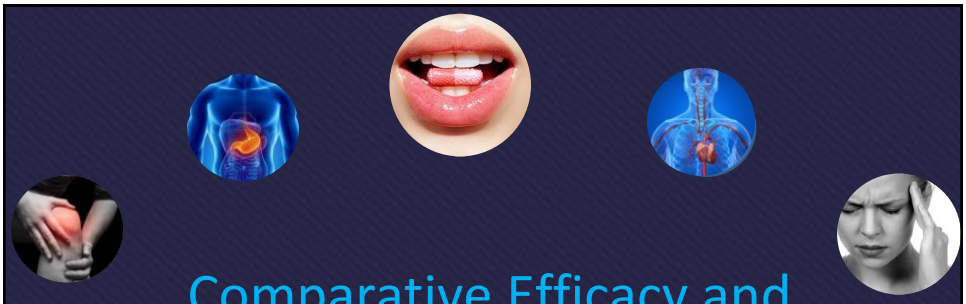

Comparative Efficacy and Toxicity of NSAIDs

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Division of Rheumatology
Department of Medicine and Therapeutics
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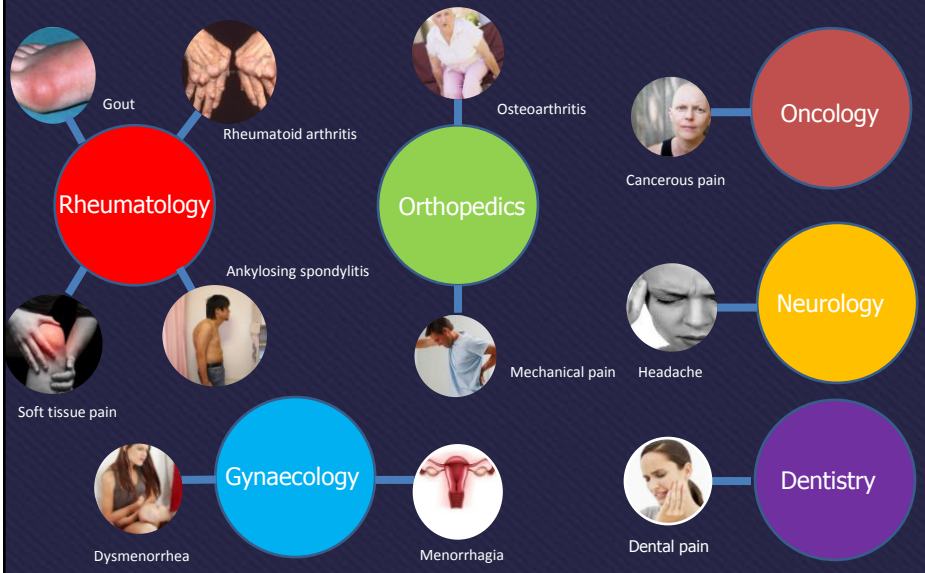
NSAID Consumption in the US

- ***17 MILLION*** Americans use various NSAIDs on a daily basis
- Number of prescriptions for older patients is approximately 3.6 fold higher than that for younger patients
- ***5% hospital admission*** are related to adverse effects of NSAIDs

NSAID therapeutic use



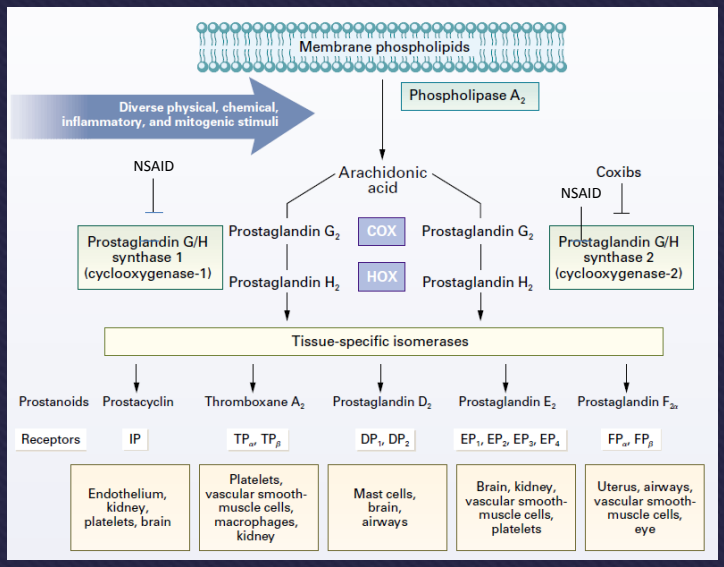
Questions to be answered…

- Are there clinically importance differences in the efficacy and toxicity between the different NSAIDs?
- If there are differences, which are the ones that are more effective and associated with fewer adverse effects?
- What are the effective therapeutic approaches that could reduce the adverse effects of NSAIDs?

Themes - NSAIDs

- Mechanism of action
- Classification
- Comparative analgesic efficacy
- Comparative gastrointestinal (GI) toxicity
- Comparative cardiovascular (CV) toxicity
- Strategies for prevention of toxicity

NSAID - Mechanism of action



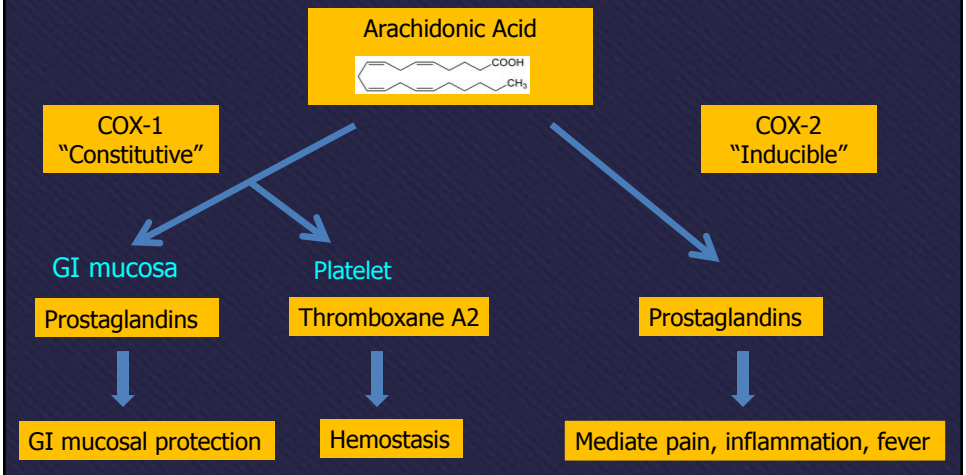
Garret A et al. N Engl J Med 2001;345:433-442.

Functions of cyclo-oxygenase (COX)

COX-1: Constitutive	COX-2: Inducible
• Present in every organ	• Present in inflammatory and neoplastic sites • Also in small intestine, kidney, brain, uterus, ovary

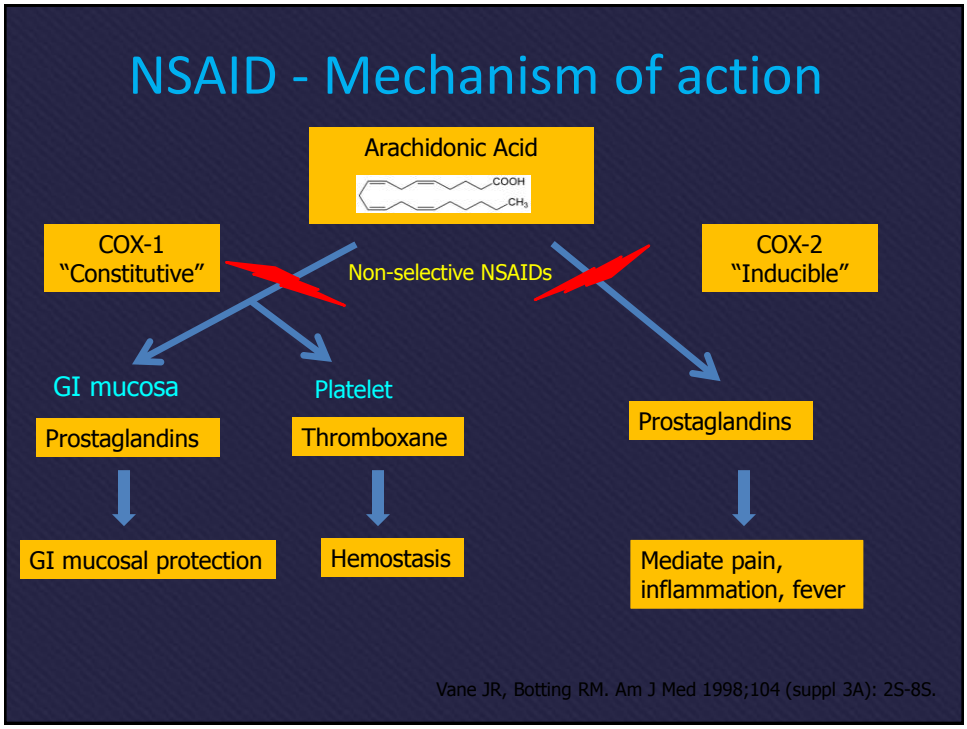
• Homeostasis
  • Protection of gastric mucosa
  • Platelet activation
  • Renal functions
  • Macrophage differentiation
	• Pathologic:
	  • Inflammation
	  • Pain
	  • Fever
	• Tissue Repair
	• Physiologic:
	  • Reproduction
	  • Renal function

NSAID - Mechanism of action



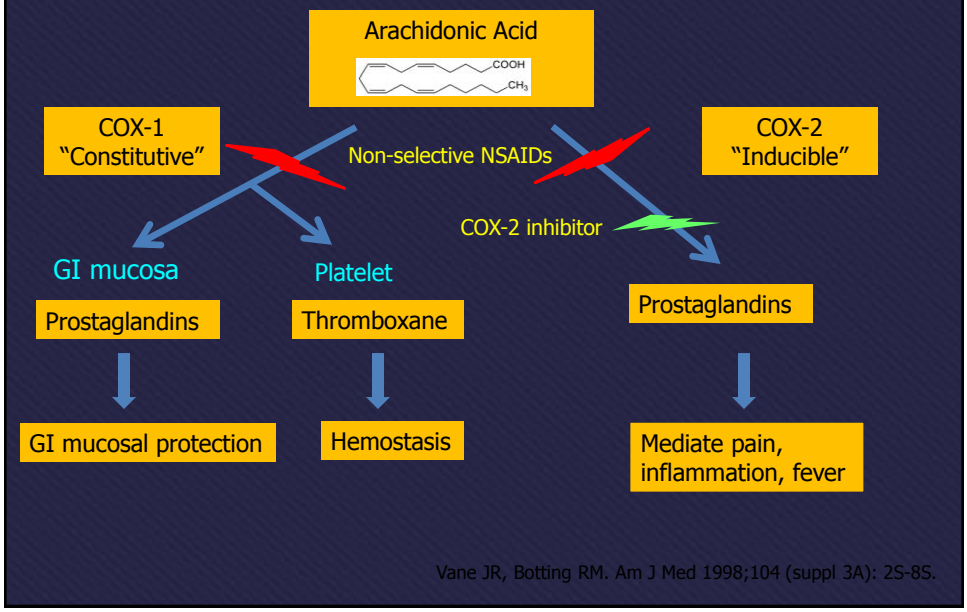
Vane JR, Botting RM. Am J Med 1998;104 (suppl 3A):2S-8S.

NSAID - Mechanism of action



Vane JR, Botting RM. Am J Med 1998;104 (suppl 3A): 2S-8S.

NSAID - Mechanism of action



Vane JR, Botting RM. Am J Med 1998;104 (suppl 3A): 2S-8S.

Classification of NSAIDs by chemical structures

Propionic acid

Ibuprofen (Advil, Brufen)
Naproxen (Naprosyn, Synflex)
Ketoprofen (Oruvail)

Acetic acids

Diclofenac (Arthrotec, Cataflam, Voltaren)
Indomethacin (Indocid)
Sulindac (Clinoril)
Tolmetin

Oxicams

Meloxicam (Mobic)
Piroxicam (Feldene)

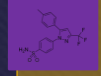
Fenamic acid

Mefenamic

Non-acidic

Nabumetone

COX-2 inhibitors



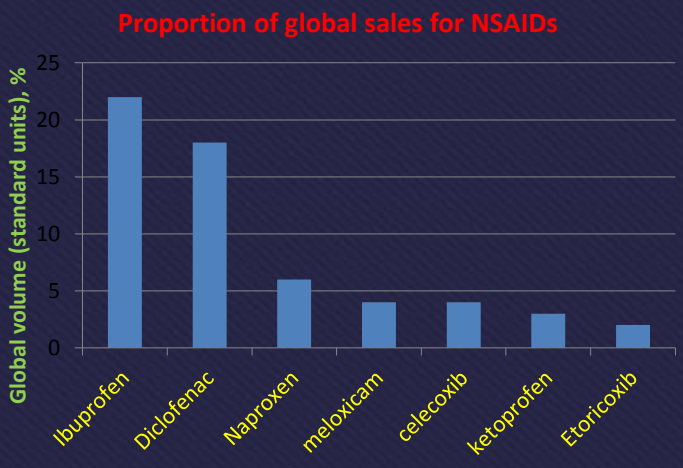
Celecoxib (Celebrex)
Etoricoxib (Arcoxia)

Classification of NSAID by pharmacokinetic properties

NSAID	Bio-availability (%)	Half-life (hr)	Volume of distribution	Clearance	Peak (hr)	Renal elimination	Clinical dose (mg)
Ibuprofen	>80	2	0.15 L/kg	3.0-3.5 L/h	1-2	45-79	1200-3200
Diclofenac	50-60	2	0.1-0.2 L/kg	21.0 L/h	2	65	100-150
Naproxen	95	12-17	0.16 L/kg	0.13 mL/min/kg	2-4	95	500-1000
Meloxicam	89	15-20	10L	0.4-0.5 L/h	4-5	50	7.5-15.0
Celecoxib	Not specified	11	400L	27.7 L/h	3	27	200
Ketoprofen	90	2.1	0.1 L/kg	6.9 L/h	≤2	80	200-300
Etoricoxib	100	22	120L	50 mL/min	1	75	60

Philip G. Conaghan. Rheumatol Int 2012;32:1491-1502.

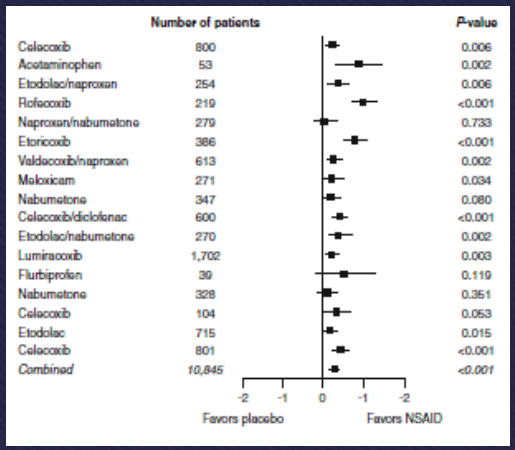
Epidemiology of NSAID prescription



IMS Health (2008) IMS MIDAS Quantum based on selected markets

Comparative analgesic efficacy: Placebo vs. NSAIDs

NSAIDs have demonstrated short-term efficacy compared with placebo in the treatment of OA



Bjordal JM et al. BMJ 2004;329:1317.

Comparative analgesic efficacy: non-selective (ns) NSAIDs

Agency for Health-care Research and Quality Effective Healthcare Program (UK):

- No clear differences in efficacy among nsNSAIDs at standard doses in treatment of knee, back, or hip pain

Chou R et al. http://effectivehealthcare.ahrq.qov/repFliles/AnalgesicsFinal.pdf. Accesssed 29 June 2010

Chou R et al. http://www.ncbi.nlm.nih.qov/pubmed/20496448. Accessed 2 July 2010.

Comparative analgesic efficacy: COX-2 inhibitors vs. nsNSAIDs

- No significant differences in efficacy between COX-2 inhibitors and nsNSAIDs in treatment of knee, back, or hip pain

Chou R et al. http://effectivehealthcare.ahrq.qov/repFliles/AnalgesicsFinal.pdf. Accesssed 29 June 2010

Comparative analgesic efficacy: COX-2 inhibitors vs. nsNSAIDs

- COX-2 inhibitors had equivalent efficacy to nsNSAIDs for treatment of rheumatoid arthritis (RA) and osteoarthritis (OA)
  - Celecoxib 200-800 mg/day
  - Naproxen 1000 mg/day
  - Diclofenac 100-150 mg/day
  - Ibuprofen 2400 mg/day
  - Etoricoxib 60-120 mg/day

Chen Y-F et al. Health Technol Assess 2008; 12:1-278.

Comparative analgesic efficacy Celecoxib vs. nsNSAIDs

In Successive Celecoxib Efficacy and Safety Study (SUCCESS):

- Celecoxib 200-400 mg/day have efficacy comparable to naproxen 1000 mg/day and diclofenac 100 mg/day for treatment of more than 13,000 patients with OA over 12 weeks

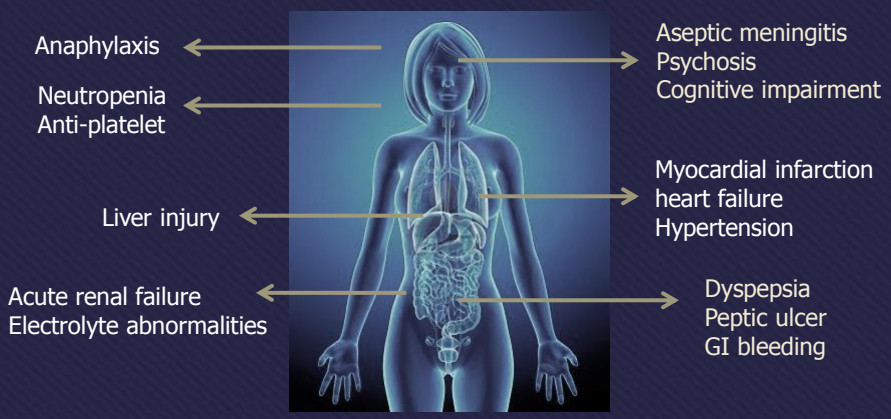
Singh G et al. 2006. Am J Med 119;255-266.

Comparative analgesic efficacy: Etoricoxib vs. nsNSAIDs

- Etoricoxib 90-120 mg/day have greater efficacy compared with naproxen 1000 mg/day over 12 weeks, but similar efficacy over 121 weeks

Matsumoto et al. Curr Med Res Opin 2007;23:2259-2268.

Overview of adverse effect of NSAIDs



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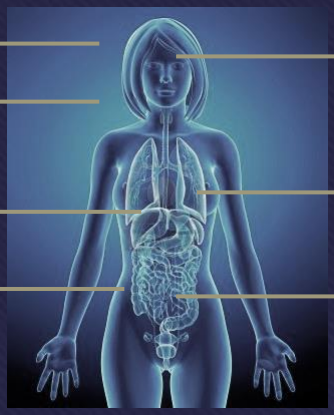


Anaphylaxis

Neutropenia
Anti-platelet

Liver injury

Acute renal failure
Electrolyte abnormalities

Aseptic meningitis
Psychosis
Cognitive impairment

Myocardial infarction
heart failure
Hypertension

Dyspepsia
Peptic ulcer
GI bleeding

GI toxicity of NSAID

60%
Dyspepsia

10-30%
Endoscopic ulcers

1-2%
Serious ulcer complications

Silverstein FE et al. Ann Intern Med 1995;123:241-249.

Risk stratification for GI toxicity

High risk

1. History of a previously complicated ulcer, especially recent
2. Multiple (>2) risk factors

Moderate risk (1-2 risk factors)

1. Age >65
2. High dose NSAID therapy
3. A Previous history of uncomplicated ulcer
4. Concurrent use of aspirin (including low dose), corticosteroids, anticoagulants

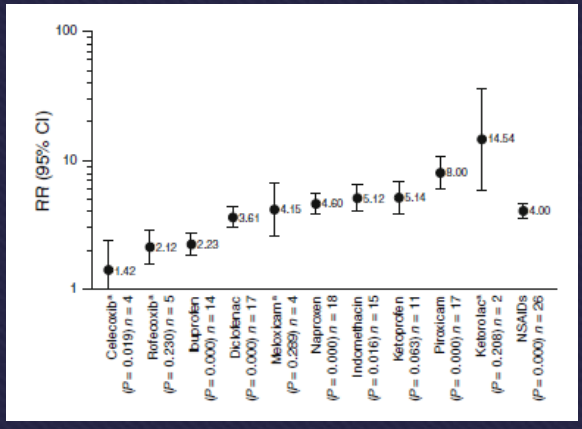
Low risk

1. No risk factors

Helicobacter pylori is an independent and additive risk factor

Frank L. Lanza et al. Am J Gastroenterol 2009;104:728-738.

Comparative GI toxicity



Risk of upper gastrointestinal bleeding/perforation with individual NSAIDs from published studies since 1990

Masso Gonzalez EL et al. Arthritis Rheum 2010;62:1592-1601.

Comparative GI toxicity

	nsNSAID	COX-2 inhibitors
Upper GI bleed or perforation	RR 4.50; 95% CI 3.82, 5.31	RR 1.88; 95% CI 0.96, 3.71

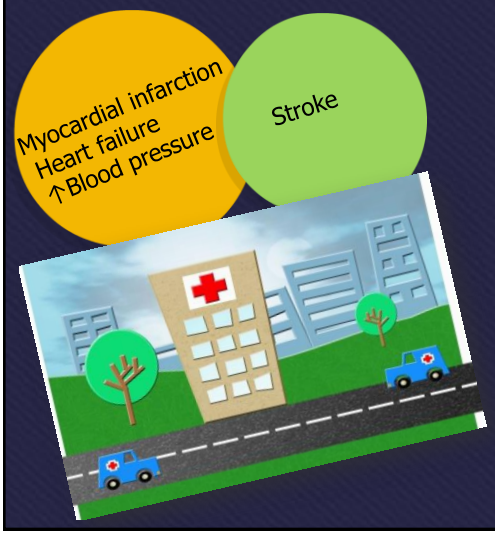
Masso Gonzalez EL et at. Arthritis Rheum 2010:62;1592-1601.

Concomitant use of low-dose aspirin increases the risk of mucosal damage and eliminates the GI benefits of COX-2 inhibitors

	COX-2 inhibitors	Aspirin + COX-2 inhibitors
Upper GI bleed or perforation	RR 0.6; 95% CI 0.4, 0.9	RR 1.9; 95% CI 10, 3.6

Garcia rodriguez LA et al. Gastroenterology 2007;132:498-506.

CV toxicity of NSAID



CV toxicity with nsNSAID

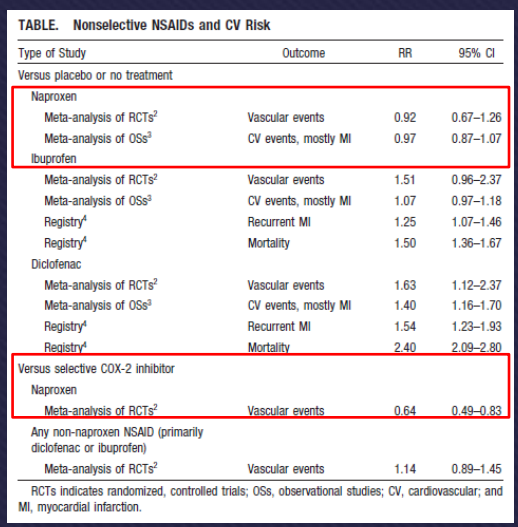
TABLE. Nonselective NSAIDs and CV Risk

Type of Study	Outcome	RR	95% CI
Versus placebo or no treatment			
Naproxen			
Meta-analysis of RCTs[2]	Vascular events	0.92	0.67–1.26
Meta-analysis of OSs[3]	CV events, mostly MI	0.97	0.87–1.07
Ibuprofen			
Meta-analysis of RCTs[2]	Vascular events	1.51	0.96–2.37
Meta-analysis of OSs[3]	CV events, mostly MI	1.07	0.97–1.18
Registry[4]	Recurrent MI	1.25	1.07–1.46
Registry[4]	Mortality	1.50	1.36–1.67
Diclofenac			
Meta-analysis of RCTs[2]	Vascular events	1.63	1.12–2.37
Meta-analysis of OSs[3]	CV events, mostly MI	1.40	1.16–1.70
Registry[4]	Recurrent MI	1.54	1.23–1.93
Registry[4]	Mortality	2.40	2.09–2.80
Versus selective COX-2 inhibitor			
Naproxen			
Meta-analysis of RCTs[2]	Vascular events	0.64	0.49–0.83
Any non-naproxen NSAID (primarily diclofenac or ibuprofen)			
Meta-analysis of RCTs[2]	Vascular events	1.14	0.89–1.45

RCTs indicates randomized, controlled trials; OSs, observational studies; CV, cardiovascular; and MI, myocardial infarction.

McGetitigan P et al. JAMA 2006;296:1633-1644.

CV toxicity with nsNSAID



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RCTs indicates randomized, controlled trials; OSs, observational studies; CV, cardiovascular; and MI, myocardial infarction.

McGetitigan P et al. JAMA 2006;296:1633-1644.

Comparative CV toxicity: nsNSAIDs

- High dose ibuprofen (rate ratio 1.51; 95% CI 0.96, 2.37) and high dose diclofenac (rate ratio 1.63; 95% CI 1.12, 2.37) were associated with a moderately increased risk of any vascular events compared with placebo
- Risks associated with naproxen was substantially lower (rate ratio 0.92; 95% CI 0.67, 1.26)

Kearny PM et al. BMJ 2006;332:1302-1308.

Comparative CV toxicity: Placebo vs. COX-2 inhibitors

- Significant increased risk of myocardial infarction with COX-2 inhibitors compared with placebo

Kearney PM et al. BMJ 2006;332:1302-1308.

Comparative CV toxicity: rofecoxib vs. naproxen

- In Vioxx Gastrointestinal Outcomes Research (VIGOR) study, rofecoxib 50 mg/day was associated with a 4 fold increase in incidence of myocardial infarction compared with naproxen 1000 mg/day in patients with RA

Bombardier C et al. N Engl J Med 2000;369:465-473.

Comparative CV toxicity: rofeoxib vs. naproxen

- In Adenomatous Polyp Prevention On Vioxx (APPROVe) study, rofecoxib 25 mg/day was associated with increased RR of thrombotic events compared with placebo in patients with a history of colorectal adenomas after 18 months of treatment and an increased risk of myocardial infarction after 15 months of treatment

Bresalier RS et al. N Engl J Med 2005;352:1092-1102.


VIOXX® 25 mg
(Rofecoxib Tablets)
MERCK & CO., INC.
Whitehouse Station, NJ 08889
BEXTRA
Valdecoxib


BANNED!
2004
MERCK & CO., INC.
BEXTRA
Valdecoxib

Comparative CV toxicity: Celecoxib

- Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)
- Adenoma Prevention with Celecoxib (APC) study
- Prevention of colorectal Sporadic Adenomatous Polyps (PreSAP) study

  - Celecoxib 200-400 mg/day was associated with a significant and dose-related increase in death from CV causes in APC, but not in PreSAP or ADAPT
  - All 3 studies were subsequently suspended

ADAPT Research Group. PLoS Clin Trials 2006;1:e33.

Bertagnolli MM et al. N Engl J Med 2006;355:873-884.

Arber N et al. N Engl J Med 2006;355:885-895.

Comparative CV toxicity: Etoricoxib

- In a pooled analysis of data from 3 trials in Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program, etoricoxib 60 or 90mg/day was compared with diclofenac 150 mg/day
  - ➢ No significant risk of thrombotic CV events (hazard ratio 0.95; 95% CI 0.81, 1.11)

Cannon CP et al. Lancet 2006;368:1771-1781.

Strategies for prevention of NSAID-related GI toxicity

- NSAIDs should be used at the lowest effective dose for the shortest duration of time
- Long-term use should be avoided

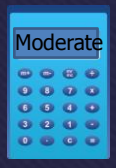
- GI risk stratification
- Treat with gastroprotective agent

- PPIs have superior efficacy to H2RA
- Misoprostol has similar efficacy with PPIs in ulcer prevention

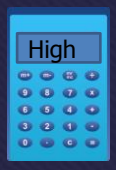
Frank L. Lanza et al. Am J Gastroenterol 2009;104:728-738.

Strategies for prevention of NSAID-related GI toxicity

- nsNSAID alone



- nsNSAID + PPI/misoprostol
- COX-2 inhibitor alone



- Alternative therapy if possible
- COX-2 inhibitor + PPI/misoprostol

Frank L. Lanza et al. Am J Gastroenterol 2009;104:728-738.

Strategies for prevention of NSAID-related CV toxicity

- NSAIDs should be avoided in patients with risk factors for CV disease
- NSAIDs should be used at their lowest effective dose for the shortest duration of time
- Naproxen is the drug of choice for patients with CV risk factors

Strategies for prevention of NSAID-related GI & CV toxicity

	Low GI risk	Moderate GI risk	High GI risk
Low CV risk	NSAID lone	NSAID + PPI / Misoprostol	Alternative therapy if possible or COX-2 inhibitor + PPI/misoprostol
High CV risk (low-dose aspirin required	Naproxen + PPI / misoprostol	Naproxen + PPI / Misoprostol	Avoid NSAIDs or COX-2 inhibitors Use alternative therapy

- High CV risk is arbitrarily defined as requirement for low-dose aspirin for prevention of serious CV events
- All patients with a history of ulcers who require NSAIDs should be tested for H. pylori, and if the infection is present, eradication therapy should be given

Frank L. Lanza et al. Am J Gastroenterol 2009;104:728-738.

Summary

- No significant difference in efficacy between various NSAIDs in treatment of arthritis pain relief
- NSAIDs are associated with GI and CV adverse effects
- Identify risk factors for GI and CV adverse effects before prescribing NSAID
- Therapy should be tailored according to risk
- Naproxen is the drug of choice for patients with CV risk factors

THANK YOU!

FOR YOUR ATTENTION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