Aspirin Dose for the Prevention of Cardiovascular Disease
A Systematic Review

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Approximately 36% of the adult US population—more than 50 million people—is estimated to take aspirin regularly for cardiovascular disease (CVD) prevention. Among individuals with known CVD, this percentage increases to more than 80%. This translates into roughly 10 billion to 20 billion aspirin tablets consumed annually in the United States alone, solely for CVD prevention.

A number of aspirin preparations are available, but patients in the United States are typically prescribed either 81 mg/d or 325 mg/d. Although aspirin is generally a very well-tolerated drug, like most medications it carries a risk of significant adverse effects, many of which are dose-related. With long-term aspirin therapy so widely used to treat and prevent CVD, maximizing benefits and minimizing risks by providing optimal dosing is of great importance.

Placebo-controlled trials to confirm the benefit of aspirin in the treatment and prevention of atherosclerotic disease complications have used dosages ranging from 50 mg/d to 1300 mg/d. Other clinical trials in CVD patients have evaluated dosages as low as 30 mg/d and as high as 1500 mg/d. In the United States, the US Food and Drug Administration recommends dosages ranging from 50 mg/d to 1300 mg/d for treatment of the clinical manifestations of atherosclerotic disease. Because of this, there is substantial controversy and debate regarding what represents the "correct" dosage of aspirin and whether it is the same in all patients.

Evidence Acquisition
We performed a systematic review of peer-reviewed publications identified through MEDLINE and EMBASE (searched through February 2007) and the search term aspirin or acetylsalicylic acid and dose. The search was limited to clinical trials and was extended by a review of bibliographies of pertinent reports of original data and review articles. Published prospective studies using different aspirin dosages in the setting of cardiovascular disease were included.

Evidence Synthesis
Although pharmacodynamic data demonstrate that long-term aspirin dosages as low as 30 mg/d are adequate to fully inhibit platelet thromboxane production, dosages as high as 1300 mg/d are approved for use. In the United States, 81 mg/d of aspirin is prescribed most commonly (60%), followed by 325 mg/d (35%). The available evidence, predominantly from secondary-prevention observational studies, supports that dosages greater than 75 to 81 mg/d do not enhance efficacy, whereas larger dosages are associated with an increased incidence of bleeding events, primarily related to gastrointestinal tract toxicity.

Conclusions
Currently available clinical data do not support the routine, long-term use of aspirin dosages greater than 75 to 81 mg/d in the setting of cardiovascular disease prevention. Higher dosages, which may be commonly prescribed, do not better prevent events but are associated with increased risks of gastrointestinal bleeding.

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Context
More than 50 million US adults take aspirin regularly for long-term prevention of cardiovascular disease, typically either 81 mg/d or 325 mg/d. Controversy remains regarding the most appropriate long-term daily dose.

Objective
To review the mechanism of action of aspirin and the clinical literature for relationships among aspirin dosage, efficacy, and safety.

Evidence Acquisition
A systematic review of the English-language literature was undertaken using MEDLINE and EMBASE (searched through February 2007) and the search term aspirin or acetylsalicylic acid and dose. The search was limited to clinical trials and was extended by a review of bibliographies of pertinent reports of original data and review articles. Published prospective studies using different aspirin dosages in the setting of cardiovascular disease were included.

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Evidence Acquisition
We performed a systematic review of peer-reviewed publications identified...
through the MEDLINE and EMBASE databases (searched through February 2007). The search term was aspirin or acetylsalicylic acid and dose, and the search was limited to clinical trials or randomized clinical trials among humans and articles in English. The search was extended by review of bibliographies from pertinent original reports of data and review articles. Unpublished trials and data presented only in abstract form were not included. A total of 2415 references were identified and manually sorted using the abstracts or full-text publications (Figure). The primary focus was on prospective studies with clinical end points evaluating different aspirin dosages in the setting of CVD. Statistics regarding trends in the consumption of aspirin were provided by the National Disease and Therapeutic Index,4 a continuous survey of office-based physicians in the United States that provides information on their drug prescription patterns. The data used in this report represent the 12-month period ending in September 2006.

**EVIDENCE SYNTHESIS**

**Mechanism of Action**

Aspirin, or acetylsalicylic acid, was first synthesized in 1897 at Friedrich Bayer & Company as a more palatable formulation of salicylic acid—a pain reliever used in some form dating back to ancient Egypt. Aspirin was initially sold to pharmacists in 250-g bottles and was dispensed to patients as a powder. Imitators and adulterated versions of the powder led Bayer to develop an aspirin tablet in 1900.5 In the United States, this was sold as a 3-grain (approximately 325-mg) pill—the genesis of the dose commonly used today. The 81-mg/d children’s doage, which is one quarter of the adult dosage and was arbitrarily determined, first became available in 1922.

Both the beneficial and detrimental effects of aspirin are believed to be primarily due to inhibition of prostanoid biosynthesis, in particular that of thromboxane A2 (TXA2) and prostaglandins (eg, PGE2 and PGI2). Aspirin irreversibly inhibits platelet cyclooxygenase 1 (COX-1) through acetylation of the amino acid serine at position 529,6 thereby preventing arachidonic acid access to the COX-1 catalytic site through steric hindrance. By inhibiting COX-1, the platelet is unable to synthesize prostaglandin H2, which, under normal circumstances, is then converted to TXA2 via the enzyme thromboxane synthase. Although anucleate platelets possess some capacity for protein synthesis, they are incapable of overcoming COX-1 inhibition with new protein synthesis, and the aspirin-induced defect spans the 8- to 10-day life span of the platelet. Because of platelet turnover, approximately 10% of platelets with normal COX activity will be recovered daily following cessation of aspirin therapy.7 Therefore, up to 10 days can be required for complete recovery of platelet COX activity; however, it may require only 20% of normal COX activity to exhibit normal hemostasis.8 COX-1 is constitutively expressed in most cells and plays important roles beyond TXA2 production in platelets. Of particular importance is the production of the cytoprotective prostaglandins by gastric mucosa. Unlike platelets, gastric mucosal cells possess the biosynthetic machinery necessary to overcome COX-1 inhibition and, therefore, recover the ability to synthesize prostaglandins within a few hours after exposure to aspirin. COX-2, a second cyclooxygenase isoenzyme primarily responsible for synthesis of the platelet inhibitor PGI2 by endothelial cells9 and induced in response to inflammatory stimuli, is less sensitive to the effects of aspirin. Aspirin is 170-fold less effective at inhibiting COX-2 than COX-1.10

It has been postulated that aspirin’s anti-inflammatory properties may explain at least part of its mechanism of benefit in CVD.11 However, with aspirin’s much greater selectivity for COX-1 and the central role of COX-2 in inflammation, dosages that achieve measurable anti-inflammatory activity—up to several grams daily—are much higher than those proven clinically effective in the prevention of atherothrombotic events.12 Consistent with this is the lack of an effect on high-sensitivity C-reactive protein levels in most studies.13,14

**Pharmacokinetics and Pharmacodynamics**

Aspirin taken orally is rapidly absorbed in the stomach and upper intestine. Acetylation of platelet COX-1 begins to occur in the portal circulation prior to any measurable systemic level; thus, the measurement of plasma levels of the inactive form of acetylsalicylic acid is an incomplete measure of efficacy.13 Nonetheless, peak plasma levels are achieved rapidly, within approximately 30 minutes, followed by rapid clearance with a half-life of 15 to 20 minutes.13,16 The systemic bioavailability of aspirin is about 50% for single oral doses ranging from 20 mg to 1300 mg.15

Multiple methods of measuring the platelet inhibitory effects of aspirin have been studied, with conflicting results. While no single measure of aspirin’s effect on platelets has yet been proven to correlate with clinical efficacy in a large population, several small studies have suggested a relationship.17-19 Currently, however there is no gold-
to completely inhibit serum TXB₂ production in healthy individuals. In patients with chronic stable angina, in whom thromboxane synthesis is chronically elevated, 50 mg/d of aspirin normalizes thromboxane production and prevents release in the setting of pacing-induced ischemia. Limited pharmacodynamic data also suggest that 100 mg of aspirin every other day is also effective at suppressing platelet function.

Clinical Efficacy
Paul Gibson proposed in 1948 that salicylic acid might be useful in treatment of coronary thrombosis, and the following year he presented case reports detailing the potential role of aspirin in the treatment of coronary thrombosis and angina. In 1953, L. L. Craven, a general practitioner, noticed that tonsillectomists patients experienced increased bleeding after using aspirin for pain relief and was the next to study the efficacy of aspirin in prevention of “coronary occlusion.” It was another 30 years, however, before the striking clinical benefit of aspirin in the short-term treatment and long-term prevention of the manifestations of atherosclerotic disease was conclusively demonstrated in randomized placebo-controlled trials. Dosages as low as 30 mg/d and as high as 1300 mg/d have been shown to significantly lower the risk of cardiovascular disease.

Several meta-analyses have indirectly compared the dosage-related relative risk reduction of aspirin in placebo-controlled trials. In an analysis of 11 clinical trials including 5228 patients randomized to aspirin or placebo following a TIA or stroke, similar effi-
cacy was found for aspirin dosages ranging from 50 mg/d to 1500 mg/d. In the Antithrombotic Trialists’ Collaboration, a meta-analysis of more than 60 aspirin trials also found no relationship between dose and efficacy. In this analysis, the greatest risk reduction was found in trials using a 75- to 150-mg dose of aspirin. An analysis of acute coronary syndrome trials evaluating aspirin vs placebo, in which a random-effects method was used to adjust for heterogeneity among the trials, also found that lower dosages of aspirin were associated with improved outcomes.

Retrospective analyses of several recent large-scale clinical trials are also consistent with the lack of any increase in benefit with higher dosages of aspirin. In the BRAVO (Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion) trial, 9190 patients with vascular disease were randomized to receive 1 of 2 doses of the glycoprotein IIb/IIIa antagonist lortiaplanin or placebo in addition to aspirin at dosages ranging from 75 mg/d to 325 mg/d at the discretion of the treating physician. Among patients randomized to receive placebo, 2410 patients received 75 mg/d to 162 mg/d and 2179 were treated with more than 162 mg/d. At a mean follow-up of 366 days, there was no difference in the primary end point of death, MI, stroke, recurrent ischemia requiring hospitalization, and urgent revascularization, with a trend favoring lower dosages. The combined end point of all-cause mortality, MI, or stroke outcomes occurred equally between these 2 cohorts (TABLE 2). Although a multivariate regression analysis identified higher aspirin dosage as being associated with lower mortality (hazard ratio, 0.74; 95% CI, 0.56-0.97; P = .03), these results have never been duplicated. In a combined analysis from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb and the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Antagonism Using Integrilin Therapy (PURSUIT) trials (n = 20 521), aspirin dosages of less than 150 mg/d were associated with a trend toward a lower incidence of the primary end point of death, MI, or stroke at 6 months, although in one adjusted analysis, aspirin dosages of 150 mg/d or more were associated with significantly fewer MIs but more strokes and no difference in mortality. In the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, 12 562 patients with a non–ST-elevation acute coronary syndromes were randomized to clopidogrel or matching placebo in addition to long-term aspirin therapy of 75 mg/d to 325 mg/d, at the discretion of the investigator. Among patients randomized to either dual antiplatelet therapy or placebo (aspirin only), the lowest event rates were in patients treated with 100 mg/d or less of aspirin (Table 2). It is

### Table 1. Prospective Trials Studying the Effect of Different Dosages of Aspirin on Clinical Outcomes

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Population</th>
<th>Mean Follow-up</th>
<th>Clinical End Point</th>
<th>Aspirin Dosages</th>
<th>No. of Patients</th>
<th>Clinical End Point Event Rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farrell et al, 1991</td>
<td>TIA or minor stroke</td>
<td>4 y</td>
<td>Vascular death, MI, or major stroke</td>
<td>Placebo</td>
<td>814</td>
<td>22.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>300 mg/d</td>
<td>806</td>
<td>20.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>600 mg/d twice daily</td>
<td>815</td>
<td>19.9</td>
</tr>
<tr>
<td>Dutch TIA Study Group, 1991</td>
<td>TIA or minor stroke</td>
<td>2.6 y</td>
<td>Vascular death, MI, or stroke</td>
<td>30 mg/d</td>
<td>1555</td>
<td>14.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>283 mg/d</td>
<td>1576</td>
<td>15.2</td>
</tr>
<tr>
<td>Taylor et al, 1999</td>
<td>Scheduled for carotid</td>
<td>3 mo</td>
<td>Death, MI, or stroke</td>
<td>81 mg/d</td>
<td>709</td>
<td>6.2*</td>
</tr>
<tr>
<td></td>
<td>endarterectomy</td>
<td></td>
<td></td>
<td>325 mg/d</td>
<td>708</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>325 mg twice daily</td>
<td>715</td>
<td>8.4† (P = .03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>650 mg twice daily</td>
<td>717</td>
<td></td>
</tr>
<tr>
<td>Hoffman and Forster, 1991</td>
<td>Following acute</td>
<td>2 y</td>
<td>Death/reinfarction</td>
<td>30 mg/d</td>
<td>179</td>
<td>7.3/6.7‡</td>
</tr>
<tr>
<td></td>
<td>myocardial infarction</td>
<td></td>
<td></td>
<td>60 mg/d</td>
<td>245</td>
<td>8.7/8.2‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1000 mg/d</td>
<td>277</td>
<td>11.2/15.9‡</td>
</tr>
<tr>
<td>Husted et al, 1989</td>
<td>Acute MI</td>
<td>3 mo</td>
<td>Cardiac death or nonfatal MI</td>
<td>Placebo</td>
<td>97</td>
<td>20.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>100 mg/d</td>
<td>99</td>
<td>15.1</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1000 mg/d</td>
<td>97</td>
<td>23.7</td>
</tr>
<tr>
<td>Lee et al, 1990</td>
<td>TIA, RIND, or ischemic</td>
<td>24 mo</td>
<td>TIA, fatal and nonfatal cerebrovascular</td>
<td>100 mg/d</td>
<td>145</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>stroke</td>
<td></td>
<td>accident, or fatal and nonfatal MI</td>
<td>300 mg/d</td>
<td>138</td>
<td>10.8</td>
</tr>
<tr>
<td>Minar et al, 1995</td>
<td>Following peripheral</td>
<td>24 mo</td>
<td>Death</td>
<td>100 mg/d</td>
<td>109</td>
<td>12.3</td>
</tr>
<tr>
<td></td>
<td>angioplasty</td>
<td></td>
<td></td>
<td>1000 mg/d</td>
<td>107</td>
<td>13.4</td>
</tr>
<tr>
<td>O’Connor et al, 1996</td>
<td>Acute MI treated with</td>
<td></td>
<td>Death</td>
<td>81 mg/d</td>
<td>79</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>thrombolytics</td>
<td></td>
<td></td>
<td>325 mg/d</td>
<td>83</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Abbreviations: MI, myocardial infarction; RIND, reversible ischemic neurologic deficit; TIA, transient ischemic attack.

*Event rate in patients receiving 81 mg or 325 mg daily.
†Event rate in patients receiving 325 mg or 650 mg twice daily.
‡Reinfarction was significantly less likely among patients randomized to 30 or 60 mg of aspirin daily compared with patients randomized to 1000 mg daily (P<.01).
important to note that aspirin dosage was not randomized in any of these trials, but these observational data involving nearly 35,000 patients support the lack of efficacy with increasing dosages of aspirin.

**Adverse Effects**

Aspirin is such a routine part of our lives that little thought is regularly given to the adverse events associated with its long-term use. The major risk of aspirin, as with other nonsteroidal anti-inflammatory drugs (NSAIDs), is the risk of bleeding. Although the antiplatelet effects of aspirin likely contribute to an increase in the risk of bleeding, as highlighted by an increased risk of hemorrhagic stroke of 0.2 events per 1000 patient-years,45 the majority of the increased bleeding has a gastrointestinal etiology. While the majority of data support that any increase in dose of aspirin is associated with an increased risk of gastrointestinal bleeding when only contemporary doses (75-325 mg) are used remains poorly defined. However, considering that more than 50 million patients take a daily aspirin pill for CVD prevention in the United States alone, if the differences in major bleeding found in the aspirin-only group of the CURE trials are reflective of this was more reflective of contemporary dosing, a trend toward less bleeding was noted in the 30-mg group (2.6%) than the 283-mg group (3.2%).33

Observational data from the BRAVO and CURE trials also demonstrated an increased risk of bleeding with higher doses of aspirin, even when doses no greater than 325 mg were used (Table 2).42,44 More support for this relationship comes from a meta-analysis of 31 clinical trials with more than 192,000 patients involving aspirin therapy in which doses of less than 100 mg/d were associated with a significantly lower mean rate of major bleeding events than doses greater than 200 mg/d (1.56% [95% CI, 1.2%-1.9%] vs 2.29% [95% CI, 1.9%-7.0%]; P<.001).52 However, not all pooled study analyses have come to the same conclusion. In an analysis involving 24 trials with nearly 66,000 individuals, no relationship was found between aspirin dose and strictly gastrointestinal bleeding.53

While the majority of data support that any increase in dose of aspirin is associated with an increased risk of gastrointestinal bleeding, the clinical importance associated with the differences in gastrointestinal bleeding when only contemporary doses (75-325 mg) are used remains poorly defined. However, considering that more than 50 million patients take a daily aspirin pill for CVD prevention in the United States alone, if the differences in major bleeding found in the aspirin-only group of the CURE trials are reflective of this

### Table 2. Retrospective Observational Results From GUSTO IIb/PURSUIT\(^\text{43}\) and the Aspirin-Only Arms of the BRAVO\(^\text{42}\) and CURE\(^\text{44}\) Trials

<table>
<thead>
<tr>
<th>Source</th>
<th>Study Population</th>
<th>Follow-up</th>
<th>Aspirin Dosages</th>
<th>No. of Patients</th>
<th>End Point Event Rate, %</th>
<th>Deaths, MI, or Stroke</th>
<th>Major or Serious Gastrointestinal Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topol et al,(^\text{42}) 2003</td>
<td>Recent MI, stroke, or TIA or double vascular bed disease</td>
<td>Maximum, 2 y Mean, 366 d</td>
<td>75-162 mg/d</td>
<td>2410</td>
<td>6.2</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>162-325 mg/d</td>
<td>2179</td>
<td>6.1</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Quinn et al,(^\text{43}) 2004</td>
<td>ACS</td>
<td>Hospital discharge to 6 mo</td>
<td>&lt;150 mg/d</td>
<td>6128</td>
<td>6.2</td>
<td>Not measured</td>
<td></td>
</tr>
<tr>
<td>Peters et al,(^\text{44}) 2003*</td>
<td>Non–ST-elevation ACS</td>
<td>Mean, 9 mo Maximum, 1 y</td>
<td>75-100 mg/d</td>
<td>2695</td>
<td>10.5</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>101-199 mg/d</td>
<td>1525</td>
<td>9.8</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>200-325 mg/d</td>
<td>2071</td>
<td>13.6†</td>
<td>3.7‡</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACS, acute coronary syndromes; MI, myocardial infarction; TIA, transient ischemic attack.

*For this study, the outcome of death included only cardiovascular death.

‡P = .002 for trend.

†P<.001 for trend.
ASPIRIN DOSE FOR CARDIOVASCULAR DISEASE PREVENTION

population, daily treatment with 325 mg of aspirin would lead to an excess of more than 900,000 major bleeding events per year compared with a daily dose of 81 mg.

**Should the Dose of Aspirin Be the Same for Everyone?**

Although studies of patient populations seem to demonstrate that the clinical benefit of aspirin is not increased when doses of more than 75 mg to 81 mg are used, and that the potential for harm may increase, it remains unclear how to apply these data to an individual patient. Intercurrent variability in response to aspirin has been recognized for almost 40 years, longer than the clinical benefit of aspirin has been appreciated. Since that time, numerous small studies using a wide variety of ex vivo methods have consistently found substantial variability in individual response to aspirin, with several, but not all, trials suggesting a correlation between ex vivo “nonresponsiveness” and clinical outcomes. Not only has it been hypothesized that specific groups of patients (such as those with diabetes) may require higher doses of aspirin, but several studies using ex vivo measures of platelet responsiveness to aspirin have found a wide range of dose responses among individuals. These results have prompted some to conclude that measuring aspirin responsiveness and increasing the dosage of aspirin accordingly (to as high as 1300 mg/d) may be of clinical benefit. However, the results of these small studies, some of which have found nearly 50% of patients treated with low-dose aspirin to be “nonresponsive,” are very difficult to reconcile with large-scale clinical trials that have not even found a trend toward a benefit of higher doses. Large-scale clinical trials in this area are clearly needed.

Differences in acetylsalicylic acid pharmacokinetics and pharmacodynamics related to sex may also affect aspirin dosing and efficacy. Women are reported to have slower clearance of acetylsalicylic acid and, therefore, higher circulating levels.

In a study of 130 healthy volunteers, consumption of low-dose aspirin had a greater effect on arachidonic acid–induced aggregation in women than in men, despite higher baseline platelet aggregation among women. There is also emerging data suggesting that the clinical efficacy of aspirin may be sex-dependent. In a meta-analysis of 6 trials randomizing patients to aspirin or placebo in the setting of primary prevention, aspirin therapy was associated with a significant reduction in MI among men but had no effect on stroke rate. In contrast, women taking aspirin experienced a lower stroke rate with no effect on MI.

**CONCLUSION**

No drug is used by a greater number of people worldwide than aspirin. Although it is safe in general, when used in such a large population, even a low overall incidence of adverse effects can have a substantial impact. An association between increases in aspirin dose and risk of adverse events has been confirmed in multiple studies, whereas no such dose relationship has been identified for efficacy. This suggests that following the rapid, acute inhibition of platelet COX-1 with 160 to 325 mg of aspirin, every effort should be made to minimize the long-term dosage. Currently, the clinical data are most supportive of a 75- or 81-mg daily dose.

The greatest challenge for the future is to determine the optimal method for identifying the best antiplatelet regimen for the individual patient. The ability to routinely assess a clinically relevant measure of platelet function during treatment with aspirin or any other antiplatelet therapy and its relation to clinical outcome will be central to accomplishing this.

**Access to Data:** Dr Campbell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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