CI 0.85–0.96); $p = 0.0006$ MI: RR 0.86 (95 % CI 0.74–1.00); $p = 0.06$ All-cause stroke: RR 0.94 (95 % CI 0.84–1.06); $p = 0.31$ Ischemic stroke: RR 0.87 (95 % CI 0.73–1.02); $p = 0.09$	Hemorrhagic stroke: RR 1.35 (95 % CI 1.01–1.81); $p = 0.04$ Major bleeding: RR 1.62 (95 % CI 1.31–2.00); $p < 0.00001$	No heterogeneity for all endpoints except MI, owing to a significant 63 % variation ($p = 0.006$)	No bias

Table 4 continued

Meta-analysis	Main CV outcomes (aspirin versus control)	Bleeding outcomes (aspirin versus control)	Heterogeneity in outcomes	Risk of publication bias
Raju et al. [7]	All-cause mortality: RR 0.94 (95 % CI 0.88–1.00); $p = 0.05$ CV mortality: RR 0.96 (95 % CI 0.84–1.09); $p = 0.51$ Major CV events: RR 0.88 (95 % CI 0.83–0.94); $p < 0.0001$ MI: RR 0.83 (95 % CI 0.69–1.00); $p = 0.05$ All-cause stroke: RR 0.93 (95 % CI 0.82–1.05); $p = 0.23$ Ischemic stroke: RR 0.86 (95 % CI 0.75–0.98); $p = 0.02$	Hemorrhagic stroke: RR 1.36 (95 % CI 1.01–1.82); $p = 0.04$ Major bleeding: RR 1.66 (95 % CI 1.41–1.95); $p < 0.00001$ GI bleeding: RR 1.37 (95 % CI 1.15–1.62); $p = 0.0003$	MI: $p = 0.0006$ (heterogeneity not evident when PHS was removed from analyses	No bias (Egger test p value > 0.05)
Seshasai et al. [8]	All-cause mortality: OR 0.94 (95 % CI 0.88–1.00) CV mortality: RR 0.99 (95 % CI 0.88–1.00) Total CVD: OR 0.90 (95 % CI 0.85–0.96) Total CHD: OR 0.86 (95 % CI 0.74–1.01) Stroke: OR 0.94 (95 % CI 0.84–1.06)	Total bleeds: OR 1.70 (95 % CI 1.17–2.46) Non-trivial bleeds: OR 1.31 (95 % CI 1.14–1.50)	CVD mortality: $I^2 = 36.1$ % (95 % CI 0.0–70.6 %) Total CHD: $I^2 = 64.8$ % (95 % CI 28.1–82.7 %) Stroke: $I^2 = 14.8$ % (95 % CI 0.0–56.9 %) Total bleeds: $I^2 = 98.0$ % (95 % CI 97.3–98.5 %) Nontrivial bleeds: $I^2 = 65.7$ % (95 % CI 30.3–83.1 %)	No bias (Egger test p value > 0.05)
Diabetes meta-analyses				
Butalia et al. [9]	MACE: RR 0.91 (95 % CI 0.82–1.00) Total MI: RR 0.85 (95 % CI 0.66–1.10) Total stroke (ischemic and non-ischemic): RR 0.84 (95 % CI 0.63–1.11) CV death: RR 0.95 (95 % CI 0.71–1.27) All-cause mortality: RR 0.95 (95 % CI 0.85–1.06) Other GI events not resulting in bleeding: RR 2.92 (95 % CI 0.17–50.23)	Hemorrhage: RR 2.50 (95 % CI 0.77–8.10) GI bleeding: RR 2.13 (95 % CI 0.63–7.25)	MI: $I^2 = 53.1$ % ($p = 0.046$)—exclusion of WHS and PHS reduced heterogeneity (14.2 %; $p = 0.324$) Ischemic stroke: $I^2 = 47.4$ % ($p = 0.091$)—exclusion of WHS diminished heterogeneity CV death: $I^2 = 41.1$ % ($p = 0.148$) exclusion of JPAD diminished heterogeneity	No bias (Egger test p value > 0.05)

Table 4 continued

Meta-analysis	Main CV outcomes (aspirin versus control)	Bleeding outcomes (aspirin versus control)	Heterogeneity in outcomes	Risk of publication bias
De Berardis et al. [10]	Major CV event: RR 0.90 (95 % CI 0.81–1.00); $p = 0.06$ MI: RR 0.86 (95 % CI 0.61–1.21); $p = 0.37$ Stroke: RR 0.83 (95 % CI 0.60–1.14); $p = 0.25$ CV mortality: RR 0.94 (95 % CI 0.72–1.23); $p = 0.68$ All-cause mortality: RR 0.93 (95 % CI 0.82–1.05); $p = 0.22$ GI symptoms: RR 5.09 (95 % CI 0.08–314.39)	Any bleeding: RR 2.50 (95 % CI 0.76–8.21) GI bleeding: RR 2.11 (95 % CI 0.64–6.95)	MI: $I^2 = 62.2$ %; $p = 0.02$—which may be explained by the WHS (weight 17 %) Stroke: $I^2 = 52.5$ %; $p = 0.08$—which may be explained by the WHS (weight 16 %) CV death: $I^2 = 56.6$ %; $p = 0.07$—which may be explained by the JPAD study	N/A
Stavrakis et al. [11]	Major CV events: HR 0.89 (95 % CI 0.70–1.13); $p = 0.33$ MI: HR 0.83 (95 % CI 0.40–1.72); $p = 0.62$ Stroke: HR 0.70 (95 % CI 0.44–1.11); $p = 0.13$ CV mortality: HR 0.99 (95 % CI 0.62–1.60); $p = 0.98$ All-cause mortality: HR 0.99 (95 % CI 0.82–1.20); $p = 0.91$	Major bleeding: statistically significant increase with aspirin with the fixed-effect pooled estimate [RR 2.51 (95 % CI 1.11–5.70); $p = 0.028$], but non-significant increase with aspirin in the random-effects pooled estimate [RR 3.02 (95 % CI 0.48–18.86); $p = 0.24$] GI bleeding: RR 2.12 (95 % CI 0.63–7.08); $p = 0.22$	No significant heterogeneity reported across the studies (note: power may be low to detect significant heterogeneity in this study)	N/A
Younis et al. [12]	Major CV events: RR 0.90 (95 % CI 0.78–1.05); $p = 0.17$ MI: RR 0.95 (95 % CI 0.76–1.18); $p = 0.63$ Ischemic stroke: RR 0.75 (95 % CI 0.55–1.02); $p = 0.07$ All-cause mortality: RR 0.96 (95 % CI 0.78–1.18); $p = 0.71$	Risk of bleeding: RR 2.49 (95 % CI 0.70–8.84); $p = 0.16$	MI: $Q = 13.20$	N/A
Zhang et al. [13]	Major CV event: RR 0.92 (95 % CI 0.83–1.02); $p = 0.11$ CV death: RR 0.95 (95 % CI 0.71–1.27); $p = 0.71$ MI: RR 0.85 (95 % CI 0.65–1.11); $p = 0.24$ Stroke: RR 0.83 (95 % CI 0.63–1.10); $p = 0.20$ All-cause mortality: RR 0.95 (95 % CI 0.85–1.06); $p = 0.33$	Major bleeding: RR 2.46 (95 % CI 0.70–8.61); $p = 0.16$	CV death: $I^2 = 41$ %; $p = 0.15$ MI: $I^2 = 55$ %; $p = 0.04$ Stroke: $I^2 = 44$ %; $p = 0.11$ Major bleeding: $I^2 = 82$ %; $p = 0.002$	No bias (Egger test p value > 0.05)

CHD coronary heart disease, *CI* confidence interval, *CV* cardiovascular, *CVD* cardiovascular disease, *GI* gastrointestinal, *HR* hazard ratio, *JPAD* Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes Trial, *MACE* major adverse cardiac events, *MI* myocardial infarction, *N/A* not applicable, *OR* odds ratio, *PHS* Physicians' Health Study, *RCT* randomized controlled trial, *RR* relative risk, *WHS* Women's Health Study

risk of major extracranial bleeding with aspirin [RR 1.54 (95 % CI 1.30–1.82); $p < 0.0001$], which was greater (non-significant) in patients with higher cholesterol. The excess risk of bleeds was mostly non-fatal. Perhaps by chance, fatal gastrointestinal (GI) or other fatal extracranial bleeds were lower in the aspirin group versus control [9 vs. 20; RR 0.48 (95 % CI 0.17–1.34)] [5]. Of the other four meta-analyses, one reported significant increases in hemorrhagic stroke [RR 1.36 (95 % CI 1.01–1.82); $p = 0.04$], major bleeding [RR 1.66 (95 % CI 1.41–1.95); $p < 0.00001$], and GI bleeding [RR 1.37 (95 % CI 1.15–1.62); $p = 0.0003$] [7], while another reported comparable increases in hemorrhagic stroke and major bleeding [16]. The meta-analysis by Seshasai et al. [8] reported a 70 % excess risk in total bleeds and 30 % of non-trivial bleeds (Table 4). One did not report pooled data for bleeding events [6].

3.2 Prophylactic Use of Aspirin for Prevention of CV Events in Patients With Diabetes

3.2.1 CV Events

Table 4 shows the main CV outcomes from five meta-analyses that focused on data from patients with diabetes. None of these analyses reported a significant protective effect of aspirin for prevention of CV events [9–13]. All of the point estimates for the major CV and mortality-related outcomes in these meta-analyses favored aspirin, and in the meta-analysis of Butalia et al. [9], the reduction in major adverse cardiac events (MACE) was of borderline significance ($p = 0.05$) (Table 4). No significant protective effect of aspirin has been observed in patients with diabetes, according to findings from the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) and Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trials [15, 19]. In a subanalysis of the JPAD trial, in patients with diabetes, the outcomes of patients with hypertension were compared with those of normotensive patients [27]. While the incidence of cerebrovascular events was higher in patients with hypertension relative to those without [HR 2.84 (95 % CI 1.52–5.52); $p = 0.0008$], use of aspirin reduced the incidence rate in patients with hypertension to a similar level to that in patients without hypertension [HR 1.64 (95 % CI 0.83–3.29); $p = 0.15$]. However, aspirin use did not significantly decrease the incidence of cerebrovascular events in the group of patients with hypertension [27].

3.2.2 Bleeding Events

The meta-analyses that focused on patients with diabetes also reported incidence of bleeding events (Table 2). Stavrakis et al. [11] reported a statistically significant increased risk of major bleeding with aspirin using a fixed-effect pooled estimate [RR 2.51 (95 % CI 1.11–5.70); $p = 0.028$]; however, the difference was no longer significant using a random-effects pooled estimate [RR 3.02 (95 % CI 0.48–18.86); $p = 0.24$]. Although the other meta-analyses reported numerically higher incidences of a range of bleeding categories with aspirin in patients with diabetes, none of these increases was statistically significant [9, 10, 12, 13]. This included the category of GI bleeding, for which a non-significant RR of 2.1 was reported in three of the meta-analyses [9–11]. Indeed, considering the bleeding risk in the two individual RCTs in patients with diabetes, in the POPADAD trial, the incidence of GI bleeding was not significantly increased in patients receiving aspirin [OR 0.90 (95 % CI 0.53–1.52); $p = 0.69$] [15]. In the JPAD trial, there was no significant difference in the composite of hemorrhagic stroke and severe GI bleeding between patients in the aspirin and non-aspirin groups, based on 17 such events that occurred during the study [19].

3.3 Prophylactic use of Aspirin in Colorectal Cancer

The search terms retrieved 80 articles, of which six were relevant meta-analyses (Table 4) [32–37]. Two additional meta-analyses evaluated data on aspirin for the prevention of colorectal adenoma, but these publications were not analyzed further because they were secondary prevention trials [38, 39]. Of the additional articles that were excluded, the most common reasons for exclusion were study on aspirin/non-steroidal anti-inflammatory drugs in other types of cancer ($n = 28$ articles), (pharmaco)genetic study ($n = 5$), and review article ($n = 3$). One article reported a systematic comparison of evidence from observational studies versus randomized trials [40]; however, there was no clear statement that the non-randomized studies included were primary prevention studies, and pooled data on the randomized trials in this article are already included in the meta-analysis by Rothwell et al. [34], which is included in Table 5. Five of the retrieved articles were RCTs [41–44].

3.3.1 Incidence

In a pooled analysis of six trials of daily low-dose aspirin for the primary prevention of CV events, during a follow-up period of 4–8 years, overall cancer incidence was reduced by 19 % [OR 0.81 (95 % CI 0.67–0.98); $p = 0.03$] after 3–4.9 years of aspirin use, increasing to 29 % at ≥5 years of use [OR 0.71 (95 % CI 0.57–0.89); $p = 0.003$], independent of age, sex, and smoking status [34]. In a related meta-analysis of five UK trials, a protective effect of aspirin against the development of new cancer was accompanied by a significant reduction in the

Table 5 Summary of meta-analyses evaluating the effect of aspirin use on cancer incidence and cancer-related mortality

Meta-analysis	Publication year	Mean duration of follow-up (years)	Studies included	Main study eligibility criteria	Aspirin doses included	Number of patients	Main findings	Heterogeneity	Publication bias
Rothwell et al. [32]	1991–2010	≥4	8 (BDS, UK-TIA, ETDRS, SAPAT, TPT, JPAD, POPADAD, AAAT)	Randomized trials of daily aspirin versus no aspirin Mean duration of treatment ≥4 years	75–1,200 mg; daily and alternate days	25,570	*Mortality* Overall OR for cancer-related death: 0.79 (95 % CI 0.68–0.92); $p = 0.003$ In 3 trials with long-term follow-up, OR for 20-year risk of death from CRC: 0.60 (95 % CI 0.45–0.81); $p = 0.0007$	Mortality: very small heterogeneity, *phet* = 0.84 No significant heterogeneity across the different gastrointestinal cancers ($p = 0.26$)	N/A
Rothwell et al. [33]	1988–2010	6.5 years	5 (BDS, AAAT, POPADAD, UK-TIA, TPT)	Randomized trials of aspirin versus no aspirin for prevention of vascular events UK trials only	≥75 mg/day	17,285	*Incidence* OR for new cancer: 0.88 (95 % CI 0.78–0.99); $p = 0.04$ HR for any cancer with distant metastasis: 0.64 (95 % CI 0.48–0.84); $p = 0.001$ *Mortality* OR for fatal incident cancer: 0.77 (95 % CI 0.65–0.91); $p = 0.002$ HR for fatal adenocarcinoma: 0.65 (95 % CI 0.53–0.82); $p = 0.0002$	No significant heterogeneity in the effect of aspirin on distant metastases	N/A
Rothwell et al. [34]	1998–2008	≥4 years	6 (TPT, POPADAD, AAAT, PPP, HOT, JPAD)	Randomized trials of low-dose aspirin for primary prevention	75–100 mg/day	35,535	*Incidence* Cancer incidence reduced from 3 years onwards [OR 0.76 (95 % CI 0.66–0.88); $p = 0.0003$] *Mortality* Cancer deaths reduced from 5 years onwards [OR 0.63 (95 % CI 0.47–0.86); $p = 0.004$] *Bleeding* Increased risk of major extracranial bleeds diminished over time [OR for 0–2.9 years 1.95 (95 % CI 1.47–2.59); OR for ≥5 years 0.63 (95 % CI 0.34–1.16)] *Net clinical benefit* Reduced risk of composite of major vascular events, cancer, or fatal extracranial bleed [HR 0.88 (95 % CI 0.82–0.94); $p = 0.0002$]	Non-vascular deaths: significant heterogeneity; $p < 0.0001$ No significant heterogeneity in the absolute annual risks	

Table 5 continued

Meta-analysis	Publication year	Mean duration of follow-up (years)	Studies included	Main study eligibility criteria	Aspirin doses included	Number of patients	Main findings	Heterogeneity	Publication bias
Bosetti et al. [35]	1988–2010	Not reported	139 in total; 30 evaluating CRC	Observational studies on aspirin use and cancer	Not reported	37,519	*Incidence* RR for CRC: 0.73 (95 % CI 0.67–0.79); $p < 0.001$	Heterogeneity between studies, p value < 0.001 for CRC studies (overall [including case–control and cohort] $I^2 = 75.5$ %)	Publication bias (Egger's test $p = 0.003$; Begg's test $p = 0.053$)
Mills et al. [36]	1983–2009	2.5	24 in total; 11 reporting cancer deaths	Randomized trials evaluating low-dose aspirin	75–325 mg/day	16,066 in cancer mortality trials	*Mortality* RR for cancer mortality: 0.77 (95 % CI 0.63–0.95); $p = 0.019$ Significant benefit of aspirin observed after a mean of 4 years' follow-up	No heterogeneity reported	N/A
Ye et al. [37]	1995–2012	Not reported	12 in total (5 reporting data on dose, 10 reporting data on frequency of use, 9 reporting data on duration)	Cohort (epidemiological) studies Providing data on aspirin use and CRC ≥3 exposure categories of aspirin (e.g., dose, frequency and duration)	162.5 to >4,500 mg/week	Not reported	*Incidence* Inverse relationship observed between CRC incidence and aspirin dose [RR 0.74 (95 % CI 0.64–0.83)], aspirin frequency [RR 0.80 (95 % CI 0.75–0.85)], and years of aspirin use [RR 0.75 (95 % CI 0.68–0.81)]	No evidence of heterogeneity among all studies included in this analysis	Slight publication bias for studies on frequency (Begg's test $p = 0.076$; Egger's test $p = 0.019$) and duration (Begg's test $p = 0.283$; Egger's test $p = 0.025$)

AAAT Aspirin for Asymptomatic Atherosclerosis Trial, *BDS* British Doctors' Study, *CI* confidence interval, *CRC* colorectal cancer, *ETDRS* Early Treatment Diabetic Retinopathy Study, *HOT* Hypertension Optimal Treatment study, *HR* hazard ratio, *JPAD* Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial, *N/A* not applicable, *POPADAD* Prevention of Progression of Arterial Disease and Diabetes trial, *OR* odds ratio, *PPP* Primary Prevention Project, *RR* relative risk, *SAPAT* Swedish Angina Pectoris Aspirin Trial, *TPT* Thrombosis Prevention Trial, *UK-TIA* UK Transient Ischemic Attack trial

incidence of cancer with distant metastasis [HR 0.64 (95 % CI 0.48–0.84); $p = 0.001$], with a significant benefit for adenocarcinomas, but not for other solid cancers [33]. Additional meta-analyses of observational and epidemiological studies provide supporting evidence for the protective effect of aspirin against cancer [35, 37]. In a meta-analysis of observational studies (case–control and cohort studies), there was a 27 % reduction in the risk of CRC with regular aspirin use [RR 0.73 (95 % CI 0.73–0.79); $p < 0.001$]; in terms of duration of aspirin use, the RR was 0.80 (95 % CI 0.71–0.91) for <5 years and 0.75 (95 % CI 0.70–0.80) for ≥5 years (P for heterogeneity = 0.369) [35]. Overall, risk reductions were stronger in case–control studies versus cohort studies, corresponding with a significant heterogeneity observed ($p < 0.001$). The authors believed the high variability of aspirin use definitions across studies may partly explain the heterogeneity observed in risk estimates across studies. Moreover, this meta-analysis included case–control studies, which might be subject to selection and recall bias, leading to heterogeneous results. Publication bias was also significant. Despite the publication bias reported, a consistent cancer risk reduction was apparent, supporting the causality of this association.

In order to elucidate the public health implication of aspirin use in cancer prevention, the dose–risk and duration–risk relationships were assessed by Ye et al. [37] in a separate meta-analysis. Based on their findings, Ye et al. [37] concluded that the threshold effect is a dose of 75–325 mg daily and 2–7 times per week; there was a non-linear relation between dose of aspirin use and CRC risk (P for non-linearity = 0.020). According to a random effects cubic spline model, there was stronger risk reduction for higher aspirin dose [RR 0.80 (95 % CI 0.74–0.88) for 325 mg per day, and RR 0.74 (95 % CI 0.65–0.83) for 650 mg per day]. This model, which included all studies on frequency of aspirin use (times per week), also indicated a non-linear relation between CRC risk and frequency of aspirin use (P for non-linearity = 0.007). Notably, there was a stronger risk reduction for people taking aspirin 7 times a week [RR 0.82 (95 % CI 0.78–0.87)] compared with twice per week [0.92 (95 % CI 0.88–0.95)]; this benefit was not strengthened in people taking aspirin more than 7 times a week [RR 0.82 (95 % CI 0.78–0.87) for 10 times per week] [37]. This meta-analysis included cohort studies only, with no evidence of heterogeneity observed across these studies.

3.3.2 *Mortality*

In a meta-analysis of eight trials including 25,570 patients, aspirin use significantly reduced the overall incidence of cancer-related death by 21 % [32]. When the analysis was confined to the three trials with long-term follow-up (≥5 years), a reduction in cancer mortality with aspirin was observed for all solid cancers [OR 0.80 (95 % CI 0.72–0.88); $p < 0.0001$] and GI cancers [OR 0.65 (95 % CI 0.54–0.78); $p < 0.0001$], but not hematological cancers [OR 1.03 (95 % CI 0.74–1.43); $p = 0.87$] (Fig. 1) [20, 23,

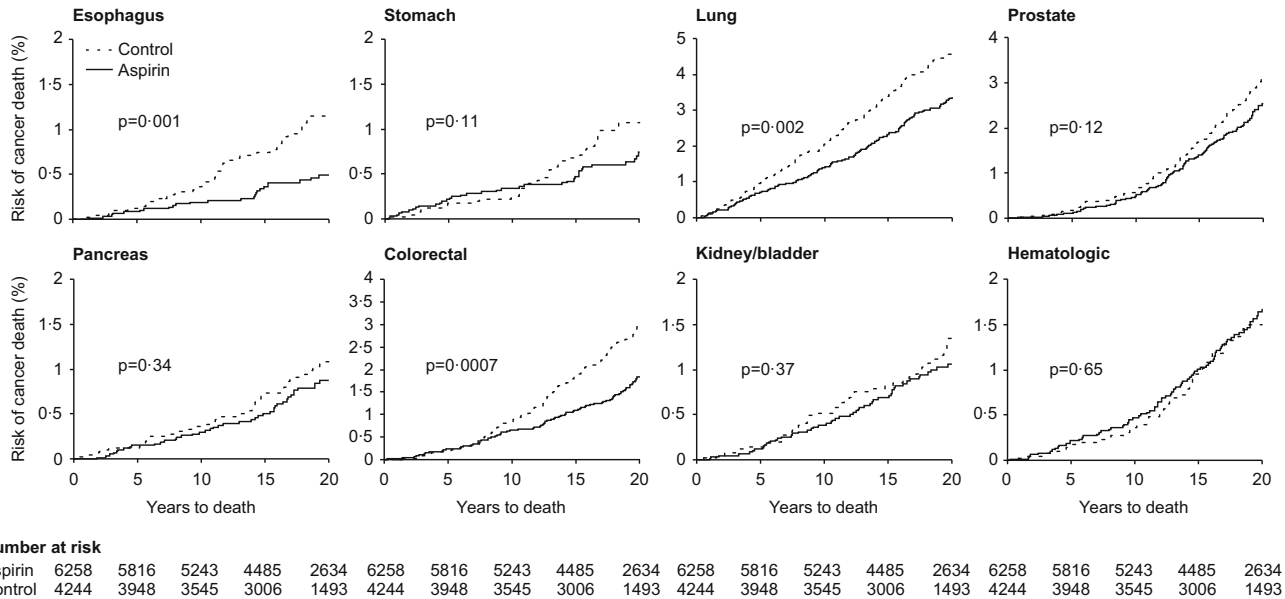

Fig. 1 Effect of allocation to aspirin versus control on the 20-year risk of death due to the most common fatal cancers in 10,502 patients with scheduled treatment duration of ≥5 years in three trials with long-term follow-up. Figure originally published in Rothwell et al. [32]. Reproduced with permission. Data are from a pooled analysis of three long-term follow-up trials [20, 23, 45]. All were randomized trials, during which patients received daily aspirin (75–1,200 mg) for ~4 to 6.8 years (mean follow-up). Long-term data for deaths due to cancer following completion of the trials were collected via the national death certification and cancer registration systems

32, 45]. There was a significant effect of aspirin on the 20-year risk of death from CRC [OR 0.60 (95 % CI 0.45–0.81); $p = 0.0007$], with a reduction in death evident from about 10 years onward. For deaths due to other cancers, such as esophageal or lung cancer, the benefit of aspirin was observed from 5 years onwards. In the meta-analysis of six trials of low-dose aspirin for primary prevention of CV events, cancer deaths were significantly reduced by 37 % from 5 years onwards [OR 0.63 (95 % CI 0.47–0.86); $p = 0.004$] [34]. In a further meta-analysis, aspirin also significantly reduced overall cancer mortality [RR 0.77 (95 % CI 0.63–0.95); $p = 0.019$] [36].

3.3.3 Bleeding Events

Of the included cancer-related meta-analyses, only one included results for adverse events attributable to aspirin use. In the meta-analysis of six trials, an increased risk of extracranial bleeding was observed with low-dose aspirin; however, the analysis of extracranial bleeding stratified by period of follow-up revealed that the risk of extracranial bleeding decreases over time, becoming comparable to that of placebo or no aspirin from 3 years onwards: <3 years, OR 1.95 (95 % CI 1.47–2.59); 3–4.9 years, 1.37 (0.87–2.14); ≥5 years, 0.63 (0.34–1.16) ($p = 0.003$ for interaction) [34]. In this same analysis, fewer cases of fatal bleeding were associated with aspirin use, compared with controls [8/203 vs. 15/132, respectively; OR 0.32 (95 % CI 0.12–0.83); $p = 0.009$] [34].

3.4 Aspirin Utilization

Our search string for this topic identified 13 publications, of which only three publications were deemed relevant.

In a cross-sectional study of aspirin use in Wisconsin, USA, for primary prevention (with data from the Survey of the Health of Wisconsin), only 31 % of the 268 participants (aged 35–74 years) for whom aspirin was indicated, according to United States Preventive Services Task Force (USPSTF) guidelines, were using it regularly (defined as ≥4 times per week) [46]. Among these participants with an aspirin indication, older patients and women had a significantly higher likelihood of regular aspirin intake compared with younger participants and men (OR 1.07, $p < 0.001$, and 3.49, $p = 0.021$, respectively) [46]. In a retrospective, cross-sectional cohort study in community outpatients in Italy, only 15.2 % of 151,526 patients free from CVD received an aspirin prescription for primary prevention, despite being eligible for regular aspirin use according to the official guidelines stipulated by the Italian Medicine Agency. Indeed, patients with either type 2 diabetes and age >40 years or without type 2 diabetes but aged ≥55 years (men) or ≥65 years (women) with at least one risk factor (obesity, dyslipaemia, smoking cigarettes, hypertension, family history of CVD) were considered eligible [47]. A study conducted in the USA between 2005 and 2007 showed that the prevalence of regular aspirin (≥3 days per week) use for primary prevention was only 31 and 44 % for the 3,431 individuals at increased and high risk of coronary heart disease (CHD), respectively, with important racial and ethnic disparities [48].

3.5 Aspirin Adherence

Data on adherence to aspirin therapy for primary prevention of CV events are relatively scant. Indeed, the authors of a 2012 meta-analysis of studies that assessed patient adherence to CV preventive treatment for either primary or secondary prevention reported that no trials reporting adherence to aspirin therapy for primary prevention were identified [49].

A post hoc analysis of the WHS (study detailed in Table 2) [21] used statistical models to estimate the effect of continuous aspirin treatment on CV events [50]. Whereas the intent-to-treat population had small but non-significant reductions in total CV events [RR 0.91 (95 % CI 0.81–1.03); $p = 0.13$] and CV mortality [RR 0.95 (95 % CI 0.74–1.22); $p = 0.68$], adjustment for aspirin non-compliance strengthened the effect of aspirin on CVD mortality, albeit without statistical significance [RR 0.76 (95 % CI 0.54–1.08); $p = 0.13$].

3.6 What Do the Guidelines Say?

A summary of current guidelines for aspirin use in primary prevention is provided in Table 6 [51–55]. The majority of existing guidelines are based on meta-analyses and systematic reviews of the nine clinical trials for aspirin in primary prevention. The assessment and interpretation of these data can vary, leading to different outcomes for overall aspirin risk–benefit. Because of their basis on the nine aspirin primary prevention of CVD trials, most guidelines {European Society of Cardiology (ESC) [52], USPSTF [55], American Heart Association/American Stroke Association (AHA/ASA) [54], American Diabetes Association (ADA) [51]} only consider the benefits of a reduction in CV risk versus potential harms from bleeding. However, recommendations from different guideline bodies are sometimes conflicting. For example, the ESC 2012 guidelines state that aspirin cannot be recommended for primary prevention in patients without overt CVD, because of the increased risk of major bleeding (although it is recommended for some special patient groups, i.e., hypertensive patients without a history of CVD, patients with reduced renal function, and those at high CV risk) [52]. In contrast, the American College of Chest Physicians

Table 6 Overview of current guidelines on the use of aspirin in primary prevention

Organization	Recommendation
European Society of Cardiology (ESC) [52]	In patients without overt CVD, aspirin cannot be recommended in primary prevention because of increased risk of major bleeding
	Antiplatelet therapy may be considered in hypertensive patients without a history of CVD, but with reduced renal function or at high CV risk
	Antiplatelet therapy with aspirin is not recommended for people with diabetes who do not have clinical evidence of atherosclerotic disease
American Diabetes Association (ADA) [51]	Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased CV risk (10-year risk >10 %). This includes most men aged >50 years or women aged >60 years who have at least one additional major risk factor (family history of CVD), hypertension, smoking, dyslipidemia, or albuminuria
American College of Chest Physicians (ACCP) [53]	Persons aged ≥50 years without symptomatic CVD: low-dose aspirin 75–100 mg daily
American Heart Association/American Stroke Association (AHA/ASA) [54]	Use of aspirin CV prophylaxis is recommended for persons whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment (i.e., 10-year risk of CV event = 6–10 %)
	Aspirin can be useful for the prevention of a first stroke among women whose risk is sufficiently high for the benefits to outweigh the risks associated with treatment
	Aspirin is not useful for preventing a first stroke in persons at low risk
	Aspirin is not useful for preventing a first stroke in persons with diabetes or diabetes plus asymptomatic peripheral artery disease in the absence of any other CVD
United States Preventive Services Task Force (USPSTF) [55]	Encourage men aged 45–79 years to use aspirin when the potential benefit of a reduction in MI outweighs the potential harm
	Encourage women aged 55–79 years to use aspirin when the potential benefit of a reduction of ischemic stroke outweighs the potential harm

CVD cardiovascular disease, *CV* cardiovascular, *MI* myocardial infarction

(ACCP) 2012 guidelines suggest daily low-dose aspirin (75–100 mg) in people aged ≥50 years without symptomatic CVD [53]. The latter recommendations are based on an evaluation of the preventive benefit of aspirin on both CVD and cancer. The remaining guidelines cited in Table 6 recommend, in one way or another, the use of aspirin in specific groups of patients in primary prevention.

Both the USPSTF [55] and AHA/ASA [54] guidelines have specific recommendations for men and women. The USPTF guidelines recommend aspirin for men age 45–79 years when the potential benefit due to a reduction in MI outweighs the potential harm, while aspirin is only recommended for women age 55–79 years when the potential benefit of a reduction in ischemic strokes outweighs the potential harm. AHA guidelines also specifically recommend against aspirin use in men for stroke prevention, while stating that aspirin can be useful in women whose risk of stroke is sufficiently high enough for the benefits to outweigh the harms of treatment. When considering patients with diabetes, both ADA and AHA recommend aspirin therapy (75–162 mg/day) for primary prevention of heart disease for people with diabetes aged >40 years or who have additional risk factors for CVD and no contraindications to aspirin therapy [51, 54]. Currently, only the ACCP guidelines also mention data showing a reduction in cancer risk with aspirin [53].

4 Discussion

4.1 CV Benefits

Recent meta-analyses provide evidence of a modest benefit for aspirin in primary CV prevention, with a number of studies reporting statistically significant reductions in serious CV events, which did not extend to a reduction in CV or all-cause mortality across these studies [5–7]. The lack of statistical significance for outcomes related to mortality in some of these analyses might be attributed to the fact that the majority of patients included in these studies were not at high risk of CVD.

Although CV benefit was not observed in patients with diabetes enrolled in primary prevention trials, it has been suggested that these trials were not adequately powered to attain a reliable answer [56]. Indeed, in the JPAD trial, the investigators predicted 52 primary CV events per 1,000 person-years, but the actual rate was only 17 events per 1,000 person-years, therefore reducing the statistical relevance. Another possible explanation for the poor level of prevention afforded by aspirin in this patient population could be a reduced efficacy of low-dose aspirin in suppressing platelet function. It is hypothesized that faster resynthesis of platelets in patients with diabetes and thereby a faster resynthesis of megakaryocyte/platelet

cyclooxygenase (COX) isozymes may allow sufficient recovery of COX-1 activity during the 24-h dosing interval (particularly between 12–24 h), to overcome the antiplatelet effect of aspirin [57, 58]. Evidence from human pharmacokinetic studies suggests that twice-daily administration of low-dose aspirin in patients with diabetes reverses this pattern of insufficient COX-1 activity inhibition seen with a single daily aspirin dose [58]; however, trials with a clinical outcome parameter are required to confirm these preliminary findings. Another approach might be to increase the aspirin dose in resistant patients with diabetes. Results from a recent subanalysis of the Aspirin Versus/Or Clopidogrel in Aspirin-resistant Diabetics inflammation Outcomes (AVOCADO) trial showed that doubling the aspirin dose from 75 mg to 150 mg once daily improved platelet reactivity suppression in patients with type 2 diabetes and high platelet reactivity versus aspirin 75 mg once daily [59].

4.2 Cancer Benefit

Evidence from primary RCTs demonstrate a reduction in the incidence of CRC and mortality from CRC with daily aspirin therapy [32–34, 36, 60]. In the meta-analysis by Rothwell et al. [32], aspirin reduced mortality by about 20 %. The reduction in cancer-related mortality observed was consistent across trials, despite the different populations included in the trials. Furthermore, the benefit of aspirin seems to be limited to certain cancers, with the most apparent benefit observed in adenocarcinomas, and by the length of treatment. Indeed, aspirin was only found to reduce cancer incidence from 3 years onwards [324 vs. 421 cases; OR 0.76 (95 % CI 0.66–0.88); $p = 0.0003$], and benefit of aspirin on reducing cancer mortality was only apparent from 5 years onwards of treatment [66 vs. 104 deaths; OR 0.63 (95 % CI 0.47–0.86); $p = 0.004$] [34]. Of note, as a reduced cancer mortality is not observed in people treated with warfarin, which has a similar bleeding profile to aspirin, it is unlikely that diagnostic procedures carried out early on in the investigations due to unexpected bleeding were the reason for lower cancer mortality [32].

Unlike the meta-analysis of RCTs observing no dose-response effect on cancer outcomes [32], the meta-analysis of cohort studies by Ye et al. [37] reported an inverse relationship between CRC incidence and aspirin dose and aspirin frequency [37], with a 75- to 325-mg daily dose 2–7 times per week considered to provide optimal benefit. In the same analyses, there was also suggestion that longer-term (>5 years) use of aspirin is necessary in order to demonstrate a protective effect on cancer risk [37], which is concordant with conclusions drawn by Rothwell et al. [32, 33] and consistent with 'true' prevention of the disease. On the topic of duration of aspirin exposure, a more clear cancer benefit in women has been observed with aspirin use lasting for 10 or more years, such as in the 82,911 women in the Nurses' Health Study [61]. The benefit observed in this study appears to be dose dependent, with a trend ($p < 0.001$ for trend) in benefit observed by number of aspirin taken in a week [risk reduction in women taking aspirin >14 times a week 0.68 (95 % CI 0.49–0.95)]. Moreover, women who took more than 14 aspirin a week, 10 years preceding the study, had an even lower RR of 0.47 (95 % CI 0.31–0.71). That said, the incidence of major GI bleeding was also dose related, which again highlights the consideration required when determining the optimal dose of aspirin for benefit to supersede risk.

Similarly, and more recently, during the development of our review article, an update of the WHS on alternate-day aspirin use and cancer incidence, which was outside the time points given in our search criteria, was published [62]. Understanding of the apparent lag time before cancer benefit is observed; the WHS aimed to decipher whether alternate-day, low-dose aspirin use for 10 years [median active treatment of 10.3 years (range 8.2–10.9)] is associated with reduced risk of CRC in a post-treatment follow-up period (median follow-up of up to 18 years) [62]. A total of 33,682 women agreed to continue participation, with slightly more women in the aspirin arm compared with the placebo arm [16,913 (89.1 %) vs. 16,769 (88.2 %); $p = 0.006$]. Unlike the original WHS [21] not showing clear CRC benefits during the active 10-year treatment phase, a post-treatment benefit in incidence of CRC was observed. Indeed, cancer incidence was lower in those taking aspirin [HR 0.80 (95 % CI 0.67–0.97); $p = 0.021$] than placebo, primarily due to a reduction in proximal colon cancer [HR 0.73 (95 % CI 0.55–0.95); $p = 0.022$], with the effect emerging after 10 years. The post-trial reduction in CRC was 42 % [HR 0.58 (95 % CI = 0.42–0.80); $p < 0.001$] [62]. Women who used aspirin during the active treatment phase but did not use aspirin post-trial had a 33 % lower rate of CRC [HR 0.67 (95 % CI 0.43–1.02)], while those who continued with aspirin use had a 43 % lower rate of CRC [HR 0.57 (95 % CI 0.35–0.93)].

Understanding that the effects of aspirin are not apparent until at least 3 years after starting aspirin treatment, a couple of studies have aimed to estimate the overall benefits and harms of aspirin over a 5- or 10-year period. A review of aspirin in cancer prevention conducted a 5-year risk analysis of the combined vascular and major bleeding events obtained from the ATT analysis of the six primary prevention trials (primary prevention trials of aspirin versus placebo) with a hypothetical 10 % reduction in cancer incidence by age and sex. This analysis showed a net benefit of aspirin use for both men and women, with an

even greater benefit for men aged ≥65 years, compared with women or subjects of a younger age [3]. It is important to note, the authors' calculations of benefits after 5 years of use were based on an assumed reduction in overall cancer incidence with aspirin and not on empirical data. This may underestimate the reduction in cancer incidence that would occur with continued aspirin use beyond 10 years. A separate review that was published during the development of this article aimed to explore the 'best estimates' for individuals taking aspirin for 10 years by synthesizing data from available evidence on cancer, CVD (data obtained from ATT analysis) and its harm, and modeled these effects using general population data from the UK [63]. For individuals taking aspirin for 10 years, Cuzick et al. [63] estimated a 'relative' reduction of ~9 % in the number of men and 7 % in the number women with a cancer, MI or stroke event over a 15-year period. Absolute reductions (conservative estimate) ranged from 0.68 to 3.09 % in men and women; reductions in cancer incidence were estimated to account for 61–80 % of the overall benefit, with reductions in CRC accounting for 30–36 % of it. Major bleeding events increased by between 0.16 and 0.81 % from baseline rates of 0.57–2.37 % over a 15-year period. Based on these harms, the net relative benefit was calculated to be about 6 %. Relative reductions in cancer mortality were greater than that calculated for incidence (4 % relative reduction all deaths); concordant with trial data, no net reduction in CV-related deaths was reported. The relative benefit for mortality was more profound in men than in women, because of the lower baseline death rate from these diseases. Overall, these analyses suggest a net benefit for a minimum of 5 years of aspirin use, which heightens with 10 years of use in both men and women ranging between ages 50 and 65.

So what renders aspirin seemingly cancer protective? The mechanism of action of aspirin in cancer prevention is not yet fully understood. Although the inflammatory-related gene COX-2 has been found to be over-expressed in adenomas, the protective effect of low-dose aspirin has been found to predominate in patients whose COX-2 expression was initially low [64]. Indeed, the main characteristics of the chemopreventive effect of low-dose aspirin are not consistent with either a direct inhibitory effect on COX-2 or with a COX-independent mechanism of action. Instead, it is hypothesized that aspirin may reduce the metastatic spread by acting through platelet-mediated mechanisms; indeed, permanent inactivation of platelet COX-1 may play a key role in preventing colorectal adenoma formation, by suppressing the induction of COX-2 expression in adjacent cells [3, 65]. Aspirin may also have a role in directing modulation of oncogene-induced expression of transcription factors and promotion of tumor cell apoptosis [66].

4.3 Establishing the Benefit Versus Bleeding Risk

The meta-analyses and randomized trial evidence demonstrate the increased risk of bleeding with aspirin is unequivocal, with most reporting a consistently high bleeding risk profile with aspirin use compared with control. However, data regarding the influence of age, underlying comorbidities (e.g., uncontrolled hypertension), and duration of use and dose of aspirin on bleeding risk are limited and conflicting.

Previous reviews of the literature have cited that increasing age per se should not be considered a significant risk factor for bleeding induced by low-dose aspirin [67]; rather, older patients in general have a much greater absolute risk of GI complications (GICs) than their younger counterparts [67], because there is a sharp increase in baseline risk of upper GICs (UGICs) in general among individuals aged ≥70 years [68]. Moreover, evidence shows that rates of UGICs are higher in subjects with non-complicated or complicated ulcers, compared with those without GI symptoms, and bleeding risk increases with age, irrespective of type of ulcer [68]. Notwithstanding, deaths from GI bleeding attributable to aspirin appear not to be increased [34]. Another aspect that should be considered is the possibility of concomitant *Helicobacter pylori* infection influencing bleeding risk. Evidence addressing the role of *H. pylori* and bleeding risk is currently conflicting [69, 70]. Future studies (discussed in the next section) should help to qualify whether determining *H. pylori* status, in addition to age, sex and history of bleeds, is an important step towards profiling the right patient, with the least risk of bleeding, prior to commencement of aspirin prophylaxis.

4.4 Limitations

There exist some differences in trial design and patient characteristics among the RCTs that explored aspirin in CVD primary prevention; indeed, the primary endpoints and treatment regimens (e.g., aspirin once-daily vs. every other day) differed across each of the RCTs. Subsequent to these differences, when these RCTs were analyzed in the meta-analyses discussed in our review, statistical heterogeneity was reported among some of the efficacy and safety outcomes. Notably, when Butalia et al. [9] from their analyses of seven RCTs removed PHS and WHS, being the largest of the trials, heterogeneity substantially decreased. Thus, these meta-analyses have taught us that appropriately sized trials, with more specific patient segregation designed to consider different CVD risk profiles, are warranted to aid more definitive conclusions on the patient group that would likely benefit from aspirin in primary prevention of CVD.

Moreover, when considering the cancer benefit with aspirin use, although promising findings have been

observed in meta-analyses of RCTs [32–34, 36, 60], a limitation of these analyses is that they are derived from studies analyzing aspirin in CVD protection where cancer was in most (with exception of WHS) not the primary outcome. In addition, we place caution on findings retrieved from a meta-analysis of observational studies; we need to consider the limitations inherent to observational studies, related in particular to measurement errors in the exposure to aspirin and the variability of aspirin use.

Regarding limitations of our own review, despite having rigorously reviewed the eligible articles extracted utilizing the specific search strings given in Table 1, we limited our search to the PubMed database, and restricted the search between two particular time points (between the years 2008 and 2013). However, we are confident of aspirin in primary prevention being well catalogued between these time points, and that the key articles of interest have been reviewed here. During the preparation of our manuscript, a robust systematic review by Sutcliffe et al. [71] re-evaluated aspirin use in primary prevention by estimating event rates, performing modeling on specific outcomes (i.e., all-cause mortality) and estimated heterogeneity in order to further rationalize the benefit of aspirin use according to the much scrutinized existing evidence base. Beyond analyzing the current data, our objective was to also review the evidence on studies on adherence of aspirin and on the recommendations of international guidelines, as well as presenting a hypothesis on the future direction of aspirin in primary prevention in anticipation of prospective and ongoing trials that may shed greater light on this subject.

4.5 Future Direction and Study Needs

A net benefit of aspirin that outweighs the risk of bleeding has been demonstrated when considering reductions in CV events and cancer together [34], thus one can speculate that aspirin may have a greater role in the primary prevention of both of these diseases in the near future. As such, it has been suggested that CRC benefits should be incorporated into CHD risk scores in order to determine the benefit-to-risk ratio for aspirin use [72].

To identify those patients for whom aspirin is most appropriate, it is of our opinion a new individual approach to assessment that considers the combined benefits of aspirin as well as bleeding risk is required. Future criteria that might define a subject eligible for primary prevention with aspirin may include:

- Healthy subjects with a significantly increased risk of CVD using available risk charts.
- Healthy subjects with a significantly increased risk of cancer, in particular, CRC.
- Healthy subjects with a combined moderate risk of both CVD and cancer.

The ASPREE trial, an ongoing randomized, double-blind study in the USA and Australia (expected to be completed by December 2018), should provide further evidence as to whether the benefits of daily aspirin use in healthy, elderly people outweigh the risks. The study is recruiting 19,000 healthy individuals aged over 70 years who will receive 100 mg of aspirin or placebo daily for 5 years. The composite primary endpoint termed 'disability-free life' includes onset of dementia, total mortality, or persistent disability in at least one of the Katz Activities of Daily Living, and the secondary endpoints [all-cause specific mortality, fatal and non-fatal CV events, fatal and non-fatal cancer (excluding non-melanoma skin cancer), dementia, mild cognitive impairment, depression, physical disability, and clinically significant bleeding] will be compared. The results of this large trial should provide further insight into the risks versus overall benefits of aspirin prophylaxis. However, we note that any trial with short follow-up could potentially miss the net benefit, especially of fatal and non-fatal cancer. Indeed, aspirin for cancer prevention has a long lag time before benefits are observed, while conversely the harms appear in the early part of the treatment, particularly in those above 70 years of age.

To resolve some of the uncertainties around aspirin use in patients with diabetes, the results of ongoing clinical trials of aspirin in patients with diabetes, such as the Aspirin and Simvastatin Combination for CV Events Prevention Trial in Diabetes (ACCEPT-D; International Standard Randomized Controlled Trial Number: 48110081) and A Study of Cardiovascular Events iN Diabetes (ASCEND; ClinicalTrials.gov identifier: NCT00135226), are keenly awaited. Notably, these trials are more powered to assess the efficacy in reducing CV events than the past investigative trials discussed in our review, and should shed better light on the role aspirin plays in this clinical scenario.

Strategies to improve the bleeding profile of aspirin are recommended for appropriate patients. For example, co-administration of aspirin with a gastroprotective drug, such as proton pump inhibitors, should be considered for patients at high risk of UGICs, as these can lead to non-adherence and discontinuation with aspirin therapy [73]. While there are conflicting data on the role of *H. pylori* as a risk factor for UGICs with low-dose aspirin [69, 70], the ongoing large-scale outcomes study Helicobacter Eradication Aspirin Trial (HEAT; ClinicalTrials.gov identifier NCT01506986) promises to provide more definitive information on the relationship between *H. pylori* infection and GI bleeding during aspirin use. However, the limitation

of this trial is that it investigates current users of aspirin and does not account for the proportion of individuals who discontinue aspirin because of GI symptoms.

Aspirin is currently underutilized in primary prevention [47]. The full extent, reasons, and consequences of aspirin underuse is poorly understood; reasons for underutilization may be related to the patient, condition, therapy or healthcare system. The highest-risk patients are frequently older with cognitive or physical impairments, or multiple comorbidities requiring polypharmacy. They may also hold negative perceptions about aspirin bleeding risk or have a low motivation to take indefinite therapy.

Since 'healthy' individuals are asymptomatic from a CV viewpoint, and the benefits of aspirin for primary prevention are not visible, while adverse events are obvious, counseling is important and should include discussion of the benefits of prophylaxis with patients prior to starting aspirin use. Adherence should be monitored and effective strategies to encourage therapeutic adherence employed. There is also a need for greater public education on aspirin for primary prevention, including information on the risks of inappropriate aspirin use and the consequences of discontinuation [47].

5 Conclusions

Emerging data from prospective studies of the protective effect of aspirin on cancer, combined with its proven effect on reduction of CV events, are likely to be included in future evaluations of benefit versus risk conducted by guideline bodies. This may influence recommendations on the use of aspirin for primary prevention, not only for CV events, but also cancer. Since CVD and cancer share a number of common risk factors, including a sedentary lifestyle, obesity, diabetes, poor diet, and smoking [74], and also share some disease mechanisms, a combined approach to prevention would be logical. However, unlike CVD risk assessment, there is some difficulty in assessing cancer risk (except for cases with familial and genetic factors) in clinical practice. Thus, profiling a patient who would benefit from aspirin in primary prevention of cancer should be based on their risk of bleeding rather the risk factors for cancer.

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Conflicts of interest Dr Carlos Brotons is a member of the Executive Committee for the ARRIVE trial, which is sponsored by Bayer HealthCare. Professor Limmroth has received honoraria as a speaker or consultant from Allergan, Bayer HealthCare, BiogenIdec, Bristol-Myers Squibb, Novartis, Pfizer, Roche, Merck Serono, and Teva. All authors participated as paid consultants in a roundtable meeting on the use of aspirin in primary prevention, sponsored by Bayer HealthCare. The authors declare that there are no other conflicts of interest, that they have full control of the primary data, and that they agree to allow the journal to review the data if requested.

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