

NSAIDs and the GI Tract- Can we Protect

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THE CENTRAL ROLE OF CYCLOOXYGENASE PRODUCTS (PROSTAGLANDINS)

- COX, the rate-limiting enzyme in prostaglandin (PG) synthesis, converts the unsaturated fatty acid arachidonic acid (C20:4) — derived from phospholipids in cell membranes — into PGG₂ and then to PGH₂.
- The gastric and duodenal mucosa proceed to convert PGH₂ to various PGs such as PGE₂ that protect the mucosal lining from injury by luminal acid-pepsin.

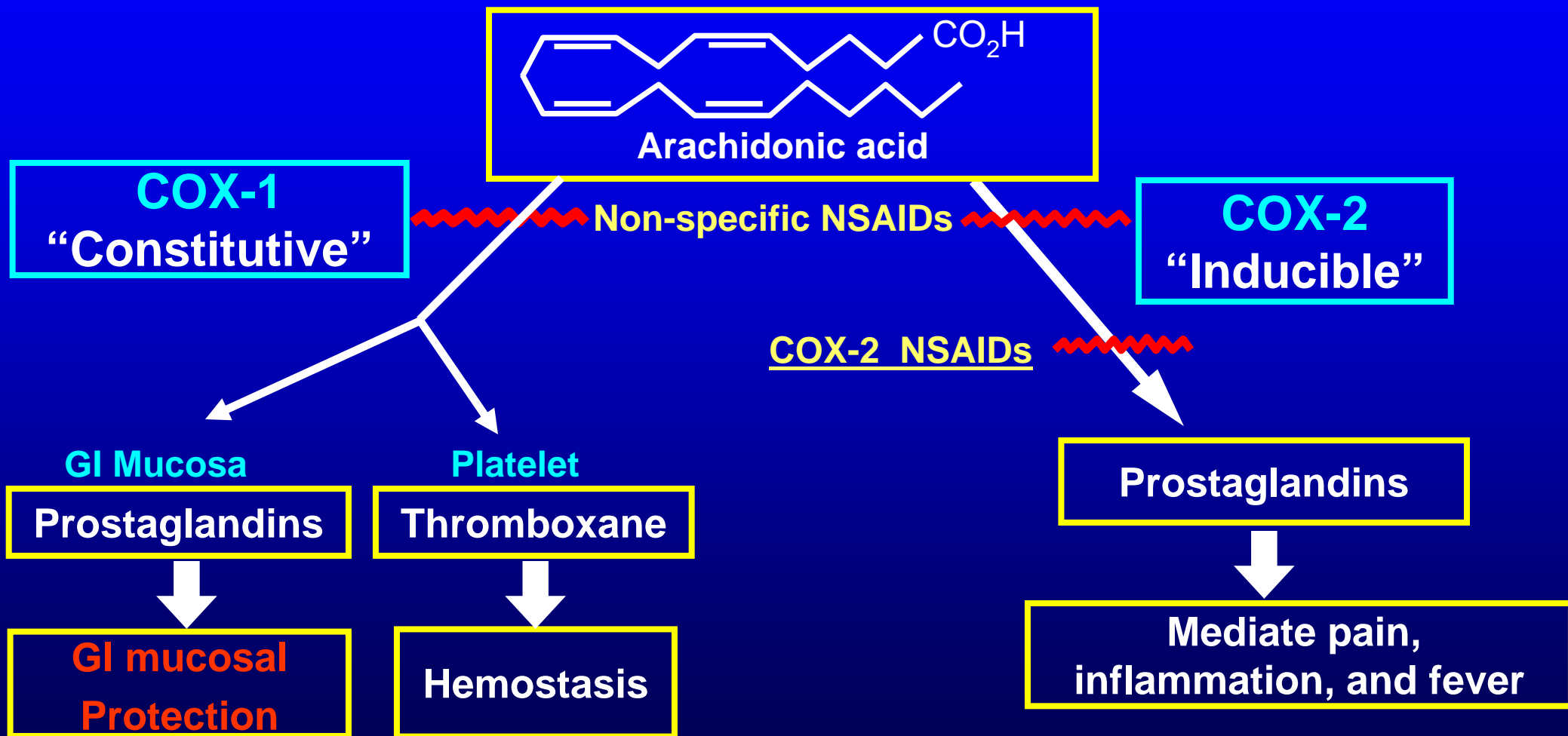
MECHANISMS OF GASTRODUODENAL PROTECTION BY ENDOGENOUS PGs

- Stimulation of glycoprotein (mucin) secretion.
- Stimulation of bicarbonate secretion.
- Stimulation of phospholipid secretion.
- Enhancement of mucosal blood flow and oxygen delivery to cells via local vasodilation.
- Increased epithelial cell migration towards the luminal surface (restitution).
- Enhanced epithelial cell proliferation.

ROLE OF NITRIC OXIDE

- Mediation of the release of gastric mucus.
- Stimulation of fluid secretion.
- Maintenance of epithelial barrier function.
- Enhancement of mucosal blood flow.

Mechanism of Action of NSAIDs: New Concept



Bakhle et al. *Med Inflamm*. 1996;5:305-323.

Vane et al. *Inflamm Res*. 1995;44:1-10.

Spectrum of NSAID-Induced GI Mucosal Injury

Upper GI

- Subepithelial petechial hemorrhages
- Erosions
- Ulcers
 - Stomach > duodenum
- Bleeding
 - Stomach » duodenum
- Perforations/obstruction

Small Intestine

- Ulcers
- Strictures
- Diaphragms
- Enteropathy

Colon

- Colitis
- Ulcers
- Strictures
- Diverticular bleed or perforation
- Collagenous colitis
- Relapse of IBD

NSAID Induced Ulceration

- Inhibition of prostoglandin synthesis is the principal mechanism of GI damage.
- Ulcer prevalence is 10 - 40% per year.
- Symptomatic ulcers or ulcer complications are 2 - 4% per year.

NSAID-Induced Gastropathy: Morbidity, Mortality and Costs in the U.S.

- Total hospitalizations/year: 107,000
- Total costs of hospitalization
(~\$12,500/hospitalization): ~\$1.4
billion
- Deaths/year: 16,500

Singh. *Am J Med.* 1998;105(suppl 1B):31S-38S.
Johnson et al. *Pharmacoeconomics.* 1997;12:76-88.

Assessment of NSAID GI Injury

- Healthy volunteers
 - Intermediate markers of injury (prostaglandins)
 - Fecal red blood cell loss
 - Short-term endoscopy study

Assessment of NSAID GI Injury

- Arthritis Patients
 - Long-Term Endoscopy studies:
 - Endoscopic ulcers, mostly asymptomatic
 - Clinical events:
 - Symptomatic ulcers
 - GI Bleeding
 - Perforation
 - Obstruction

Prevalence of Endoscopic NSAID-Induced Ulceration

| | Mean | Range |
|-------------------------------|--------|-----------|
| NSAID Gastropathy | > 90 % | |
| Gastric Ulcer | 15 % | 10 to 30% |
| Duodenal Ulcer | 5 % | 4 to 10 % |
| Clinically Significant Ulcers | 2% | 1 to 4% |

Reducing the Risk of GI Complications with NSAIDS

- Identify risk factors
- Use of gastroprotective drugs
- Safer NSAIDS

List of NSAIDs Available by Prescription

NON-SALICYLATES

Diclofenac (Voltaren)
Diclofenac/Misoprostol (Arthrotec)^b
Fenoprofen (Nalfon)
Flurbiprofen (Ansaid)
Ibuprofen (Motrin)^a
Indomethacin (Indocin)
Ketoprofen (Orudis)^a
Meclofenamate
Mefenamic acid (Ponstel)
Nabumetone (Relafen)
Naproxen (Naprosyn, Anaprox)^a
Oxaprozin (Daypro)
Piroxicam (Feldene)
Sulindac (Clinoril)
Tolmetin (Tolectin)

SALICYLATES

Aspirin^a (Zorprin, Easprin)
Diflunisal (Dolobid)
Salsalate (Disalcid, Salflex)
Choline salicylate (Trilisate)
Magnesium salicylate (Magan)

COX-2 INHIBITORS

Celecoxib (Celebrex)
Valdecoxib (Bextra)

In Development

Etoricoxib
Parecoxib^c
Lumiracoxib

Previously Available

Rofecoxib (Vioxx)

- ^a Also available as over-the-counter preparations in the U.S.
^b Combination tablet of NSAID/synthetic prostaglandin E₁
^c Parenterally administered

A committee appointed by the American College of Gastroenterology identified the five most important risk factors

- A history of an ulcer or GI hemorrhage increases risk four- to fivefold.
- Age >60 increases risk five- to sixfold.
- High (more than twice the customary) dosage of a NSAID increases risk 10-fold.
- Concurrent use of glucocorticoids increases risk four to fivefold.
- Concurrent use of anticoagulants increases risk 10- to 15-fold.

Multiple Risk Factors

- Patients with several of these risk factors are at highest risk for NSAID-induced GI toxicity.
- Up to 9 percent after six months of NSAID exposure.

Other Important Risk Factors

- Concomitant SSRI
- Multiple NSAIDS (OTC NSAIDS)
- NSAID plus ASA
- H-pylori positive
- Long term exposure
- Specific type of NSAID

NONSELECTIVE NSAIDs

- The risk of gastrointestinal complications:
- indomethacin (RR 2.25)
- naproxen (RR 1.83)
- diclofenac (RR 1.73)
- piroxicam (RR 1.66)
- tenoxicam (RR 1.43)
- ibuprofen (RR 1.43)
- meloxicam (RR 1.24)

Duration of Treatment

- The longer the patient is on NSAIDs the higher the risk of complications.
- The average duration of treatment before observing a significant risk of GI effects was 84 days.
- An increased risk was apparent as early as seven days with indomethacin.

Dose of NSAID

- Low dose ibuprofen (RR 1.6, 95% CI 0.8-3.2)
- High dose ibuprofen (RR 4.2 (95% CI 1.8-9.8)
- Low dose naproxen (RR 3.7 (95% CI 1.7-7.7)
- High dose naproxen (RR 6.0, 95% CI 3.0-12.2)
- Low dose indomethacin (RR 3.0, 95% CI 2.2-4.2)
- High dose indomethacin (RR 7.0, 95% CI 4.4-11.2)

Strategies for the primary prevention of gastroduodenal toxicity due to NSAIDs

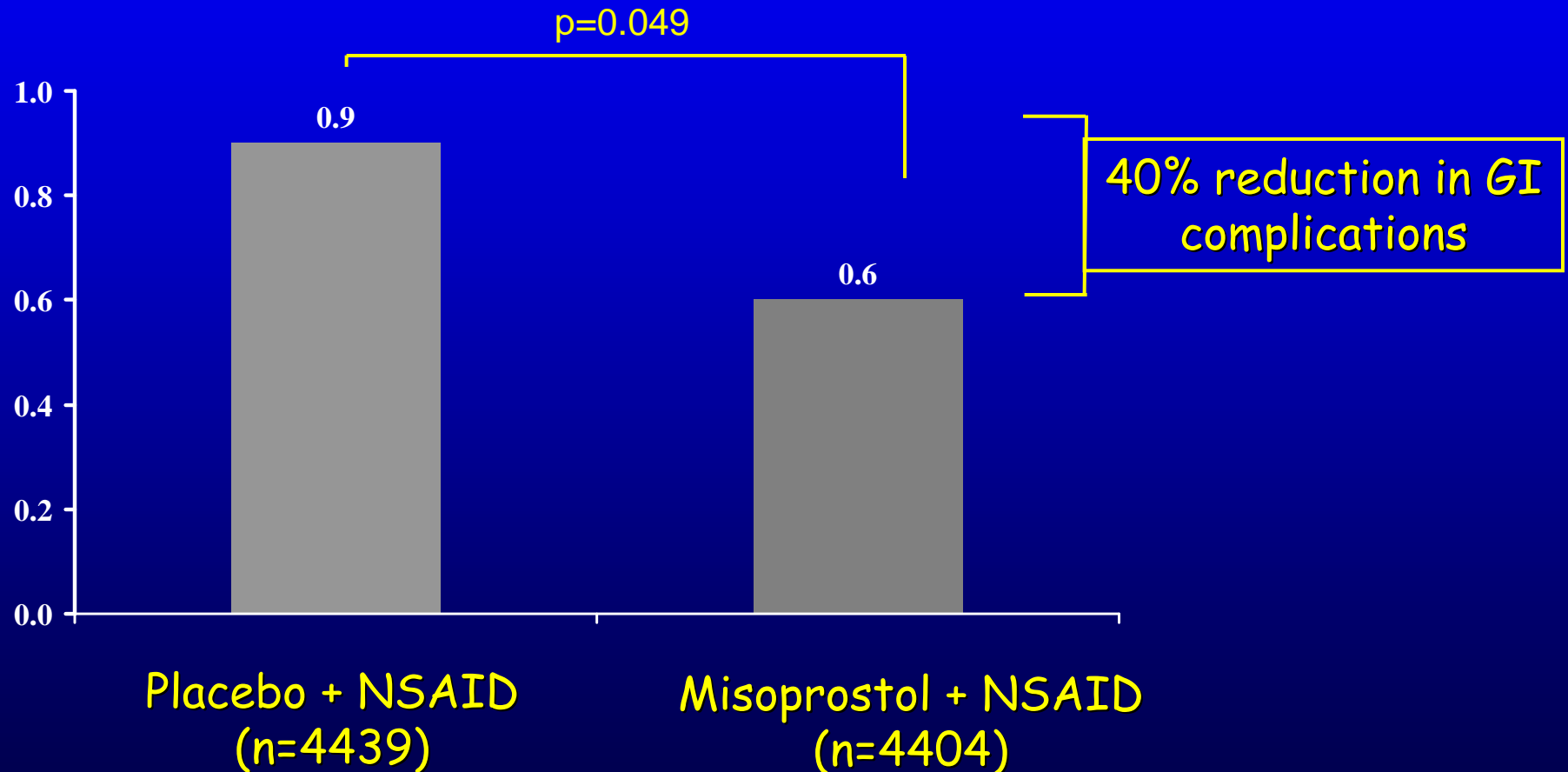
- Misoprostol, proton pump inhibitors, and H₂ receptor antagonists have all been evaluated as prophylactic therapies for patients taking NSAIDs.
- Selective COX-2 inhibitors.
- Decrease dose of NSAID.
- Decrease duration of NSAID.
- Eradicate *H. pylori*.

Misoprostol

- Prostaglandin E analog.
 - Largest trial, 8,843 patients with rheumatoid arthritis receiving continuous therapy with any of 10 NSAIDs.
 - Randomly assigned to receive 200 μ g of misoprostol or placebo four times daily for six months .
 - Reduction in serious upper gastrointestinal complications with misoprostol (bleeding, perforation, gastric outlet obstruction). A relative risk reduction of 40 percent, an absolute risk reduction of 0.57 percent.
-
- Silverstein FE; Graham DY; Senior JR; Davies HW; Struthers BJ; Bittman RM; Geis GS. *Ann Intern Med* 1995 Aug 15;123(4):241-9.

Gastroprotection: Misoprostol (MUCOSA trial)

% of patients with serious upper GI complications at 6 months

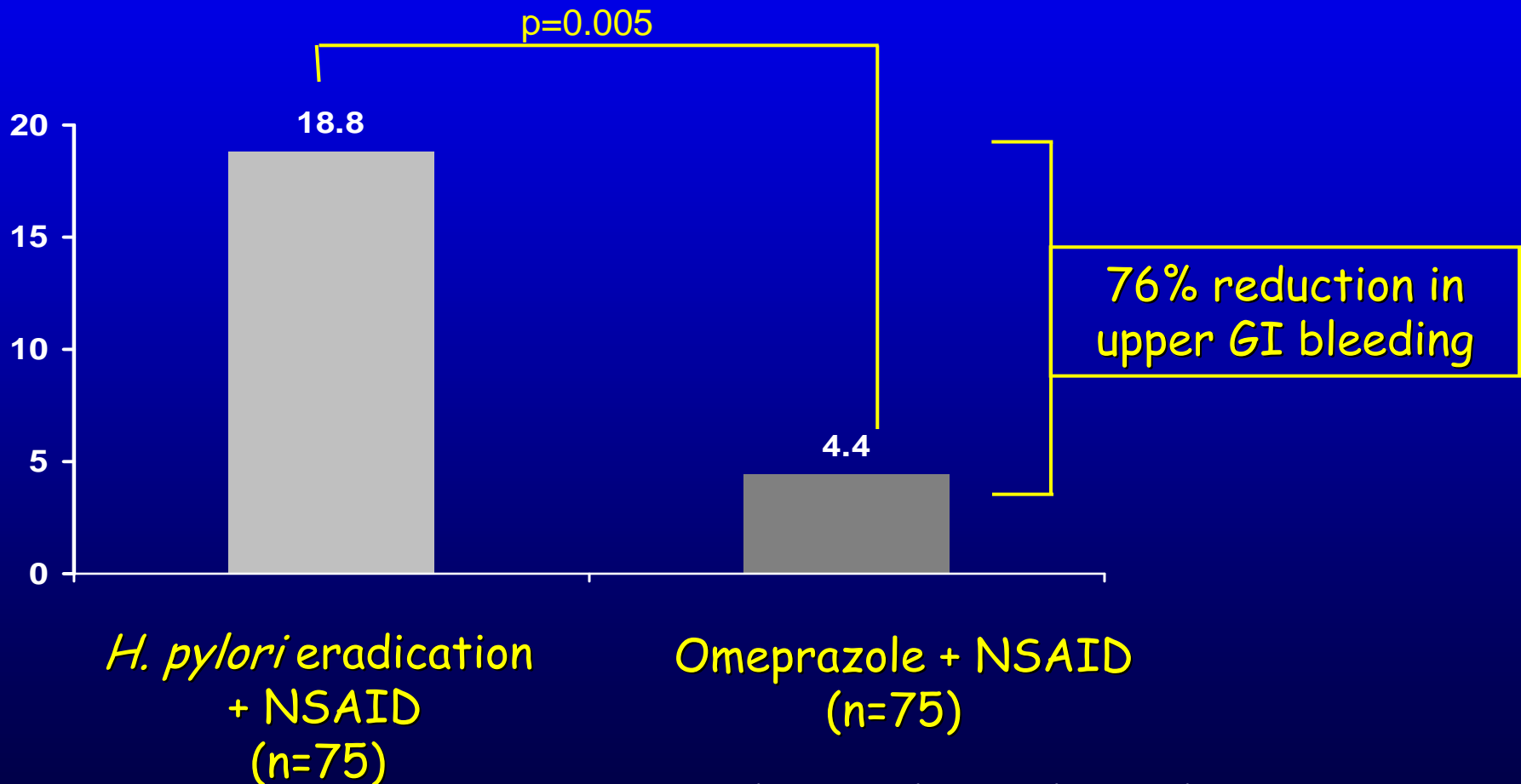


Proton pump inhibitors

- Esomeprazole was approved for prevention of NSAID-associated ulcers based upon the results of two multicenter trials
- 1429 patients taking NSAIDs continuously (both nonselective or COX-2 selective, with or without low-dose aspirin).
- The cumulative proportion of patients developing ulcers at six months was significantly reduced with PPI co-therapy (17 percent with placebo versus 5.2 and 4.6 percent with the 20 and 40 mg dose of esomeprazole, respectively).

Gastroprotection: Proton Pump Inhibitors

% of patients with recurrent upper GI bleeding at 6 months



H2 receptor antagonists

- Standard doses of H2 receptor antagonists are not effective for the prevention of NSAID-induced gastric ulcers, although they may prevent duodenal ulcers.

SELECTIVE COX-2 INHIBITORS

- COX-2 inhibitors are associated a reduced risk of gastrointestinal bleeding compared with nonselective NSAIDs.
- The risk is increased compared with placebo.
- Thus, COX-2 inhibitors may be safer than conventional NSAIDs but are still associated with an increased risk.
- Gastroduodenal sparing effects are negated when used concurrently with low dose aspirin therapy.

GI Outcomes Trials: Design

VIGOR (n=8076)

CLASS (n=7982)

| | | |
|--------------|---|---|
| Drug | Rofecoxib 50 mg QD (2x max chronic dose) | Celecoxib 400 mg BID (2x max chronic dose) |
| Patients | RA | OA (72 %), RA (28 %) |
| Comparator | Naproxen 500 mg BID | Ibuprofen 800 mg TID Diclofenac 75 mg BID |
| Low dose ASA | No | Yes (21 %) |
| Duration | Median 9 months Maximum 13 months | Median 9 months Maximum 13 months 6 months reported |

CLASS Trial: Upper GI Complications Alone and With Symptomatic Ulcers

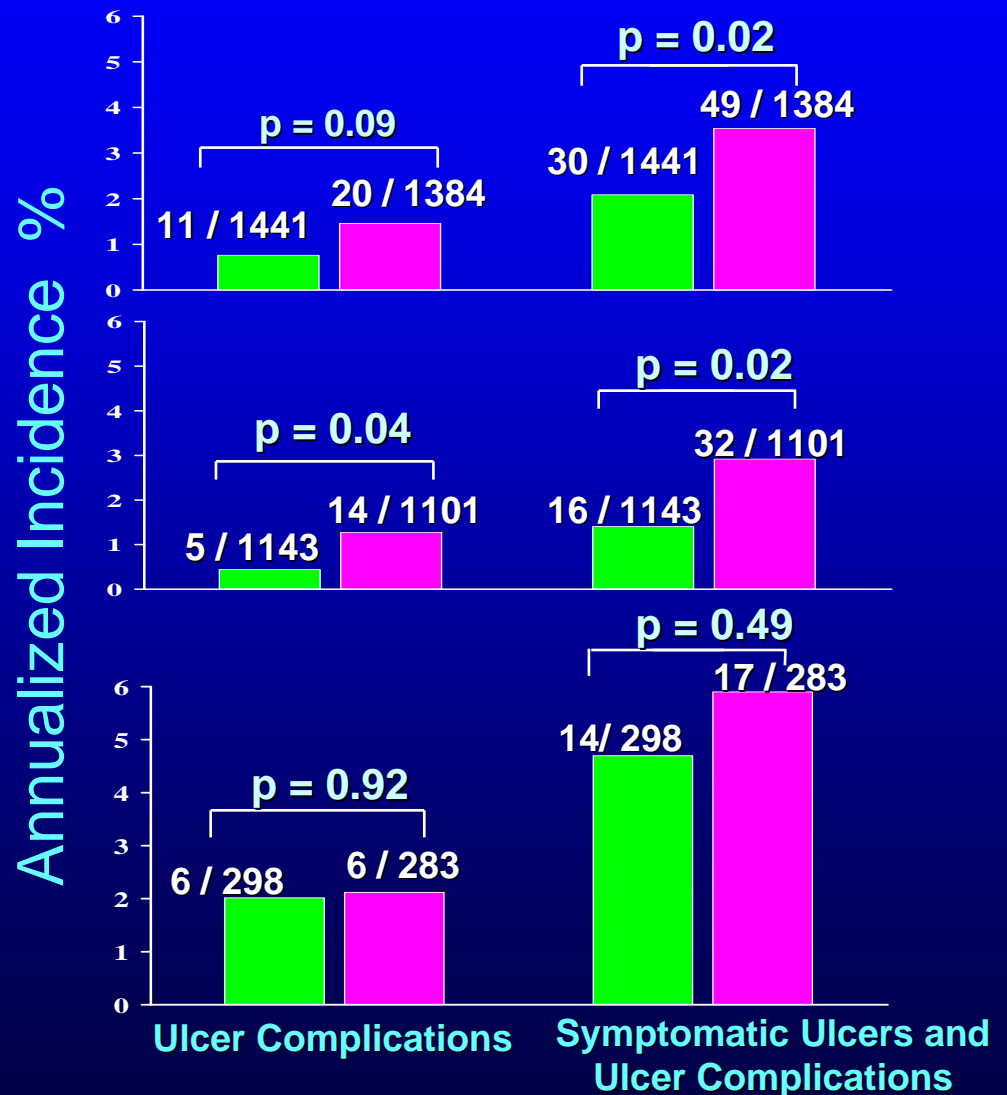
■ = celecoxib

■ = NSAIDs (ibuprofen + diclofenac)

All Patients

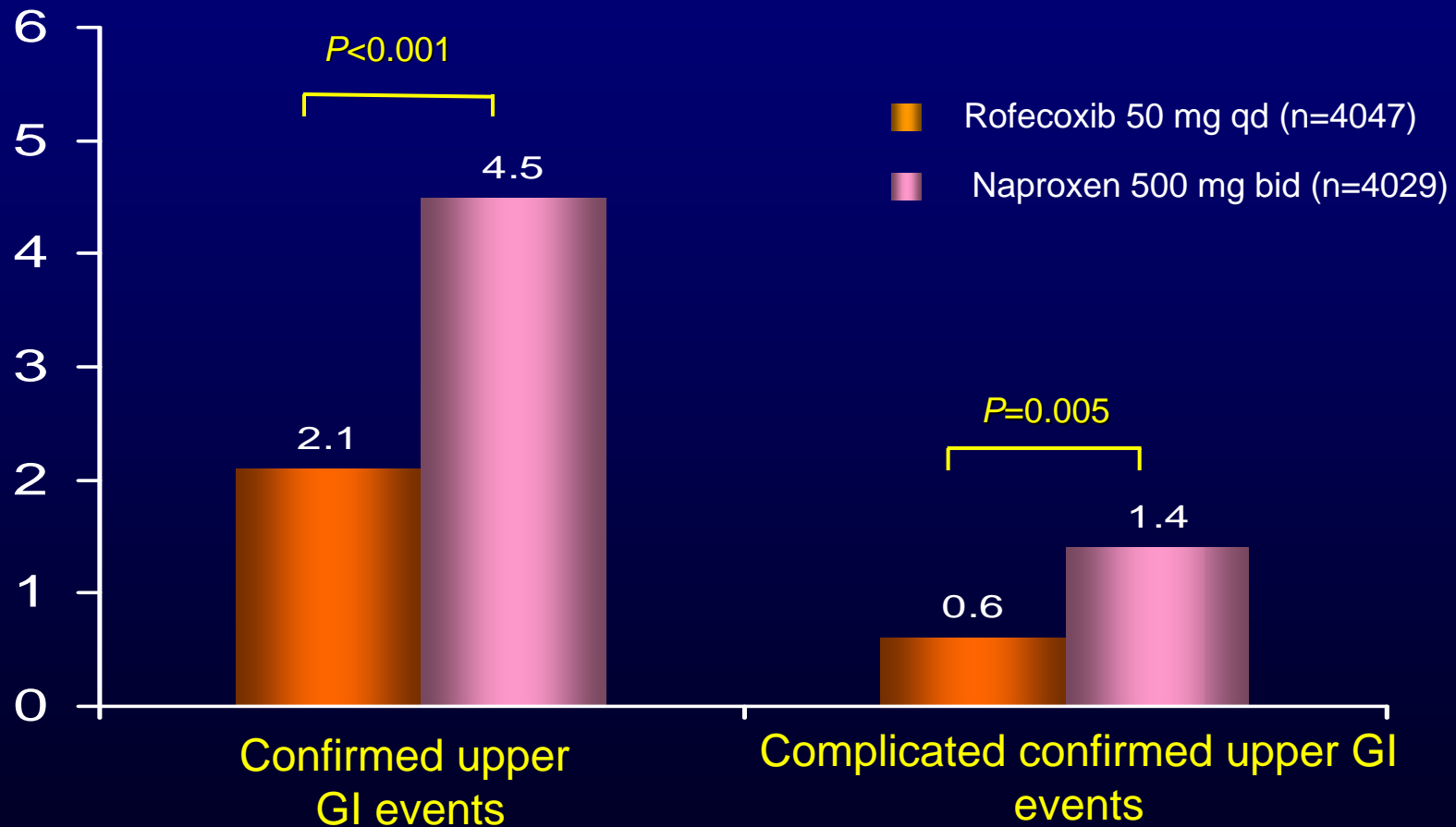
Patients Not Taking Aspirin

Patients Taking Aspirin



VIGOR: Upper GI Events at 9 Months*

Events per 100 patient years



*Median follow-up period.
Bombardier et al. *N Engl J Med.* 2000;343:1520-1528

From a lecture by Cryer B.

Low Dose Aspirin:
What Are the GI Risks?

Daily Aspirin Dose and Admission for Ulcer Bleeding

| <u>Aspirin Dose</u> | <u>Odds Ratio (95% CI)</u> |
|---------------------|----------------------------|
| 75 mg (n=27) | 2.3 (1.2-4.4) |
| 150 mg (n=22) | 3.2 (1.7-6.5) |
| 300 mg (n=62) | 3.9 (2.5-6.3) |

Risk of Combining Low-Dose Aspirin with NSAIDs

- National cohort study in Denmark
- 27,694 people on aspirin 100-150 mg qd

| Treatment regimen | Increased incidence over general population | 95% CI |
|---------------------------|---|-----------|
| Low-dose aspirin | 2.6 | 2.2 - 2.9 |
| Low-dose aspirin + NSAIDs | 5.6 | 4.4 - 7.0 |

ENTERIC-COATED AND BUFFERED ASPIRIN

- Does not protect against the clinically relevant end point of gastrointestinal bleeding.
- The systemic effect of aspirin probably explains why buffered aspirin is no more effective than plain aspirin in preventing ulcer bleeding.

ROLE OF HELICOBACTER PYLORI INFECTION

- The risk of uncomplicated peptic ulcer disease was significantly higher among *H. pylori* positive compared with *H. pylori* negative NSAID users (OR 1.81).
- The risk of uncomplicated peptic ulcer disease was 17.5 times higher among *H. pylori* positive NSAID users compared with *H. pylori* negative non-users.
- Ulcers were common in *H. pylori* positive compared with *H. pylori* negative patients irrespective of NSAID use (OR 4.03) and in NSAID users compared with nonusers irrespective of *H. pylori* status (OR 3.10).

ROLE OF HELICOBACTER PYLORI

- Patients with a history of uncomplicated or complicated peptic ulcers should be tested for *H. pylori*.
- If present, *H. pylori* should be treated with appropriate therapy.
- Even in patients with no history of PUD it is possible that successfully treating *H. pylori* infection will reduce the risk of NSAID-related ulcer complications.

Treatment and secondary prevention of gastroduodenal toxicity

- If a patient develops an ulcer while on NSAIDs, the NSAIDs should be stopped if possible.
- Traditional ulcer therapy with a proton pump inhibitor or an H2 antagonist started.
- The patient's *H. pylori* status should be assessed and if positive, appropriate therapy should be instituted.

Treatment and secondary prevention of gastroduodenal toxicity

- Among patients who must remain on NSAID therapy, randomized trials have shown that ulcer healing occurs more rapidly with a proton pump inhibitor than an H₂ blocker.

SECONDARY PREVENTION

- Patients with gastroduodenal ulcers or numerous erosions who must continue NSAID or aspirin should be treated with a proton pump inhibitor.
- Followed by maintenance therapy for as long as the NSAID or aspirin is used.

Conclusions Regarding Upper GI Effects of NSAIDs

- Untoward GI effects of NSAIDs result in considerable morbidity, mortality and costs.
- COX-2 inhibitors were developed to reduce NSAIDs' GI toxicity.
- However, COX-2 inhibitors have been widely used by patients not at high risk of NSAIDs' GI effects.
- Limitations of COX-2 Inhibitors:
 - No great need for COX-2s in patients at low GI risk
 - No GI benefit in patients concurrently taking aspirin
 - CV concerns may exist for some patients

Conclusions Regarding Upper GI Effects of NSAIDs (continued)

- Strategies to reduce risk of GI effects of NSAIDs should focus on patients at greatest GI risk.
- For such patients, COX-2 inhibitors are an attractive option from the GI perspective.
- However, for patients taking low-dose aspirin or when CV concerns exist clinicians may consider other strategies to reduce NSAIDs' GI effects.

Secondary Prevention

- Patients with gastroduodenal ulcers or numerous erosions who must continue NSAID or aspirin therapy should be treated with a proton pump inhibitor,
- followed by maintenance therapy for as long as the NSAID or aspirin is used.
- *H. pylori* infection should be eradicated, if present.

SUMMARY AND CLINICAL IMPLICATIONS

- Mucosal damage by aspirin and NSAIDs is primarily a consequence of inhibition of COX-1 in the upper GI tract.
- COX-1 inhibition reduces mucosal generation of protective prostaglandins such as PGE₂.
- Strategies to avoid this damage include using antiinflammatory or analgesic drugs that have minimal effects on COX-1 at usual doses, such as selective COX-2 inhibitors, acetaminophen, or non-acetylated salicylates, and prescribing either a prostaglandin E analog such as misoprostol or a potent inhibitor of gastric acid production such as a proton pump inhibitor together with the NSAID.

Treatment for NSAID-induced injury

- Discontinuation of the NSAID.
- Endoscopically accessible strictures or diaphragms may be amenable to TTS balloon dilatation .
- However, the diaphragm-like strictures tend to be multiple, often requiring resection of the involved intestinal segment.

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The distal small bowel and colon are susceptible to the deleterious effects of NSAIDs

- The ileocecal region is a potential site for a variety of NSAID-induced injuries including erosions, ulcers, strictures, perforation, and the formation of diaphragms, which can lead to bowel obstruction.
- NSAIDs can also lead to colitis resembling inflammatory bowel disease (IBD), exacerbate preexisting IBD, or complicate diverticular disease (ie, perforation or bleeding).
- The elderly and those on long-term NSAID therapy appeared to be at highest risk.

NSAID Induced Diaphragm-Like Stricture

- A lesion thought to be pathognomonic of NSAID injury is the diaphragm-like stricture.
- These lesions are thin, concentric, diaphragm-like septa with pinhole-sized lumen.
- They are usually multiple, found mostly in the mid-intestine, but have also been described in the ileum and colon.
- Characterized by submucosal fibrosis with normal overlying epithelium.





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