

# Low-Dose Aspirin in Patients with Stable Cardiovascular Disease: A Meta-analysis

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## ABSTRACT

**OBJECTIVE:** Many recommendations for aspirin in stable cardiovascular disease are based on analyses of all antiplatelet therapies at all dosages and in both stable and unstable patients. Our objective was to evaluate the benefit and risk of low-dose aspirin (50-325 mg/d) in patients with stable cardiovascular disease.

**METHODS:** Secondary prevention trials of low-dose aspirin in patients with stable cardiovascular disease were identified by searches of the MEDLINE database from 1966 to 2006. Six randomized trials were identified that enrolled patients with a prior myocardial infarction (MI) (n = 1), stable angina (n = 1), or stroke/transient ischemic attack (n = 4). A random effects model was used to combine results from individual trials.

**RESULTS:** Six studies randomized 9853 patients. Aspirin therapy was associated with a significant 21% reduction in the risk of cardiovascular events (nonfatal MI, nonfatal stroke, and cardiovascular death) (95% confidence interval [CI], 0.72-0.88), 26% reduction in the risk of nonfatal MI (95% CI, 0.60-0.91), 25% reduction in the risk of stroke (95% CI, 0.65-0.87), and 13% reduction in the risk of all-cause mortality (95% CI, 0.76-0.98). Patients treated with aspirin were significantly more likely to experience severe bleeding (odds ratio 2.2, 95% CI, 1.4-3.4). Treatment of 1000 patients for an average of 33 months would prevent 33 cardiovascular events, 12 nonfatal MIs, 25 nonfatal strokes, and 14 deaths, and cause 9 major bleeding events. Among those with ischemic heart disease, aspirin was most effective at reducing the risk of nonfatal MI and all-cause mortality; however, among those with cerebrovascular disease, aspirin was most effective at reducing the risk of stroke.

**CONCLUSION:** In patients with stable cardiovascular disease, low-dose aspirin therapy reduces the incidence of adverse cardiovascular events and all-cause mortality, and increases the risk of severe bleeding.

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**KEYWORDS:** All-cause mortality; Aspirin; Dose; Meta-analysis; Myocardial infarction; Secondary prevention; Stable angina; Stroke

The importance of platelets in the pathophysiology of cardiovascular disease and thrombus formation is well established.<sup>1-5</sup> Medications with antiplatelet activity clearly decrease cardiovascular morbidity and mortality across a wide spectrum of patients.<sup>6-11</sup> In the largest investigation to date, the Antiplatelet Trialists' Collaboration (ATC) demonstrated a reduction in myocardial infarction (MI), stroke, and death with antiplatelet therapy in patients at "high risk" (history of MI, unstable angina, stable angina, prior percutaneous or surgical

coronary revascularization, stroke, transient ischemic attack, atrial fibrillation, valvular heart disease, or peripheral vascular disease) of cardiovascular events.<sup>6,7</sup> On the basis of these data, the American College of Cardiology, American Heart Association, and Seventh American College of Chest Physicians Consensus Conference on Antithrombotic Therapy recommend indefinite oral aspirin therapy for the secondary prevention of cardiovascular events.<sup>12,13</sup> However, the beneficial effect of therapy was derived from all antiplatelet medications combined, not only aspirin. Among 278 trials examined in the ATC meta-analysis, 64 (23%) evaluated the affect of aspirin alone versus placebo or control, and 37 (13%) used a dose of aspirin that is currently recommended for the secondary prevention of cardiovascular disease (75-325 mg).<sup>7</sup> Furthermore, among the 37 trials that evaluated

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low-dose aspirin, only 6 included patients with stable cardiovascular disease (history of MI, stroke/transient ischemic attack, or stable angina).<sup>7</sup> Thus, the effect of low-dose aspirin in patients with stable cardiovascular disease for the secondary prevention of cardiovascular events is poorly defined. The current analysis studies the effect of low-dose aspirin on major cardiovascular events, all-cause mortality, and bleeding risk in patients with stable cardiovascular disease.

## MATERIALS AND METHODS

### Data Sources and Searches

The primary aim of this meta-analysis was to determine the effect of aspirin in the secondary prevention of cardiovascular disease in patients with stable cardiovascular disease. A comprehensive MEDLINE database search using Ovid software (Ovid Technologies Inc, New York, NY) was performed to find human studies published between 1966 and March 2006 using the search terms *aspirin*, *secondary prevention*, *myocardial infarction*, *stroke*, and *randomized controlled trials*, as well as combinations of these terms. The bibliographies of retrieved articles were searched for other relevant studies, and major scientific meetings were monitored for the results of trials still under way at the time of the MEDLINE search. Data concerning study design, baseline patient characteristics, treatment, follow-up, and results were extracted from these reports.

### Study Selection

Trials that met the following criteria were included: prospective, randomized, controlled, open, or blinded trials; blinded assignment of participants with stable cardiovascular disease (excluding trials that included patients during the acute presentation of an MI, stroke/transient ischemic attack, or unstable angina) to aspirin treatment or a control group for the secondary prevention of cardiovascular disease; and data on cardiovascular death, MI, and stroke. Quality was assessed using criteria that were previously published (adequate blinding of randomization, completeness of follow-up, and objectivity of outcome assessments).<sup>14,15</sup> A total of 126 potentially eligible studies were identified, and 89 were excluded because they were not randomized controlled trials (eg, review articles, editorials, letters to the editor, case reports, case-control studies, and meta-analyses). Of the randomized trials, 36 trials included patients in the acute setting, did not report end points of interest (eg, platelet function), used aspirin as

an adjunct to dipyridamole, were not secondary prevention, or included duplicate results and were excluded (Figure 1).

## Data Extraction

We abstracted data on demographics, inclusion and exclusion criteria, treatment regimen, duration of follow-up, and clinical end points from published data. Two of the studies<sup>16,17</sup> included treatment arms in addition to those of interest for this analysis (eg, aspirin plus dipyridamole), but we abstracted data from low-dose aspirin-only and placebo-only treatment arms.

## Clinical End Points

The clinical end point definitions were similar among the trials. Outcomes examined in the current overview were a composite end point of any major cardiovascular event (cardiovascular mortality, nonfatal MI, or nonfatal stroke), each of the individual components of the composite end point separately, and all-cause mortality. All 6 trials<sup>16-21</sup> reported outcomes on cardiovascular events, all-cause mortality, and MI, whereas 5 trials reported outcomes on stroke.<sup>16-19,21</sup>

The safety end point was major bleeding, as defined by each individual trial. Major bleeding was reported by 4 of the 6 trials.<sup>16-18,21</sup>

## Data Synthesis and Analysis

All statistical analyses were performed using the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ).

## CLINICAL SIGNIFICANCE

- This is the first study to cumulatively evaluate the benefit and risk of low-dose aspirin (50-325 mg/d) in patients with stable cardiovascular disease.
- Low-dose aspirin significantly reduces all-cause mortality, adverse cardiovascular events, nonfatal MI, and nonfatal stroke, and increases the risk of major bleeding in patients with stable cardiovascular disease.
- The benefit of aspirin was driven by a reduction in all-cause mortality and nonfatal MI in patients with ischemic heart disease and by a reduction in stroke in patients with cerebrovascular disease.
- No additional benefit was observed with a higher dose (300 mg vs 50-100 mg/d).

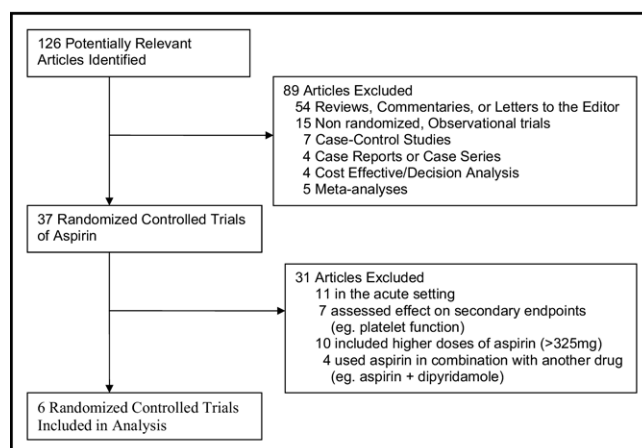


Figure 1 Flow diagram of the trial selection process.

**Table 1** Design of Trials Included in the Meta-Analysis

Source	No. of Individuals	Patient Population	Aspirin mg/d	Follow-up
Cardiff-I, 1974	1239	Men with a prior MI	300	13 mo
Danish Low Dose, 1988	301	Prior carotid endarterectomy	50-100	23 mo
UK-TIA, 1991	1620	Prior TIA or minor stroke	300	50 mo
SALT, 1991	1360	Prior TIA or stroke	75	32 mo
ESPS-2, 1996	3298	Prior TIA or stroke	50	24 mo
SAPAT, 1992	2035	Chronic stable angina	75	50 mo

UK-TIA = United Kingdom Transient Ischemic Attack; SALT = Swedish Aspirin Low-Dose Trial; ESPS-2 = European Stroke Prevention Study-2; SAPAT = Swedish Angina Pectoris Aspirin Trial; MI = myocardial infarction; TIA = transient ischemic attack.

Data were analyzed according to the intention-to-treat principle. The Cochrane Q statistic was calculated to assess heterogeneity among the trials. The Q statistic failed to indicate statistical heterogeneity for any end point. However, because the lack of heterogeneity does not necessarily indicate homogeneity, a summary odds ratio (OR) was calculated using a random effects model from the ORs and the 95% confidence intervals (CIs) for each end point in each study using Mantel-Haenszel methods. A *P* value of less than .05 was judged as statistically significant. To assess publication bias, we generated a funnel plot of the logarithm of effect size and compared it with the standard error for each trial.

Subgroup analyses were conducted to examine whether the results were different in studies with lower dose aspirin (50-100 mg) versus those with higher dose aspirin (300 mg); in studies in which patients were enrolled for cerebrovascular accident (stroke/transient ischemic attack) versus those enrolled for ischemic heart disease (prior MI or stable angina); and in studies with a mean follow-up exceeding 2 years versus those with a

follow-up of up to 2 years. Subgroup estimates were compared by general variance methods.

## Role of the Funding Source

This was an investigator-initiated unfunded study. All authors had access to the data and the statistical analysis report. Each author approved the final article and attests to the validity of the results.

## RESULTS

### Overview of Trials

We identified 6 randomized trials for inclusion.<sup>16-21</sup> Four trials enrolled patients following a cerebrovascular event,<sup>16-19</sup> 1 following an MI,<sup>20</sup> and 1 trial included patients with chronic stable angina.<sup>21</sup> Four of the studies<sup>18-21</sup> included 2 study arms: low-dose aspirin versus placebo. Two studies had multiple arms; the United Kingdom Transient Ischemic Attack trial<sup>17</sup> had 3 arms (low-dose aspirin, high-dose aspirin, and placebo); and the European Stroke Prevention Study-2<sup>16</sup> had 4 arms (low-dose aspirin, dipyridamole, low-dose aspirin plus dipyridamole, and placebo). For the current analysis we included only those subjects who were receiving low-dose aspirin monotherapy and placebo. In total, 13,972 subjects were enrolled in the 6 trials, of whom 9853 were included in this analysis. Details of the included studies are shown in Table 1. Aspirin dose ranged from 50 mg to 300 mg daily. Duration of follow-up ranged between 13 and 50 months. Patient characteristics in each of the studies are presented in Table 2.

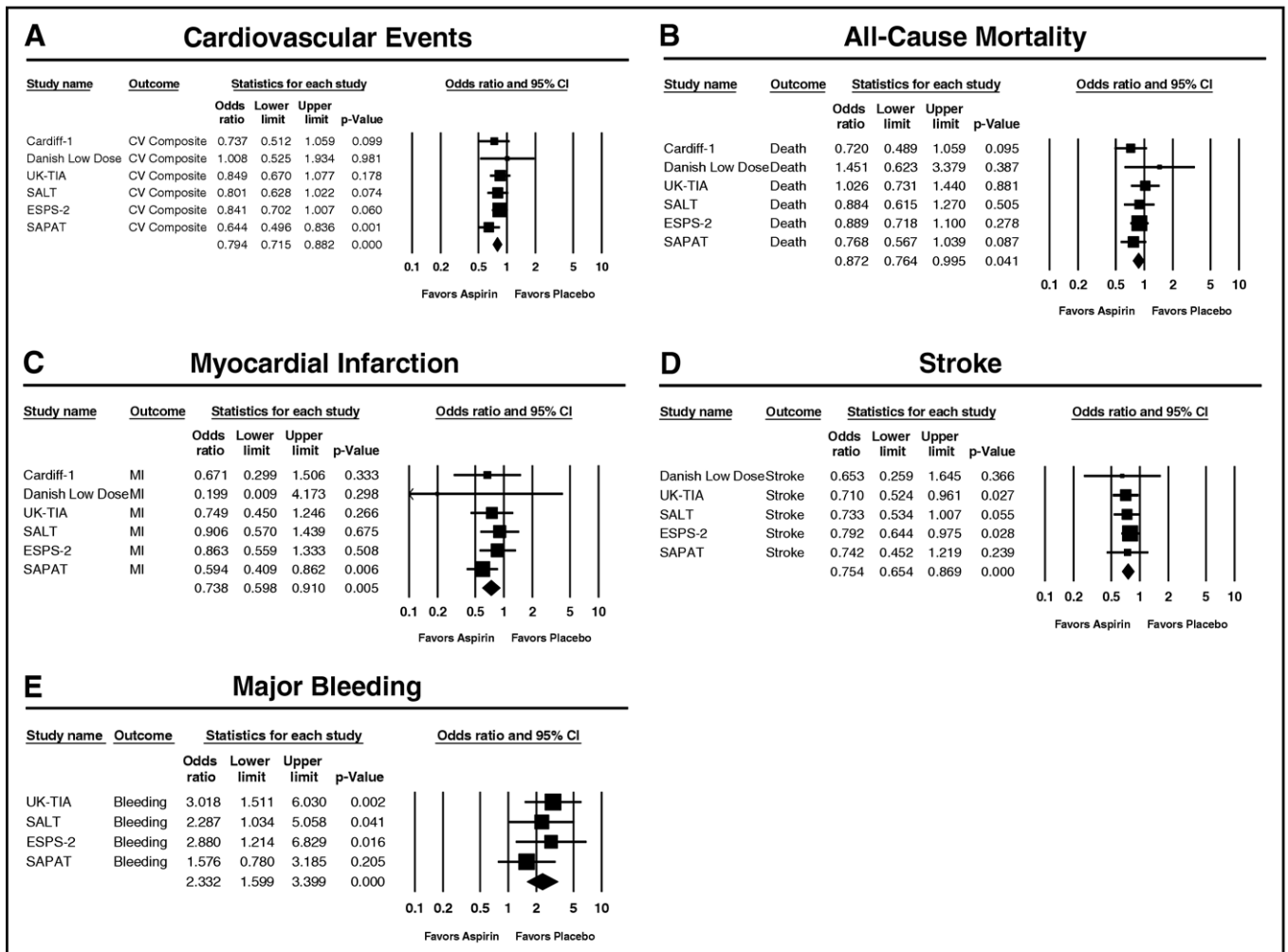
### Study Quality

Randomized treatment allocation sequences were generated in all 6 studies. All trials were placebo controlled. Five of the 6 trials used a fixed aspirin dose; the Danish Low Dose trial<sup>19</sup> titrated aspirin dose to maintain platelet inhibition at more than 80%, in which 76% received 50 mg/d, 13% received 60 mg/d, 8% received 70 mg/d, and 3% received 100 mg/d. Four of the 6 trials<sup>16-18,21</sup> maintained a blinded adjudication committee for the outcomes of interest. Five of the 6 trials had more than 99% follow-up.<sup>16-19,21</sup> Cardiff-1<sup>20</sup> reported a 9% withdrawal

**Table 2** Characteristics of Subjects Included in Trials of Low-Dose Aspirin for the Secondary Prevention of Cardiovascular Disease

	Cardiff-I	Danish Low Dose	UK-TIA	SALT	ESPS-2	SAPAT
Age in years (SD)	55.0	59.0 (8.0)	59.8 (9.0)	66.9 (7.2)	66.7	67
Female	0	35	27	34	42	48
Smoker	–	76	52	27	24	16
Hypertension	–	36	40	47	61	41
Hyperlipidemia	–	–	37	–	23	–
Diabetes	–	8	4	13	15	7
Claudication/PVD	–	21	12	8	22	–

UK-TIA = United Kingdom Transient Ischemic Attack; SALT = Swedish Aspirin Low-Dose Trial; ESPS-2 = European Stroke Prevention Study-2; SAPAT = Swedish Angina Pectoris Aspirin Trial; PVD = peripheral vascular disease; SD = standard deviation.



**Figure 2** Effect of aspirin on (A) major cardiovascular events, (B) all-cause mortality, (C) MI, (D) stroke, and (E) major bleeding in patients with stable cardiovascular disease. Sizes of data markers are proportional to the amount of data contributed by each trial. Test for heterogeneity for major cardiovascular events,  $P = .571$ ; all-cause mortality,  $P = .557$ ; MI,  $P = .650$ ; stroke,  $P = .974$ ; major bleeding,  $P = .581$ . CI = confidence interval; CV = cardiovascular; UK-TIA = United Kingdom Transient Ischemic Attack; SALT = Swedish Aspirin Low-Dose Trial; ESPS-2 = European Stroke Prevention Study-2; SAPAT = Swedish Angina Pectoris Aspirin Trial.

rate secondary to illness (4%), adverse event (3%), and refusal to continue (2%). Four of the trials were partially or completely funded by pharmaceutical companies.<sup>16,17,19,21</sup> There was no evidence of publication bias.

**Clinical End Points**

A total of 1718 cardiovascular events (nonfatal MI, nonfatal stroke, and cardiovascular death) occurred during a mean follow-up of 33.3 months. The cardiovascular event rate was 15.8% among patients randomized to aspirin and 19.1% among patients randomized to placebo. Aspirin therapy was associated with a significant 21% reduction in the odds of cardiovascular events (OR 0.79; 95% CI, 0.72-0.88;  $P < .01$ ). Absolute risk reduction was 3.3%, and the number needed to treat was 30 (Figure 2A).

A total of 1067 deaths occurred during follow-up, 10.1% among aspirin users and 11.5% among placebo

users. Aspirin therapy was associated with a significant 13% reduction in the odds of all-cause mortality (OR 0.87; 95% CI, 0.76-0.98;  $P = .03$ ). Absolute risk reduction was 1.4%, and the number needed to treat was 71 (Figure 2B).

A total of 375 MIs occurred during follow-up, 3.2% among aspirin users and 4.4% among placebo users. Aspirin therapy was associated with a significant 26% reduction in the odds of MI (OR 0.74; 95% CI, 0.60-0.91;  $P < .01$ ). Absolute risk reduction was 1.2%, and the number needed to treat was 83 (Figure 2C).

A total of 873 strokes occurred during follow-up, 8.9% among aspirin users and 11.4% among placebo users. Aspirin therapy was associated with a significant 25% reduction in the odds of stroke (OR 0.75; 95% CI, 0.65-0.87;  $P < .01$ ). Absolute risk reduction was 2.5%, and the number needed to treat was 40 (Figure 2D).

**Table 3** Random Effects Risk Ratios (95% Confidence Intervals) for Aspirin Therapy Versus Placebo in Subgroup Analyses

	Major Cardiovascular Event	All-Cause Mortality	Myocardial Infarction	Stroke	Major Bleeding
Aspirin dose					
50-100 mg	0.78 (0.69-0.90)	0.87 (0.75-1.01)	0.74 (0.58-0.96)	0.77 (0.65-0.90)	2.09 (1.33-3.28)
300 mg	0.81 (0.67-0.99)	0.87 (0.62-1.23)	0.73 (0.47-1.12)	0.71 (0.52-0.96)	3.02 (1.51-6.03)
Enrollment criteria					
CVA	0.84 (0.74-0.95)	0.93 (0.80-1.09)	0.83 (0.64-1.09)	0.76 (0.65-0.88)	2.73 (1.75-4.27)
IHD	0.67 (0.55-0.83)	0.75 (0.59-0.95)	0.61 (0.43-0.85)	0.74 (0.45-1.22)	1.58 (0.78-3.19)
Mean follow-up					
≤24 mo	0.82 (0.72-0.94)	0.87 (0.74-1.03)	0.84 (0.63-1.13)	0.77 (0.65-0.91)	2.54 (1.42-4.56)
>24 mo	0.74 (0.57-0.98)	0.87 (0.66-1.17)	0.64 (0.48-0.87)	0.72 (0.56-0.93)	2.19 (1.34-3.59)

CVA = cerebrovascular accident (stroke/transient ischemic attack); IHD = ischemic heart disease (MI/stable angina).

## Safety End Point

A total of 98 major bleeds occurred during follow-up, 1.6% among aspirin users and 0.7% among placebo users. Aspirin therapy was associated with a significant increase in the odds of major bleeding (OR 2.18; 95% CI, 1.41-3.35;  $P < .01$ ). Absolute risk increase was 0.9%, and the number needed to harm was 111 (Figure 2E).

## Subgroups

Subgroup analyses (Table 3) reveal that aspirin dose and length of follow-up do not affect any of the 5 end points considered. The 2 trials that enrolled patients with ischemic heart disease showed a statistically significant reduction in the risk of major cardiovascular events, all-cause mortality, and MI.<sup>20,21</sup> The 4 trials that enrolled patients after cerebrovascular accidents demonstrated a significant reduction in the risk of major cardiovascular events, primarily driven by a reduction in the risk of stroke.<sup>16-19</sup>

## DISCUSSION

The major finding of this study is that low-dose aspirin is associated with a significant reduction in the risk of major cardiac events, all-cause mortality, nonfatal MI, and nonfatal stroke among patients with stable cardiovascular disease. Low-dose aspirin also is associated with a significant increase in the risk of major bleeding. The effect of aspirin was similar in the low-dose group (50-100 mg) and the higher dose group (300 mg). Unlike prior analyses that combined various populations with different antiplatelet therapies and dosages, our study focuses on low-dose aspirin in a population with stable cardiovascular disease. Within this cohort, we demonstrated a significant reduction of major cardiac events in patients with either ischemic heart disease or cerebrovascular disease. Of interest, the benefit was driven by a reduction in the risk of MI among the ischemic heart disease group and a reduction in the risk of stroke among the cerebrovascular disease group.

Aspirin is one of the most widely used cardioprotective drugs.<sup>22</sup> More than 75 randomized trials of aspirin have been conducted during the past 40 years. Much of the data

on aspirin have been summarized by the ATC in a comprehensive analysis in 1994 and updated in 2002.<sup>6,7</sup> However, by design, the ATC combined studies that evaluated various antiplatelet agents, multiple clinical settings, and a wide range of dosages. A wide discrepancy exists in the number of randomized trials performed and the number of subjects included between all antiplatelet studies and studies of low-dose aspirin (Table 4). Although 34 studies have been conducted using an antiplatelet regimen for the secondary prevention of cardiovascular disease (prior MI/stroke/stable angina), only 6 of these studies studied the effect of low-dose aspirin in this cohort.<sup>7</sup> To date, no study has collectively reviewed the effect of low-dose aspirin in this high-risk group of subjects.

In the 2007 American Heart Association update on heart disease and stroke statistics,<sup>23</sup> 1 in 3 adult men and women have a diagnosis of cardiovascular disease. Cardiovascular disease remains the leading cause of death in men and women throughout the industrial world. With the aging of the population and the increased risk of cardiovascular disease with age, there is an increasing need for cardiovascular protection. In addition to diet, exercise, and smoking cessation, special emphasis should be placed on inexpensive and readily available cardioprotective agents. Aspirin is one such agent and has been extensively studied. However, its cumulative effect in a high-risk population for secondary prevention has not been fully evaluated. Consistent with the findings of the ATC, our study demonstrated that aspirin was associated with a significant reduction in the risk of cardiovascular adverse events, as well as each individual end point of death, MI, and stroke. Few therapies have been noted to have such cardioprotective properties. Statin therapy and angiotensin-converting enzyme inhibitors all have been proven to decrease the risk of adverse cardiovascular events in patients with stable cardiovascular disease.<sup>24,25</sup> In an attempt to compare the effects of aspirin with other proven medications, Figure 3 illustrates the number of patients needed to treat to prevent adverse cardiovascular events. Aspirin is comparable to these other proven therapies; however, aspirin is readily available over the counter and inexpensive.

**Table 4** Number of Trials and Participants Included in Randomized Control Trials of All Antiplatelet Therapies, Aspirin (Any Dose), and Aspirin (Low Dose) Versus Placebo/Control

Setting	All Trials		Aspirin Trials* (Any Dose)		Aspirin Trials* (50-325 mg/d)	
	No. of Trials	No. of Patients	No. of Trials	No. of Patients	No. of Trials	No. of Patients
<b>Unstable population</b>						
Acute MI	15	19,288	6	17,979	5	17,926
Acute stroke	7	40,821	3	40,399	3	40,399
Unstable angina	12	4681	6	2957	5	2478
Total	34	64,790	15	61,335	13	60,803
<b>Stable population†</b>						
Previous MI	12	18,573	6	10,983	1	1239
Prior stroke/TIA	21	18,270	11	9960	4	6579
Stable angina	1	2035	1	2035	1	2035
Total	34	38,878	18	22,978	6	9853

MI = myocardial infarction; TIA = transient ischemic attack.

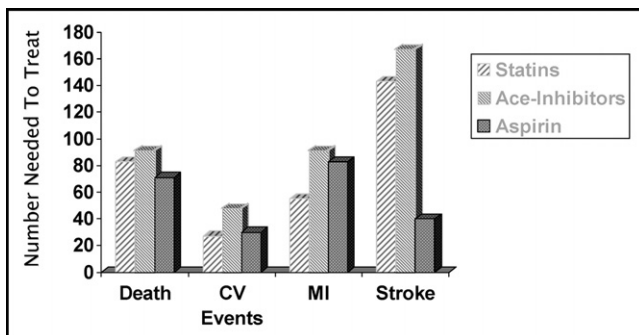
\*Included any trial that included aspirin as monotherapy (not in combination with another drug).

†Defined as patients with stable angina, prior MI, or prior stroke/TIA.

In addition to its benefit, one must be mindful of the risk of low-dose aspirin.<sup>12</sup> From our analysis, aspirin is associated with a more than 2-fold risk of major bleeding. Recent attention has focused on the relationship between bleeding and risk of death.<sup>26,27</sup> It remains unclear whether bleeding contributes to death or is associated with other factors that contribute to death, including cessation of therapy and/or transfusions. However, because of the low absolute risk of major bleeding in this population, the number needed to harm (eg, the number needed to treat to cause a major bleed) is 111. Furthermore, on the basis of the absolute risk reduction and absolute risk increase among 1000 patients treated with low-dose aspirin, one would prevent approximately 33 adverse cardiovascular events (nonfatal MI, nonfatal stroke, or cardiovascular deaths) and 14 deaths, and cause approximately 9 major bleeds.

Despite the protective effect of aspirin, many patients continue to have cardiac events while receiving aspirin therapy.<sup>6,7,12</sup> For the secondary prevention of cardiovascular

disease, aspirin reduces cardiovascular events by approximately 20%. Conversely, this implies that approximately 80% cardiovascular events are not prevented by aspirin. This is somewhat intuitive because aspirin blocks only one of several pathways of platelet activation and aggregation.<sup>28,29</sup> Nevertheless, between 5% and 65% of the population has an inadequate platelet response to aspirin, sometimes known as aspirin resistance.<sup>30,31</sup> Much interest has focused on the variability in response to aspirin therapy. Factors such as gender, body mass index, and smoking status have been shown to be associated with platelet response to aspirin therapy.<sup>30,31</sup> Aspirin dose also has been shown to influence platelet response.<sup>32</sup> Nevertheless, in subgroup analyses, we found no difference in any of the clinical outcomes between aspirin doses of 50 to 100 mg and 300 mg. Furthermore, although a recent review concluded there are no data to support the routine use of doses greater than 81 mg/d for cardiovascular protection, the optimal dose of aspirin in certain high-risk groups remains elusive and a major topic of debate.<sup>33</sup>



**Figure 3** How does aspirin compare? Number needed to treat with aspirin, statins, and ACE inhibitor to prevent a death, major cardiovascular event, MI, or stroke. CV = cardiovascular; MI = myocardial infarction; ACE = angiotensin-converting enzyme.

## Limitations

The present study has several potential limitations. First, as in most meta-analyses, these results should be interpreted with caution because aspirin dose, duration of treatment, and lengths of follow-up were not uniform. However, these differences did not result in any statistical difference in the effect size between the trials. Second, the data used are from randomized trials conducted 10 to 30 years ago. However, much of these data drove regulating agencies to approve and recommend aspirin in this setting. Because of ethical concerns, future studies of aspirin versus placebo are unlikely; therefore, to evaluate the role of aspirin in this setting, one must reevaluate the original data. However, because many of these trials occurred 10 to 30 years ago with limited follow-up, included predominantly older Northern Europeans, and

may not represent today's patients with cardiovascular disease, we are limited in our conclusion to current practicing physicians. Finally, meta-analysis remains retrospective research that is subject to the methodologic deficiencies of the included studies. We minimized the likelihood of bias by developing a detailed protocol before initiating the study, performing a meticulous search for published and unpublished studies, and using explicit methods for study selection, data extraction, and data analysis.

## CONCLUSIONS

This meta-analysis of patients with stable cardiovascular disease indicates that low-dose aspirin therapy is associated with a significant reduction in the risk of cardiovascular events and all-cause mortality. Our results are particularly noteworthy for the significant reduction in each individual end point and all-cause mortality. Although aspirin significantly increased the risk of major bleeding, the totality of evidence demonstrated the benefit of aspirin in this high-risk group of subjects. Future research should focus on proper patient selection and management options to reduce the bleeding risk and the most optimal aspirin dose in each clinical setting for the long-term reduction in cardiovascular disease and mortality.

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