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

Kati Copley-Merriman,[1] Bimpe Olanrewaju,[1] Susan Hogue[2]

[1]RTI Health Solutions, Ann Arbor, MI, United States; [2]RTI Health Solutions, Research Triangle Park, NC, United States

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.[1]

NSAID Classes and COX Enzymes

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 result in an increased risk of adverse events; therefore, use should be limited to the shortest duration possible, especially in individuals with known risk factors.[2]

FDA Black Box Warning and Medication Guide

As early as April 2002, the Division of Drug Risk Evaluation 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.[3] 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.[4] Additionally, the FDA mandated that information be provided to all patients, highlighting the importance of using the lowest effective dose for the shortest duration.[4]

OBJECTIVE

- To perform a systematic review of the literature evaluating the temporal relationship between start of treatment with NSAIDs and GI, CV, and renal events.

METHODS

Data Source

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, if necessary.

Inclusion and Exclusion Criteria

Table 1. Inclusion and Exclusion Criteria (Defined a Priori)

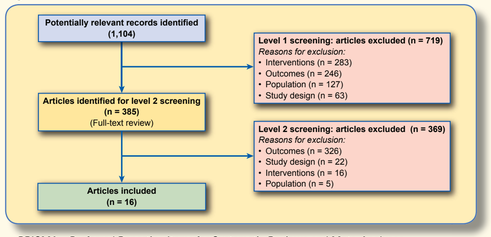
	Inclusion Criteria	Exclusion Criteria
Population	• Adult patients (aged ≥ 18 years) • History of NSAID use due to acute or chronic pain	• Pediatric patients (aged < 18 years) • No history of NSAID use
Study design	• Clinical trials • Cross-sectional studies • Cohort studies • Case-control studies • Retrospective studies • Observational studies • Systematic literature reviews • Meta-analyses • Treatment guidelines	• Preclinical studies (animal) • Commentaries • Letters • Editorials • Consensus statements • Non–English language articles
Outcomes	• GI events (nausea, vomiting, dyspepsia, gastric ulceration, GI bleed) • CV events (myocardial infarction, stroke, angina, heart failure, hypertension) • Renal event (salt and water retention, interstitial nephritis, nephritic syndrome, acute renal failure, acute tubular necrosis)	• Outcomes other than those specified as inclusion criteria

RESULTS

Literature Review

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

Figure 1. PRISMA Flowchart



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

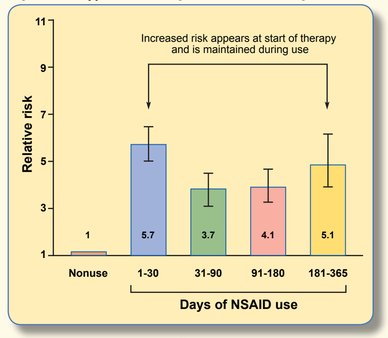
Table 2. Articles Selected for Inclusion in Full Report

Study	Adverse Event Reported in Study		
	GI	CV	Renal
Ahmad et al., 2002[5]			✓
Ailabouni and Eknoyan, 1996[6]			✓
Bak et al., 2003[7]		✓	
Baraf et al., 2007[8]		✓	
Bueno et al., 2010[9]		✓	
Garcia Rodriguez et al., 1998[10]	✓		
Garcia Rodriguez and Hernandez-Diaz, 2001[11]	✓		
Helin-Salmivaara et al., 2006[12]		✓	
Helin-Salmivaara et al., 2007[13]	✓		
Hernandez-Diaz and Rodriguez, 2000[14]	✓		
Hunt et al., 2003[15]	✓		
Juhlin et al., 2004[16]			✓
Levesque et al., 2006[17]		✓	
Richy et al., 2004[18]	✓		
Schjerning Olsen et al., 2011[2]		✓	
Schneider et al., 2006[19]			✓

GI Event

- Four studies and two systematic reviews were identified evaluating the temporal relationship between NSAID use and GI events.
- Risk was greatest in current users,[14] and GI events generally occurred within the first 30 days of treatment.[10,11,14]
- The risk of developing NSAID-induced upper GI complications is generally higher soon after initiating treatment and slowly decreases as treatment duration increases.[10,11,14]
- Risk remained constant over the first year and quickly returned to baseline within 2 months of NSAID discontinuation.[11,14]

Figure 2.
High Risk of Upper GI Bleeding is Maintained During NSAID Use

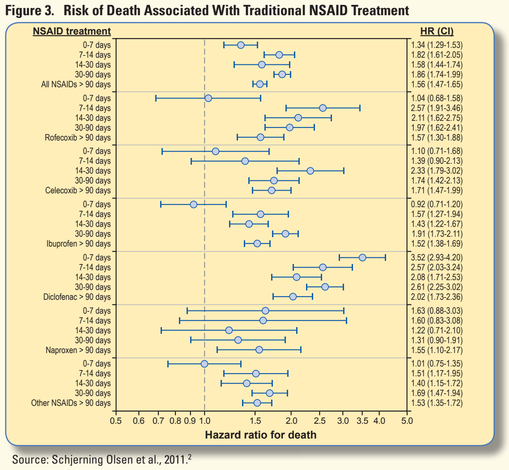


Source: Hernandez-Diaz et al., 2000.[14]

CV Event

- Six studies were included in the CV assessment: four retrospective studies, one randomized clinical trial (occurrence of CV adverse events was a secondary endpoint), and one prospective survey.
- Even short-term use of NSAIDs was associated with increased risk of death from MI (Figure 3), specifically a statistically significant increased risk starting early in and persisting throughout the treatment.[2]
- The risk of developing CV adverse events was greater in patients with a history of ischemic heart disease.[8,9]
- The risk of first myocardial infarction was more evident early in the treatment period and remained elevated for up to a week after the last prescription.[13,17]
- Only one study[17] assessed the time to CV event in a specific number of days, finding that events occurred a median of 9 days from first time prescription (rofecoxib). Risk remained elevated for the first 7 days after discontinuation and returned to baseline between days 8 and 30.

Figure 3. Risk of Death Associated With Traditional NSAID Treatment



Source: Schjerning Olsen et al., 2011.[2]

Renal Event

- 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 ($P < 0.05$).[16]
- 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.[5]
- The risk of acute renal failure for all NSAIDs combined was highest within 30 days of treatment initiation (adjusted rate ratio, 2.05; 95% CI, 1.61-2.60) and receded thereafter. There was a twofold increase in the risk of acute renal failure with any NSAID within 1 month of a first prescription; this risk decreased after at least 30 days without an NSAID prescription (Table 3).[19]

Table 3. Descriptive Statistics of Cases of NSAID-Induced Renal Failure

	Celecoxib (n = 122)	Rofecoxib (n = 142)[a]
Age (years)		
Median	72	75
Mean	69.7	73.1
Range	14-101	33-101
Dose (mg/day)		
Median	200	25
Mean	224	26.6
Range	100-800	12.5-50
Time to onset (days)		
Mean	18	10
Median	41.7	32.7
Range	1-300	1-450
Cases with onset at		
≤ 3 days	4	32
≤ 14 days	33	65

Source: Ahmad et al., 2002.[5]

[a] Withdrawn from worldwide marketplace.

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 NSAID 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 also was reported.

LIMITATIONS

Few studies were identified assessing the temporal relationship between NSAID use and risk of 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.

FUNDING

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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.

CONTACT INFORMATION

Kati Copley-Merriman
Vice President, Market Access and Outcomes Strategy

RTI Health Solutions
3005 Boardwalk Street, Suite 105
Ann Arbor, MI 48108

Phone: +1.734.213.5429
Fax: +1.734.213.6169
E-mail: kcmerriman@rti.org

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