Aspirin for the Prevention of Cancer Incidence and Mortality: Systematic Evidence Reviews for the U.S. Preventive Services Task Force

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Abstract

Background: Cancer is the second leading cause of death in United States; colorectal cancer (CRC) is the third most commonly diagnosed cancer in men and women.

Purpose: To conduct systematic reviews on aspirin's effects on total cancer and CRC mortality and incidence.

Data Sources: MEDLINE, PubMed, and the Cochrane Collaboration Registry of Controlled Trials from January 2004 (CRC) or January 2011 (total cancer) through January 2015.

Study Selection: Two investigators independently reviewed abstracts and articles against inclusion and quality criteria.

Data Extraction: Data from 20 trials were abstracted by one reviewer and checked by another.

Data Synthesis: Based on 10 cardiovascular disease (CVD) primary prevention trials (n=103,787), we found a non-significantly slightly reduced cancer mortality risk in individuals randomized to aspirin compared to no aspirin over 3.6-10.1 years (relative risk [RR], 0.96 [95% CI, 0.87 to 1.06]). Among 72,926 participants in six trials, cancer incidence was similar between groups (RR, 0.98 [95% CI, 0.93 to 1.04]). Data from two CVD primary prevention and two CVD secondary prevention trials (n=14,033) showed reduced long-term (0-20+ year) CRC mortality among persons assigned to aspirin (RR, 0.67 [95% CI, 0.52 to 0.86]). Three primary and one CVD secondary prevention trials (n=69,535) suggested no effect on CRC incidence within approximately 10 years of aspirin initiation (RR, 0.99 [95% CI, 0.85 to 1.15]). Pooled analyses of two primary and one CVD secondary prevention trials (n=47,464) showed a reduced risk of CRC incidence 10-19 years after aspirin initiation (RR, 0.60 [95% CI, 0.47 to 0.76]).

Limitations: Most data in our review were collected from CVD trials in primary prevention populations with clinical and methodological heterogeneity across studies. Limited data were available to assess cancer-specific effects and subgroup differences.

Conclusions: In CVD primary prevention populations, aspirin appears to reduce risk of and perhaps mortality from CRC 10 or more years after initiation, but does not clearly affect total cancer incidence or mortality.

Primary Funding Source: Agency for Healthcare Research and Quality

Introduction

In the United States (U.S.), the lifetime risk of cancer is 43.3% in men and 37.8% in women (1) and cancer is the second leading cause of death (2). In 2015, there will be an estimated 1,658,370 new cancer cases and 589,430 cancer deaths (3). As such, primary prevention of cancer is an important public health objective. Chemoprevention (4) of cancer with aspirin is of particular interest as a primary prevention strategy.

We found no established groups who currently recommend aspirin use for prevention of cancer, in general or for specific cancers (5-9), except for consideration in certain groups at high risk for CRC, such as persons with Lynch syndrome (10). Consistent with the U.S. Preventive Services Task Force's (USPSTF's) 2007 findings (11), the American Cancer Society recommends against aspirin use for colorectal cancer (CRC) prevention in the general population (3). In updating its recommendation, the USPSTF considered cancer prevention, including CRC, as contributing to an assessment of the net benefits and harms of aspirin use in a population eligible for the primary prevention of cardiovascular disease (CVD). This manuscript summarizes two concurrent systematic reviews (12, 13) that addressed the effects of aspirin use on total cancer incidence and mortality and on CRC incidence and mortality specifically. These reviews were used in conjunction with the full evidence review on cardiovascular disease events (14) and a decision model (15) to update USPSTF recommendations on aspirin use. Companion manuscripts addressing complementary issues of cardiovascular disease (16) and bleeding harms (17) should be considered alongside this manuscript for a complete picture of benefits and harms in a CVD primary prevention population.

Methods

We developed an analytic framework and key questions to evaluate the relationship between aspirin use and 1) cancer-related and all-cause mortality; 2) cancer incidence; 3) CRC mortality; 4) CRC incidence; 5) colorectal adenoma incidence; 6-7) and harms of aspirin use specific to the review focus (**Web Appendix Figure 1**). This manuscript focuses on cancer mortality and incidence, with all-cause mortality and harms in companion papers. Results on adenoma incidence and CRC incidence and mortality in persons with prior adenomas are available in the full report (12). The full reports for the USPSTF also describe our methods in detail (12, 13).

Data Sources and Searches

We conducted literature searches separately for total cancer and CRC but used similar methods. For total cancers, we based our review on two individual patient data meta-analyses (18, 19) of randomized controlled trials (RCTs) that tested the effects of daily aspirin on cancer incidence and/or mortality (13), supplemented through a comprehensive bridge search of PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials (January 1, 2011-January 6, 2015). We also reviewed of bibliographies of previous and concurrent USPSTF reviews (12, 14, 20, 21) and other recent relevant reviews. Similarly, for CRC we assessed all studies from the previous USPSTF review (20), performed a comprehensive search using the databases listed above from January 1, 2004-January 6, 2015, and examined reference lists of relevant literature.

Study Selection

Total cancer. Pairs of investigators independently reviewed titles, abstracts, and full-text articles of studies against pre-specified criteria (12, 13). We included RCTs or controlled clinical trials conducted in adults (aged ≥40 years) that compared regular oral aspirin use (≥75 milligrams [mg] at least every other day) for ≥1 year for any indication to placebo or no treatment. We excluded randomized arms that included other antithrombotic or chemopreventive agents and trials in adults with a personal history of cancer or a high prevalence of familial cancer syndromes (e.g., Lynch syndrome). We limited the review to trials published in English and conducted in countries with a "very high" Human Development Index in 2013 (22).

Colorectal cancer. Inclusion and exclusion criteria were similar to the total cancer review with a few exceptions: we included prospective cohort studies in the full report (not reported here as they did not alter conclusions (12)); we did not exclude studies of patients with prior cancers other than CRC; and we did not restrict by country.

Data Extraction and Quality Assessment

Pairs of investigators independently assessed the quality of included studies using USPSTF criteria (23) and supplemented the quality criteria for systematic reviews with the Assessment of Multiple Systematic Reviews (24). Good-quality studies met the majority of criteria. Fair quality studies did not meet, or did not clearly meet, all criteria for a good-quality study. Poor quality studies (i.e., greater than 40% attrition, greater than 10% difference in attrition between groups, other fatal flaws, or multiple minor flaws or missing important information significant enough to limit our confidence in the validity of results) were excluded.

One investigator abstracted data from included studies and another checked the data for accuracy.

Data Synthesis and Analysis

Our full reports contain more detailed analysis to consider the applicability of cancer results to the CVD primary prevention clinical topic (12, 13). For all cancer results, we focus this paper on results from CVD primary prevention trials, except when results suggested by individual patient-data meta-analysis of a broader set of studies require context through additional analyses. For CRC, we analyzed all trials together due in part to the limited number of studies and present results stratified by follow-up period after aspirin initiation (early onset: 0-10 years; late-onset: 10-20 years; long-term 0-20+ years) because of apparent differences in effect by time since initiation of aspirin. Study population (primary versus secondary prevention) and dosage are noted for clarity.

We defined aspirin use by dose: high-dose as >325 mg per day; low-dose as ≤325 mg per day; and very low-dose as ≤100 mg per day (14). We defined intended duration of aspirin use as the mean in-trial followup if it was not reported. We use "duration" as short-hand in the text for this concept.

We used the Mantel-Haenszel fixed effects model to estimate effects when combining studies (25). We used Stata 12.0 (StataCorp LP, College Station, TX) for all statistical analyses. We conducted sensitivity analyses by aspirin dose (≤325 mg, ≤100 mg), frequency (daily use), and intended duration of treatment.

We explored pre-specified subgroups of interest including age, sex, race/ethnicity, baseline cancer risk (family history and other cancer risk factors), and diabetes status. We were unable to pool results due to the limited number of contributing studies.

Role of Funding Source

Agency for Healthcare Research and Quality staff provided oversight for the project. USPSTF liaisons helped to resolve issues around the scope of the review, but were not involved in the conduct of the review.

Results

Description of Included Trials

We identified 20 fair- or good-quality randomized controlled trials (RCTs) of aspirin that provided cancer outcomes (**Table 1**) (26-45). Nine were RCTs of daily aspirin in CVD primary prevention populations (26-34), two were of alternate day aspirin use for primary CVD and cancer prevention (35, 36), and nine were RCTs of daily aspirin for CVD secondary prevention (37-45). Persistence of aspirin use was generally high (≥85%) in the first year of the studies, declining to 50%-83% after 3-5 years, with substantial variability across studies; these results are detailed in our full report (12).

Ten CVD primary prevention studies included in the companion review (14) provided total cancer mortality data and six provided total cancer incidence data (**Table 1**). Analyses of CRC mortality and incidence included six and four of the CVD primary prevention trials, respectively, as well as two CVD secondary prevention trials. For CRC, most outcomes came from three individual patient data meta-analyses by Rothwell and colleagues (18, 46, 47) of daily aspirin in either primary or secondary prevention of CVD studies. Separate CRC outcomes were

reported for Women's Health Study (WHS) (35) and the Physicians Health Study (PHS) (**Table 2**).

Effect of aspirin on total cancer mortality

Within trial. Across 10 fair- or good-quality RCTs of aspirin for CVD primary prevention, mean duration ranged from 3.6 to 10.1 years (1,513 total cancer deaths among 103,787 participants; **Table 1**) (27-36). While participants randomized to aspirin tended towards slightly fewer cancer deaths, these differences were not statistically significant (relative risk [RR], 0.96 [95% CI, 0.87 to 1.06]; **Figure 1**).

Dose, frequency and duration of use. In sensitivity analyses, we found few differences from our main analysis, whether restricting to trials of daily use, lower dosage, or longer duration, or adding in additional trials primarily conducted in CVD secondary prevention populations (**Web Appendix Table 1**). An individual patient-data meta-analysis (18) using seven primary prevention trials of daily aspirin with a median ≥4 years duration reported reduced total cancer mortality in aspirin arms by 18% (hazard ratio [HR], 0.82 [95% CI, 0.70 to 0.95]), with effects mainly after five years. Three of these seven trials tested high-dose daily aspirin (28, 33, 43). When we included CVD secondary prevention populations (**Web Appendix Figure 2**) *and* allowed any dosage daily aspirin for a median ≥4 years (7 trials (28, 29, 31-34, 43); 559 cancer deaths; n=20,990), we found a similar 17% reduction in cancer mortality (RR, 0.83 [95% CI, 0.70 to 0.98). However, these data represented less than 25% of participants in the CVD primary prevention trials, due to exclusion of alternate day aspirin users and shorter duration studies.

In a separate meta-analysis of CVD primary and secondary prevention trials of daily aspirin that included trials with shorter durations (≥90 days) (k=34 trials; n=69,224, 1,226 cancer deaths) (19) *a priori* stratified analysis showed no differences in cancer deaths until ≥5 years, except for an effect during the first three years among trials of high-dose aspirin. Analyses of various categories of cancer deaths in both individual patient-data analyses suggested reductions among solid gastrointestinal cancers and adenocarcinomas (but not hematological, solid non-gastrointestinal cancers, or non-adenocarcinomas) after ≥5 years of aspirin. Analyses were limited, however, by relatively few site-specific cancer deaths and lack of testing for subtype effects. Both individual patient-data analyses (18, 19) excluded data from two large good-quality U.S. trials of alternate day aspirin for CVD primary prevention (35, 36).

Post-trial follow-up. WHS (n=39,876) reported a cumulative risk of cancer death after 17.5 years from randomization (~4%) that was similar between groups (HR, 0.97 [95% CI, 0.88 to 1.07] (48). While 11% of randomized women opted out from post-trial observation, adjusting the sensitivity analyses to account for imbalances between groups using inverse probability weighting did not impact other main study findings.

An individual patient-data meta-analysis (18) reported cancer mortality 20-years after randomization in two CVD primary prevention trials in men (31, 33) and a CVD secondary prevention trial in men and women (43) (n=14,033), with median duration of 4 to 6.8 years. Longer treatment duration was significantly related to decreased 20-year risk of non-hematological cancers (interaction, p=0.01), with no benefit for <5 years intended use and greatest benefit for ≥7.5 years. Among the 10,502 (83%) randomized participants with ≥5 years of intended treatment (1,378 cancer deaths), those allocated to aspirin had 22% fewer deaths due to all cancers after approximately 0 to 10, 10 to 20, or 0 to 20 years (HR, 0.78 [95% CI, 0.70 to

0.87]). No data were reported to determine if groups remained comparable at baseline after excluding 17% of originally randomized participants who had <5 years intended treatment. Specific cancer mortality findings were limited by power and methodological and clinical heterogeneity; however, exploratory analyses suggested minimal treatment duration (5 to 10 years) and latency to mortality reduction (5 to 20 years) may vary across cancer types.

Effect of aspirin on total cancer incidence

Within trial. End-of-trial cancer incidence results (4,294 incident cancers among 72,926 participants) were available for six fair- or good-quality RCTs of aspirin for primary prevention of CVD after a mean duration of 3.6 to 10.1 years (**Table 1**) (27, 29, 30, 33-35). Cancer risk was similar in the aspirin versus no aspirin groups (RR, 0.98 [95% CI, 0.93 to 1.04]; **Web Appendix Figure 3**). These results did not change when we included the results from four additional RCTs among CVD secondary prevention populations (**Web Appendix Figure 4**) (38, 41, 44, 45). Sensitivity analyses that were identical to those for cancer mortality yielded parallel unchanged results (**Web Appendix Table 1**). Similarly, we found a marginally statistically significant reduction in cancer incidence only when we restricted this analysis to selected trials of daily aspirin that had a median ≥4 years intended duration and simultaneously included CVD secondary prevention studies (45) (k=4; n=11,800; RR, 0.86 [95% CI, 0.74 to 0.99]).

In time-to-event individual patient-data meta-analysis (19) of six trials of daily low-dose aspirin in primary prevention populations (27, 29-32, 34), overall cancer incidence (combining fatal and nonfatal cancers) was reduced (HR, 0.88 (95% CI, 0.80 to 0.98) with effects beginning after 3 to 4 years, with statistically significant greater effects as follow-up duration increased beyond three years (interaction with duration, p=0.04) (19). Estimating the cumulative risk at the

end of study follow-up (after *a priori* exclusion of studies reporting fatal cancers only (32) and warfarin co-treatment (31)), we found an attenuated effect (RR, 0.92 [95% CI, 0.82 to 1.02]) (27, 29, 30, 34).

Post-trial follow-up. Overall cancer incidence (5,071 cases, excluding non-melanoma skin cancers) was not reduced among aspirin users in age-adjusted analyses (HR, 0.97 [95% CI, 0.92 to 1.03]) after a median of 17.5 years in WHS (48), whether data were analyzed over the entire follow-up period or stratified by within-trial or post-trial period. Cancer incidence was not reduced at any specific non-CRC site (including *a priori* secondary study outcomes of breast or lung cancer) either cumulatively, within, or post-trial period, though most other cancer types were relatively uncommon and the lack of significant findings may be due to power. Even when grouped by type, only gastrointestinal cancer incidence was reduced in the post-trial follow-up period, while incidence of urinary tract, respiratory tract, reproductive tract, and hematologic cancers was unaffected.

Effect of aspirin on CRC mortality

All pooled data come from a mixture of primary and secondary CVD populations, only two of which had cancer has an *a priori* outcome (35, 36). Pooled data from two CVD primary prevention trials (31, 33) and two CVD secondary prevention trials (40, 43) (n=14,033) showed a reduced long-term cumulative risk of CRC mortality (0 to ≥20 years) among patients assigned to take 75 to 1,200 mg/day of aspirin ≥1 year (median intended duration ≥2.5 years) compared to non-users (RR, 0.67 [95% CI, 0.52 to 0.86]) (**Figure 2**) (46). Based on data from three of these trials with ≥5 years daily treatment (31, 33, 43), aspirin reduced CRC mortality beginning 10 to 20 years after randomization (HR, 0.51 [95% CI, 0.35 to 0.74]), but not before (HR, 0.79 [95%

CI, 0.49 to 1.26]) (18). An individual patient-data meta-analysis (18) used data from six trials for the primary or secondary prevention of CVD with a median intended duration ≥4 years (29, 31-34, 43) (n=19,824) to examine the effect of 75 to 1,200 mg/day aspirin. It did not report a statistically significant effect on CRC mortality during the first 5 years after randomization (HR, 0.78 [95% CI, 0.39 to 1.56]), but did find an effect after ≥5 years of in-trial follow-up (HR, 0.41 [95% CI, 0.17 to 1.00]) (18). WHS found no effect on CRC mortality with very low-dose aspirin taken on alternate days during the first 10 years of follow-up (data not shown) but they did not report on late or long-term risk of CRC mortality (35).

Dose, frequency, and duration of use. Evidence on dose was limited to four trials of daily aspirin for CVD primary (31, 33) or secondary prevention (40, 43) that employed dosages varying from 75 to 1,200 mg per day (n=14,033). All included RCTs randomized patients to daily aspirin use and could not, therefore, compare daily to alternate-day use. Analyses, described in more detail in the full report, did not clearly suggest an effect of dose (12). An individual patient-data meta-analysis (46) of the same trials observed a significant association between longer scheduled duration of daily aspirin use and greater CRC mortality reduction (p=0.04) (31, 33, 40, 43) .

Effect of aspirin on CRC incidence

Based on three primary (33, 48, 49) and one secondary (43) CVD prevention trial (n=69,535), there was no effect on CRC risk within approximately 10 years of aspirin initiation (RR, 0.99 [95% CI, 0.85 to 1.15]) (**Figure 3a**). Our pooled analyses of two primary and one secondary prevention CVD trial (n=47,464) suggested that aspirin reduced the risk of CRC incidence by about 40% between approximately 10 to 19 years after initiation (33, 43, 47, 48)

(RR, 0.60 [95% CI, 0.47 to 0.76]) (**Figure 3b**). An individual patient-data meta-analysis of four CVD primary and secondary prevention trials (46) showed a reduced long-term cumulative risk (0 to ≥20 years) of CRC (HR, 0.76 [95% CI, 0.63 to 0.94]) (31, 33, 40, 43). The estimate in WHS after a median of 17.5 years was similar (HR, 0.80 [95% CI, 0.67 to 0.97]) (48).

Dose, frequency, and duration of use. None of the trials directly compared aspirin dosages. An individual patient-data meta-analysis that conducted preplanned analyses of aspirin dose, however, observed similar effects on CRC incidence whether restricting to patients randomized to 75 or 300 mg/day or overall (results not shown) (46). No trial directly compared the effect daily versus alternate-day aspirin use on CRC incidence. We found little data on the effect of treatment duration (46, 47); our findings are described in detail in the full report (12).

Subgroup Differences

Limited evidence did not clearly suggest variation in the effect of aspirin on total cancer or CRC mortality or incidence by age, sex, or other subgroups. Details are described in the full reports (12, 13).

Discussion

Summary of Evidence

Based on 10 CVD primary prevention trials that reported end-of-trial cancer-related outcomes, we found no significant reduction in total cancer mortality (RR, 0.96 [95% CI, 0.87 to 1.06]). Others have concluded no established protective effect for aspirin on total cancer mortality in the CVD primary prevention population based on similar analyses (50). In four trials of primary and secondary CVD prevention populations, we found that aspirin reduced CRC

mortality over approximately 20 years of follow-up (RR, 0.67 [95% CI, 0.52 to 0.86]). This effect occurred only after 5 years of follow-up. A large U.S. trial of women taking very low-dose alternate day aspirin for CVD and cancer primary prevention reported no total cancer mortality effect after 10.1 years of treatment and 17.5 years of follow-up, but did not report results for CRC mortality separately.

Effects of aspirin on total cancer incidence within 10 years of aspirin initiation were generally small (2% reduction) and not statistically significant, even when restricted to studies with daily dosing and median ≥4 years of scheduled treatment. Only the analysis that included either CVD primary or secondary prevention populations assigned to daily aspirin (75 to 500 mg) for ≥4 years showed a statistically significant reduction in cancer incidence after 4.2 to 8.2 years. Longer-term follow-up data were available on CRC incidence in three studies, including WHS, and suggested a 40% reduction in risk approximately 10 to 19 years after randomization. A pooled analysis of these studies plus one another showed no effect during the first 10 years after randomization. Over a 20-year period, the cumulative effect was an approximately 20% reduction in CRC incidence in persons assigned to take aspirin.

Data were too limited to generate consistent or definitive results for any specific type of cancer beyond CRC. Nonetheless, exploratory analyses suggested that adenocarcinomas and/or solid cancers of gastrointestinal origin may respond to aspirin chemoprevention. Additional data from applicable populations using low-dose aspirin will likely clarify and extend these findings.

Our findings on aspirin's effect on total cancer differed from those reported in a widely reported meta-analysis that found a 21% statistically significant reduction (95% CI, 8% to 32%) in cancer mortality (18). However, this meta-analysis used a somewhat different set of included studies than our CVD primary prevention trials analysis by allowing trials in CVD secondary

prevention but restricting analyses to daily aspirin use for a median treatment duration of ≥4 years (18). Similarly, other analyses of cancer outcomes from the same group have often relied on subsets of trials that could provide longer-term followup (13). However, these analyses also differ in terms of the populations and interventions they represent from the body of CVD primary prevention trials, which could impact findings away from those that would be expected in the population of interest (51).

Cuzick and colleagues used a modeling approach to conclude that benefits of initiating at least 5 years of 75-325 mg/day of aspirin at ages 50-65 years outweighed risks (52). Model inputs (RRs) were qualitatively derived from recent reviews of RCTs and observational studies. Comparing our two reviews has limitations as Cuzick and colleagues did not present an overall estimate for total cancers, and we do not present estimates for individual cancers other than CRC as they were not frequently reported. RR estimates for aspirin and CRC incidence and mortality differ from ours in part because Cuzick and colleagues focused on daily use (i.e., did not include WHS or PHS) and included observational studies.

Limitations

Several limitations in available data impacted our review. Most data used in our review were collected *post hoc* as part of follow-up studies of CVD trials (18, 19, 46, 47). Clinical and methodological heterogeneity across studies complicated interpretation of subsets of trials with longer-term data needed to study aspirin's effect on cancer. Limited data were available to assess cancer-specific effects (18, 35) and subgroup differences. Data on cancer risk factors, such as family history, were generally unavailable. We also could not address questions about how long the effects of aspirin continue after the end of treatment.

Aspirin is one of the most extensively studied medications. As such, establishing appropriate exclusion criteria was essential to managing this review's scope. Thus, we focused on RCTs and individual patient-data meta-analysis of CVD primary prevention trials to enhance validity for total cancer outcomes and to ensure applicability to the clinical context of primary prevention of CVD and cancer combined. Observational studies may provide information on subgroup effects once efficacy is established, particularly for individual cancers. We did consider prospective cohort studies in our review of aspirin and CRC incidence and mortality, and, despite imprecision of exposure data, findings were generally consistent with trial data (12).

The perspective of our review does not inform the consideration of potential cancer benefits in those taking aspirin for secondary prevention of CVD or those who might take aspirin long-term for other reasons.

Emerging directions and areas for future research

Longer-term follow-up from trials could provide important information on cancer-specific and overall cancer effects of aspirin, particularly with respect to the size and timing of chemopreventive benefits, dose-response relationships, effect of duration of use, and differences across subgroups. The primary data for aspirin's effects on a range of health outcomes has not changed substantially over the past several years, but the field is poised to provide additional data in the near future. Several large trials are in progress (53-56), for example, and future syntheses of existing and emerging evidence should be forthcoming from the Non-Vascular outcomes on Aspirin (NoVA) Collaboration, which aims to collate all data from previous and ongoing trials of aspirin in order to provide as complete data as possible on short-term and long-term effects of aspirin (57). Observational studies or trials focused on subgroups defined by

genotype, lifestyle factors, or biomarkers may also provide important data to understand which subgroups are more or less likely to benefit from aspirin use (58-61).

Conclusion

In CVD primary prevention populations taking low-dose aspirin for chemoprevention, a beneficial effect on total cancer mortality or incidence is not clearly established. Data remain limited for effects on specific cancers, except perhaps for CRC. Evidence from primary and secondary prevention studies suggests that aspirin reduces the risk of CRC incidence, and perhaps mortality with an apparent time to preventive effect of approximately 10 or more years.

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Table 1. Brief description of included studies, limited to trials reporting cancer outcomes

Author, Year	Population	N rand	Mean Age and Range (years)	% Female	Aspirin Dose, Concomitant Treatment, and Frequency	Mean Intended Treat-ment Duration (years)	Cancer-specific Key Question
CVD Primary Prevention Trials (reporting CVD and cancer outcomes)							
Belch, 2008 (POPADAD) (34)	Diabetics and ABI ≤ 0.99	1,276	60.3 (≥ 40)	55.9	100 mg alone or with antioxidants qd*	6.7†	1, 2, 3
Cook, 2005 (WHS) (35) Cook, 2013 (48)	Health professionals	39,876	54.6 (≥ 45)	100	100 mg alone or with vitamin E or beta-carotene qod*	10.1	1, 2, 3, 4
de Gaetano, 2001 (PPP) (27)	≥ 1 CVD risk factor	4,495	64.4 (≥ 50)	57.5	100 mg alone or with 300 mg vitamin E qd*	3.6	1, 2
ETDRS, 1992 (28)	Diabetics and diabetic retinopathy	3,711	NR (18-70)	43.5	650 mg qd*	5	1
Fowkes, 2010 (AAA) (29)	ABI ≤ 0.95	3,350	62.0 (50-75)	71.5	100 mg qd	8.2	1, 2, 3
Hansson, 1998 (HOT) (30)	Hypertension	19,193	61.5 (50-80)	47	75 mg qd*	3.8	1, 2
MRC, 1998 (TPT) (31)	High-risk for IHD	2,540 (5,085)‡	57.5 (45-69)	0	75 mg alone or with warfarin started at 2.5 mg qd*	6.9†	1, 3, 4
Ogawa, 2008 (JPAD) (32)	Diabetics	2,539	64.5 (30-85)	45.4	81 or 100 mg qd	4.4†	1, 3
Peto, 1988 (BMD) (33)	Physicians	5,139	61.6 (NR)	0	500 mg, or 300 mg if requested qd	6	1, 2, 3, 4
PHS, 1989 (36, 49)	Physicians	22,071	53.2 (40-84)	0	325 mg alone or with 50 mg beta-carotene qod*	5.0	1, 4
CVD Primary Prevention Trials (reporting cancer outcomes only)							
DAMAD, 1989 (26)	Diabetics and diabetic retinopathy	314	46.7 (17-67)	35.4	330 mg tid (990 mg total per day)	3	1
CVD Secondary Prevention Trials							
AMIS, 1980 (44)	Prior MI	4,745	54.8 (30-69)	11.1	500 mg bid (1,000 mg total per day)	3.2	2
Brighton, 2012 (ASPIRE) (41)	Prior DVT or PE	822	54.5 (≥ 18)	45.6	100 mg qd	3.1†	1, 2
CDPRG, 1980 (CDPA) (37)	Prior MI	1,529	NR (NR)	0	324 mg tid (972 mg total per day)	1.8	1

Author, Year	Population	N rand	Mean Age and Range (years)	% Female	Aspirin Dose, Concomitant Treatment, and Frequency	Mean Intended Treat-ment Duration (years)	Cancer-specific Key Question
Diener, 1997 (ESPS-2) (38)	Prior TIA or stroke	3,298	66.7 (≥ 18)	42.2	25 mg bid (50 mg total per day)	2	1, 2
EAFT, 1993 (39)	Prior TIA or stroke	782	73 (> 25)	44	300 mg qd	2.3	1
Farrell, 1991 (UK-TIA) (43)	Prior TIA or stroke	2,449	60.3 (≥ 40)	27.0	300 mg qd or 600 mg bid (1,200 mg total per day)	4.4†	1, 3, 4
Juul-Moller, 1992 (SAPAT) (45)	Stable angina	2,035	67 (30-80)	48	75 mg qd	4.2	2
PARIS, 1980 (42)	Prior MI	1,216	56.3 (30-74)	13.2	324 mg tid (972 mg total per day)	3.4	1
SALT, 1991 (40)	Prior TIA or stroke or retinal artery occlusion	1,363	67 (50-79)	34.2	75 mg qd	2.7	1, 3, 4

*Multifactorial design

†Median

‡Total n randomized when warfarin arms included

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis ; ABI = ankle brachial index; AMIS = Aspirin Myocardial Infarction Study; ASPIRE = Aspirin to Prevent Recurrent Venous Thromboembolism; bid = twice daily; BMD = British Medical Doctors; CDPA = Coronary Drug Project Aspirin; CDPRG = Coronary Drug Project Research Group; CVD = cardiovascular disease; DVT = deep vein thrombosis; EAFT = European Atrial Fibrillation Trial; ESPS = European Stroke Prevention Study; ETDRS = Early Treatment Diabetic Retinopathy; HOT = Hypertension Optimal Treatment; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; mg = milligram(s); MI = myocardial infarction; NR = not reported; PARIS = Persantine-Aspirin Reinfarction Study; PE = pulmonary embolism; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; qd = once daily; qod = every other day; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; TIA = transient ischemic attack; tid = three times daily; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischemic Attack; WHS = Women's Health Study

Table 2. Comparison of inclusion criteria of included meta-analyses*

Criteria	Rothwell 2011 (18) Analysis 1	Rothwell 2011 (18) Analysis 2	Rothwell 2011 (18) Analysis 3	Rothwell 2012 (19) Analysis 1	Rothwell 2012 (19) Analysis 2	Rothwell 2010 (46)	Flossman 2007 (47)
Inclusion Criteria							
Included populations	1° and 2° CVD prevention	1° and 2° CVD prevention	1° and 2° CVD prevention	1° and 2° CVD prevention	1° CVD prevention	1° and 2° CVD prevention	1° and 2° CVD prevention
ASA dose	Any dose (75-1,200 mg/day)	Any dose (75-1,200 mg/day)	Any dose (75-1,200 mg/day)	Any dose (75-1,200 mg/day)	< 300 mg/day	Any dose (75-1,200 mg/day)	300-1,200 mg/day
Frequency	Daily	Daily	Daily	Daily	Daily	Daily	Daily
Median intended Intervention duration	≥ 4 years	≥ 4 years	≥ 4 years	> 90 days**	> 90 days**	≥ 2.5 years	Not specified
Included Studies							
Total number of studies; participants; cancer outcomes	k=7, n=23,535; 657 cancer deaths	k=3; n=12,659†; 1,634 cancer deaths, CRC deaths NR	k=6; n=19,824 54 CRC deaths	k=34‡; n=69,224; 1,226 cancer deaths	k=6; n=35,535; 1,632 incident cancers	k=4, n=14,033 391 incident CRCs 240 CRC deaths	k=2; n=7,588; 216 incident CRCs
1° CVD prevention studies	AAA, BMD, ETDRS, JPAD, POPADAD, TPT§	BMD, TPT§	AAA, BMD, JPAD, TPT§, POPADAD	AAA, BMD, ETDRS, HOT, JPAD, POPADAD, PPP, TPT	AAA, HOT, JPAD‖, POPADAD, PPP, TPT	BMD, TPT§	BMD
2° CVD prevention studies	UK-TIA*	UK-TIA	UK-TIA	UK-TIA, EAFT, SALT, ESPS-2, SAPAT, 21 "small trials"	None	UK-TIA, SALT	UK-TIA

*Included data from SAPAT for trial-level meta-analyses

†Also conducted sub-analyses on 10,502 patients who had 5 or more years of treatment.

‡Also analyzed nonvascular death among 77,549 participants in 51 trials

§Includes arms of TPT in which anticoagulant was co-administered with ASA

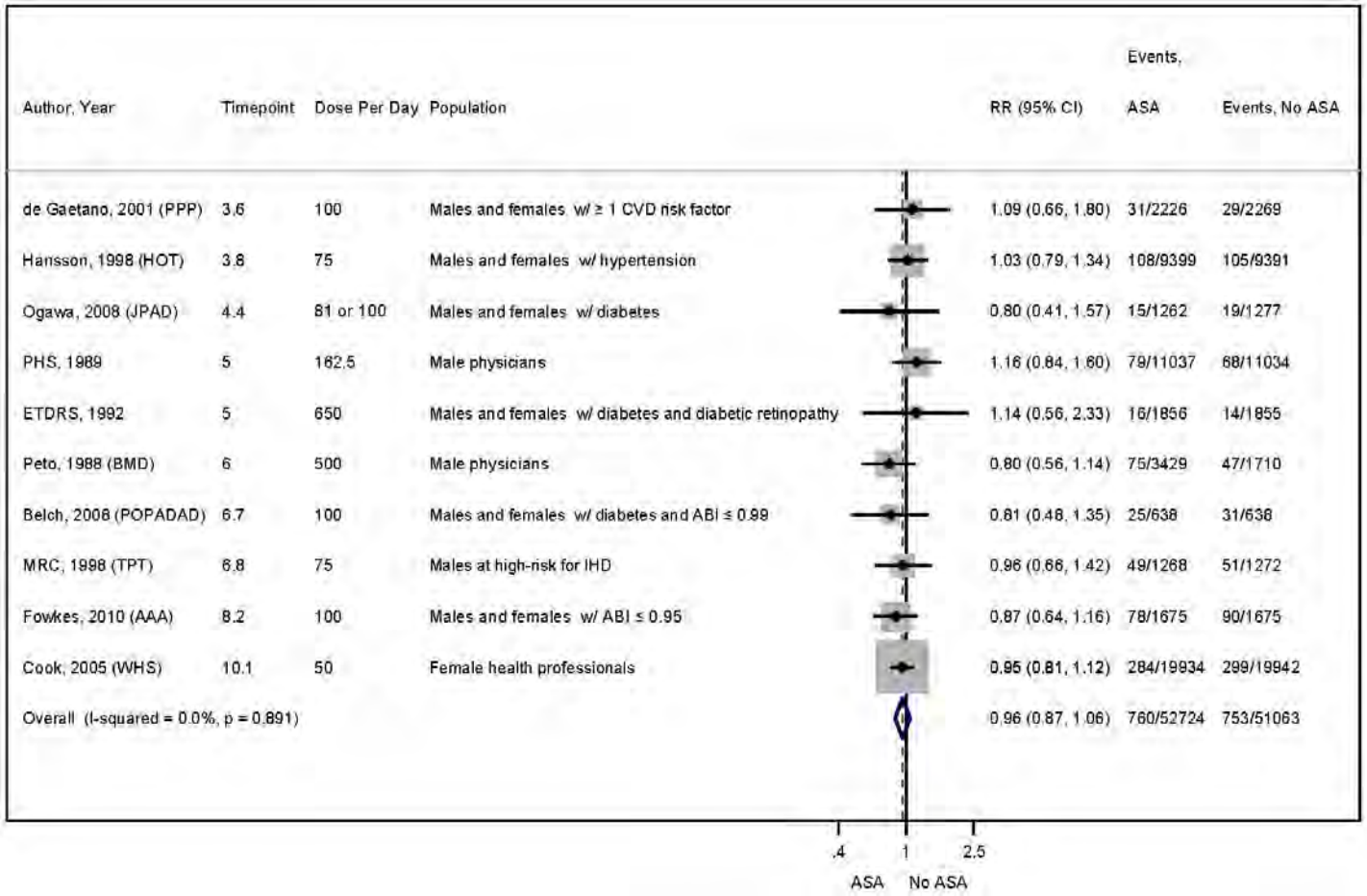
‖Substituted cancer mortality for nonfatal cancer

¶Not included for cancer mortality

**Minimum intended intervention duration

Abbreviations: ASA = acetylsalicylic acid; CRC = colorectal cancer; CVD = cardiovascular disease; mg = milligram(s)

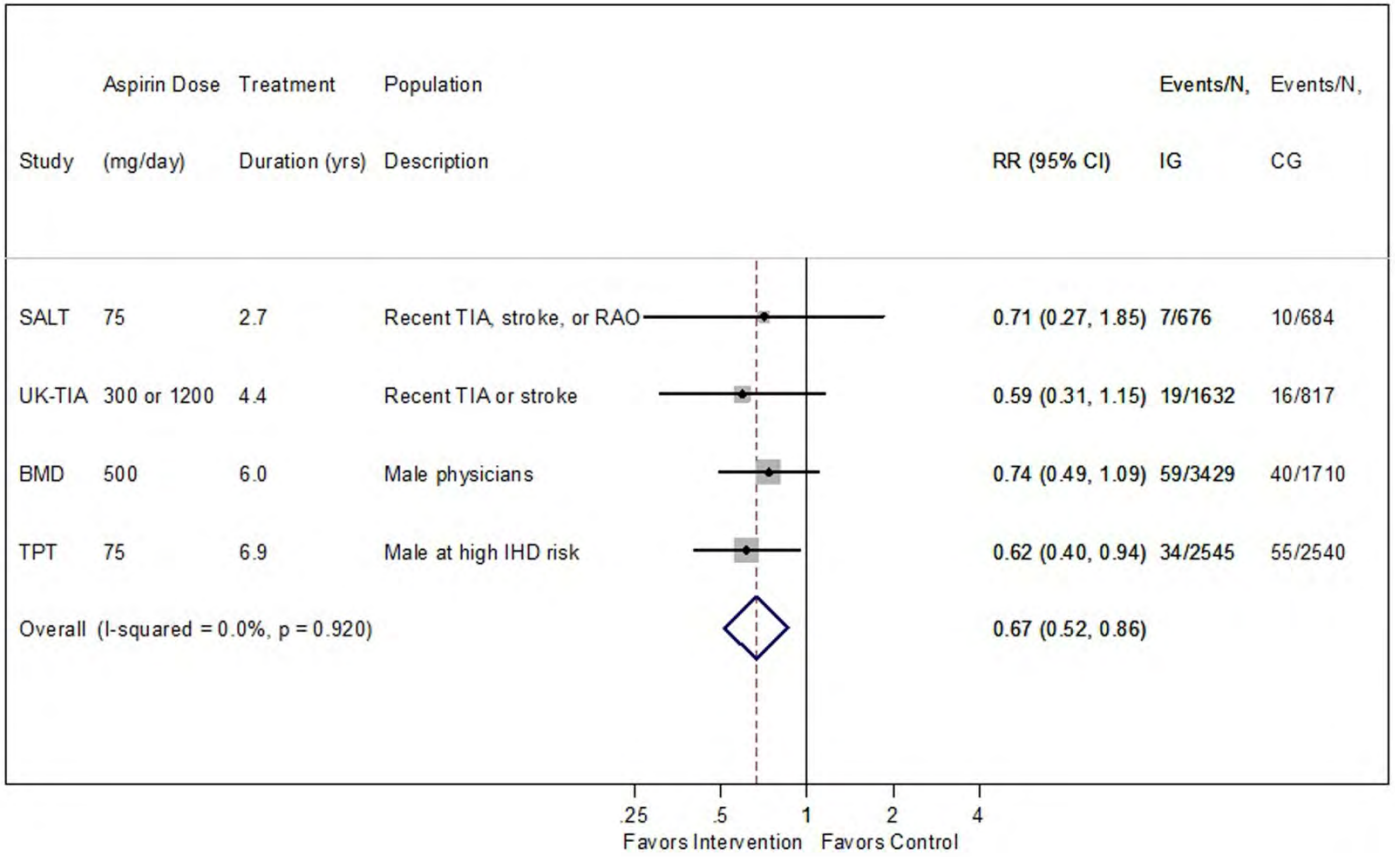
Figure 1. Forest plot of aspirin and cancer mortality, CVD primary prevention trials



Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively); TPT data does not include the warfarin arms

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis ; ABI = ankle brachial index; ASA = acetylsalicylic acid; BMD = British Medical Doctors; CI = confidence interval; CVD = cardiovascular disease; ETDRS = Early Treatment Diabetic Retinopathy; HOT = Hypertension Optimal Treatment; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; TPT = Thrombosis Prevention Trial; w/ = with; WHS = Women's Health Study

Figure 2. Forest plot of aspirin and long-term risk (0 to 20+ year) of colorectal cancer mortality

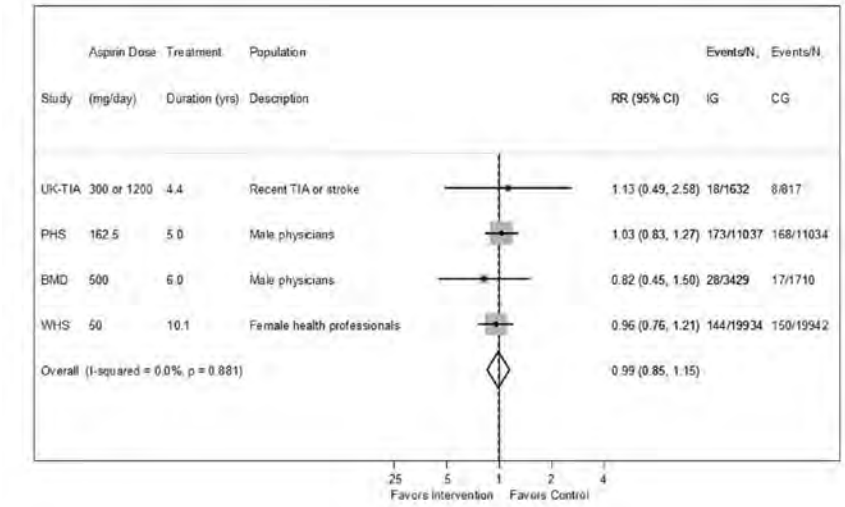


Note: Differences from point estimates or 95% confidence intervals reported in studies are due to use of different statistical programs, and are minor and of no clinical or statistical significance

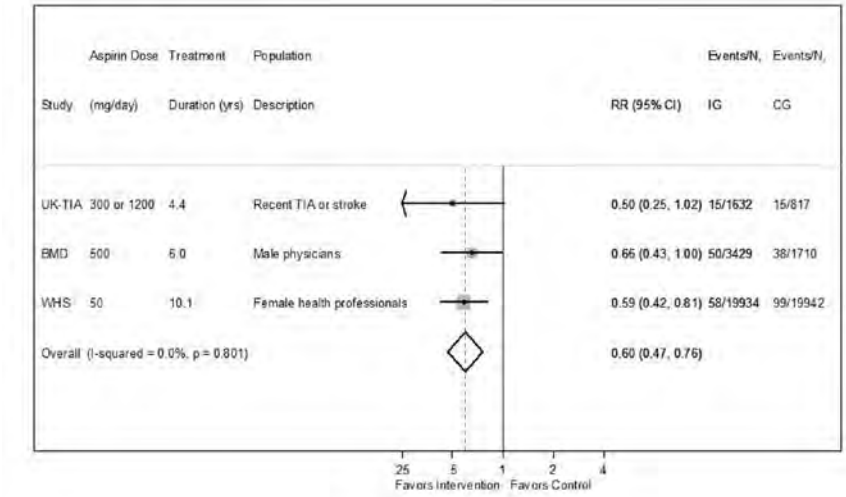
Abbreviations: BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; IG = intervention group; IHD = ischemic heart disease; mg = milligram; RAO = retinal artery occlusion; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack; yrs = years

Figure 3. Forest plots of aspirin and colorectal cancer incidence

a. early risk (0 to 12 years)



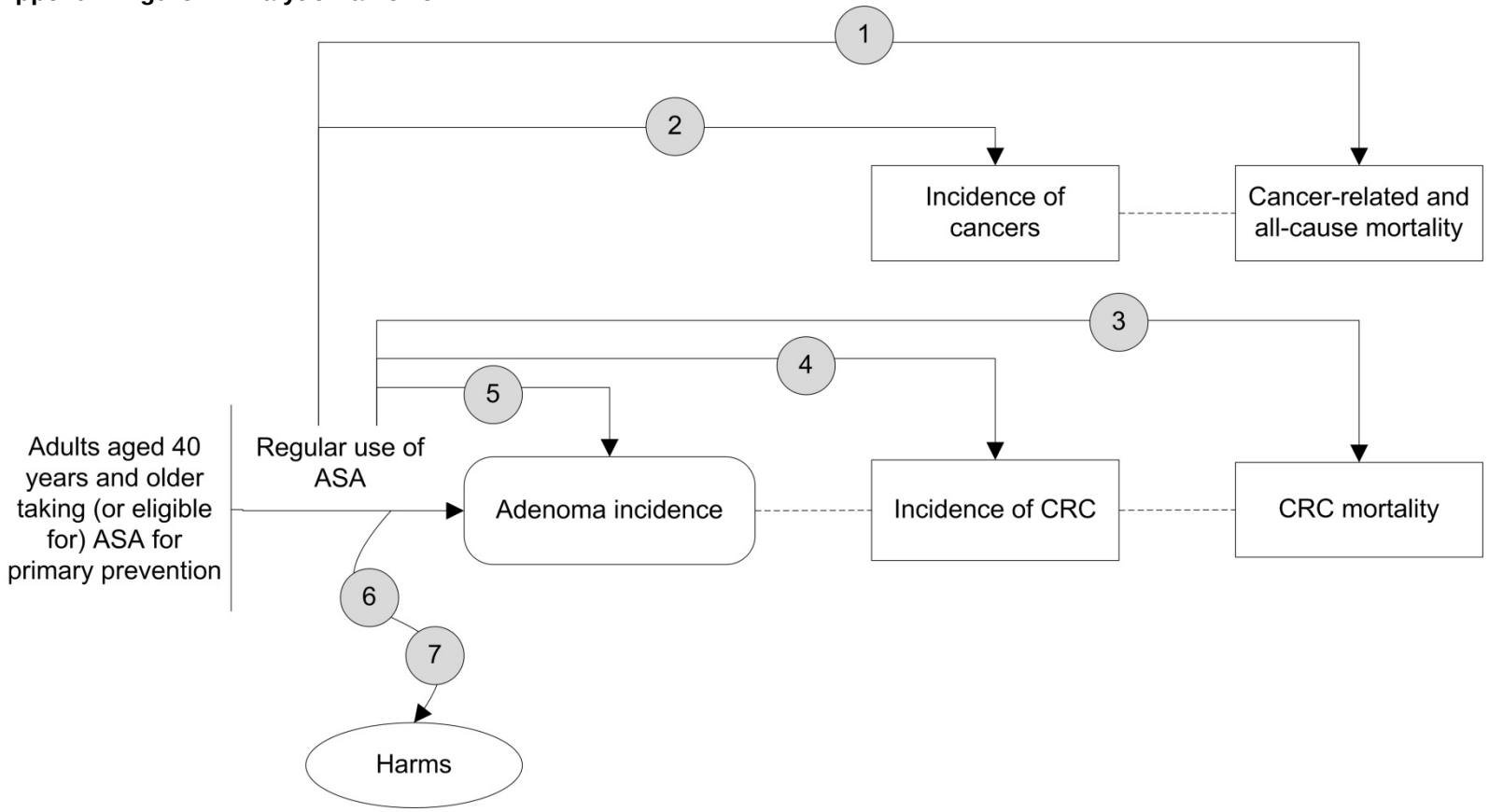
b. late risk (10 to 19 years)



Note: Differences from point estimates or 95% confidence intervals reported in studies are due to use of different statistical programs, and are minor and of no clinical or statistical significance

Abbreviations: BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; IG = intervention group; mg = milligram; PHS = Physicians' Health Study; RR = relative risk; TIA = transient ischemic attack; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study; yrs = years

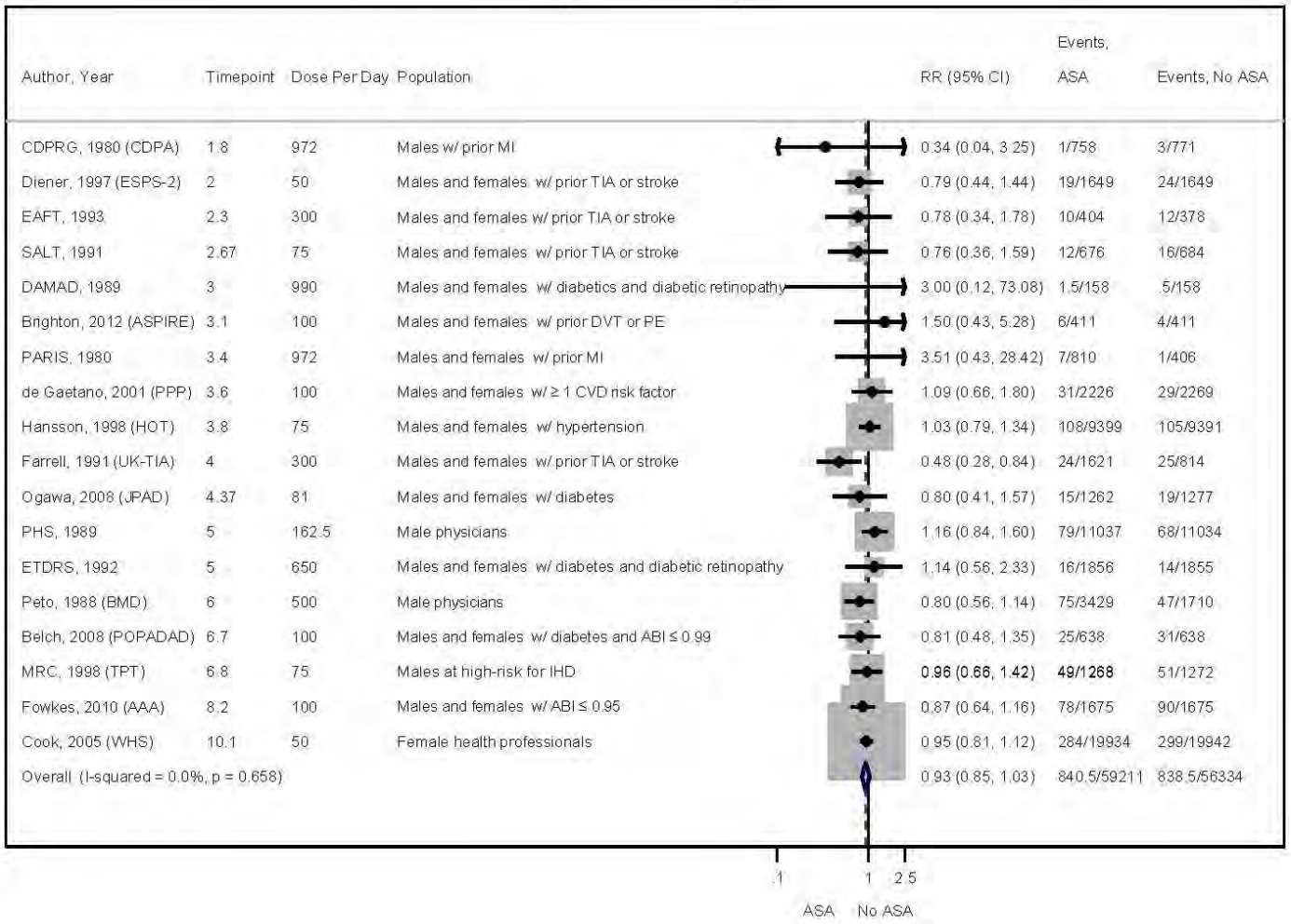
Appendix Figure 1. Analytic framework



Abbreviations: ASA = acetylsalicylic acid, CRC = colorectal cancer

Note: The numbers on the analytic framework correspond to the Key Questions listed in the Methods section

Appendix Figure 2. Forest plot of aspirin and cancer mortality, CVD primary and secondary prevention trials

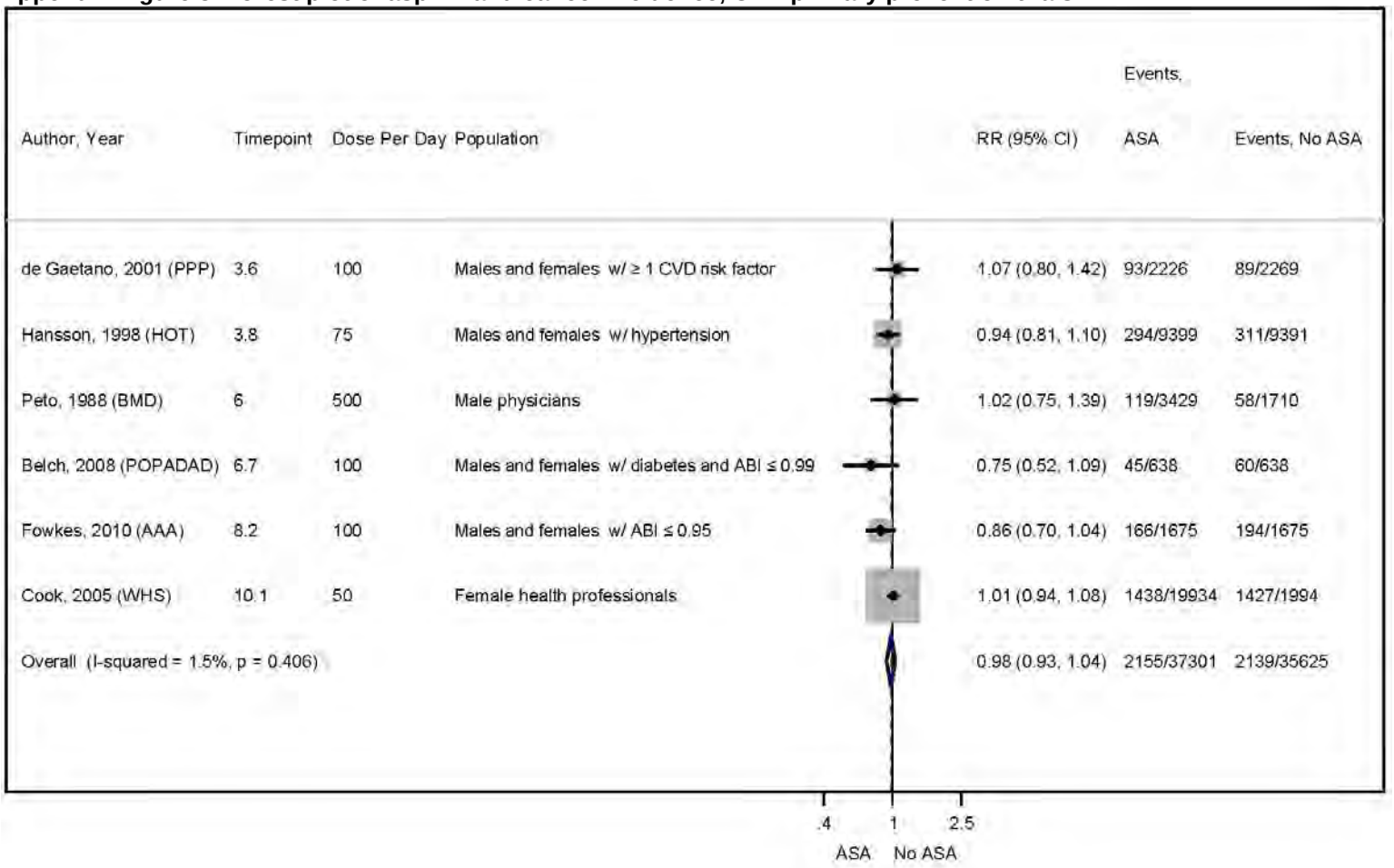


Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively). Continuity correction used a continuity correction factor of 0.5 if an arm reported no events

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis ; ABI = ankle brachial index; ASA = acetylsalicylic acid; ASPIRE = Aspirin to Prevent Recurrent Venous Thromboembolism; BMD = British Medical Doctors; CDPA = Coronary Drug Project Aspirin; CDPRG = Coronary Drug Project Research Group; CI = confidence interval; CVD = cardiovascular disease;; EAFT = European Atrial Fibrillation Trial; ESPS = European Stroke Prevention Study; ETDRS = Early Treatment Diabetic Retinopathy; HOT =

Hypertension Optimal Treatment; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; MI = myocardial infarction; PARIS = Persantine-Aspirin Reinfarction Study; PE = pulmonary embolism; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; SALT = Swedish Aspirin Low-dose Trial; RR = relative risk; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischemic Attack; w/ = with; WHS = Women's Health Study

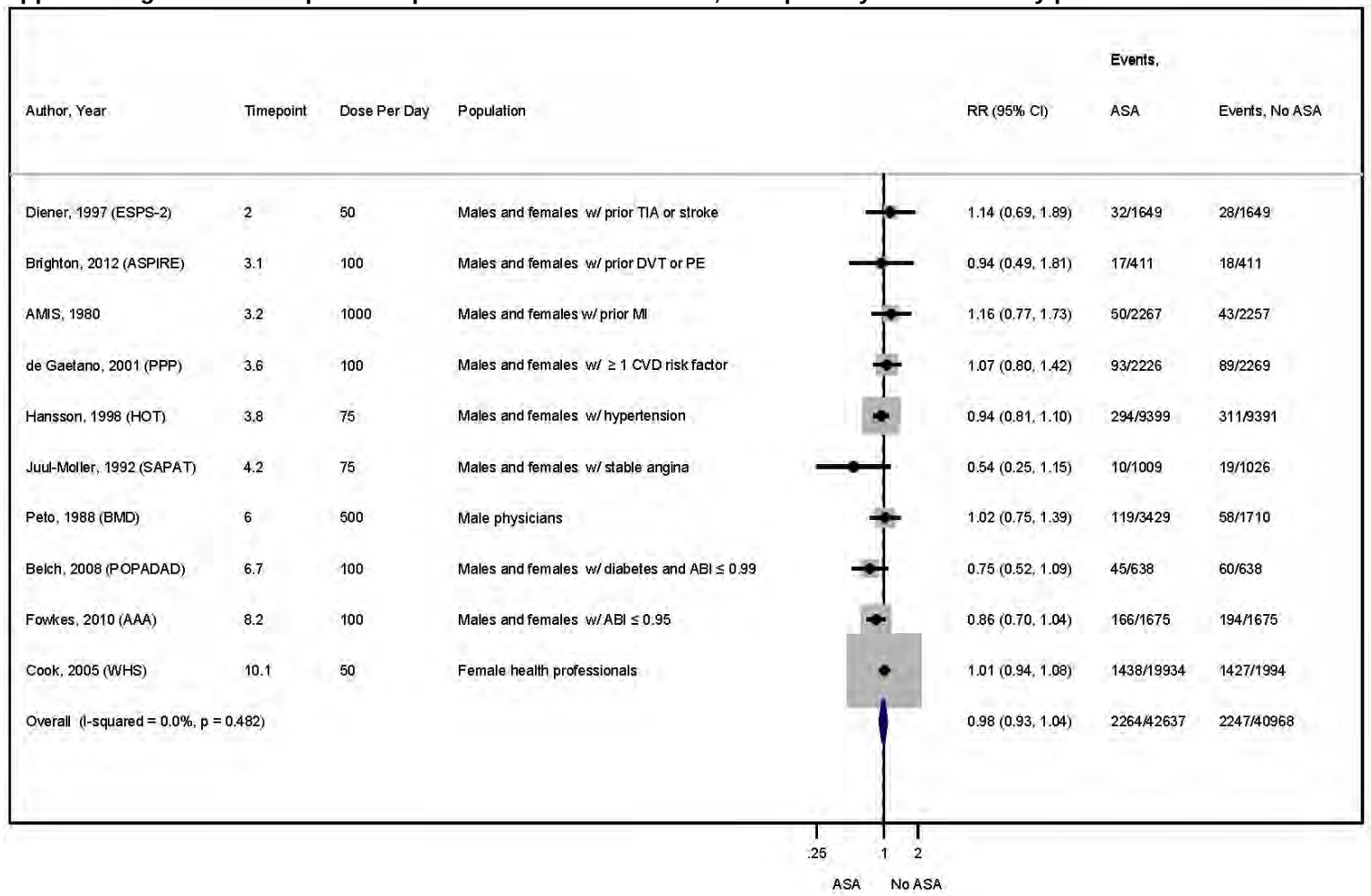
Appendix Figure 3. Forest plot of aspirin and cancer incidence, CVD primary prevention trials



Note: PHS and WHS are alternate day dosage studies (100 mg qod and 325 mg qod, respectively)

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis ; ABI = ankle brachial index; ASA = acetylsalicylic acid; BMD = British Medical Doctors; CI = confidence interval; CVD = cardiovascular disease; ETDRS = Early Treatment Diabetic Retinopathy; HOT = Hypertension Optimal Treatment; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; WHS = Women's Health Study

Appendix Figure 4. Forest plot of aspirin and cancer incidence, CVD primary and secondary prevention trials



Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis ; ABI = ankle brachial index; AMIS = Aspirin Myocardial Infarction Study; ASA = acetylsalicylic acid; ASPIRE = Aspirin to Prevent Recurrent Venous Thromboembolism; BMD = British Medical Doctors; CI = confidence interval; CVD = cardiovascular disease; DVT = deep vein thrombosis; ESPS = European Stroke Prevention Study; HOT = Hypertension Optimal Treatment; MI = myocardial infarction; PE = pulmonary embolism; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; SAPAT = Swedish Angina Pectoris Aspirin Trial; TIA = transient ischemic attack; w/ = with; WHS = Women's Health Study

Appendix Table 1. Sensitivity analyses for aspirin and cancer mortality and incidence

Analysis	CVD Prevention Level	Mean Follow-up (y)	Dose Schedule	k	n	Pooled RR (95% CI)	Included CVD Primary Prevention Trials (*CVD Secondary Prevention Trials*)
Cancer mortality							
Main Analysis	Primary	≥ 1	Any	10	103,787	0.96 (0.87, 1.06)	AAA, BMD* , ETDRS*, HOT, JPAD, PHS, POPADAD, PPP, TPT, WHS
Sensitivity Analyses	Primary and secondary	≥ 1	Any	18	116,484	0.93 (0.85, 1.03)	AAA, BMD* , ETDRS*,HOT, JPAD, PHS, POPADAD, PPP, TPT, WHS, (*AMIS, ASPIRE, CDPA*, DAMAD*, EAFT, ESPS-2, PARIS*, SALT, SAPAT, UK-TIA**)
	Primary	≥ 1	Daily	8	41,840	0.93 (0.81,1.07)	AAA, BMD* , ETDRS*, HOT, JPAD, POPADAD, PPP, TPT,
	Primary	≥ 4	Any	8	80,502	0.94 (0.84,1.05)	AAA, BMD* , ETDRS*, JPAD, PHS, POPADAD, TPT, WHS
	Primary	≥ 4	Daily	6	18,555	0.87 (0.73,1.03)	AAA, BMD* , ETDRS*, JPAD, POPADAD, TPT
	Primary and secondary	≥ 4	Daily	7	20,990	0.83 (0.70, 0.98)	AAA, BMD* , ETDRS*, JPAD, POPADAD, TPT, (*UK-TIA*)*
Rothwell 2011 (18)	Primary and secondary	≥ 4	Daily	7	23,535	HR, 0.82 (0.70, 0.95) ≤5 years: HR, 0.86 (0.71, 1.04) >5 years: HR, 0.66 (0.50, 0.87)	AAA, BMD* , ETDRS*, JPAD, POPADAD, TPT‡, *(UK-TIA*)*
Rothwell 2012 (19)	Primary and secondary	> 90 days	Daily	34	69,224	OR, 0.85 (0.76, 0.96) <3 years: OR, 0.90 (0.76, 1.06) 3-4.9 years: OR, 0.93 (0.75, 1.16) 5 years: OR, 0.63 (0.49, 0.82)	AAA, BMD* , ETDRS*, HOT, JPAD, POPADAD, PPP, TPT‡, (*UK-TIA*, EAFT, SALT, ESPS-2, SAPAT), 21 "small trials"*
Cancer incidence							
Main Analysis	Primary	≥ 1	Any	6	72,926	0.98 (0.93, 1.04)	AAA, BMD* , HOT, POPADAD, PPP, WHS
Sensitivity Analyses	Primary and secondary	≥ 1	Any	10	83,605	0.98 (0.93, 1.04)	AAA, BMD* , HOT, POPADAD, PPP, WHS, (*AMIS, ASPIRE, ESPS-2, SAPAT*)
	Primary	≥ 1	Daily	5	33,050	0.93 (0.84, 1.03)	AAA, BMD* , HOT, POPADAD, PPP
	Primary	≥ 4	Any	4	49,641	0.98 (0.92, 1.05)	AAA, BMD* , POPADAD, WHS
	Primary	≥ 4	Daily	3	9,765	0.88 (0.75, 1.02)	AAA, BMD*, POPADAD
	Primary and secondary	≥ 4	Daily	4	11,800	0.86 (0.74, 0.99)	AAA, BMD*, POPADAD, (*SAPAT*)

Analysis	CVD Prevention Level	Mean Follow-up (y)	Dose Schedule	k	n	Pooled RR (95% CI)	Included CVD Primary Prevention Trials (*CVD Secondary Prevention Trials*)
Rothwell 2012† (19)	Primary	> 90 days	Daily§	6	35,535	HR, 0.88 (0.80, 0.98) 0-2.9 years: HR, 1.00 (0.88, 1.15) 3-4.9 years: HR, 0.81 (0.67, 0.98) ≥ 5 years: HR, 0.71 (0.57, 0.89) ≥ 5 years (scheduled treatment duration): HR, 0.81 (0.70, 0.93) 0-2.9 years: OR, 1.01 (0.88, 1.15) ≥ 3.0 years: OR, 0.76 (0.66, 0.88)	AAA, HOT, JPAD, PPP, POPADAD, TPT‡
	Primary and secondary	> 90 days	Daily	32	65,973	0-3 years: OR, 0.91 (0.81, 1.02) > 3 years: OR, 0.79 (0.70, 0.90)	AAA, BMD* , ETDRS*, HOT, JPAD, POPADAD, PPP, TPT‡, (*UK-TIA*, EAFT, SALT, ESPS-2, SAPAT), 21 "small trials"*

*Trials testing high-dose aspirin (≥325 mg/day)

†Overall cancer incidence combining fatal and nonfatal cancers

‡Includes warfarin arms

§Analyses listed were not restricted by dose except for one which was limited to trials with aspirin dose less than 300 mg/day

Italics indicates secondary prevention trials

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis ; AMIS = Aspirin Myocardial Infarction Study; ASPIRE = Aspirin to Prevent Recurrent Venous Thromboembolism; BMD = British Medical Doctors; CDPA = Coronary Drug Project Aspirin; CDPRG = Coronary Drug Project Research Group; CI = confidence interval; CVD = cardiovascular disease; EAFT = European Atrial Fibrillation Trial; ESPS = European Stroke Prevention Study; ETDRS = Early Treatment Diabetic Retinopathy; HOT = Hypertension Optimal Treatment; HR = hazard ratio; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; OR = odds ratio; PARIS = Persantine-Aspirin Reinfarction Study; PHS = Physician's Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischemic Attack; WHS = Women's Health Study