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Which Aspirin Dose and Preparation Is Best for the Long-Term Prevention of Cardiovascular Disease and Cancer? Evidence From a Systematic Review and Network Meta-Analysis

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ABSTRACT

The evidence base on aspirin in primary prevention suggests that it can reduce significantly the risk of cardiovascular disease (CVD) events and cancer, especially colorectal, albeit increasing bleeding. There is, however, uncertainty on the optimal aspirin dose and preparation for primary prevention. We thus aimed to review main sources of evidence informing on daily dosage and preparation of aspirin for primary prevention of CVD and cancer. We collected and elaborated aspirin effectiveness and safety data from U.S. Preventive Services Task Force reports on aspirin in primary prevention, distinguishing average daily dose in <100 mg, 100 mg, and >100 mg. The following preparations were also systematically compared: enteric coated, controlled release, non-coated, or otherwise unspecified. Fixed-effect pairwise and network meta-analytic models were run in a frequentist framework. Eleven randomized trials were shortlisted, enrolling 104,101 subjects, followed for a median of 60 months. At pairwise analysis, aspirin was associated with significant reductions in death and CVD events, non-significant reductions in cancer death or incidence, and significant increases in the risk of intracranial and gastrointestinal (GI) bleeding. An average daily dose of 100 mg had the highest probability of reducing death, cancer death, and cancer incidence, whereas higher doses seemed superior for reducing CVD events, and 100 mg or less daily proved better tolerated. Coated preparations appeared more beneficial for death, cancer death, cancer incidence, and GI bleeding, whereas controlled release preparations appeared better for CVD events and non-coated ones for intracranial bleeding. In conclusion, an average daily dose of 100 mg of coated aspirin seems more likely to confer favorable preventive effects on death and cancer, with higher doses more appealing for CVD prevention and lower doses better tolerated.

Statement of Conflict of Interest: see page 501.

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Abbreviations and Acronyms
CV = cardiovascular
CVD = cardiovascular disease
GI = gastrointestinal

Despite major breakthroughs in reducing the burden of cardiovascular (CV) disease (CVD) and cancer, they still represent the main cause of mortality, morbidity, and resource use worldwide.[1–5] Even acknowledging past and present successes, an aging population will always face a substantial risk of CVD or oncologic events.[6–11] The management of CVD and cancer has seen important developments, and preventive efforts have also being successful, albeit more so for CVD events than for cancer.[7,8,12] Indeed, few, if any, effective and affordable preventive strategies are available for cancer death and incidence.[7,13]

Aspirin, i.e. acetyl-salicylic acid, is an oral irreversible inhibitor of cyclo-oxygenase, with established antiplatelet effects.[14,15] While aspirin remains a mainstay in the secondary prevention of atherothrombosis, several trials have tried to address the role of aspirin in primary CVD prevention, and others are ongoing.[16,17] Most recently, multiple sources of evidence have highlighted that aspirin may have pleiotropic non-CV effects, even reducing the risk of cancer incidence and mortality.[18–22] Multiple efforts at summarizing the evidence base on aspirin in primary prevention of CVD and cancer are ongoing or have just been completed, confirming prior preliminary data that aspirin is beneficial for both preventive goals, thus representing a major shift for researchers as well as policy makers in comparison to prior evidence-based guidelines.[23–26]

Even if this is taken for granted, uncertainty persists on which aspirin dose and preparation should be chosen to minimize CVD and oncologic risk, as well as bleeding. Indeed, preliminary evidence suggests that daily doses of 100 mg or less may be better tolerated,[27] without significant differences in terms of CV effectiveness or efficacy.[28–30] Notably, the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events–Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT–OASIS 7) trial did not find significant differences between high- vs low-dose aspirin in secondary prevention when focusing on CVD events or major bleeding, despite an increased risk of minor bleeding with high aspirin.[31] On the other hand, enteric coating aims at reducing gastrointestinal (GI) complications, including pain and erosions with the ensuing risk of bleeding, in comparison to non-coated preparations,[32,33] without unfavorably impacting on systemic thromboxane synthesis inhibition.[34]

Systematic reviews encompassing pairwise and network meta-analysis may offer important insights for evidence synthesis, informing decision making, highlighting potential inconsistencies between evidence sources, and guiding further research.[35,36] We thus aimed to review and appraise the comparative safety and efficacy of different doses and preparations of aspirin in primary prevention using state of the art meta-analytic methods.

Methods and results

We collected and extracted study features, procedural details and outcome data from randomized trials on aspirin in primary prevention as recently reported by the updated U.S. Preventive Services Task Force reports,[23–25] distinguishing studies with average daily aspirin doses in <100 mg, 100 mg, and >100 mg, and preparations in coated, controlled release, non-coated, or otherwise unspecified. The outcomes of interest were death, major adverse CV events (the composite of CV death or myocardial infarction), cancer death, cancer incidence, intracranial bleeding, and major GI bleeding, all at the longest available follow-up. Meta-analysis was conducted in a frequentist framework with fixed-effect pairwise and network meta-analytic models, computing risk ratios (RR, i.e. relative risks) with 95% confidence intervals, heterogeneity tests, tests for small study effects, and P-scores, which represent the probability that any given treatment is better than the others, and can be interpreted similarly to estimates from the surface under the cumulative ranking area (SUCRA).[35] Computations were performed with the meta, metaphor and netmeta packages in R 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

Eleven randomized controlled trials with a placebo or standard care control arm were included (Figs 1 and 2), which enrolled 104,101 patients, followed for a median of 60 months (Table 1).[37–47] Most trials included subjects at increased vascular risk, despite three (67,086 patients) including apparently healthy subjects without a specific risk profile. The majority of studies included both men and women, despite three (29,750 subjects) including only males and one (39,876) only females. Average daily doses <100 mg were used in 4 trials (63,745 patients), 100 mg in 3 (9121 subjects), and >100 mg in 4 (31,235 patients). Coated aspirin was used in two studies (7845 patients), controlled-release aspirin in one (2540 subjects), non-coated aspirin in four (47,402 patients), and otherwise unspecified preparations in four (46,314 subjects).

Pairwise meta-analysis mirrored results reported elsewhere,[23–25] with aspirin significantly reducing the risk of death (RR = 0.94 [0.88–0.99]) (Tables 2 and 3; Figs 3–5) and

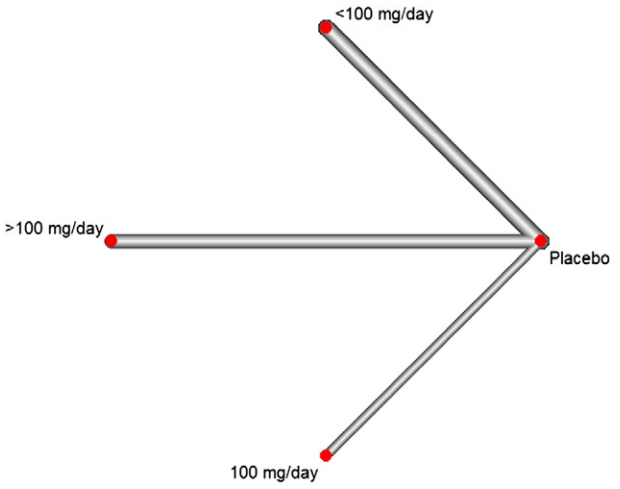

Fig 1 – Evidence network for average daily doses of aspirin in randomized trials for primary prevention. Dot size is proportional to the number of patients receiving a specific treatment, and line thickness is proportional to the number of trials comparing the treatments.