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.

Evidence Acquisition
We performed 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.

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.

EVIDENCE ACQUISITION
We performed a systematic review of peer-reviewed publications identified

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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 endpoints 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, 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. 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 dosage, 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, 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. 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.

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 secondary cyclooxygenase isoenzyme primarily responsible for synthesis of the platelet inhibitor PGI2 by endothelial cells 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.

It has been postulated that aspirin’s anti-inflammatory properties may explain at least part of its mechanism of benefit in CVD. 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. Consistent with this is the lack of an effect on high-sensitivity C-reactive protein levels in most studies.

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. Nonetheless, peak plasma levels are achieved rapidly, within approximately 30 minutes, followed by rapid clearance with a half-life of 15 to 20 minutes. The systemic bioavailability of aspirin is about 50% for single oral doses ranging from 20 mg to 1300 mg.

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. Currently, however there is no gold-
standard measure of aspirin's pharmacodynamics.

**Pharmacodynamic Studies of Aspirin**

**Short-term Therapy.** A wide range of aspirin doses, preparations, and methods of ingestion have been evaluated to determine the best way to achieve maximal antiplatelet activity in the acute setting. In a study that evaluated the acute antiplatelet effects of 40-mg, 100-mg, 300-mg, and 500-mg doses of aspirin, the 300-mg and 500-mg doses were found to achieve equal levels of platelet inhibition 2 hours following ingestion, suggesting that there is no added benefit for doses of more than 300 mg. However, at very low doses (0.45 mg/kg, corresponding to about 30 mg in an adult), it may take 10 days to effectively suppress TXA₂ production. Aspirin absorption and the onset of antiplatelet activity are significantly shortened by chewing or drinking solubilized aspirin (eg, Alka-Seltzer), with maximal inhibition of serum thromboxane B₂ (TXB₂) production achieved within 20 to 30 minutes compared with swallowing a whole pill that required approximately 60 minutes. In another study of 18 volunteers, chewing an 81-mg, 162-mg, or 324-mg aspirin pill led to equivalent reduction in TXB₂ production, but maximal inhibition by 15 minutes after ingestion was achieved only with the 162-mg and 324-mg doses. The results of these and other studies suggest that to rapidly (within 15 minutes) achieve the maximal effects of aspirin, at least 162 mg should be chewed or dissolved, then swallowed.

**Long-term Therapy.** Due to its irreversible inactivation of platelet COX-1 and presumably minimal de novo synthesis of new COX-1 by platelets, the effects of long-term aspirin dosing are cumulative. Once complete inhibition of COX-1 is achieved, only minimal doses of aspirin are required to ensure adequate acetylation of COX-1 activity arising in newly formed platelets entering the circulation (approximately 10% daily). Because of this, dosages of as little as 30 mg/d have been shown 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.

Enteric-coated products are also routinely used in the setting of long-term aspirin therapy. However, questions have arisen regarding the effect of enteric coating on the bioavailability and biological activity of aspirin. There is conflicting evidence regarding the effectiveness of routinely administered enteric-coated products, even among trials with similar designs. In a study comparing 3 different enteric preparations with uncoated aspirin, it was noted that despite high levels (>96%) of TXB₂ suppression by all preparations, the uncoated form led to a significantly higher level of inhibition.

**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 tonsillectomy 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 studied in these trials, as have daily and alternate-day dosing schedules.

A number of large, blinded, controlled trials as well as several meta-analyses of placebo-controlled trials have evaluated the optimal aspirin dosage in various clinical settings. The one nearly constant finding among all of these studies has been the lack of a relationship between increasing aspirin dosage and improved efficacy. In fact, the trend in benefit has almost uniformly favored lower dosages.

Pharmaceutical market research suggests that the dosage selected by physicians is relatively well divided, with the majority (about 60%) choosing 81 mg/d and a substantial minority (about 35%) prescribing 325 mg/d. The dosage used does not appear to be affected by physician specialty, although cardiologists tend to use 325 mg/d slightly more frequently.

Clinical outcomes trials directly comparing different dosages of aspirin have included patients with virtually every clinical manifestation of atherosclerotic disease: stroke, transient ischemic attack (TIA), percutaneous coronary and peripheral interventions, carotid endarterectomy, and myocardial infarction (MI). As shown in Table 1, together these trials include nearly 10 000 patients at dosages ranging from 30 mg/d to 1300 mg/d. A significant benefit of higher dosages of aspirin was not demonstrated in any trial, and in most trials the lowest event rates were realized among patients randomized to the low-dosage groups. In perhaps the best trial of long-term therapy comparing the contemporary dosage with a very low dosage of aspirin, 3131 individuals were randomized to receive either 283 mg/d or 30 mg/d of aspirin following a TIA or stroke. After a mean of 2.6 years of follow-up, the combined end point of vascular death, MI, or stroke was similar in the 2 groups (14.7% for 30 mg/d vs 15.2% for 283 mg/d; hazard ratio, 0.91; 95% confidence interval [CI], 0.76-1.09).

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

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 anti-platelet 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, the majority of the increased bleeding has a gastrointestinal etiology. Although this increased risk of gastrointestinal bleeding is more commonly attributed to nonaspirin NSAIDs, a recent evaluation of patients hospitalized for ulcer bleeding found that low-dose aspirin therapy was responsible for as much ulcer bleeding as all other NSAIDs combined. In another prospective evaluation of 18,820 hospitalized patients, 1225 were admitted as a result of adverse drug reactions, and low-dose aspirin was identified as one of the most common causal agents, with 18% of the hospitalizations and 61% of the fatal cases associated with aspirin.

Through the inhibition of COX-1 in gastric mucosal cells, aspirin decreases the production of cytoprotective prostaglandins. The influence of aspirin on gastric prostaglandin levels is dosage-dependent, with almost 50% inhibition at just 30 mg/d, but maximal inhibition requires approximately 1300 mg/d. Consistent with these data, all conventional dosages of aspirin are associated with an increased risk of gastrointestinal bleeding compared with placebo. In a case-control study of patients admitted with gastrointestinal bleeding, the odds ratio for admission with a bleeding ulcer was increased among aspirin users regardless of dosage. Treatment with a 75-mg/d dosage of aspirin was associated with an odds ratio of 2.3 for a bleeding ulcer (95% CI, 1.2-4.4), whereas 300 mg/d increased the odds ratio to 3.9 (95% CI, 2.5-6.3). Unfortunately, enteric-coated or buffered aspirin preparations do not appear to influence the risk of major bleeding in the upper GI tract.

A relationship between aspirin dosage and bleeding has also been demonstrated in clinical trials. An analysis of aspirin-treated patients from the UK-TIA trial found almost double the risk of gastrointestinal bleeding among patients randomized to 1200 mg/d of aspirin compared with 300 mg/d (odds ratio, 6.4 [95% CI, 2.5-16.5] vs 3.3 [95% CI, 1.2-9.0]). In the Dutch-TIA trial, where the higher aspirin dose 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%).

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). 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). 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.

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 trial are reflective of this...
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. Intertreatment 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 1300 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 antplatelet regimen for the individual patient. The ability to routinely assess a clinically relevant measure of platelet function during treatment with aspirin or any other antplatelet therapy and its relationship 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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