Nonsteroidal Anti-Inflammatory Drugs: Adverse Effects and Their Prevention

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Objectives: To discuss nonsteroidal anti-inflammatory drugs (NSAIDs), their history, development, mode of action, toxicities, strategies for the prevention of toxicity, and future developments.

Methods: Medline search for articles published up to 2007, using the keywords acetylsalicylic acid, aspirin, NSAIDs, cyclooxygenase 2, adverse effects, ulcer, and cardiovascular.

Results: NSAIDs are 1 of the oldest, most successful drugs known to modern medicine. They are effective for alleviating pain, fever, and inflammation by inhibiting prostaglandin synthesis. Aspirin, by its irreversible inhibition of blood platelet function, is also effective in the prevention of cardiovascular disease. NSAIDs may cause gastrointestinal ulcers, serious cardiovascular events, hypertension, acute renal failure, and worsening of preexisting heart failure. These adverse effects may be prevented by limiting NSAID dosage and duration and by performing individual risk assessments and treating patients accordingly. Those at risk for gastroduodenal ulcers may be treated with concomitant proton-pump inhibitors, misoprostol and/or COX-2 selective NSAIDs. Those at risk for cardiovascular events may be treated with naproxen and a proton-pump inhibitor or misoprostol, but should best avoid NSAID use altogether.

Conclusions: Physicians should always prescribe the lowest effective dose for the shortest possible time and must take into account both the gastrointestinal and the cardiovascular risks of individual patients when prescribing NSAIDs.

 Semin Arthritis Rheum 39:294-312

Keywords: *NSAIDs, review, history, toxicity, prevention*

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been successfully used for the alleviation of pain, fever, and inflammation for at least 3500 years and continue to be used daily by millions of patients worldwide. NSAID use is, however, associated with several serious treatment side effects, with considerable associated morbidity and mortality. Many of these side effects may be prevented by careful consideration of the patient's risk factors and by subsequent implementation of preventive strategies.

METHODS

We searched Medline for English-language articles published up to 2007, using the keywords acetylsalicylic acid, aspirin, NSAIDs, cyclooxygenase-2, adverse effects, ulcer, and cardiovascular. The abstracts were screened for relevance and the publications relating to aspirin and NSAIDs were obtained. Additional references were identified from the bibliographies of the retrieved reports and from review articles. Further sources of information were retrieved from the internet.

RESULTS

The Age of Aspirin

The use of nonsteroidal anti-inflammatory substances predates the dawn of modern medicine. The earliest

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There are no conflicts of interest and no sources of support.

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 0049-0172/10/$-see front matter
doi:10.1016/j.semarthrit.2008.08.001

known references to the medicinal use of myrtle and willow tree bark, original sources of aspirin-like compounds, can be traced back to the ancient Egyptians. The application of willow tree bark for stiff and painful joints is recommended in the Ebers papyrus, a comprehensive 110-page medical text, containing 877 treatises on various physical, mental, and spiritual diseases, which is dated to the reign of Amenhotep I around 1534 BC (1). Hippocrates of Cos (460-377 BC), who had spent several years in Egypt studying medicine, also noted that chewing the bitter leaves of the willow tree reduced pain, and he recommended this remedy for women in labor. Subsequent ancient Greek physicians recommended willow tree preparations, especially from the inner bark, for alleviating pain, fever, and inflammation (1-4).

Advocates of the Doctrine of Signatures attributed the healing force of nature to Divine Providence, which often placed the cure next to the malady and left clues for its discovery (5). Christian metaphysics expanded this early European philosophy in theology. According to the Christian version, God had so set his mark on Creation that by careful observation one could learn the medicinal uses of a plant from some aspect of its form or place of growing. The willow tree grows in damp regions where fever (possibly malaria) was endemic and the flexibility of its "weeping" branches might suggest a further effect in reducing stiffness and inflammation of joints (2). As late as 1763 AD, the reverend Edward Stone, a vicar from Chipping Norton in Oxfordshire, England, in following the Doctrine of Signatures, successfully treated fever in 50 patients using "twenty grains (1 g) of powdered willow bark in a dram of water every four hours" (6). In a letter to the Earl of Macclesfield, then president of the Royal Society in London, he subsequently presented the first scientific description of the effects of willow bark. However, the report was regretfully attributed to the mathematician Edmund Stone, due to a misprint.

The following 100 years brought the industrial revolution and in its wake the birth of modern pharmaceutical medicine. In 1828 Johann Andreas Buchner first isolated salacin from willow bark. It was named after its source (*Salix alba*; the white willow) and was also discovered in other *Salicaea*, such as poplars and aspens (1,3). In 1838 Raffaelle Piria treated salacin to yield salicylic acid, which was also found to occur naturally in some species of *Spiraea* (*Spiraea ulmaria*; meadowsweet). Salicylic acid was found to possess profound medicinal properties and soon became a panacea despite causing severe gastric irritation, bleeding, and diarrhea (2). In 1853 a French chemist named Charles Frederic Gerhardt managed to buffer salicylic acid to make it less gastrotoxic, a discovery that remained obscure for nearly 50 years. In 1857 Hammond Kolbe discovered how to synthesize salicylic acid de novo and, subsequently, by 1874 salicylic acid was produced on an industrial scale (1,3).

Meanwhile, in 1863 Friedrich Bayer and Friedrich Weskott had founded a dye manufacturing company in Wuppental-Barmen in Germany. In 1886, the Bayer company started producing phenacetin from dye manufacturing byproducts. Phenacetin was the first real analgesic to be marketed and Bayer's pharmaceutical branch would eventually become the company's core business (7). Phenacetin use, however, proved to be associated with increased risk of death due to urologic or renal disease and cancers, and its use was temporarily banned but is restrictedly allowed at present. In 1948 paracetamol was discovered to be phenacetin's major metabolite (8).

In 1899, a German chemist working for the Bayer company named Felix Hoffmann rediscovered and perfected Gerhardt's formula for acetylating salicylic acid. After trying the result on his father who was suffering from arthritic pain, Hoffmann convinced Heinrich Dreser, head of Bayer's pharmacological division, to conduct animal experiments to establish the drug's analgesic and anti-inflammatory properties, properties that were confirmed by subsequent tests on patients at the Deaconess Hospital in Halle an der Saale (9). Acetyl salicylicacid, the world's first truly synthetic drug, was patented on March 6, 1899 and was called Aspirin: "A" from acetyl, "spir" from *Spiraea ulmaria*, and "in" as a then-typical name ending for medicines (10).

Heinrich Dreser was initially reluctant to support aspirin, preferring to push another of Hoffmann's discoveries (1). As it happened, 11 days after discovering aspirin in an attempt to manufacture codeine, again by acetylation, Hoffmann produced a potent acetylated synthetic of morphine, which Bayer called heroin after the "heroic" feeling it induced in volunteering Bayer employees. Aspirin and heroin were initially marketed side by side, heroin being the more successful painkiller, and commonly believed to be the healthier of the 2. Heroin found a large market share as a supposedly nonaddictive morphine substitute and as children's cough remedy. By 1899 Bayer was producing a ton of heroin yearly, with exports to 23 countries. Eventually in 1913, heroin's obvious addictiveness and a sharp increase in heroin-related hospitalizations caused Bayer to end production. Recreational use however continued to expand. Supposedly, the term "junky" was coined to describe recreational heroin users who financed their addiction by selling scrap (junk) metal.

As aspirin became ever more popular, Bayer opened a production plant in 1903 in Albany, New York. As a first example of mass marketing of a pharmaceutical product, Bayer energetically promoted the drug to more than 30,000 doctors and also introduced the concept of celebrity endorsement by recruiting Caruso and Kafka, the latter claiming that aspirin "eased the unbearable pain of being" (7). Aspirin was relatively expensive at first, being sold as a powdered drug that was available over the counter from 1911. Cheaper mass produced aspirin tablets were introduced in 1915.

From 1914 through 1916, pending the 1917 loss of patent, Bayer introduced aggressive direct to consumer

marketing to establish the brand name, but United States sales collapsed when the U.S. entered the First World War and Bayer was accused of secretly attempting to poison the American people. Under the "Trading with the Enemy" Act, Bayer U.S. was sold for $5.31 million to Sterling Products, a company that would ultimately be acquired by Bayer in 1994 (1). In the interim, however, the U.S. trademark was lost after a 1921 U.S. federal court ruled "aspirin" a genericized trademark. Nonetheless, aspirin continued generating huge revenues. In 1940, the sales of Bayer aspirin were approximately 100 million Deutsche Mark a year; in 1990 Bayer aspirin sold approximately 800 million, while current estimates approximate €2 billion a year. The Aspirin Foundation states that annual production is approximately 35,000 metric tons, equivalent to over 100 billion standard aspirin tablets every year, and that, since it was patented, a trillion (a million billion) tablets have been consumed (11). However, aspirin's inventor Felix Hoffmann reaped little rewards. The German patent office had refused to patent aspirin in 1900, considering the industrial process to be insufficiently novel. Hoffmann's contract with Bayer stated that royalties would only be paid on patented products, and therefore, he received none. Conversely, Heinrich Dreser's contract stated payment of royalties on marketed products, allowing him to retire early a rich man (3).

Aspirin's road to pharmaceutical glory was interrupted by a 1938 publication in the *Lancet* by Douthwaite and Lintott, who used rigid endoscopy to demonstrate aspirin-induced gastric damage in a series of patients (12). Concern was raised further by subsequent reports on increased bleeding during aspirin use. However, aspirin's emergent side effects were soon to be overshadowed by a huge unexpected benefit; the inhibition of platelet aggregation. In the late 1940s, Lawrence L. Craven, a general practitioner from Glendale, California, observed increased bleeding in children who chewed aspirin gum after tonsillectomy. Craven inferred aspirin to be an effective prophylaxis of cardiovascular events and started prescribing an aspirin a day to overweight middle-aged men with sedentary lifestyles and also to patients who had recovered from previous heart attacks. After supposedly having treated nearly 8000 patients and noting not a single myocardial infarction or stroke among them, Craven recommended aspirin as "a safe and effective method of preventing coronary thrombosis" (13). His recommendations were largely ignored by the medical profession, partly because they were published in rather obscure medical journals such as the *Mississippi Valley Medical Journal*. In 1968 O'Brian showed aspirin to inhibit human platelet aggregation (14), and in 1974 systematic data showed that aspirin use was associated with a reduction in myocardial infarction and stroke (15). But it was not until the 1980s that the U.S. Food and Drug Administration (FDA) would finally endorse Dr. Craven's recommendation (1).

A Nobel Mode of Action

While aspirin's analgesic, antipyretic, and anti-inflammatory properties had been well recognized by the beginning of the 20th century, its mode of action remained obscure until the 1970s. Several pieces of the puzzle were still missing. In 1935 the eminent Swedish physiologist Ulf von Euler, and independently the British pharmacologist M.W. Goldblatt, had isolated prostaglandin from seminal fluid (16,17). Although in actuality produced in the seminal vesicles, prostaglandin was initially thought to be a prostatic secretion, thus acquiring its name. In 1945, von Euler met the young biochemist Sune Bergström at a meeting of the Physiological Society of the Karolinska Institute in Stockholm, Sweden, and asked if he might be interested in studying some of his lipid extracts of sheep vesicular glands (18). Bergström purified the crude extract and in 1957, with his graduate student Bengt Ingemar Samuelsson, was able to isolate small amounts of prostaglandin E_1 and prostaglandin $F_{1\alpha}$.

By 1962, Bergström and Samuelsson had isolated and determined the structure of 6 different prostaglandins. They showed that the rapidly metabolized prostaglandins act locally and are involved in many processes that cause inflammation after injury or illness, affect constriction and relaxation of blood vessels, regulate the constriction of the uterus, and help to clot blood. Some unusual features were found, namely that the same prostaglandins may act differently in different tissues, and that prostaglandins often come in pairs with opposite actions. Bergström and Samuelsson went on to demonstrate how prostaglandins were produced in the body from essential fatty acids: gamma-linolenic acid, arachidonic acid, and eicosapentaenoic acid.

Progress was slow as prostaglandins were in limited supply and their production time consuming. Fortunately, Bergström's efforts were greatly enhanced by a generous mode of international collaboration (19). In the early 1960s David van Dorp and Henk Vonkeman working at Unilever Research Laboratories in The Netherlands elucidated the biosynthesis of prostaglandins from their essential fatty acid precursors, findings that they agreed to share and simultaneously published with Bergström in 1964 (20,21).

In 1971, Sir John Robert Vane, then at the Royal College of Surgeons in London and not yet Sir, showed that aspirin-like compounds act by inhibiting the production of prostaglandins (22). For this discovery Vane shared the 1982 Nobel Prize in Physiology or Medicine with Bergström and Samuelsson and received his subsequent knighthood. Essentially, in humans, arachidonic acid is mobilized from cell-membrane glycerophospholipids by phospholipase A_2. The subsequent biotransformation of arachidonic acid is catalyzed by prostaglandin G_2/H_2 synthase, resulting in the sequential formation of prostaglandin G_2 (PGG_2) and prostaglandin H_2 (PGH_2) via the cyclooxygenase (COX) activities of the protein. Addi-

tional tissue-specific prostaglandin synthases subsequently convert PGH_2 into other prostaglandins and thromboxane, each with different functions in different tissues. For example, PGD_2 is involved in sleep regulation and allergic reactions; PGF_2 controls the contraction of the uterus during birth and menstruation, and thromboxane A_2 (TXA_2) stimulates the constriction of blood vessels and induces platelet aggregation. Prostacyclin (PGI_2) dilates blood vessels, inhibits platelet aggregation, and may protect against damage to the stomach lining; prostaglandin E_2 (PGE_2) is involved in pain, inflammation, and fever and also protects against damage to the stomach. John Vane and ensuing researchers demonstrated that by blocking the COX enzyme and consequently inhibiting the biotransformation of arachidonic acid into prostaglandin H_2, aspirin effectuates its analgesic, antipyretic, and anti-inflammatory properties while conversely causing gastric damage and increased bleeding (23,24).

Nonsteroidal Anti-Inflammatory Drugs

In 1959 John Nicholson from the Boots Company had, in collaboration with Stuart Adams, synthesized a drug with analgesic, antipyretic, and anti-inflammatory properties similar to aspirin. The drug was named ibuprofen and was marketed in 1969 under the brand name Brufen, despite performing no better than placebo in an initial clinical trial among 18 rheumatoid arthritis patients (25,26). Ibuprofen would, however, prove to be one in a long series of very successful nonaspirin NSAIDs. Currently, approximately 50 different NSAID preparations are available and, as a class, they are among the most commonly prescribed drugs worldwide.

NSAIDs are mainly indicated for mild to moderate pain of somatic origin. Due to their anti-inflammatory effect, NSAIDs may be especially effective in inflammatory diseases such as rheumatoid arthritis. Other indications include osteoarthritis, soft-tissue injury, renal colic, postoperative pain, and dental procedures. The efficacy of NSAIDs may vary by patient and by indication. In case of inefficacy, substitution by a NSAID from a different chemical class is a reasonable therapeutic option.

NSAIDs may be grouped as salicylates (with as prominent member aspirin itself), arylalkanoic acids (diclofenac, indomethacin, nabumetone, sulindac), 2-arylproprionic acids or profens (ibuprofen, flurbiprofen, ketoprofen, naproxen), *N*-arylanthranilic acids or fenamic acids (mefenamic acid, meclofenamic acid), pyrazolidine derivates (phenylbutazone), oxicams (piroxicam, meloxicam), sulfonanilides (nimesulide), and others. As a group, NSAIDs are structurally diverse and differ in pharmacokinetic and pharmacodynamic properties, but ultimately they share the same mode of action. Like aspirin, nonaspirin NSAIDs inhibit the production of prostaglandins by blocking the COX enzyme, causing analgesic, antipyretic, and anti-inflammatory benefits, but at a risk for increased gastric bleeding (27).

However, aspirin and nonaspirin NSAIDs differ fundamentally in the way the COX enzyme is inhibited. Aspirin inhibits COX by noncompetitive and irreversible acetylation, where an acetyl group is covalently attached to a serine residue in the active site of the COX enzyme, rendering the COX enzyme permanently inaccessible for the biotransformation of arachidonic acid into PG H_2. Conversely, nonaspirin NSAIDs competitively and reversibly inhibit the COX enzyme during only part of their dosage interval. This distinction is exemplified by their differential effects on platelet aggregation. Blood platelets, unlike inflammatory cells, have no cellular nucleus and are therefore unable to newly synthesize COX. Aspirin will irreversibly block all COX on blood platelets, permanently preventing the production of TXA_2 and subsequently inhibiting platelet aggregation for the duration of the platelets' lifecycle, making aspirin a potent cardiovascular protective agent. Conversely, as a result of their competitive reversible binding of the COX enzyme, nonaspirin NSAIDs do not provide significant long-term inhibition of blood platelet aggregation.

The COX-2 Hypothesis

The suggestion of distinct isoforms of the COX enzyme, with differing sensitivities to NSAIDs, had been around for some time when in 1989 Phillip Needleman identified a second cyclooxygenase isozyme, COX-2 (28). Apparently, COX-1 was constitutionally present in low abundance in most human tissues, acting as a housekeeping enzyme by regulating normal physiological processes such as the maintenance of gastric mucosal integrity, kidney function, and platelet aggregation. Conversely, COX-2 was undetectable in most tissues under normal physiological circumstances and was selectively upregulated after exposure to inflammatory mediators or trauma, causing subsequent inflammatory responses and mediation of pain. If this "COX-1 good, COX-2 bad" hypothesis were true, then a COX-2-selective NSAID would be an ideal drug, with analgesic, antipyretic, and anti-inflammatory benefits without gastric or other side effects.

In the early 1990s, radiograph crystallography clarified the COX 3-dimensional structure, showing a long narrow channel, ending in a hairpin bend (Fig. 1) (29,30). Both COX isozymes are membrane-associated and internalize adjacent arachidonic acid, which is released when membrane damage occurs. Arachidonic acid is bound high within the COX enzyme and is biotransformed via PG G_2 into PG H_2, which is a subsequent substrate for other cell- and tissue-specific terminal enzymes, such as PGI_2 synthase, which produces prostacyclin, thromboxane synthase, which produces thromboxane, and glutathione S-transferase, for the conversion to PG E_2.

Most nonaspirin NSAIDs inhibit PG G_2/H_2 synthase by blocking both COX-1 and COX-2 isozymes halfway up their channel by binding an arginine molecule at po-

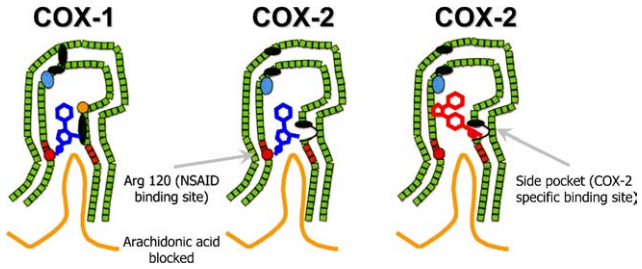

Figure 1 Left: schematic representation of the inhibition of COX-1 (large grey figure) by a nonselective NSAID (central black figure). The entrance channel to COX-1 is blocked by the NSAID. Binding and transformation of arachidonic acid (bottom grey figure) within COX-1 is prevented. Middle: inhibition of COX-2 by a nonselective NSAID (central black figure). Right: inhibition of COX-2 by COX-2 selective NSAID (central black figure). The COX-2 side pocket allows specific binding of the COX-2 selective NSAID's rigid side extension. The entrance channel to COX-2 is blocked. The bulkier COX-2-selective NSAID will not fit into the narrower COX-1 entrance channel, allowing uninhibited access of arachidonic acid into COX-1. Adapted from Hawkey CJ. (31). (Color version of figure is available online.)

sition 120, thereby inhibiting access of arachidonic acid to the catalytic site and thus ultimately inhibiting the synthesis of prostaglandin, PGI_2, and thromboxanes. NSAID binding at the arginine 120 site is competitive and reversible; the extent and duration of COX inhibition depends on the drug's half-life and concentration. COX-1 and COX-2 share the arginine 120 site but differ with respect to position 523. In COX-1, position 523 is taken up by a bulky isoleucine molecule, while a smaller valine molecule at the same position in COX-2 leaves room for a gap, or side-pocket, in the channel's wall (31). It was this side-pocket that provided the target for COX-2-selective NSAIDs. Specifically, rather bulky NSAIDs with a rigid side extension that would bind within the side-pocket would be able to access and block COX-2, but not the narrower COX-1 enzyme. Also, the COX-2-selective covalent binding within the COX-2 side-pocket would be semi-irreversible, thus lastingly inhibiting access of arachidonic acid to the catalytic site (32). A number of pharmaceutical companies tested and developed this hypothesis and by 1995 the first generation of COX-2-selective NSAIDs, celecoxib (Celebrex®) and rofecoxib (Vioxx®), entered clinical trials.

NSAID-Induced Gastroduodenal Toxicity

NSAIDs are effective analgesic, antipyretic, and anti-inflammatory drugs, especially in arthritic diseases. However, their use is limited by serious side effects, most common of which is gastroduodenal toxicity. The spectrum of NSAID-related gastroduodenal toxicity may be categorized into 3 groups: (i) subjective symptoms like heartburn, dyspepsia, nausea, and abdominal pain are most common, occurring in 15 to 40% of NSAID users and causing 10% to change or discontinue their NSAID use; (ii) superficial gastroduodenal mucosal lesions such as erosions and asymptomatic ulcers, occurring in 5 to 20% of NSAID users, which may heal spontaneously; (iii) serious gastroduodenal ulcers with life-threatening complications like perforation, symptomatic ulcers, and bleeding (perforation, ulcer, bleeding; PUB) occur in 1 to 2% of chronic NSAID users, with an associated mortality rate of 10 to 15% (33-35).

Although topical gastroduodenal injury may occur, postabsorptive inhibition of gastrointestinal COX probably plays a more central role in the pathogenesis of NSAID-associated gastroduodenal ulcers. By inhibiting gastric COX-1, NSAIDs may reduce mucosal blood flow, causing local ischemic injury. NSAIDs may also impair specific prostaglandin-dependent defenses, which protect the gastric mucosa, such as the thick bicarbonate-containing mucous layer lining the interior of the stomach, which buffers luminal gastric acid and thus protects the stomach wall. When these defenses have been weakened by NSAID inhibition of gastrointestinal COX-1, a second wave of injury caused by luminal gastric acid may facilitate deeper ulceration, bleeding, and even perforation of the stomach wall (36). Strategies aimed at preventing NSAID gastropathy either help to maintain the integrity of the stomach wall and mucous lining, such as the use of COX-2-selective NSAIDs and the concomitant administration of prostaglandin analogues, or alternatively inhibit the secretion of gastric acid, such as concomitant histamine H_2-receptor antagonists or proton-pump inhibitors (PPI).

Multiple studies have identified additional risk factors for the development of NSAID ulcers (37,38). Assessment of these risk factors is recommended for identifying patients who should be considered for ulcer prophylaxis (37). Risk factors include the following: a prior history of gastrointestinal events (increases risk 4- to 5-fold), patient's age over 60 years (risk, 5- to 6-fold), high dosage of NSAID (risk, 10-fold), concomitant use of corticosteroids (risk, 4- to 5-fold), anticoagulants (risk, 10- to 15-fold), aspirin, platelet inhibitors, and serotonin reuptake inhibitors (risk, 12- to 15-fold),

Table 1 The Five Most Important Risk Factors for the Development of NSAID Ulcers, as Identified by a Committee Appointed by the American College of Gastroenterology

Additional Risk Factors for the Development of NSAID Ulcers	
Prior history of gastrointestinal events	Risk 4- to 5-fold
Patient's age over 60 years	Risk 5- to 6-fold
High dosage of NSAID	Risk 10-fold
Concomitant use of corticosteroids	Risk 4- to 5-fold
Concomitant anticoagulants	Risk 10- to 15-fold

Assessment of these risk factors is recommended for identifying patients who should be considered for ulcer prophylaxis. Adapted from ref. 37.

infection with *Helicobacter pylori*, and comorbid conditions such as diabetes mellitus, heart failure, and rheumatoid arthritis (Table 1) (37,38). Several studies have ranked commonly prescribed NSAIDs for their relative gastrointestinal toxicity. The order in which NSAIDs are ranked differs among studies. In 1 study the risk for gastrointestinal complications appeared highest with indomethacin, followed by naproxen, diclofenac, piroxicam, ibuprofen, and meloxicam (39). The risk is also related to the duration of treatment.

The Role of *Helicobacter pylori* Infection

In the early 1980s, at a time that prevailing dogma stated "no acid, no ulcer," the Australian pathologist John Robin Warren observed the presence of proliferating bacteria on the gastric mucosa from mucosal biopsies and established its close relationship to active chronic gastritis. In 1982 a young gastroenterology fellow, Barry Marshall, successfully collaborated with Warren and cultured and classified the gastric pathogen as an S-shaped campylobacter-like organism, now known as *H. pylori* (40,41). In fulfilling Koch's third and fourth postulates, Marshall demonstrated that the bacteria could colonize normal mucosa and could induce gastritis by ingested *H. pylori* (42) and developed acute gastritis, which was endoscopically and histologically confirmed 10 days later, after which he easily treated himself. The further association of *H. pylori* with peptic ulceration, and possibly with gastric adenocarcinoma, was first suggested by Marshall (40). For their discovery Warren and Marshall were awarded the 2005 Nobel Prize in Physiology or Medicine.

The interaction between *H. pylori* and the use of NSAIDs in the development of gastroduodenal ulcers is less clear. *H. pylori* infection and NSAID use may represent independent but synergistic risk factors (43,44). A recent meta-analysis of 21 studies that evaluated the relationship between *H. pylori* and NSAIDs in the development of gastroduodenal ulcers found that the risk for uncomplicated ulcers was 4 times as high in *H. pylori*-positive compared with *H. pylori*-negative patients, irrespective of NSAID use (odds ratio, 4.03), and 3 times as high in NSAID users compared with nonusers, irrespective of *H. pylori* status (odds ratio, 3.10) (44). Furthermore, the risk of uncomplicated ulcers was almost twice as high among *H. pylori*-positive compared with *H. pylori*-negative NSAID users (odds ratio, 1.81), and 17.5 times higher among *H. pylori*-positive NSAID users compared with *H. pylori*-negative nonusers. Possible explanations for the increased risk of ulcers in *H. pylori*-positive NSAID users are deterioration of the mucosal barrier caused by inflammation, increased acid secretion, a higher level of apoptosis in the infected mucosa, and decreased gastric adaptation to NSAIDs (45).

Whether eradication of *H. pylori* before, or during, NSAID treatment can reduce the risk of gastroduodenal ulcers has yet to be determined. Several studies have addressed these issues but results are inconsistent (46-50). In a study by Francis Chan, 100 *H. pylori*-positive patients without previous exposure to NSAIDs and no preexisting ulcers on endoscopy were randomized to naproxen 750 mg per day for 8 weeks or to a 1-week course of triple therapy for *H. pylori*, followed by naproxen treatment (46). *H. pylori* eradication was successful in 89% in the eradication group, and 0% in the naproxen group. At repeated endoscopy after 8 weeks, 7% in the *H. pylori* eradication group and 26% in the naproxen-only group had ulcers ($P = 0.01$). In the eradication group, 2 of the 3 patients with ulcers had failure of *H. pylori* eradication.

In a second study by the same authors, 100 NSAID-naïve patients with a positive urea breath test, dyspepsia, or an ulcer history were randomized to omeprazole triple therapy or omeprazole with placebo for 1 week, and subsequent diclofenac slow release 100 mg per day for 6 months, followed by endoscopy (47). *H. pylori* had been eradicated in 90% in the eradication group, and 6% in the placebo group. The 6-month probability of endoscopic ulcers was 12% in the eradication group and 34% in the placebo group ($P = 0.009$). The 6-month probability of complicated ulcers was 4% in the eradication group and 27% in the placebo group ($P = 0.003$).

In a third study, 660 *H. pylori*-positive patients without previous or current ulcers received diclofenac 50 mg twice per day for 5 weeks and were randomized to 1 of 4 strategies; triple therapy for 1 week followed by placebo for 4 weeks, triple therapy for 1 week followed by omeprazole 20 mg per day for 4 weeks, omeprazole 20 mg per day for 5 weeks, or placebo for 5 weeks (48). At repeated endoscopy, all 3 active therapies were equally effective in reducing the occurrence of NSAID ulcers as compared with placebo ($P < 0.05$). In this study, lack of significant difference between the active therapy groups might have been due to the overall low incidence of ulcers (6% in the placebo group) and the short study duration.

In a study by Chris Hawkey, 285 *H. pylori*-positive NSAID users with current or previous ulcers or with dyspepsia were randomized to omeprazole triple therapy or omeprazole with placebo for 1 week (49). All patients were subsequently treated with omeprazole 20 mg daily for another 3 weeks, at which time ulcer healing was endoscopically confirmed. NSAID use was continued throughout the study and endoscopy was repeated at 3 and 6 months. Patients in both groups were equally likely to remain ulcer free at 6 months (56% on placebo and 53% on triple therapy), and time to treatment failure also did not differ. Unexpectedly, fewer baseline gastric ulcers healed among patients who underwent *H. pylori* eradication.

In a study by de Leest, 347 *H. pylori*-positive long-term NSAID users were randomized to omeprazole triple therapy or placebo for 1 week (50). NSAID use was continued throughout the study and 48% were on concomitant gastroprotective medication. At endoscopy after 3 months, 4% in the *H. pylori* eradication group and 5% in the placebo group had ulcers ($P = 0.65$). During 12 months

follow-up, no symptomatic ulcers or ulcer complications occurred. In this study, lack of significant difference between the active therapy and placebo groups might again have been due to the overall low incidence of ulcers.

The role of *H. pylori* seems to be different in NSAID-naïve patients than in those on long-term NSAID treatment. In NSAID-naïve patients, *H. pylori* increases the risk for ulcers, whereas in long-term NSAID users, ulcers occur irrespective of *H. pylori* status. Epidemiological studies have shown that the risk for ulcers is substantially increased during the first months of NSAID therapy. Possibly this excess risk occurs in a susceptible subgroup of *H. pylori*-positive patients (47). These susceptible *H. pylori*-positive patients will likely discontinue their NSAID use, creating a residual population of those who can tolerate long-term NSAID treatment irrespective of their *H. pylori* status. Consequently, eradication of *H. pylori* does not affect the ulcer risk in patients who are already on long-term NSAIDs. However, *H. pylori* eradication before NSAID therapy might lower the ulcer risk in NSAID-naïve patients.

Current recommendations regarding *H. pylori* testing and treatment in patients requiring NSAIDs are that patients with a history of gastroduodenal ulcers should be tested for *H. pylori* before starting NSAID or aspirin therapy, and if present, *H. pylori* should be eradicated. In asymptomatic patients with no ulcer history and not currently taking NSAIDs, physicians may consider *H. pylori* testing before starting long-term NSAID therapy. It is possible that successful *H. pylori* eradication in such individuals will reduce the risk of NSAID-related ulcer complications. This "test-and-treat" approach may be most effective in populations with high prevalence of *H. pylori* infection.

Prevention of NSAID Gastroduodenal Toxicity

When reviewing the evidence for gastroprotective strategies in NSAID users, one has to make several distinctions. First, efficacy may be proven for the prevention of subjective symptoms, for endoscopic ulcers, or for serious NSAID ulcer complications such as PUB. The prevention of subjective symptoms, such as dyspepsia and abdominal pain, is very relevant to clinical practice as it affects up to 40% of NSAID users and may influence adherence to NSAID therapy (51). However, in NSAID users the occurrence of subjective symptoms is poorly correlated with the development of gastroduodenal ulcers. Most NSAID users with subjective symptoms show no endoscopic gastroduodenal damage, while up to 58% of patients who present with life-threatening NSAID ulcer complications did not have prodromal symptoms (52). Nonetheless, endoscopy is recommended in NSAID-using patients presenting with subjective symptoms like heartburn, dyspepsia, and abdominal pain.

Many gastroprotective strategies have proven efficacy for the prevention of endoscopic ulcers. However, most endoscopic ulcers cause neither symptoms nor complications and may heal spontaneously, even during continued NSAID use. The clinically relevant target for gastroprotective strategies is therefore the prevention of serious NSAID ulcer complications (PUBs), as these are associated with significant morbidity, mortality, and costs (53). Conversely, one may argue that an endoscopic ulcer is an intermediate in the causal chain from NSAID use to PUBs. In that case, the prevention of endoscopic ulcers may be viewed as a pseudo-outcome for the prevention of PUBs. However, none of the preventive strategies entirely eliminates the risk for endoscopic ulcers and one may postulate that it is exactly these remaining ulcers that may perforate and bleed. In that case, extrapolation of the prevention of endoscopic ulcers to the prevention of PUBs may be a fallacy. Efficacy for the prevention of serious NSAID ulcer complications has only been directly proven for a few strategies, as PUBs are relatively rare, making the necessary studies very large and expensive.

A second distinction to be made is the difference between primary and secondary prevention of NSAID ulcers. Primary prevention concerns the prevention of NSAID ulcers in all patients starting on NSAID therapy, or in those on NSAID therapy who have not had previous NSAID ulcers. Secondary prevention concerns the prevention of recurrent NSAID ulcers in those with a (recent) history of NSAID ulcers. Some of the studies proving the efficacy of gastroprotective strategies in preventing PUBs have been secondary prevention studies. Patients with a history of NSAID ulcers are by definition high-risk patients. Extrapolation of results from secondary prevention studies to the primary prevention of NSAID ulcers may overestimate efficacy and underestimate costs.

Primary Prevention of NSAID Ulcers

NSAID-induced depletion of local endogenous gastrocytoprotective prostaglandins may be reversed by coadministration of prostaglandin E analogues such as misoprostol. Concomitant use of misoprostol has been shown to decrease the risk for both endoscopic NSAID ulcers and serious NSAID ulcer complications. In 1 large study, 8843 elderly NSAID-using rheumatoid arthritis patients were randomized to misoprostol 200 μg 4 times daily or placebo for 6 months (36). Serious NSAID ulcer complications (perforation, gastric outlet obstruction, bleeding) were reduced by 40% (odds ratio, 0.598; 95% CI, 0.364 to 0.982; $P = 0.049$; absolute risk reduction, 0.57%; number needed to treat, 175) among patients receiving misoprostol compared with those receiving placebo. However, during the first month of treatment more patients receiving misoprostol (20%) than placebo (15%) withdrew from the study, primarily because of diarrhea and abdominal discomfort.

Other studies have demonstrated that the efficacy and side effects of misoprostol are dose dependent. In 1 study,

1200 long-term NSAID users were randomized to 1 of 4 regimens; placebo 4 times daily, 200 μg misoprostol twice daily, and placebo twice daily, 200 μg misoprostol 3 times daily and placebo once daily, and 200 μg misoprostol 4 times daily, with upper gastrointestinal endoscopy for ulcers at 4, 8, and 12 weeks (54). The incidence of gastric ulcers was 15.7% with placebo, 8.1% with 400 μg misoprostol, 3.9% with 600 μg, and 4% with 800 μg. The incidence of duodenal ulcers was 7.5% with placebo, 2.6% with 400 μg misoprostol, 3.3% with 600 μg, and 1.4% with 800 μg. Withdrawal due to adverse events was 20% with 800 μg of misoprostol compared with 12% with 400 or 600 μg.

In a 2002 Cochrane systematic review, all doses of misoprostol significantly reduced the risk of endoscopic NSAID ulcers (55). Misoprostol 800 μg/d was superior to 400 μg/d for the prevention of endoscopic gastric ulcers, while a dose–response relationship was not seen for duodenal ulcers. Misoprostol caused diarrhea at all doses, although significantly more at 800 μg/d than 400 μg/d. Misoprostol 800 μg/d significantly reduced the risk of NSAID ulcer complications, such as perforation, bleeding, or obstruction (55).

NSAID-induced gastroduodenal damage partly depends on a low intraluminal gastric pH, and elevation of the intragastric pH reduces the risk of gastroduodenal ulcers. The production of gastric acid can be inhibited with PPIs and histamine H_2-receptor antagonists (H2RAs). PPIs are significantly more effective than H2RAs in achieving and sustaining an intragastric pH above 4.0 (56). Several studies have evaluated the efficacy of concomitant use of PPIs on reducing the risk of NSAID ulcers. Concomitant PPIs have been shown to prevent endoscopic NSAID ulcers (55,57,58). PPIs are better tolerated but have lower efficacy than high-dose misoprostol (57,59).

In one study, 537 long-term NSAID users were randomized to placebo, misoprostol 800 μg/d, lansoprazole 15 mg/d, or lansoprazole 30 mg/d, with upper gastrointestinal endoscopy for ulcers at 12 weeks (57). The incidence of endoscopic ulcers was 49% with placebo, 20% with lansoprazole 15 mg, 18% with lansoprazole 30 mg, and 7% with misoprostol. However, if withdrawals were classified like ulcers as treatment failures, misoprostol and lansoprazole had equal efficacy.

One study directly compared the pharmacodynamic efficacies of different PPIs in controlling intragastric acidity in NSAID users (60). The mean percentage of time during a 24-hour pH monitoring period that the gastric pH was >4.0 was significantly greater with esomeprazole (74%) compared with lansoprazole (67%) and pantoprazole (61%). However, there have been few studies directly comparing the efficacies of different PPIs in reducing the risk of NSAID ulcers. In 1 study, 595 NSAID-using rheumatoid arthritis patients were randomized for pantoprazole 20 mg once daily, pantoprazole 40 mg once daily, or omeprazole 20 mg once daily (61). At 6 months, incidence of endoscopic ulcers was 10% with pantoprazole 20 mg, 7% with pantoprazole 40 mg, and 11% with omeprazole 20 mg.

There have been no studies demonstrating the efficacy of PPIs in the primary prevention of serious NSAID ulcer complications.

Several studies have evaluated the efficacy of concomitant use of H2RAs on reducing the risk of NSAID ulcers. Standard doses of H2RAs are not effective for the prevention of gastric NSAID ulcers, although they may prevent duodenal ulcers (55,62). High doses of H2RAs may prevent both gastric and duodenal endoscopic NSAID ulcers (55,63). In 1 study, 285 long-term NSAID users with rheumatoid arthritis or osteoarthritis were randomized for famotidine 40 mg twice daily, famotidine 20 mg twice daily, or placebo (63). At 24 weeks, the incidence of endoscopic gastric ulcers was 8% with famotidine 80 mg, 13% with famotidine 40 mg, and 20% with placebo, and the incidence of duodenal ulcers was 2%, 4%, and 13%, respectively.

Several studies have directly compared the effects of concomitant misoprostol and H2RAs on the risk of NSAID ulcers. Misoprostol 400 to 800 μg/d was shown to be more effective than ranitidine 150 mg twice daily in preventing endoscopic NSAID ulcers (64,65). Furthermore, in direct comparison PPIs have also been shown to be more effective than H2RAs in preventing endoscopic NSAID ulcers (66).

There have been no studies demonstrating the efficacy of H2RAs in the primary prevention of serious NSAID ulcer complications.

With the discovery of the 2 COX isoenzymes, COX-1 and COX-2, it was hypothesized that the continuous production of local gastroprotective prostaglandins is mainly COX-1 dependent, while the inducible production of inflammatory prostaglandins is mainly COX-2 dependent. Most traditional NSAIDs were found to be nonselective inhibitors of both COX isoforms (67). An ideal NSAID would selectively inhibit the inducible COX-2 isoform, thereby reducing inflammation and pain, without acting on the constitutive COX-1 isoform, thereby minimizing toxicity. On the basis of this hypothesis, several COX-2-selective NSAIDs were developed in the 1990s. Celecoxib (Celebrex®), rofecoxib (Vioxx®), and valdecoxib (Bextra®) received FDA approval for use in rheumatoid arthritis and osteoarthritis, while celecoxib and rofecoxib were also approved for use in acute pain. Two other COX-2 selective NSAIDs, etoricoxib (Arcoxia®) and lumircoxib (Prexige®), received European approval for use in rheumatoid arthritis, osteoarthritis, and acute gout or osteoarthritis, respectively.

COX-2-selective NSAIDs demonstrate comparable analgesia and anti-inflammatory effects to nonselective NSAIDs in patients with rheumatoid arthritis and osteoarthritis (67-71). At their defined therapeutic doses, COX-2-selective NSAIDs show at least a 200- to 300-fold selectivity for inhibition of COX-2 over COX-1

(67). Many studies have evaluated the efficacy of COX-2-selective NSAIDs on reducing the risk of NSAID ulcers. In 2000, 2 pivotal outcome studies, the Celecoxib Long-term Arthritis Safety Study (CLASS) and VIoxx Gastrointestinal Outcome Research study (VIGOR), demonstrated that COX-2-selective NSAIDs decrease the risk for both endoscopic NSAID ulcers and serious NSAID ulcer complications when compared with nonselective NSAIDs (72,73).

In the CLASS study, 8059 rheumatoid arthritis and osteoarthritis patients were randomized to celecoxib 400 mg twice daily (2 and 4 times the maximal dose approved for rheumatoid arthritis and osteoarthritis, respectively), ibuprofen 800 mg 3 times daily, or diclofenac 75 mg twice daily (72). Prophylactic aspirin use was permitted. At 6 months, the annualized incidence rates of NSAID ulcer complications alone and combined with symptomatic ulcers for celecoxib versus NSAIDs were 0.76% versus 1.45% ($P = 0.09$) and 2.08% versus 3.54% ($P = 0.02$), respectively. For patients not taking aspirin, the annualized incidence rates were 0.44% versus 1.27% ($P = 0.04$) and 1.40% versus 2.91% ($P = 0.02$), respectively. For patients taking aspirin, there were no significant differences (72). However, at the primary study endpoint at 12 months there was no statistically significant reduction in NSAID ulcers or ulcer complications among patients taking celecoxib. These final results of the CLASS study were never officially published.

In the VIGOR study, 8076 rheumatoid arthritis patients were randomized for rofecoxib 50 mg daily (twice the maximal dose approved for long-term use) or naproxen 500 mg twice daily (73). During a median follow-up of 9.0 months, 2.1 gastrointestinal events per 100 patient-years (gastroduodenal perforation, obstruction, bleeding, and symptomatic ulcers) occurred with rofecoxib, as compared with 4.5 per 100 patient-years with naproxen (relative risk, 0.5; 95% CI, 0.3 to 0.6; $P < 0.001$). The rates of complicated events (perforation, obstruction, and severe bleeding) were 0.6 per 100 patient-years and 1.4 per 100 patient-years, respectively (relative risk, 0.4; 95% CI, 0.2 to 0.8; $P = 0.005$). However, the incidence of myocardial infarction was higher in the rofecoxib group than in the naproxen group (0.4% versus 0.1%). Overall toxicity was higher with rofecoxib than with naproxen (73).

The Multinational Etoricoxib and Diclofenac Arthritis Long-term program was a pooled intent-to-treat analysis of 3 randomized comparisons of etoricoxib (60 or 90 mg daily) and diclofenac (150 mg daily) in 34,701 rheumatoid arthritis or osteoarthritis patients (74). Overall, gastrointestinal events were significantly less common with etoricoxib than with diclofenac (hazard ratio, 0.69; 95% CI, 0.57 to 0.83; $P = 0.0001$). This was due to a significant decrease in uncomplicated ulcers with etoricoxib (hazard ratio, 0.57; 95% CI, 0.45 to 0.74; $P < 0.0001$), but there was no difference in perforation, obstruction, or bleeding (hazard ratio, 0.91; 95% CI, 0.67 to 1.24; $P = 0.561$). PPIs were used concomitantly for at least 75% of the study period by 40% of the patients and low-dose aspirin by 33%, but treatment effects did not differ significantly in these subgroups (74).

In the Therapeutic Arthritis Research and Gastrointestinal Event Trial, 18,325 osteoarthritis patients were randomized to lumiracoxib 400 mg once daily, naproxen 500 mg twice daily, or ibuprofen 800 mg 3 times daily for 52 weeks (75). In the patients not taking aspirin, the cumulative incidence of serious NSAID ulcer complications (bleeding, perforation, or obstruction) was significantly lower with lumiracoxib than with naproxen or ibuprofen (hazard ratio, 0.21; 95% CI, 0.12 to 0.37). However, there was no significant difference in the patients concurrently taking aspirin. Furthermore, there were more myocardial infarctions with lumiracoxib, especially as compared with naproxen (0.38% versus 0.21%), although the differences were not statistically significant (75).

Several tentative conclusions may be drawn from these and other studies. First, the use of COX-2-selective NSAIDs significantly reduces the risk of NSAID ulcers and of serious NSAID ulcer complications. However, long-term efficacy remains debatable. Second, concurrent use of low-dose aspirin for primary or secondary prevention of cardiovascular or cerebrovascular disease negates the gastroprotective effect of COX-2-selective NSAIDs. This observation may be directly related to effect of aspirin, which irreversibly blocks COX-1 in the gastrointestinal tract (76). Third, the use of COX-2-selective NSAIDs increases the risk of myocardial infarction, as compared with the nonselective NSAID naproxen.

Treatment of NSAID Ulcers

The development of upper gastrointestinal ulcer disease in a patient on NSAID therapy should result in prompt discontinuation of the drug, followed by the initiation of medical therapy to promote ulcer healing. Treatment options include gastric acid suppressants such as PPIs or H2RAs, and possibly cytoprotective drugs such as sucralfate and misoprostol. The patient's *H. pylori* status should also be assessed, and if present, *H. pylori* should be eradicated (37).

In certain patients discontinuation of NSAID therapy may not be possible. Several studies have evaluated the efficacy of the medical therapy for ulcer healing during continued NSAID therapy. Ulcer healing may occur more rapidly with PPIs than with H2RAs, misoprostol, or sucralfate (77-79). In 1 study, 541 patients with NSAID ulcers or multiple gastroduodenal erosions who required continuous NSAID therapy were randomized for treatment with omeprazole 20 mg daily, omeprazole 40 mg daily, or ranitidine 150 mg twice daily (77). At 8 weeks, the rates of endoscopic ulcer healing were 80% with omeprazole 20 mg, 79% with omeprazole 40 mg, and 63% with ranitidine 300 mg.

In a second study, 935 patients with NSAID ulcers or multiple erosions who required continuous NSAID therapy were randomized for treatment with omeprazole 20 mg daily, omeprazole 40 mg daily, or misoprostol 200 μg 4 times daily (78). At 8 weeks, endoscopic healing rates were comparable in all 3 groups, with successful treatment in 76% with omeprazole 20 mg, 75% with omeprazole 40 mg, and 71% with misoprostol.

In a third study, 98 patients with NSAID ulcers who required continuous NSAID therapy were randomized for treatment with omeprazole 20 mg daily or sucralfate 2 g twice daily (79). At 8 weeks, the rates of gastric ulcer healing were 87% with omeprazole versus 52% with sucralfate, while the rates of duodenal ulcer healing were 95% versus 73%.

Secondary Prevention of NSAID Ulcers

The aim of secondary prevention strategies is the prevention of recurrent NSAID ulcers in patients with a (recent) history of gastroduodenal ulcers who require continued NSAID therapy. A prior history of gastroduodenal ulcers is a strong predictor for the occurrence of NSAID ulcers, and careful assessment of alternative treatment options should be undertaken before NSAID therapy is reinitiated or continued.

Several studies have compared the efficacy of the concomitant use of PPIs, H2RAs, and misoprostol on reducing the risk of recurrent endoscopic NSAID ulcers (77,78,80). In the previously mentioned study on NSAID ulcer healing with omeprazole 20 mg, omeprazole 40 mg, or ranitidine 300 mg, the 432 patients in whom initial treatment had been successful were then randomized for 6 months of maintenance therapy with either omeprazole 20 mg daily or ranitidine 150 mg twice daily (77). The proportion of patients who remained in remission at 6 months was significantly higher with omeprazole (72%) than with ranitidine (59%).

Likewise, in the study on NSAID ulcer healing with omeprazole 20 mg, omeprazole 40 mg, or misoprostol 800 μg, the 732 patients in whom initial treatment had been successful were then randomized for 6 months of maintenance therapy with either omeprazole 20 mg daily, misoprostol 200 μg twice daily, or placebo (78). The proportion of patients who remained in remission at 6 months was significantly higher with omeprazole (61%) than with misoprostol (48%) or placebo (27%). Halving the misoprostol dosage for the maintenance phase may have biased the study in favor of omeprazole. However, omeprazole was still better tolerated than misoprostol.

These 2 studies allow some interesting additional observations. First, during continued NSAID use following successful initial treatment, the rate of recurrent endoscopic ulcers was very high at 73% in 6 months with placebo. Second, although the efficacy of omeprazole 20 mg daily was significantly better than ranitidine 150 mg twice daily or misoprostol 200 μg twice daily, the rate of recurrent endoscopic ulcers was still high at 28% and 39% in 6 months.

In 2 similarly designed studies, Verification of Esomeprazole for NSAID Ulcers and Symptoms (VENUS) (United States) and Prevention of Latent Ulceration Treatment Options (PLUTO) (multinational), 844 and 585 NSAID users, including COX-2-selective NSAIDs, were randomized to esomeprazole 20 mg, esomeprazole 40 mg, or placebo for 6 months (80). Patients were 60 years or older and/or had documented ulcers in the previous 5 years (VENUS 20%, PLUTO 36%), but no ulcer complications in the 6 months before study entry, no endoscopic ulcers at baseline, and were *H. pylori* negative. At 6 months, the estimated proportions developing endoscopic ulcers were 20% and 12% with placebo, 5% and 5% with esomeprazole 20 mg, and 5% and 4% with esomeprazole 40 mg, for VENUS and PLUTO, respectively. In these studies, ulcer rates for COX-2 selective NSAID users would have been expected to be lower than for nonselective NSAID users. Interestingly, however, the pooled ulcer rates for the 400 COX-2-selective NSAID users and 978 nonselective NSAID users were similar, 16.5% and 17% with placebo, 1% and 7% with esomeprazole 20 mg, and 4% and 5% with esomeprazole 40 mg. Patients using COX-2-selective NSAIDs did not have a higher risk for developing NSAID ulcers than those using nonselective NSAIDs. The COX-2-selective and nonselective groups had similar proportions of patients with an ulcer history (34 and 33%); mean age was slightly higher in the COX-2 selective group (mean, 66.6 and 64.2 years), but there were fewer low-dose aspirin users in the COX-2-selective group (3% and 12%) (80).

Several studies have compared the efficacy of either a COX-2-selective NSAID or the combination of a nonselective NSAID with a PPI for the secondary prevention of NSAID ulcer complications (81-83). In 1 study, 287 *H. pylori*-negative arthritis patients who had presented with NSAID ulcer bleeding were randomized after endoscopically confirmed ulcer healing to celecoxib 200 mg twice daily plus placebo or diclofenac 75 mg twice daily plus omeprazole 20 mg (81). The probability of endoscopically confirmed recurrent ulcer bleeding during a 6-month follow-up was 4.9% with celecoxib and 6.4% with diclofenac plus omeprazole. Therefore, among high-risk patients with a recent history of ulcer bleeding, treatment with celecoxib was as effective as treatment with diclofenac plus omeprazole for the prevention of recurrent bleeding, but neither strategy completely eliminated the risk (81).

In an extension to the previous study, 222 (86%) of the patients without recurrent bleeding within the study period agreed to undergo follow-up endoscopy at their last study visit (82). The probability of recurrent endoscopic ulcers in 6 months was 19% with celecoxib and 26% with diclofenac plus omeprazole. With a combined endpoint of bleeding and endoscopic ulcers, 24% with celecoxib

and 32% with diclofenac plus omeprazole had recurrent ulcers. Therefore, among high-risk patients with a recent history of ulcer bleeding, neither celecoxib nor diclofenac plus omeprazole adequately prevented ulcer recurrence (81,82).

In a similar study, 224 *H. pylori*-negative patients who had presented with NSAID ulcer bleeding were randomized after endoscopically confirmed ulcer healing to celecoxib 200 mg once daily or naproxen 250 mg 3 times daily plus lansoprazole 30 mg once daily (83). The cumulative incidence of recurrent ulcer complications at 24 weeks was 3.7% with celecoxib and 6.3% with naproxen plus lansoprazole.

One study compared the efficacy of either *H. pylori* eradication or concomitant PPI treatment for the secondary prevention of NSAID ulcer bleeding (84). This study enrolled 400 *H. pylori*-positive patients, 150 with NSAIDs, and 250 with low-dose aspirin for cardiovascular prophylaxis, who had presented with ulcer bleeding. Only the data for the 150 NSAID users will be presented here. After endoscopically confirmed ulcer healing with omeprazole 20 mg daily for 8 weeks or longer, patients were given naproxen 500 mg twice daily and then randomized to omeprazole 20 mg daily for 6 months or 1 week of *H. pylori* eradication therapy followed by placebo for 6 months. The probability of recurrent NSAID ulcer bleeding during the 6-month follow-up period was 19% for patients receiving eradication therapy and 4% for those treated with omeprazole (84).

Another study evaluated the efficacy of combination treatment with a COX-2-selective NSAID and a PPI for the secondary prevention of NSAID ulcer complications in patients at very high risk for ulcer bleeding (85). In this study, 441 *H. pylori*-negative arthritis patients who had presented with NSAID ulcer bleeding were treated with celecoxib 200 mg twice daily after endoscopically confirmed ulcer healing and were randomized for additional esomeprazole 20 mg twice daily or placebo. The 13-month cumulative incidence of recurrent ulcer bleeding was 0% with celecoxib and esomeprazole combination therapy and 9% with celecoxib monotherapy (85). Therefore, patients at very high risk for recurrent ulcer bleeding who need continued NSAID treatment might benefit from combination treatment with a COX-2-selective NSAID and a PPI.

Secondary Prevention of Aspirin Ulcers

Aspirin 75 to 325 mg daily has proven efficacy in the secondary prevention, and in selected patients primary prevention, of cardiovascular disease. However, patients using low-dose aspirin have a small increase in the risk of major gastrointestinal bleeding. A meta-analysis of adverse events of low-dose aspirin in 22 randomized placebo-controlled trials found a relative risk of 2.07 for major gastrointestinal bleeding with aspirin, with an absolute annual increase of 0.12% (86). With this low absolute risk increase, the number needed to treat with aspirin to cause 1 major gastrointestinal bleeding is 833. Therefore, strategies for the prevention of gastrointestinal bleeding should be targeted at high-risk patients. However, the general increase in use of aspirin, and particularly the increasing use of aspirin for primary prevention of cardiovascular disease, may now make it a bigger cause of ulcer bleeding than NSAIDs.

Different strategies have been evaluated for the prevention of recurrent gastrointestinal bleeding in patients who continue aspirin therapy (84,87,88). In 1 study, 123 *H. pylori*-positive patients who had developed bleeding ulcers with low-dose aspirin were treated with *H. pylori* eradication therapy and then randomized to lansoprazole 30 mg daily or placebo in addition to aspirin 100 mg daily (87). At 12 months follow-up, the rate of recurrent ulcer complications was 1.6% with lansoprazole and 14.8% with placebo.

In another study, 320 *H. pylori*-negative patients who presented with ulcer bleeding with low-dose aspirin were randomized after endoscopically confirmed ulcer healing to aspirin 80 mg daily plus esomeprazole 20 mg daily or clopidogrel 75 mg daily plus placebo (88). Clopidogrel had previously been recommended as an alternative in patients with major gastrointestinal complications with aspirin. At 12 months follow-up, the rate of recurrent ulcer bleeding was 0.7% with aspirin plus esomeprazole and 8.6% with clopidogrel.

One previously mentioned study compared the efficacy of either *H. pylori* eradication or concomitant PPI treatment for the secondary prevention of aspirin ulcer bleeding (84). This study enrolled 400 *H. pylori*-positive patients, 250 with low-dose aspirin and 150 with NSAIDs, who had presented with ulcer bleeding. Only the data for the 250 aspirin users will be presented here. After endoscopically confirmed ulcer healing with omeprazole 20 mg daily for 8 weeks or longer, patients were given aspirin 80 mg daily and then randomized to omeprazole 20 mg daily for 6 months or 1 week of *H. pylori* eradication therapy followed by placebo for 6 months. The probability of recurrent ulcer bleeding during the 6-month follow-up period was 1.9% for patients receiving eradication therapy and 0.9% for those treated with omeprazole (84).

Possible NSAID Prevention of Colon Cancer

A large body of evidence has shown that aspirin and NSAIDs may inhibit colorectal carcinogenesis (89). The evidence derives from animal models, epidemiological studies, intervention trials with NSAIDs in patients with familial polyposis, and randomized controlled trials with aspirin and COX-2-selective NSAIDs (90). Aspirin and NSAIDs may inhibit colorectal carcinogenesis by increasing the rate of apoptosis in colon cancer cells, inhibiting tumor angiogenesis, inhibiting cell proliferation and tumor growth, and decreasing metastatic potential.

A systematic review of controlled and observational

studies examining the use of aspirin for the primary prevention of colorectal cancer found that regular use of aspirin was associated with a significantly reduced incidence of colonic adenomas in randomized controlled trials (relative risk, 0.82), case-control studies (relative risk, 0.87), and cohort studies (relative risk, 0.72) (91). In cohort studies, regular use of aspirin was associated with relative risk reductions of 22% for incidence of colorectal cancer. Benefits from chemoprevention were more evident when aspirin was used at a high dose and for periods longer than 10 years (91).

A systematic review of controlled and observational studies examining the use of nonselective and COX-2-selective NSAIDs for primary prevention of colorectal cancer found that nonselective NSAIDs were associated with a significantly reduced incidence of colorectal adenomas in cohort studies (relative risk, 0.64) and case-control studies (relative risk, 0.54) (92). COX-2-selective NSAIDs were also associated with a significantly reduced incidence of colorectal adenomas in randomized controlled trials (relative risk, 0.72). Nonselective NSAIDs were associated with a significant reduction in colorectal cancer in cohort studies (relative risk, 0.61) and in case-control studies (relative risk, 0.70) (92).

NSAID-Induced Cardiovascular Toxicity

Within the endovascular lumen COX-1 and COX-2 appear to play important roles in thrombogenesis (93). Activated blood platelets produce COX-1-dependent thromboxane TXA_2, which acts as a prothrombotic platelet agonist and vasoconstrictor. Nearby endothelial and smooth muscle cells produce COX-2-dependent prostaglandin I_2 (PGI_2), especially after cell damage has occurred (94). PGI_2 is an antithrombotic platelet inhibitor and vasodilator and thus modulates the interaction between activated platelets and the endovascular wall. COX-2-selective NSAIDs may, by their irreversible covalent binding of COX-2, strongly impair the synthesis of antithrombotic prostacyclin while lacking COX-1-inhibiting effects, thus tipping the scales of homoeostasis in favor of thrombogenesis and vasoconstriction (94). As their effect is temporary and reversible, only continuous high dosage of nonselective NSAIDs will considerably inhibit COX-1 and COX-2. Under normal circumstances, nonselective NSAIDs would not greatly influence the endovascular homeostasis. However, cell damage, atherosclerotic plaques, and laminar shear forces selectively up-regulate the expression of COX-2 by endothelial cells in an attempt to maintain homoeostasis (95). Therefore, in clinical syndromes associated with platelet activation, COX inhibition by any NSAID, but especially by COX-2-selective NSAIDs, could be expected to increase the risk for cardiovascular events (94).

On 30 September 2004, Merck Sharp and Dohme removed its COX-2-selective NSAID rofecoxib (Vioxx®) from the market because of a raised risk for cardiovascular events, especially myocardial infarctions. Overnight, direct-to-consumer advertising was replaced by direct-to-litigant advertising. The VIGOR study had already shown that rofecoxib, compared with naproxen, carried an increased risk for thrombotic cardiovascular events (73). In this study, the incidence of myocardial infarction was 0.4% with rofecoxib 50 mg and 0.1% with naproxen 1000 mg, but these results were heavily debated.

The expectancy of a lower incidence of gastrointestinal side effects and a superior therapeutic index with COX-2-selective NSAIDs had led to studies assessing their efficacy for the prevention of adenomatous polyps in patients who had undergone endoscopic polypectomy. Although these studies showed COX-2-selective NSAIDs to be effective for the prevention of colorectal neoplasia, they also confirmed the suspected increase in cardiovascular risk. In the Adenomatous Polyp PRevention On Vioxx study, the 18-month rates of thrombotic events were 1.5 per 100 patient-years with rofecoxib and 0.78 per 100 patient-years with placebo (relative risk, 1.92), prompting the withdrawal of rofecoxib (96). Likewise, in the Adenoma Prevention with Celecoxib study, which was terminated early by the National Institutes of Health, the risk for having major cardiovascular events was increased 2.3-fold with celecoxib 400 mg and 3.4-fold with celecoxib 800 mg, compared with placebo (97).

In a study assessing the safety of parecoxib and valdecoxib after cardiac surgery, 1671 patients were randomized to intravenous parecoxib or placebo for 3 days after coronary artery bypass grafting, followed by oral valdecoxib or placebo for 10 days (98). All patients also received low-dose aspirin and were followed for up to 30 days. Cardiovascular events occurred in 0.5% with placebo only, 1.1% with placebo followed by valdecoxib (relative risk, 2.0), and 2.0% with parecoxib followed by valdecoxib (relative risk, 3.7).

In the Therapeutic Arthritis Research and Gastrointestinal Event Trial, 18,325 osteoarthritis patients were randomly assigned to lumiracoxib 400 mg once daily, naproxen 500 mg twice daily, or ibuprofen 800 mg 3 times daily and followed for 1 year (99). Patients with prior myocardial infarction, stroke, coronary bypass grafting, angioplasty or stenting, angina, or significant heart failure were excluded. The rates of cardiovascular events were not significantly different for lumiracoxib and nonselective NSAIDs (0.86 and 0.75 per 100 patient-years; hazard ratio, 1.14; 95% CI, 0.78 to 1.66). Compared with naproxen, the relative risk for lumiracoxib was increased but did not reach statistical significance (hazard ratio, 1.5; 95% CI, 0.9 to 2.4) (99).

The Multinational Etoricoxib and Diclofenac Arthritis Long-term program evaluated the cardiovascular safety of etoricoxib in a prespecified analysis of 3 separate trials comparing etoricoxib with diclofenac in 24,913 osteoarthritis patients and 9787 rheumatoid arthritis patients (100). After 18 months, 320 patients with etoricoxib (1.24 per 100 patient-years) and 323 with diclofenac

(1.30 per 100 patient-years) had thrombotic cardiovascular events (hazard ratio, 0.95; 95% CI, 0.81 to 1.11) (100). However, interpretation of these results is problematic since diclofenac itself is strongly associated with an increased risk of cardiovascular outcomes (101).

One meta-analysis assessed the effects of COX-2-selective and nonselective NSAIDs on the risk of vascular events in published and unpublished tabular data from 138 randomized trials that included a comparison of a COX-2-selective NSAID versus placebo or a COX-2-selective NSAID versus a nonselective NSAID, of at least 4 weeks' duration (102). Selective COX-2 inhibitors were associated with a moderate increase in the risk of serious vascular events compared with placebo (rate ratio, 1.42), which was chiefly attributable to an increased risk of myocardial infarction (rate ratio, 1.86). High-dose regimens of nonselective NSAIDs were associated with a similar increase in risk of vascular events compared with placebo (rate ratio, 1.51 for ibuprofen, 1.63 for diclofenac), with the exception of high-dose naproxen (rate ratio, 0.92) (102).

A systematic review and meta-analysis assessed the risks of serious cardiovascular events with individual COX-2-selective and nonselective NSAIDs in 17 case-control studies and 6 cohort studies (101). Rofecoxib was associated with a significant dose-related relative risk of serious cardiovascular events during the first month of treatment (relative risk, 1.33 with 25 mg or less daily; relative risk, 2.19 with more than 25 mg daily). Celecoxib was not associated with an elevated risk (relative risk, 1.06). Among the nonselective NSAIDs, diclofenac had the highest risk (relative risk, 1.40). Other nonselective NSAIDs that had relative risks close to 1 include ibuprofen (relative risk, 1.07) and piroxicam (relative risk, 1.06). The risk appeared lowest for naproxen (relative risk, 0.97) (101).

One meta-analysis assessed the comparative risk of myocardial infarctions with COX-2-selective and nonselective NSAIDs in case-control studies, cohort studies, and randomized controlled trials in colonic adenomas and arthritis (103). Fourteen case-control studies with 74,673 myocardial infarction patients and 368,968 controls showed no significant association of NSAIDs with myocardial infarctions in a random effects model and a small risk in a fixed effects model (odds ratio, 1.32). Six cohort studies with 387,983 patient-years and 1120,812 control-years showed no significant risk of myocardial infarctions with NSAIDs, except for rofecoxib (relative risk, 1.25). Four randomized controlled trials of NSAIDs in colonic adenomas with 6000 patients showed increased risks of myocardial infarctions with NSAIDs (relative risk, 2.68). Fourteen randomized controlled trials in arthritis with 45,425 patients showed more myocardial infarctions with COX-2-selective NSAIDs (odds ratio, 1.6), but fewer serious upper gastrointestinal events (odds ratio, 0.40) (103).

Based on a review of available data from long-term placebo- and active-controlled clinical trials of NSAIDs, the FDA has concluded that an increased risk of serious adverse cardiovascular events may be a class effect for all NSAIDs, COX-2-selective and nonselective alike (excluding aspirin). The FDA has subsequently requested that the package insert for all NSAIDs be revised to include a boxed warning highlighting the potential increased risk of cardiovascular events and the well-described risk of serious, and potentially life-threatening, gastrointestinal bleeding. The FDA has also requested that the package insert for all NSAIDs include a contraindication for use in patients immediately postoperative from coronary artery bypass graft surgery (104).

NSAID Interference with Aspirin

The beneficial effect of aspirin may be attenuated by concomitant administration of NSAIDs such as ibuprofen or naproxen (105,106). In 1 study, patients were treated with ibuprofen 2 hours before or 2 hours after aspirin (105). Serum thromboxane B2 levels and platelet aggregation were maximally inhibited with aspirin before ibuprofen. In contrast, inhibition of serum thromboxane B2 formation and platelet aggregation by aspirin was prevented with a single daily dose of ibuprofen before aspirin, as well as when multiple daily doses of ibuprofen were given. The concomitant administration of rofecoxib, acetaminophen, or diclofenac before or after aspirin did not affect the pharmacodynamics of aspirin (105). Similar effects have been described with naproxen. In 1 study, a single dose of naproxen 2 hours before aspirin interfered with the antiplatelet effect of aspirin (106).

Nonselective NSAIDs compete with aspirin for a common binding site on COX-1. The presence of a nonselective NSAID at this site prevents aspirin from binding and irreversibly acetylating a serine residue on COX-1 (107,108). This pharmacodynamic interaction is not seen with COX-2-selective NSAIDs. Aspirin causes an irreversible and nearly complete blockade of COX at low doses, while the blockade caused by ibuprofen at therapeutic doses is reversible and much less complete, declining rapidly between doses (109). The inhibitory effect of naproxen on platelet function is greater than that of ibuprofen and its half-life is significantly longer.

These findings may have strong clinical relevance in patients with cardiovascular disease. Concomitant use of aspirin and ibuprofen or naproxen should be avoided, or at least the NSAID should be administered 2 hours after aspirin.

NSAID-Induced Exacerbation of Heart Failure

NSAID use is not associated with a first occurrence of heart failure but may exacerbate preexisting disease (110,111). In patients with preexisting heart failure, NSAID use may induce systemic vasoconstriction, causing an increase in afterload with further reduction in cardiac contractility and cardiac output (107). Advanced

heart failure is associated with increased secretions of antidiuretic hormone, angiotensin II, and norepinephrine. The ensuing renal ischemia may lead to water retention and hyponatremia, resulting in further worsening of heart failure and increased risk for acute renal failure.

In the prospective Rotterdam cohort study, 7277 subjects over 55 years of age were followed up from the interview date until a diagnosis of incident heart failure, death, or end of the follow-up period (110). During follow-up, 345 participants had incident heart failure. Current use of NSAIDs was associated with a relative risk of incident heart failure of 1.1 (95% CI, 0.7 to 1.7). However, in NSAID users with prevalent heart failure the adjusted relative risk of a relapse was 9.9 (95% CI, 1.7 to 57.0). Another study found a similar 10-fold increased risk of exacerbating heart failure in elderly patients with recent NSAID use (111). In this study, the risk was related to the dose of NSAID consumed within the week before hospitalization for heart failure.

One population-based retrospective cohort study compared the rates of hospital admission for heart failure in 38,882 elderly patients who were newly dispensed COX-2-selective or nonselective NSAIDs and 100,000 randomly selected non-NSAID using controls (112). The crude rate of hospitalization for heart failure was 0.9 per 100 patient-years for the controls, 1.3 per 100 patient-years with celecoxib (adjusted rate ratio compared with controls 1.0), 1.6 per 100 patient-years with nonselective NSAIDs (rate ratio, 1.4), and 2.4 per 100 patient-years with rofecoxib (rate ratio, 1.8).

NSAID-Induced Hypertension

Patients with hypertension may have increased activation of the renin-angiotensin and sympathetic nervous system, with subsequent release of vasodilator prostaglandins from the kidney, which act locally to lessen the degree of renal ischemia (113). When this compensatory response is inhibited by NSAIDs, the increase in renal and systemic vascular resistance can cause an elevation in blood pressure averaging 3 to 6 mm Hg (114). This effect may be most pronounced in patients who are salt-sensitive and ingesting a relatively high salt diet and appears to be smallest in patients taking calcium channel blockers.

In the Nurses' Health Study II, a prospective study of over 80,000 women of 31 to 50 years of age without an initial history of hypertension, the relative risk for the development of hypertension after 2 years of follow-up was 1.86 with NSAIDs compared with non-NSAIDs, except with aspirin (115).

In a meta-analysis of 19 randomized trials with COX-2-selective NSAIDs involving 45,451 participants in whom blood pressure data were available, the rate of incident hypertension was 2.63 with rofecoxib compared with placebo (114). The weighted mean increase in blood pressure was 5.66 mm Hg with rofecoxib and 2.6 mm Hg with celecoxib. However, celecoxib was associated with a 0.99 mm Hg increase in diastolic blood pressure (114).

NSAID-Induced Acute Renal Failure

In normal subjects the basal rate of renal prostaglandin synthesis is relatively low and does not play a major role in the regulation of renal hemodynamics (116). The release of renal PGI_2 and PGE_2 is increased by glomerular disease, renal insufficiency, and hypercalcemia and by increases in the vasoconstrictors angiotensin II and norepinephrine in states of effective volume depletion, such as heart failure, cirrhosis, and true volume depletion (117). In these situations, renal vasodilator prostaglandins maintain renal blood flow and glomerular filtration rates by relaxing preglomerular resistance and antagonizing the vasoconstrictor effects of angiotensin II and norepinephrine. Under such conditions NSAID inhibition of prostaglandin synthesis may cause reversible renal ischemia, a decline in glomerular hydraulic pressure and glomerular filtration rate, and acute renal failure (116).

Acute renal failure may occur with any COX-2-selective or nonselective NSAID. In 1 nested case-control study, hospitalization for acute renal failure was correlated with initiation of NSAID use among 121,722 patients older than 65 years of age (118). The risk of acute renal failure was highest within 30 days of starting treatment and receded thereafter. The relative risk for acute renal failure was comparable among rofecoxib (relative risk, 2.31; 95% CI, 1.73 to 3.08), naproxen (relative risk, 2.42; 95% CI, 1.52 to 3.85), and nonselective, nonnaproxen NSAIDs (relative risk, 2.30; 95% CI, 1.60 to 3.32) but was slightly lower with celecoxib (relative risk, 1.54; 95% CI, 1.14 to 2.09). In another study, 60 elderly patients receiving a low-salt diet were randomized to rofecoxib 12.5 mg daily, rofecoxib 25 mg daily, indomethacin 50 mg 3 times daily, or placebo for 5 days (119). Compared with placebo, glomerular filtration rate was significantly lowered with rofecoxib 12.5 mg (8.4 mL/min lower), with rofecoxib 25 mg (7.8 mL/min lower), and with indomethacin 150 mg (6.0 mL/min lower).

NSAID use is also associated with acute interstitial nephritis, membranous nephropathy, and nephrotic syndrome due to minimal change disease. The underlying pathophysiologic mechanisms are not known. Affected patients typically present with hematuria, pyuria, white cell casts, proteinuria, and acute renal insufficiency. Spontaneous recovery usually occurs within weeks to months after therapy is discontinued (120). Subsequent administration of NSAIDs should be avoided as relapse may occur with rechallenge.

Future Developments

Most cells routinely make prostaglandins through the action of COX-1 on arachidonic acid. Arachidonic acid is converted to the endoperoxide PGH_2, which is subsequently converted by additional prostaglandin synthases

Table 2 Prescribing NSAIDs According to the Risk for Gastrointestinal (GI) and Cardiovascular (CV) Events

Guideline for Prescribing NSAIDs According to the Risk for Gastrointestinal (GI) and Cardiovascular (CV) Events			
	Low GI risk (no risk factors)	Moderate GI risk (1 or 2 risk factors)	High GI risk (more than 2 risk factors)
Low CV risk	Nonselective NSAID	COX-2/NSAID + PPI	COX-2 + PPI
High CV risk	Naproxen + PPI	Naproxen + PPI	No NSAIDs

GI risk factors include history of ulcers, age over 60 years, high dosage of NSAID, concomitant corticosteroids, anticoagulants, aspirin, platelet inhibitors, and serotonin reuptake inhibitors, *Helicobacter pylori*, diabetes mellitus, heart failure, and rheumatoid arthritis. Proton pump inhibitor (PPI) may also be read as misoprostol 400 to 800 μg. 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. COX-2: COX-2 selective NSAID. Adapted from ref. 124.

into other prostaglandins, such as PGD_2, involved in sleep regulation and allergic reactions; PGF_2, involved in uterus contraction; PGI_2, involved in dilation of blood vessels, platelet inhibition, and stomach protection; PGE_2, involved in pain, inflammation, and fever, and in stomach protection; and thromboxane, TXA_2, involved in constriction of blood vessels and platelet aggregation.

When tissue injury occurs, a chemical signal instructs macrophages and inflammatory cells to increase the activity of COX-2, which subsequently increases the conversion of PGH_2 to PGE_2 by PGE_2 synthases (PGES). Aspirin and nonselective NSAIDs act by blocking both COX isoforms, COX-1 and COX-2, early in the prostaglandin synthesis pathway, consequently inhibiting the entire synthesis of prostaglandins downstream of PGH_2. Inflammatory PGE_2 synthesis was found to be mainly COX-2 dependent, while gastroprotective PGE_2 synthesis was found to be mainly COX-1 dependent, prompting the development of the COX-2-selective NSAIDs. However, COX-2-selective NSAIDs still interact early in the prostaglandin synthesis pathway and inadvertently inhibit other COX-2-dependent prostaglandins, such as the cardioprotective PGI_2, with the consequential elevated risk for cardiovascular events.

More specific targets for anti-inflammatory action would have to be sought downstream from the COX enzymes in the prostaglandin synthesis pathway (121). Recent discoveries have found different forms of PGES (122). A cytosolic form of PGES couples preferentially with COX-1 to convert PGH_2 into gastroprotective PGE_2, while 1 of 2 membrane-bound forms of PGES (mPGES-1) couples with COX-2 to convert PGH_2 into inflammatory PGE_2. Several agents, still under development, specifically block mPGES-1. Inhibiting mPGES-1 but not the enzymes that make normal levels of prostaglandins may thus control inflammatory PGE_2 levels, providing analgesic, antipyretic, and anti-inflammatory benefits, without concurrent cardiovascular or gastrointestinal harms. Alternative strategies being developed for third-generation NSAIDs involve drugs that would bind to PGE_2 receptors, directly blocking them from functioning (121).

DISCUSSION

In summary, NSAIDs are among the oldest, most successful drugs known to modern medicine. NSAIDs are effective for alleviating pain, fever, and inflammation, by inhibiting prostaglandin synthesis. Aspirin, by its irreversible inhibition of blood platelet function, is also effective in the secondary prevention and, in selected patients, primary prevention of cardiovascular disease. In addition, NSAIDs may also inhibit colorectal carcinogenesis.

NSAIDs are mainly indicated for mild to moderate pain of somatic origin and may be especially effective in inflammatory diseases such as rheumatoid arthritis. The efficacy of NSAIDs may vary by patient and by indication. In case of inefficacy, substitution by a NSAID from a different chemical class is a reasonable therapeutic option.

NSAID use is associated with several serious treatment side effects, with considerable associated morbidity and mortality. NSAIDs may cause gastrointestinal ulcers, which may be complicated by ulcer bleeding, perforation, and obstruction. COX-2-selective NSAIDs and high-dose nonselective NSAIDs may cause serious cardiovascular events, especially myocardial infarction, with the possible exception of naproxen. NSAIDs use is also associated with the development of hypertension, acute renal failure, and worsening of preexisting heart failure.

Concurrent use of low-dose aspirin for primary or secondary prevention of cardiovascular disease may negate the gastroprotective effect of COX-2-selective NSAIDs. Conversely, the beneficial effect of aspirin may be attenuated by concomitant use of nonselective NSAIDs, such as ibuprofen or naproxen.

Physicians must take into account both the gastrointestinal and the cardiovascular risks of individual patients when prescribing NSAIDs. Interestingly, in a study among Canadian osteoarthritis patients, most patients were willing to accept some additional risk of ulcer bleeding and heart attacks or stroke to gain pain relief but were generally willing to accept a greater additional risk of ulcer bleeding than of heart attacks or stroke (123).

As a central dictum in NSAID treatment, physicians should always prescribe the lowest effective dose for the shortest possible time.

Patients with a history of gastroduodenal ulcers should

be tested for *H. pylori* before starting NSAID or aspirin therapy, and if present, *H. pylori* should be eradicated. In asymptomatic patients with no ulcer history and not currently taking NSAIDs, physicians may consider *H. pylori* testing before starting long-term NSAID therapy. This "test-and-treat" approach may be most effective in populations with high prevalence of *H. pylori* infection.

In patients with a low cardiovascular risk, NSAIDs can be prescribed according to the risk for gastrointestinal events (Table 2) (124). Patients with a low gastrointestinal risk may be treated with a nonselective NSAID. Patients with a moderate gastrointestinal risk (1 or 2 gastrointestinal risk factors) may be treated with a nonselective NSAID plus a PPI or misoprostol 800 μg, or with a COX-2-selective NSAID. In patients with a high gastrointestinal risk (more than 2 gastrointestinal risk factors or prior ulcer complications) alternative treatment options should be explored. If NSAID therapy is required in these patients, a combination of a COX-2-selective NSAID with a PPI twice daily should be considered.

Patients with a high cardiovascular risk should receive prophylactic low-dose aspirin. If additional NSAID therapy is required, naproxen is the preferred NSAID, in combination with a PPI or misoprostol 800 μg, irrespective of the presence of additional gastrointestinal risk factors (Table 2) (124). Naproxen should be taken 2 hours after aspirin. Patients with both a high cardiovascular risk and a high gastrointestinal risk should avoid NSAID therapy.

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