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# Aspirin Dosing for the Prevention and Treatment of Ischemic Stroke: An Indication-Specific Review of the Literature

Alexander J Ansara, Sarah A Nisly, Sally A Arif, Julia M Koehler, and Sarah T Nordmeyer

**OBJECTIVE:** To evaluate the efficacy of aspirin for the treatment and prevention of ischemic stroke and identify the minimum dose proven to be effective for each indication.

**DATA SOURCES:** PubMed and MEDLINE searches (January 2009–January 2010) were performed to identify primary literature, using search terms including aspirin, stroke prevention, acute ischemic stroke, acetylsalicylic acid, atrial fibrillation, myocardial infarction, and carotid endarterectomy. Additionally, reference citations from publications identified were reviewed.

**STUDY SELECTION AND DATA EXTRACTION:** Articles published in English were evaluated and relevant primary literature evaluating the efficacy of aspirin in the prevention of stroke was included in this review.

**DATA SYNTHESIS:** Antiplatelet therapy is the benchmark for the prevention of ischemic stroke. Aspirin has been proven to prevent ischemic stroke in a variety of settings. Despite the frequency at which aspirin continues to be prescribed in patients at risk of ischemic stroke, there remains confusion in clinical practice as to what minimum dose is required in various at-risk patients. A thorough review of the primary literature suggests that low-dose (50–81 mg daily) aspirin is insufficient for some indications. Acute ischemic stroke treatment requires 160–325 mg, while atrial fibrillation and carotid arterial disease require daily doses of 325 and 81–325 mg, respectively.

**CONCLUSIONS:** Available evidence suggests that aspirin dosing must be individualized according to indication. Recommendations provided by national guidelines at times recommend lower doses of aspirin than have been proven effective. Higher doses are indicated for stroke prevention in atrial fibrillation (325mg) and acute ischemic stroke patients (160–325 mg). Aspirin has not yet been proven effective for primary prevention of strokes in men, and a minimum dose for these patients cannot be determined from the available data.

Nearly 800,000 strokes occur yearly in the US. Stroke is the third leading cause of death in the US and accounted for 1 of every 18 deaths in 2006.<sup>1</sup> Stroke is a leading cause of disability, impaired functionality, and lessened quality of life. In a utilities survey of people at high risk for stroke, more than 45% of respondents viewed a major stroke as a worse outcome than death.<sup>2</sup>

Nearly 85% of all strokes are ischemic, with atherosclerotic disease accounting for most cases.<sup>1</sup> The mainstay of stroke prevention is pharmacologic treatment with antiplatelet agents. Several antithrombotic agents have been proven efficacious in the prevention of ischemic stroke. These include clopidogrel, ticlopidine, extended-release dipyridamole, warfarin, and aspirin. Aspirin is often initially prescribed due to affordability, lack of the need for extensive monitoring, and evidence of clinical efficacy in various settings.

Although aspirin is frequently prescribed, there remains confusion in clinical practice as to the optimal dose for stroke prevention and treatment. While doses of 50 mg daily are beneficial in some patients, others warrant higher doses (160–325 mg).

This literature review identifies the minimum dose of aspirin necessary for stroke prevention and treatment in each of the following settings: primary prevention, acute ischemic stroke, secondary prevention of stroke or transient ischemic attack (TIA), post-myocardial infarction (MI), atrial fibrillation (AF), and carotid arterial disease with or without endarterectomy.

## Pathophysiology of Atherosclerosis

In order to appreciate the benefits of aspirin, one must understand its mechanism of action and the pathophysiology of atherosclerosis. Atherosclerosis, a chronic inflammatory response, leads to the hardening of and loss of elasticity in arterial vessels. Atherosclerotic plaques develop over time and can rupture suddenly, causing platelet activation and thrombus formation, a phenomenon known as atherothrombosis.<sup>3,4</sup>

The role of platelets in the pathophysiology of atherosclerosis begins with endothelial dysfunction, which stimulates the deposition, accumulation, and oxidation of low-density lipoprotein cholesterol within intimal cells. Inflammatory cells are recruited to the endothelium and promote growth of the plaque. Subsequently,

smooth muscle cells migrate toward the lesion, multiply, and cause accumulation of lipid-laden foam cells, which are joined together by a matrix of collagen and elastin. Platelets undergo a conformational change and thereby become activated. Upon activation, thromboxane A<sub>2</sub> (TXA<sub>2</sub>) synthesis is amplified and multiplication of the surface population of glycoprotein IIb/IIIa receptors ensues. Consequently, more fibrinogen is bound, as thrombin-mediated conversion to fibrin attracts more platelets. Although platelet adhesion and activation are essential processes during the course of vascular injury repair, overt expression and progression of such processes can lead to vascular thrombus formation, intraluminal occlusion, and transient ischemia or infarction.<sup>4</sup>

### **Mechanism of Action of Aspirin**

Aspirin prevents vascular complications by inhibiting the effects of platelets. Full antiplatelet effects occur within 30 minutes after ingestion and persist for the platelet lifespan.<sup>5</sup> Aspirin prevents thrombosis by inhibiting the production of the prostanoid TXA<sub>2</sub> through direct effects on the cyclooxygenase (COX) enzymes.<sup>6-8</sup> TXA<sub>2</sub> induces platelet aggregation and promotes vasoconstriction.<sup>9</sup> The specific mechanism and site of aspirin action are illustrated in Figure 1.<sup>6-10</sup> In addition to inhibiting production of TXA<sub>2</sub> through direct effects on the COX enzymes, aspirin affects hemostasis and thrombogenesis beyond its ability to inactivate COX-1. Additional mechanisms attributed to aspirin's efficacy as an antithrombotic entity include dose-dependent platelet inhibition, promotion of fibrinolysis, and suppression of plasma coagulation factors.<sup>8</sup> While these mechanisms play a role in aspirin's efficacy, its effect on the COX enzymes (particularly COX-1) is believed to be most essential to its ability to prevent arterial thrombosis.<sup>8</sup>

### **Primary Prevention**

The efficacy of aspirin for the primary prevention of stroke has been evaluated in men and women. Five pivotal trials are often cited in recommendations for the use of aspirin in high-risk patients. Of these, 2 included men only, 1 randomized women only, and 2 randomized both men and women.

Peto and colleagues randomized 5139 British male doctors to treatment for 6 years with aspirin 500 mg daily or no aspirin to evaluate the incidence of mortality from vascular events.<sup>11</sup> Nearly half of the subjects were younger than 60 years and 2.7% had a history of TIA or cerebrovascular disease besides stroke. Patients with coronary artery disease were excluded. Within the first year, 19% of doctors allocated to the aspirin group stopped taking aspirin and an additional 5% stopped therapy throughout the study. Halfway through the study, only 70% of subjects in the aspirin arm were still taking the drug. Gastrointestinal symptoms were the primary reason for discontinuation. Nearly 2% of participants instructed to avoid aspirin began taking it each year due to the development of vascular disease. After 6 years, aspirin reduced the incidence of TIA by nearly 42% ( $p < 0.05$ ). There were no significant differences in the frequencies of MI or occlusive stroke. The lack of benefit of aspirin may have been a consequence of the relatively healthy population without underlying vascular disease.

The subsequent Physician's Health Study (PHS) was a double-blind, placebo-controlled trial in which 22,071 male US physicians aged 40 years and older were randomized to receive either aspirin 325 mg every other day or placebo.<sup>12</sup> The study was terminated early after 5 years due to significant reductions in the incidence of MI (RR 0.56; 95% CI 0.45 to 0.70;  $p < 0.00001$ ) and exceptionally low rates of death from cardiovascular causes (81 deaths in aspirin group, 83 in placebo group; RR 0.96; 95% CI 0.84 to 5.69;  $p = 0.11$ ). Subgroup analyses revealed this reduction was present only in patients aged 50 years and older. There was a nonsignificant increase in the risk of total stroke, with 119 strokes (1.1%) occurring in the aspirin group and 98 (0.9%) in the placebo group (RR 1.22; 95% CI 0.93 to 1.60;  $p = 0.15$ ). A nonsignificant risk of hemorrhagic stroke (RR 2.14; 95% CI 0.96 to 4.77;  $p = 0.06$ ) was associated with aspirin use. While aspirin was undoubtedly effective at reducing rates of MI, the results of this study in the context of stroke prevention are inconclusive, as there were insufficient numbers of subjects who suffered strokes to sufficiently evaluate this endpoint. The lack of ischemic events is explained by the relatively healthy population, as nearly half of the participants were less than 50 years of age.

In contrast to the study by Peto and colleagues, the PHS was larger, blinded, used different doses of aspirin (325 mg every other day compared to 500 mg daily), and had higher rates of adherence to study medications

(85% vs 70%).<sup>11,12</sup> Neither trial, however, demonstrated that aspirin confers a protective effect against ischemic stroke.

The Hypertension Optimal Treatment (HOT) trial was the first to investigate the impact of aspirin in hypertensive patients.<sup>13</sup> A total of 18,790 patients (53% men) aged 50–80 years (mean 61.5) with hypertension were randomly assigned to receive aspirin 75 mg daily or placebo. The use of aspirin provided only a 0.1% absolute risk reduction (ARR) in the incidence of stroke (4.2% vs 4.1%; CI 0.78 to 1.24;  $p = 0.88$ ). Overall, the use of aspirin was associated with a 36% relative risk reduction (RRR) in MI and a 15% RRR in major cardiovascular events, but had no effect on mortality. Closer examination revealed that fewer women experienced MIs compared to men ( $p = 0.034$ ). No other endpoint yielded a statistically significant difference when adjusted for sex.

In the Primary Prevention Project (PPP), 4495 patients (75% men) aged 50 years and older (mean 64.4) with one major cardiovascular risk factor (age >65 y, hypertension, diabetes, hyperlipidemia, obesity, and family history of MI before age 55 in a first-degree relative) were randomly assigned in an open 2 × 2 factorial trial to aspirin 100 mg daily and vitamin E 300 mg daily.<sup>14</sup> After 3.6 years of followup, the trial was prematurely stopped after the results of the HOT trial<sup>13</sup> and Thrombosis Prevention Trial<sup>15</sup> demonstrated overwhelmingly beneficial effects of aspirin on the primary prevention of coronary events in men. At the conclusion of the PPP, there was an overall reduction in total cardiovascular events (RR 0.77; 95% CI 0.62 to 0.95;  $p = 0.014$ ) and cardiovascular deaths (RR 0.56; 95% CI 0.31 to 0.99;  $p = 0.049$ ) with the use of aspirin, but no significant reductions in the incidence of stroke (0.7% vs 1.1%) in men or women.<sup>14</sup> The authors concluded that further analysis is warranted to evaluate the efficacy of aspirin in primary stroke prevention.

The Women's Health Study (WHS) was designed to evaluate the efficacy of aspirin in women.<sup>16</sup> This trial randomized 39,876 women to receive aspirin 100 mg every other day or placebo for 10 years. The incidence of the primary endpoint, the combination of major cardiovascular events and death from cardiovascular causes, was not statistically significantly different between treatment groups, with an overall RRR of 9% ( $p = 0.13$ ). An analysis of individual endpoints revealed that patients receiving aspirin had a 17% RRR in total stroke ( $p = 0.04$ ) and a 24% reduction in the risk of ischemic stroke (1.1% with placebo, 0.85% with aspirin;  $p = 0.009$ ). Due to the low incidence of stroke, this correlates with a number needed to treat of 400 patients to prevent 1 stroke. A prespecified subgroup analysis demonstrated the strongest cardiovascular benefit in patients older than 65 years at study entry; however, no reduction in stroke was observed.

Aspirin 100 mg every other day should be considered for primary prevention in women over 45 years of age without a history of heart or cerebrovascular disease. Current guidelines from the American Heart Association (AHA) include a class IIa recommendation for aspirin use in high-risk women and recommend against its use in men for primary prevention of stroke.<sup>17</sup> Despite the lack of efficacy for primary stroke prevention in men, aspirin is recommended by the AHA at a minimum dose of 75 mg daily for patients at risk for cardiovascular events.<sup>18</sup>

### **Acute Ischemic Stroke**

Aspirin is the only antiplatelet agent with literature supporting its benefit in the acute ischemic stroke setting. Two large trials, conducted concurrently, provide the evidence to support aspirin's efficacy in this setting: the Chinese Acute Stroke Trial (CAST) and the International Stroke Trial (IST).

In CAST, conducted exclusively in China, 21,106 Chinese patients (64% male) were randomized to receive aspirin 160 mg daily or placebo within 48 hours of suspected acute ischemic stroke.<sup>19</sup> Mean time to randomization was 25 hours and patients were followed for 4 weeks. Aspirin was crushed or chewed to facilitate rapid onset of activity. The primary endpoints were mortality at 4 weeks and death or dependence at hospital discharge. Secondary endpoints included fatal or nonfatal stroke and the composite of death or nonfatal stroke. Treatment with aspirin was associated with significant reductions in mortality (3.3% vs 3.9%;  $p = 0.04$ ), an absolute difference of 5.4 fewer deaths per 1000 cases. Aspirin reduced the risk of recurrent ischemic stroke (1.6% vs 2.1%;  $p = 0.01$ ) without an increased risk of hemorrhagic stroke (1.1% vs 0.9%;  $p >$

0.1). Aspirin did not reduce rates of death or dependence at discharge (30.5% vs 31.6%;  $p = 0.08$ ). The secondary endpoint of death or nonfatal stroke was significantly reduced with aspirin (5.3% vs 5.9%;  $p = 0.03$ ). Nearly 29% of patients experienced lacunar infarct, a form of small artery occlusive stroke associated with the lowest rates of early recurrence and best rates of survival and motor deficit improvements among the various types of strokes.<sup>20</sup> The findings of this trial demonstrate that aspirin 160 mg taken within 48 hours of ischemic stroke provides small but significant reductions in mortality and recurrent stroke.

The IST was conducted in over 450 hospitals in 36 countries to assess the effects of aspirin and 2 unfractionated heparin (UFH) doses in patients with acute ischemic stroke.<sup>21</sup> IST assigned 19,435 patients (54% male), via a 3x2 factorial design, to 1 of 6 treatments: aspirin 300 mg plus UFH 12,500 units subcutaneously twice daily ( $n = 2430$ ), aspirin 300 mg plus UFH 5000 units subcutaneously twice daily ( $n = 2432$ ), aspirin 300 mg and no UFH ( $n = 4858$ ), UFH 12,500 units twice daily and no aspirin ( $n = 2426$ ), UFH 5000 units twice daily and no aspirin ( $n = 2,429$ ), or no aspirin or UFH ( $n = 4860$ ). Atrial fibrillation was present in 16% of patients. The median time to randomization was 19 hours and patients were treated for 14 days or until hospital discharge. Average treatment duration for both heparin and aspirin was 11 days. The primary endpoints of IST, similar to those of CAST, were death at 14 days and death or dependency at 6 months. Secondary outcomes included symptomatic intracranial hemorrhage or ischemic stroke within 14 days, major extracranial hemorrhage, and 6-month mortality. Heparin provided no benefit on stroke reduction. Aspirin also failed to demonstrate significant reductions in 14-day (9.0% vs 9.4%) or 6-month mortality (21.5% vs 22.5%). Death and dependency at 6 months was less frequent (61.2% vs 63.5%) with aspirin but failed to meet statistical significance. The incidence of recurrent ischemic stroke within 14 days, however, was significantly reduced with the use of aspirin 300mg daily (2.8% vs 3.9%;  $p < 0.001$ ). The proportion of patients who reported a complete recovery at 6 months did not improve with aspirin (17.6% vs 16.6%;  $p = 0.07$ ).

The combined results of CAST and IST demonstrate that aspirin doses of 160–300 mg daily administered within 48 hours of ischemic stroke provide small but certain reductions in death and recurrent ischemic stroke rates. The American College of Chest Physicians (ACCP) recommends early aspirin therapy (Grade 1A) at doses of 150–325 mg for patients with acute ischemic stroke who have not received thrombolysis with tissue plasminogen activator, while guidelines for the early management of acute ischemic stroke from the AHA and American Stroke Association recommend an initial dose of 325 mg. It is unclear why ACCP guidelines recommend 150 mg instead of the 160-mg dosage utilized in CAST. The use of aspirin after thrombolysis should be reserved until 24 hours have elapsed.<sup>22,23</sup>

### **Secondary Prevention of Stroke**

The efficacy of aspirin for secondary stroke prevention has been studied in numerous trials. Several were underpowered and failed to demonstrate benefits. Fields et al. failed to demonstrate reductions in stroke or death with aspirin in 178 patients with prior TIA.<sup>24</sup> This study was too small and short to draw practical conclusions. The Canadian Co-operative Study randomized 585 stroke patients to receive aspirin or sulfipyrazone, alone or in combination, for 26 months.<sup>25</sup> Aspirin reduced the risk of stroke or death by 31% ( $p < 0.05$ ), but benefits were sex-dependent. The risk of stroke or death was reduced by 48% in men ( $p < 0.005$ ), with no benefit among women, perhaps due to small sample size. Sulfipyrazone failed to reduce stroke or death rates.

The UK-TIA trial was a randomized, double-blind trial that compared 2 aspirin dosages (600 mg twice daily, 300mg daily) vs placebo in 2435 patients (73% male) 40 years and older with presumed TIA or minor ischemic stroke.<sup>27</sup> Patients were followed for 4 years and the primary endpoint was the time to a composite of major stroke (modified Rankin scale score  $\geq 3$ ), MI, or vascular death. Patients with adverse gastrointestinal effects received reduced doses. There was no significant difference in efficacy between the doses or between aspirin and placebo.

Similar to results in the UK-TIA trial, there was no significant difference in stroke rates in the Dutch TIA trial.<sup>28</sup> In this double-blind, randomized, multicenter trial, 2437 patients with a history of TIA or minor stroke

underwent double randomization with aspirin 30 mg versus 283 mg and atenolol 50 mg versus placebo. After a mean followup of 2.6 years, annual stroke rates were 3.6% in each group.

The Accidents Ischémiques Cérébraux Liés à l'Athérosclérose (AICLA) trial failed to demonstrate benefits with aspirin 1000 mg with or without dipyridamole 225mg in comparison to placebo in 604 patients with prior TIA or stroke.<sup>29</sup> Conflicting results were seen in the European Stroke Prevention Study (ESPS), a multicenter, double-blind trial in which 1861 patients with a history of stroke, TIA, or reversible ischemic neurologic deficit were randomized to receive dipyridamole 75 mg and aspirin 325mg 3 times daily or placebo.<sup>30</sup> Significant 33% reductions in mortality (108 deaths with dipyridamole/aspirin and 156 with placebo;  $p < 0.01$ ) and stroke (114 strokes with dipyridamole/aspirin and 184 with placebo;  $p < 0.001$ ) were observed.

The lack of an aspirin-only arm in the ESPS study left questions as to whether the combination of dipyridamole/aspirin was superior to aspirin monotherapy. Therefore, the ESPS-2 study randomly assigned 6602 patients (58% male) with prior stroke or TIA within the previous 3 months to treatment with one of the following: dipyridamole 200mg twice daily, aspirin 25mg twice daily, aspirin 25mg twice daily and extended-release dipyridamole 200 mg twice daily, or placebo.<sup>31</sup> Before the ESPS-2 trial was completed, data from the EAFT trial demonstrated that treatment with anticoagulation was superior to aspirin in patients with AF<sup>32</sup> (see Atrial Fibrillation section). Investigators in the ESPS-2 trial were informed of this finding and allowed patients with AF to switch from aspirin to anticoagulation.<sup>31</sup> Primary endpoints included the incidence of stroke, death, and stroke or death at 2 years. The risk of stroke, compared to placebo, was reduced by 18% with aspirin ( $p < 0.013$ ), 16% with dipyridamole ( $p < 0.039$ ), and 37% with the combination ( $p < 0.001$ ) (24-month stroke rates were 12.9% in the aspirin group, 12.2% in the dipyridamole group, 9.9% in the combination group, and 15.8% in the placebo group). Stroke or death rates were also significantly reduced by 13% with aspirin, 15% with dipyridamole, and 24% with the combination.<sup>31</sup> No sex-specific differences were reported. Mortality rates were similar. The risk of TIA was significantly reduced with each treatment, with the largest reduction of 36% provided by the combination ( $p < 0.001$ ). The ESPS-2 trial was the first to demonstrate additional stroke reductions by using 2 antiplatelet agents together. Criticisms of this trial include the low aspirin dose and whether stroke reduction would have been more drastic with higher doses. In addition, adherence to aspirin was only 84% compared to 97% in the dipyridamole arm. Despite these limitations, the combination of aspirin 25 mg and extended-release dipyridamole 200 mg is approved by the Food and Drug Administration for stroke prevention in patients with prior TIA or ischemic stroke.<sup>33</sup>

Questions remained regarding the most appropriate regimen for a patient who suffered an ischemic stroke despite already receiving antiplatelet therapy. Clinicians sometimes used a combination of aspirin and clopidogrel, despite a lack of supporting data. The efficacy of this combination was investigated in the Management of Atherothrombosis with Clopidogrel in High-Risk Patients (MATCH) trial. This randomized, double-blind trial compared aspirin 75mg and clopidogrel 75mg daily versus clopidogrel 75mg daily in 7599 patients with previous stroke or TIA within 90 days and at least 1 additional risk factor (ischemic stroke, angina, MI, diabetes, or symptomatic peripheral vascular disease in the previous 3 years).<sup>34</sup> Patients were treated for 18 months and the primary endpoint was a composite of ischemic stroke, MI, vascular death, and rehospitalization for an acute ischemic event. Ischemic stroke alone was a secondary endpoint. For the primary endpoint, combination therapy with aspirin and clopidogrel offered no benefit over monotherapy ( $p = 0.244$ ). There was no benefit with the combination of clopidogrel plus aspirin versus monotherapy for ischemic ( $p = 0.353$ ) or any stroke ( $p = 0.790$ ). Combination therapy was associated with higher rates of major, minor, and life-threatening bleeds (2.6% vs 1.3%;  $p < 0.0001$ ). Based on these findings, a regimen of aspirin and clopidogrel for the secondary prevention of stroke or TIA cannot be recommended.

The CAPRIE trial compared the safety and efficacy of aspirin 325 mg daily vs clopidogrel 75 mg daily in 19,185 patients with symptomatic peripheral arterial disease or recent stroke or MI. Patients were followed for 1–3 years and the primary endpoint was a composite of ischemic stroke, MI, or vascular death.<sup>35</sup> Treatment with clopidogrel yielded an RRR of 8.7% (CI 0.3 to 16.5%) compared with aspirin therapy ( $p = 0.043$ ) for the primary endpoint; however, this difference was driven by reductions in ischemic events due to peripheral arterial disease. In addition, the ARR of 0.5% suggests that nearly 200 patient-years are needed to prevent 1 event with clopidogrel compared to aspirin. Stroke occurred in 338 and 315 patients treated with aspirin and

clopidogrel, respectively (RRR 7.3%; CI -5.7 to 18.7; p = 0.26). These data suggest that aspirin 325 mg daily and clopidogrel equally reduce the risk of stroke in patients at high risk for atherothrombotic events.

While equal reductions in stroke were observed between aspirin and clopidogrel in the CAPRIE trial and more significant reductions in stroke were demonstrated with aspirin and extended-release dipyridamole in the ESPS-2 trial, there was no significant difference in secondary stroke rates between clopidogrel and aspirin plus extended-release dipyridamole in the PROFESS trial.<sup>36</sup> This study, however, did not include an aspirin-only arm.

Evidence demonstrates that dosages of aspirin from 30 to 1300 mg daily prevent strokes in patients with prior TIA or stroke; however, higher doses are associated with greater risk of gastrointestinal hemorrhage.<sup>13,26</sup> Based on the results of the ESPS-2 trial it can be concluded that the minimum dose needed for secondary stroke prevention is 50 mg daily. AHA/American Stroke Association guidelines recommend aspirin 50–325 mg daily for the secondary prevention of ischemic stroke or TIA.<sup>37</sup> Clopidogrel and extended-release dipyridamole are both appropriate first-line agents for primary and secondary stroke prevention in patients who cannot tolerate aspirin.

### Secondary Prevention of Stroke in Post-Myocardial Infarction Patients

The incidence of ischemic stroke is increased 44-fold in the first month following MI.<sup>38</sup> Diabetes, previous stroke, age >75 years, AF, African American race, hypertension, and peripheral arterial disease further increase the risk of stroke and death during the 6 months following an MI.<sup>39</sup>

The ATC is the largest meta-analysis (>135,000 patients in 287 studies) to investigate the lowest effective dose of aspirin in patients at high risk of cardiovascular events. A risk reduction in MI, stroke, and death was most prominent with doses of 75–325 mg daily. There was no additional benefit, but there was increased minor bleeding risk, associated with dosages >325 mg daily.<sup>26</sup>

Revascularization using percutaneous coronary intervention has become the standard of care in high-risk patients with acute coronary syndromes.<sup>40</sup> The implementation of intracoronary bare metal and drug-eluting stents has made long-term antiplatelet therapy mandatory. Randomized controlled trials utilizing clopidogrel and aspirin together following acute coronary syndrome have demonstrated minimal additional benefit with dual antiplatelet therapy. However, data suggest that the addition of aspirin may reduce the incidence of stroke in post-MI patients.<sup>37</sup> Most post-MI trials used composite cardiovascular primary endpoints and reported stroke outcomes within subgroup analyses. These trials are outlined in Table 1.<sup>41-43</sup>

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study demonstrated no significant benefit, but a significant increase in major bleeding, in the clopidogrel plus aspirin arm compared to aspirin alone.<sup>41</sup> Increased bleeding risk was also demonstrated with dual antiplatelet therapy used in the MATCH trial described previously.<sup>34</sup>

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study demonstrated no significant benefit, but a significant increase in major bleeding, in the clopidogrel plus aspirin arm compared to aspirin alone.<sup>41</sup> Increased bleeding risk was also demonstrated with dual antiplatelet therapy used in the MATCH trial described previously.<sup>34</sup>

**Table 1.** Post-Myocardial Infarction Trials Using Dual Antiplatelet Therapy with Secondary Endpoints of Stroke

Trial	Patients (N)	ACS Type	Stroke Incidence (%) Aspirin +		p Value	Aspirin Dose (mg/day)
			Aspirin	Clopidogrel		
CURE <sup>41</sup>	12,562	NSTEMI	1.4	1.2	NS	75–325
CLARITY-TIMI 28 <sup>42</sup>	3,491	STEMI	1.7	0.9	0.052	75–162
COMMIT/CCS-2 <sup>43</sup>	45,852	STEMI (93%); NSTEMI (7%)	1.1	0.9	0.11	162

ACS = acute coronary syndrome; NS = not significant; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

A prespecified subgroup of post–ST elevation MI patients undergoing percutaneous coronary intervention with fibrinolysis was randomized to receive clopidogrel plus aspirin or aspirin 75–162 mg alone in the CLARITY TIMI 28 trial.<sup>42</sup> The clopidogrel arm showed a 68% reduction in the rate of stroke at 30 days compared to aspirin alone, but was not significant (OR 0.32; 95% CI 0.1 to 1.01). The COMMIT/CCS-2 trial found a nonsignificant reduction in stroke rates in ST-elevation MI patients at 4 weeks when treated with aspirin 162 mg daily.<sup>43</sup>

A strong correlation exists between recurrent cardiovascular events and death. Therefore, the ideal approach in post-MI patients is to initiate aspirin therapy for prevention of both recurrent MI and stroke. In regard to duration of use, the AHA recommends indefinite oral aspirin therapy at doses of 75–162 mg daily for the secondary prevention of cardiovascular events in post–acute coronary syndrome patients.<sup>44,45</sup> As such, post-MI patients should be treated with aspirin 75 mg daily for the prevention of cardiovascular events, despite the lack of stroke prevention.

### **Stroke Prevention in Atrial Fibrillation**

While warfarin has demonstrated superiority for primary stroke prevention in AF patients, aspirin is recommended by the current *Chest* and American College of Cardiology (ACC)/AHA/European Society of Cardiology (ESC) guidelines as an alternative to warfarin in patients with  $\geq 1$  of the following risk factors: age  $>75$  years, hypertension, diabetes, moderate/severe impaired left ventricular systolic function, or heart failure.<sup>46,47</sup> The quandary for practitioners lies in choosing the appropriate aspirin dose.

Several trials have compared aspirin to placebo for primary stroke prevention in AF patients.<sup>32,48–51</sup> Results of these major trials are summarized in Table 2. Only the SPAF (Stroke Prevention in Atrial Fibrillation) trial demonstrated superior efficacy of aspirin over placebo in the prevention of stroke in AF patients.<sup>48</sup> SPAF 1 followed patients for 2 years before being terminated early due to superior efficacy of warfarin and aspirin over placebo.<sup>48</sup> Compared to placebo, aspirin reduced the risk of the combined primary event by 42% ( $p = 0.02$ ).

The remaining trials evaluated in Table 2 failed to show a reduction in stroke rates. Overall, study populations were similar; however, the EAFT trial was designed as a secondary prevention trial and included only patients with a history of stroke.<sup>32</sup> Differences in results could be attributed to lower doses of aspirin, unknown concomitant medications, or smaller trial enrollment.

To address these concerns, several meta-analyses have subsequently been performed.<sup>52–54</sup> The first meta-analysis by Hart et al. utilized 6 studies in an effort to confirm the SPAF 1 results on a larger scale.<sup>52</sup> The primary endpoint was stroke. With respect to the aspirin arm, average age was 70 years, most patients were male, and 40% had a prior stroke. This meta-analysis demonstrated a stroke reduction of 22% (CI 2 to 38) in patients receiving aspirin compared with placebo. Combined trial results yielded an annual ARR of 1.5%, requiring 67 patients to be treated to prevent one stroke. An update to the aforementioned analysis was published by Aguilar et al. in 2005.<sup>53</sup> This analysis included unpublished data from several clinical trials restricting the results to primary stroke prevention. The authors concluded that aspirin decreased stroke incidence by about 25%; however, the results showed statistical significance only when stroke incidence was combined with the incidence of MI or vascular death. Finally, a third metaanalysis by Segal and colleagues additionally failed to demonstrate a difference in stroke rates between aspirin and placebo.<sup>54</sup>

Encompassing the aforementioned trials and meta-analyses, the current *Chest* AF guidelines recommend aspirin 75–100 mg daily in certain patient populations to decrease the risk of cardioembolic events.<sup>47</sup> The ACC/AHA/ESC guidelines recommend a wider range of 81–325 mg daily.<sup>46</sup> The rationale behind the differing recommendations in *Chest* includes a detailing of aspirin's mechanism to selectively inhibit COX-1 at lower doses, efficacy of smaller doses for other indications, and an analysis of aspirin's risk for hemorrhage versus potential benefit.<sup>47</sup>



Strict evaluation of the available literature suggests that only aspirin 325 mg daily as used in SPAF 1 reduces the incidence of stroke in the AF setting.<sup>48</sup> Therefore, when used as monotherapy for primary prevention in AF patients not receiving vitamin K antagonists, the minimum effective dose of aspirin is 325 mg daily. Lower doses may be warranted when used in conjunction with other antithrombotic agents in an effort to decrease bleeding risks.

**Table 2. Atrial Fibrillation Trials Utilizing Aspirin for the Prevention of Stroke**

Study	Patients (N)	Patient Characteristics	Aspirin Dose	Primary Endpoint	Results	P Value
SPAF 1 <sup>48</sup>	1330	71% male; 56% aged 61–75 y; 68% AF >1 y; 7% prior stroke/TIA; 52% history of hypertension	325 mg/day	Any of the following: (1) ischemic stroke or (2) systemic embolism	Combined endpoint: aspirin 3.6%/y vs placebo 6.3%/y	0.02
AFASAK <sup>49</sup>	1007	53% male; median age 74.2 y; chronic AF; 1.6% prior stroke/TIA; 32% history of hypertension	75 mg/day	Any of the following: (1) TIA, (2) stroke, or (3) systemic embolism	Combined endpoint: aspirin 5.5%/y vs placebo 5.5%/y	NS
LASAF <sup>50</sup>	285	53% male; mean age 62 y; AF duration unknown; no prior stroke or TIA; 51% history of hypertension	125 mg/day or 125 mg every other day	Any of the following: (1) stroke of any kind; (2) major cardiovascular events; or (3) cardiovascular mortality	Stroke: aspirin 2.6% vs placebo 3.3%	0.07
JAST <sup>51</sup>	871	70% male; mean age 65 y; all AF >1 y; 2.5% prior stroke or TIA; 38% history of hypertension	150–200 mg/day	Any of the following: (1) cardiovascular death; (2) symptomatic brain infarction; or (3) TIA	Combined endpoint: aspirin 6.3%/y vs placebo 5.1%/y TIA only: aspirin 3.9% vs placebo 4%	0.458 0.967
EAF <sup>32</sup>	1007	56% male; mean age 73 y; AF duration unknown; 100% prior stroke; 47% history of hypertension	300 mg/day	Any of the following: (1) death from vascular disease; (2) nonfatal stroke; (3) nonfatal MI; or (4) systemic embolism	Combined endpoint: aspirin 15%/y vs placebo 19%/y All stroke: aspirin 10%/y vs placebo 12%/y	0.12 0.31

AF = atrial fibrillation; MI = myocardial infarction; NS = not significant; TIA = transient ischemic attack.

### Stroke Prevention in Carotid Artery Disease Following Carotid Endarterectomy

Carotid artery stenosis is a major risk factor for ischemic stroke and TIA. The prevalence of carotid stenosis ranges from 0.5% in the 6th decade of life up to 10% in the 9<sup>th</sup> decade.<sup>55-57</sup> Most carotid stenoses and subsequent strokes result from atherosclerotic plaque formation and rupture.<sup>58</sup> Most patients with carotid stenosis are asymptomatic. Asymptomatic carotid stenosis with <75% luminal loss carries an estimated annual stroke risk of 1.3% and a combined risk of cardiovascular ischemia and death due to vascular causes of 10%.<sup>59</sup> Patients with symptomatic carotid stenosis with >75% occlusion carry an annual risk of stroke or TIA of approximately 11%.<sup>60,61</sup>

Carotid endarterectomy is the standard treatment for revascularization of carotid disease, particularly in patients with >70% occlusion.<sup>37,62</sup> The goal of aspirin therapy in patients undergoing carotid endarterectomy

following TIA or stroke includes reducing perioperative coronary event and stroke rates and long-term post-procedure risks of recurrent stroke or coronary events.<sup>62</sup>

Boysen et al. compared low-dose aspirin (50–100 mg daily) to placebo in patients following carotid endarterectomy.<sup>63</sup> Treatment was initiated 1–12 weeks after carotid endarterectomy. No differences in mortality rates were observed. Although there was a trend in favor of the aspirin group with respect to probability of stroke, stroke and TIA combined, and all vascular events combined, the differences were not significant ( $p = 0.34$ ).

Lindblad et al. conducted a double-blind, randomized, placebo-controlled trial to evaluate the efficacy of low-dose aspirin following carotid endarterectomy for secondary stroke prevention.<sup>64</sup> In the study, 232 patients were randomized to receive aspirin 75 mg daily or placebo initiated before surgery. The results revealed a significant ( $p = 0.01$ ) decrease in post-surgical stroke rates at 6 months in patients who received aspirin (1.7% vs 9.6% placebo). Additionally, a nonsignificant ( $p = 0.12$ ) decrease in mortality (0.8% vs 4.3%) was observed in the aspirin group at 30 days.

In a retrospective evaluation of the results of the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the association between aspirin dose and perioperative stroke rates in patients with 70–99% carotid occlusion who underwent carotid endarterectomy was assessed.<sup>65</sup> The 30-day postoperative stroke rates were 7.8%, 6.5%, 1.1%, and 2.1% in patients receiving no aspirin, 81–325 mg, 650 mg, or 1300 mg, respectively. As the primary intervention being evaluated in NASCET was surgical, the statistical significance of stroke-related outcomes relative to aspirin doses was not described.

In a larger, randomized, double-blind, prospective trial including 2849 patients scheduled to undergo carotid endarterectomy, the efficacy of low- and high-dose aspirin in reducing the incidence of secondary stroke, MI, or death was evaluated.<sup>66</sup> In this study, the ACE Trial Collaborators randomized patients to receive low- (81 or 325 mg daily) or high-dose aspirin (650 or 1300 mg daily), begun prior to surgery and continued 3 months postoperatively. The rate of stroke or death was not significantly lower in the low-dose groups compared to the high-dose groups, either at 30 days (4.7% vs 6.1%, respectively;  $p = 0.1$ ) or at 3 months (5.7% vs 7.1%, respectively;  $p = 0.12$ ). However, in an efficacy analysis that excluded patients taking aspirin  $\geq$  650 mg prior to randomization, the rate of stroke or death was statistically lower in the low-dose groups compared to the high-dose groups (3.4% vs 6.9%, respectively, at 30 days;  $p = 0.007$ ; and 3.9% vs 8.2%, respectively, at 3 months;  $p = 0.003$ ). Also, the combined rate of stroke, MI, and death was lower in the low-dose groups compared to the high-dose groups at 3 months (6.2% vs 8.4%, respectively;  $p = 0.03$ ). In the efficacy analysis, the combined rates of stroke, MI, and death were also statistically lower in the low-dose groups compared to the high-dose groups, both at 30 days and at 3 months (3.7% vs 8.2%, respectively, at 30 days,  $p = 0.002$ ; and 4.2% vs 10%, respectively, at 3 months,  $p = 0.0002$ ). Bleeding complications were not correlated with dose.

The findings of these studies suggest a clear benefit with aspirin following carotid endarterectomy for secondary stroke or TIA prevention, as well as a possible mortality reduction. Current guidelines from the AHA and American Stroke Association on the secondary prevention of stroke or TIA generally recommend, without regard to whether carotid endarterectomy was performed, aspirin doses of 50–325 mg daily.<sup>37,67</sup> Although a wide range of dosing has been evaluated, based specifically on the findings of the ACE trial, aspirin doses ranging from 81 to 325 mg daily are recommended for patients undergoing carotid endarterectomy.<sup>66</sup>

### **Dose-Related Bleeding Rates with Aspirin**

A meta-analysis by Serebruany et al. evaluated the risk of bleeding complications with varying doses of aspirin in 192,036 patients from 31 randomized controlled trials.<sup>68</sup> The meta-analysis included 3 trials that focused on aspirin use in the acute treatment of stroke, 2 trials in primary prevention, and 9 trials for secondary prevention of stroke. Other trials focused on aspirin use in the prevention of cardiovascular events, with stroke included in the primary or secondary endpoints. The objective was to compare the risk of hemorrhage due to low (<100 mg), moderate (100–200 mg), and high (>200 mg) doses. Bleeding complications were divided into 6 non-mutually exclusive categories: minor (12 trials), major (22 trials), gastrointestinal (12 trials), stroke (22 trials),

fatal/life threatening (9 trials), and total (12 trials). The most frequently used criteria to assess bleeding severity in the studies were those developed by the Thrombolysis In Myocardial Infarction study group. The Global Use of Strategies To Open coronary arteries criteria were used less often. The results of the study are reported in Table 3.

This meta-analysis demonstrates that low doses of aspirin (<100 mg) were associated with the lowest risk of bleeding. Doses  $\square$ 200 mg caused fewer major bleeds, especially gastrointestinal bleeds, when compared with doses >200 mg (equivalent to 325 mg in the US).<sup>68</sup>

## Summary

Aspirin has been proven to reduce the risk of stroke in a wide variety of settings but has not been proven efficacious for the primary prevention of stroke in men or in post-MI patients. The net absolute reductions in stroke in women are very small in the setting of primary prevention but more substantial for secondary prevention in both men and women. Guidelines sometimes vary regarding the dosage recommended for stroke prevention. It is therefore essential to ascertain the minimum dose proven to be effective according to the primary literature. Based on the literature presented in this review, the minimum aspirin dosage proven to prevent strokes in each at-risk population is listed in Table 4.

While bleeding risk, comorbidities, contraindications, and concurrent treatment with other antithrombotics must be considered when selecting an aspirin dosage, prescribing must be individualized to select a dosage that has been proven to be efficacious for each patient's indication. Highdose aspirin is warranted acutely for the treatment of ischemic stroke and chronically for stroke prevention in the setting of AF. Due to increased bleeding risks associated with higher doses, maintenance doses should be reduced to less than 100 mg daily when possible.

Indication	Minimum Daily Dose
Primary prevention men women	None identified 100 mg every other day
Acute ischemic stroke	160 mg daily
Secondary stroke prevention	50 mg daily
Post-myocardial infarction	75 mg daily <sup>a</sup>
Atrial fibrillation	325 mg daily
Post-carotid endarterectomy	81 mg daily
<sup>a</sup> This dose is recommended for cardiovascular risk reduction and has not been proven to prevent ischemic stroke in the post-myocardial infarction population.	

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