Low Dose Aspirin for Prophylaxis of Cardiovascular Disease
Use of Low Dose Aspirin to Treat and Prevent Cardiovascular Disease

In recent decades, aspirin has become one of the most widely used pharmacologic agents. A major role for this drug is in the treatment and prevention of cardiovascular (CV) disease. The Nobel Prize winner Sir John Vane first elucidated the mechanism by which aspirin helps to prevent occlusive vascular disease (e.g., the blockage of arteries by atherosclerotic plaque). Sir John demonstrated that small amounts of aspirin irreversibly acetylate the active site of cyclooxygenase (COX) in platelets. The presence of COX in platelets is required for the production of thromboxane A2 (TxA2), which induces irreversible platelet aggregation. Platelets only have the COX-1 isoform and not COX-2. TxA2 is the major COX-1 product of arachidonic acid metabolism in platelets. Platelet activation can lead to the development of thrombotic events. Diseases such as unstable angina and occlusive peripheral vascular disease are associated with activated platelets (due to increased production of TxA2).

As shown in the arachidonic acid pathway diagram below, when aspirin is given to permanently inactivate cyclooxygenase, TxA2 will not be produced. This leads to a reduction in platelet aggregation and a significantly lower incidence of cardiovascular events [i.e., cardiovascular death, myocardial infarction (MI) and cerebrovascular accident (CVA)] in high-risk patients. (MI is defined as heart attack; CVA is defined as a stroke.)
Use of Aspirin in the Secondary Prevention of Cardiovascular Disease

More than 100 randomized trials have demonstrated that low dose aspirin can be used to prevent cardiovascular events in individuals who have already had an MI, stroke, unstable angina, or transient ischemic attack (TIA); TIA is defined as a reversible loss of blood flow to a portion of the brain. This is referred to as secondary prevention. Specifically, aspirin is indicated in:

Vascular Disorders (Ischemic Stroke, TIA, Acute MI, Prevention of Recurrent MI, Unstable Angina Pectoris and Chronic Stable Angina Pectoris).

- To reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli.
- To reduce the risk of vascular mortality in patients with a suspected acute MI.
- To reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris
- To reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris

Revascularization Procedures (Coronary Artery Bypass Graft (CABG), Percutaneous Transluminal Coronary Angioplasty (PTCA), and Carotid Endarterectomy).

- Aspirin is indicated in patients who have undergone revascularization procedures (i.e., CABG, PTCA, or carotid endarterectomy) when there is a preexisting condition for which aspirin is already indicated.

The recommendation for use of aspirin in secondary prevention of CV disease includes women as well as men with prior TIA, prior occlusive stroke, MI, unstable angina, and chronic stable angina.

The Antiplatelet Trialists’ Collaboration was a meta-analysis of 133 antiplatelet therapy trials in approximately 53,000 patients with a history of CV disease. High-risk patients showed a statistically significant benefit from antiplatelet therapy with a 35% decrease in subsequent nonfatal MI, a 31% decrease in nonfatal stroke, an 18% decrease in vascular death and a 27% decrease in the combined outcome of important vascular events. Aspirin by itself was found to be as effective as the combination of aspirin with other antiplatelet agents (such as dipyridamole or sulfinpyrazone). In addition, low dose aspirin (75 to 325 mg/day) was just as effective as high dose aspirin (900 to 1500 mg/day).
Primary Prevention of Cardiovascular Disease with Low Dose Aspirin

Low dose aspirin has also been used to prevent the occurrence of cardiovascular thromboembolic disease in apparently healthy individuals who have no prior history of a cardiovascular event (primary prevention). Evidence from primary prevention trials supports a clear reduction (at least 32%) in first MI among men, but the balance of benefits versus risks for stroke and cardiovascular disease-related mortality has yet to be definitively evaluated.

The US Physicians’ Health Study involved 22,071 male physicians, aged 40 to 84 years. The study was prematurely terminated in 1988 after only 5 years, primarily because of the emergence of an extreme 44% reduction in first MI among those assigned to aspirin (325 mg taken every other day, p<0.001). As a result, there were insufficient numbers of strokes or cardiovascular disease-related deaths to evaluate these end points definitively. There also was the suggestion of a possible increased risk of hemorrhagic stroke (a stroke that involves bleeding) in the aspirin group vs the placebo group (23 events vs 12 events in the placebo group, p=0.06).

The beneficial effect of low dose aspirin, to prevent cardiovascular disease, has not been proven in women and is currently being evaluated (100 mg aspirin every other day) in the large-scale, long-term Women’s Health Study.

Potential risks of primary prevention therapy with low dose aspirin include gastrointestinal effects, such as bleeding, heartburn, nausea (all dose-related) and possibly hemorrhagic stroke.

Currently, there are no approved indications for aspirin in primary cardiovascular prevention and these should not be expected until the results are available from the Women’s Health Study.

Aspirin should always be used as an adjunctive therapy in the management of cardiovascular disease risk factors and never as an alternative therapy.
Gastrointestinal Injury and Very Low Dose Aspirin

Cryer and Feldman evaluated the long-term effects of very low doses of aspirin on the gastrointestinal tract in normal volunteers. They studied 29 healthy volunteers randomized into 3 groups which received either 10 mg aspirin (n=8; ages 24–81, mean age 49), 81 mg aspirin (n=11; ages 24–78, mean age 46), or 325 mg aspirin (n=10; ages 27–81, mean age 46) daily for 3 months. The study did not include a placebo group. Thus, it is unclear how many patients on placebo alone would have developed erosions and ulcers. Individuals were evaluated by endoscopy at baseline, 6 weeks, and 12 weeks for gastric, duodenal, and rectal erosions and ulcers. Ulceration was defined as ≥5 mm mucosal breaks associated with depth and exudate. The following results were seen:

Table 1: Effect of Aspirin on Gastric Erosions and Ulcers

<table>
<thead>
<tr>
<th>Aspirin dose (mg)</th>
<th>Baseline</th>
<th>6 weeks</th>
<th>12 weeks</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>81</td>
<td>325</td>
</tr>
<tr>
<td>Gastric erosions (n)</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Gastric ulcers (n)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The data show that for the 81 mg dose of aspirin, no gastric ulcers were detected after 6 or 12 weeks of treatment. One gastric ulcer was observed in the 10 mg aspirin group at 6 weeks but not at 12 weeks. Furthermore, in the patients receiving 81 mg aspirin, 7 of the 10 gastric erosions detected at 6 weeks were no longer seen at 12 weeks. No significant disease was seen for the 81 mg aspirin dose in either the duodenum or rectum. The authors discussed the possibility of gastric adaptation.

Use of NSAIDs as Anti-Platelet Agents

Although NSAIDs that inhibit COX-1 also inhibit platelets to varying degrees, depending upon their selectivity, they are not a substitute for low dose aspirin for the prevention of cardiovascular disease. Furthermore, not all NSAIDs inhibit platelets. NSAIDs that selectively inhibit COX-2 such as VIOXX do not inhibit platelet function.
Studies on Platelet Activity

Studies were performed by Merck Research Laboratories to ascertain the effects of NSAIDs on platelet function. Healthy volunteers were treated with VIOXX 12.5 mg qd (n=12), VIOXX 25 mg qd (n=12), naproxen 550 mg bid (n=8), diclofenac 50 mg tid (n=8), ibuprofen 800 mg tid (n=8), meloxicam 15 mg qd (n=12) or placebo (n=16). All treatments were administered for 5 days plus 1 morning dose on Day 6. The effect of treatment on platelet aggregation was determined in vitro (outside of the body) using arachidonic acid as the primary agonist (the agent used to promote platelet aggregation via TxA2 generation). The effect of NSAID treatment on bleeding time was also determined in the same treatment groups.

The results of the studies showed that the effect on platelet aggregation for VIOXX and meloxicam was not significantly different from that of placebo. Diclofenac, ibuprofen and naproxen significantly inhibited platelet aggregation compared with placebo (p<0.001).

For the bleeding time studies, meloxicam, diclofenac and VIOXX treatments showed no significant change in bleeding time from Day 1 to Day 6 compared to placebo. In contrast, ibuprofen and naproxen treatments significantly prolonged mean bleeding time by 1.57 and 2.41 minutes, respectively (p<0.002, p<0.001).

Conclusion

Agents that selectively inhibit COX-2 such as VIOXX do not affect platelets. VIOXX cannot be used to prevent cardiovascular disease and is not a substitute for low dose aspirin.