Willow Bark was used thousands of years ago to treat pain, fever and inflammation and it was not discovered until later that the active compounds in willow bark were natural salicylates. In 1897, Felix Hoffman, working at the Bayer company in Germany, made the acetylated form of salicylic acid, and named the compound "Aspirin." Aspirin became the most widely used medicine of all time. 1

In 1971, John Vane discovered the mechanism of action of aspirin and how it exerts its anti-inflammatory, analgesic and antiplatelet properties. He proved that aspirin and other Non Steroidal Anti-Inflammatory Drugs (NSAIDs) inhibit the activity of the Cyclooxygenase (COX) enzyme which leads to the formation of prostaglandins (PGs) that cause inflammation, swelling, pain and fever. However, by inhibiting this key enzyme in PG synthesis, these drugs also prevented the production of PGs which protect the stomach mucosa from damage by hydrochloric acid, maintain kidney function and aggregate platelets when required. 1

This discovery provided an explanation for the therapeutic actions and shared side effects of the aspirin-like drugs. Twenty years later, with the discovery of a second COX gene, it became clear that there are two isoforms of the COX enzyme: COX-1 supports beneficial homeostatic functions, whereas COX-2 becomes upregulated by inflammatory mediators and, its products cause many of the symptoms of inflammatory diseases such as rheumatoid and osteoarthritis. 1

Aspirin is a potent cardiovascular protective agent and is used today to prevent occlusive cardiovascular disease. Aspirin permanently inhibits the COX-1 enzyme by non-competitive and irreversible binding, helping to cause the unique effect of inhibiting platelet aggregation. 2

Non-selective NSAIDs competitively and reversibly inhibit both COX-1 and COX-2 enzymes. Because of the competitive and reversible inhibition of COX-1, the non-aspirin NSAIDs do not cause significant inhibition of platelet aggregation seen with aspirin use. 2 However, since the non-selective agents inhibit both forms of COX, they possess therapeutic and side effects profile associated with each mechanism of inhibition.

COX-2 selective NSAIDs were developed to inhibit COX-2 (reducing inflammation and pain) without inhibiting COX-1, which would minimize the side effect and toxicity profile associated with the other NSAIDs (mainly the gastrointestinal effects seen with COX-1 inhibition). The irreversible covalent binding of COX-2, however, impairs the synthesis of endothelium derived anti-thrombotic and vasodilatory prostacyclin which can cause thrombogenesis and vasoconstriction, leading to cardiovascular adverse effects. 3

NSAIDs are one of the most commonly used classes of medications in the world. NSAIDs are used to treat fever, inflammation and pain associated with many disease states but, their use can be limited by adverse drug events associated with this class of medication.

304,844 NSAID prescriptions were filled for the Connecticut Medical Assistance Program patients during 2011 and of those prescriptions 10,032 were considered an instance of therapeutic duplication with another NSAID a patient was concurrently being prescribed.

As a class, NSAIDs are associated with a range of side effects which can include: renal toxicity, hepatotoxicity, exacerbation of hypertension, fluid retention, gastrointestinal (GI) complications, and cardiovascular (CV) events. 4,5,6 High doses, prolonged use, and therapeutic duplication of NSAIDs can lead to an increase in adverse events and complications associated with this class of medications. For the purpose of this article, we will focus on GI and CV complications caused by NSAIDs.

Because of the inhibition of COX-1, aspirin and the non-selective NSAIDs share a similar GI side effects profile. In general, it is recommended that patients with GI risk factors (Table 1) be treated with COX-2 selective agents or non-selective NSAIDs plus concurrent gastroprotective therapy. Gastroprotective therapy agents include H-2 antagonists, misoprostol, and Proton Pump Inhibitors (PPIs).

Recently, there has been an increased awareness of CV risk associated with use of NSAIDs (excluding aspirin), especially in patients with a history of CV disease. NSAIDs currently carry the following black box warning from the FDA: "Cardiovascular Risk: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk."

NSAID use is associated with an increased risk of hypertension, edema, congestive heart failure, and myocardial infarction and the risk appears to be dependent on the duration of exposure. 12 Both COX-2 selective agents and non-selective NSAIDs inhibit COX-2 at traditional doses and have the potential to cause cardiovascular toxicity. Therefore, COX selectivity does not define the risk of NSAID-associated cardiovascular complications.

Table 1: Patients at Risk for Developing GI Bleeds 4,3,5,7

| Patients with a previous GI bleed | Patients > 60 years of age | Patients receiving high dose NSAIDs | Concomitant use of corticosteroids, aspirin, anticoagulants, platelet inhibitors, and SSRIs | Infections with Helicobacter pylori | Comorbid diabetes, heart failure, and rheumatoid arthritis |

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American Heart Association and the American College of Rheumatology recommend that all NSAIDs, and particularly COX-2 selective agents, be avoided in patients with cardiovascular risk factors. In addition they should be used only when sufficient pain relief is not achieved with other therapies and the benefit outweighs the increased cardiovascular risk. Where NSAID therapy is required for patients at risk of cardiovascular complications, naproxen is recommended as the NSAID of choice. 9-13

Cardiovascular Risk Factors include the following9-13:

- Hypertension
- Hypercholesterolemia
- Angina
- Edema
- Recent bypass surgery
- History of myocardial infarct
- Other cardiovascular events

Meek, et. al. published an algorithm to assist in the selection of an NSAID based on a patient’s gastrointestinal (GI) and cardiovascular (CV) risk factors. The algorithm was published in a 2010 issue of Pharmaceuticals (Table 2). 14

In May 2011, Circulation printed a study regarding the impact of treating patients with NSAIDs and the risk of death and recurrent myocardial infarction (MI) in patients with a previous MI. The study concluded that NSAID use should be limited to the absolute minimum in patients with established cardiovascular disease.

NSAIDs are effective at treating mild to moderate pain and drugs within the class provide unique options for individual patients and their concurrent disease states. Non-selective NSAIDs pose an increased risk of GI side effects, and both non-selective NSAIDs and COX-2 Inhibitors have been shown to increase rates of CV events. In general practice, the lowest dose and shortest duration should be used when prescribing NSAIDs, and a patient’s GI and CV status should be taken into account when choosing the right treatment.4

References

### Table 2

<table>
<thead>
<tr>
<th>Low GI Risk</th>
<th>Moderate GI Risk (1-2 risk factors)</th>
<th>High GI Risk (3-5 risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CV Risk**</td>
<td>Non-Selective NSAIDs</td>
<td>Non-Selective NSAID + PPI* or COX-2 + PPI*</td>
</tr>
<tr>
<td>High CV Risk**</td>
<td>Naproxen + PPI**</td>
<td>Naproxen + PPI**</td>
</tr>
</tbody>
</table>

*PPI can be substituted with Misoprostol 400–800 mg or an H-2 Antagonist.

**Evaluation of CV risk is according to the judgment of the prescribing physician. Patients with a high CV risk should receive prophylactic low-dose aspirin. If additional NSAID therapy is required, naproxen is the preferred NSAID. Naproxen should be taken 2 hours after aspirin.