Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute a highly effective form of treatment used to manage a number of painful and inflammatory conditions. Serious adverse effects that result from use of NSAIDs most commonly affect the gastrointestinal (GI) tract, the cardiovascular (CV) system, and the kidneys.\(^1\)\(^-\)\(^3\) Evidence suggests that there is a strong correlation between the relative risk (RR) for these serious events and the dose and duration of NSAID therapy.

**GI Events**

Several studies have found an association between NSAID use and the risk for serious GI-related adverse events. For example, a meta-analysis of 28 case-control studies published between 1980 and 2011 calculated the pooled RRs for upper GI complications associated with NSAID use for 8 different prescription NSAIDs. Data from these studies showed that the RR of upper GI complications was approximately 2- to 3-fold greater with use of high daily doses versus low or medium daily doses (Figure 1).\(^1\)

A strong dose-dependent risk was also observed in a separate meta-analysis of individual patient data from 3 case-control studies utilizing conventional dose ranges. The increase in risk for upper GI bleeding was 4- to 8-fold higher for high- versus low-dose indomethacin, naproxen, and diclofenac. This study also found that the RR was highest among short-term users, who had taken an NSAID 1 week previous to the bleed, but had not taken an NSAID 2 to 4 weeks prior.\(^4\)

**CV Events**

The CV risks associated with NSAIDs also increase with dose, as shown in a large case-control study of more than 58,000 individuals in Denmark. Researchers examined the dose-related risk of death or reinfarction with NSAID use among patients who experienced a first-time myocardial infarction (MI). The most frequently used cyclooxygenase-2 (COX-2) inhibitors were rofecoxib and celecoxib. For traditional NSAIDs, ibuprofen and diclofenac were most frequently used. Researchers identified NSAID dose-related increases in the risk of death following hospital discharge for all 4 of these medications. Overall, the elevated risk of death was greatest with rofecoxib use. A daily dose of less than 25 mg of rofecoxib was associated with a hazard

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**Abstract**

Effective pain relief with use of nonsteroidal anti-inflammatory drugs (NSAIDs) may come at the cost of an increased risk for serious cardiovascular (CV), gastrointestinal (GI), and renal complications. Research has shown that these adverse events are more likely to occur with higher NSAID dosing and in individuals with a preexisting risk for CV and GI complications. To minimize the potential risk for an adverse event, numerous regulatory bodies and medical societies recommend using the lowest effective NSAID dose for the shortest time necessary. One potential strategy is to offer patients lower doses of standard NSAID formulations. However, efforts to modify physician prescribing behavior may be challenging because of concerns regarding the potential for suboptimal pain management. Another strategy has emerged through use of new technology that produces submicron NSAID formulations. This new technology is also an approach that could provide effective pain relief at low doses. This article reviews the role of dose and duration in the risk for NSAID-associated adverse events, and discusses the potential benefits associated with new low-dose submicron NSAID formulations.

ratio (HR) of 2.49 (95% CI, 2.11-2.94; \( P < .0001 \)). By comparison, a higher daily dose of 25 mg or more was associated with a 2-fold greater risk of death (HR, 5.26; 95% CI, 3.90-7.09; \( P < .0001 \)).

A recent meta-analysis of data from 30 case-control studies that included 184,946 CV events and 21 cohort studies with more than 2.7 million exposed individuals also showed a dose-dependent risk for CV events among NSAID users. Significant increases in the RR of CV events were observed between low and high doses of rofecoxib, diclofenac, and ibuprofen (Figure 2). A separate retrospective, case-control study of 716,395 individuals aged 50 to 85 years found an increased RR of MI of 1.35 for NSAID users compared with nonusers. This study also found that duration of treatment played a role in the CV risks associated with NSAID therapy. Users who stopped treatment between 3 months and 1 year in advance had a risk level similar to that of nonusers (RR, 1.02). When duration of NSAID treatment increased from 1 month to 3 or more years, the RR of MI increased from 1.13 to 1.53.

**Acute Renal Failure**

Several studies have reported a dosage effect for NSAID use and nephrotoxicity. A nested case-control study of 386,916 individuals aged 50 to 84 years in the general population in the United Kingdom examined several factors to determine the RR for renal failure associated with NSAID use. Data showed that dose; duration of use; and previous history of hypertension, heart failure, and diabetes were among the factors associated with an elevated risk for renal failure. The study found a dose-dependent effect regardless of the type of NSAID used. When compared with nonusers of NSAIDs, the RR of renal failure among individuals using NSAIDs was 2.51 with low/medium daily doses and 3.38 with high daily doses.

A separate study examined the association between NSAID use and hospitalization for acute renal failure among 4228 new NSAID users and 84,540 matched control subjects older than 65 years in Quebec. The adjusted RR of acute renal failure for rofecoxib was 6.64 for daily doses greater than 25 mg and 1.94 for daily doses less than 25 mg. A dose-depen-
The Role of Dose Reduction With NSAID Use

Figure 2. Pooled-Adjusted Relative Risk of Cardiovascular Events With Low-Medium Dose NSAIDs Versus High-Dose NSAIDs, Compared With Nonuse

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.05</td>
<td>1.78&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>1.22</td>
<td>1.98&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>1.37</td>
<td>2.17&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1.26</td>
<td>1.69</td>
</tr>
<tr>
<td>Naproxen</td>
<td>0.97</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Gastrointestinal (GI) indicates gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.
<sup>a</sup><sub>P<0.05 for dose effect</sub>

Figure 3. Relative Risk of Acute Renal Failure for High- and Low-Dose NSAID Use

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Low Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib</td>
<td>1.94</td>
<td>6.64</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1.33</td>
<td>2.00</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.65</td>
<td>3.62</td>
</tr>
</tbody>
</table>

NSAID indicates nonsteroidal anti-inflammatory drug.
<sup>a</sup>Adjusted for several covariates including age, sex, comorbidities, current use of aspirin, and healthcare utilization.

Dent trend for increased risk was also seen with celecoxib and naproxen (Figure 3).<sup>8</sup>

Recommendations From Regulatory Bodies and Medical Societies

Following recognition of the potentially serious adverse CV and GI events associated with nonselective NSAIDs, numerous regulatory bodies and medical organizations from around the world issued guidance on appropriate use of these agents for symptom control. The US Food and Drug Administration (FDA) issued an advisory in 2005 warning of the risks associated with NSAID use. The FDA recommended using “the lowest effective dose for the shortest duration consistent with individual patient treatment goals.”<sup>9</sup> A few months later, the European Medicines Agency issued a press release recommending that patients “take the lowest effective dose of non-selective NSAIDs for the shortest time necessary to control symptoms.”<sup>10</sup>
Other regulatory bodies issued similar recommendations,\(^{11,12}\) as did several medical organizations, including the American College of Rheumatology and the American Gastroenterological Association.\(^{13,14}\) A consistent message from all of these organizations is that NSAIDs are effective in treating pain, but should be used at the lowest effective dose for the shortest time necessary. The Table provides a summary of these recommendations.\(^{9-17}\)

### Strategies for Dose Reduction

Until recently, the only option for lower-dose oral NSAID use was for physicians to offer a lower dose of an existing standard NSAID formulation. However, this approach could lead to suboptimal pain management.\(^7\)

One novel approach to improving safety through lower dosing involves the use of a new technology. This technology relies on a manufacturing process that can produce drug particles that are approximately 10 times smaller than conventional drug particles.\(^{18}\) The decreased particle size increases the total surface area of the particle, which allows for faster dissolution of the drug.\(^{19}\)

### Conclusion

Although NSAIDs are associated with serious GI, CV, and renal adverse events, these side effects tend to occur most often at high NSAID doses. Physicians should also be mindful that the increased risks are present even with short-term therapy. Utilizing low NSAID doses for the shortest duration necessary to control symptoms, in accordance with regulatory and medical society recommendations, may lead to better outcomes by mitigating the risk for potentially serious side effects. For patients at risk of developing NSAID-associated side effects, additional risk reduction may be obtained by selecting an NSAID with a minimal GI or vascular risk profile. Use of new NSAID formulations is also an approach that could provide effective pain relief at low doses.

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REFERENCES


