The Temporal Relationship Between NSAIDs and Risk of Gastrointestinal, Cardiovascular, and Renal Events: A Systematic Review

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BACKGROUND
Overview of NSAIDs
Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat pain associated with both acute and chronic conditions. More than 70 million NSAID prescriptions and 30 billion over-the-counter NSAID tablets are sold annually in the United States. NSAIDs are divided into two major classes: nonselective NSAIDs, which inhibit both COX-1 and COX-2 enzymes, and COX-2 inhibitors, which were developed to mitigate the adverse gastrointestinal (GI) side effects associated with conventional NSAIDs. However, COX-2 inhibitors have been associated with an increased risk of cardiovascular (CV) events.

Evidence suggests that even a short-term use of NSAIDS can increase the risk of cardiovascular events; therefore, use should be limited to the shortest duration possible, especially in individuals with known risk factors.

FDA Black Box Warning and Medication Guide
As early as April 2002, the Division of Drug Risk Management within the Food and Drug Administration (FDA) issued a memorandum about the GI toxicity of NSAIDs and its occurrence early in the course of therapy. In 2005, the FDA required a boxed warning and a medication guide for all marketed NSAIDs, highlighting the potential for increased risk of CV events, as well as serious and potentially life-threatening GI bleeds. Additionally, the FDA mandated that information be provided to all patients, highlighting the importance of using the lowest effective dose for the shortest duration.

OBJECTIVE
To perform a systematic review of the literature evaluating the temporal relationship between NSAID use and GI, CV, and renal events.

METHODS
Data Sources
A PubMed literature search strategy with the following limits was prepared to support the literature reviews:

• Conducted in humans
• Published in English language
• No date limit was applied to the literature search.

Study Selection Process
• Level 1 screening was performed to identify titles and abstracts to determine their eligibility for inclusion based on the criteria provided in Table 1.
• Full-text versions of articles deemed potentially eligible for inclusion were then obtained for level 2 screening; their eligibility for inclusion was based on the same criteria.
• Two staff members performed each level screening; discrepancies were addressed by a third reviewer, as necessary.

RESULTS
Literature Review
A total of 16 full-text articles were selected for inclusion in the report (Table 1 and Table 2): GI (6), CV (6), and renal (4).

Table 1. Articles Selected for Inclusion in Full Report

Study
Ansell et al.,2008
Bueno et al.,2010
Baraf et al.,2007
Bak et al.,2003
Hunt et al.,2005
Helin-Salmivaara et al.,2006
Hunt et al.,2006
Helin-Salmivaara et al.,2007
Schneider et al.,2009
Reasons for exclusion:
• Population (n = 127)
• Interventions (n = 16)
• Study design
• Observational studies
• Retrospective studies
• Preclinical studies
• Clinical trials
• Randomized controlled studies
• Cohort studies
• Case-control studies
• Prospective studies
• Retrospective studies

Reasons for inclusion:
• Level 1 criteria
• Prevalence of GI complications
• Temporal relationship
• Prevalence of CV complications
• Temporal relationship
• Prevalence of renal complications
• Temporal relationship

Table 2. Articles Selected for Inclusion in Full Report

Study
Ansell et al.,2008
Bueno et al.,2010
Baraf et al.,2007
Bak et al.,2003
Hunt et al.,2005
Helin-Salmivaara et al.,2006
Hunt et al.,2006
Helin-Salmivaara et al.,2007
Schneider et al.,2009

OBJECTIVE
To perform a systematic review of the literature evaluating the temporal relationship between NSAID use and CV events. CV events appeared the highest risk among the three endpoints.

RESULTS
• Three studies were identified evaluating the temporal relationship between use of NSAIDs and acute renal failure; one study evaluated acute tubular interstitial nephritis.
• Acute administration of diclofenac has a rapid, profound, negative impact on renal function in patients with heart failure, specifically, significant decrease in glomerular filtration rate, urine flow, and excretion rates of sodium and potassium in patients with congestive heart failure treated with an ACE inhibitor (P < 0.05).
• Celecoxib and rofecoxib have a relatively short median time to onset of adverse renal events from the start of therapy: 18 days and 10 days, respectively.
• The risk of acute renal failure for all NSAIDs combined was highest within 30 days of treatment initiation (adjusted rate ratio, 2.06; 95% CI, 1.69-2.46). Ten studies were evaluated to determine the risk of ischemic heart disease when two studies were excluded for the following reasons:

DISCUSSION
The temporal relationship between NSAID use and risk of an adverse event is complex due to heterogeneity of study methodology. The risk of developing GI adverse events was greatest in current users and was elevated over the first 30 days and up to 12 weeks of treatment. Risk remained constant over the first year of treatment but quickly returned to baseline after NSAID discontinuation.

Our research yielded limited findings pertaining to the temporal relationship between NSAID use and CV events. CV events appeared to occur somewhat earlier than previously reported, with the highest risk occurring within the first few weeks and decreasing as treatment duration increased. Acute renal failure has a fairly rapid onset upon administration of first dose but was often reversible upon discontinuation of the NSAID. Evidence suggests an increase in the risk of acute renal failure with any NSAID within 1 month of a first prescription. A shorter median time of 10 to 18 days of onset was also reported.

LIMITATIONS
Few studies were identified assessing the temporal relationship between NSAID use and GI, CV, and renal harm. Across all studies reviewed, there was a lack of specific assessment of when the event occurred and a large variability of the study periods by event. Most studies were retrospective analyses, which have inherent limitations such as unmeasured events or data availability pertaining to confounders such as patient risk factors, use of over-the-counter NSAIDs, and adequate power to assess differences.

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CONCLUSION
In assessing the temporal relationship with NSAIDs to the development of GI and renal adverse events, there is significant heterogeneity in measurement, although a temporal relationship was reported in all three categories.

REFERENCES
Please see handout.

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