

CLASS

Celecoxib Long-term Arthritis Safety Study

Agenda

Introduction

Philip Needleman, Ph.D.
Senior Executive Vice President
Chief Scientist and Chairman
Research and Development

UGI Safety Profile of NSAIDs and Celecoxib: Rationale for CLASS Study

G. Steven Geis, Ph.D., M.D.
Vice President
Arthritis Clinical R&D

Safety Profile of Celecoxib: CLASS, Long Term Safety Trial

James Lefkowitz, M.D.
Senior Director
Arthritis Clinical R&D

Summary

Fred Silverstein, M.D.
Chairman
CLASS Executive Committee

Introduction

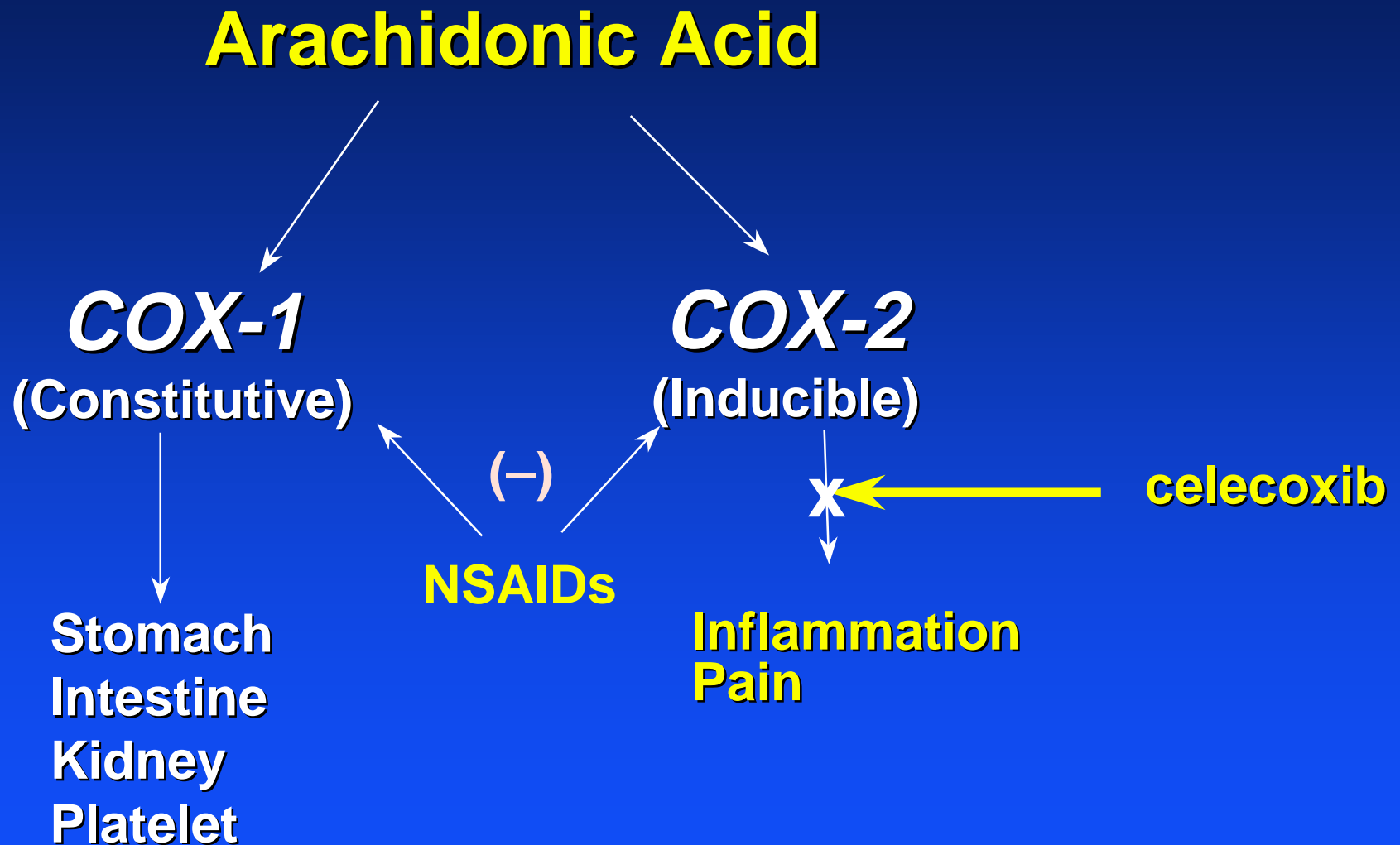
Philip Needleman, Ph.D.

Pharmacia

Research and Development

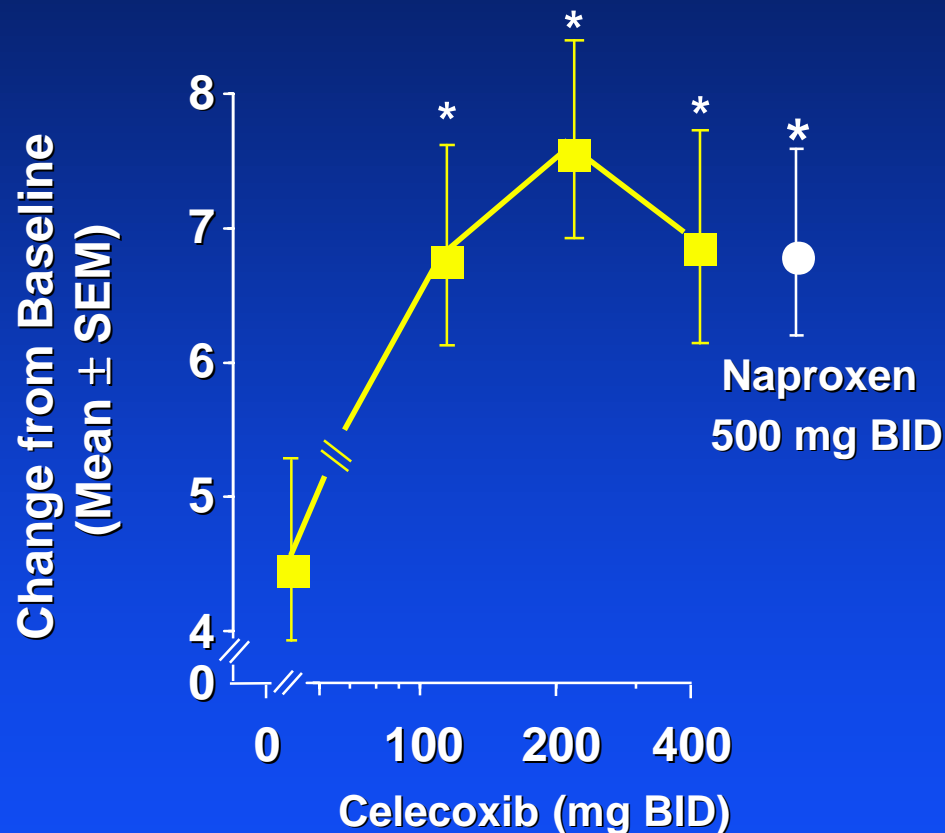
The COX-2 Hypothesis: ca. 1990

Mechanism-Based Drug Targeting

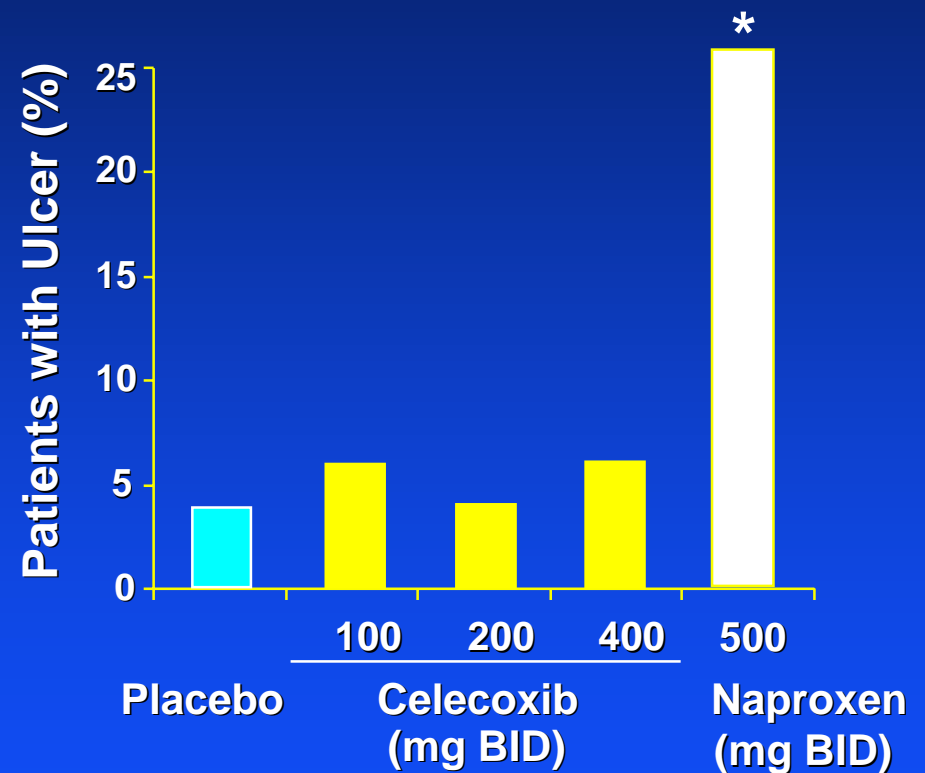


Clinical Efficacy of Celecoxib in RA Patients

Reduction in Number of Swollen Joints



Incidence of Gastroduodenal Ulcers



* Significantly different from 0 mg; $P \leq 0.05$

* $P < 0.001$ vs other treatments

Simon LS, et al. JAMA 282 20:1921-1928, 1999

Celecoxib NDA Perspective

- **Advisory Committee unanimously recommended approval of celecoxib (Celebrex) for signs and symptoms of OA and adult RA; approved Dec 29, 1998 by FDA.**
- **Celebrex demonstrated greater UGI safety than conventional NSAIDs**
- **Key unresolved issue:**

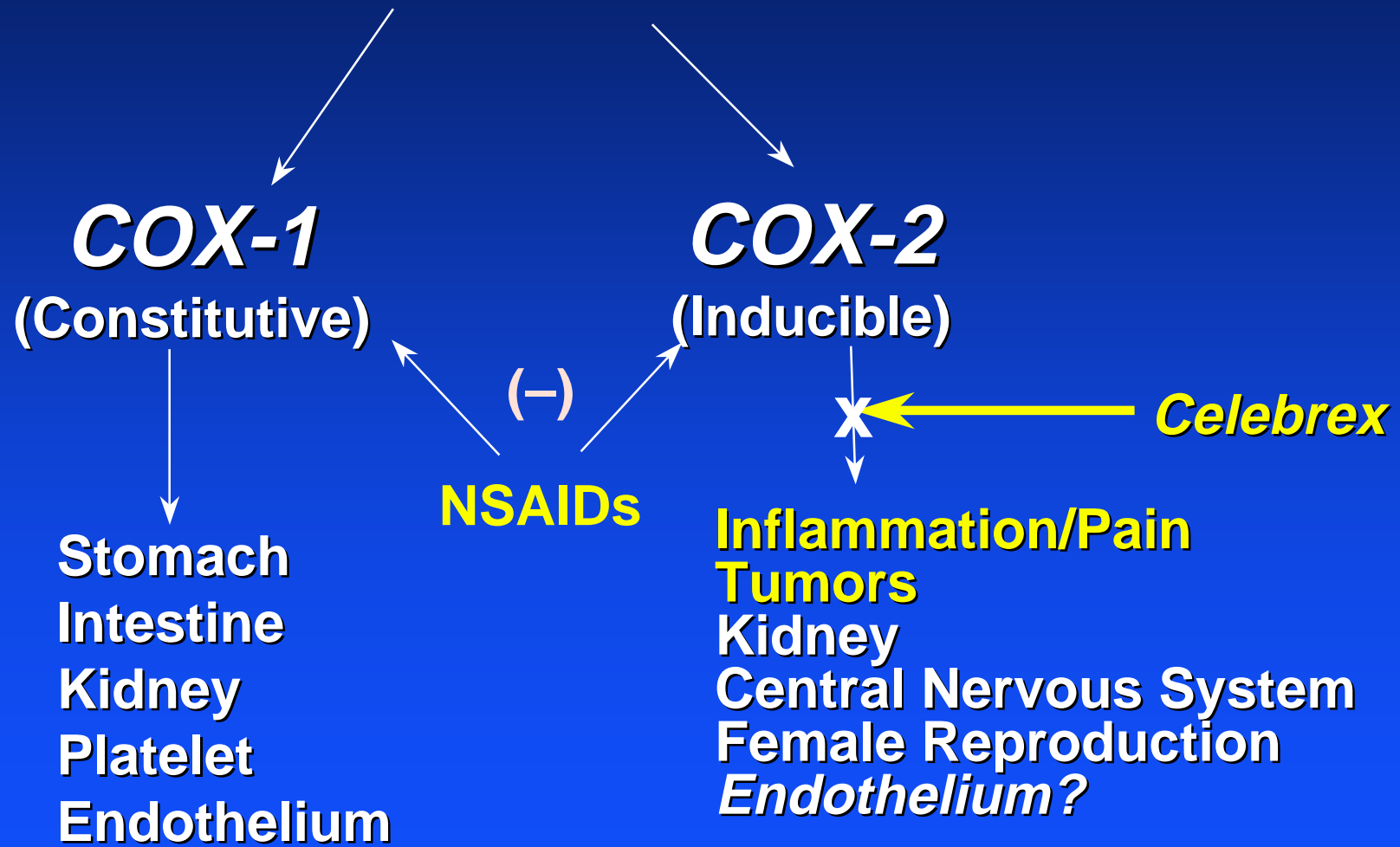
Would the decrease in endoscopic ulcers with celecoxib translate into improved, clinically meaningful GI safety in a large, well controlled outcomes trial?

CLASS Trial Design: Collaboration with FDA

- **Primary objective: assess GI safety profile of Celebrex; may provide insight into other COX-related safety issues**
- **Rigorous trial of OA and RA patients that mimicked clinical practice – allowed cardioprotective aspirin**
- **Utilized two NSAIDs, including ibuprofen, at commonly used doses**
- **Studied Celebrex at 2 to 4 times the maximally effective therapeutic doses in arthritis**

The COX-2 Hypothesis 2001

Arachidonic Acid



Areas where CLASS data may shed light on the roles of COX-1 and COX-2

- **Definitely:**
 - GI events
 - Blood loss
- **Possibly:**
 - Effects of Low Dose Aspirin
 - Renal
 - Cardiovascular/Thrombosis
- **Unlikely:**
 - Female Reproduction
 - Central Nervous System
 - Cancer

Low Dose Aspirin

- Aspirin covalently inhibits platelet COX-1, providing cardioprotection and increased bleeding potential
 - NSAIDs transiently inhibit platelet COX-1
- Aspirin causes direct damage to the GI mucosa
- Low dose aspirin shown to increase risk of GI ulcer complications (Lanas et al., NEJM 2000; 343: 834)

CLASS data can provide insight into the GI effects of aspirin

Renal COX-1/COX-2

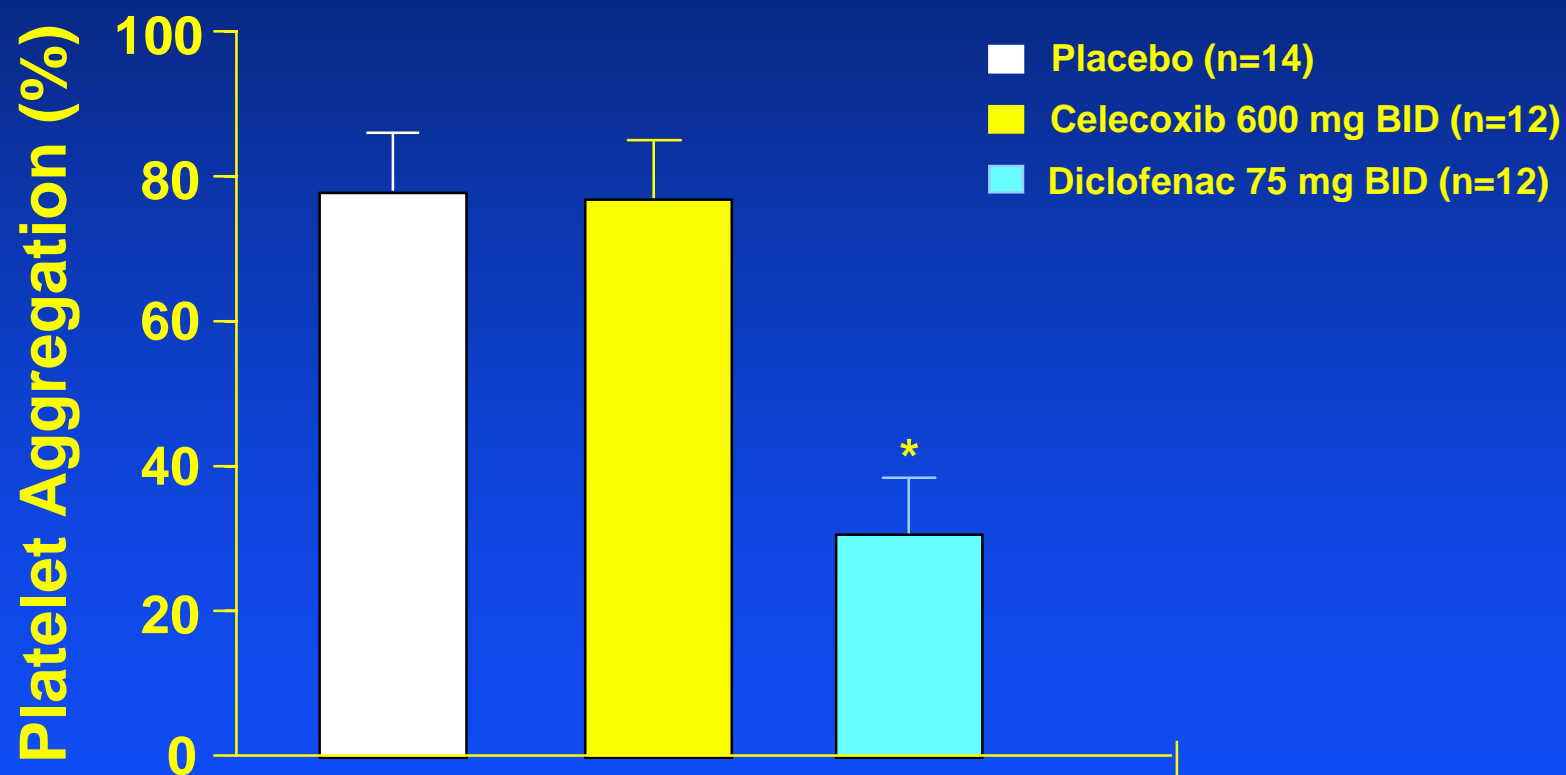
- Both COX isoforms are expressed constitutively
- Localization in laboratory animals is distinct from that in primate
- NDA database did not distinguish Celebrex from NSAIDs

CLASS database may provide further insight

Cardiovascular/Thrombosis

- **Low dose aspirin reduces risk of a myocardial infarction by inhibiting platelet COX-1**
 - Clear benefit during an acute MI, unstable angina, and in secondary prevention of MI
 - Marginal benefit in primary prevention of MI
- **Blood vessels and endothelium produce PGI₂ predominantly by COX-1**
- **Endothelium also produces the potent anti-thrombotic nitric oxide (NO)**

Platelet Aggregation



*p < 0.05 vs placebo

Effect of Celecoxib on Human Urinary PGI₂ Metabolites

Potential for COX-2 and the Endothelium?

<u>PGI-M (pg/mg creatinine)</u>	
<u>Treatment</u>	
Placebo	117 +/- 49
Celecoxib, 400 mg	34 +/- 7
Celecoxib, 800 mg	23 +/- 9
Ibuprofen, 800 mg	51 +/- 19

McAdam,....FitzGerald PNAS 1999, 96:272-277.

Effect of Celecoxib on Human Urinary PGI₂ Metabolites

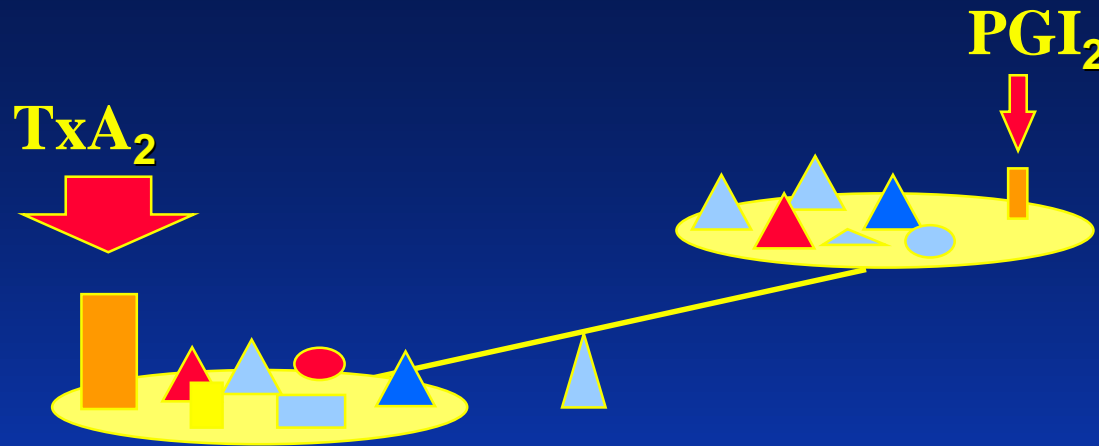
Potential for COX-2 and the Endothelium?

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Placebo	117 +/- 49
Celecoxib, 400 mg	34 +/- 7
Celecoxib, 800 mg	23 +/- 9
Ibuprofen, 800 mg	51 +/- 19

- PGI₂ is a potent vasodilator and inhibits platelet aggregation
- McAdam et al. suggested that the endothelium is the source of the COX-2 and PGI₂

McAdam,....FitzGerald PNAS 1999, 96:272-277.

FitzGerald Hypothesis



- NSAIDs inhibit both COX-1 and COX-2
 - No net effect on thrombosis
- COX-2 inhibitors allow unopposed production of TxA₂
 - Potential for increased risk for thrombotic events

If the hypothesis is correct, the expected effect would be similar to that of not taking aspirin in an “at risk” population

CLASS Trial: Potential for assessing CV risk

- The cardioprotective benefits of aspirin in reducing primary CV event (MI) - or for a COX-2 inhibitor to cause a CV event - requires a sample size of >20,000 patients, treated for five years (NEJM 321:129,1989)
- Therefore, the CLASS trial (~4000 pts) was not large enough to detect small CV effects due to COX-2 inhibition of endothelial PGI₂ production
- However, the CLASS trial was large enough to establish the general CV safety profile of Celebrex

Summary

- **The preponderance of the clinical data supports the safety of the COX-2 inhibitor – Celebrex compared to NSAIDs**
 - Endoscopy
 - Evaluation of ulcers and complications
 - Post-marketing surveillance
- **Evaluation of exaggerated doses of Celebrex in a large controlled trial revealed no new safety signals.**
- **Celebrex did not increase thromboembolic events when compared to NSAIDs, in the absence or presence of aspirin.**

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Upper GI Safety Profile of NSAIDs and Celecoxib:

Rationale for CLASS Study

G. Steven Geis, PhD MD
Vice President, Arthritis Clinical R&D

Overview

- **NSAID-associated upper GI toxicity**
- **Prospective trials to evaluate upper GI safety**
- **Upper GI safety of celecoxib**

Overview

- **NSAID-associated upper GI toxicity**
 - Definition
 - Incidence
 - Patients at Risk
- Prospective trials to evaluate upper GI safety
- Upper GI safety of celecoxib

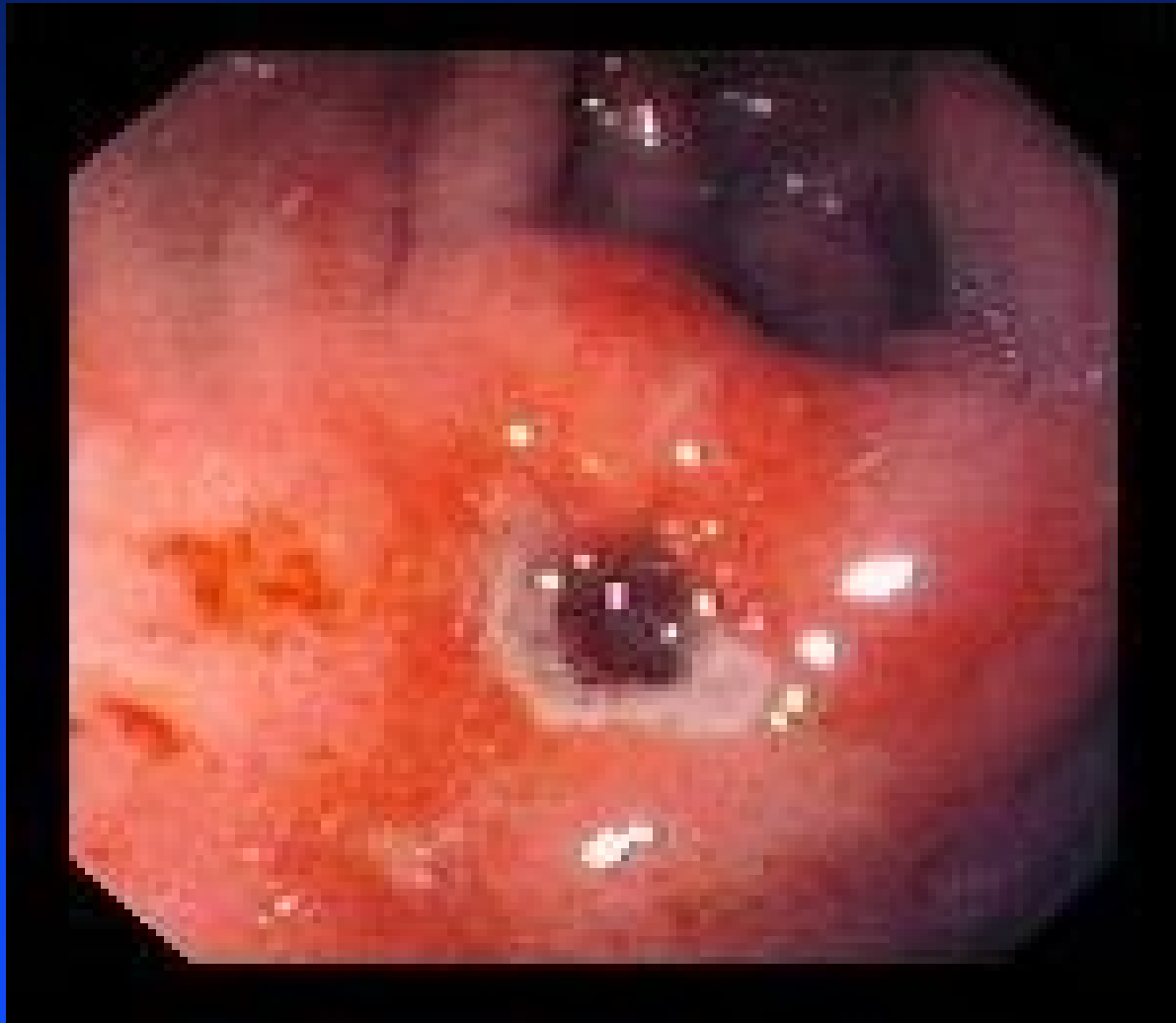
Clinical Evidence of NSAID-Related Upper GI Injury

- **Symptomatic ulcers**
- **Ulcer complications**
 - Perforation
 - Bleeding
 - Outlet obstruction

Symptomatic Ulcer



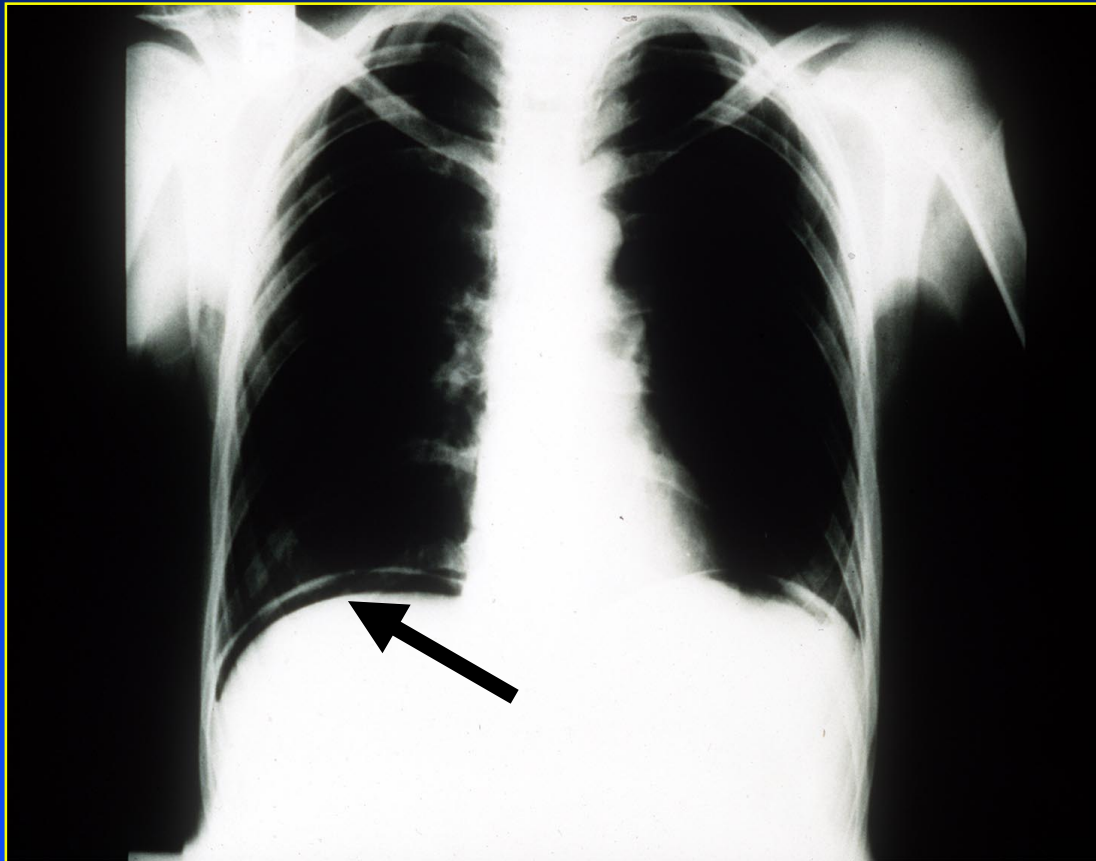
Ulcer with Visible Vessel



Bleeding Ulcer



Ulcer Perforation

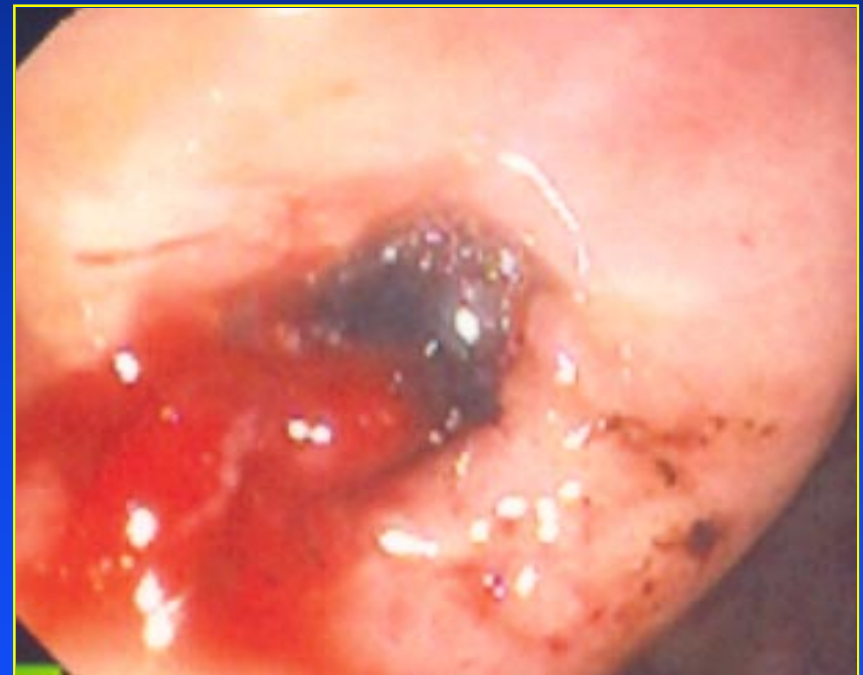


Spectrum of NSAID-Related Upper GI Injury


Symptomatic Ulcer



Ulcer Complication



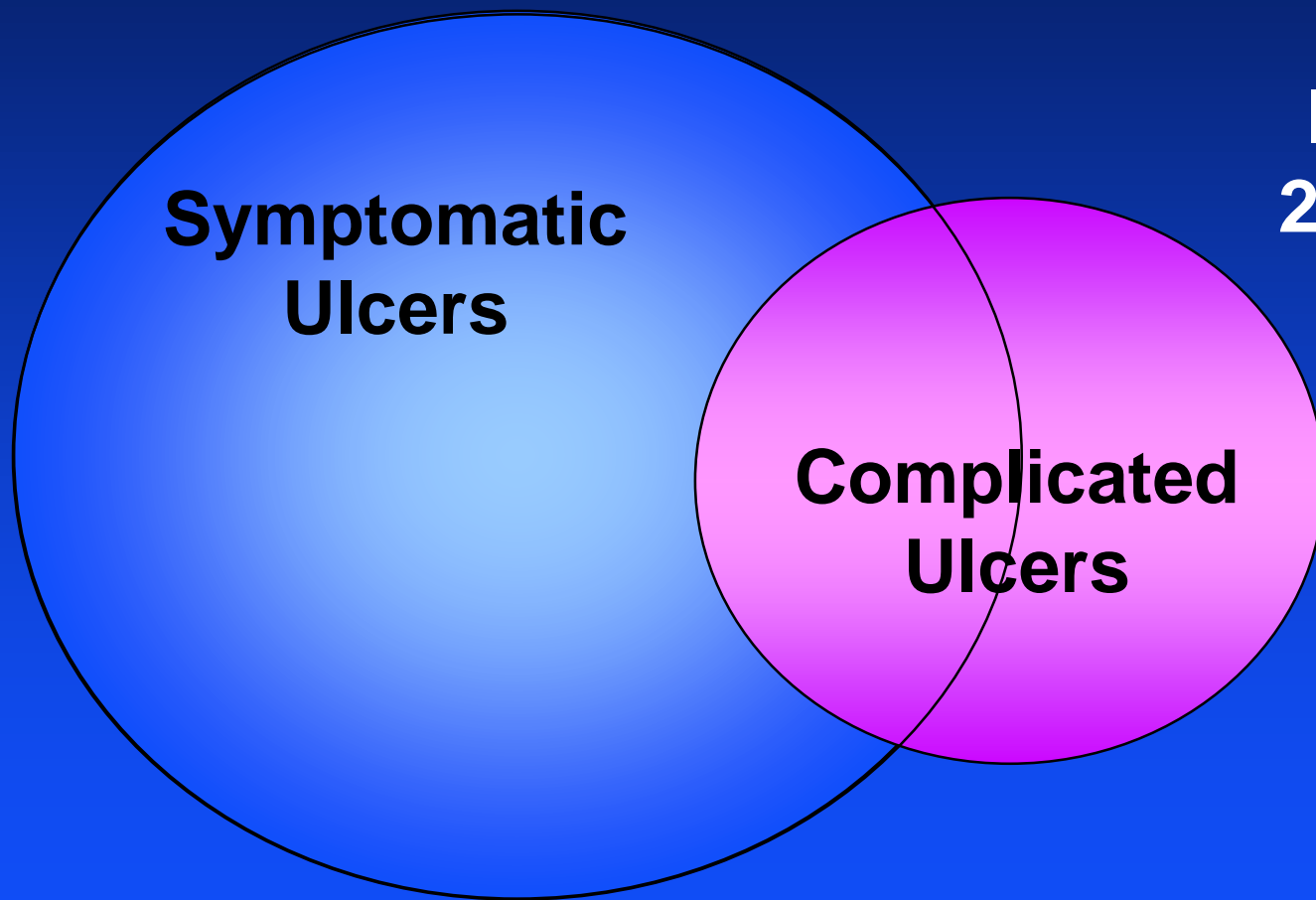
Clinical Evidence of NSAID-Related Upper GI Injury

- **Symptomatic ulcers**
 - **Ulcer complications**
 - Perforation
 - Bleeding
 - Outlet obstruction
- POB**
- PUB**
- 

Magnitude of NSAID-Related Upper GI Toxicity

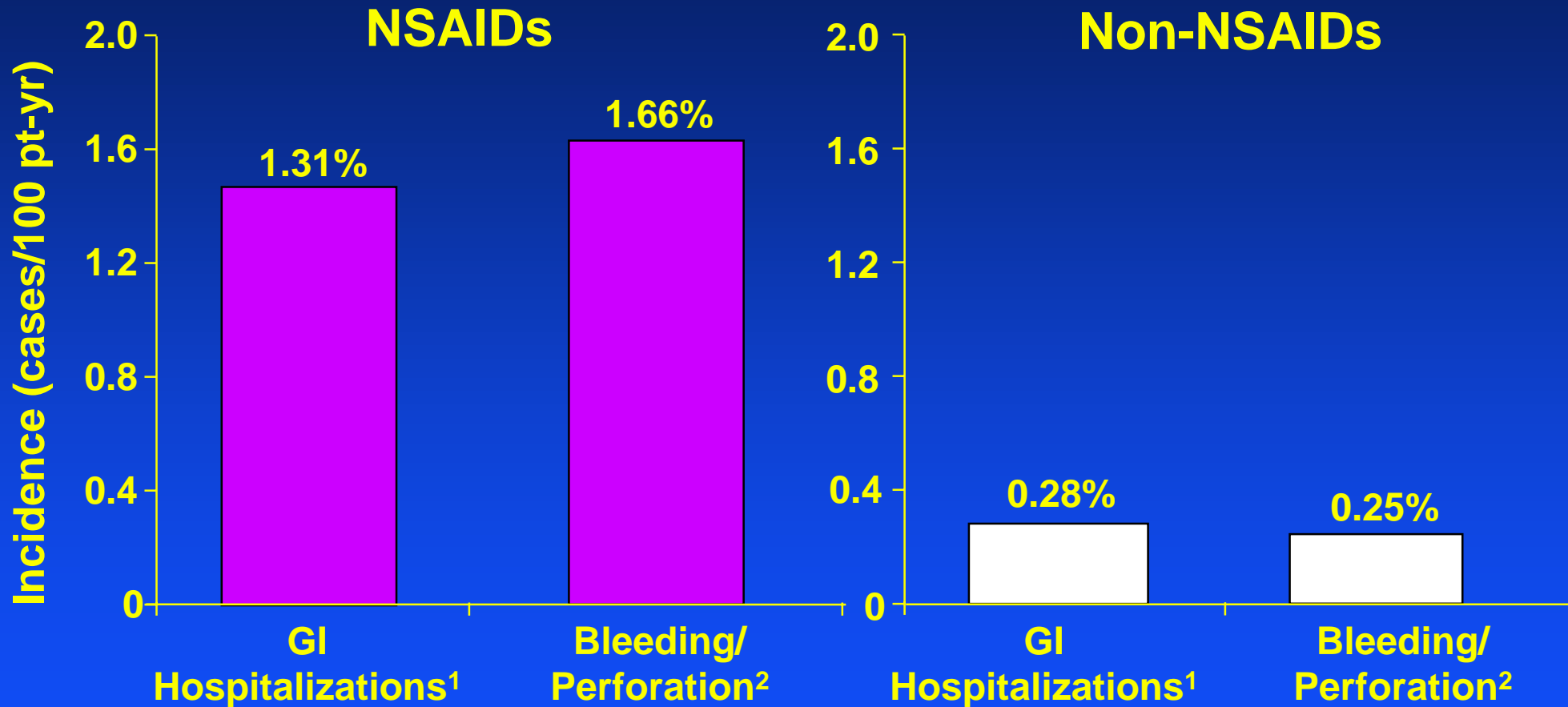
- **Observational cohort and retrospective cohort or case control studies**
 - Examined hospital records for diagnoses of:
 - Symptomatic ulcers
 - Ulcer complications

Magnitude of NSAID-Related Upper GI Toxicity



**Overall
Incidence
2-4% per yr**

Incidence of Ulcer Complications



1. Singh and Rosen Ramey, J Rheumatol Suppl 51:8-16, 1998

2. Perez-Gutthahn et al. Epidemiology 1997;8:18-24

NSAIDs: GI Morbidity and Mortality

	<u>Patient Years</u>	<u>Hospitalizations No. (Rate*)</u>	<u>Deaths No. (Rate*)</u>
Tennessee			
Medicaid- ≥ 65 yrs ¹ (est.)	2,340,000	41,000 (17.5)	3,300 (1.41)
Aramis ² (est.)	13,000,000	107,000 (8.2)	16,500 (1.27)

* Per 1000 patient-years

1. Ray, Griffin and Shorr, Health AFF 1990;3:114-122

2. Singh and Ramey, J Rheum 1998;25(Suppl 51):8-16

Risk Factors for NSAID-Related Symptomatic Ulcers/Ulcer Complications

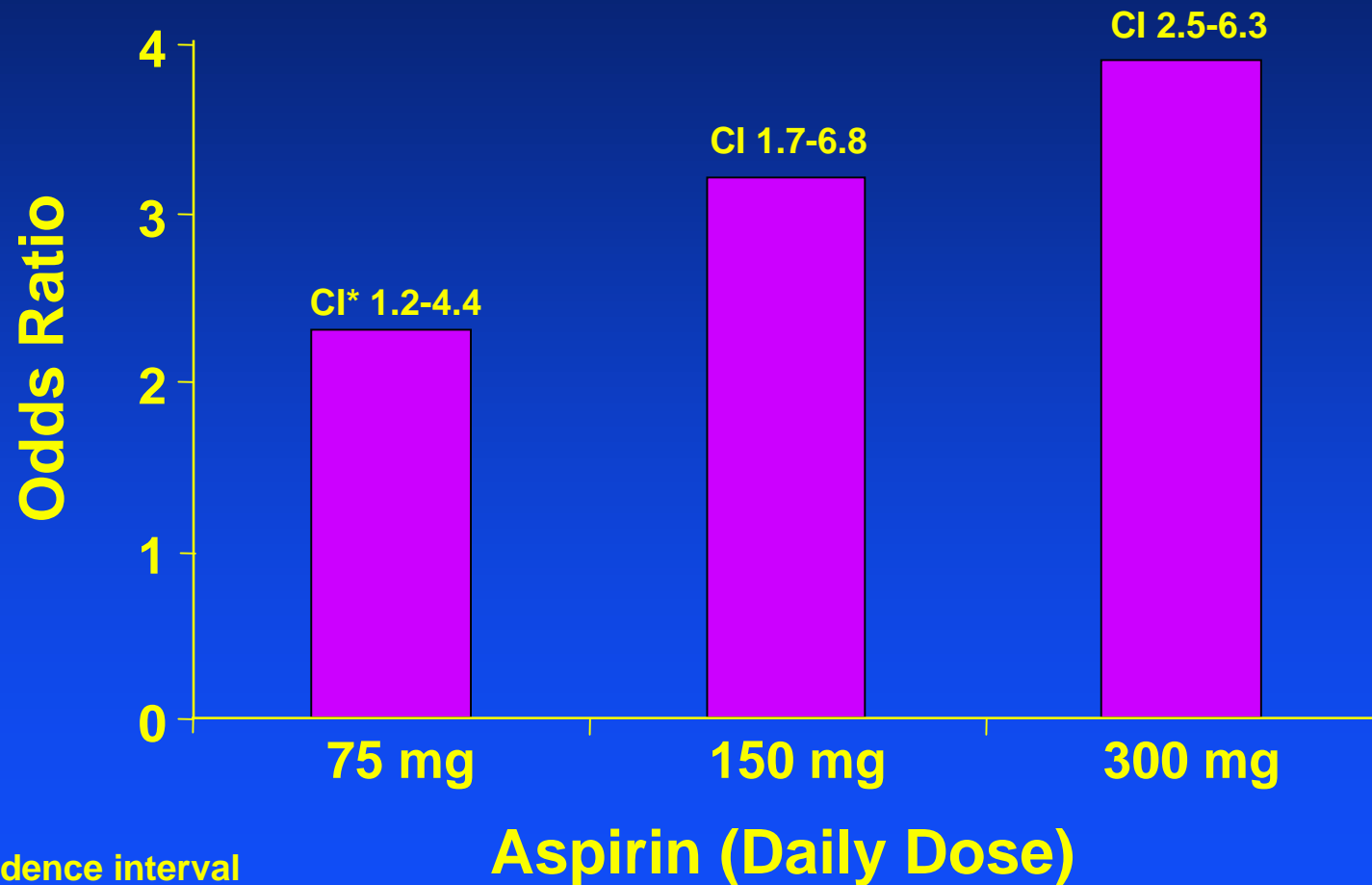
	<u>Evidence</u>
Increasing Age	+++
Female	+
Concomitant Disease	
RA	++
CV Disease	++
History of Ulcer or GI Bleed	+++
Alcohol or Smoking	+
Medications	
High dose, long-term NSAIDs	+++
Low dose ASA	+++
Anticoagulants	++
Corticosteroids	+

Odds Ratios for Ulcer Complications: Effect of NSAID Use and Age

	Age (Years)		
	15-59	60-79	≥80
Female Nonusers	1.0	3.3	8.8
Female NSAID Users	4.9	16.6	57.2
Male Nonusers	2.0	4.8	18.4
Male NSAID Users	10.4	19.4	50.6

Perez-Guttham et al. Epidemiology 1997;8:18-24

Risk of Upper GI Bleeding Related to Prophylactic Aspirin



* CI - Confidence interval

Weil et al. BMJ 1995;310:827-830

Risk of Upper GI Bleeding – Meta Analysis

	Odds Ratio (95% CI)
Ibuprofen	1.0 (ref)
Diclofenac	1.8 (1.4-2.3)
Diflunisal	2.2 (1.2-4.1)
Naproxen	2.2 (1.7-2.9)
Indomethacin	2.5 (1.5-4.1)
Sulindac	2.1 (1.6-2.7)
Piroxicam	3.8 (2.7-5.2)
Ketoprofen	4.2 (2.7-6.4)

Conclusions: NSAID-Related Upper GI Toxicity

- **Symptomatic ulcers and ulcer complications are on a continuum of GI toxicity**
- **All NSAIDs are associated with symptomatic ulcers and ulcer complications**
- **Approximately 16,500 deaths/year due to NSAID GI toxicity**

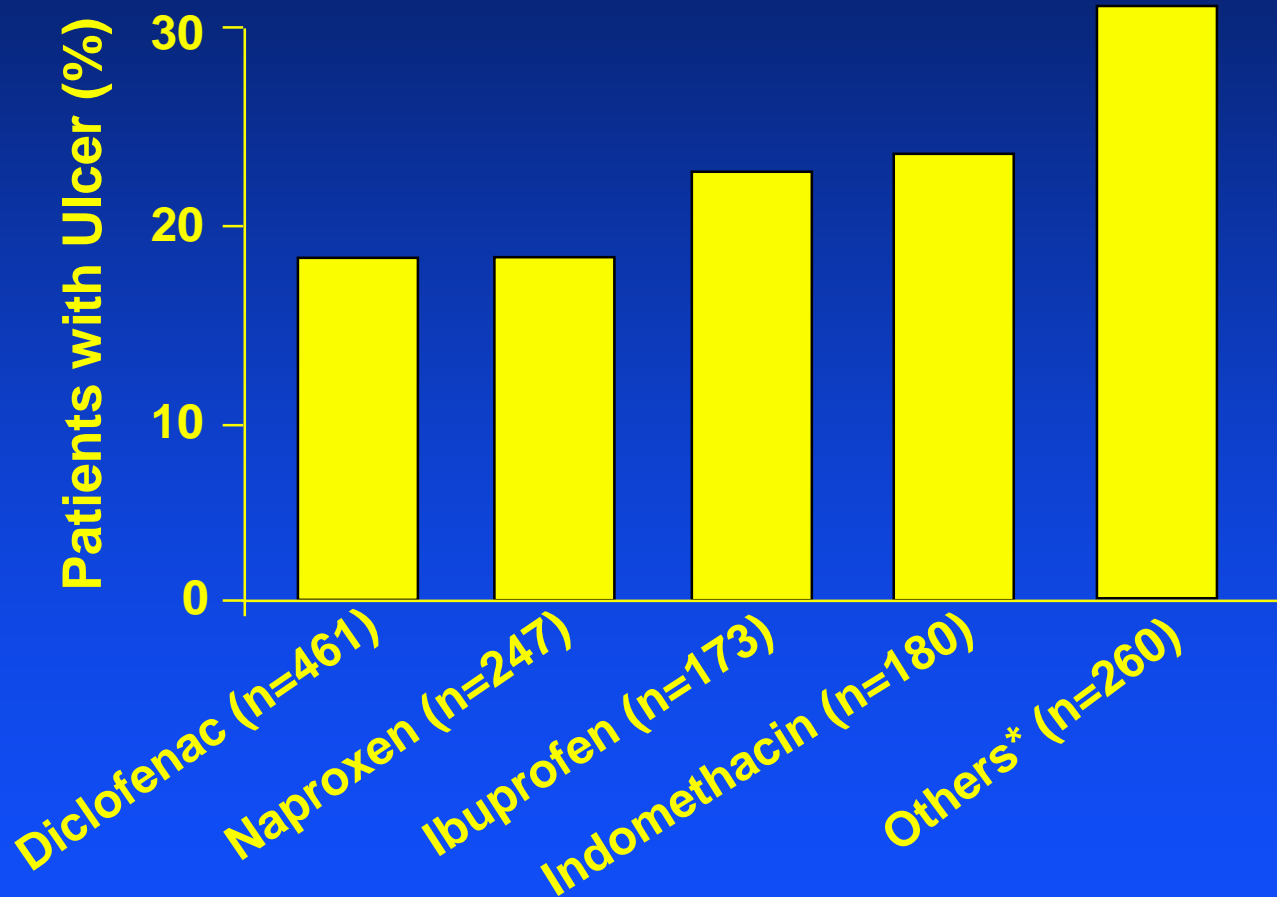
Overview

- NSAID-associated upper GI toxicity
- **Prospective trials to evaluate upper GI safety**
 - Endoscopic ulcers
 - Ulcer complications
- Upper GI safety of celecoxib

Definitions: NSAID-Related Upper GI Toxicity

- **Symptomatic ulcers**
 - GI toxicity encountered in clinical practice
 - Identified by “for cause” endoscopy
- **Endoscopic ulcers**
 - Measure of GI toxicity in clinical investigations
 - Identified by scheduled endoscopy in a clinical trial

Prevalence of Endoscopic Gastroduodenal Ulcers in NSAID Users



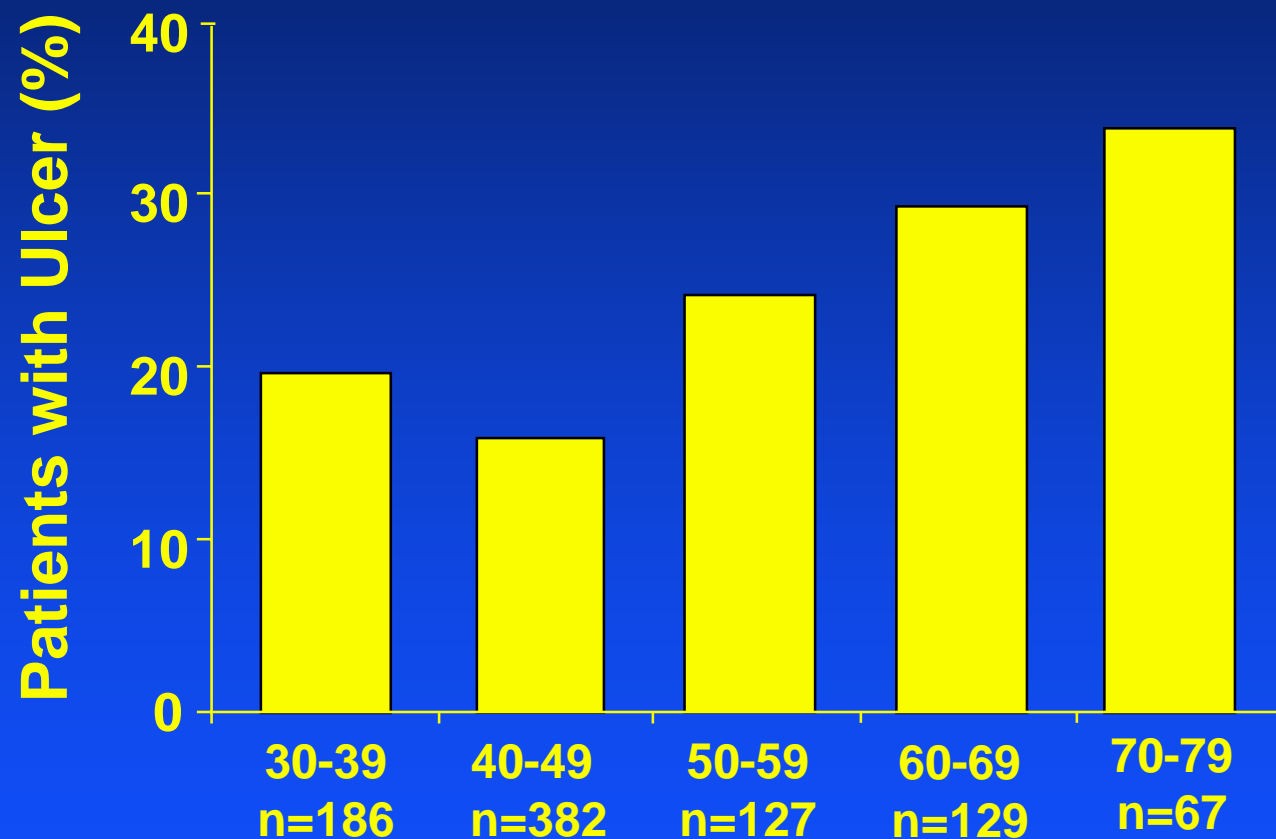
Cheatum et al. Clin Ther 1999;21:992

*Fenoprofen, sulindac, flurbiprofen, etodolac, ketoprofen, aspirin

Prevalence of Endoscopic Ulcers in NSAID Users

	<u>No. of Patients</u>	<u>Gastric Ulcer (%)</u>	<u>Duodenal Ulcer (%)</u>
Cheatum et al.	1826	14	9
Nobunaga et al.	1008	24	5
Roth et al.	239	23	6
Farah et al.	18	19	7
Collins et al.	150	28	18
Sontag et al.	140	30	10

Prevalence of Endoscopic Gastroduodenal Ulcers by Age in NSAID Users



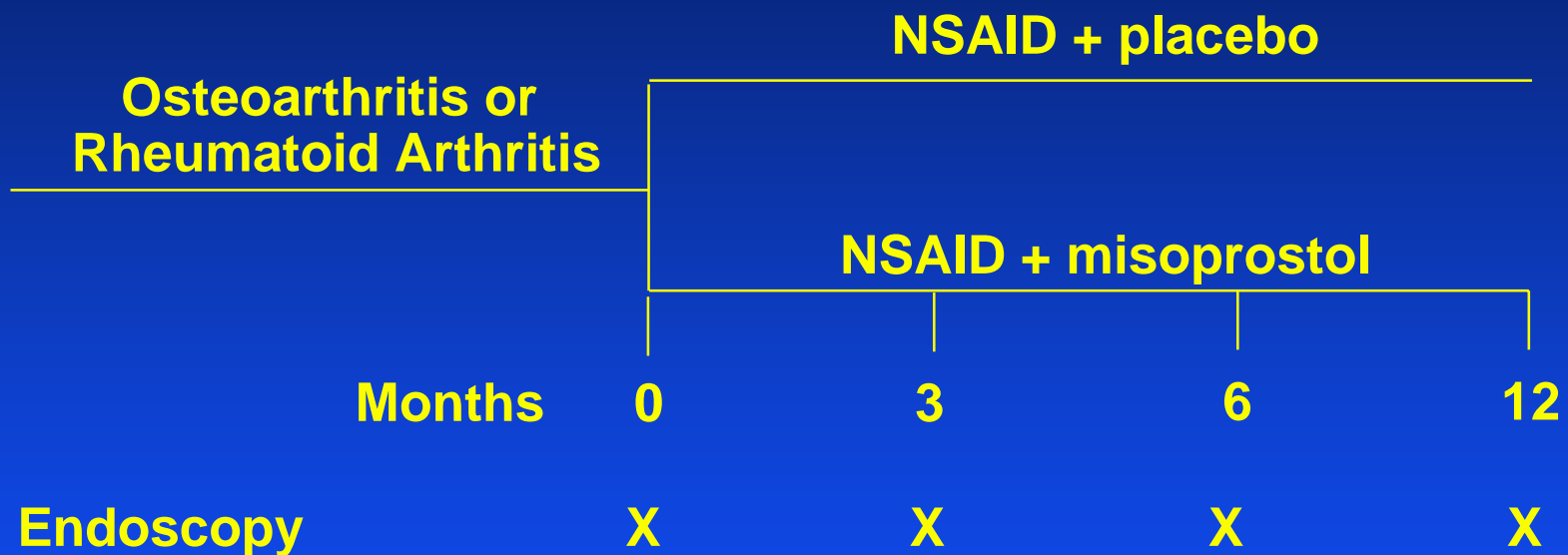
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Endoscopic Ulcers: Surrogates for Ulcer Complications?

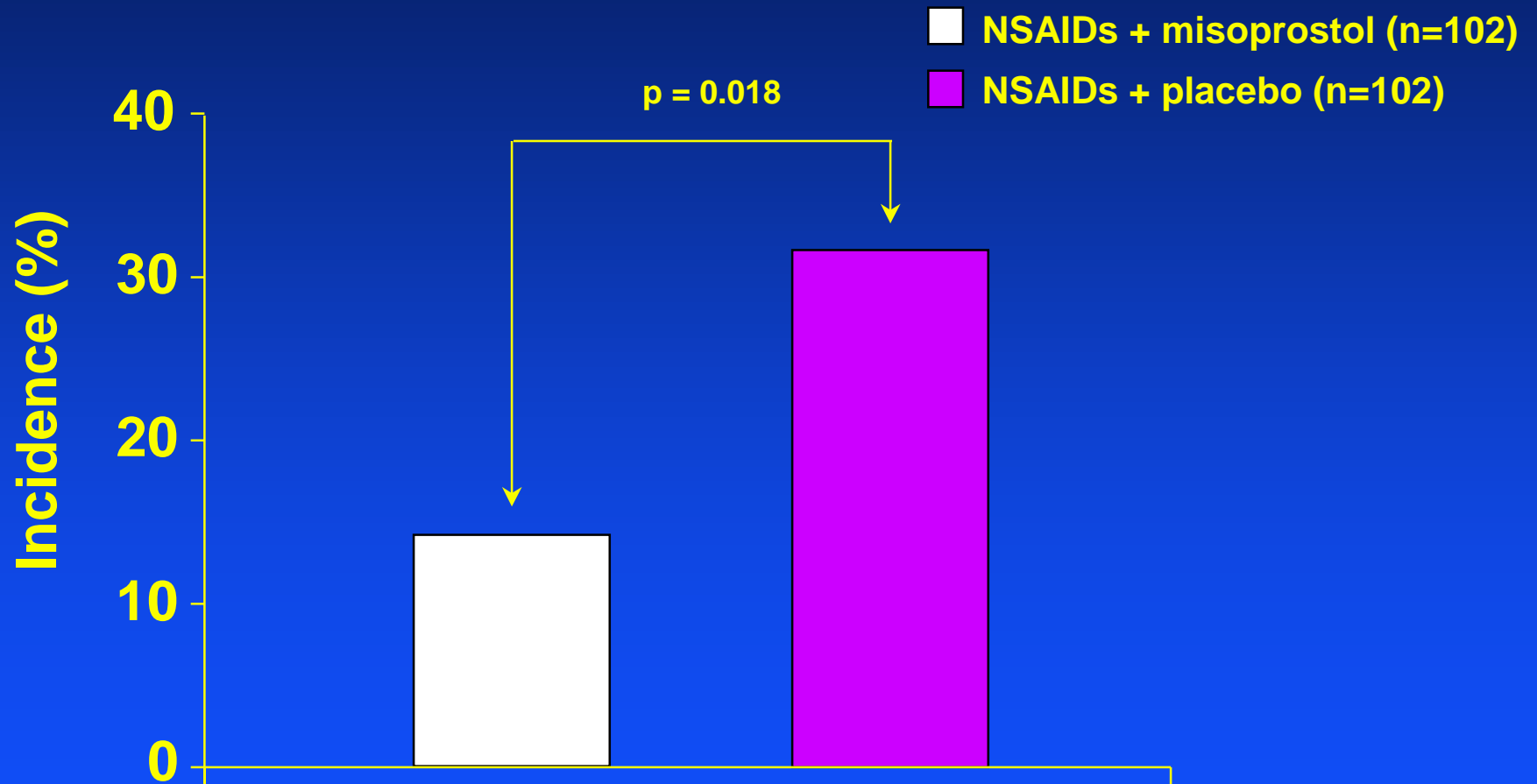
Endoscopic Ulcers: Surrogates for Ulcer Complications?

- **Rationale:**
 - NSAIDs reduce mucosal prostaglandins and cause ulcers
 - Ulcers can result in bleeding, perforation or outlet obstruction
- **Development program for misoprostol (synthetic prostaglandin) investigated the relationship**

Design: 52-Week Endoscopy Study



Incidence of Endoscopic Gastroduodenal Ulcers Developing Over One Year



Agrawal et al. Dig Dis Sci 1995;40:1125-1131

MUCOSA: A Study of Relevant Outcomes

- **Prospective randomized double-blind trial**
- **Primary endpoint**
 - Ulcer complications (bleeding, perforation, obstruction)

MUCOSA: Trial Design

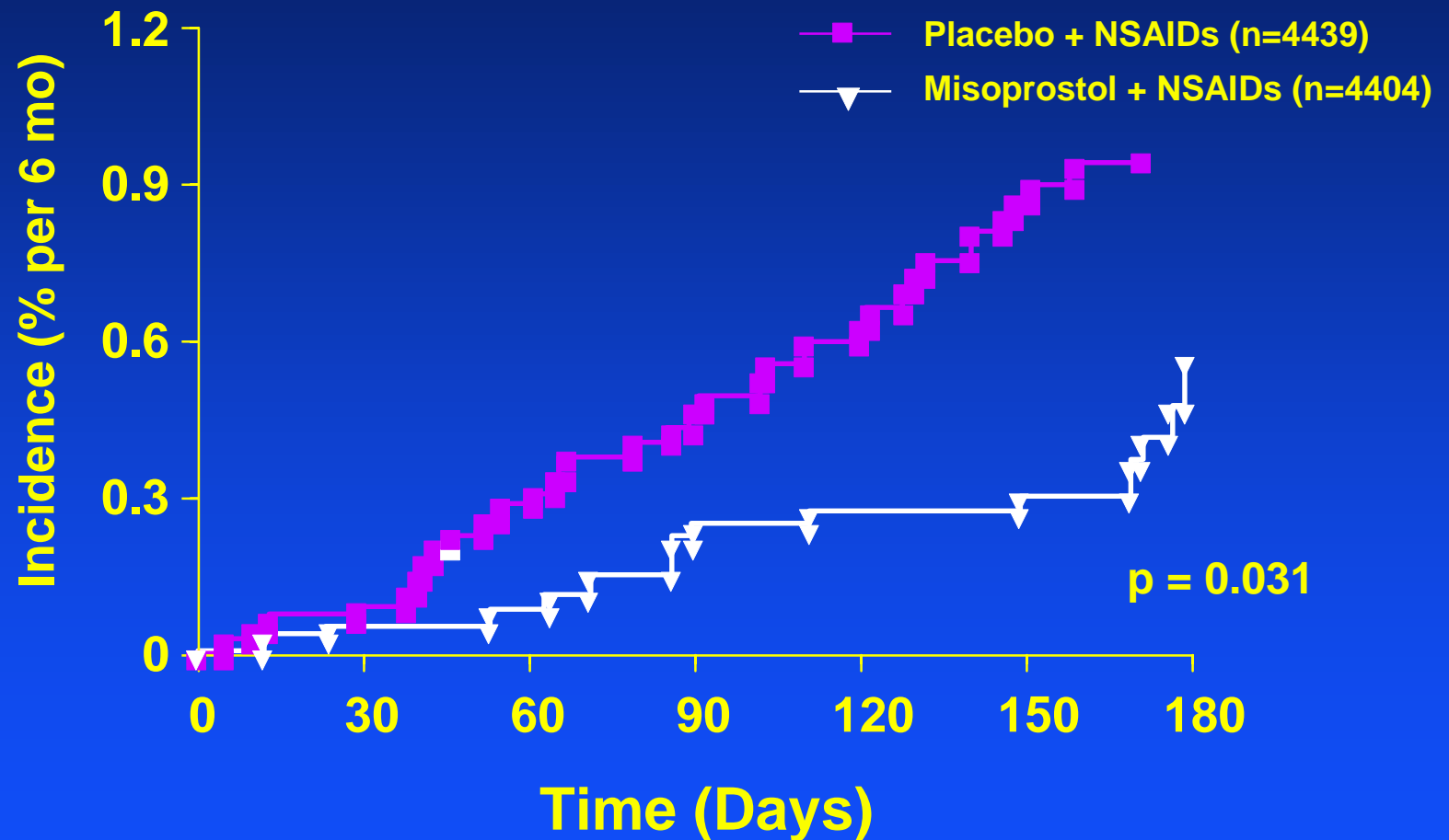
- **The design paralleled normal medical practice**
- **No scheduled endoscopy**

Ulcer Complications: MUCOSA Definitions

1. **Perforation**
2. **Gastric outlet obstruction**
3. **Lesion + hematemesis**
4. **Lesion+ melena**
5. **Lesion + evidence of bleeding (active bleeding, signs of recent hemorrhage, blood in the stomach)**
6. **Lesions + hemoccult positive stool + evidence of recent bleed (drop in hematocrit, orthostasis)**
7. **Hematemesis without identified lesion; no alternate cause**
8. **Melena plus hemoccult positive stool**

MUCOSA

Ulcer Complications: Time to Event Analysis



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

Conclusions: Prospective GI Safety Trials

- **Endoscopic ulcers and ulcer complications are reliable endpoints for investigating GI safety**
- **Endoscopic ulcers are predicative of ulcer complications**
 - **Exogenous prostaglandins reduce both endoscopic ulcers and ulcer complications by ~50%^{1,2}**

1. Agrawal et al. Dig Dis Sci 1995;40:1125-1131

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

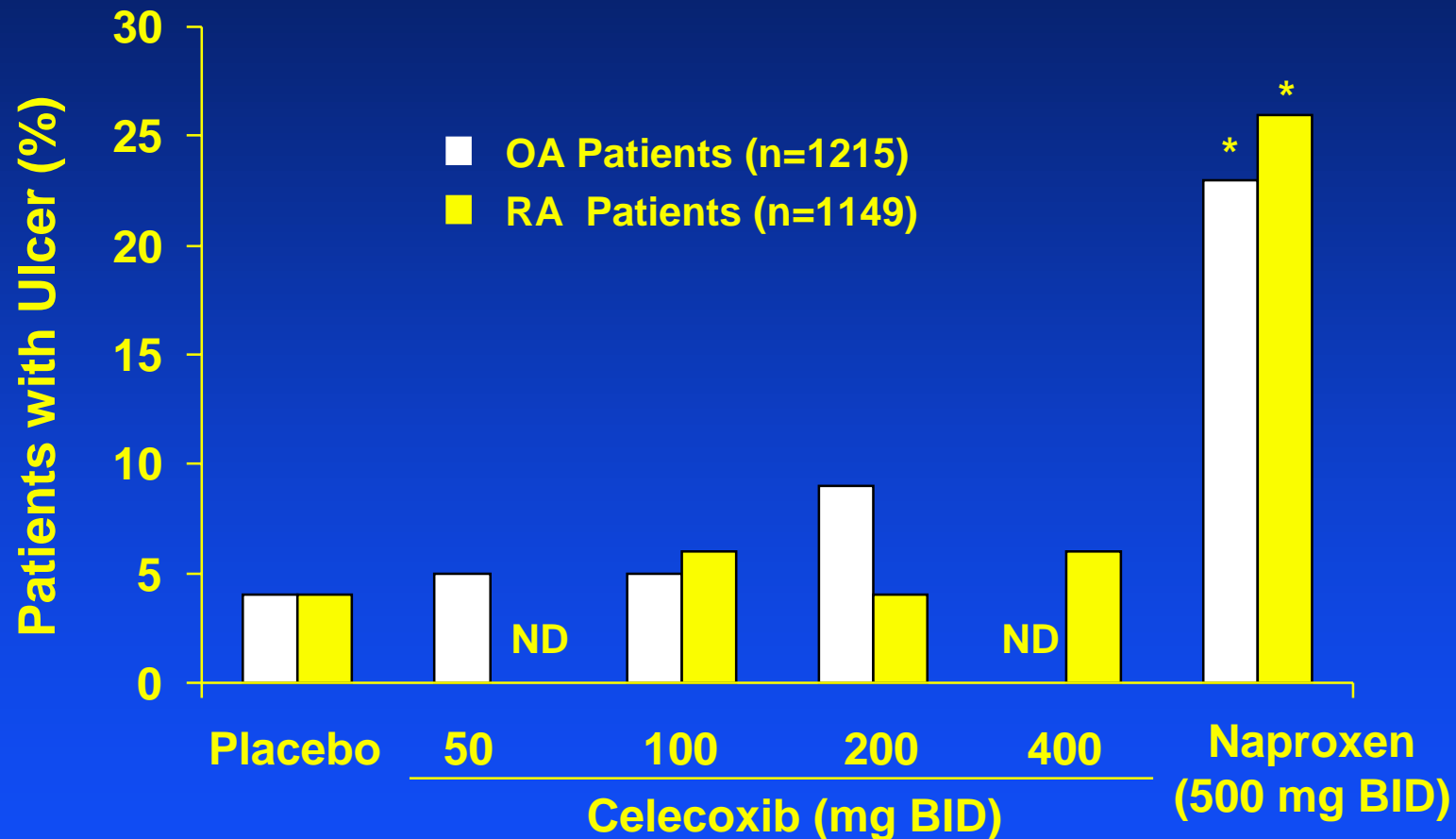
Overview

- NSAID-associated upper GI toxicity
- Prospective Trials to Evaluate Upper GI Safety
- **Upper GI Safety of Celecoxib**

NDA: Celecoxib Endoscopy Studies

- Endoscopies in over 4,700 arthritis patients
- Incidence of upper GI ulcers
 - similar to placebo in replicate studies
 - statistically lower compared to:
 - naproxen
 - diclofenac
 - ibuprofen

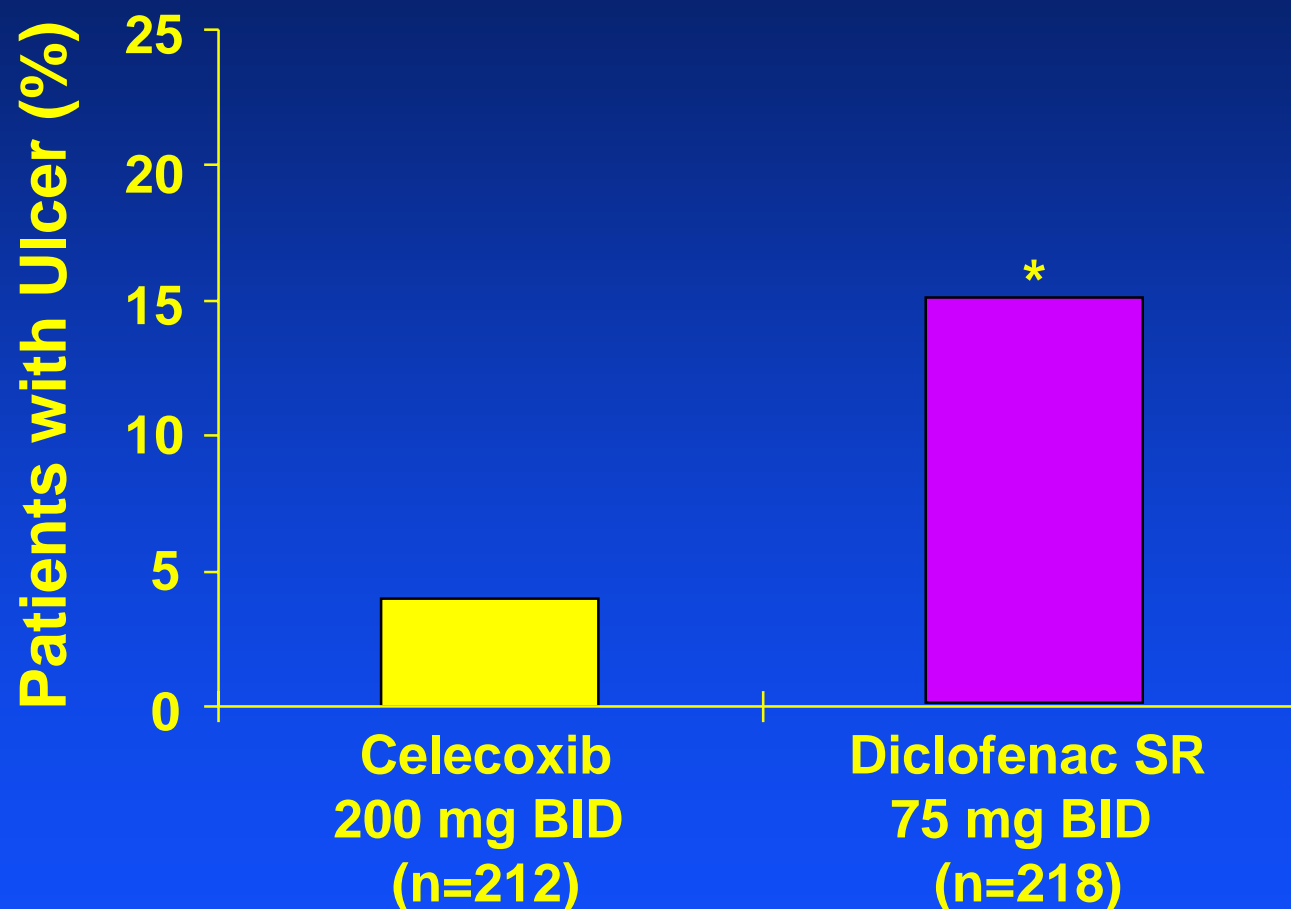
NDA: Incidence of Gastroduodenal Ulcers 3 Month Endoscopy Trials



ND = Not Done

* Significantly different from all other treatments; $p < 0.05$

NDA: Incidence of Gastroduodenal Ulcers 6-Month Endoscopic Study



* Significantly different from celecoxib; $p < 0.001$

NDA: Prospective Evaluation of GI Effects

- **Endoscopy findings**
 - 5 arthritis trials
- **Analyses of upper GI ulcer complications**

Methods: Analyses of Ulcer Complications

- 14 randomized controlled trials and one open-label trial of OA and RA patients
- Criteria for upper GI ulcer complications were prospectively developed
- Cases were adjudicated by Events Committee
 - Blinded to the trial and
 - Blinded to the study drug

Upper GI Ulcer Complications- Definitions

- **Upper GI Perforation**
- **Gastric Outlet Obstruction**
- **Upper GI Bleeding**

NDA: Ulcer Complications

Controlled Trials

Open Label Trial

No. Patients

11,008

5155

Duration

12 weeks

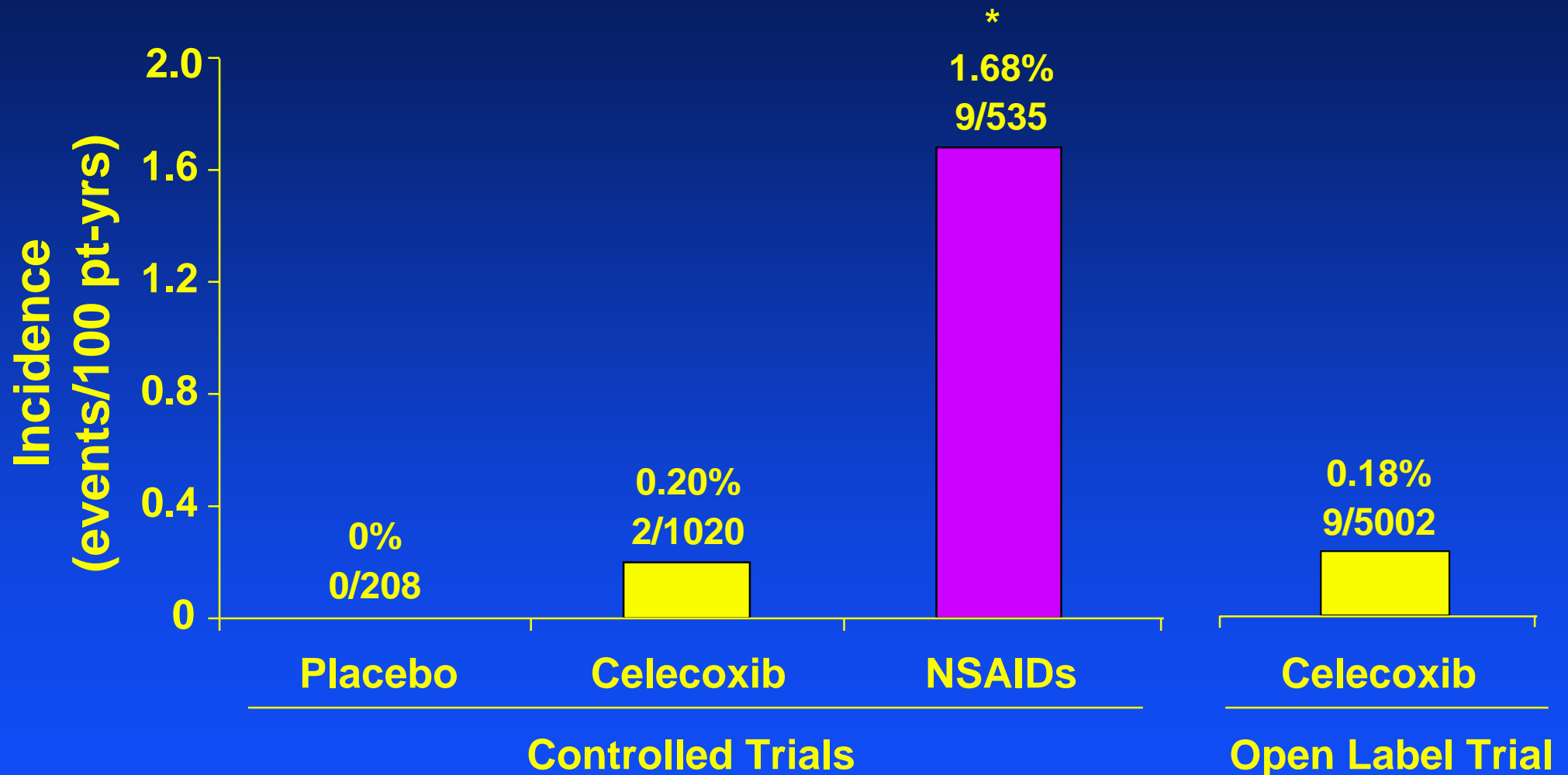
2 years

Primary

Celecoxib Doses

200 – 400 mg /day

NDA: Incidence of Ulcer Complications



* Significantly different from all other treatments; $p < 0.05$

Goldstein et al. *Am J Gastroenterol* 2000;95:1681-1690

NDA Conclusions: GI Effects of Celecoxib

- **Incidence of endoscopic ulcers**
 - Similar to placebo
 - Lower than NSAIDs
- **Endoscopic ulcer data were predictive of ulcer complication results**
- **Incidence of ulcer complications**
 - Lower than NSAIDs

Clinical Relevance

- **The generalizability of the ulcer complications analysis was uncertain:**
 - About 40% of patients were ulcer free by endoscopy at study entry
 - Most studies were 3 months in duration

Rationale for CLASS

- **Rigorous assessment of upper GI safety of celecoxib:**
 - Using clinically relevant outcomes
 - In patients that fully represent the intended population
 - With chronic exposure

CLASS Design

- **Large prospective randomized study**
- **Mirror usual medical practice**
 - Endoscopy performed “for cause”
- **Included:**
 - OA and RA patients
 - High risk patients
 - Low dose ASA
- **Celecoxib 400 mg BID (4X OA dose; 2X highest RA dose)**
- **Longer duration of exposure (up to 15 mo)**

The End

Safety Profile of Celecoxib:

CLASS

Celecoxib Long-term Arthritis Safety Study

James B. Lefkowitz, MD
Sr. Director, Arthritis Clinical R&D

CLASS Design Overview

- **“Real world” study**
 - Clinical practice conditions
 - Low dose aspirin allowed
 - RA and OA patients included
- **Stringent test of safety**
 - Celecoxib: 2-4x RA and OA doses
 - NSAID Comparators: Ibuprofen,
Diclofenac

CLASS Design

- Objectives
- Study design
- Analysis plan
- Oversight committees

Objectives

Celecoxib vs. NSAIDs (ibuprofen, diclofenac)

- **Compare the incidence of:**
 - ulcer complications
 - symptomatic ulcers
- **Evaluate impact of risk factors on outcome: ASA**
- **Compare general safety and tolerability**

CLASS Design

- Objectives
- Study design
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- Oversight committees

CLASS Trial

- Design:***
- Double-blind, randomized, parallel group
 - Two protocols - pooled analysis
 - Minimum 6 months exposure
- Inclusions:***
- OA and RA patients
- Exclusions:***
- History of:
 - recent or active GI disease
 - Labeled contraindications

CLASS Trial

Co-Meds:

- **Permitted:**
 - ASA \leq 325 mg/d
 - limited antacid use
- **Excluded:**
 - anti-ulcer drugs (H₂RAs, PPIs)
 - NSAIDs

Treatments:

- Celecoxib 400 mg BID
- Diclofenac 75 mg BID
- Ibuprofen 800 mg TID

CLASS Trial

- **Power calculation:**
 - **Ulcer complication rate:**
 - celecoxib vs. NSAIDs
0.3 vs. 1.2 events/100 pt-yrs
 - **assumptions:**
 - constant incidence rates
 - ASA use ~ 12%
 - **40 total events; 8000 patients**
 - 4000 celecoxib
 - 4000 NSAIDs (2000 per comparator)

CLASS Design

- Objectives
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Analysis Plan

- **Endpoints analyzed**
 - Ulcer complications
 - Symptomatic ulcers/ulcer complications
- **Statistics**
 - Intent-to-Treat Analysis
 - Log-rank test of time-to-event
 - Step-wise comparison
 - Celecoxib vs. NSAIDs combined
 - Celecoxib vs. each NSAID

Analysis Plan

- **Risk Factors**
 - ASA use
 - Risk factors defined by MUCOSA
 - Age ≥ 75 y
 - History of ulcer
 - History of GI bleeding
 - Cardiovascular disease
 - Others (e.g., alcohol intake, smoking)

CLASS Design

- Objectives
- Study design
- Analysis plan
- Oversight committees

CLASS Committees

Executive Committee

- Fred Silverstein, M.D (Chair)
- Lee Simon, M.D.
- Gerald Faich, M.D.

GI Events Committee

- Jay Goldstein, M.D. (Chair)
- Naurang Agrawal, M.D.
- William Stenson, M.D.
- Glenn Eisen, M.D.



Data Safety Monitoring Board

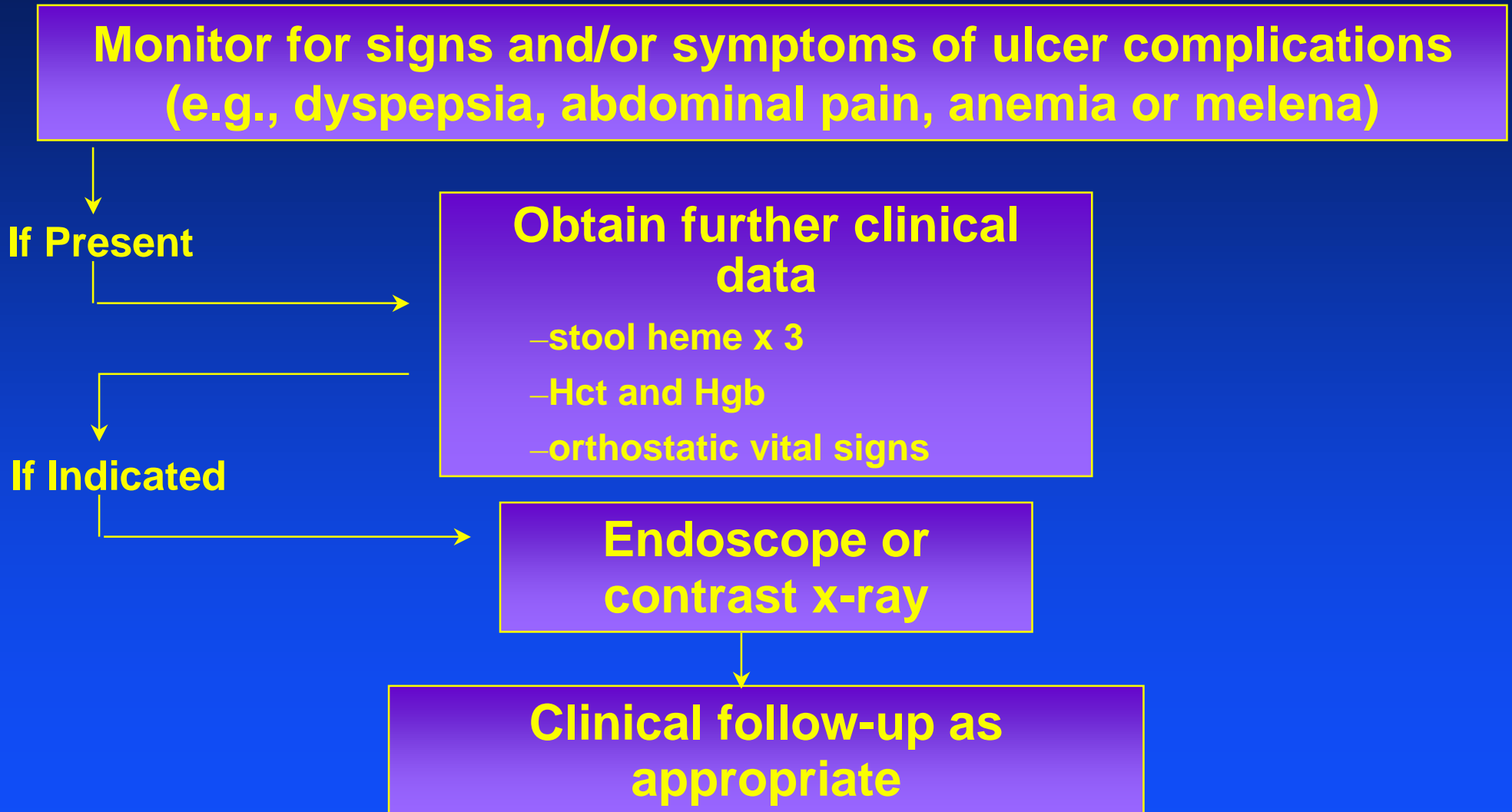
- Gerald Faich, M.D. (Chair)
- Robert Makuch, Ph.D.
- Andrew Whelton, M.D.
- Theodore Pincus, M.D.



CLASS Committee Charters

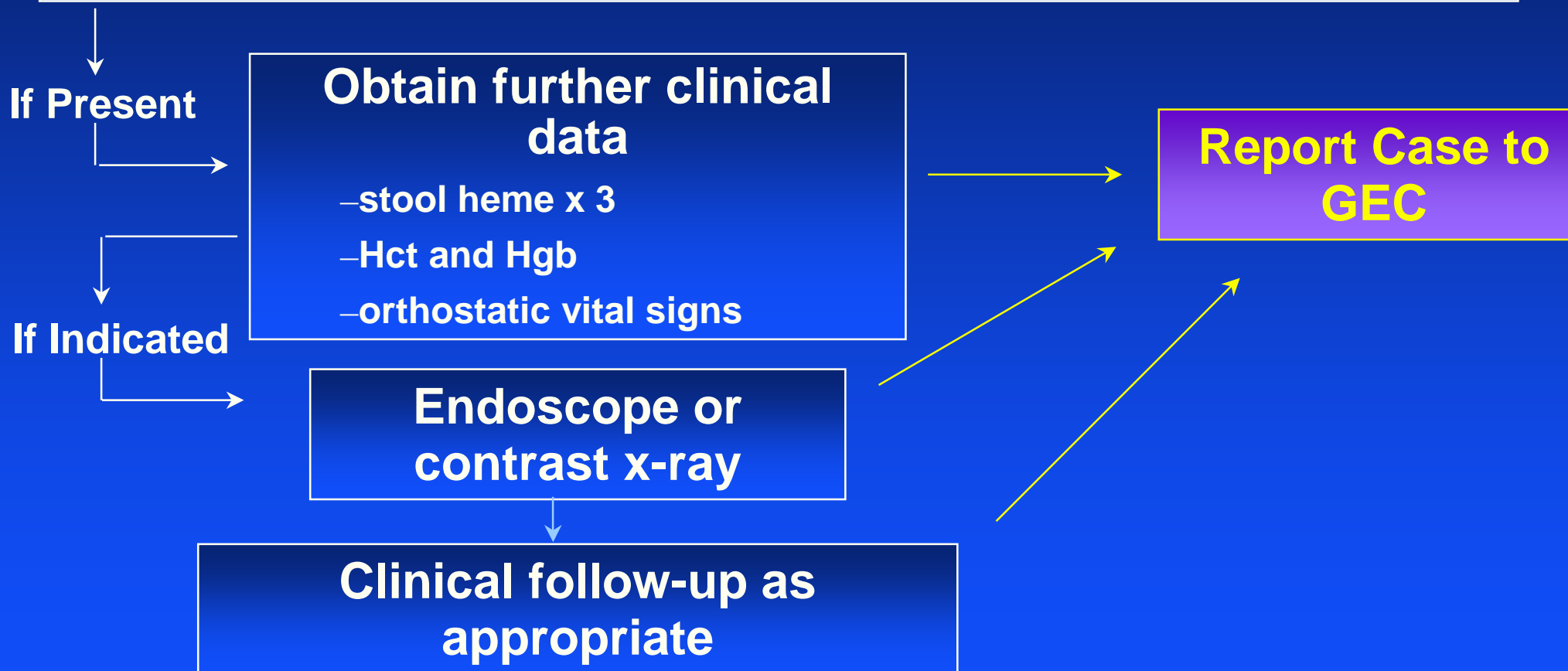
- **GI Events Committee - GEC**
 - Review potential GI events
- **Data Safety Monitoring Board - DSMB**
 - Evaluate safety data
- **Executive Committee - EC**
 - Monitor and administer study conduct

Algorithm for Work-Up of Suspected Events by Investigator

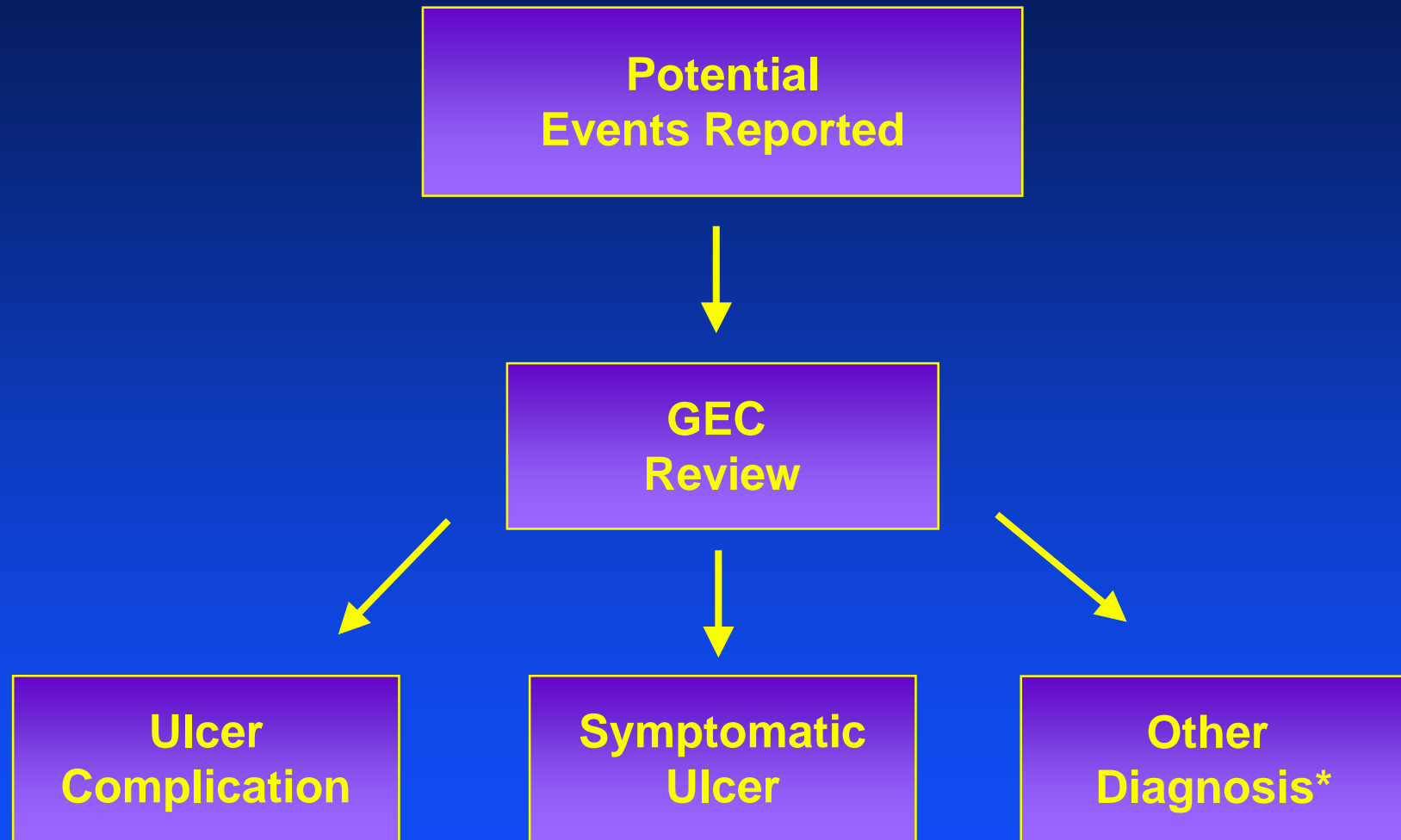


Algorithm for Work-Up of Suspected Events by Investigator

**Monitor for signs and/or symptoms of ulcer complications
(e.g., dyspepsia, abdominal pain, anemia or melena)**



Evaluation Process



***Other diagnoses: esophagitis, gastritis, duodenitis, anemia etc**

Ulcer Complications

Prospectively defined:

- Bleeding
- Perforation
- Gastric Outlet Obstruction

All ulcer complications required endoscopic/contrast x-ray evidence of an ulcer or large erosion

Ulcer Complications: Bleeding

- 1A. Hematemesis + lesion**
- 1B. Active bleeding/stigmata + lesion**
- 1C. Melena + lesion**
- 1D. Hemoccult positive stool + lesion + clinical evidence of blood loss**

Symptomatic Ulcers

Prospectively defined:

- Mucosal break with unequivocal depth
- Found on “for cause” work-up (to investigate a sign or symptom)

All ulcers required endoscopic/contrast x-ray evidence

CLASS Results

GI Outcomes

- Study population
- GI Outcomes
 - Intent-to-treat
 - Risk Factors
 - Effect of ASA Use
 - RA vs OA
- Sources of Bias

General Safety

- Overall Safety
- Analysis by System
 - GI
 - Renal
 - Hepatic
 - CV/Thromboembolic
- Analysis in ASA users
- Analysis by Age

Demographics

	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Age (yrs, mean)	60.6	60.1	59.5
Female (%)	69	67	71
Ethnicity (%)			
Caucasian	88.5	89.4	86.3
Black	7.5	7.6	8.7
Other	4.0	3.1	5.1
OA (%)	72.7	72.8	72.2

Baseline Risk Factors for Ulcer Complications

	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
≥75 years (%)	12.2	11.8	10.9
Hx GI Bleed (%)	1.7	1.5	1.4
Hx of Ulcer (%)	8.4	8.5	7.6
Hx of CV Dz (%)	40.2	40.3	40.0

Concurrent Medications

	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
ASA (%)	22.1	22.3	20.8
Steroids¹ (%)	30.6	28.5	30.6
Anticoagulants (%)	1.1	1.2	1.0
OTC NSAIDs			
Ibuprofen (%)	4.4	4.9	3.3
Naproxen (%)	1.8	1.3	1.5

1. Includes oral, IA, IM, topical and inhaled steroids

Treatment Exposure

	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Mean Duration (days)	212	197	206
Maximum Exposure (days)	446	374	456
Total Exposure (pt-yrs)	2320	1081	1123

Demographics - OA

	Celecoxib 400 mg BID (n=2898)	Diclofenac 75 mg BID (n=1453)	Ibuprofen 800 mg TID (n=1434)
Age (yrs, mean)	62.4	62.0	60.9
Female (%)	67	68	69
Duration (yrs)	10.3	10.4	9.9
Prior NSAID use (%)*	71	71	73

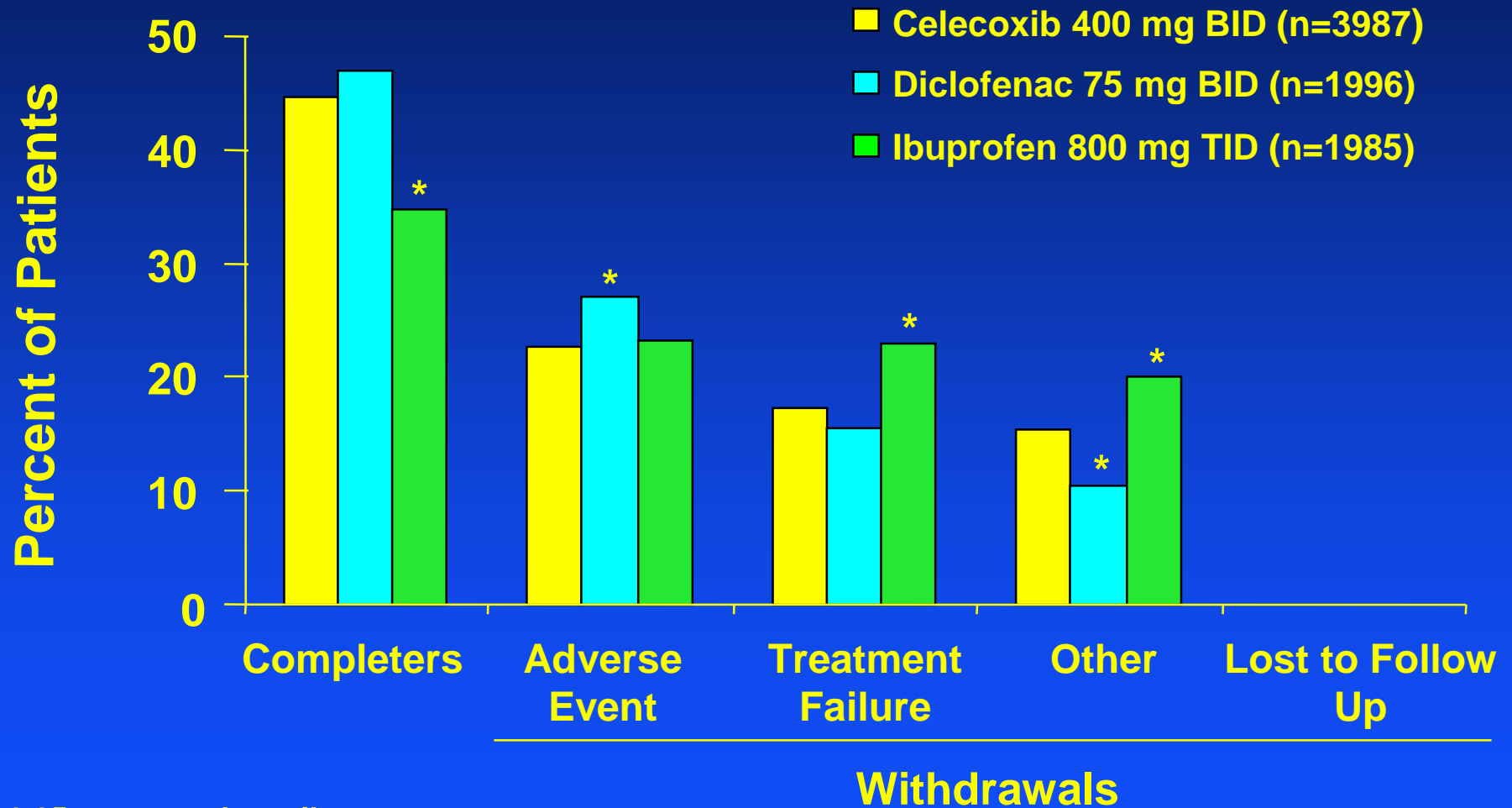
***Excluding ASA**

Demographics - RA

	Celecoxib 400 mg BID (n=1089)	Diclofenac 75 mg BID (n=543)	Ibuprofen 800 mg TID (n=551)
Age (yrs, mean)	55.8	55.1	55.8
Female (%)	71	65	74
Duration (yrs)	11.3	10.5	10.9
Prior NSAID use (%)*	76	74	78
Steroid use (oral, %)	45	43	48
Methotrexate use (%)	44	46	39

*Excluding ASA

Patient Disposition



* $p < 0.05$ versus celecoxib

Study Population - Summary

- **Representative OA/RA cohort**
 - **ASA use: 22%**
- **No lost to follow up patients**
- **Substantial exposure: up to 15 months**
- **Higher incidence of withdrawals vs. celecoxib:**
 - **ibuprofen: treatment failure**
 - **diclofenac: adverse events**

CLASS Results

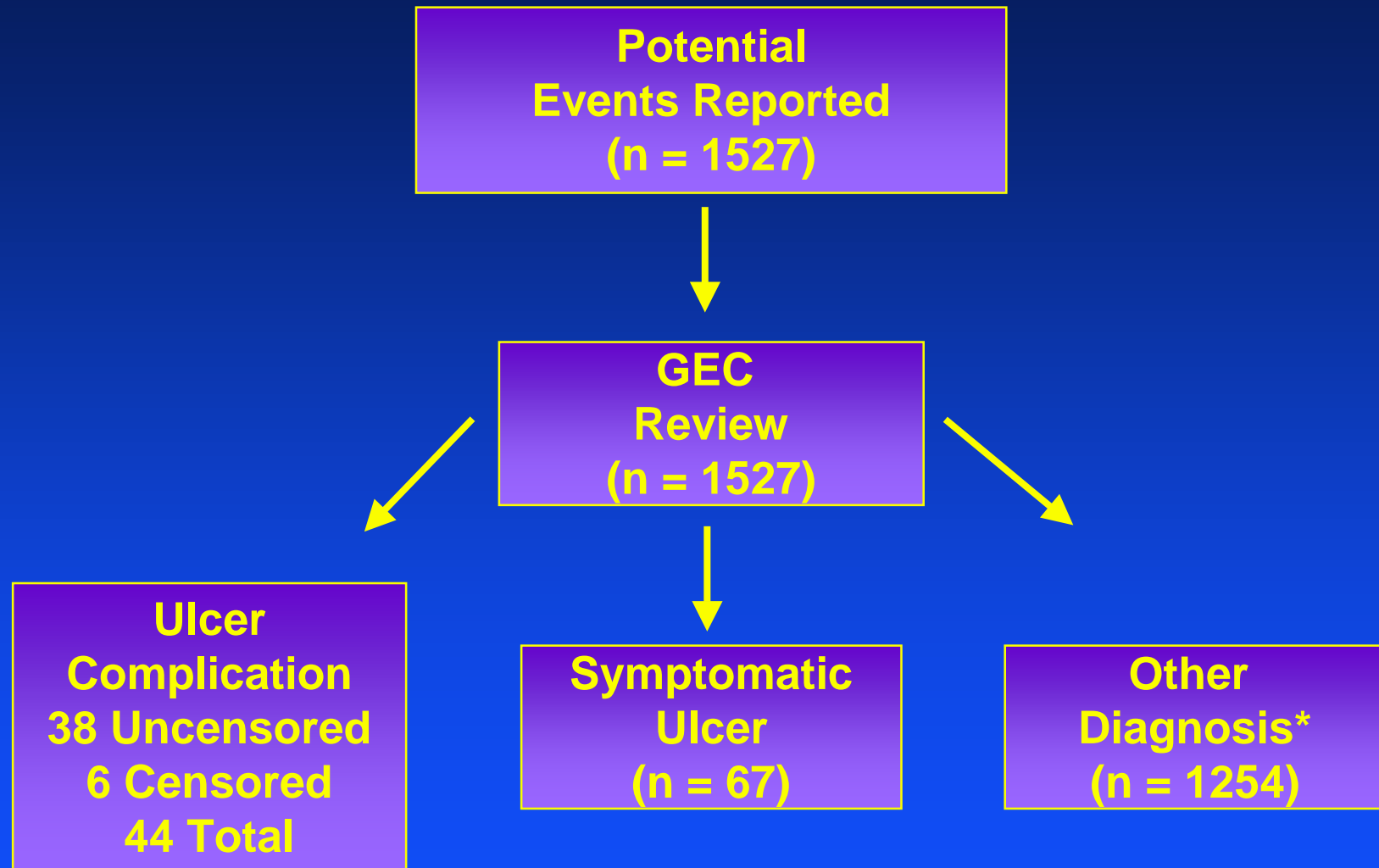
GI Outcomes

- **Study population**
- **GI Outcomes**
 - **Intent-to-treat**
 - **Risk Factors**
 - **Effect of ASA Use**
 - **RA vs OA**
- **Sources of Bias**

General Safety

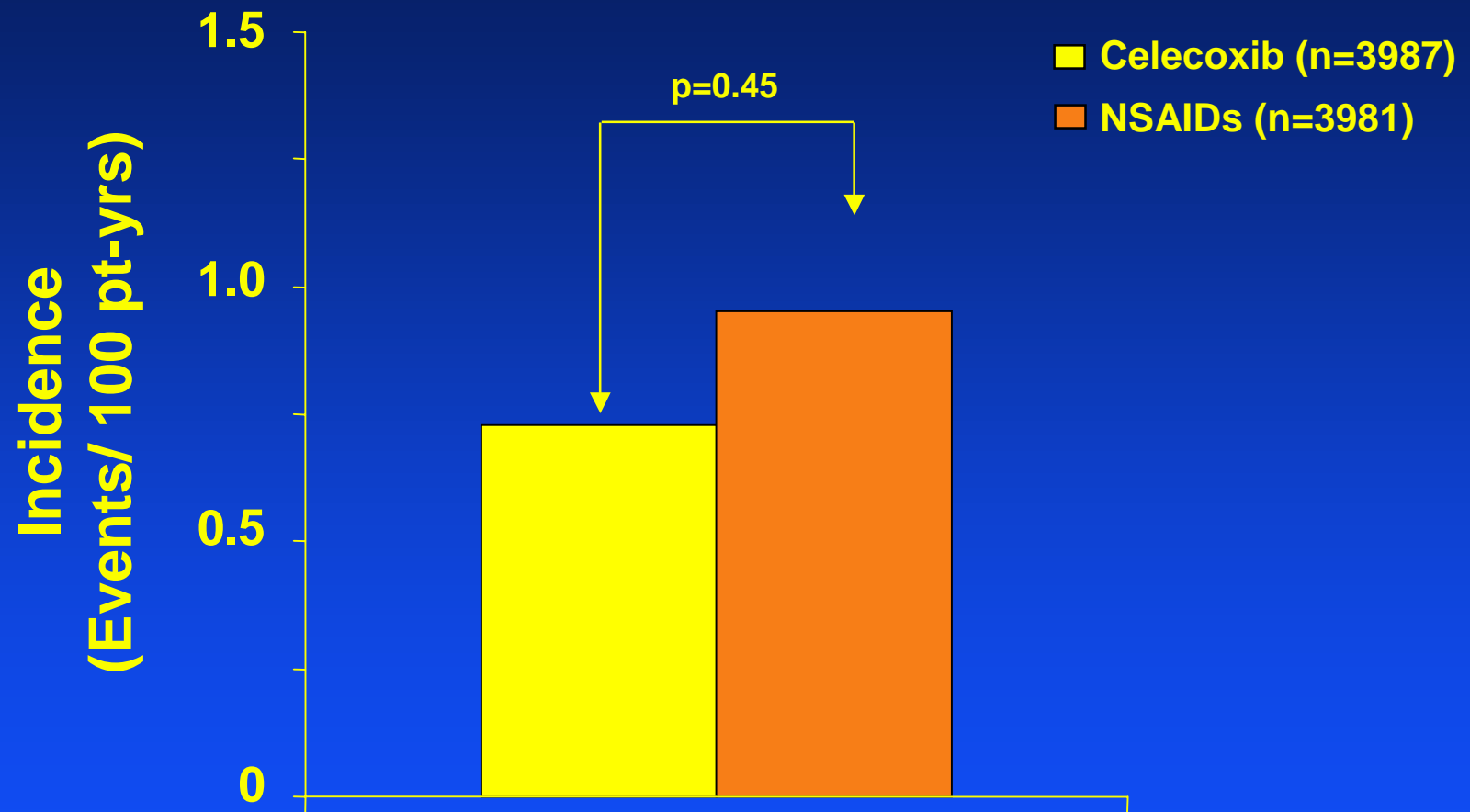
- **Overall Safety**
- **Analysis by System**
 - **GI**
 - **Renal**
 - **Hepatic**
 - **CV/Thromboembolic**
- **Analysis in ASA users**
- **Analysis by Age**

Evaluation Process



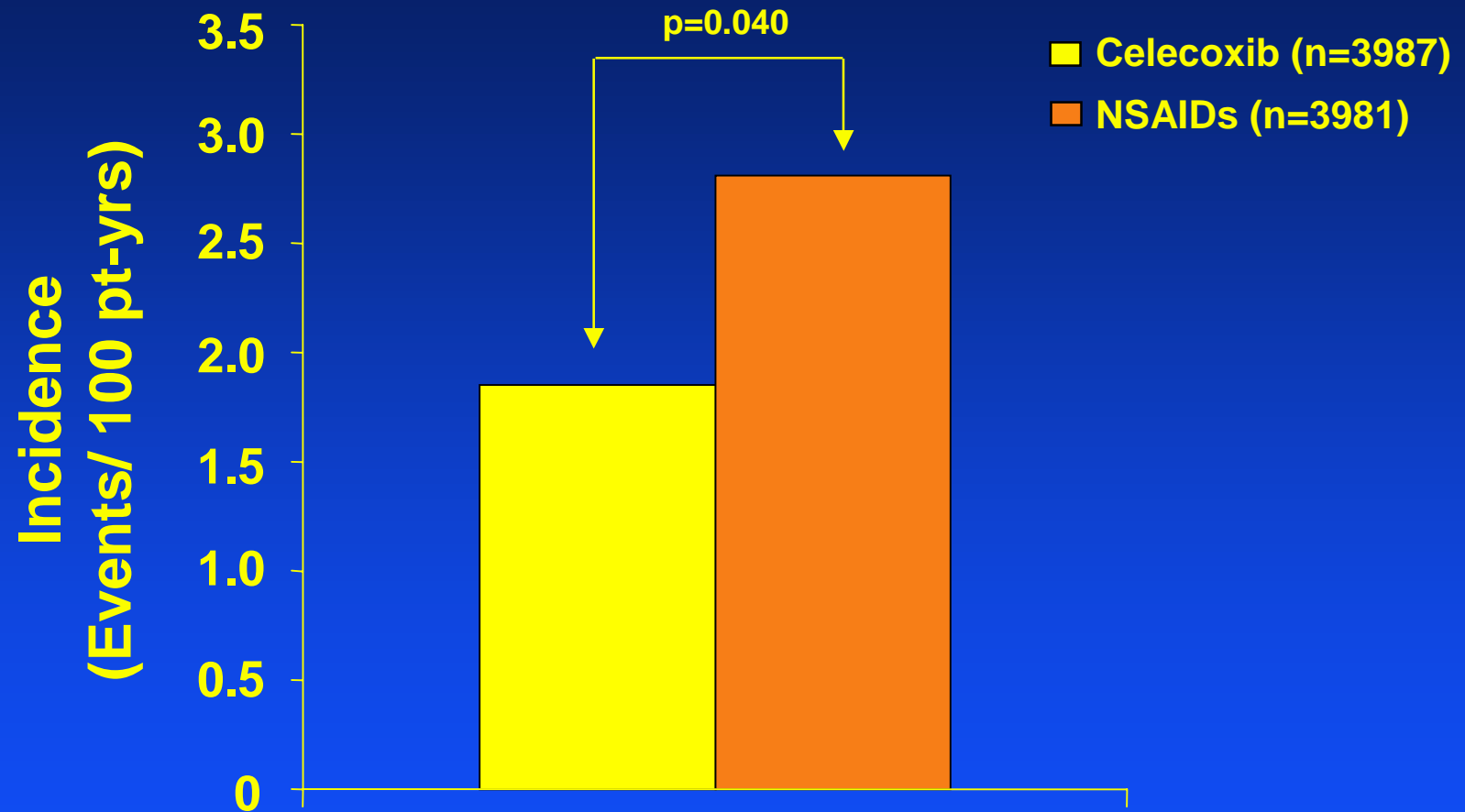
*Other diagnoses: esophagitis, gastritis, duodenitis, anemia etc

Ulcer Complications



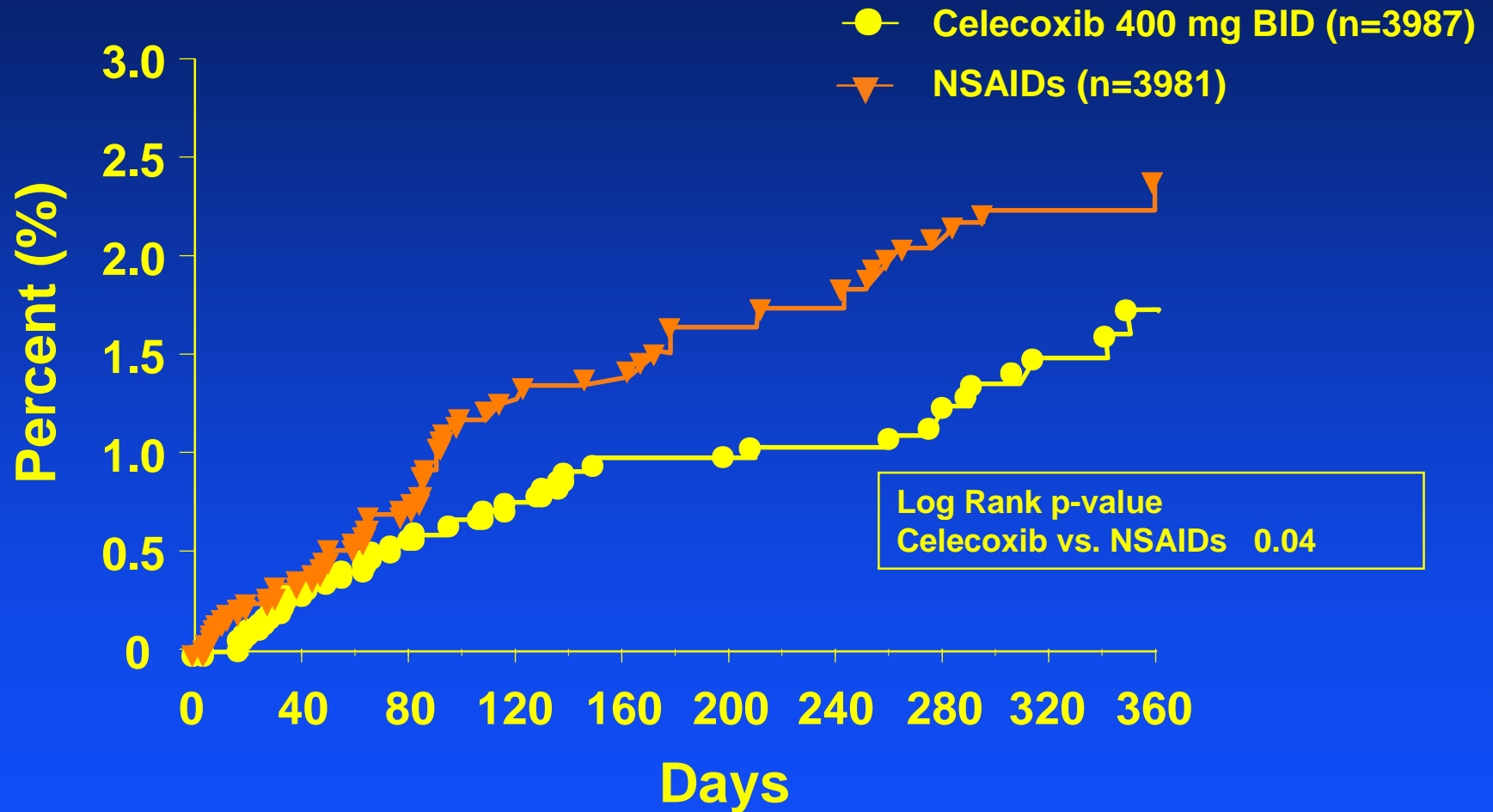
p value by log rank test

Symptomatic Ulcers/Ulcer Complications

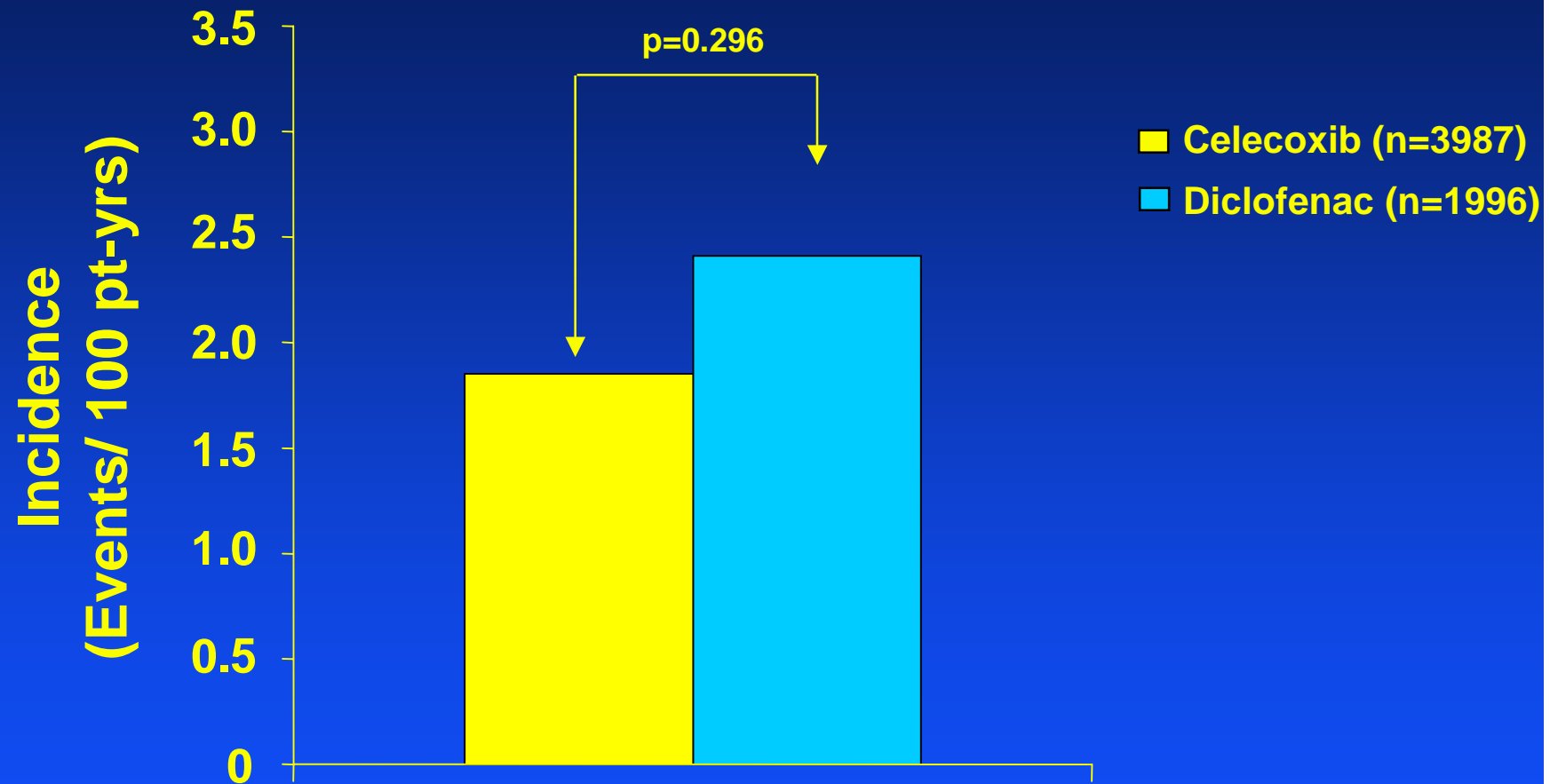


p value by log rank test

Incidence of Symptomatic Ulcers/ Ulcer Complications

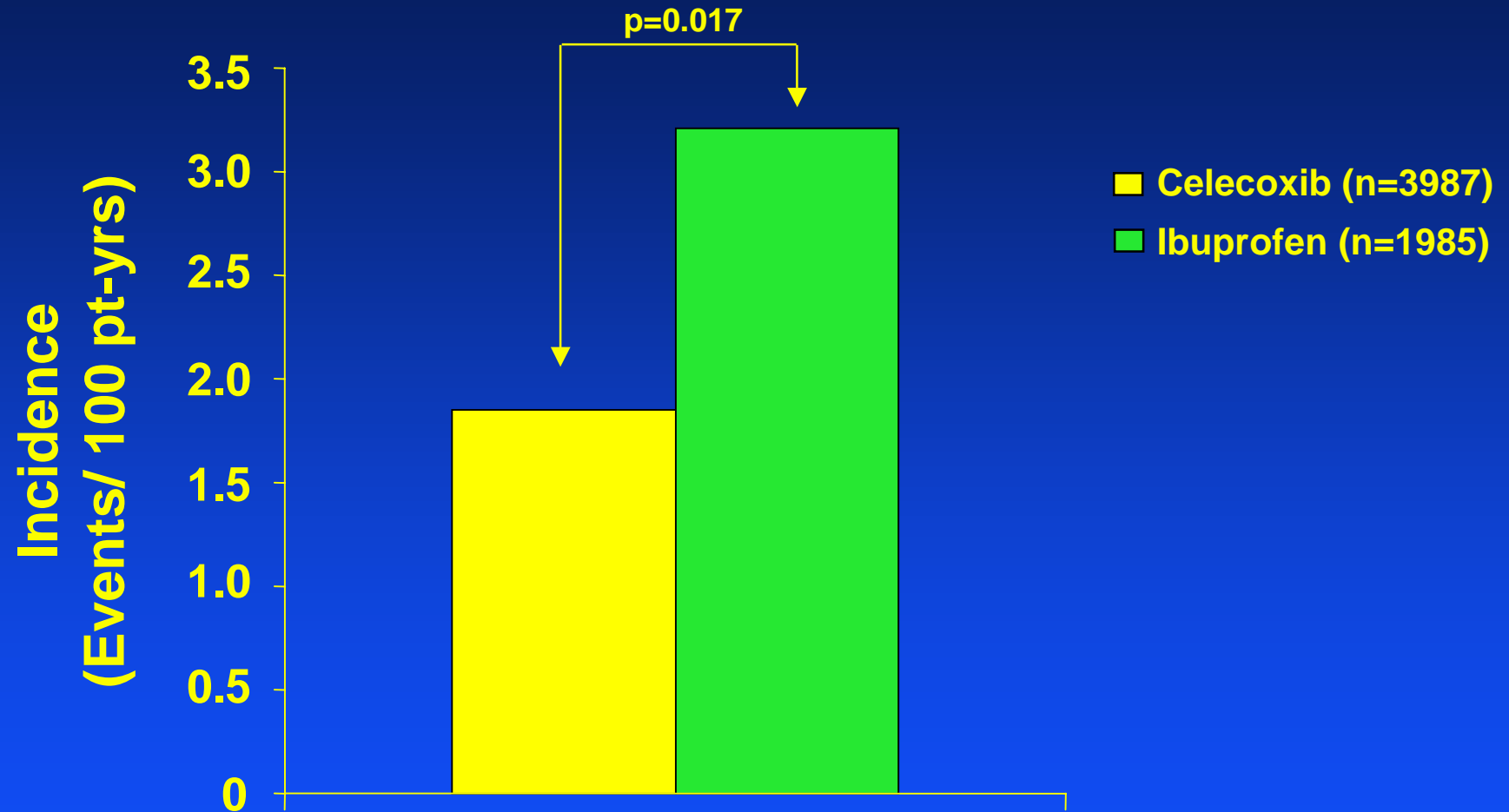


Symptomatic Ulcer/Ulcer Complications



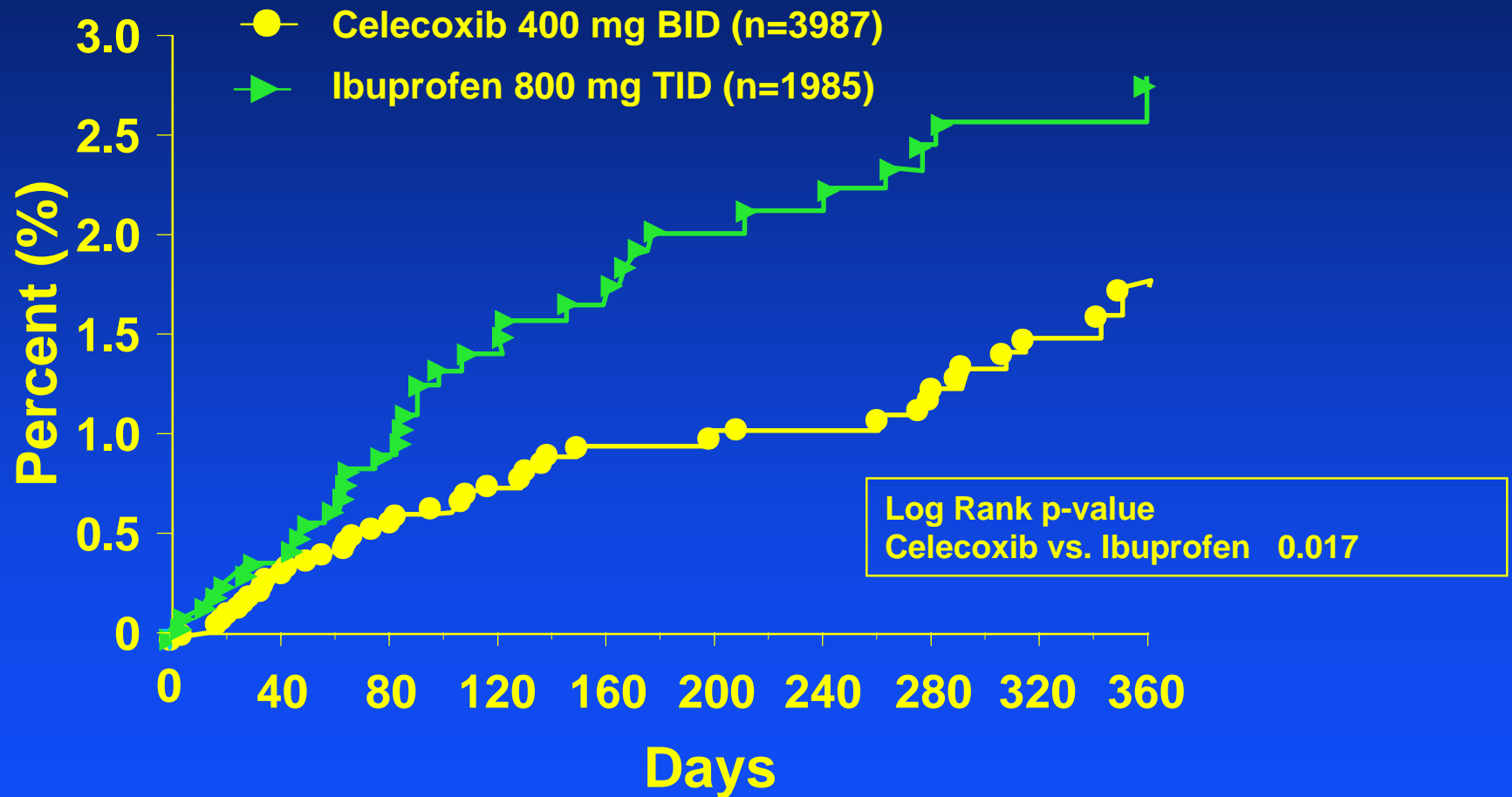
p value by log rank test

Symptomatic Ulcer/Ulcer Complications



p value by log rank test

Incidence of Symptomatic Ulcers/ Ulcer Complications



UGI Outcomes - Summary

- **Celecoxib vs. NSAIDs:**
 - Lower incidence of symptomatic ulcers/ulcer complications
- **Celecoxib vs. ibuprofen:**
 - Lower incidence of symptomatic ulcers/ulcer complications

CLASS Results

GI Outcomes

- **Study population**
- **GI Outcomes**
 - **Intent-to-treat**
 - **Risk Factors**
 - **Effect of ASA Use**
 - **RA vs OA**
- **Sources of Bias**

General Safety

- **Overall Safety**
- **Analysis by System**
 - **GI**
 - **Renal**
 - **Hepatic**
 - **CV/Thromboembolic**
- **Analysis in ASA users**
- **Analysis by Age**

Prespecified Risk Factor Analyses

- **Demographics:**
 - Age, Gender, Alcohol or Tobacco use
- **Disease:**
 - OA vs. RA, Duration, Severity
- **Concomitant medications:**
 - ASA, Steroids, Anti-coagulants
- **History of:**
 - UGI Bleed, GD Ulcer, CV Disease
- **Positive *H. pylori* serology**

Risk Factors for Symptomatic Ulcers/ Ulcer Complications

- **Significant:**
 - Age ≥ 75 yrs
 - History of ulcer disease
 - History of UGI bleeding
 - ASA use (CV disease)
- **Significant effect on treatment outcome:**
 - ASA

Risk Factors for Symptomatic Ulcers/ Ulcer Complications

- **Not significant:**
 - **Gender**
 - **Alcohol**
 - **Tobacco use**
 - **Arthritis type (OA vs RA)
or duration**
 - **Steroid use**

Risk Factors - Summary

- **Data confirm MUCOSA study risk factor analysis**
- **ASA use affects analysis of UGI outcomes**

CLASS Results

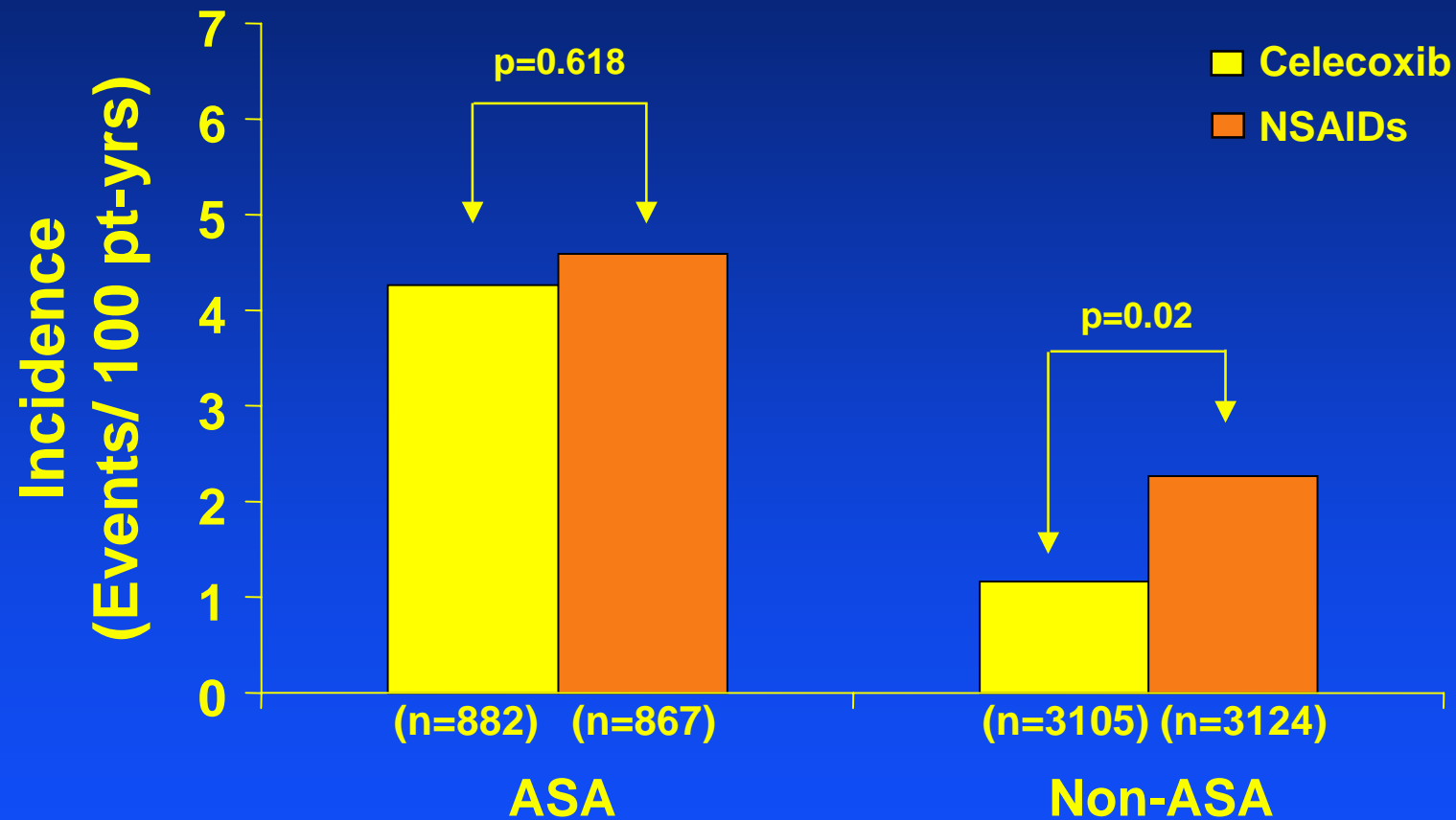
GI Outcomes

- **Study population**
- **GI Outcomes**
 - **Intent-to-treat**
 - **Risk Factors**
 - **Effect of ASA Use**
 - **RA vs OA**
- **Sources of Bias**

General Safety

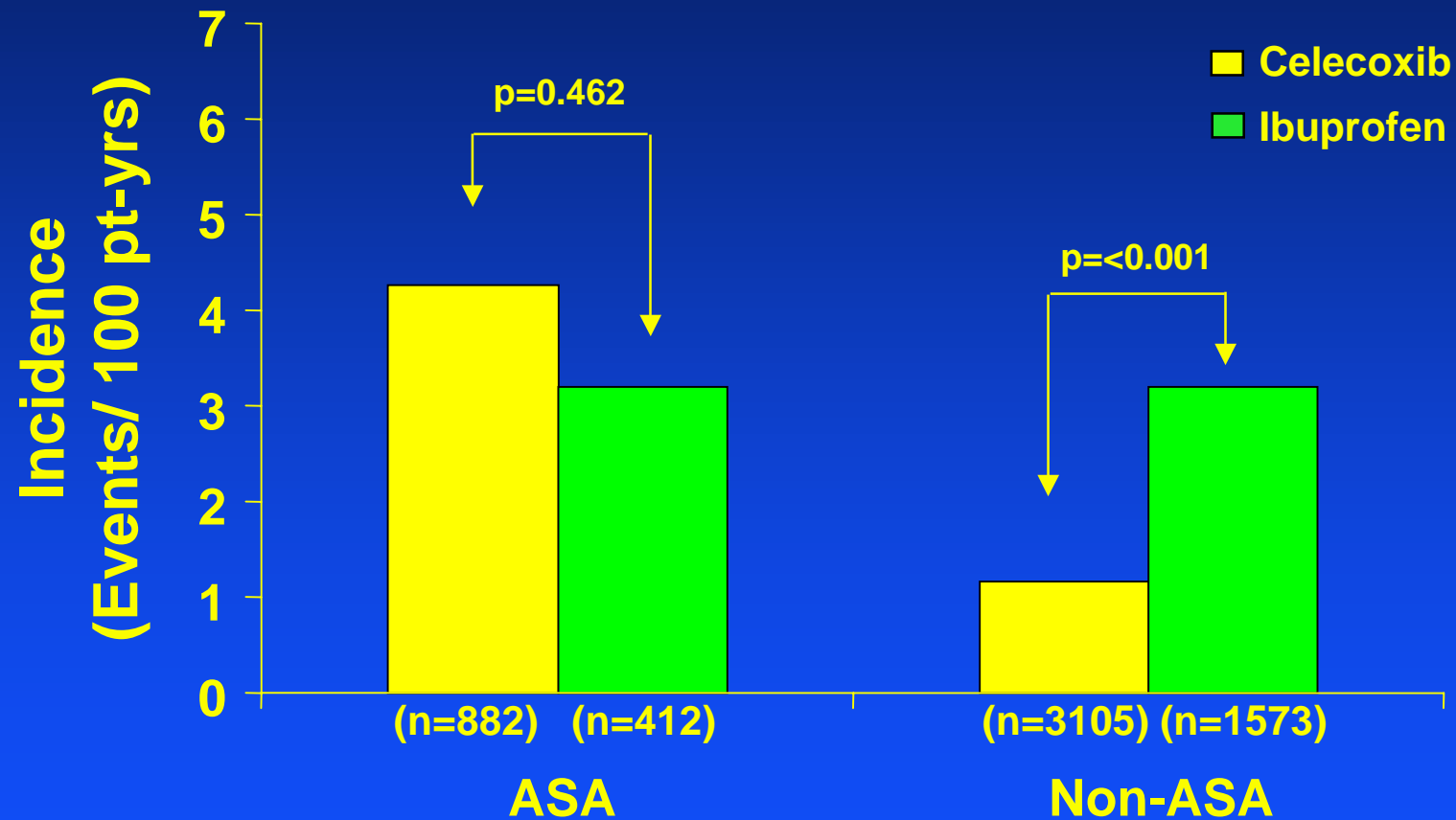
- **Overall Safety**
- **Analysis by System**
 - **GI**
 - **Renal**
 - **Hepatic**
 - **CV/Thromboembolic**
- **Analysis in ASA users**
- **Analysis by Age**

Symptomatic Ulcer/Ulcer Complications



p value by log rank test

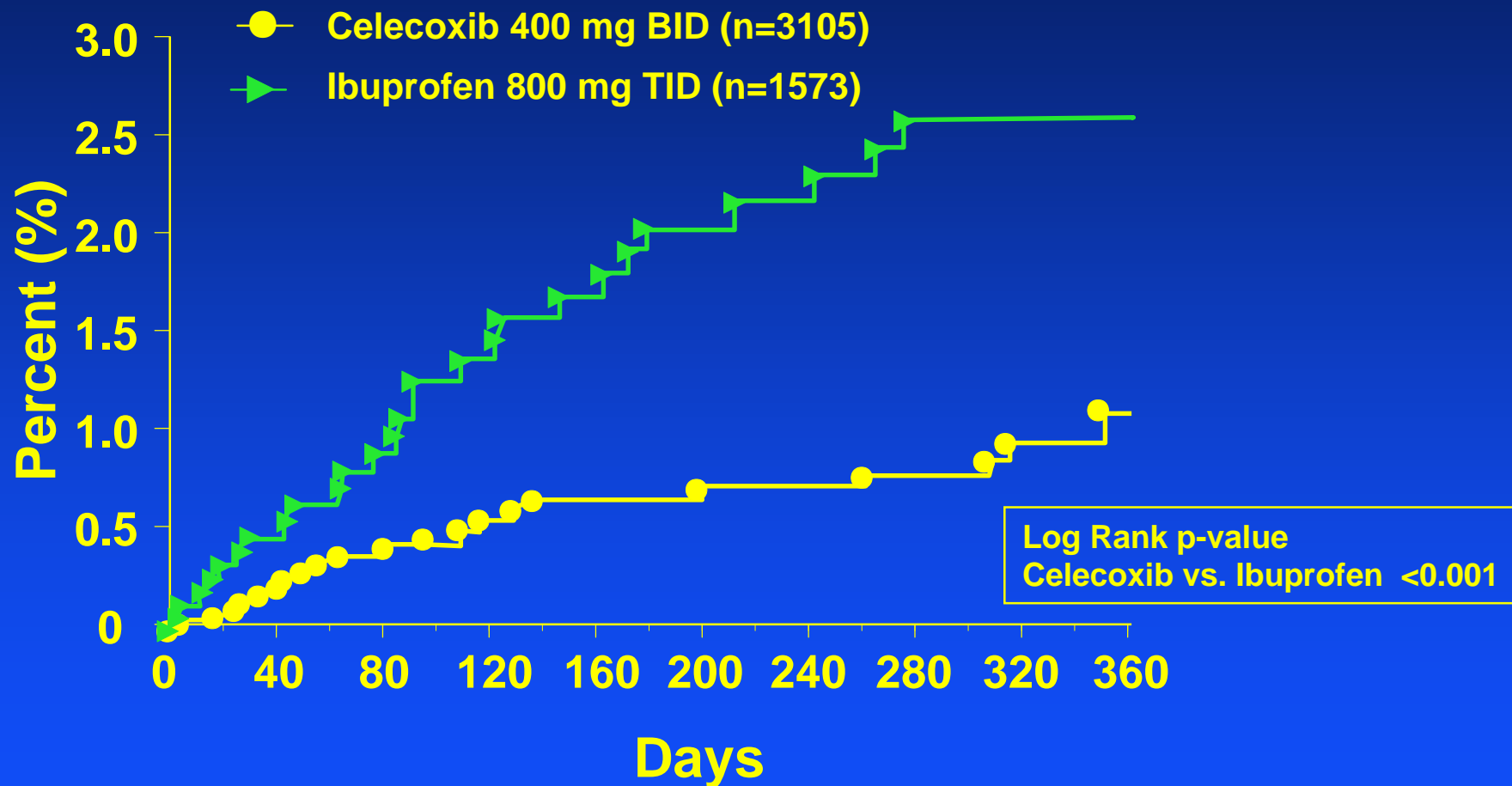
Symptomatic Ulcer/Ulcer Complications



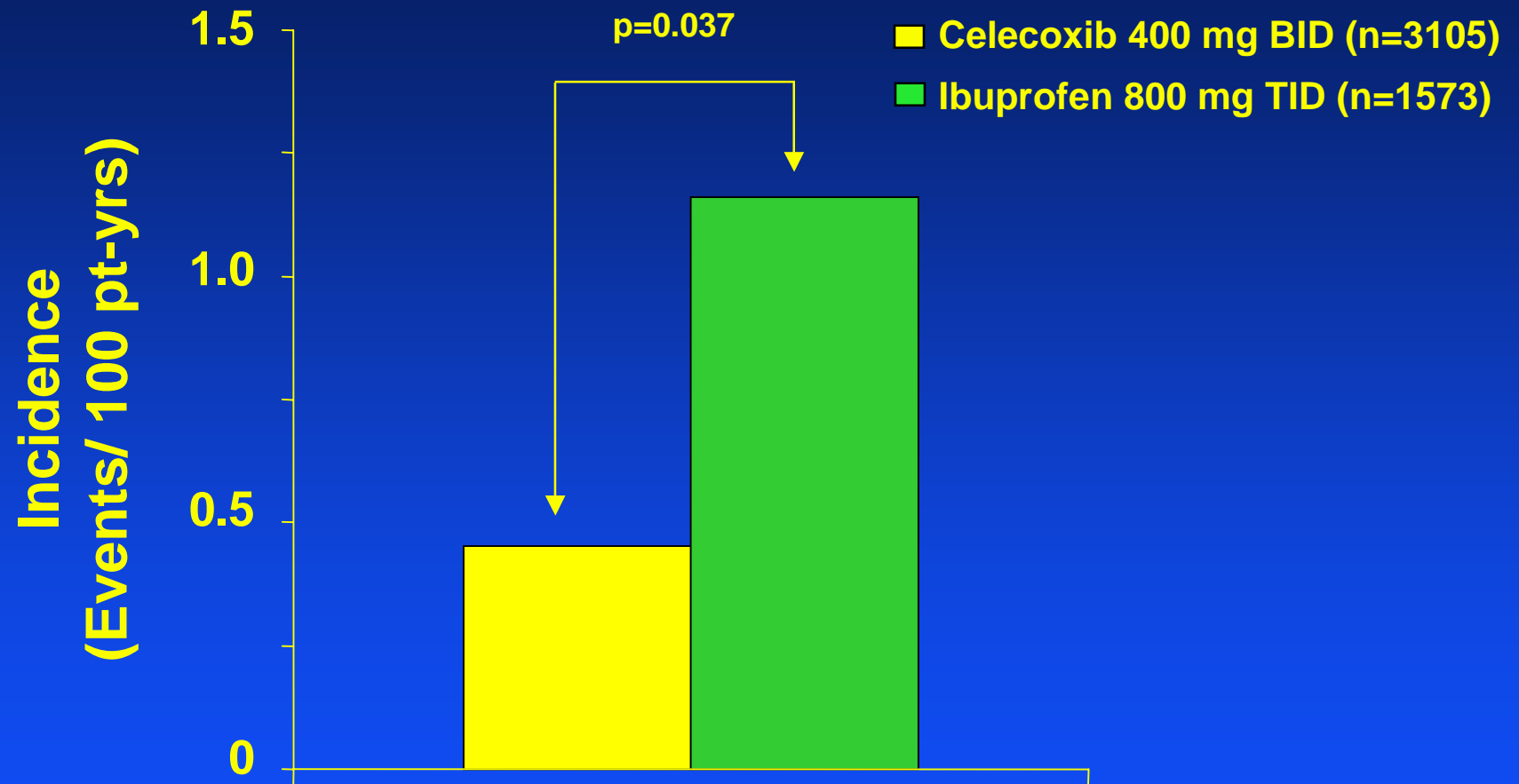
p value by log rank test

Non-ASA

Incidence of Symptomatic Ulcers/ Ulcer Complications



Ulcer Complications



p value by log rank test

ASA Use and UGI Outcomes - Summary

- **Non-ASA users:**
 - **Lower incidence of symptomatic ulcers/ulcer complications vs. NSAIDs and ibuprofen**
- **ASA users:**
 - **No difference in symptomatic ulcers/ulcer complications vs. NSAIDs and ibuprofen**

CLASS Results

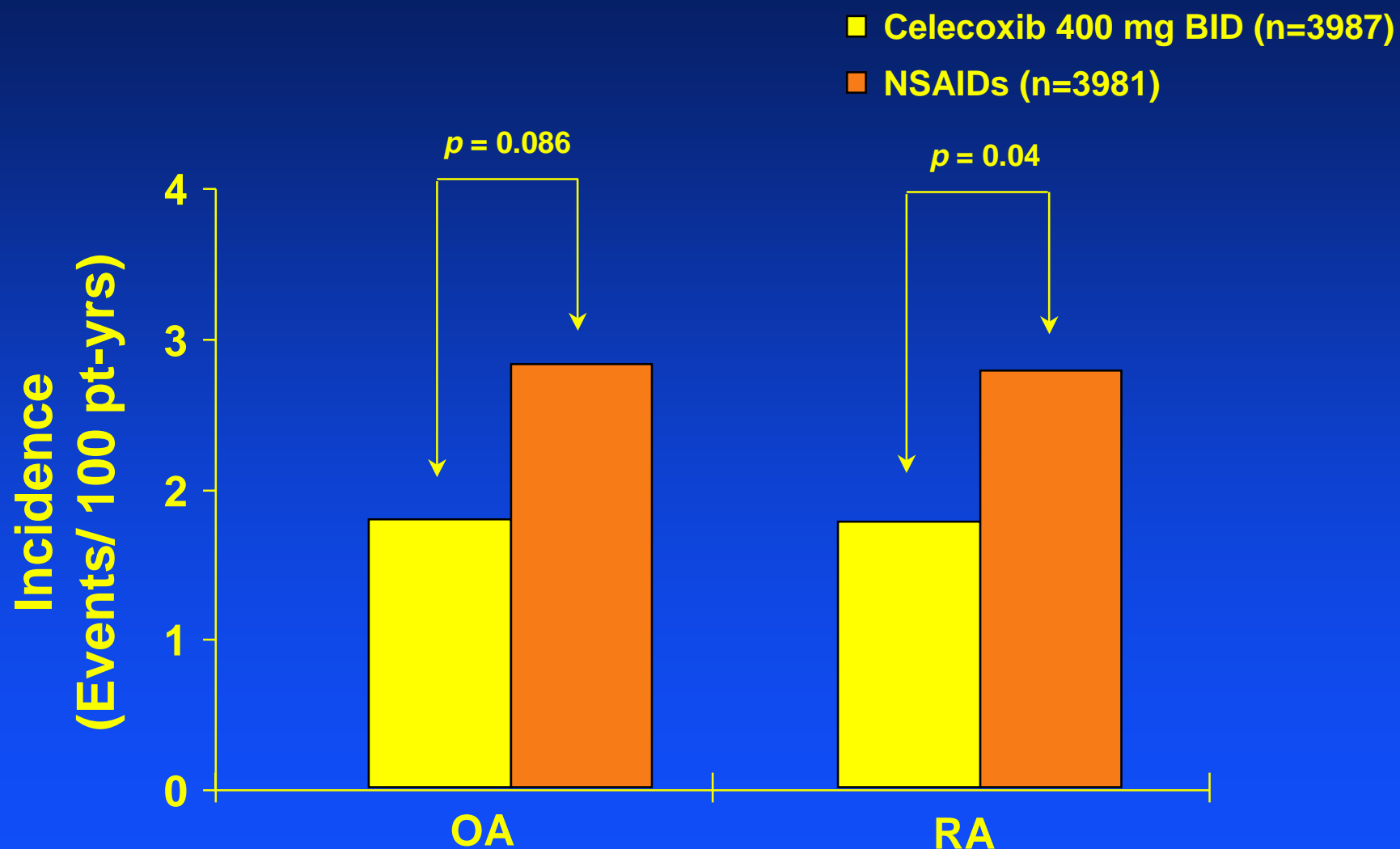
GI Outcomes

- **Study population**
- **GI Outcomes**
 - **Intent-to-treat**
 - **Risk Factors**
 - **Effect of ASA Use**
 - **RA vs OA**
- **Sources of Bias**

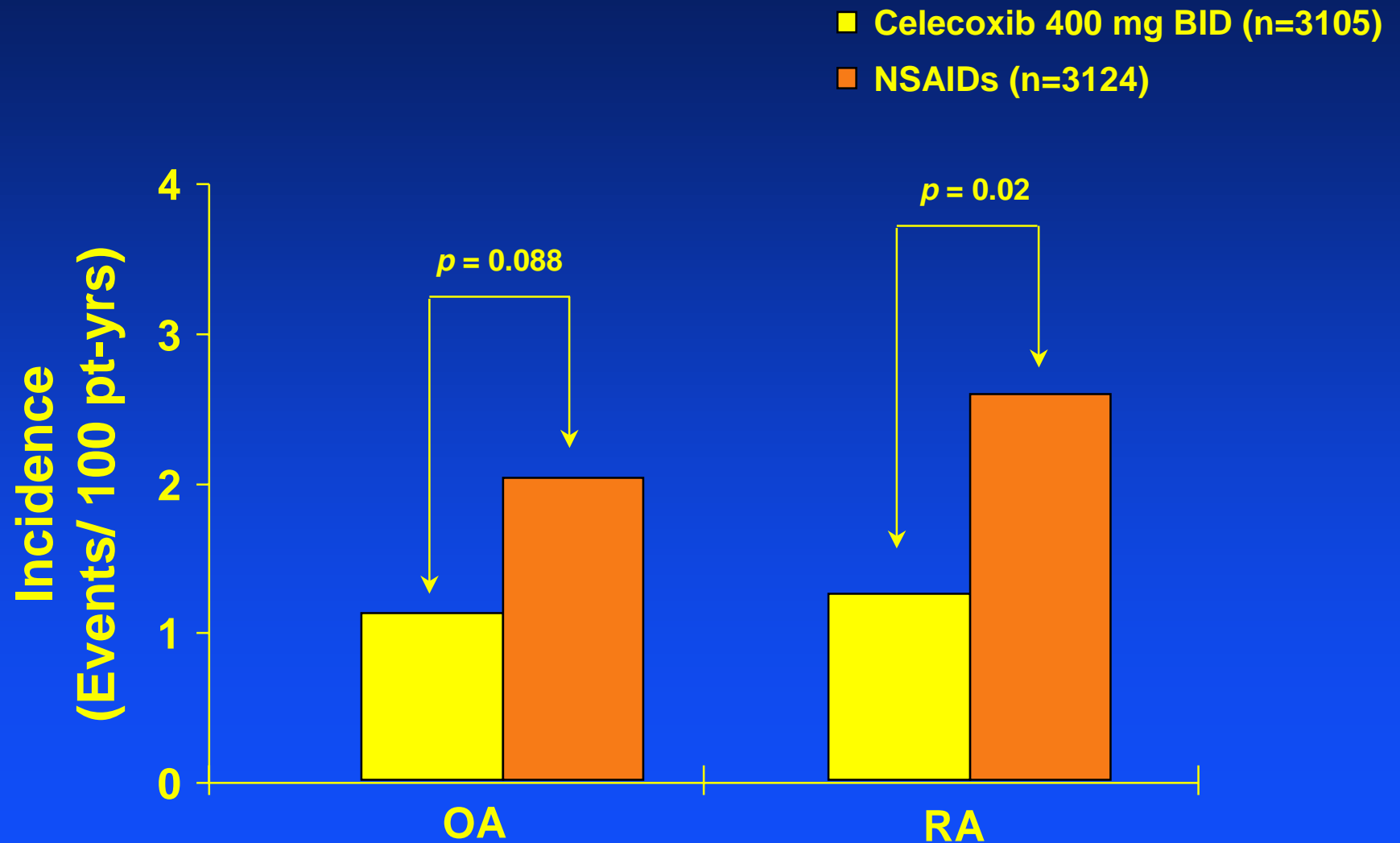
General Safety

- **Overall Safety**
- **Analysis by System**
 - **GI**
 - **Renal**
 - **Hepatic**
 - **CV/Thromboembolic**
- **Analysis in ASA users**
- **Analysis by Age**

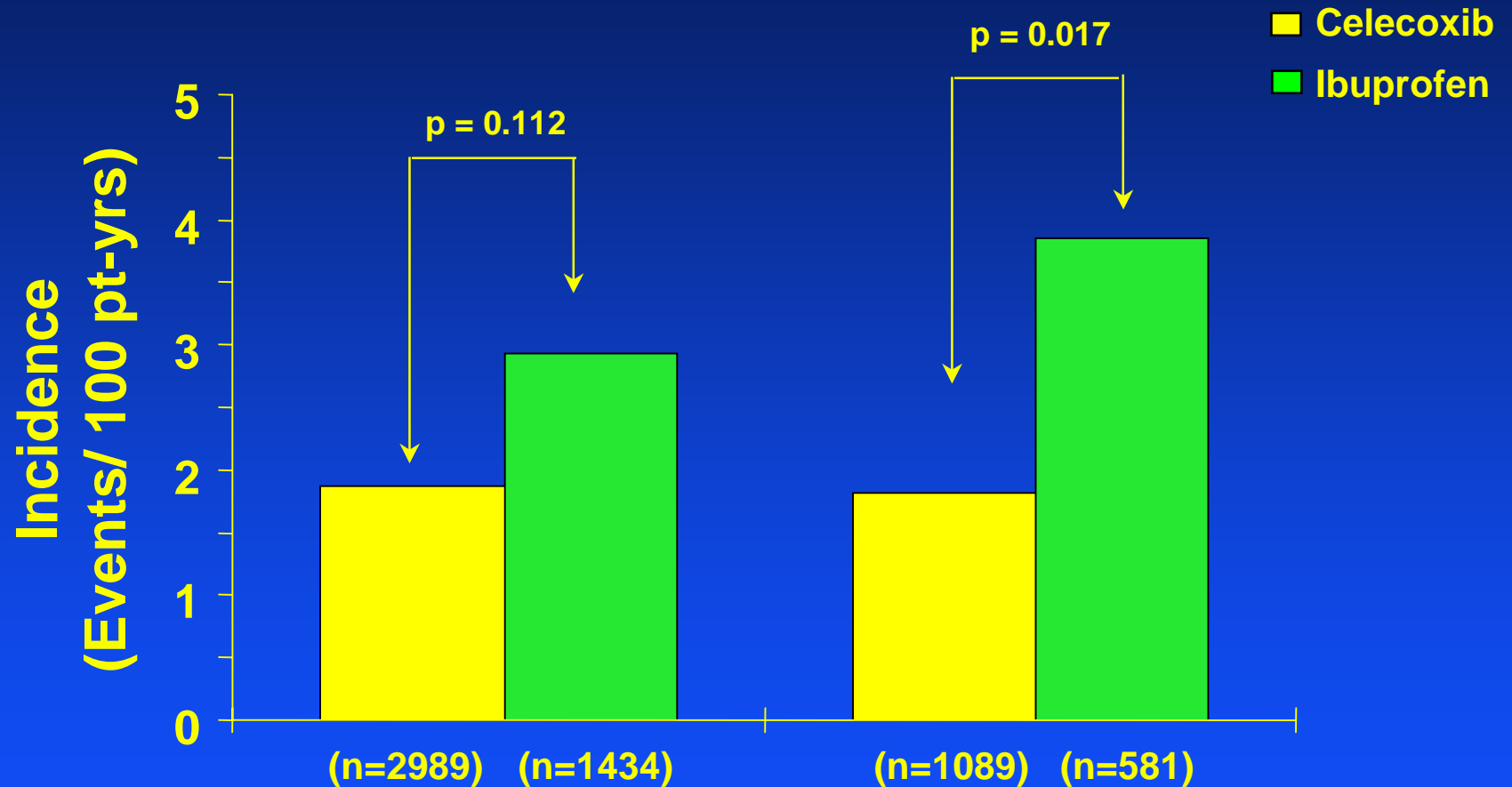
Incidence of Symptomatic Ulcers/ Ulcer Complications



Incidence of Symptomatic Ulcers/ Ulcer Complications



Incidence of Symptomatic Ulcers/ Ulcer Complications



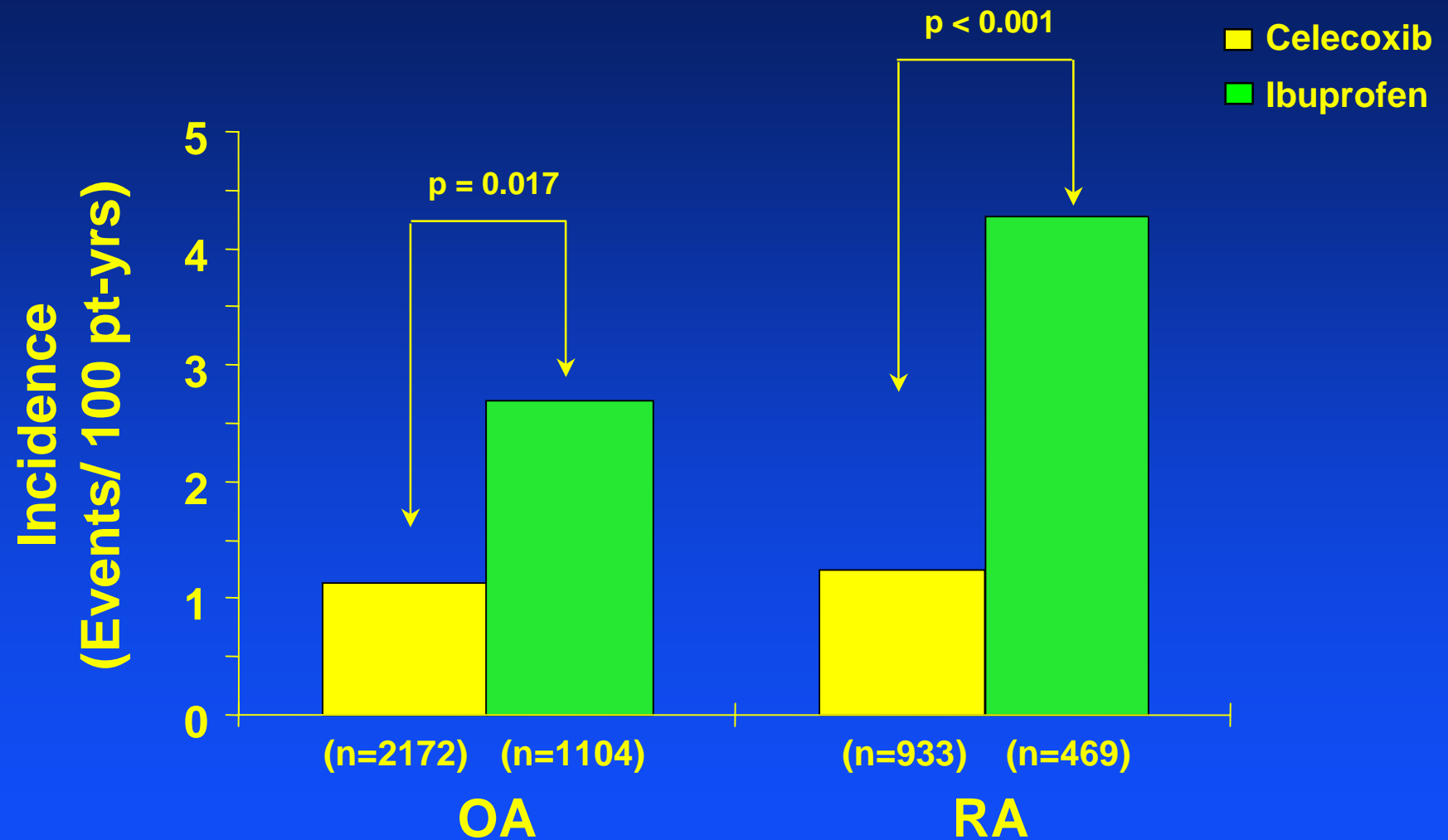
p value by log rank test

OA

RA

Non-ASA

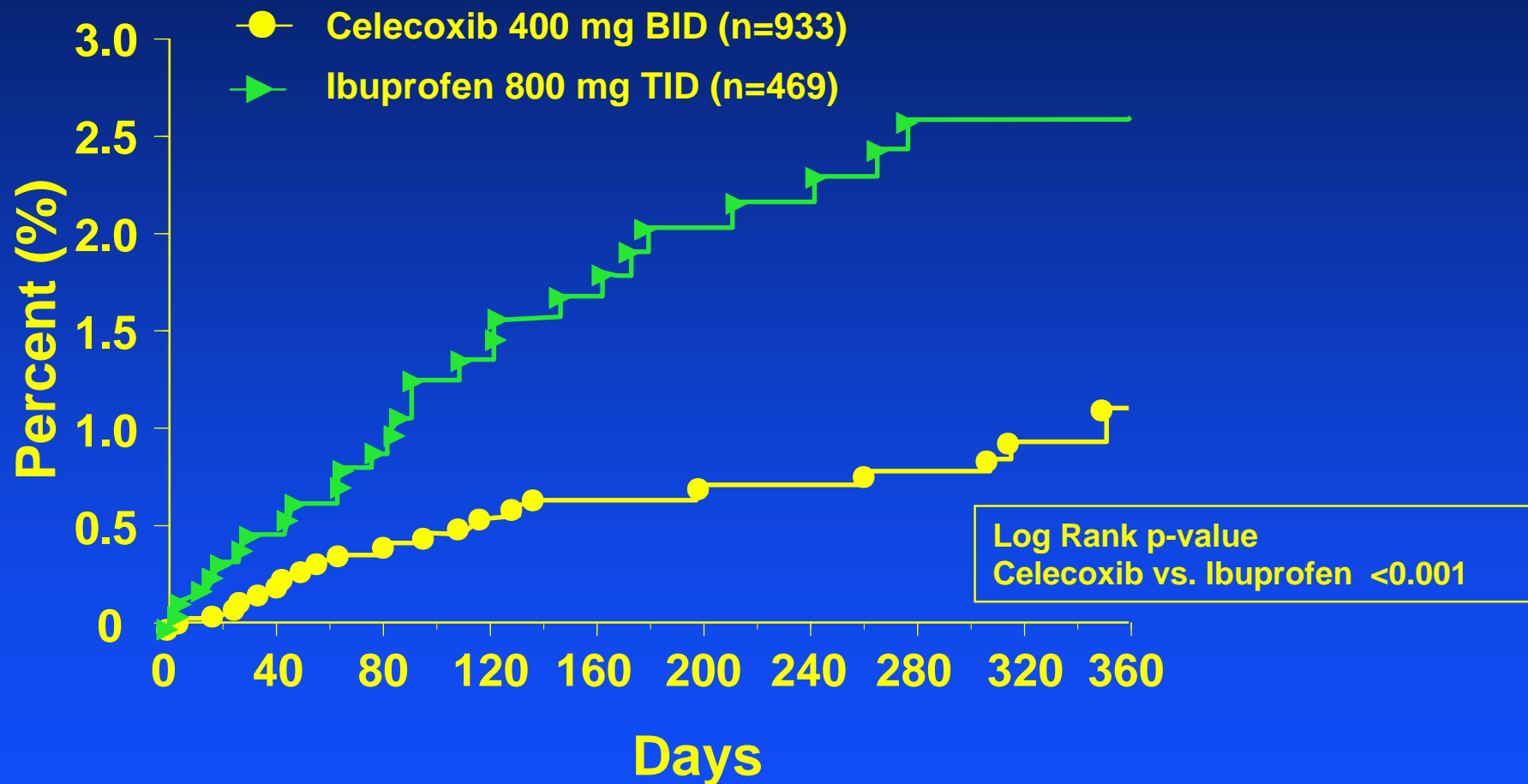
Incidence of Symptomatic Ulcers/ Ulcer Complications



p value by log rank test

Non-ASA

Incidence of Symptomatic Ulcers/ Ulcer Complications - RA



Analysis of UGI Outcomes in OA/RA - Summary

OA vs. RA:

- **Similar incidence of symptomatic ulcers/ulcer complications**
- **Similar treatment differences between celecoxib and NSAIDs**
- **Similar treatment differences between celecoxib and ibuprofen**

CLASS Results

GI Outcomes

- Study population
- GI Outcomes
 - Intent-to-treat
 - Risk Factors
 - Effect of ASA Use
 - RA vs OA
- Sources of Bias

General Safety

- Overall Safety
- Analysis by System
 - GI
 - Renal
 - Hepatic
 - CV/Thromboembolic
- Analysis in ASA users
- Analysis by Age

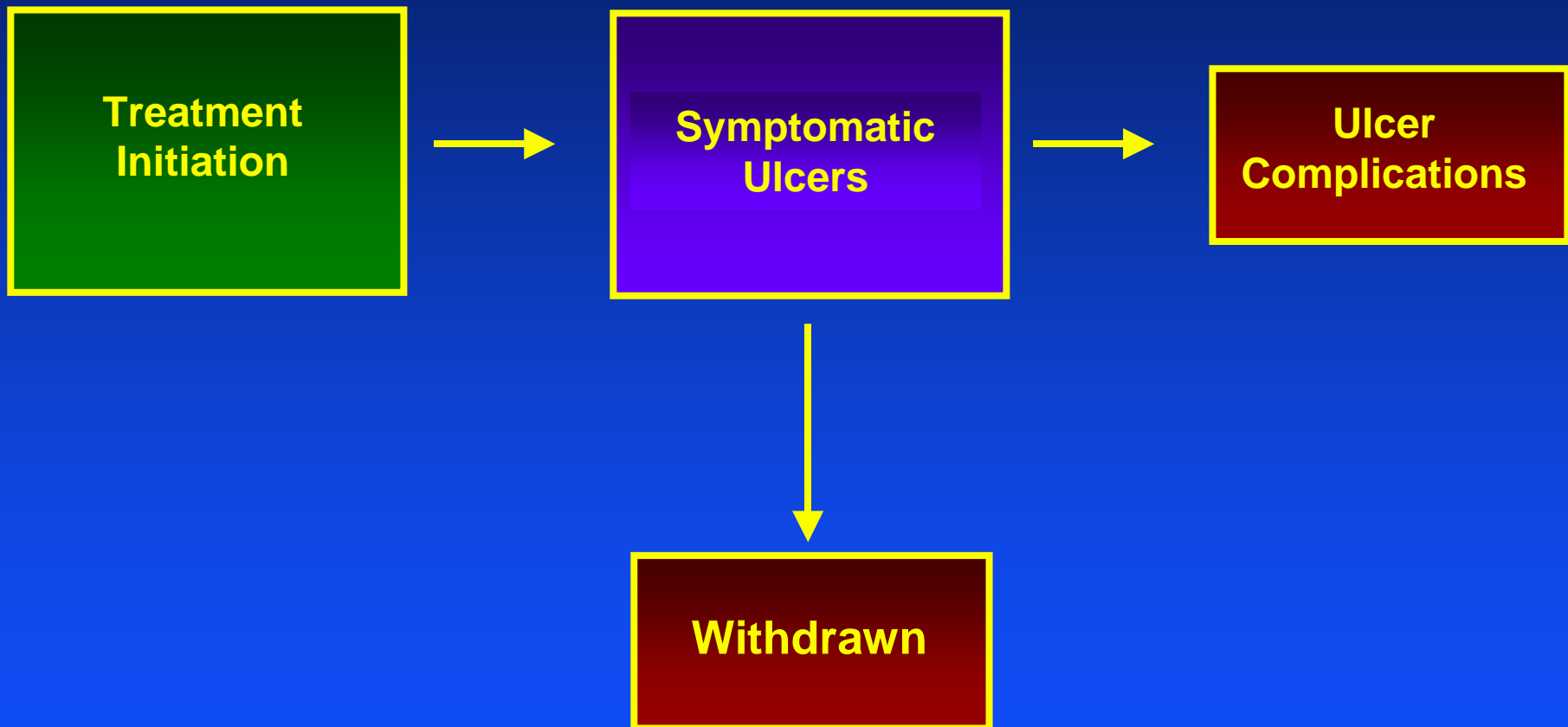
Sources of Bias In Ulcer Complications Analysis

- **ASA use**
- **Withdrawal of patients with symptomatic ulcers**

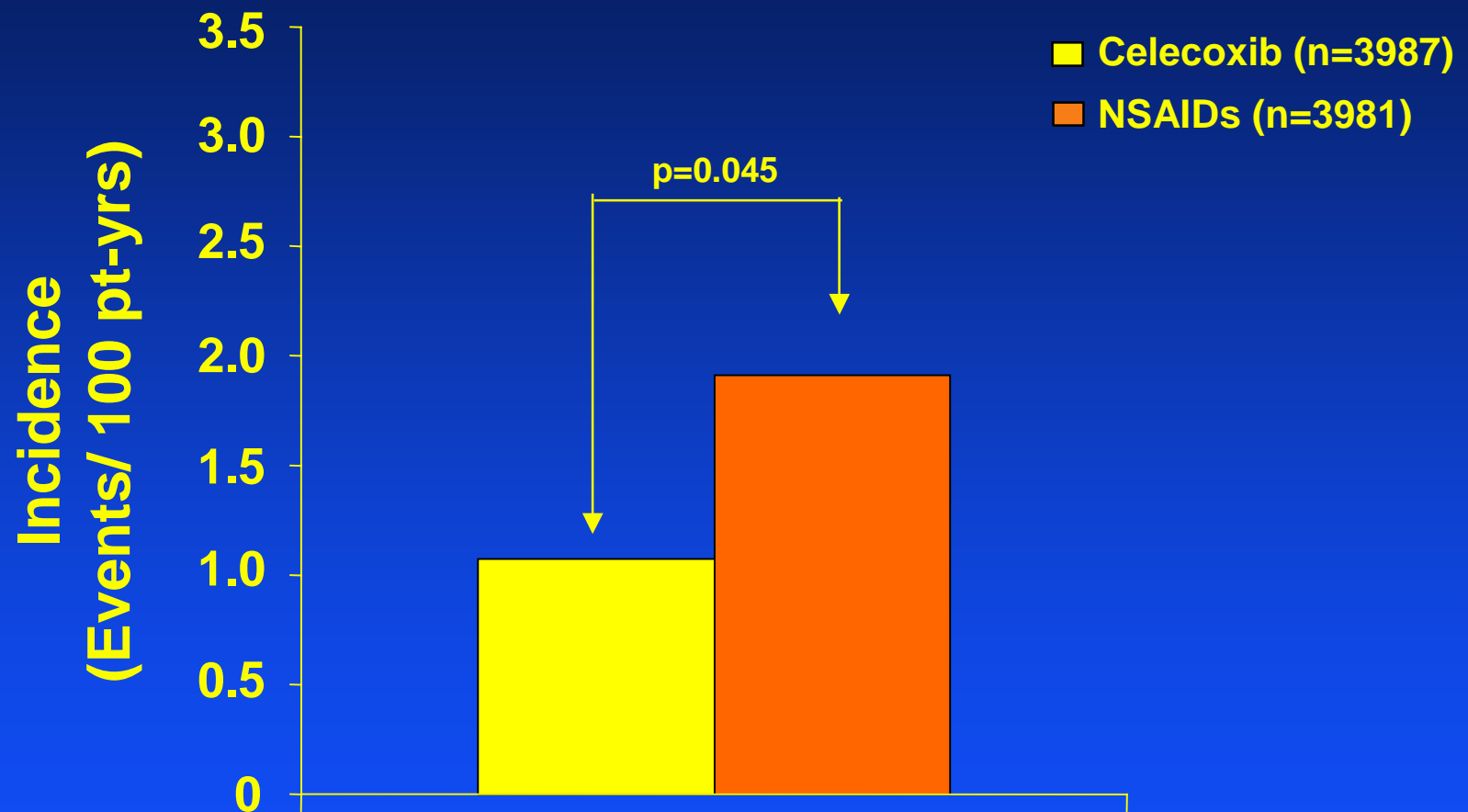
Potential Source of Bias



Potential Source of Bias



Incidence of Symptomatic Ulcers



Sources of Bias - Summary

- **Celecoxib vs. NSAIDs:**
 - Lower incidence of symptomatic ulcers
- **Withdrawals of symptomatic ulcers may bias the analysis of ulcer complications**

CLASS Results

GI Outcomes

- **Study population**
- **GI Outcomes**
 - Intent-to-treat
 - Risk Factors
 - Effect of ASA Use
 - RA vs OA
- **Sources of Bias**

General Safety

- **Overall Safety**
- **Analysis by System**
 - GI
 - Renal
 - Hepatic
 - CV/Thromboembolic
- **Analysis in ASA users**
- **Analysis by Age**

Deaths and Serious Adverse Events

	Incidence - Per 100 Pt. Yrs.		
	Celecoxib 400 mg BID (2320 pt yrs)	Diclofenac 75 mg BID (1081 pt yrs)	Ibuprofen 800 mg TID (1123 pt yrs)
Overall Deaths	0.8	0.8	0.7
Cardiac	0.5	0.5	0.4
Overall Serious AEs	11.6	10.3	10.6
Cardiac	2.1	1.6	1.7
Gastrointestinal¹	1.9	2.1	1.7
Dermatologic	0.0	<0.1	0.2
Renal	0.4	<0.1	0.4

¹Includes all esophageal, gastric, intestinal, colonic, and pancreatic SAEs

Common Adverse Events ($\geq 5\%$)

<u>Adverse Event</u>	<u>Celecoxib 400 mg BID (n=3987)</u>	<u>Diclofenac 75 mg BID (n=1996)</u>	<u>Ibuprofen 800 mg TID (n=1985)</u>
Any Event	81.8	82.9	79.5
Dyspepsia	16.5	19.5*	16.5
Headache	13.9	16.6*	13.0
Abdominal pain	11.7	18.5*	11.3
Diarrhea	10.9	15.0*	7.5*
Nausea	8.2	12.1*	9.0
Flatulence	7.3	11.4*	7.2

* p <0.05 versus celecoxib

Common Adverse Events ($\geq 5\%$) - Continued

<u>Adverse Event</u>	<u>Celecoxib 400 mg BID (n=3987)</u>	<u>Diclofenac 75 mg BID (n=1996)</u>	<u>Ibuprofen 800 mg TID (n=1985)</u>
Any Event	81.8	82.9	79.5
Rash	6.2	2.8*	3.8*
Anemia	4.4	5.3	8.7*
Bronchitis	4.0	4.1	5.1*
Edema Peripheral	3.7	3.5	5.2*
Constipation	2.2	6.8*	6.5*
ALT increased	1.0	5.1*	1.2

* p < 0.05 versus celecoxib

Adverse Events Causing Withdrawal $\geq 1\%$

<u>Adverse Event</u>	<u>Celecoxib 400 mg BID (n=3987)</u>	<u>Diclofenac 75 mg BID (n=1996)</u>	<u>Ibuprofen 800 mg TID (n=1985)</u>
Any Event	22.4	26.5*	23.0
Abdominal pain	4.3	6.5*	4.9
Rash	2.1	0.7*	1.3*
Nausea	1.7	2.8*	1.8
Diarrhea	1.4	2.7*	0.8*
Gastric Ulcer	0.3	0.7	1.0*
AST increased	0.1	2.1*	0.1
ALT increased	<0.1	2.3*	0.1
Hepatic function abn	<0.1	1.1*	<0.1

* p <0.05 versus celecoxib

Celecoxib General Safety - Summary

- **Celecoxib is well tolerated at 400 mg BID**
- **No dose- or duration-related increases in adverse events except non-serious rash**

CLASS Results

GI Outcomes

- **Study population**
- **GI Outcomes**
 - **Intent-to-treat**
 - **Risk Factors**
 - **Effect of ASA Use**
 - **RA vs OA**
- **Sources of Bias**

General Safety

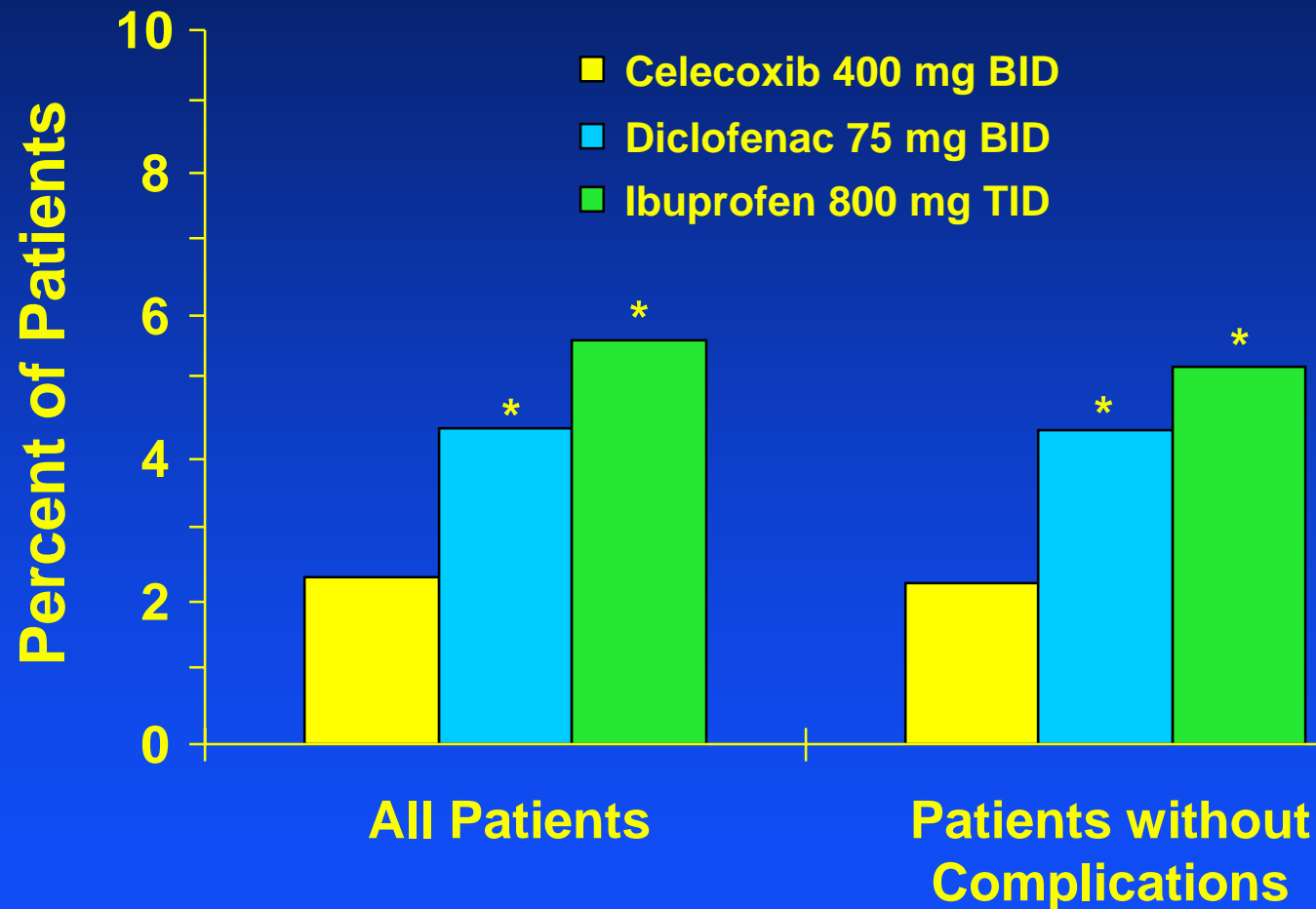
- **Overall Safety**
- **Analysis by System**
 - **GI**
 - **Renal**
 - **Hepatic**
 - **CV/Thromboembolic**
- **Analysis in ASA users**
- **Analysis by Age**

GI Adverse Events (%)

<u>Adverse Event</u>	<u>Celecoxib 400 mg BID (n=3987)</u>	<u>Diclofenac 75 mg BID (n=1996)</u>	<u>Ibuprofen 800 mg TID (n=1985)</u>
Any Event	45.6	55.0*	46.2
Dyspepsia	16.5	19.5*	16.5
Abdominal Pain	11.7	18.5*	11.3
Nausea	8.2	12.1*	9.0
Diarrhea	10.9	15.0*	7.5*
Constipation	2.2	6.8*	6.5*
Withdrawals	12.2	16.6*	13.4

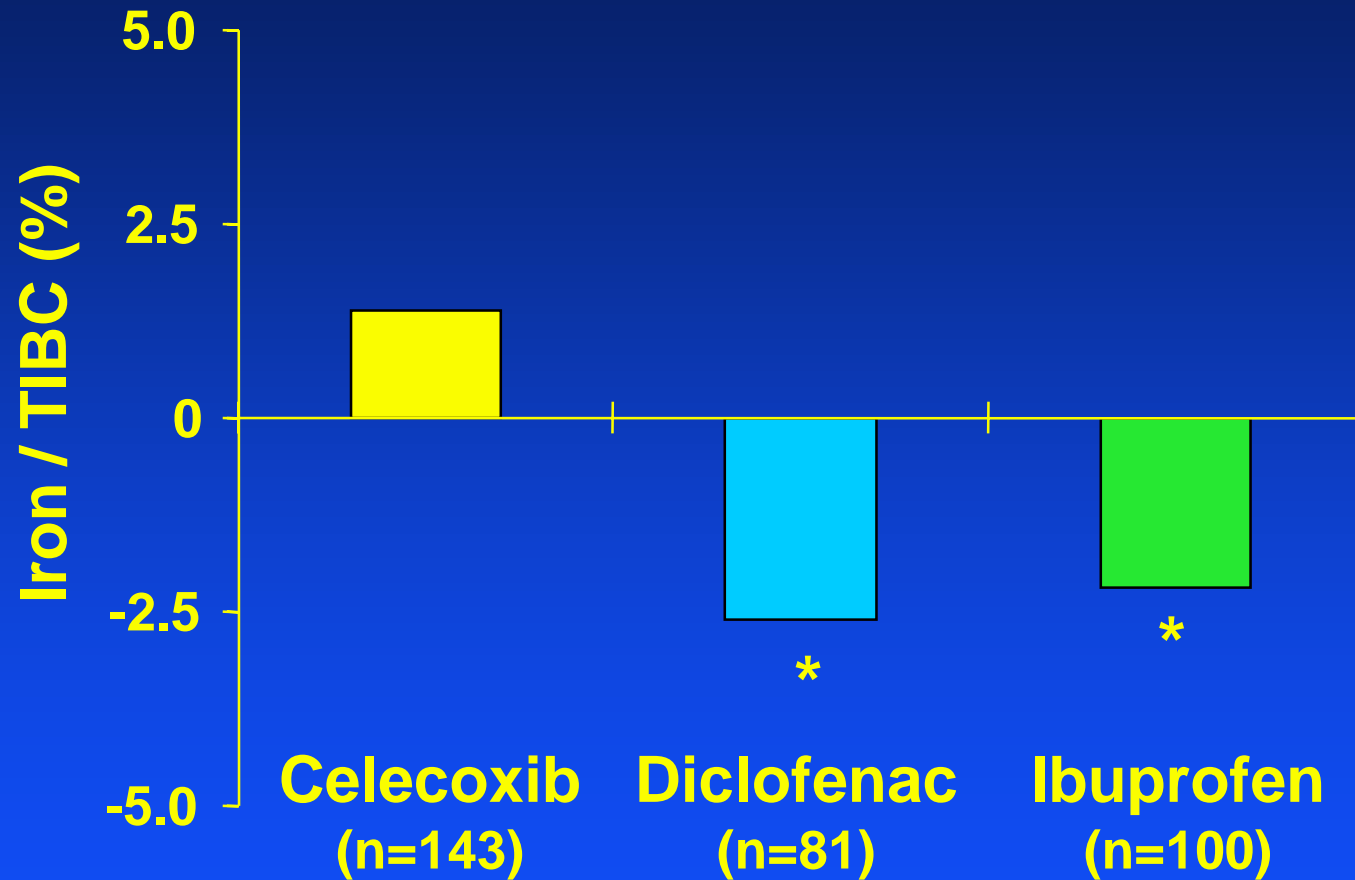
* p <0.05 versus celecoxib

Clinically Significant Changes in Hct/Hgb (Decreases in Hct ≥ 10 % points and/or Hgb > 2 g/dL)



* p < 0.05 versus celecoxib

Mean Change From Baseline of Iron / Total Iron Binding Capacity



* p < 0.05 versus celecoxib

Celecoxib GI Safety - Summary

- **Lower incidence of:**
 - **GI adverse events and withdrawals than diclofenac**
 - **Clinically significant reductions in Hgb/Hct than ibuprofen and diclofenac**
- **Decreases in iron stores and Hgb/Hct suggest chronic GI blood loss**

CLASS Results

GI Outcomes

- **Study population**
- **GI Outcomes**
 - **Intent-to-treat**
 - **Risk Factors**
 - **Effect of ASA Use**
 - **RA vs OA**
- **Sources of Bias**

General Safety

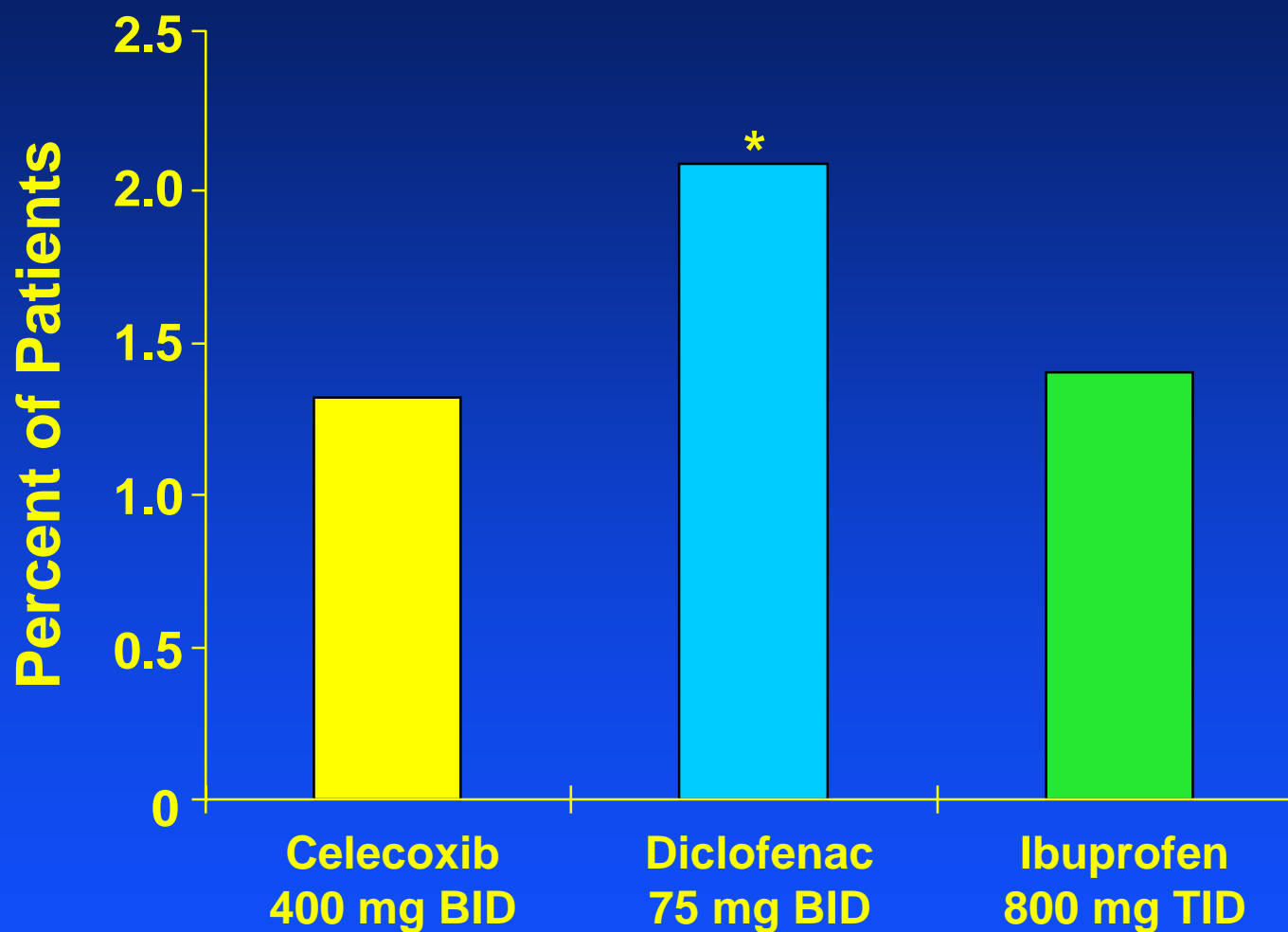
- **Overall Safety**
- **Analysis by System**
 - **GI**
 - **Renal**
 - **Hepatic**
 - **CV/Thromboembolic**
- **Analysis in ASA users**
- **Analysis by Age**

Renal Adverse Events $\geq 1\%$

	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Any Event	8.9	9.0	11.7*
Hypertension	2.0	2.0	3.1*
Hypertension aggr.	0.8	0.6	1.2
Edema generalized	0.5	0.6	1.0*
Edema peripheral	3.7	3.5	5.2*
Creatinine increased	1.3	1.9	1.2
BUN increased	1.1	1.7	0.9
Withdrawals	1.6	1.3	1.7

* p <0.05 versus celecoxib

Clinically Significant Renal Lab Abnormalities (BUN \geq 40 mg% and/or Cr \geq 1.8 mg%)



* p < 0.05 versus celecoxib

Celecoxib Renal Safety - Summary

- **Lower incidence of:**
 - **Hypertension and edema than ibuprofen**
 - **Clinically significant increases in creatinine and/or BUN than diclofenac**

CLASS Results

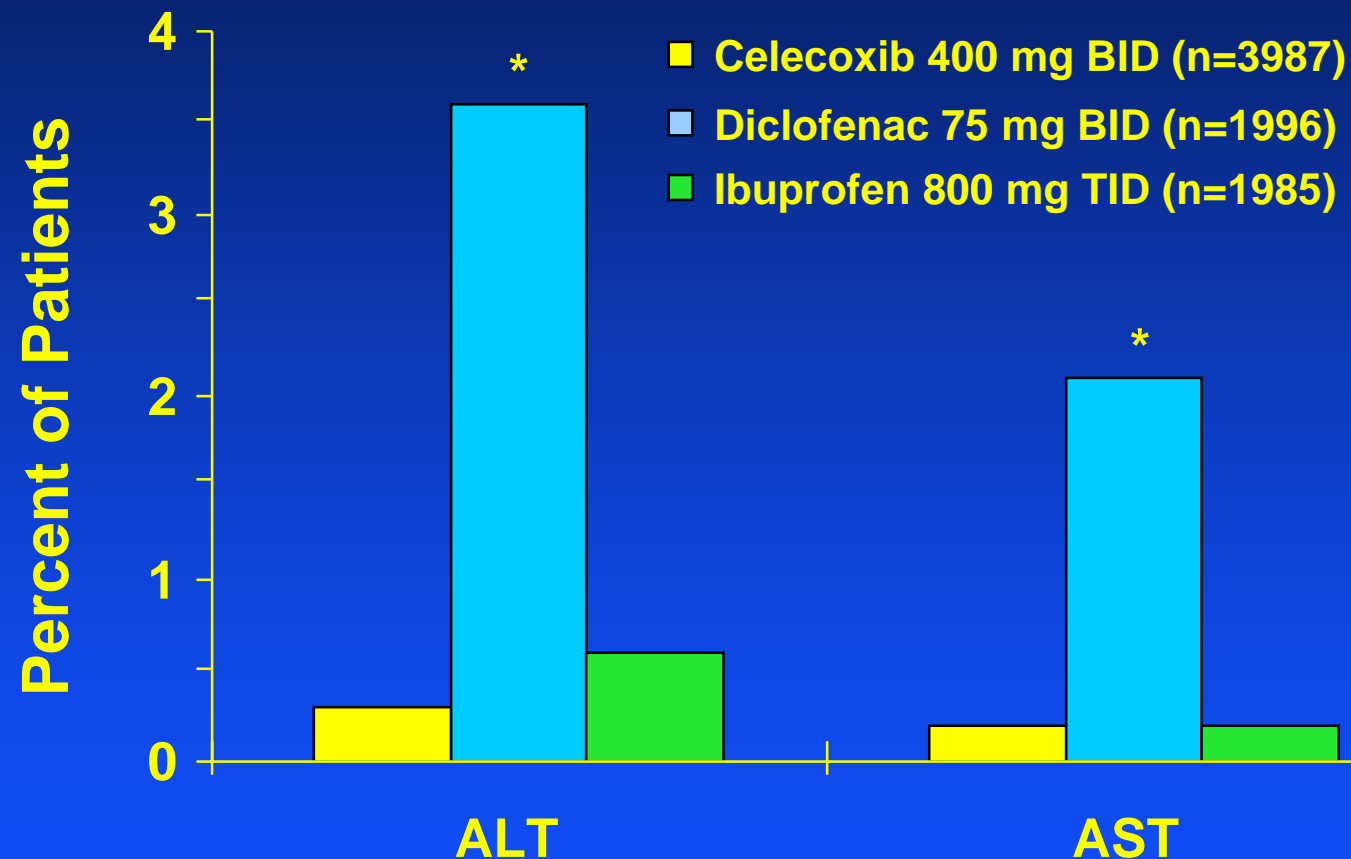
GI Outcomes

- **Study population**
- **GI Outcomes**
 - **Intent-to-treat**
 - **Risk Factors**
 - **Effect of ASA Use**
 - **RA vs OA**
- **Sources of Bias**

General Safety

- **Overall Safety**
- **Analysis by System**
 - **GI**
 - **Renal**
 - **Hepatic**
 - **CV/Thromboembolic**
- **Analysis in ASA users**
- **Analysis by Age**

Clinically Significant Elevations in Hepatic Transaminases (3x ULN)



* p < 0.05 versus celecoxib

Celecoxib Hepatic Safety - Summary

- **Lower incidence of clinically significant transaminase elevations than diclofenac**

CLASS Results

GI Outcomes

- Study population
- GI Outcomes
 - Intent-to-treat
 - Risk Factors
 - Effect of ASA Use
 - RA vs OA
- Sources of Bias

General Safety

- Overall Safety
- Analysis by System
 - GI
 - Renal
 - Hepatic
 - CV/Thromboembolic
- Analysis in ASA users
- Analysis by Age

Thromboembolic Adverse Events¹ (%)

<u>Event</u>	<u>Celecoxib (n=3987)</u>	<u>Diclofenac (n=1996)</u>	<u>Ibuprofen (n=1985)</u>
Any Event	2.5	2.1	2.2
MI	0.5	0.3	0.5
Angina	0.6	0.5	0.6
CAD	0.6	0.4	0.3
Unstable Angina	0.3	0.2	<0.1
CVA	0.2	0.5	0.5*
Withdrawals	0.8	0.7	0.8

1. Includes all arterial and venous thromboembolic events

* p <0.05 versus celecoxib

Non-ASA

Thromboembolic Adverse Events (%)

<u>Event</u>	<u>Celecoxib (n=3105)</u>	<u>Diclofenac (n=1551)</u>	<u>Ibuprofen (n=1573)</u>
Any Event	1.5	1.1	1.2
MI	0.2	0.1	0.1
Angina	0.3	0.1	0.4
CAD	0.3	0.3	<0.1
Unstable Angina	<0.1	0.0	<0.1
CVA	<0.1	0.3*	0.3
Withdrawals	0.6	0.4	0.4

1. Includes all arterial and venous thromboembolic events

* p <0.05 versus celecoxib

Other Cardiac Adverse Events (%)

	Celecoxib (n=3987)	Diclofenac (n=1996)	Ibuprofen (n=1985)
Atrial Arrhythmias			
Atrial Fibrillation	0.4	0.2	0.3
Atrial Arrhythmia	<0.1	0.0	<0.1
Bradycardia	<0.1	0.0	<0.1
SVT	<0.1	0.0	<0.1
Withdrawals	<0.1	0.0	0.2
CHF	0.3	0.2	0.5
Withdrawals	0.1	<0.1	0.3

Non-ASA

Other Cardiac Adverse Events (%)

	Celecoxib (n=3105)	Diclofenac (n=1551)	Ibuprofen (n=1573)
Atrial Arrhythmias			
Atrial Fibrillation	0.3	0.1	0.1
Atrial Arrhythmia	0.0	0.0	0.0
Bradycardia	0.1	0.0	0.1
SVT	<0.1	0.0	<0.1
Withdrawals	<0.1	0.0	0.1
CHF	0.2	0.1	0.3
Withdrawals	<0.1	0.0	0.3*

* p <0.05 versus celecoxib

Celecoxib CV Safety - Summary

- **Compared to ibuprofen or diclofenac:**
 - **No difference in thromboembolic events**
 - **No difference in atrial arrhythmias or CHF**

CLASS Results

GI Outcomes

- **Study population**
- **GI Outcomes**
 - Intent-to-treat
 - Risk Factors
 - Effect of ASA Use
 - RA vs OA
- **Sources of Bias**

General Safety

- **Overall Safety**
- **Analysis by System**
 - GI
 - Renal
 - Hepatic
 - CV/Thromboembolic
- **Analysis in ASA users**
- **Analysis by Age**

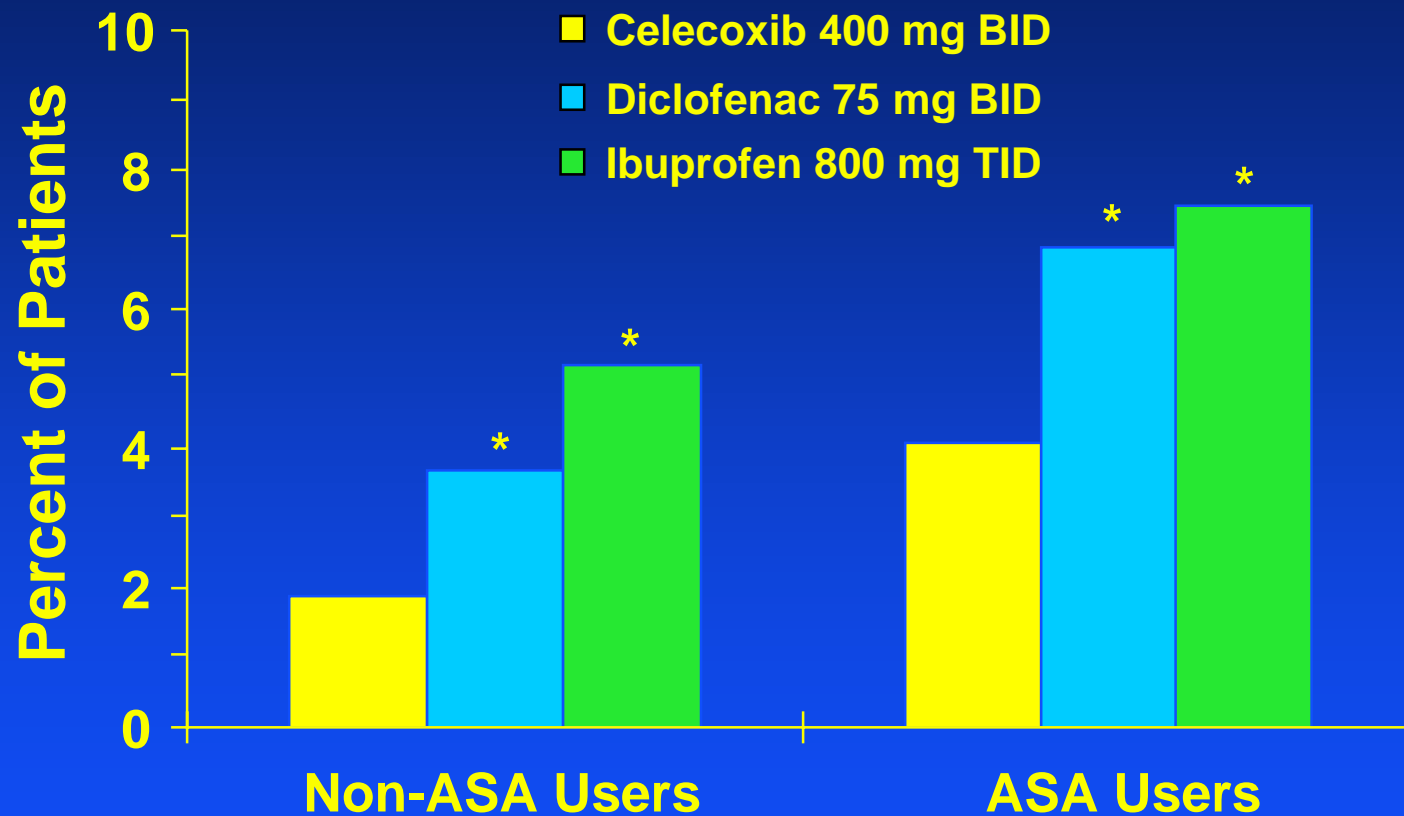
ASA Users

GI and Renal Adverse Events (%)

	Celecoxib 400 mg BID (n=882)	Diclofenac 75 mg BID (n=445)	Ibuprofen 800 mg TID (n=412)
GI			
Any Event	54.0	59.1	52.7
Withdrawals	14.9	20.7*	14.1
Renal			
Any Event	10.8	11.2	14.8*
Withdrawals	1.4	1.8	1.7

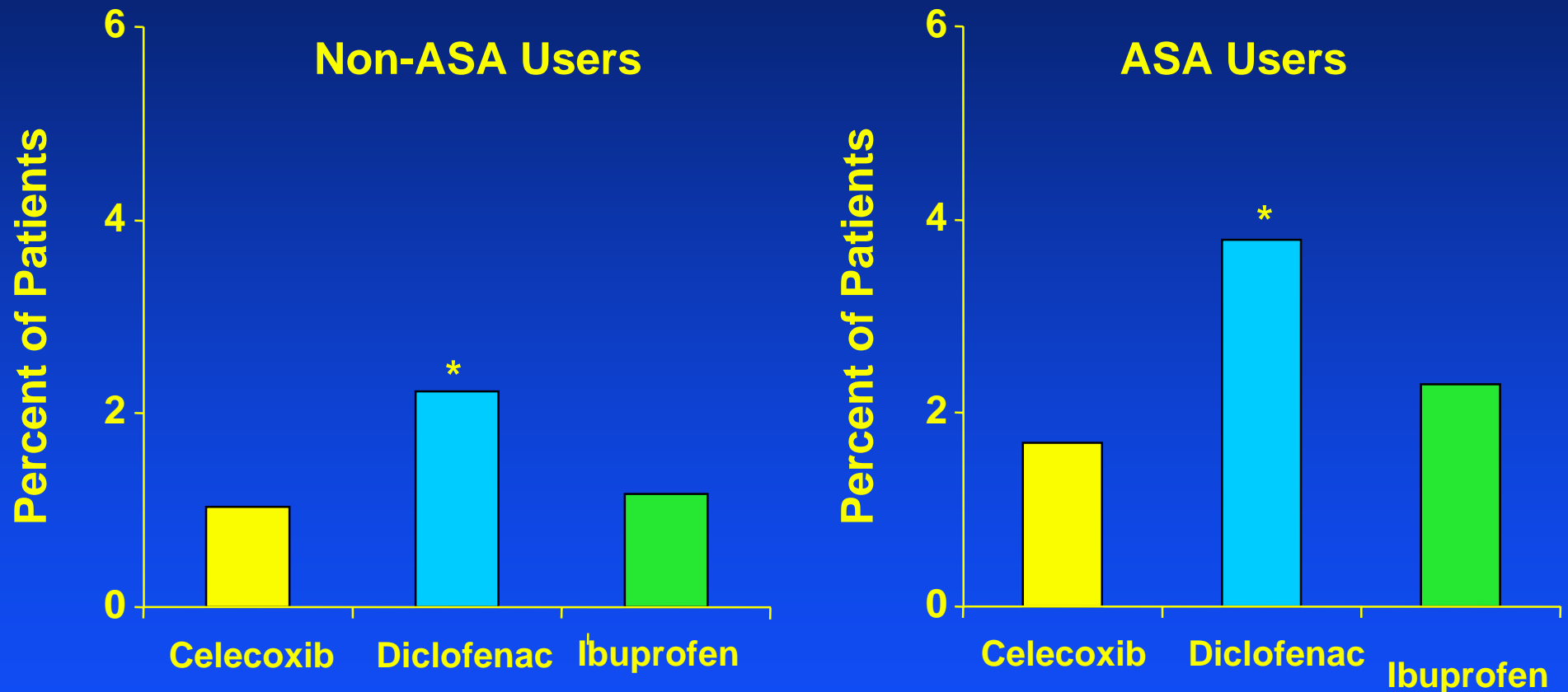
* p <0.05 versus celecoxib

Clinically Significant Changes in Hct/Hgb (Decreases in Hct ≥ 10 % points and/or Hgb > 2 g/dL)



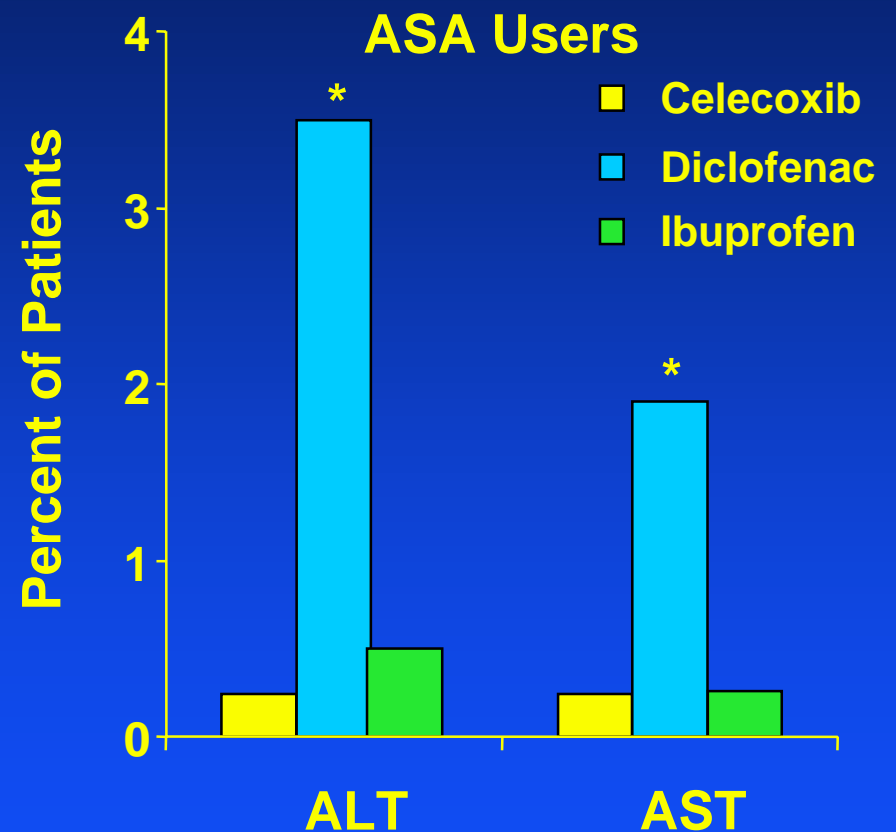
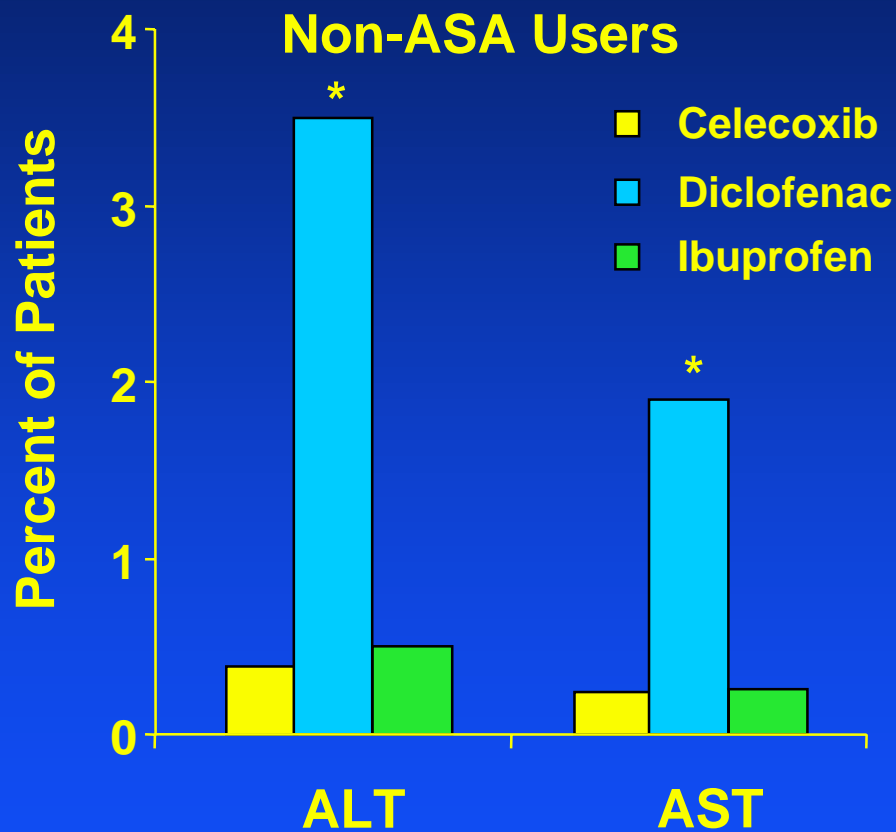
* p < 0.05 versus celecoxib

Clinically Significant Renal Lab Abnormalities (BUN ≥ 40 mg% and/or Cr ≥ 1.8 mg%)



* $p \leq 0.05$ versus celecoxib

Clinically Significant Elevations in Hepatic Transaminases (3x ULN)



* $p \leq 0.05$ versus celecoxib

Celecoxib Safety in ASA Users - Summary

- **Similar safety profile to patients not on ASA:**
 - GI
 - Renal
 - Hepatic

CLASS Results

GI Outcomes

- Study population
- GI Outcomes
 - Intent-to-treat
 - Risk Factors
 - Effect of ASA Use
 - RA vs OA
- Sources of Bias

General Safety

- Overall Safety
- Analysis by System
 - GI
 - Renal
 - Hepatic
 - CV/Thromboembolic
- Analysis in ASA users
- Analysis by Age

≥ 65 years

Safety by Body System (%)

	Celecoxib 400 mg BID (n=1599)	Diclofenac 75 mg BID (n=762)	Ibuprofen 800 mg TID (n=724)
GI - Any AE	47.3	58.0*	47.7
Hct/Hgb Decreases	2.8	5.4*	6.5*
Renal - Any AE	10.2	9.8	13.8*
BUN/Cr Increases	2.3	4.0*	3.3
Hepatic - Any AE	1.3	7.2*	1.1

* p <0.05 versus celecoxib

Celecoxib Safety by Age - Summary

- **Similar safety profile in patients in all age groups:**
 - **Patients ≥ 65 years**

CLASS SUMMARY: GI Safety Advantages of Celecoxib

	<u>NSAIDs Combined</u>	<u>Diclofenac 75 mg BID</u>	<u>Ibuprofen 800 mg TID</u>
Symptomatic Ulcers/ Ulcer complications	✓		✓
GI Blood Loss*	✓	✓	✓
GI Tolerability*	✓	✓	

* Similar results in ASA users

CLASS SUMMARY:

General Safety Advantages of Celecoxib

Diclofenac
75 mg BID

Ibuprofen
800 mg TID

Renal Safety*

Edema/Hypertension

✓

Increased Creatinine/BUN

✓

Hepatic Safety*

✓

Similar safety profile in all age groups

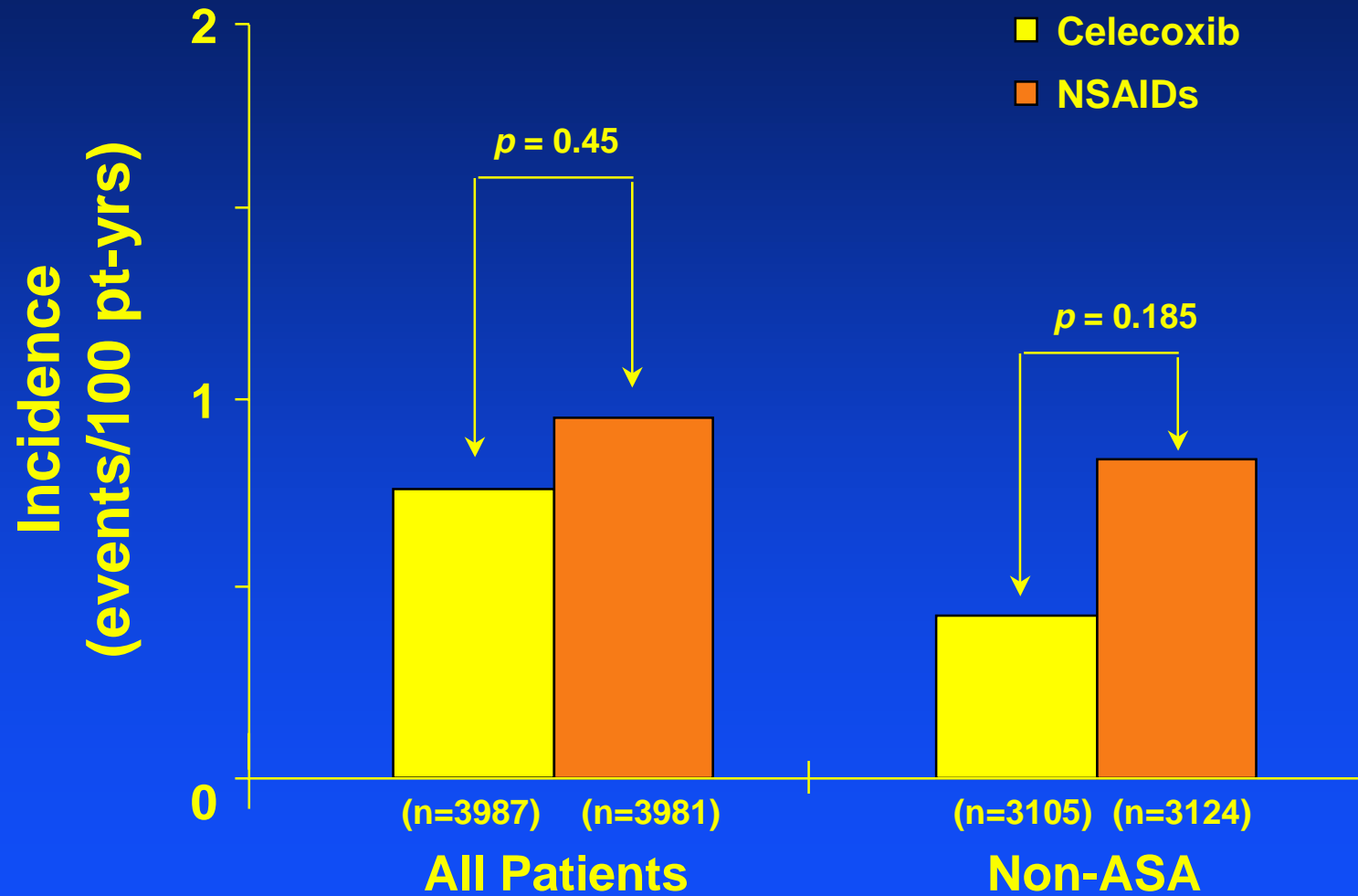
No increased risk of cardiac or thromboembolic events

*** Similar results in ASA users**

Summary

- **Trial Design**
- **Clinical Results**
- **Confirmation of Antecedent Trials**
- **Safety**
- **Conclusion**

Ulcer Complication Rate



Gastrointestinal Safety Analyses

- **Outcomes evaluated:**
 - **Ulcer complications (primary)**
 - **Symptomatic ulcers (secondary)**

Baseline NSAID Risk Factors

	Incidence (% of Patients)	
	MUCOSA ¹ 1990	CLASS ² 2000
RA patients	100	27.4
Age >75 years	16.0	11.6
History of GI Bleed	6.5	1.5
History of ulcer	14.5	8.2
History of CVD	54.6	40.2

1. Silverstein et al. Ann Int Med 1995; 123:241-249

2. Silverstein et al. JAMA 2000; 284:1247-1255

Baseline NSAID Risk Factors

	<u>Incidence (% of Patients)</u>	
	<u>NDA (14 RCTs)¹ 1998</u>	<u>CLASS² 2000</u>
RA patients	33.3	27.4
Age >75 years	10.8	11.6
History of GI Bleed	2.1	1.5
History of ulcer	11.6	8.2
History of CVD	51.2	40.2
Aspirin Use	12.0	22.0

1. Goldestein et al. Am J Gastroenterol 2000; 95:1681-1690

2. Silverstein et al. JAMA 2000; 284:1247-1255

GI Event Surveillance

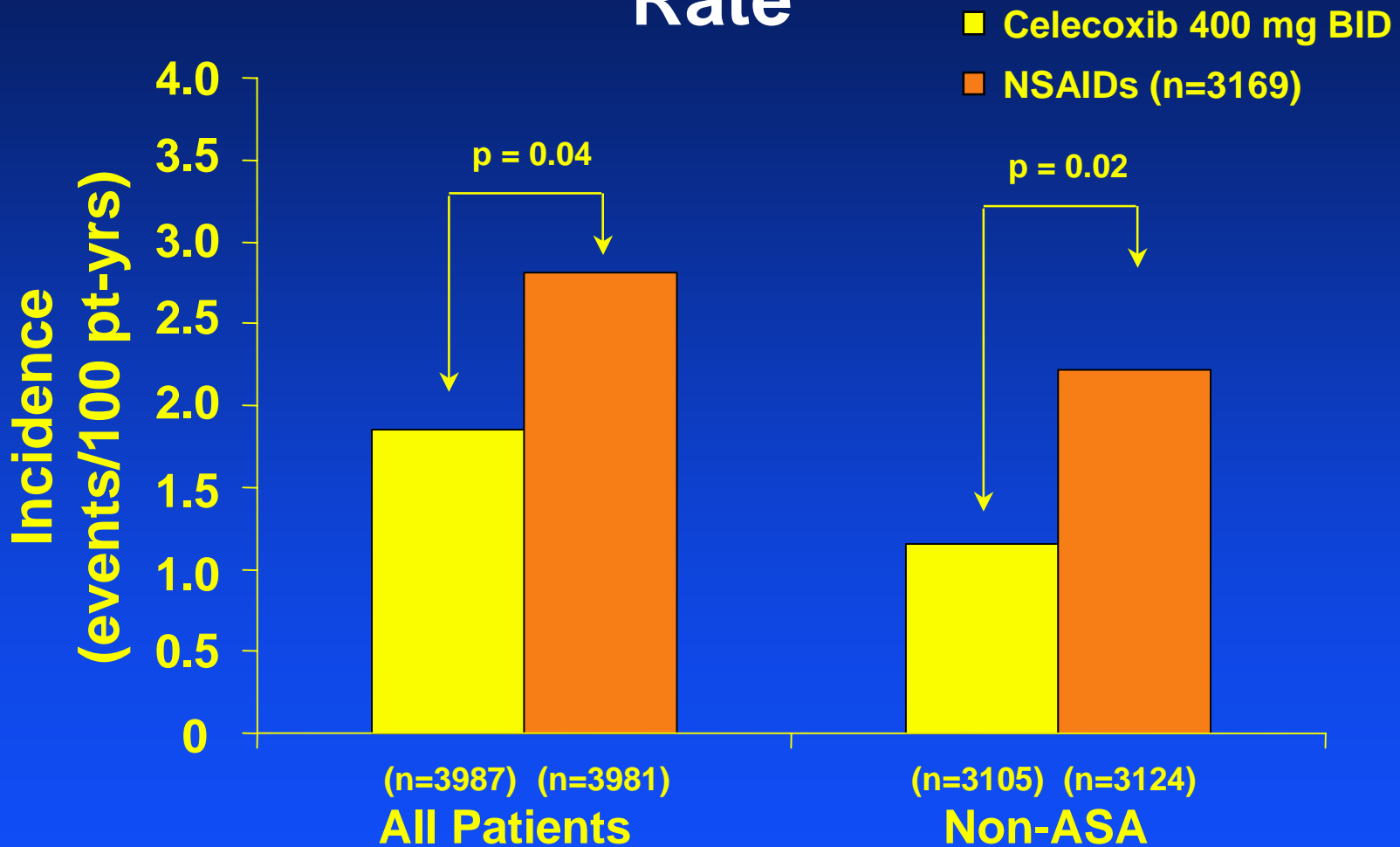
	<u>MUCOSA (1990)</u>	<u>CLASS (2000)</u>
Patients	8843	7968
Patient Years	--	4523
Reported	--	1527
Full GI Work-up	242	384
Crude Rate*	2.7%	4.8%

* Number with full GI work-up/patients

1. Silverstein et al. Ann Int Med 1995; 123:241-249

2. Silverstein et al. JAMA 2000; 284:1247-1255

Ulcer Complication and Symptomatic Ulcer Rate



Summary

- **Trial Design**
- **Clinical Results**
- **Confirmation of Antecedent Trials**
- **Safety**
- **Conclusion**