# Aspirin prophylaxis in patients at low risk for cardiovascular disease: A systematic review of all-cause mortality

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**KEY POINTS FOR CLINICIANS**

- Only 3 primary prevention studies of aspirin included low-risk subjects and measured all-cause mortality.
- Two of those studies demonstrated no significant decrease in mortality with low-dose aspirin.
- The Nurses Health Study demonstrated a dose-dependent increase in mortality with aspirin use.
- There is insufficient evidence for or against recommending aspirin to low-risk individuals.

■ OBJECTIVE We investigated whether aspirin reduces all-cause mortality in low-risk patients.
■ STUDY DESIGN We systematically reviewed studies of aspirin for primary prevention to measure total mortality. We included all clinical trials, cohort studies, and case control studies that assessed primary prevention, included low-risk subjects, and measured total mortality. The quality of studies was evaluated with a standard scale.
■ DATA SOURCES MEDLINE, the Cochrane Library, and the Internet were systematically searched for studies with the key terms *primary*, *prevention*, *aspirin*, *myocardial infarction*, *stroke*, and *mortality*. Reference lists of identified trials and reviews also were examined.
■ POPULATION Active members in the Indiana Academy of Family Physicians 2000–2001 membership database (N = 1328).
■ OUTCOMES MEASURED Primary outcomes were myocardial infarction, stroke, and mortality.
■ RESULTS Three primary prevention studies met our criteria. Two clinical trials, the United States Physicians Health Study and British Doctors Study, demonstrated no significant decrease in mortality in the aspirin group alone or when results from the 2 studies were combined. The United States Physicians Health Study showed a lower rate of myocardial infarction (odds ratio [OR], 0.58; 95% confidence interval [CI], 0.47–0.71). In the Nurses Health Study, a cohort study, taking aspirin at any dose was associated with higher rates of myocardial infarction (OR, 2.34; CI, 1.92–2.86), stroke (OR, 1.84; CI, 1.39–2.44), and all-cause mortality (OR, 1.83; CI, 1.57–2.14).
■ CONCLUSIONS There is currently no evidence to recommend for or against the use of aspirin to decrease mortality in low-risk individuals.
■ KEY WORDS Aspirin; primary prevention; mortality; low-risk patient. (*J Fam Pract 2002; 51:00–00*)

Cardiovascular disease is the leading cause of death in the United States, and aspirin, a platelet aggregate inhibitor, is often recommended as prophylaxis for cardiovascular disease.[1–3] Clinical studies have demonstrated the benefit of aspirin use for secondary prevention of cardiovascular disease and stroke.[1,4–10] In high-risk subjects, aspirin has been proven effective in primary prevention of major cardiovascular events and nonfatal ischemic heart disease.[11–13] Sanmuganathan and colleagues recently reported a meta-analysis of 4 randomized trials of aspirin for primary prevention. Although they determined that aspirin treatment is safe if the coronary event rate is at least 1.5% each year and unsafe if the rate is no higher than 0.5% each year, they did not address all-cause mortality, and 2 of the 4 trials did not include low-risk subjects.[9]

Many physicians and patients are prescribing aspirin with the expectation of reduced mortality in high-risk and low-risk individuals. Media advertisements and health programs may not clearly delineate the population for whom aspirin has clear benefits. A recent review suggested that aspirin is likely to be effective for primary prevention in yet to be defined groups.[14] This review seeks to answer 2 questions.

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First, are there any primary prevention studies using aspirin that included only low-risk subjects? Second, should aspirin be prescribed routinely to persons at low risk for cardiovascular disease to decrease total mortality?

## METHODS

### Search strategy

The MEDLINE database and the Cochrane Library were systematically searched using the terms *aspirin* or *antiplatelet therapy* and *primary prevention* or *prevention* and *primary* and *mortality*. An additional search was made with *primary prevention* and *myocardial infarction* or *stroke*. The Internet was searched (http://www.google.com) by using the same search terms. The studies were limited to human populations. Search results consisted of abstracts, complete reviews, and reference lists from articles. Morbidity associated with aspirin use also was reviewed.

### Selection criteria: end points

Only those studies that investigated primary prevention of cardiovascular disease using aspirin, had low-risk subjects, and included a measure of total mortality were part of our analysis. We used the 2001 Adult Treatment Panel III Guidelines and the recent *British Medical Journal* clinical evidence guidelines on primary prevention of cardiovascular disorders to define the low-risk patient.[15,16] Those guidelines classified major risk factors for ischemic vascular disease as hypertension, low high-density lipoprotein cholesterol, high low-density lipoprotein cholesterol, family history of premature coronary heart disease, smoking, diabetes, and advancing age (men ≥ 45 years, women ≥ 55 years). We also classified those patients with past cerebrovascular events, myocardial infarction, and angina as high risk. We defined low risk as having no more than 1 of these risk factors.

Every trial was evaluated independently by each author according to the Jadad scale.[17] Based on information in the original articles, we recalculated the odds ratios (ORs) for each study. The results of the 2 randomized trails were combined by means of the Mantel-Haenszel method for combining ORs, and StatXact 4 for Windows was used for the analysis.[18,19] The data were used to create a forest plot of mortality.[19] The decision to combine studies of like type was made a priority.

## RESULTS

MEDLINE search results for *aspirin* and *primary prevention* yielded 291 articles. *Antiplatelet therapy* and *primary prevention* yielded 64 articles. *Myocardial infarction* or *stroke* and *primary prevention* yielded 514 articles. Cross-referencing *aspirin*, *prevention*, and *mortality* yielded 690 articles. The Cochrane Library search of *antiplatelet therapy* and *prevention* and *primary* yielded 17 complete reviews and 6 abstracts of systematic reviews. No additional studies published or unpublished were identified through the Internet.

Five clinical trials and 1 cohort study that evaluated aspirin for primary prevention were identified.[11,12,20–23] One of those, a pilot study, was excluded because it did not provide mortality data for the aspirin and placebo groups.[23] Two clinical trials, the Hypertension Optimal Treatment Trial and the Thrombosis Prevention Trial, did not include low-risk subjects.[11,12] Although no studies were identified that included only low-risk subjects, 3 studies met our inclusion criteria. Characteristics of those 3 studies are reported in Table 1.

The US Physicians Health Study (USPHS) randomized physicians into 4 treatment groups: aspirin plus beta-carotene, aspirin plus placebo, beta-carotene plus placebo, and placebo plus placebo.[20]

**TABLE 1**

**Characteristics of aspirin studies that included low-risk subjects**

| | USPHS | BDS | NHS |
|---|---|---|---|
| Trial | Steering Committee[20] | Peto et al[21] | Manson et al[22] |
| Study population | Healthy US physicians | Healthy UK physicians | Healthy US nurses |
| Study type | Randomized controlled trial | Randomized controlled trial | Cohort |
| Subjects in aspirin group | 11,037 | 3429 | 35,048 |
| Subjects in control group | 11,034 | 1710 | 52,630 |
| Treatment | 325 mg aspirin every other day | 500 mg/d aspirin | 1–15 aspirin tablets/wk |
| Comparison | Placebo | No aspirin | None |
| Follow-up time (y) | 5 | 6 | 6 |
| Jadad score | | | |
| Randomization† | 1 | 2 | NA* |
| Blinding‡ | 1 | 0 | NA |
| Withdrawals§ | 1 | 0 | NA |
| Total | 3 | 2 | NA |
| Significant difference in mortality | No | No | Yes in favor of no aspirin |

*The Jadad scale does not apply to cohort studies.
†Two points maximum.
‡Two points maximum.
§One point maximum.
BDS, British Doctors Study; NA, not applicable; NHS, Nurses Health Study; USPHS, US Physicians Health Study.

Both aspirin groups took 325 mg every other day. The mean age was 53.2 years.[24] Fifty percent of the participants were current or past smokers, and 9% had hypertension. Although the rate of myocardial infarction was significantly lower in the aspirin group, there was no reduction in total cardiovascular mortality. The results are reported in Table 2. More side effects were noted in the aspirin group, including gastric ulcers, gastrointestinal bleeding, hemorrhagic stroke, and other bleeding disorders.[20] No separate analysis of low-risk subjects' risk was performed.

**TABLE 2**

**Rates of myocardial infarction, stroke, total cardiovascular mortality, and total mortality in studies of aspirin vs no aspirin that included low-risk patients**

| | Study | | |
|---|---|---|---|
| **Outcome** | **USPHS (5 y)** | **BDS (6 y)** | **NHS (6 y)** |
| Myocardial infarction | | | |
| Aspirin, n (%) | 139 (1.26) | 169 (4.93) | 244 (0.70) |
| No aspirin, n (%) | 239 (2.17) | 88 (5.15) | 157 (0.30) |
| OR (CI) | 0.58 (0.47–0.71) | 0.96 (0.73–1.24) | 2.34 (1.92–2.86)* |
| Stroke | | | |
| Aspirin, n (%) | 119 (1.08) | 91 (2.65) | 109 (0.31) |
| No aspirin, n (%) | 98 (0.89) | 39 (2.28) | 89 (0.17) |
| OR (CI) | 1.22 (0.93–1.59) | 1.17 (0.80–1.71) | 1.84 (1.39–2.44)* |
| Total cardiovascular mortality | | | |
| Aspirin, n (%) | 81 (0.73) | 148 (4.32) | 68 (0.19) |
| No aspirin, n (%) | 83 (0.75) | 79 (4.62) | 62 (0.12) |
| OR (CI) | 0.98 (0.72–1.33) | 0.93 (0.70–1.23) | 1.65 (1.17–2.33)* |
| Total mortality | | | |
| Aspirin, n (%) | 217 (1.97) | 270 (7.87) | 354 (1.01) |
| No aspirin, n (%) | 227 (2.06) | 151 (8.83) | 292 (0.55) |
| OR (CI) | 0.95 (0.79–1.15) | 0.88 (0.72–1.09) | 1.83 (1.57–2.14)* |

*OR significant at the .05 level.
BDS, British Doctors Study; CI, 95% confidence interval; n (%), number (percentage) of patients taking or not taking aspirin; NHS, Nurses Health Study; OR, odds ratio; USPHS, US Physicians Health Study.

In the British Doctors Study (BDS), 66% of patients were randomized to take aspirin once daily and 33% were to avoid aspirin.[21] More than half of the subjects were at least 60 years old. Physicians with stroke, myocardial infarction, ulcer disease, or currently taking any aspirin products were excluded. Six percent of the subjects had a history of heart disease other than myocardial infarction, 10% had hypertension, and 75% of participants were currently smoking or had a history of smoking. No significant differences were noted between groups for myocardial infarction or total mortality. By the end of the study, 44% of the aspirin group had discontinued aspirin secondary to side effects, the most common being dyspepsia. Of the control group, 2% per year started using aspirin because they developed risk factors such as vascular disease or for primary prevention. Low-risk individuals were not evaluated separately.

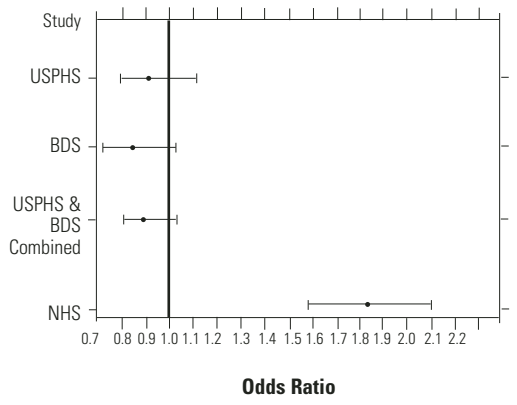
The Nurses Health Study (NHS) was a cohort study of women who were free of diagnosed coronary heart disease, stroke, and cancer at the start of the study. However, 29% of the women smoked and 15% had hypertension.[22] The mean age was 46.0 years, and the follow-up was 96.7% of total potential person years. The study respondents were asked how many aspirin tablets they took per week: 0, 1 to 3, 4 to 6, 7 to 14, or 15+. Those who smoked or were overweight were more likely to take aspirin. No separate analysis of low-risk subjects was performed. Mortality from aspirin use was clearly dose dependent. For study participants taking 1 to 6 aspirin tablets each week, mortality was 0.84% (OR, 1.51; 95% confidence interval [CI], 1.26–1.82); for those taking 7 to 14 aspirin tablets, mortality was 0.99% (OR, 1.80; CI, 1.39–2.33); and for those taking 15+ aspirin tablets, mortality was 1.82% (OR, 3.32; CI, 2.62–4.21). Rates of myocardial infarction and stroke also were higher for all groups taking aspirin (see Table 2). When combined, the USPHS and the BDS demonstrated no significant difference in mortality between aspirin and placebo groups, whereas the NHS found increased mortality from aspirin (Figure).

## DISCUSSION

To date, there has been no study of aspirin for primary prevention that included a separate analysis of patients who were free of cardiovascular risk factors. Each of the 3 studies that included low-risk subjects grouped them with subjects at higher risk, those known to benefit from aspirin.[9,11,12] Even so, none of those studies demonstrated a statistically significant decrease in all-cause mortality. Even when combined, the BDS and the USPHS demonstrated no significant improvement in mortality. Mortality in the BDS was nearly 4 times greater than that in the USPHS. This finding is likely due to the higher baseline rate of smoking and other risk factors in the British doctors. In contrast to the BDS, the USPHS

**FIGURE**

**Forest plot of mortality in healthy patients on aspirin**




BDS, British Doctors' Study; Combined, NHS, Nurses' Health Study; USPHS, United States Physicians' Health Study.

demonstrated significantly decreased rates for fatal and nonfatal myocardial infarction. Our analysis of the NHS associated aspirin with increased mortality, fatal myocardial infarction, and nonfatal myocardial infarction at any dose. The nurses on average had lower risk than the doctors, fewer smoked, and they were younger.

Many studies have clearly demonstrated the benefits of aspirin for primary prevention in high-risk subjects.[10–12,25] There may be other benefits to taking prophylactic aspirin. In the Cancer Prevention Study II, aspirin use was associated with decreased death rates from colon cancer.[26] Unfortunately, that study did not measure all-cause mortality.

There are a number of limitations to this study. There were no strictly low-risk studies of aspirin for primary prevention of cardiovascular mortality, and there was a paucity of studies that included low-risk subjects. Because the studies analyzed did not include only low-risk subjects, the results may not apply to all low-risk patients. The BDS did not include a placebo and was not blinded. Although not statistically significant, the ORs tended toward a protective effect for aspirin in the 2 randomized trials. The large difference in mortality between those 2 trials remains unexplained. The NHS was the only study to include women, and it was a cohort study, which is subject to selection and reporting biases. Therefore, aspirin users may have been at higher mortality risk due to smoking, obesity, or other illness, thus rendering the association between aspirin and higher mortality meaningless.

Many studies have shown significant side effects of aspirin, including epistaxis, peptic ulcer disease, gastrointestinal bleeds, and hemorrhagic stroke.[15,20–22,27–32] In the BDS, 17% more subjects in the aspirin group developed peptic ulcer disease, and 19% stopped treatment during the first year secondary to gastrointestinal complaints.[21]

In conclusion, there is currently no evidence to recommend for or against the use of aspirin in low-risk individuals to decrease mortality. There may be other reasons to take aspirin prophylactically such as to reduce myocardial infarction or colon cancer. However, these benefits have not been established in a low-risk population. Health care providers should ask all patients whether they are taking aspirin and evaluate the risk-benefit ratio before recommending it.

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