Analyzing the Risk of Adverse Events Associated with NSAIDs

James R. Miller DDS, MSD, PhD

State Oral Health Director
Indiana State Department of Health
Indianapolis, Indiana

Visiting Scholar
Indiana University School of Dentistry
Indianapolis, Indiana

Clinical Assistant Professor
Marian University College of Osteopathic Medicine
Indianapolis, Indiana

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Objectives

- Present an example of determining categories of baseline risk and using these to develop guidelines for prescribing NSAIDs (or not prescribing NSAIDs) while reducing the risk of adverse events
- Present basic concepts of risk useful for understanding adverse events associated with NSAIDs
- Present data from a meta-analysis of adverse events associated with NSAIDs that illustrate these concepts of risk

Source Material

(1) Lanza FL, et al. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastoenterol* 2009;104:728-238

(2) Coxib and traditional NSAID Trialists' Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomized trials. www.thelancet.com. 2013;382:769-779

(1) Lanza Article

Risk Categories and Prescription Guidelines

- Lanza et al. published an article in 2009 which included categories of risk for a patient developing an ulcer while taking an NSAID
- These categories of risk included two sets of categories:
  - One set of categories of risk, specifically related to the development of an ulcer with NSAIDs, is based on age, medical history, and treatment plan
  - The other set of categories of risk is based on a factor that generally indicates CV risk, the use of *low-dose aspirin (ASA)*
- Prescription guidelines for NSAIDs (or other medications) were developed based on these two sets of categories of risk

Reference: Lanza FL, et al. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastoenterol* 2009;104:728-238

Prescription Guidelines

- These prescription guidelines were written by Lanza et al., based on the analysis of epidemiological data available in 2009

- As the authors stated, guidelines may change as more data become available

GI Risk Factors	

Significant Risk Factor

* **HX: Complicated ulcer** (especially recent)

Less Significant Risk Factors

* AGE: > 65
* HX: Uncomplicated ulcer
* MEDS: Aspirin, Corticosteroids, Anticoagulants
* TX: Proposed High Dose NSAIDs

Note

Patients with HX of ulcer (complicated or uncomplicated) should be tested for H. pylori and, if present, treated

GI Risk Categories	
* **LOW**	***None*** of the *above risk factors*
* **MODERATE**	***1 or 2*** *Less Significant Risk Factors*
* **HIGH**	***HX of complicated ulcer*** *(Significant Risk Factor)* *OR* ***3 or more*** *Less Significant Risk Factors*

Adapted from: Lanza FL, et al. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastoenterol* 2009;104:728-238

CV Risk Factor	

* MEDS: Use of *low-dose ASA*

CV Risk Categories	
* **LOW**	***Not using*** *low-dose ASA*
* **HIGH**	***Using*** *low-dose ASA*

**Guidelines for Prevention of NSAID-related Ulcer Complications

		GI Risk		
		LOW	**MODERATE**	**HIGH**
CV Risk	**LOW**	**NSAID alone** > least ulcerogenic > lowest dose	**NSAID + PPI/misoprostol**	**Alternative therapy** *OR* **Coxib + PPI/misoprostol**
	HIGH	**Naproxen + PPI/misoprostol**	**Naproxen + PPI/misoprostol**	**Alternative therapy *only*** *(AVOID NSAIDS or Coxibs)*

There could be other risks associated with taking NSAIDs that are not addressed by these guidelines

** Adapted from: Lanza FL, et al. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastoenterol* 2009;104:728-238

(2) *Lancet* Article

Basic Concepts of Risk

- A *Lancet* article was published in 2013 which presents a meta-analysis of the adverse events associated with the use of NSAIDs, specifically with Coxibs and various traditional NSAIDs
- The article presents an opportunity to illustrate some basic concepts of risk and the utility of these concepts in choosing appropriate NSAIDs

Basic Concepts of Risk

- To make a clinical decision about whether to prescribe a NSAID, it would be beneficial to have an understanding of the benefits and risks associated with a particular medication for a particular patient

- This presentation presents some basic concepts of understanding risk and then uses the *Lancet* article to provide examples of these concepts

Measurement of Risk

- In context of the *Lancet* article, the measurement of risk includes the number of individuals with a first time adverse event within a group of individuals, at risk for that event, over a certain period of time

- To understand the risk for an adverse event associated with a specific NSAID, the risks in two groups are compared

Comparison of Risk for an Adverse Event with a NSAID among Two Groups

Exposed Group

- Group of individuals taking a NSAID

Non-exposed Group (“placebo group”)

- Group of individuals not taking a NSAID

Method of Comparing Risks

- **Relative Risk**
- **Excess Risk**

  Excess risk is also referred to as **absolute risk** or **attributable risk** (“*due to*”)

Relative Risk

- In the *Lancet* article, relative risk is a relative comparison of the risk of having an adverse event when taking a NSIAD ("exposed") to the risk of having an adverse event when not taking a NSAID ("non-exposed")
- Relative risk is the risk among the "exposed" *divided* by the risk among the "non-exposed", producing a ratio without a unit of measurement
- Relative risk provides a relative likelihood of an individual having an adverse event

Note: In the *Lancet* article, direct comparisons of NSAIDs to a placebo group were not possible for all NSAIDs; however, the authors were able to statistically use the available placebo group for *indirect* comparisons of various NSAIDs to the available placebo group (see article for details).

Excess Risk

- In the *Lancet* article, excess risk is an absolute comparison of the risk of having an adverse event when taking a NSAID ("exposed") to the risk of having an adverse event when not taking a NSAID ("non-exposed")
- Excess risk is the risk among the "exposed" *minus* the risk among the "non-exposed", producing a risk with units of measurement
- Excess risk provides the absolute risk an individual will have for an adverse event that is *due to* a NSAID

Note: In the *Lancet* article, direct comparisons of NSAIDs to a placebo group were not possible for all NSAIDs; however, the authors were able to statistically use the available placebo group for *indirect* comparisons of various NSAIDs to the available placebo group (see article for details).

Risk *due to* taking a NSAID

In the *Lancet* article:

- Excess risk was used to measure the risk *due to* taking a NSAID
- Excess risk is provided for coxibs, diclofenac, ibuprofen, and naproxen

Risk *due to* taking a NSAID

Excess Risk = Risk *due to* taking a NSAID

Note:

Excess Risk = **Risk in *Exposed* Group** – **Risk in *Non-exposed* Group**

Risk in *Exposed* Group = Risk *due to* taking a NSAID + Inherent Risk

Risk in *Non-exposed* Group = Inherent Risk

Excess Risk = (Risk *due to* taking a NSAID + Inherent Risk) – (Inherent Risk)

Excess Risk = Risk *due to* taking a NSAID

Examples

- The *Lancet* article presents a meta-analysis of the adverse events associated with the use of NSAIDs
- This article uses both relative risk and excess risk to explain the risk for adverse events associated with the use of NSAIDs
- Examples from this article will be used to illustrate the utility of using knowledge of excess risk to make clinical decisions when prescribing specific NSAIDs

Adverse Events with NSAIDs mentioned in the *Lancet* Article

Major Vascular Events

Heart:

- Myocardial infarction
- Coronary death

CNS:

- Stroke
- Stroke death

GI Complications

Upper GI:

- Bleed
- Perforation
- Obstruction

Lower GI:

- (None measured)

Relative Risk (RR) for a Major Vascular Event associated with various NSAIDs

coxibs **	RR = 1.37	p < 0.01
diclofenac **	RR = 1.41	p < 0.01
ibuprofen **	RR = 1.44	p = 0.14
naproxen	RR = 0.93	p = 0.66

- The relative risk for having a major vascular adverse event were elevated for coxibs and diclofenac
- The relative risk for having a major vascular adverse event appears elevated for ibuprofen, but was not statistically significant
- The relative risk for Naproxen indicates it is not associated with a major cardiovascular adverse event

Some of the adverse events among patients taking coxibs, diclofenac, and ibuprofen were **fatal ****

Relative Risk (RR) for a GI Complication associated with various NSAIDs

coxibs	RR = 1.81	p < 0.01
diclofenac	RR = 1.89	p ~ 0.01
ibuprofen	RR = 3.97	p < 0.01
naproxen	RR = 4.22	p < 0.01

The relative risk for having a GI complication were elevated for all four medications

Almost all of the GI complications among patients taking one of these four NSAIDs were **non-fatal**

Excess Risk

- In the *Lancet* article, the authors present an interesting summary of the excess risks associated with major vascular events and GI complications
- These risks are stratified according to categories of baseline risk for a major vascular events or a GI complication

Note: How these categories of baseline risk were determined in the *Lancet* article was not apparent

Excess Risk
Fatal and Non-Fatal Adverse Events *by* Categories of Baseline Risk

The **Baseline Risk** is the number of individuals with an adverse event per 1,000 per year, among individuals **not** taking a NSAID

The **Excess Risk** is the number of individuals with an adverse event per 1,000 per year, among individuals taking a NSAID, **which is *due to* taking a NSAID**

		Major vascular events		Upper GI complications	
	Baseline Risk	High	Low	Moderate	Low
		20	5	5	2
		Excess Risk		**Excess Risk**	
Coxib vs. placebo	Non-fatal	7	2	4	2
	Fatal	2	1	0	0
	Total	**9**	**3**	**4**	**2**
Diclofenac vs. placebo	Non-fatal	8	2	4	2
	Fatal	2	1	0	0
	Total	**10**	**3**	**4**	**2**
Ibuprofen vs. placebo	Non-fatal	9	2	15	6
	Fatal	3	1	negligible	0
	Total	**12**	**3**	**15**	**6**
Naproxen vs. placebo	Non-fatal	-1	0	16	6
	Fatal	0	0	negligible	0
	Total	**-1**	**0**	**16**	**6**

Notes: The values presented are approximations

Excess Risk
by Categories of Baseline Risk

- For each NSAID, the excess risk for a major vascular event varies according to the category of baseline risk of a patient for a major vascular event
- For each NSAID, the excess risk for a GI complication varies according to the category of baseline risk of a patient for a GI complication

Fatalities

- Most adverse events were **non-fatal**
- Some adverse events were **fatal**
  - **Most fatal adverse events** were associated with a **high baseline risk of a major vascular event**, although there were some fatalities even with a low baseline risk of a major vascular event
  - Few fatal adverse events were associated with a high or low baseline risk for GI complications, although those that did occur were mostly in the high-risk group

Different Perspectives

- **Excess risk** is a *difference* between risks and has units of measurement, which *allows calculation of the absolute risk a patient assumes* by taking a NSAID
- **Relative risk** is a *ratio* and has no units of measurement, which *does **not** allow calculation of the absolute risk a patient assumes* by taking a NSAID

Relationship between Excess Risk and Relative Risk

- The **following tables** use the baseline risk and excess risk values from the previous table on excess risk to calculate values for relative risk
- These calculated values for relative risk closely approximate the reported values for relative risk
- The excess risks and relative risks are reported according to categories of baseline risk
  - High or low for a major vascular event
  - Moderate or low for a GI complication

Note: Only ***Total*** excess risks from the previous table are used in the following two tables

Risk of a Major Vascular Event

Risk of Major Vascular Adverse Event	Medication Risk ("exposed") *risk while taking*		Placebo Risk (Baseline Risk) ("non-exposed") *risk while not taking*	**Excess Risk** *risk due to*	**Relative Risk**	
Coxib vs. placebo	29/1000/yr	High	20/1000/yr (2.0% pa)	9/1000/yr	29/20 =	1.45
	8/1000/yr	Low	5/1000/yr (0.5% pa)	3/1000/yr	8/5 =	1.60
Diclofenac vs. placebo	30/1000/yr	High	20/1000/yr (2.0% pa)	10/1000/yr	30/20 =	1.50
	8/1000/yr	Low	5/1000/yr (0.5% pa)	3/1000/yr	8/5 =	1.60
Ibuprofen vs. placebo	32/1000/yr	High	20/1000/yr (2.0% pa)	12/1000/yr	32/20 =	1.60 ←
	8/1000/yr	Low	5/1000/yr (0.5% pa)	3/1000/yr	8/5 =	1.60 ←
Naproxen vs. placebo	19/1000/yr	High	20/1000/yr (2.0% pa)	neg. 1/1000/yr	19/20 =	0.95
	5/1000/yr	Low	5/1000/yr (0.5% pa)	0/1000/yr	5/5 =	1.00

For each of the NSAIDs, the **relative risks** do not vary (statistically) across baseline risk categories, while the **excess risks** do vary.

See **arrows** for one example.

Risk of a GI Complication

Risk of GI Complication	Medication Risk ("exposed") *risk while taking*	Placebo Risk (Baseline Risk) ("non-exposed")		Excess Risk *risk due to*	Relative Risk	
Coxib vs. placebo	9/1000/yr	Moderate	5/1000/yr (0.5% pa)	4/1000/yr	9/5 =	1.80
	4/1000/yr	Low	2/1000/yr (0.2% pa)	2/1000/yr	4/2 =	2.00
Diclofenac vs. placebo	9/1000/yr	Moderate	5/1000/yr (0.5% pa)	4/1000/yr	9/5 =	1.80
	4/1000/yr	Low	2/1000/yr (0.2% pa)	2/1000/yr	4/2 =	2.00
Ibuprofen vs. placebo	20/1000/yr	Moderate	5/1000/yr (0.5% pa)	15/1000/yr	20/5 =	4.00
	8/1000/yr	Low	2/1000/yr (0.2% pa)	6/1000/yr	8/2 =	4.00
Naproxen vs. placebo	21/1000/yr	Moderate	5/1000/yr (0.5% pa)	16/1000/yr	21/5 =	4.20
	8/1000/yr	Low	2/1000/yr (0.2% pa)	6/1000/yr	8/2 =	4.00

For each of the NSAIDs, the **relative risks** do not vary (statistically) across baseline risk categories, while the **excess risks** do vary.

See **arrows** for one example.

Choice of NSAID

based on *Lancet* Article

- In a patient with a high baseline risk of a major vascular event
  - Naproxen might be acceptable for pain, while coxib(s), diclofenac, and ibuprofen likely should be avoided
- In a patient with a high baseline risk of a GI complication
  - Coxib(s) and diclofenac might be acceptable for pain, while ibuprofen and naproxen likely should be avoided

Notes for *Lancet* Article

- Excess risk varies considerably according the category of baseline risk for a patient
- Relative risk does not vary much according to the category of baseline risk for a patient
- Excess risk and relative risk provide different information
- Excess risk can be very helpful when deciding whether to prescribe a NSAID or not, and if so what NSAID to prescribe

SUMMARY

- Although NSAIDs are effective pain medications and are widely used, they are not without risk
- An evaluation of a patient's baseline risk for a major vascular event and a GI complication is prudent prior to prescribing a NSAID
- It is also prudent to carefully consider all of a patient's current medical conditions and medications before prescribing a NSAID
- Consultation with a patient's physician is often advisable