MOBIC CLINICAL OVERVIEW AND WHAT'S UP WITH THE NSAIDS????

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November 2004

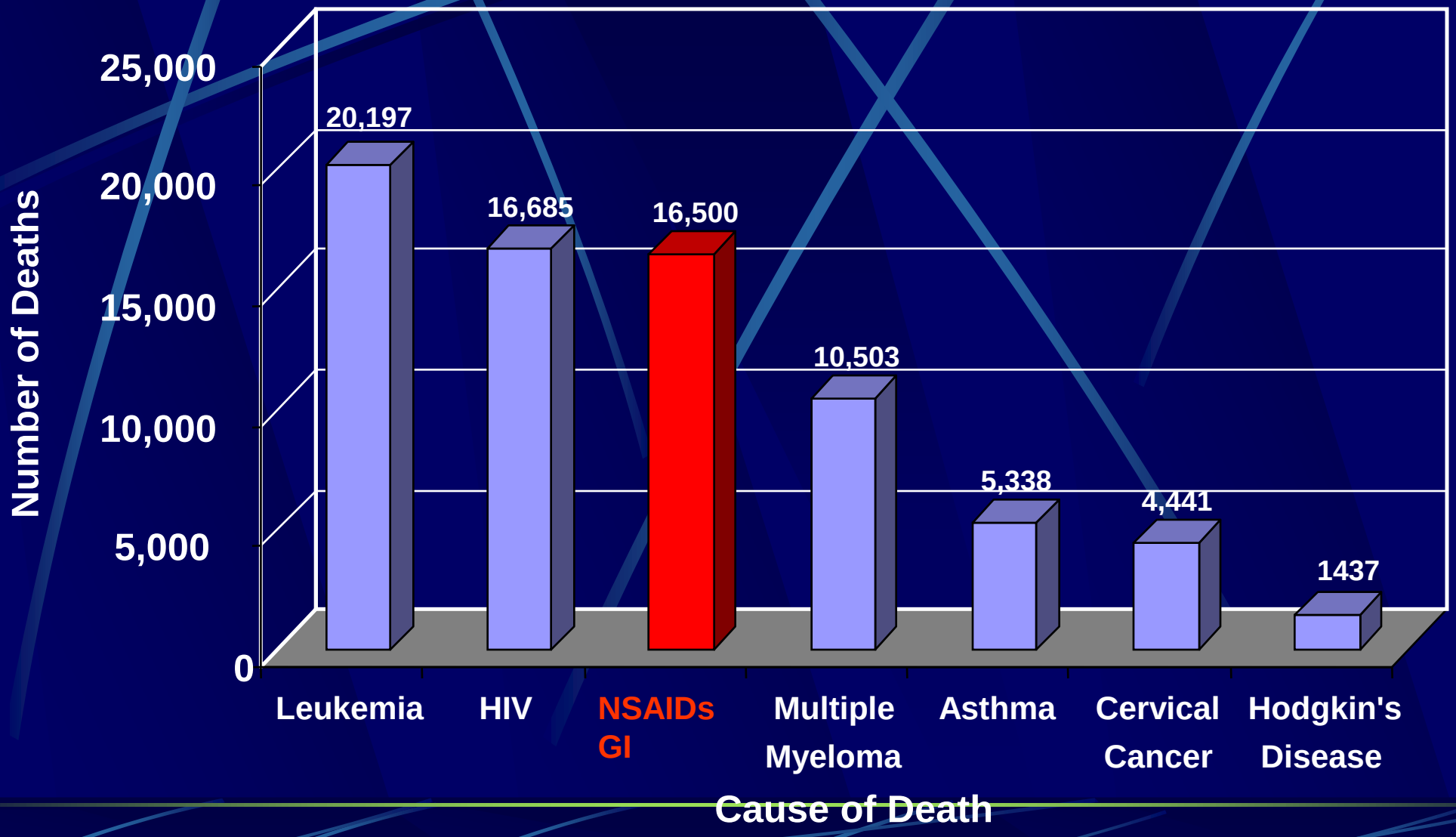
NSAID OVERVIEW

- 1 billion people world-wide have “arthritis”
- 30-50% are chronic NSAID users
- In U.S. 13 million use Rx.NSAIDS
- The same number use “over the counter” NSAIDS

NSAID RISKS

- 107,000 NSAID users hospitalized for GI
- 16,500 deaths due to GI bleeds (10-15%)
- Total cost $2 billion annually

Number of Deaths from Selected Causes US population (1997)



Wolfe, Lichtenstein, and Singh, 1999 NEJM

Cyclo-oxygenase concepts

- Arachidonic acids (AA)- unsaturated fatty acid obtained from ingested animal fats
- Cyclo-oxygenase (COX) binds AA to form prostaglandins
- In 1991 a second “type” of COX was discovered

COX-1

- Constitutive enzyme: stable body concentration
- In many tissues and function varies depending on location
- Stable gene expression
  - Thromboxane production (TxA2)
  - Stomach mucus production
  - Kidney: water, Na retention
  - Platelet aggregation, adhesion (“stickiness”)
  - Vasoconstriction

Cox -2

- Inducible by noxious (inflammation producing) stimulus
- Lives in endothelial blood vessel walls
- Variable gene expression
  - Prostacyclin production (PGI2)
  - Dilates blood vessels, permeability
  - Prevents platelet activation
  - Promotes extra- vascular phagocyte migration

Positive feedback mechanism

- In response to local platelet aggegation by thromboxane, prostacyclin is produced in vessel walls to vasodilate and to curb TxA2 production.
- Platelet aggregation doesn’t go unchecked

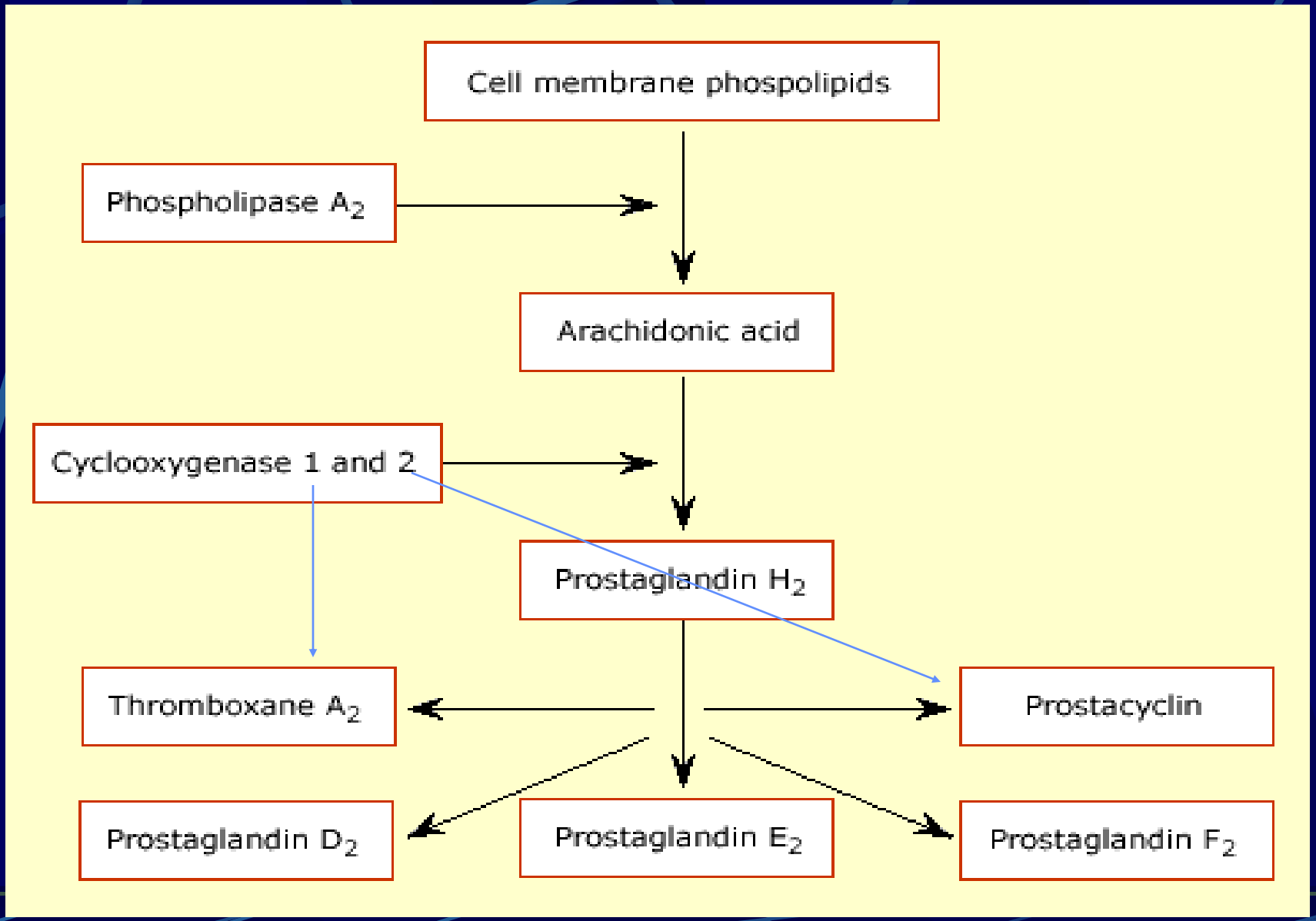
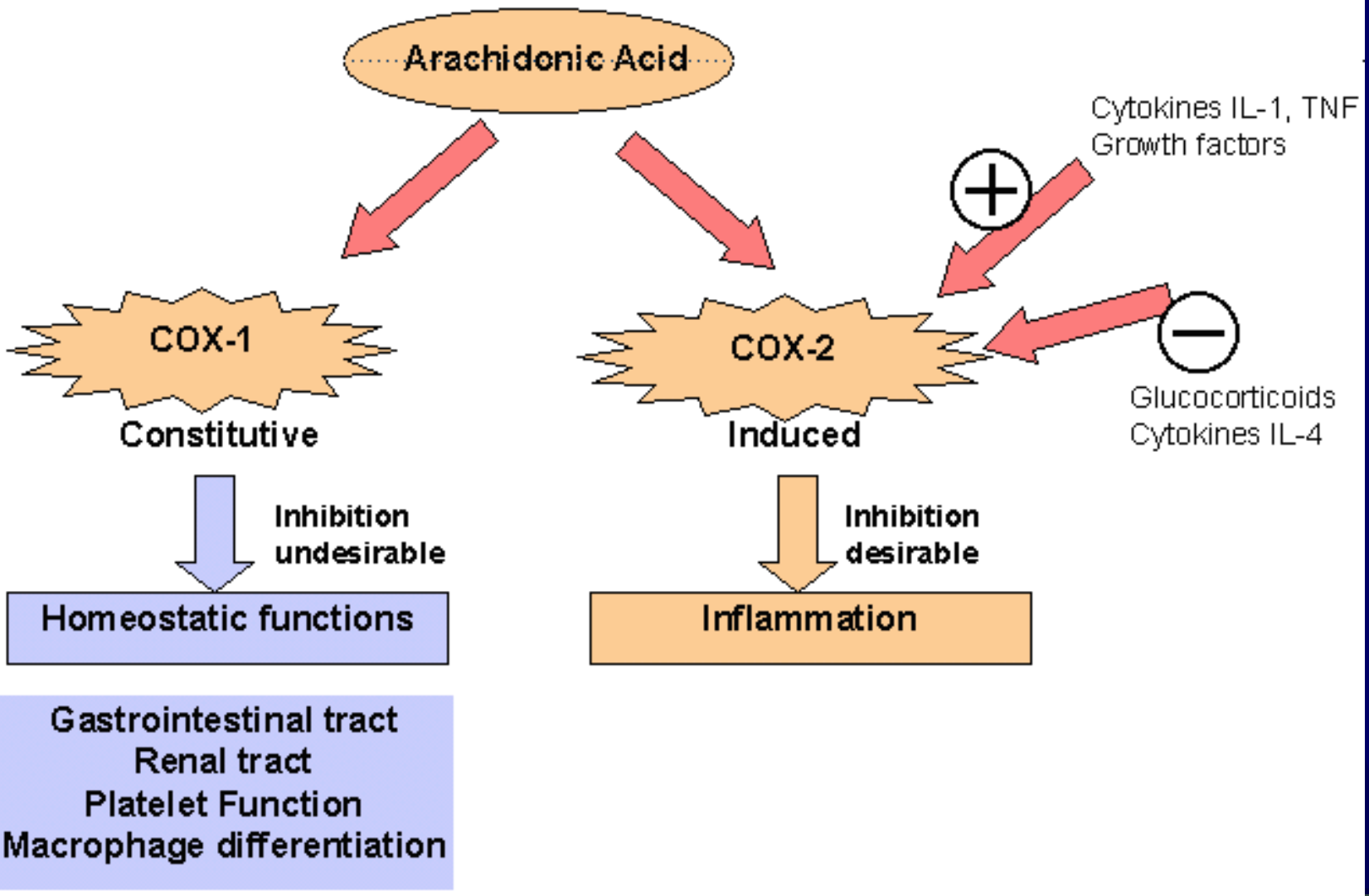
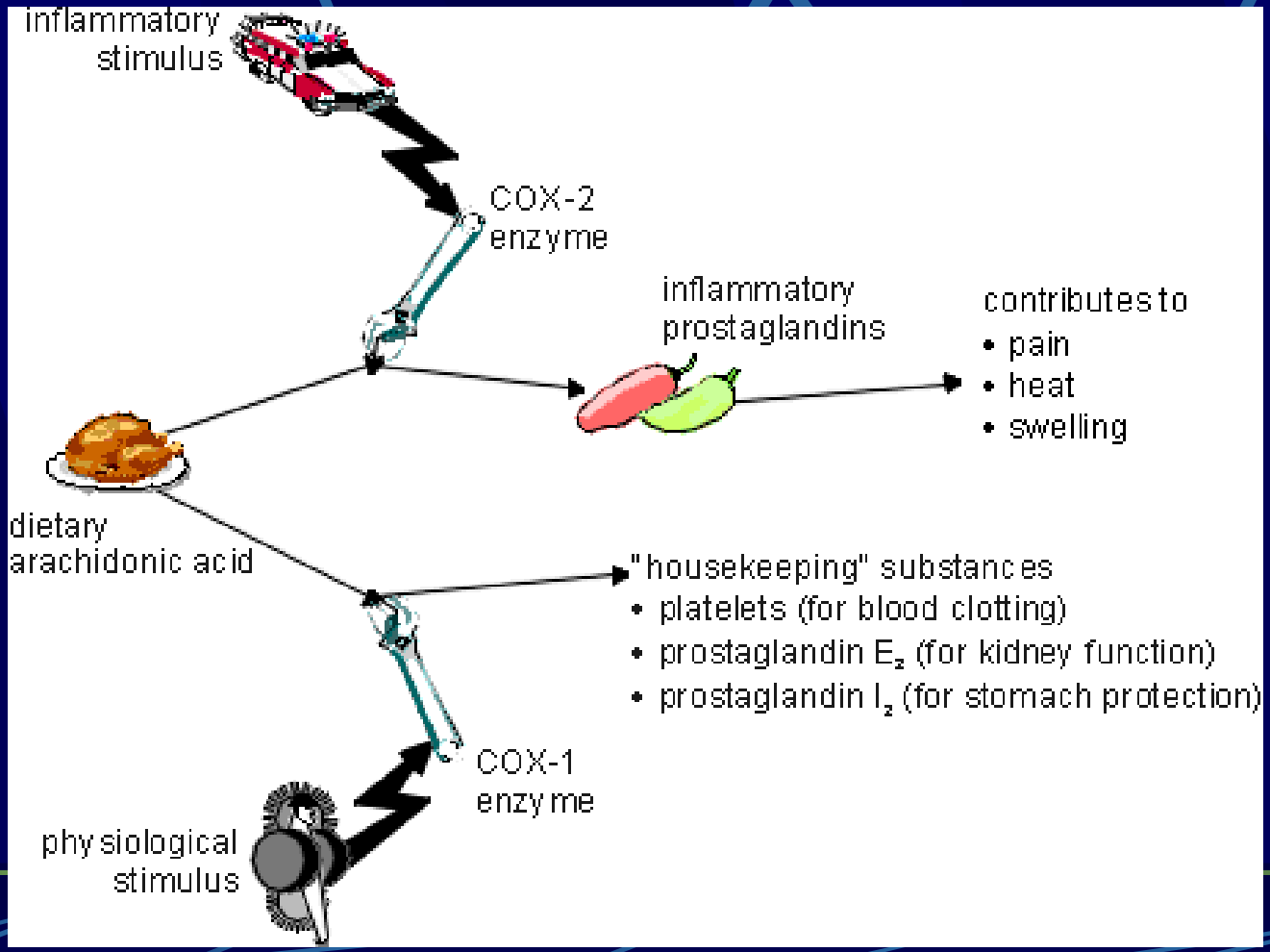
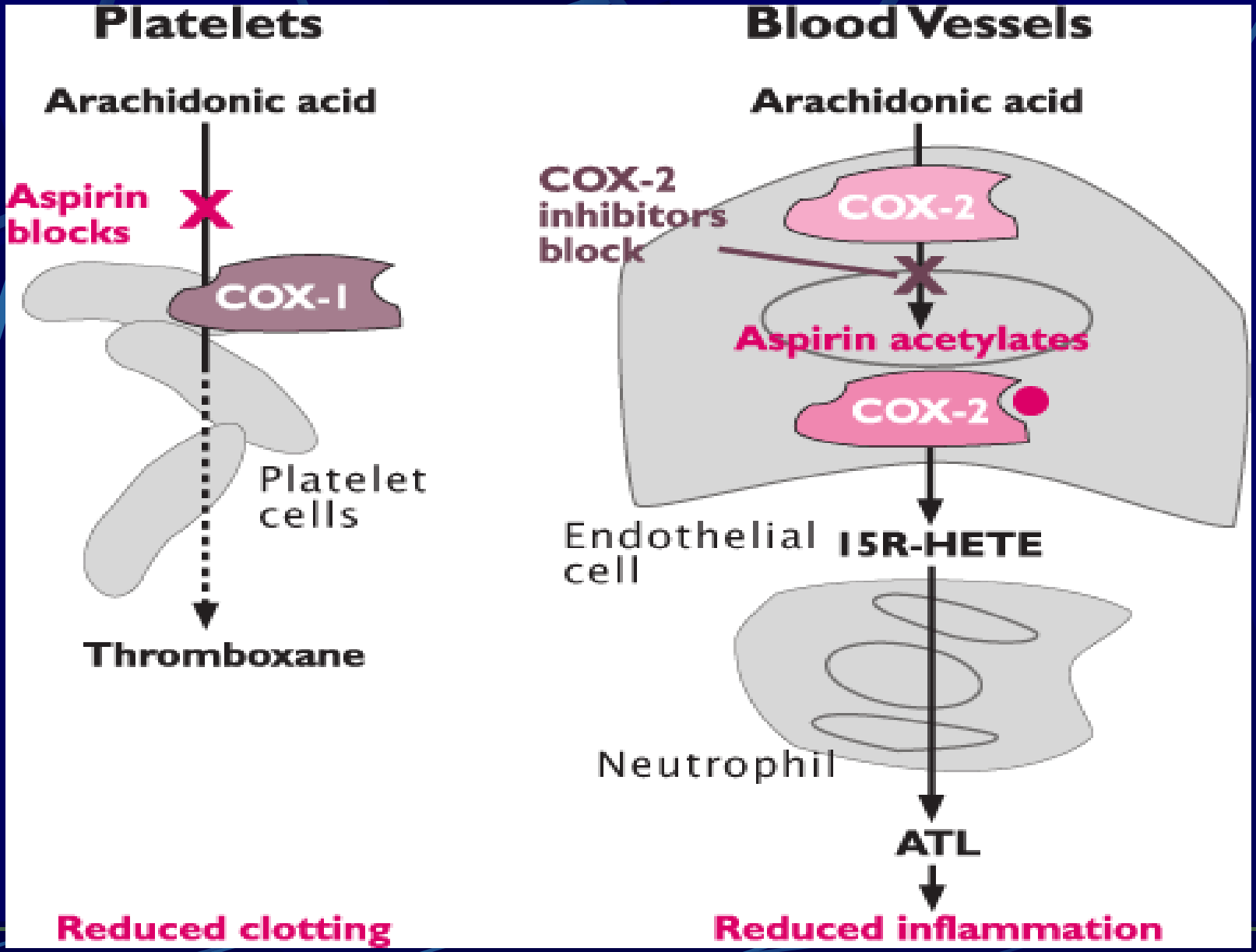

Cell membrane phospolipids
Phospholipase A_2
Arachidonic acid
Cyclooxygenase 1 and 2
Prostaglandin H_2
Thromboxane A_2
Prostacyclin
Prostaglandin D_2
Prostaglandin E_2
Prostaglandin F_2

Figure 3: The Current COX concept



Cox-1 vs. Cox-2 enzyme functions




Platelets
Arachidonic acid
Aspirin blocks
COX-1
Platelet cells
Thromboxane
Reduced clotting
Blood Vessels
Arachidonic acid
COX-2 inhibitors block
COX-2
Aspirin acetylates
COX-2
Endothelial cell
15R-HETE
Neutrophil
ATL
Reduced inflammation

NSAID ACTION

- Block the receptor site for AA on the COX molecule so that it cannot convert AA into PGE, TxA1, PGI2
- Aspirin acetylates Cox-1 permanently so it has a longer duration of action
- Blockage is incomplete for COX-2 (big receptor site) so some PGI2 still made
- You need high ASA dose for NSAID effect (4000mg.) but just 75 mg for anti platelet effect =cardio-protective

Acetominophen

- Has mild Cox-1 and Cox-2 inhibition effect
- Enough activity in the brain to relieve pain and fever
- ? Cox-3

Block COX-1

- Block production of Thromboxane
- Prevent platelet aggregation
- “Thin blood”
- Lose GI mucus “protective” effect

Block COX-2

- Diminish pain and inflammation
- Will allow Thromboxane synthesis to go unchecked by suppressing PGI2
- Vasoconstriction and runaway platelet aggregation and thrombus formation

  - Science 4/19/02

RENAL EFFETS

- Inhibiting COX –2 (PGE-2) in the kidney can cause Na+ and water retention causing hypertension

Drug Regulation in Controversy: Vioxx

November 10, 2004

Sandra L. Kweder, M.D.
Deputy Director, Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

COX-2 Inhibitors

- 1990s: tremendous hope of reducing GI morbidity and mortality
- 1998 Vioxx NDA was large
  - > 5000 pts
  - Exposure up to 86 weeks, with 371 and 381 patients taking 12.5 and 25 mg/day for one year or longer; 272 patients took 50 mg for at least six months
  - No CV signals in clinical trials, but reviewed carefully because of concern of pro-thrombotic effects *in vitro*

Vioxx 1999

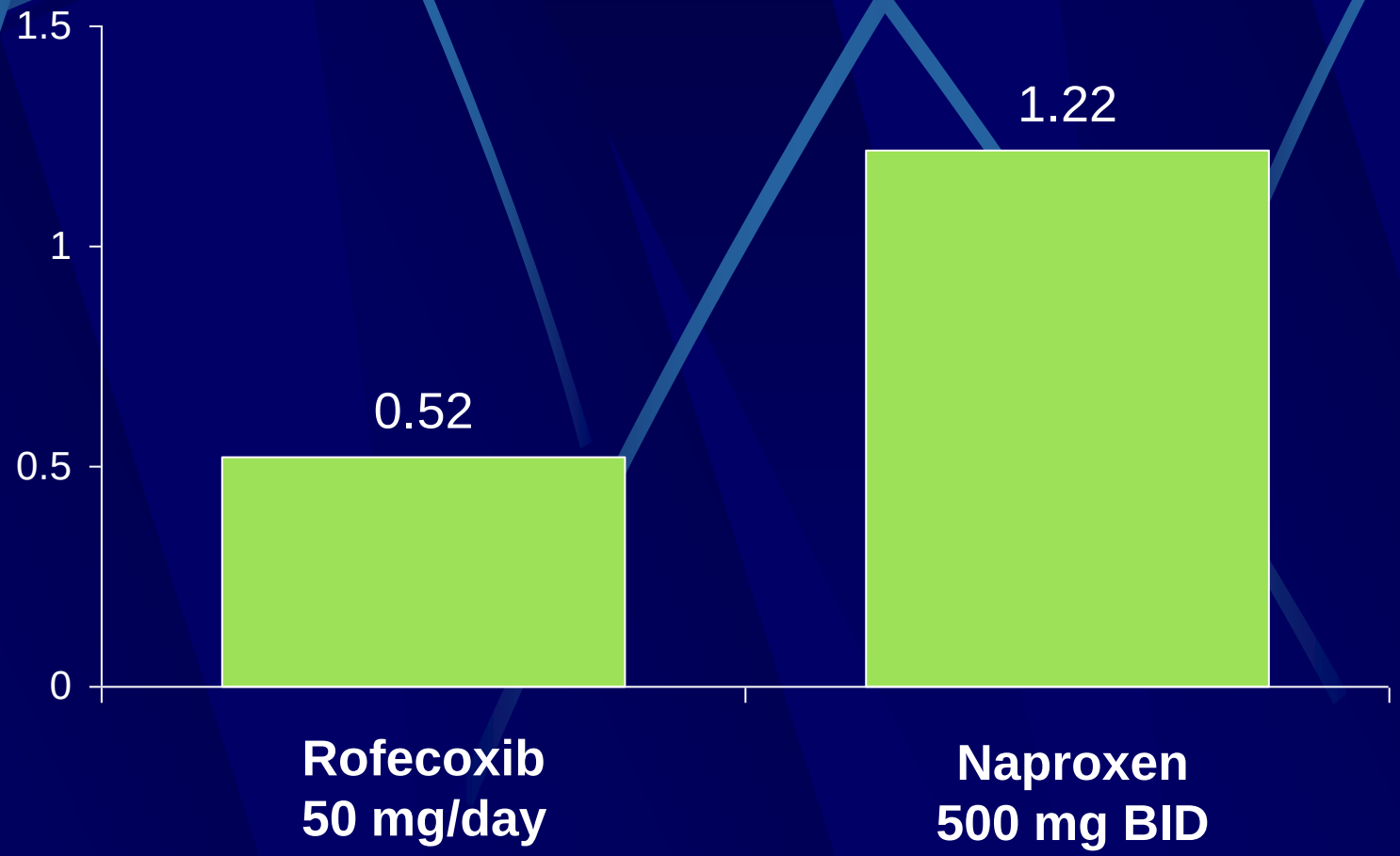
- January
  - Vioxx GI Outcomes Research trial begins (VIGOR)
- April - Arthritis Advisory Committee
  - Efficacy and multiple safety components
- May – Vioxx NDA approved
  - Acute pain, dysmenorrhea, OA
- November
  - Colon polyp prevention study (APPROVe) submitted

Coxib Study Designs

	CLASS[1] (n=7968)	VIGOR[2] (n=8076)
Drug	Celecoxib 400mg bid (4x OA dose, 2x max RA dose)	Rofecoxib 50mg qd (2x typical OA dose, 2x max chronic dose)
Patients	OA (72%), RA (28%)	RA
Comparator(s)	Ibuprofen 800mg tid Diclofenac 75mg bid	Naproxen 500mg bid
Low dose aspirin	Yes (21%)	No
Duration	Median 9 months Maximum 13 months	Median 9 months Maximum 13 months
1° endpoint	Complicated ulcers	Clinical UGI events
2° endpoint	Symptomatic ulcers	Complicated UGI events

[1] Celecoxib Long-term Arthritis Safety Study
[2] Vioxx Gastrointestinal Outcomes Research

VIGOR: Kaplan-Meier cumulative rate of complicated PUBs (per 100 patient-years)[2*†]



Vioxx 2000

- March – Preliminary results of VIGOR submitted to IND
  - Analyses of serious CV events in all NDA studies, placebo controlled Alzheimer studies and ADVANTAGE, which was almost complete
  - Letters to all investigators with information
  - Informed consent documents modified
- Multiple public venues for data

Vioxx 2000 (continued)

- June
  - APPROVe protocol changed to allow use of low dose aspirin
- June – VIGOR to FDA as NDA supplement
  - Decrease in risk of gastro-duodenal perforations, ulcers and bleeds compared to naproxen
  - Increase in CV thrombotic events, mostly MI 0.5% V vs. 0.1% not used
- November – NEJM publication of VIGOR

Vioxx 2001

- February
  - Arthritis Advisory Committee reviews VIGOR
  - Risk/Benefit review – still positive
  - Recommend labeling & additional studies of CV risk
- February**
  - NDA for Rheumatoid Arthritis submitted
  - N=1100 taking 25 or 50 mg vs naproxen for 3-12 months
- Fall
  - APPROVe completes enrollment
  - Labeling discussions with Merck ongoing

Vioxx 2001 (continued)

- All Vioxx protocols reviewed
  - Alzheimer's, polyps, prostate cancer
  - Focus on CV endpoint definition & adjudication
- Review of data sources for more definitive answer
  - NDA supplement for RA
  - Interim analyses of other clinical trials
- FDA sought large database to conduct retrospective data review
  - Contract with Kaiser

Vioxx 2002

- Label discussions between FDA and Merck
- Ongoing data review by FDA
  - Mixed picture of CV risk
  - Merck submits more data from ongoing Alzheimer's Disease trials
    - 2800 patients on Vioxx 25 mg vs placebo
    - No excess of CV events
- April
  - Label for RA, GI safety benefit and CV risk approved
  - CV risk in "Precautions" and other sections
  - 50 mg dose should not be used for more than 5 days

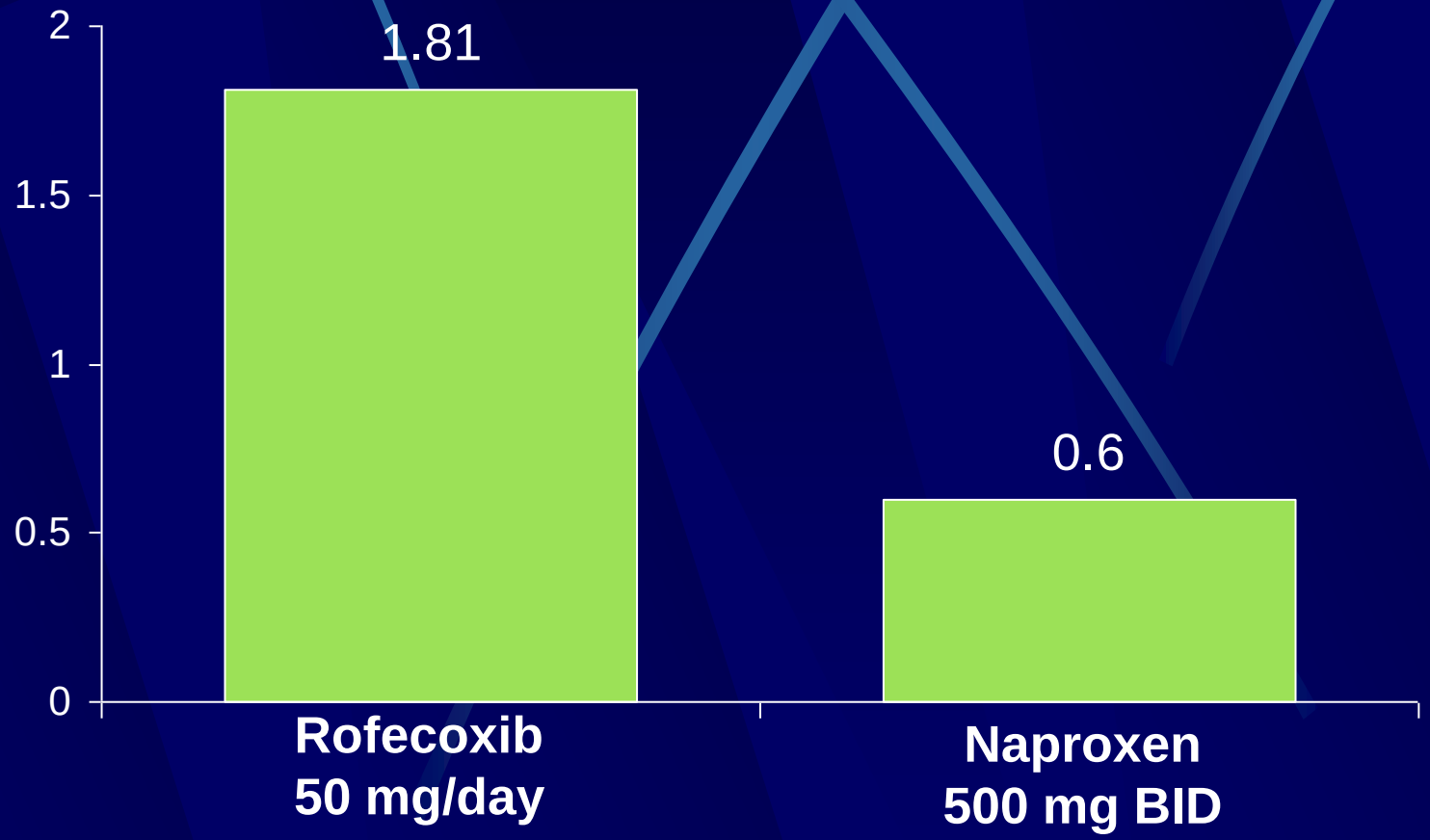
Vioxx 2003-2004

- 2003
  - Continued focus on ongoing trials and data collection and assessment for CV safety
- August 2004
  - FDA Kaiser cohort analysis neared completion
  - Abstract presented at ISPE
    - Shows risk of 50 mg dose (confirms VIGOR)
    - Risk for 25 mg dose similar to other NSAIDS
- September 2004
  - APPROVe 36 month study results reviewed by DSMB
  - Merck decision to withdraw Vioxx

What Did APPROVe Show?

- **Vioxx 25 mg** per day significantly increases risk of serious CV events (MI and stroke) compared to placebo
- Risk appears after patients are taking drug for 18 months
  - Definitive confirmation of risk not evident until 36 month assessment

VIGOR: Kaplan-Meier cumulative rate of CV thrombotic adverse events (per 100 patient-years)



Number of subjects in studies included in meta-analysis

Study	Valdecoxib	Placebo
Ott (initial CABG study)	311	151
2nd CABG	1088	548
White (placebo-controlled studies only)	4531	1142

Valdecoxib (Bextra) meta-analysis signals significant cardiovascular risk
[*Rheumawire > News;* Nov 10, 2004]

Number of cardiovascular events (MI and stroke)

Study	Valdecoxib	Placebo	RR	95% CI
Ott	14	2	3.51	0.79-16
2nd CABG	17	3	2.88	0.84-10
White	14	2	1.77	0.40-7.8
Meta-analysis, p=0.11			2.19	1.19-4.03

Valdecoxib (Bextra) meta-analysis signals significant cardiovascular risk
[*Rheumawire > News;* Nov 10, 2004]

Do Cox-2 Selective Agents Have a Different CV Risk Profile?

- No definitive evidence – except Vioxx
- Agents differ in degree of selectivity
- Dose response may be an important factor
- Traditional NSAIDs may differ in CV toxicity profiles
- Mechanism for the risk remains unclear
  - platelet effect?
  - blood pressure?
  - Other?

Difficulties in Evaluation

- Placebo controlled data most interpretable because CV effects of comparators not established
  - Issue of naproxen control loomed over VIGOR
  - Other NSAID controls would have similar concerns
- VIGOR suggested risk seems to be highest after months on treatment
  - Hard to do long term placebo controlled trials in arthritis
  - Trials in high risk groups for long periods are of concern
  - High CV risk groups take ASA, which might have mitigated any adverse risk with Vioxx

What About Other COX-2s?

Celecoxib (Celebrex)

- Approved in 1998
  - No CV risk in NDA
- Development program
  - Large scale placebo-controlled trials for prevention of colon polyps/cancer (n=3600) and Alzheimer's disease
  - Independent DSMBs for these studies with special emphasis on cardiovascular events. Both DSMB's get monthly data updates; have issued statements to investigators that they are aware of rofecoxib W/D and have determined there is no indication for stopping these trials
  - Meet again in late fall

Valdecoxib (Bextra)

- NDA database of 8,000
  - No CV signal in oral studies at doses in range and above those approved
  - No CV signal in IV studies in post operative pain
  - Excess CV events and death in single IV study in post-CABG patients
- IV and follow-on p.o. in post-op studies were 2-4X that in oral only studies

Valdecoxib (Bextra)
10/18/04

- Stevens- Johnson syndrome
- Exfoliative dermatitis
- Toxic epidermal necrolysis
- High rate with Bextra than any other NSAID
- Within first two weeks of treatment
- Very rare <1%

Bextra controversy

- Fitzgerald meta-analysis 2000 CABG patients
- 2 placebo controlled trials of Bextra
- 7500 in all, varying the NSAID for post op pain relief
- Twice the incidence of MI or CVA with Bextra than any other NSAID

Study design

- CABG patients were given IV Paracoxib post-op followed by Bextra po 40-80 mg
- Close exam of the MI's showed that most occurred intra-op ***before the drug was given.***
- ***The fun is just starting!***

FDA Next Steps

- Arthritis Advisory Committee in early 2005
  - Share all available data on Vioxx and other drugs
  - Seek advice on additional steps and studies needed
- Other COX-2s
  - Accumulating data re: celecoxib via placebo controlled trials
  - Explore ways of further evaluation of valdecoxib
  - Scrutiny of new agents (some approved in Europe)

FDA Safety Initiative 2004

- Search for Director, Office of Drug Safety
- Institute of Medicine Study
  - Assess full spectrum of drug safety in the US
  - To include operations between Office of New Drugs and Office of Drug Safety
- New procedure for review of differing professional opinions
  - When usual processes are not satisfactory to parties
- Focused effort to bring safety matters to public Advisory Committee meetings for review

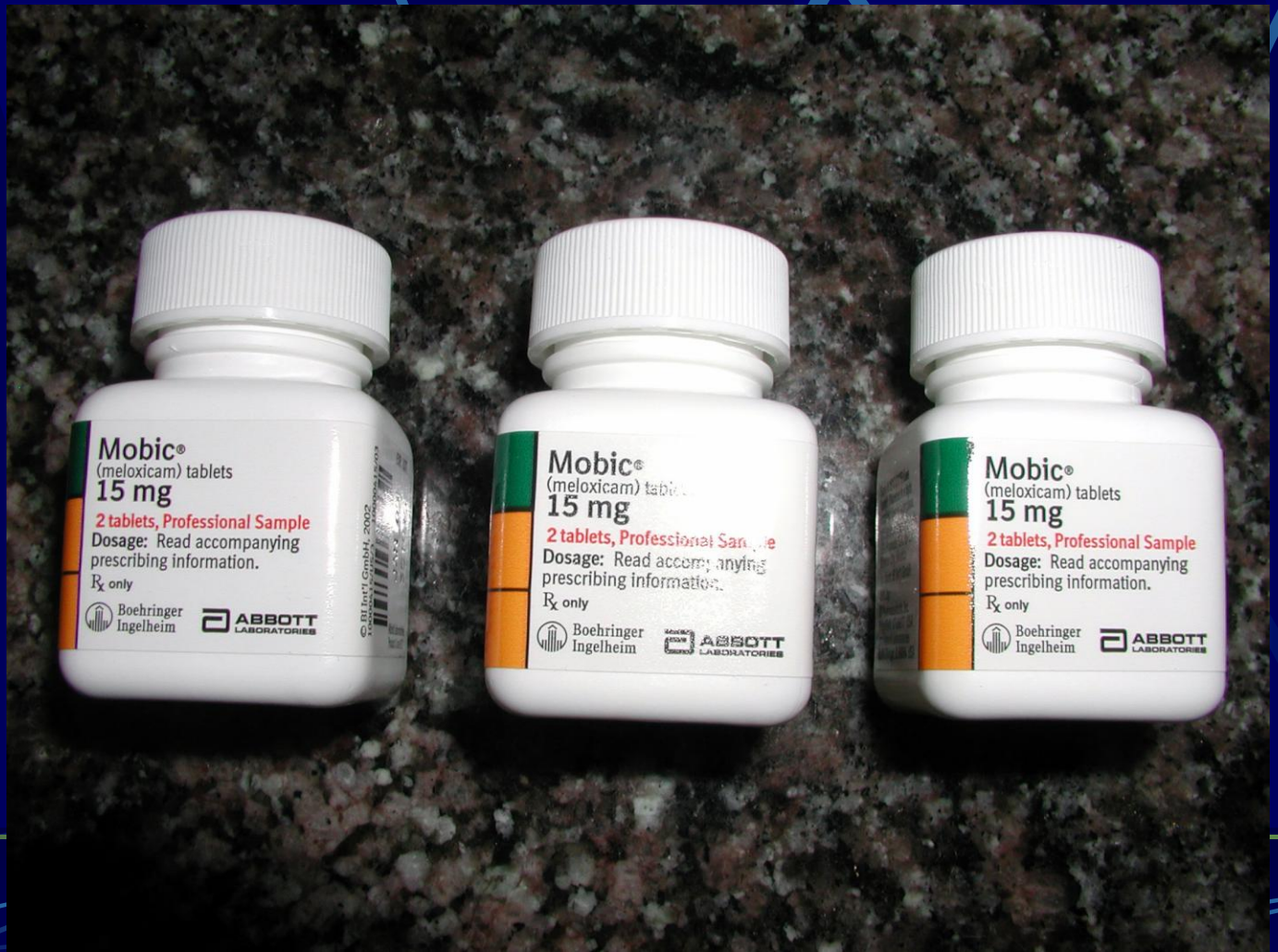
Summary

- Vioxx experience complex from scientific and regulatory standpoint
  - Data were mixed from very early on
  - Definitive trials in arthritis extremely challenging
  - Difficulty in requiring 3 year placebo controlled safety studies prior to approval
  - Placebo controlled data offered best hope for definitive answers
- The experience will be applied to review additional COX-2 inhibitors over next few months
  - Public discussion essential – Advisory Committee

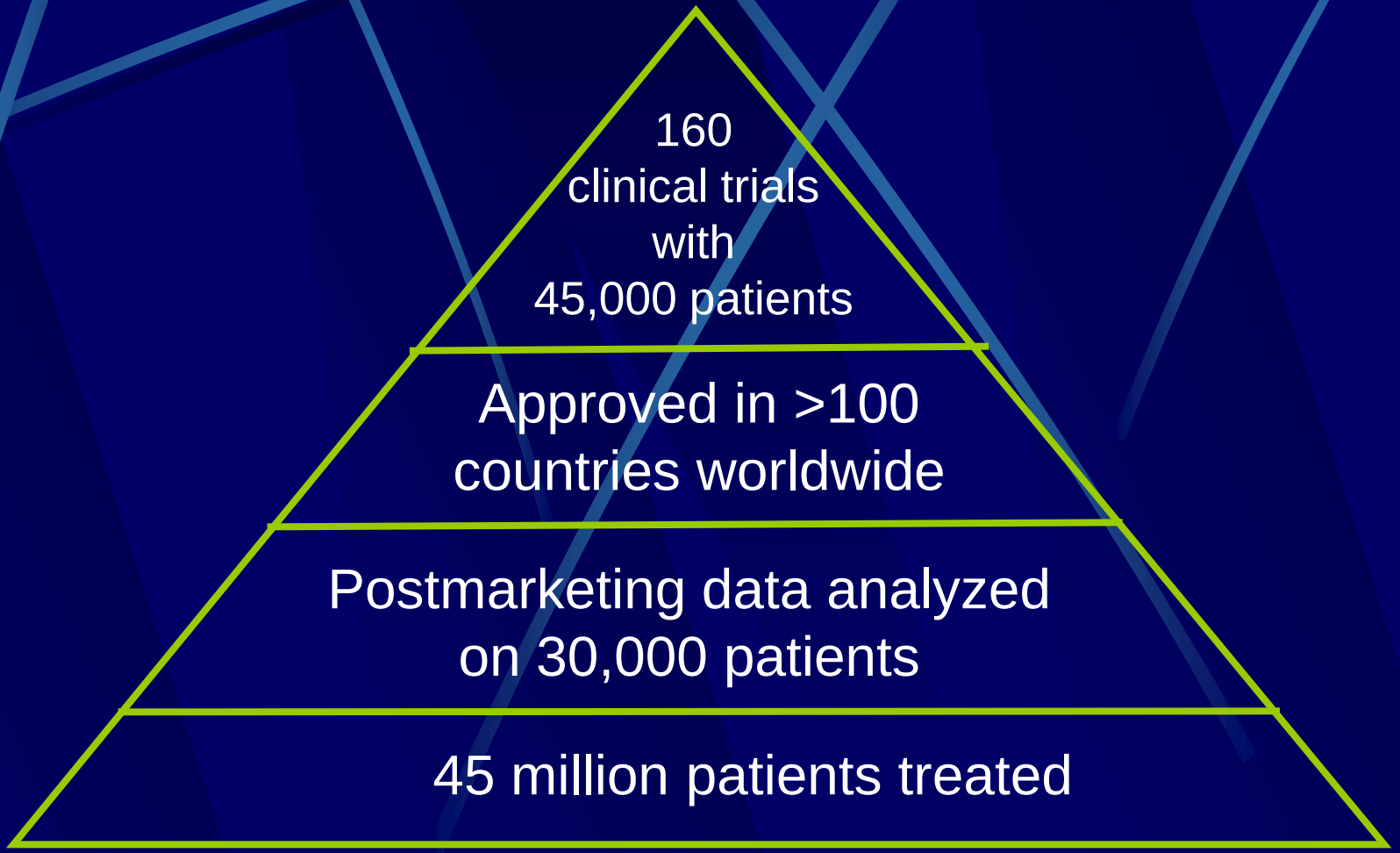
Summary (continued)

- Learning from experience is a part of public accountability
  - Role for external scrutiny (IOM), particularly of broader picture of our ability to be effective in identifying and following up on safety issues

Well, what about Mobic?



Meloxicam Worldwide Experience: December 2000



Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.

Meloxicam Pharmacokinetics

- Absorption
  - Peak plasma concentrations (C_{max}) at 5–6 hours
  - Steady state concentrations within 3–5 days
  - Half-life = 20 hours (true once-daily dosing)
  - Can be taken without regard to meals
- Distribution
  - Protein binding >99.5%
  - Synovial fluid concentration = 40%–50% of plasma concentrations
- Excretion
  - Eliminated by hepatic metabolism (no active metabolites)
  - Equal excretion via urinary and fecal routes

Türck D et al. *Arzneimittelforschung*. 1997.
Schmid J et al. *Drug Metab Dispos*. 1995.
MOBIC® (meloxicam) U.S. Product Information. 1999.

Meloxicam Drug Interactions

Methotrexate	No
Warfarin	No*
Furosemide	No
Cimetidine	No
Digoxin	No
Lithium	Yes†

* No change in INR with concomitant meloxicam therapy
†21% increase in lithium AUC

Türck D et al. *Eur J Clin Pharmacol*. 1997.
Degner F et al. *Br J Clin Pharmacol*. 1995.
Hübner G et al. *J Rheumatol*. 1997.
Müller FO et al. *Eur J Clin Pharmacol*. 1995.
Müller FO et al. *Br J Clin Pharmacol*. 1997.
MOBIC® (meloxicam) U.S. Product Information. 1999.
Busch U et al. *J Clin Pharmacol*. 1996.
Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.

COX1- COX2 Balance

- In vitro inhibition of COX 2 is 3x that of COX-1
- Diminished monocyte (COX-2) activity by 50-70%
- Diminished platelet (COX-1) activity by 25-35%

Efficacy

Efficacy Overview

- US OA Trial
- US RA Trial
- IMPROVE
- Ankylosing spondylitis

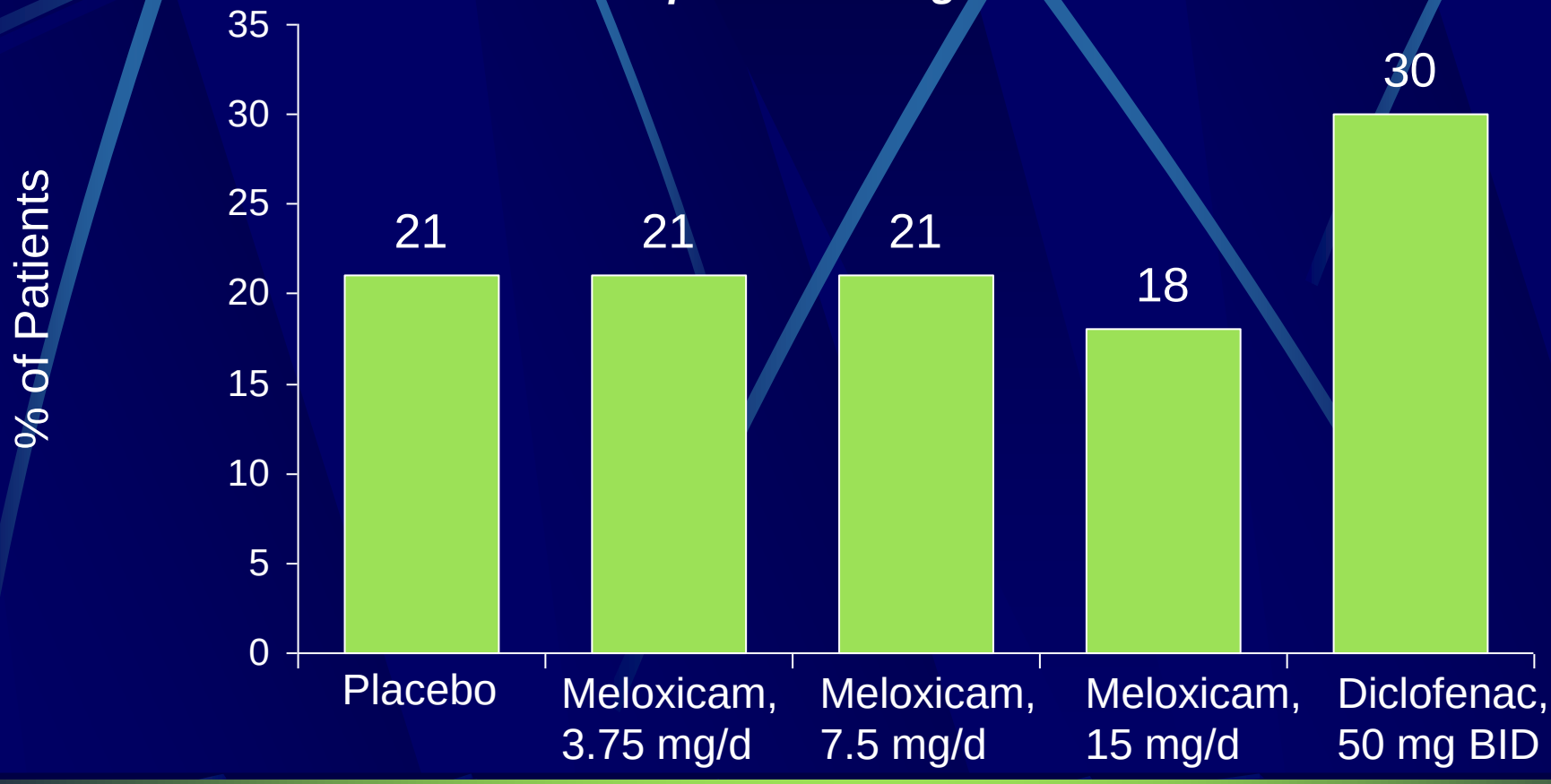
Safety and Efficacy of Meloxicam in the Treatment of Osteoarthritis: US OA Trial

Trial Design

- Double-blind, parallel group, randomized multi-center study (774 patients)
- Patient aged 62.9 +/- 10.3 years
- Diagnosis of OA of hip or knee and a flare
- Treated with meloxicam (3.75mg, 7.5 mg, 15 mg/d), diclofenac (100mg [50mg twice daily]), or placebo for 12 weeks

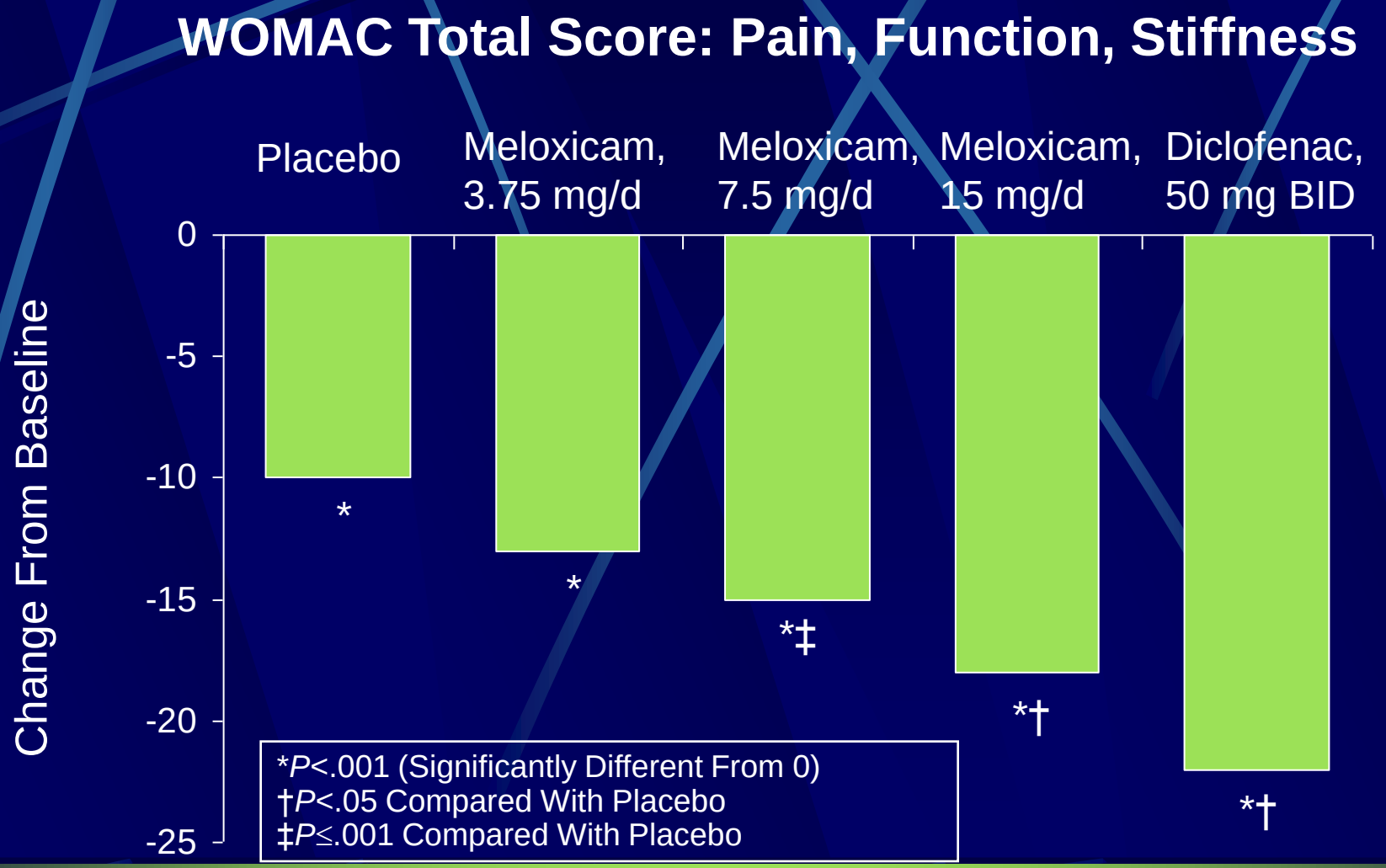
Safety and Efficacy of Meloxicam in the Treatment of Osteoarthritis: US OA Trial

Incidence of gastrointestinal adverse events estimated using the Kaplan-Meier algorithm.



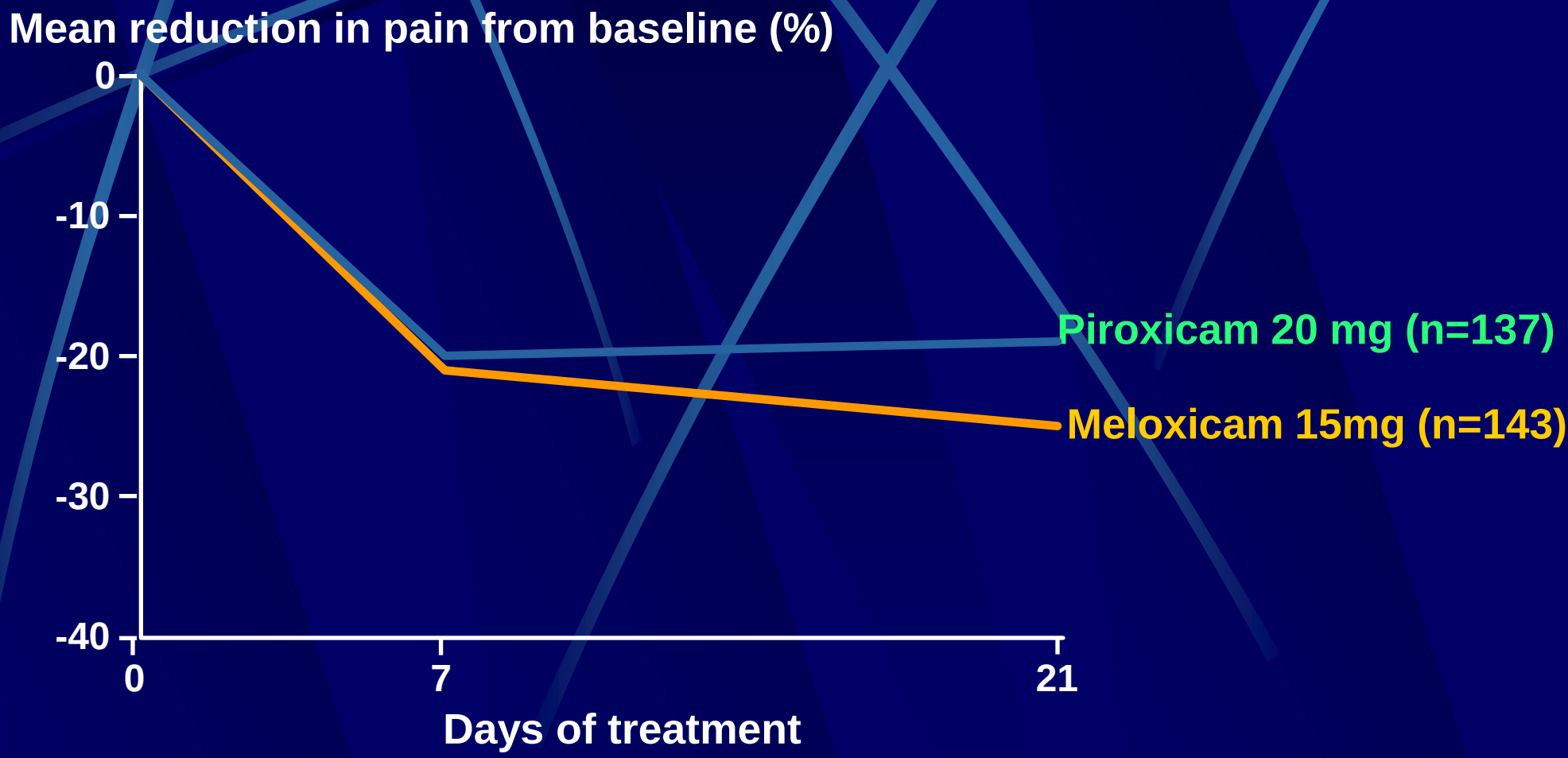
Yocum et al Arch Intern Med, Vol 160: 2947-2954.

Safety and Efficacy of Meloxicam in the Treatment of Osteoarthritis: US OA Trial



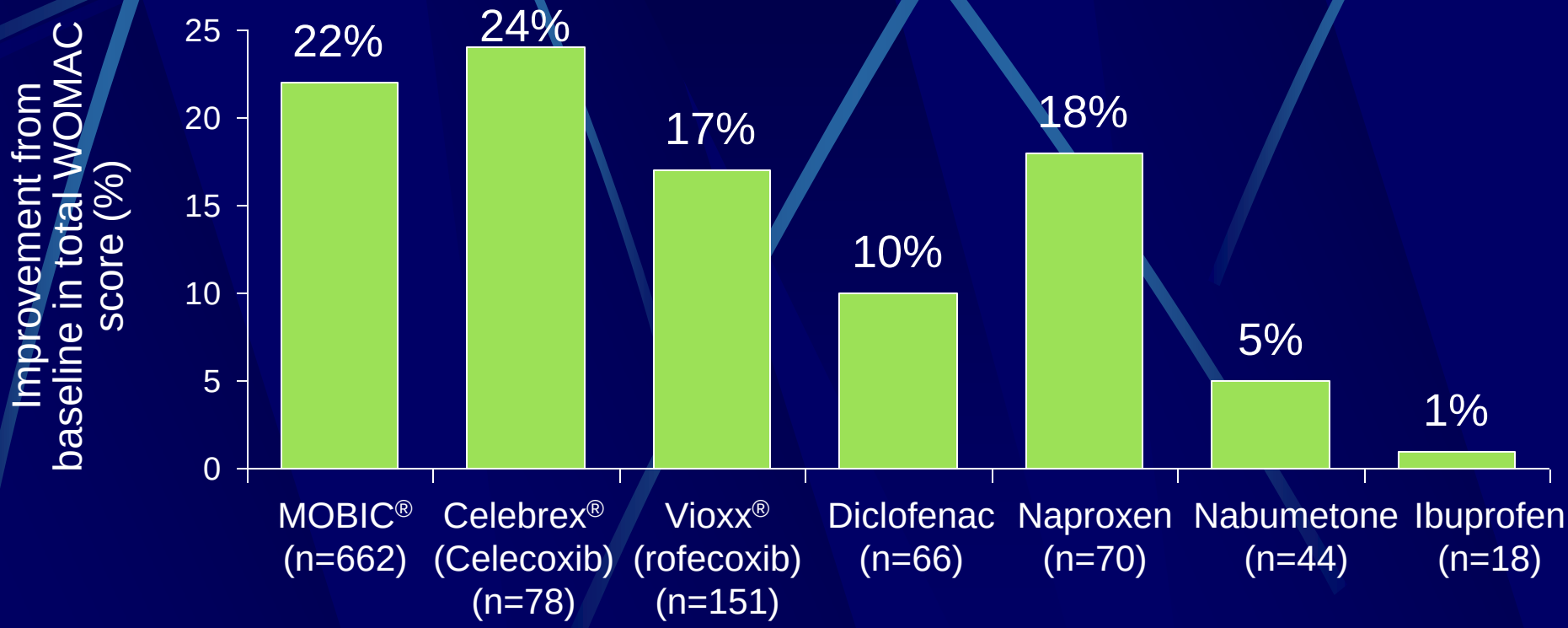
Yocum et al Arch Intern Med, Vol 160: 2947-2954.

Reduction in pain over the previous 2 days in RA for meloxicam 15 mg and piroxicam 20 mg



Huskisson et al. Scand J Rheumatol 1994 (suppl. 98): 115

IMPROVE Trial
WOMAC Improvement From Baseline



IMPROVE Trial
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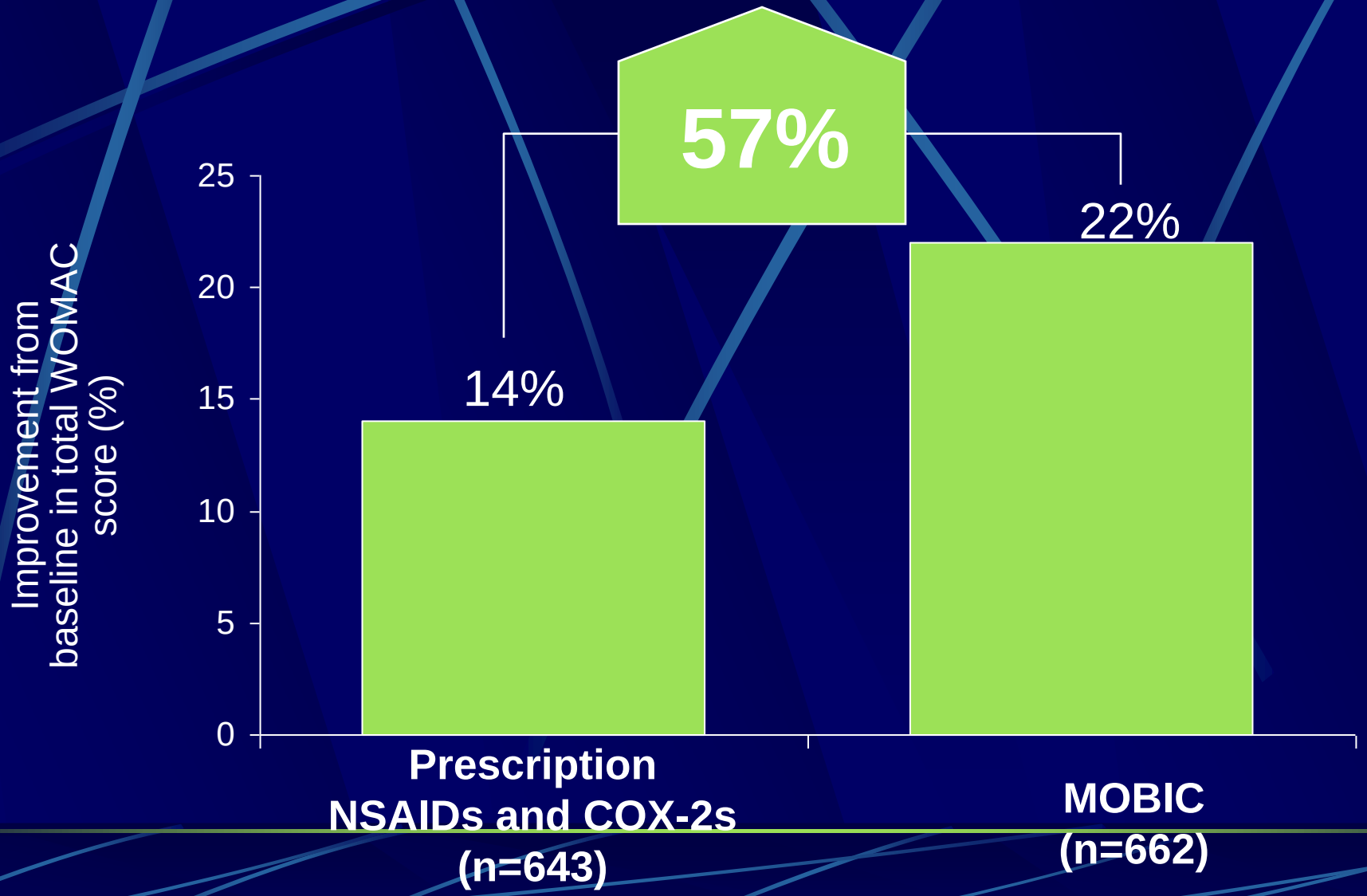
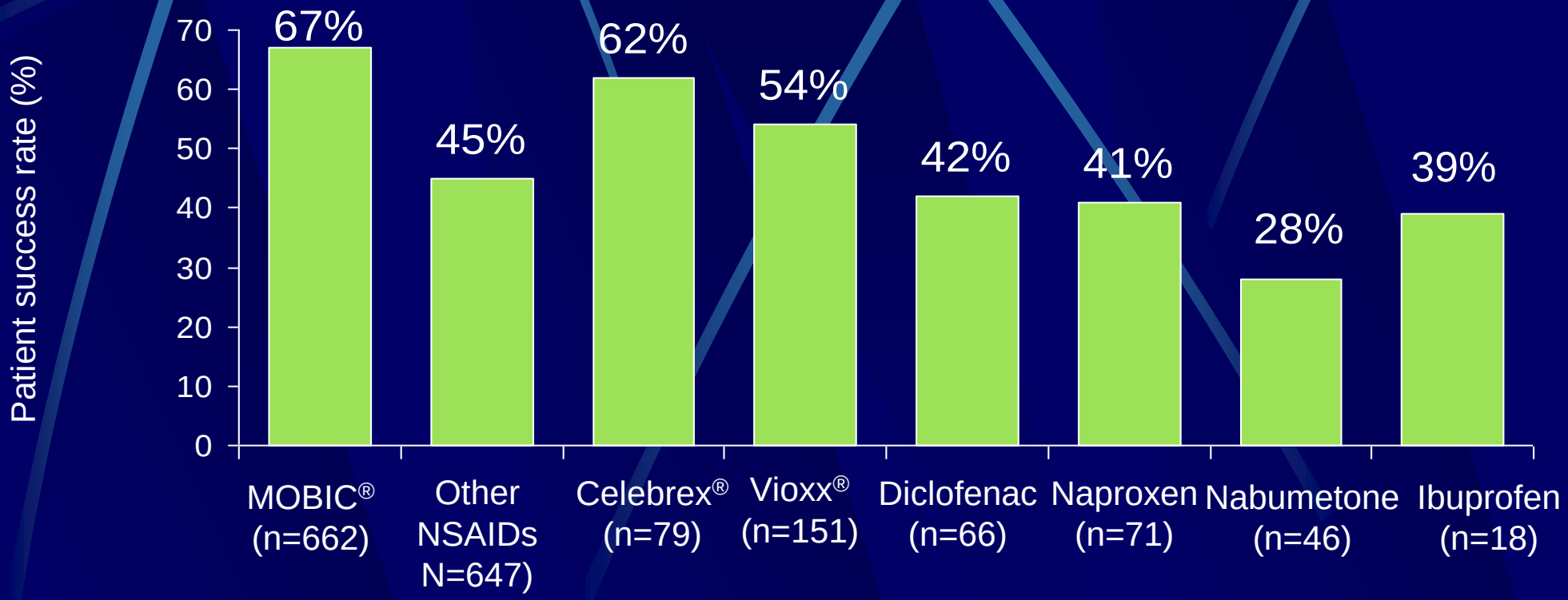
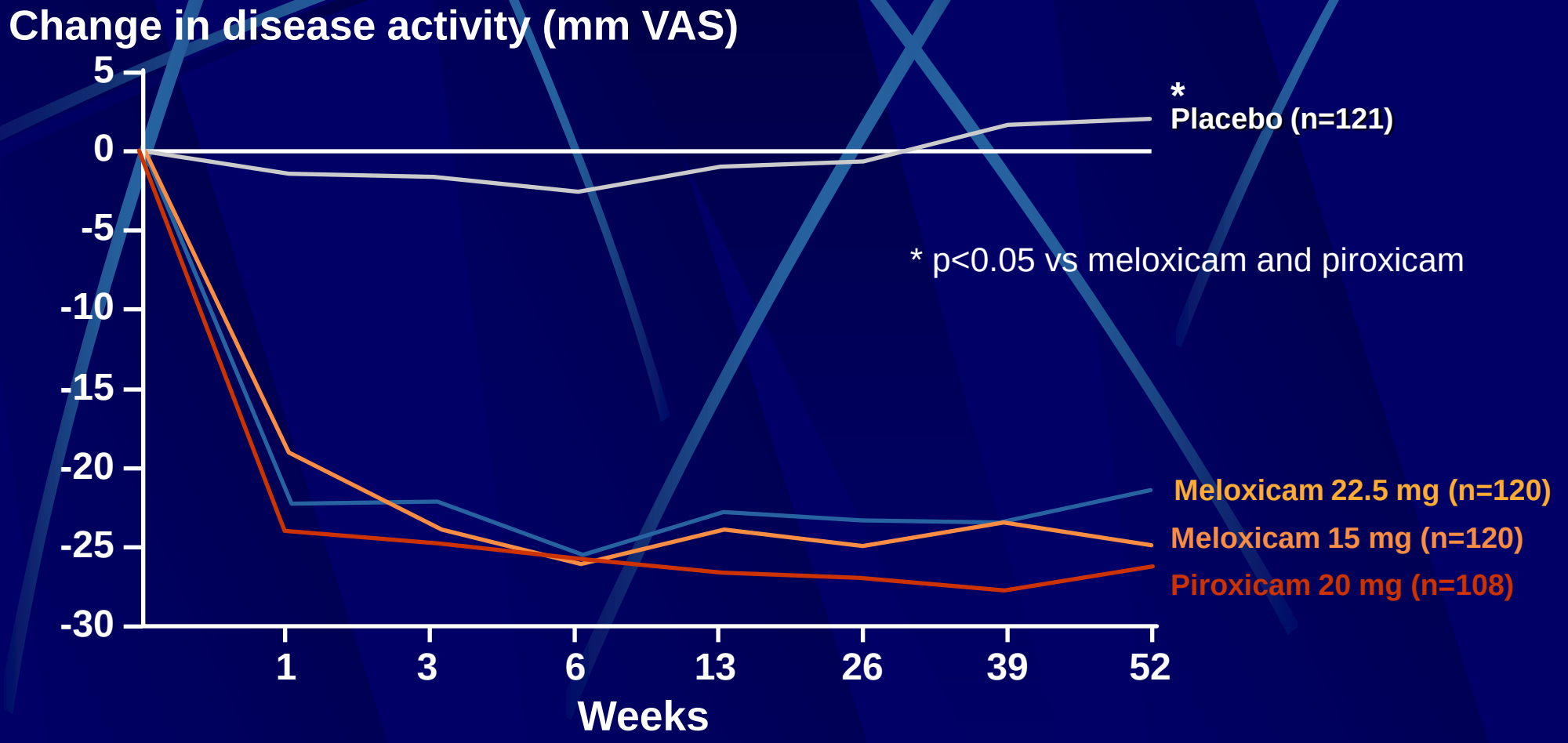


IMPROVE Trial
Patient Success



Absolute change in disease activity over 1 year of treatment in patients with AS



Dougados et al. Rheumatology 1999; 38:235-244

Efficacy Summary

- Meloxicam 7.5-mg dose demonstrates efficacy clinically comparable to diclofenac 100 mg SR and piroxicam 20 mg
- Meloxicam 7.5-mg and 15-mg doses demonstrate
  - Efficacy significantly superior to placebo for all efficacy measures
  - Significantly fewer withdrawals than placebo due to lack of efficacy

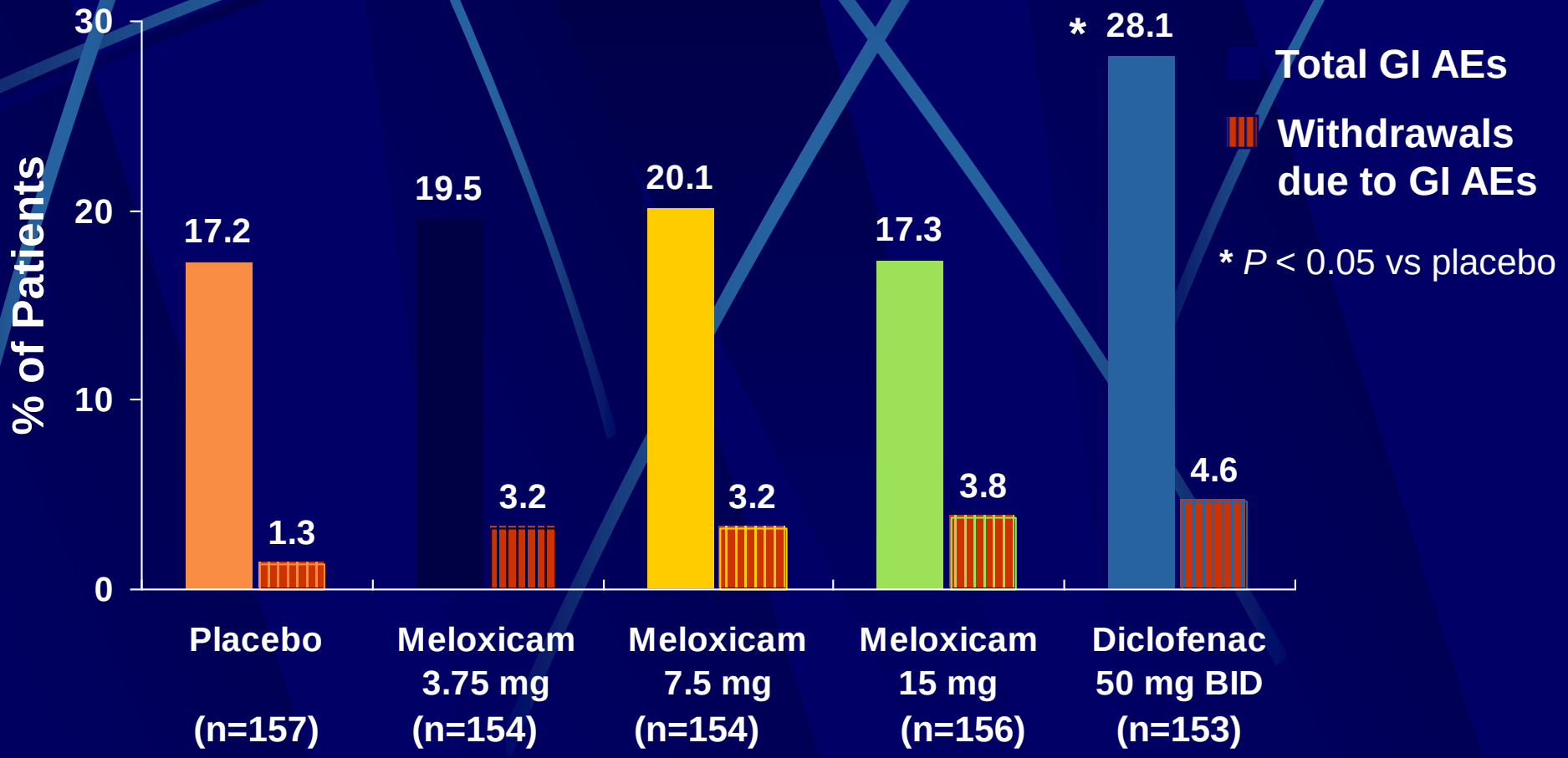
Hawkey C, Kahan A, Steinbrück C, et al. *Br J Rheumatol*. 1998.
Dequeker J, Hawkey C, Kahan A, et al. *Br J Rheumatol*. 1998.
Data on file. Boehringer Ingelheim Pharmaceuticals, Inc./Yocum et al. Pending MS submission

GI Safety and Tolerability

GI Safety and Tolerability Overview

- US OA Trial
- MELISSA/SELECT
- CLASS/VIGOR
- GI Adverse Event Meta-analysis

Total GI AEs and Withdrawals Due to GI AEs: US OA Trial



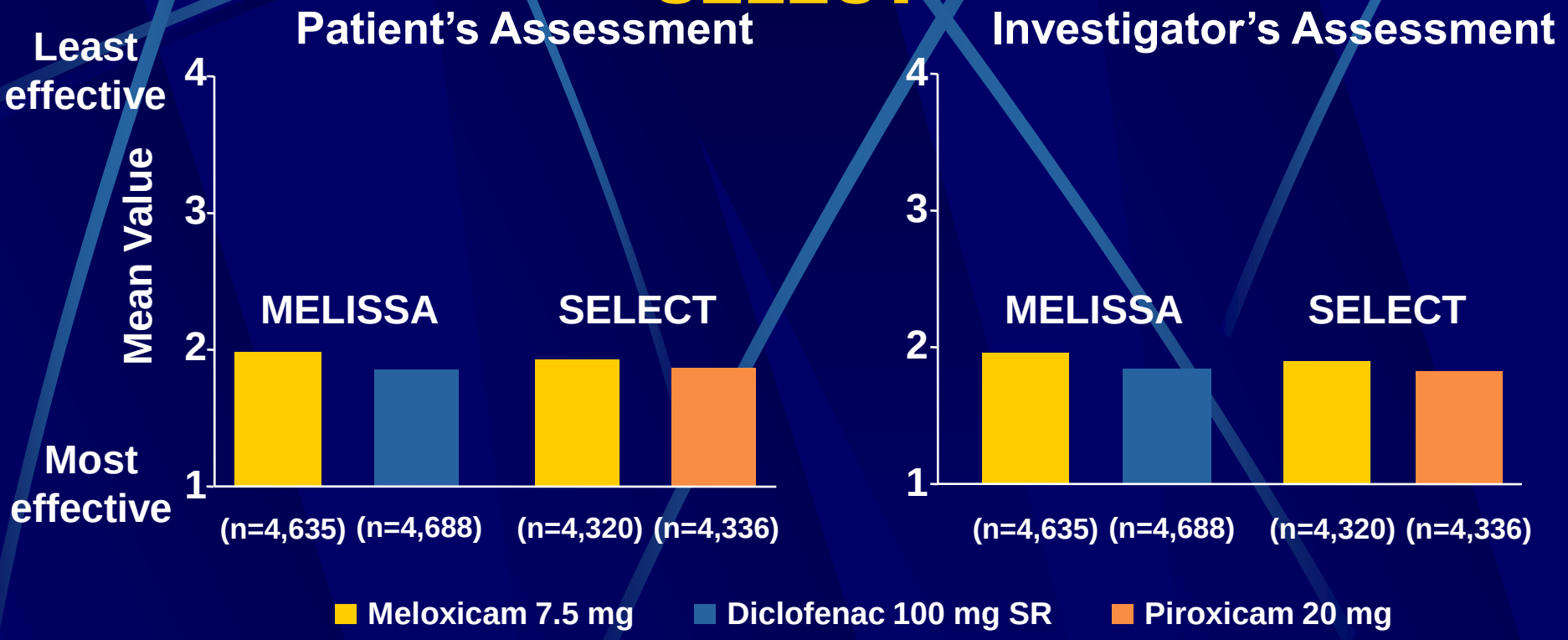
Data on file. Boehringer Ingelheim Pharmaceuticals, Inc./Yocum et al. Pending MS submission

MELISSA and SELECT Trial Design

- MELISSA:
  - International prospective trial (n=9323)
  - Double-blind, double-dummy, randomized trial
  - Purpose to investigate tolerability of meloxicam compared to diclofenac.
  - Conducted over 28 days in patients with symptomatic OA
  - Compared meloxicam 7.5mg vs. diclofenac 100mg

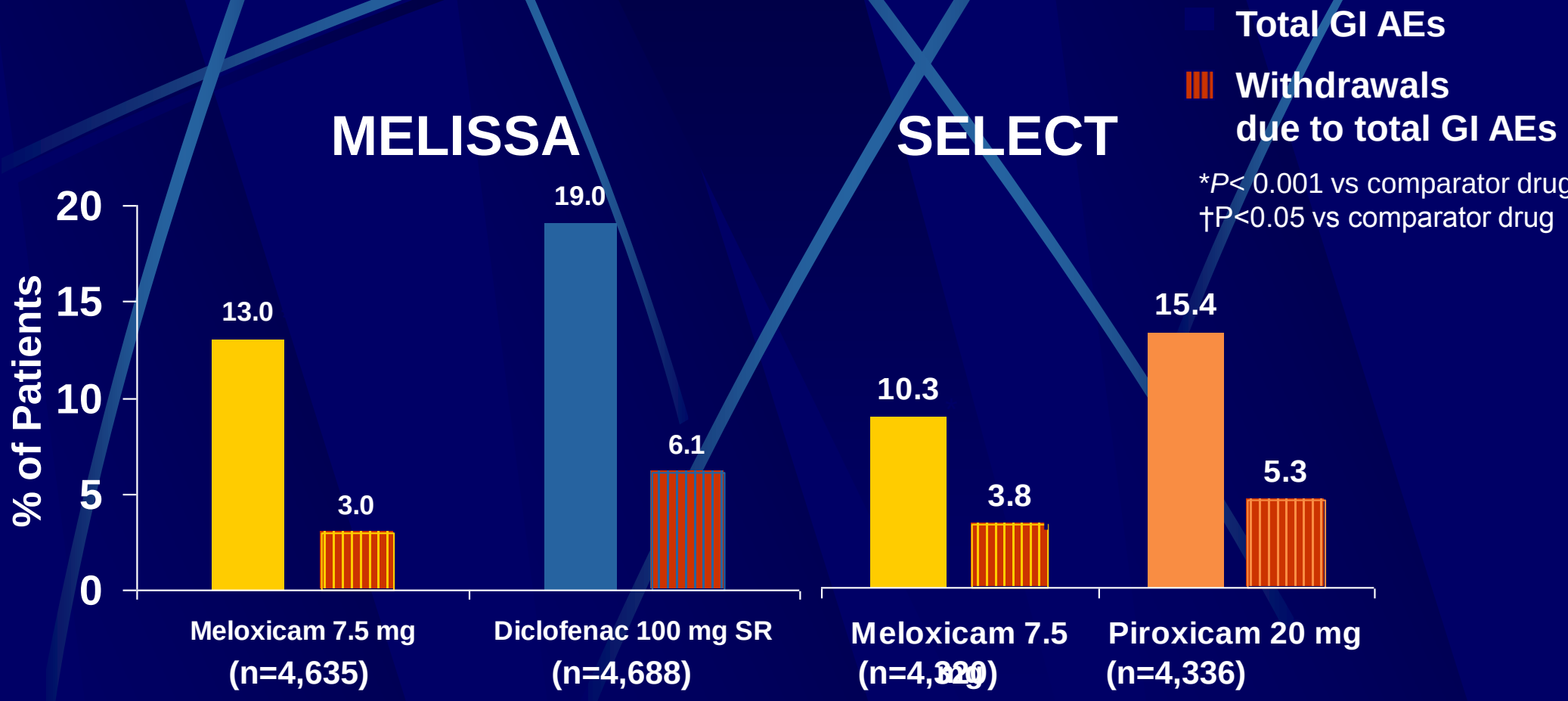
- SELECT:
  - Large-scale prospective international trial (n=8656).
  - Double-blind, double-dummy, randomized parallel group trial
  - Meloxicam 7.5mg vs. piroxicam 20mg

Patient's and Investigator's Global Efficacy Assessment: MELISSA and SELECT



Hawkey C, Kahan A, Steinbrück C, et al. *Br J Rheumatol*. 1998.
Dequeker J, Hawkey C, Kahan A, et al. *Br J Rheumatol*. 1998.

Total GI AEs and Withdrawals Due to GI AEs: MELISSA and SELECT



Hawkey C, Kahan A, Steinbrück C, et al. *Br J Rheumatol*. 1998.
Dequeker J, Hawkey C, Kahan A, et al. *Br J Rheumatol*. 1998.

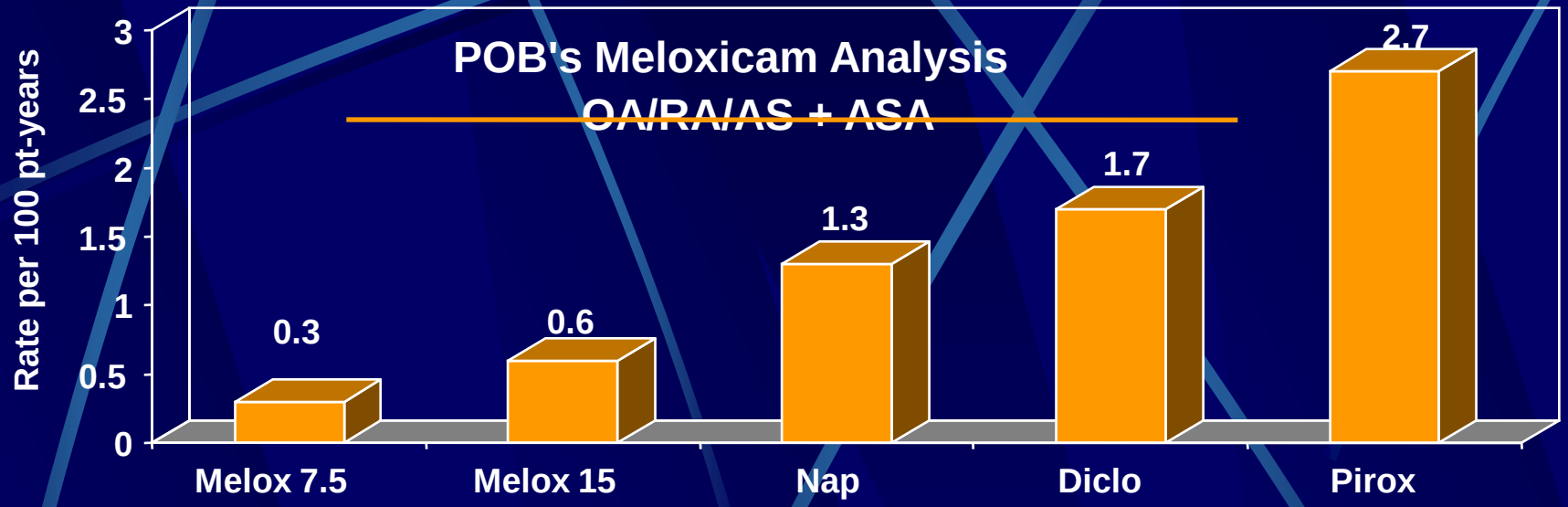
Most Common GI AEs: MELISSA and SELECT

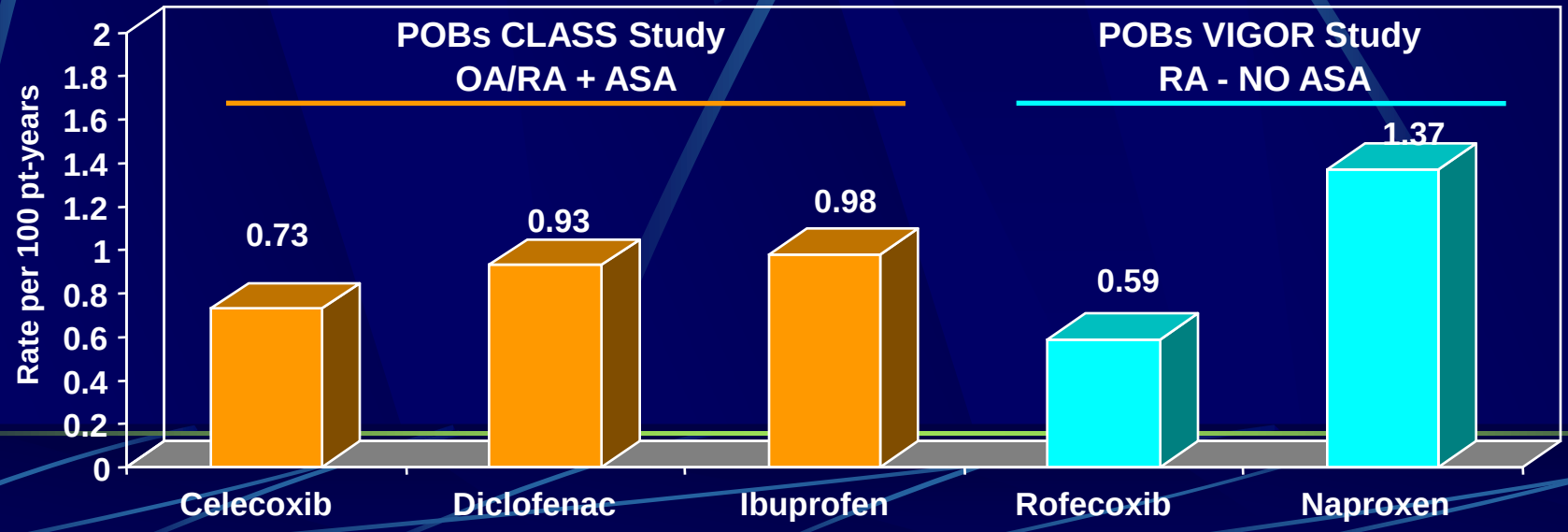
- Incidence of most common GI AEs was significantly lower with meloxicam 7.5 mg than with diclofenac 100 mg SR and piroxicam 20 mg
  - Dyspepsia ($P < 0.001$)
  - Nausea/vomiting ($P < 0.05$)
  - Abdominal pain ($P < 0.001$)
  - Diarrhea ($P < 0.001$)*

* MELISSA (diclofenac) only

Hawkey C, Kahan A, Steinbrück C, et al. *Br J Rheumatol*. 1998.
Dequeker J, Hawkey C, Kahan A, et al. *Br J Rheumatol*. 1998.

Benchmarking Summary





Meloxicam Serious GI Event Meta-Analysis Objective

- Determine the risk of clinically serious GI Events (Perforation, Obstruction, or Bleeds) in patients receiving meloxicam.

GI Safety and Tolerability Meta-Analysis Protocol

- Identification of 10 published trials (>20,000 patients) meeting the following criteria
  - Comparison of meloxicam with another NSAID
  - Adult patient population
  - Randomized trial with parallel design or crossover with washout
  - Evaluation of GI adverse events
- Test for homogeneity
  - *P* > 0.05 indicates trial homogeneity

Schoenfeld P. *Am J Med*. 1999; in press.

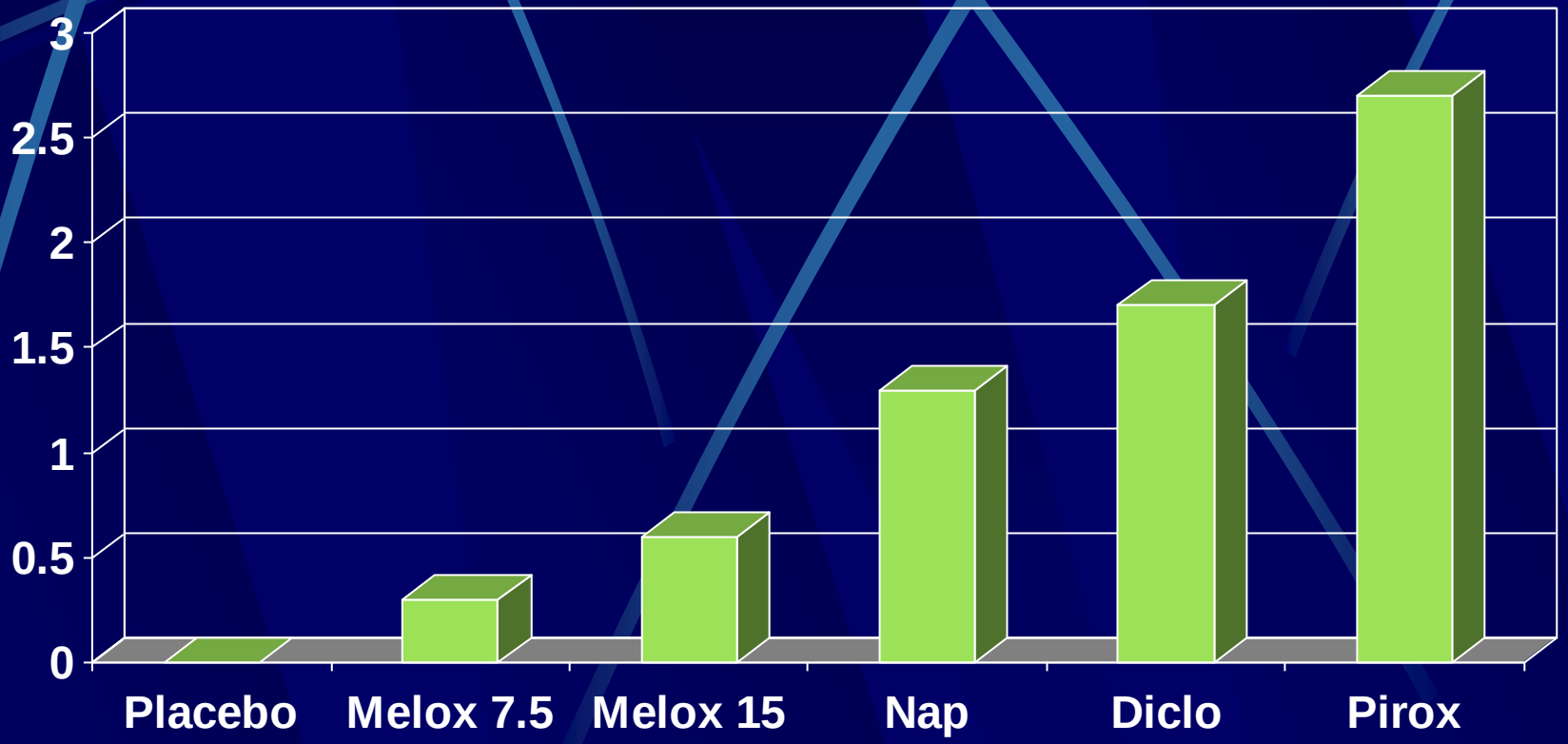
Trials Included in Meta-analysis

- 35 clinical trials (27,309 patients)
  - 21 Controlled
    - 7 Diclofenac (6 OA, 1 RA)
    - 2 Naproxen (RA)
    - 10 Piroxicam (6 OA, 2 RA, 1 AS, 1 other)
    - 2 Placebo (1 OA, 1 RA)
  - 11 Uncontrolled
  - 3 Long Term extension

Meloxicam Serious GI Event Meta-Analysis

- Total Number of patients 27,309
- Cases reviewed 448
- Confirmed GI Events 54
  - UGI source 37
  - Source unknown 10
  - Not enough data 7

Incidence of Serious GI Adverse Events



Meta-analysis Study: Limitations

- Pooling of data
  - similar results in active-controlled, placebo-controlled and uncontrolled studies, different indications
- Post-hoc analysis of prospective data
  - ascertainment bias
- Limited duration of exposure (7.5 mg)

Meta-analysis Study Strengths

- Patients not screened or selected
  - did not exclude patients with
    - a history of ulcer disease
    - asymptomatic endoscopic detectable ulcers
    - elderly
- Generalizability

Meloxicam Meta-Analysis Summary

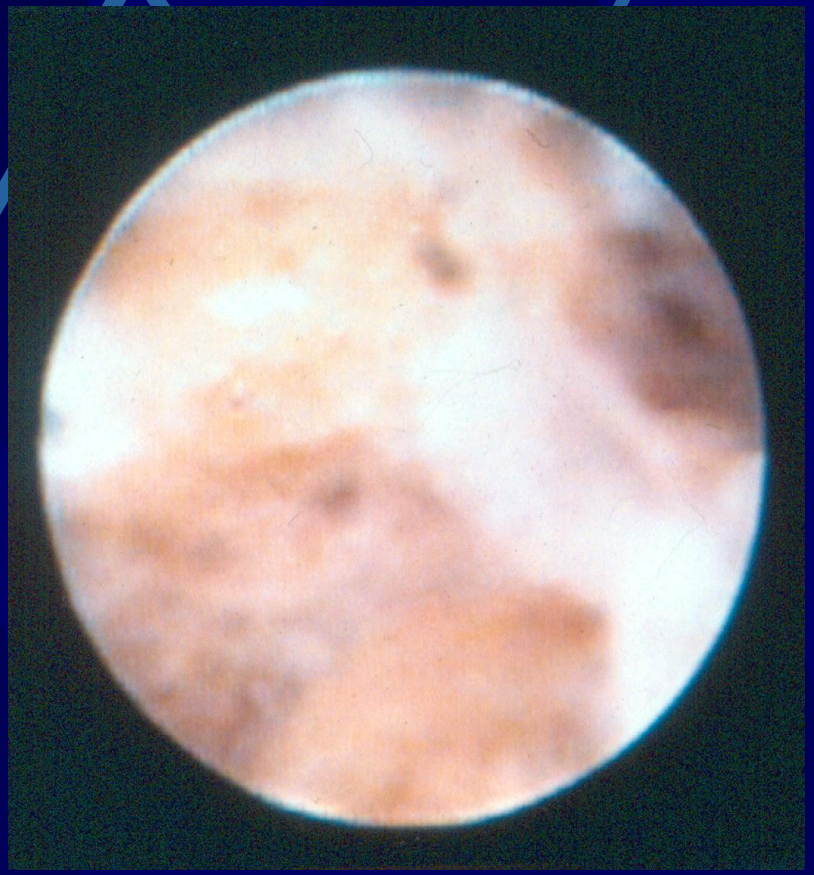
- In a meta-analysis of 10 published trials, meloxicam resulted in a lower risk for GI adverse events compared with diclofenac, piroxicam, and naproxen

GI Event	Approximate risk reduction with Meloxicam
GI AEs	36%
Withdrawals (GI AEs)	41%
PUBs	48%
Dyspepsia	27%

Schoenfeld P. *Am J Med*. 1999; in press.

Endoscopy data

- 28 day study
- Mobic 7.5 MG << 15 mg or Piroxicam 20mg with regard to ulcerations and gastric or duodenal irritation



Meloxicam Safety and Tolerability Summary

- Low incidence of GI AEs
- GI tolerability is statistically superior to that of other NSAIDs (diclofenac and piroxicam)
- GI tolerability is comparable to placebo

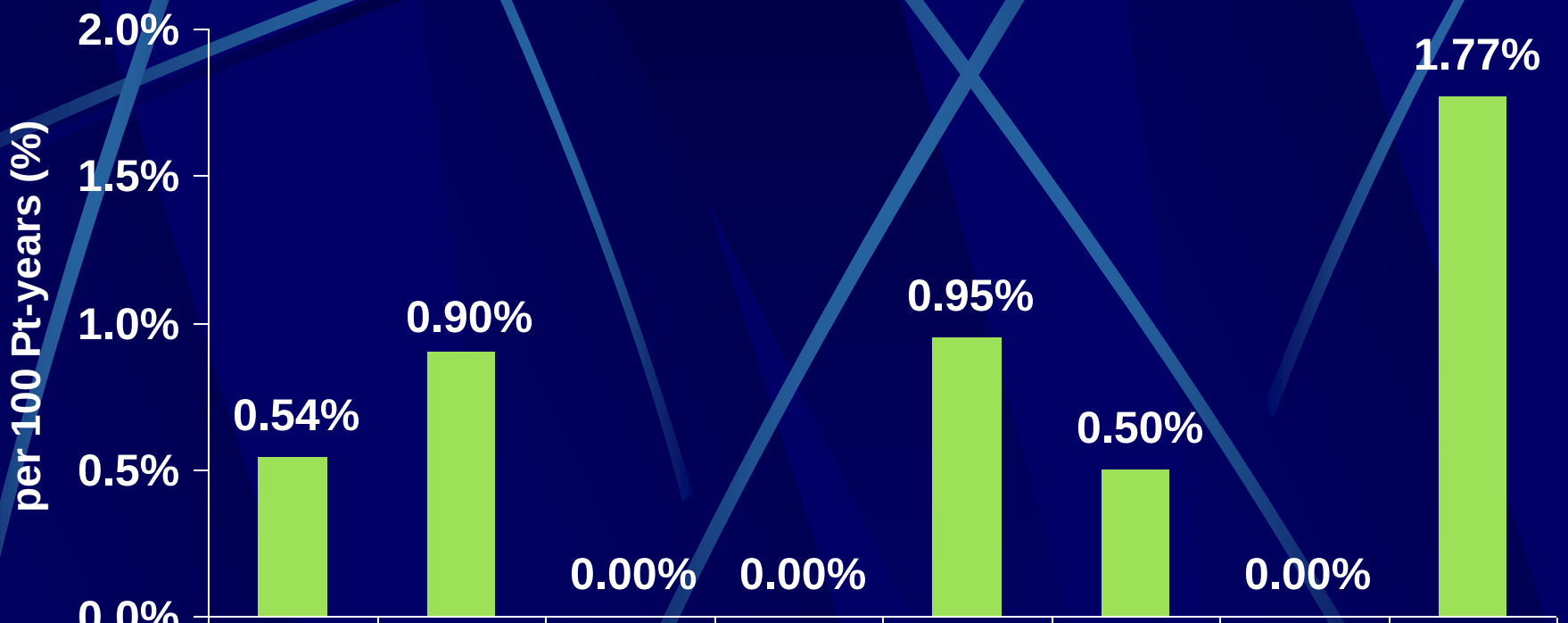
Data on file. Boehringer Ingelheim Pharmaceuticals, Inc./ Yocum et al. Pending MS submission.
Hawkey C, Kahan A, Steinbrück C, et al. *Br J Rheumatol*. 1998.
Dequeker J, Hawkey C, Kahan A, et al. *Br J Rheumatol*. 1998.
Busch U et al. *Clin Drug Invest.* 1996.
Boulton-Jones JM et al. *Br J Clin Pharmacol.* 1997.
Türck D et al. Eur J *Clin Pharmacol.* 1996.
DeMeijer A et al. Poster #5 at William Harvey Research Conference. 1998.

Cardiovascular, Renal, and Hepatic Safety

Cardiovascular, Renal, and Hepatic Safety Overview

- Myocardial Infarctions
- Blood pressure
- Thromboembolic events
- Peripheral edema
- Hepatic safety

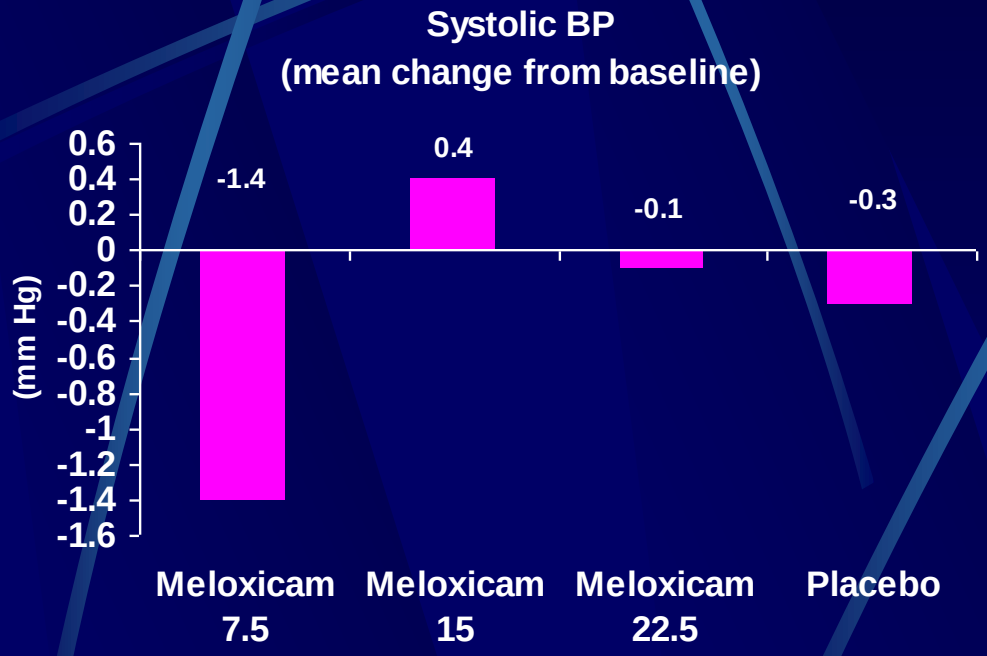
Myocardial Infarctions

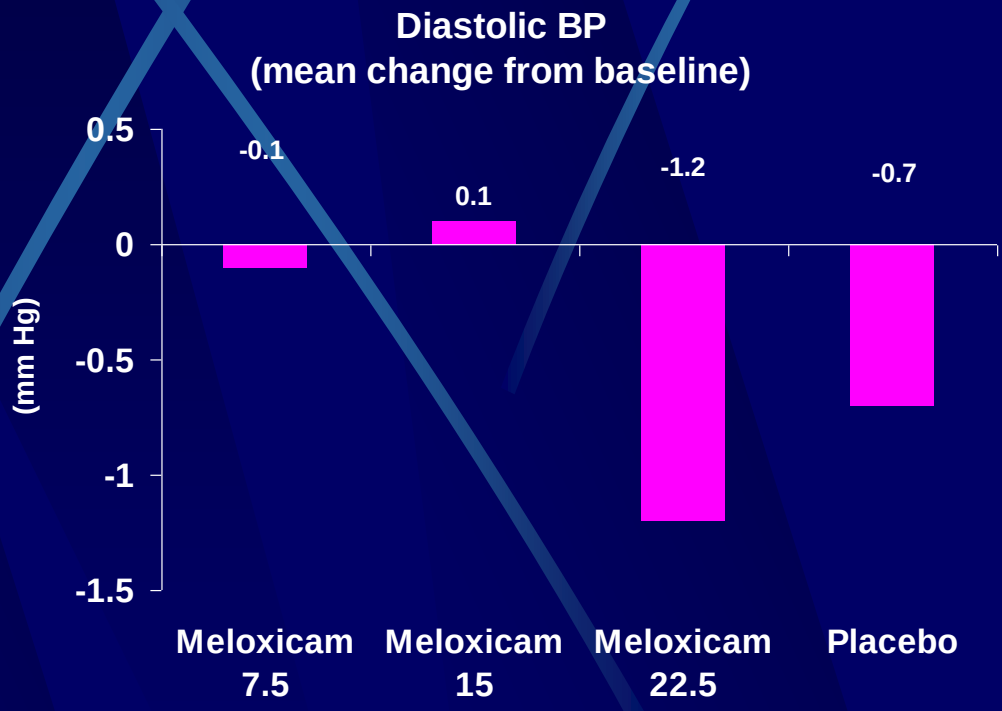


	Melox 7.5	Melox 15 mg	Melox 22.5 mg	Melox 30 mg	Diclo	Pirox	Naprox	Placebo
Total Treated	10,158	2,960	910	1,043	5,464	5,371	243	763

per 100 years POB DATABASE

Effect on Blood Pressure Change From Baseline by Dose



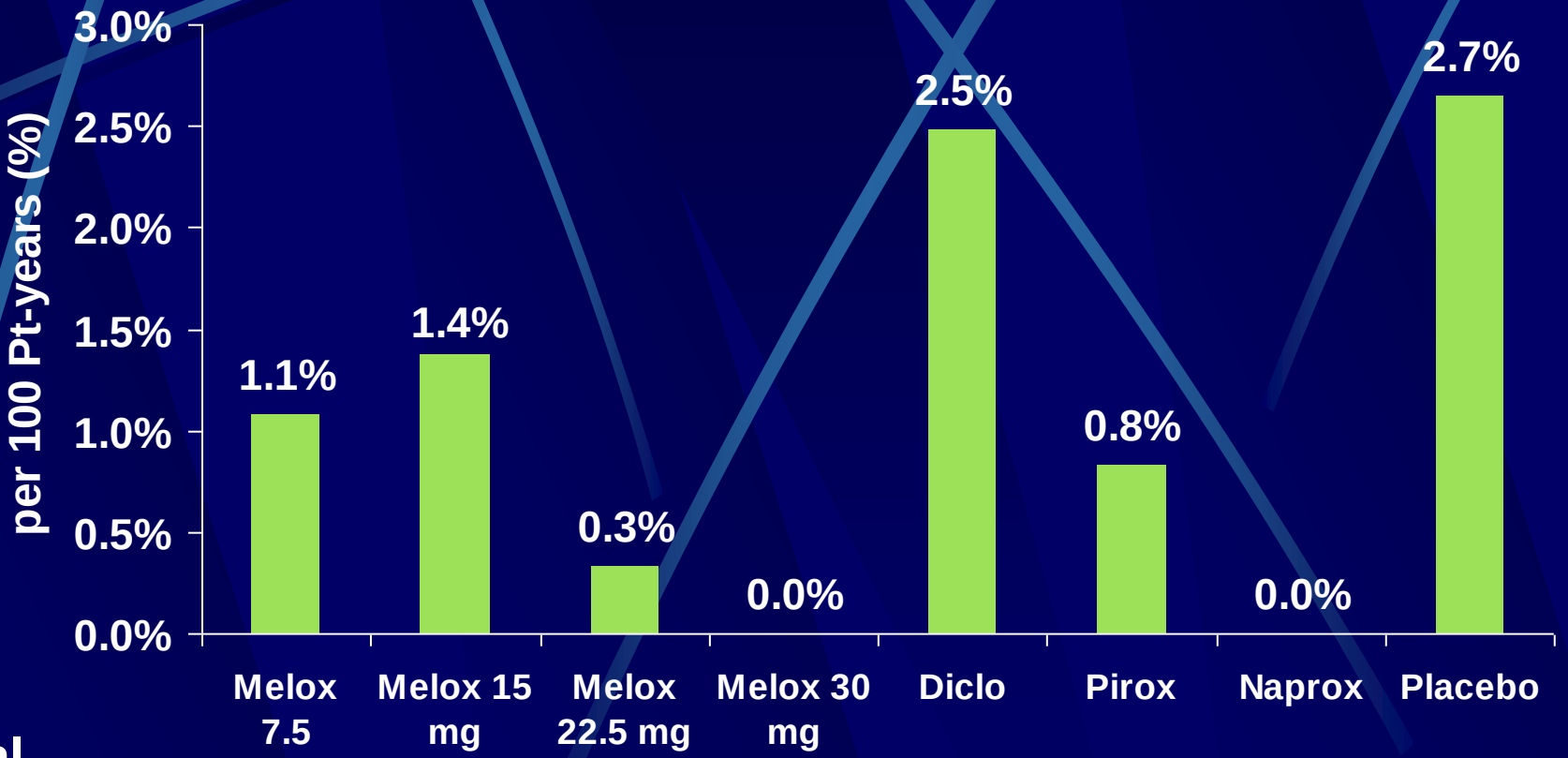


Source: OA NDA, ISS, TABLE 8.8.9.1: 1 Vital Signs Summary for Controlled Phase 2/3 Trials by Treatment Group (Integrated Safety Database)

[1] A patient must have had a baseline and at least one post-baseline vital sign measurement to be included in this table.

[2] Vital signs data were only collected in the following trials:107.013, 107.014, 107.019, 107.045, 107.046, 107.057, 107.061, 107.063, 107.076, 107.084, 107.086, 107.092, 107.094, 107.098, 107.099

Thromboembolic Events



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Total Treated	10,158	2,960	910	1,043	5,464	5,371	243	763

per 100 years POB DATABASE

Peripheral Edema

	Percent of Patients	
	Peripheral Edema	Weight Increase
MELISSA Trial		
Meloxicam (n = 4,635)	0.5	0.1
Diclofenac (n = 4,688)	0.6	0.1
SELECT Trial		
Meloxicam (n = 4,320)	0.3	0.2
Piroxicam (n = 4,336)	0.9	0.3
U.S. OA Trial		
Placebo (n = 157)	0.6	0.6
Meloxicam (n = 464)	0.6	0.4
Diclofenac (n = 153)	0.0	0.0

Hawkey C, Kahan A, Steinbrück C, et al. *Br J Rheumatol*. 1998.
Dequeker J, Hawkey C, Kahan A, et al. *Br J Rheumatol*. 1998.
Data on file. Boehringer Ingelheim Pharmaceuticals, Inc./Yocum et al. Pending MS submission

Selected Cardiorenal Adverse Events

	Meloxicam	NSAIDs	Placebo
Intent-to-treat patients (N)	15,071	11,078	736
Patient Years	3129	1202	113
Events (N, per 100 Pt yrs)			
Myocardial Infarction	18 (0.58)	8 (0.67)	2 (1.8)
Cardiac Failure	15 (0.48)	7 (0.58)	0 (0)
Edema, Peripheral	98 (3.13)	79 (6.57)	1 (0.88)
Hypertension	82 (2.62)	32 (2.66)	5 (4.42)
Hypertension, Aggravated	25 (0.8)	15 (1.25)	2 (1.77)

Singh, 2001 POB DATABASE

Risk of Serious Upper Gastrointestinal and Cardiovascular Thromboembolic Complications with Meloxicam: The POB Analysis

MB-9808B

POB Data Analysis

- Pooled analysis of 28 clinical trials evaluated GI and thromboembolic safety profile of meloxicam[2]
  - Evaluated risk estimates of thromboembolic and serious upper GI complications
  - Compared meloxicam to the traditional NSAIDs diclofenac, naproxen, and piroxicam

1. Mobic® (meloxicam) Prescribing Information, Ridgefield, CT.
2. Singh G et al. *Am J Med*. 2004;117:100-106.

Study Definitions

- Serious GI complications
  - Upper GI bleeding
  - Gastric outlet obstruction
  - Duodenal or gastric perforation
- Thromboembolic events
  - Coronary thrombosis
  - Cerebral infarction
  - Myocardial infarction
  - Transient ischemic attack
  - Stroke

Singh G et al. *Am J Med*. 2004;117:100-106.

Study Design

Trial Criteria

- Oral meloxicam therapy (7.5 mg and 15 mg)
- 21-day treatment minimum
- Sample size ≥20
- North America or Western Europe
- Study completed by April 1,1999

Study Sample

28 Trials

N=24,196

Treatment Groups

- Meloxicam 7.5 mg/15 mg (n=13,118)
- Diclofenac 100 mg/d/150 mg/d (n=5464)
- Naproxen 500 mg BID (n=243)
- Piroxicam 20 mg (n=5371)

Adapted from Singh G et al. *Am J Med*. 2004;117:100-106.

Risk Estimates

Treatment (dose)	Interval (days)	Number of Patients Entering Interval	Serious GI Events	Thromboembolic Events
			Number (Cumulative risk, %)	
Meloxicam (7.5 mg/d)	0-60	10,158	3 (0.03)	8 (0.2)
	>60	551	0 (0.03)	2 (0.8)
Meloxicam (15 mg/d)	0-60	2960	5 (0.2)	5 (0.2)
	>60	1684	4 (0.6)	7 (0.9)
Diclofenac (100-150 mg/d)*	0-60	5464	7 (0.1)	13 (0.8)
	>60	493	2 (1.3)	0 (0.8)
Piroxicam (20 mg/d)	0-60	5371	15 (0.9)	5 (0.1)
	>60	532	1 (1.1)	0 (0.1)
Naproxen (1000 mg/d)	0-60	243	1 (0.5)	0
	>60	166	0 (0.5)	0

*Includes 5283 patients treated with a 100-mg/d dose and 181 patients treated with a 150-mg/d dose.

From Singh G et al. *Am J Med*. 2004;117:100-106.

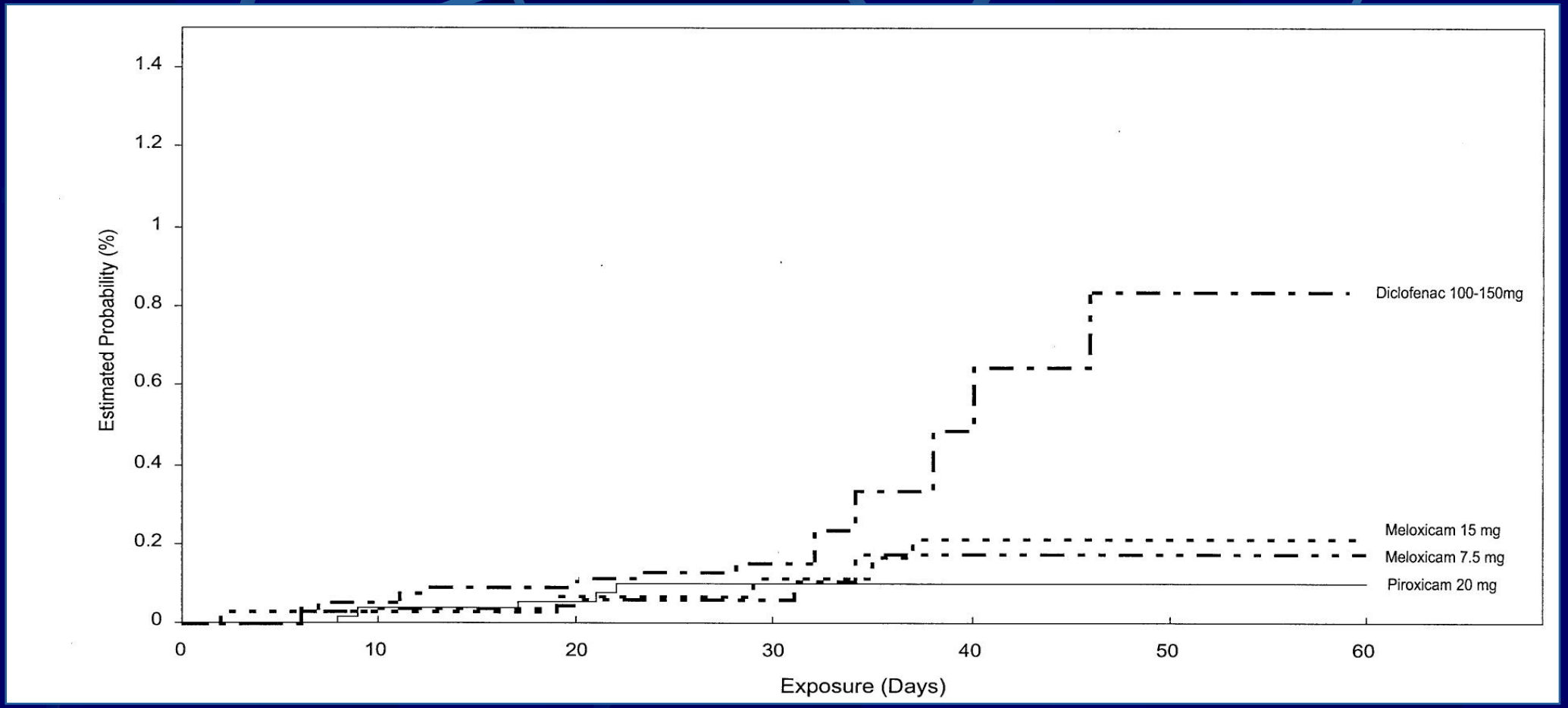
Comparisons of Treatment

Treatment Compared	GI Complications	Thromboembolic Complications
	P Value*	
Meloxicam 7.5 mg vs meloxicam 15 mg	0.06	0.8
Meloxicam 7.5 mg vs diclofenac	0.02	0.02
Meloxicam 7.5 mg vs piroxicam	<0.001	0.8
Meloxicam 7.5 mg vs naproxen	0.003	0.5
Meloxicam 15 mg vs diclofenac	0.9	0.05
Meloxicam 15 mg vs piroxicam	0.03	0.6
Meloxicam 15 mg vs naproxen	0.5	0.5
Diclofenac vs piroxicam	0.09	0.06
Diclofenac vs naproxen	0.2	0.2
Piroxicam vs naproxen	0.7	0.6

*By log-rank test.

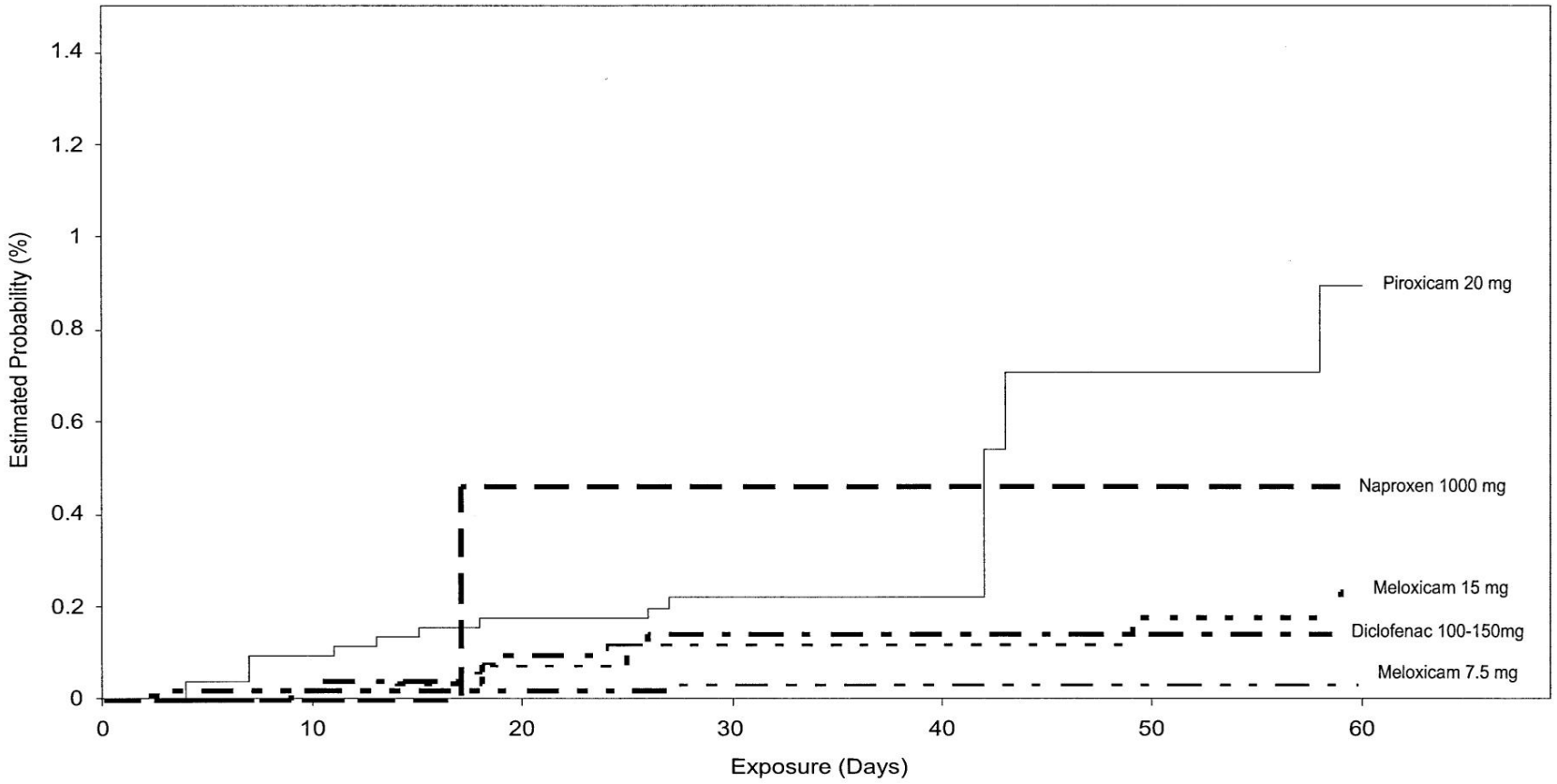
From Singh G et al. *Am J Med*. 2004;117:100-106.

Probability of Thromboembolic Complications



From Singh G et al. *Am J Med*. 2004;117:100-106.

Probability of GI Complications



From Singh G et al. *Am J Med*. 2004;117:100-106.

Study Limitations

- Majority of patients treated for <2 months
  - Long-term risk estimates are unreliable
- Absence of protocol-defined guidelines
- Randomization was not preserved with pooled analysis
- Accurate comparison would require head-to-head clinical trials

Singh G et al. *Am J Med*. 2004;117:100-106.

POB Data Analysis Conclusions

- Data analysis suggests that in the first 60 days, the risk of serious upper GI complications is significantly lower in patients taking meloxicam 7.5 mg/d compared with those taking diclofenac, naproxen, or piroxicam.
- Risk of thromboembolic events was similar in all treatment groups evaluated.
- Meloxicam has a favorable thromboembolic and GI safety profile for up to 2 months of treatment.

Meloxicam Hepatic Safety

- No dosage adjustment required for patients with mild to moderate (Pugh grade 1 or 2) hepatic impairment
- Patients with severe hepatic impairment have not been studied; therefore, use of meloxicam is not recommended
- Favorable hepatic and renal safety profile

Busch U et al. *Clin Drug Invest.* 1996.
MOBIC® (meloxicam) U.S. Product Information. 1999.

Meloxicam Cardio-Renal Safety

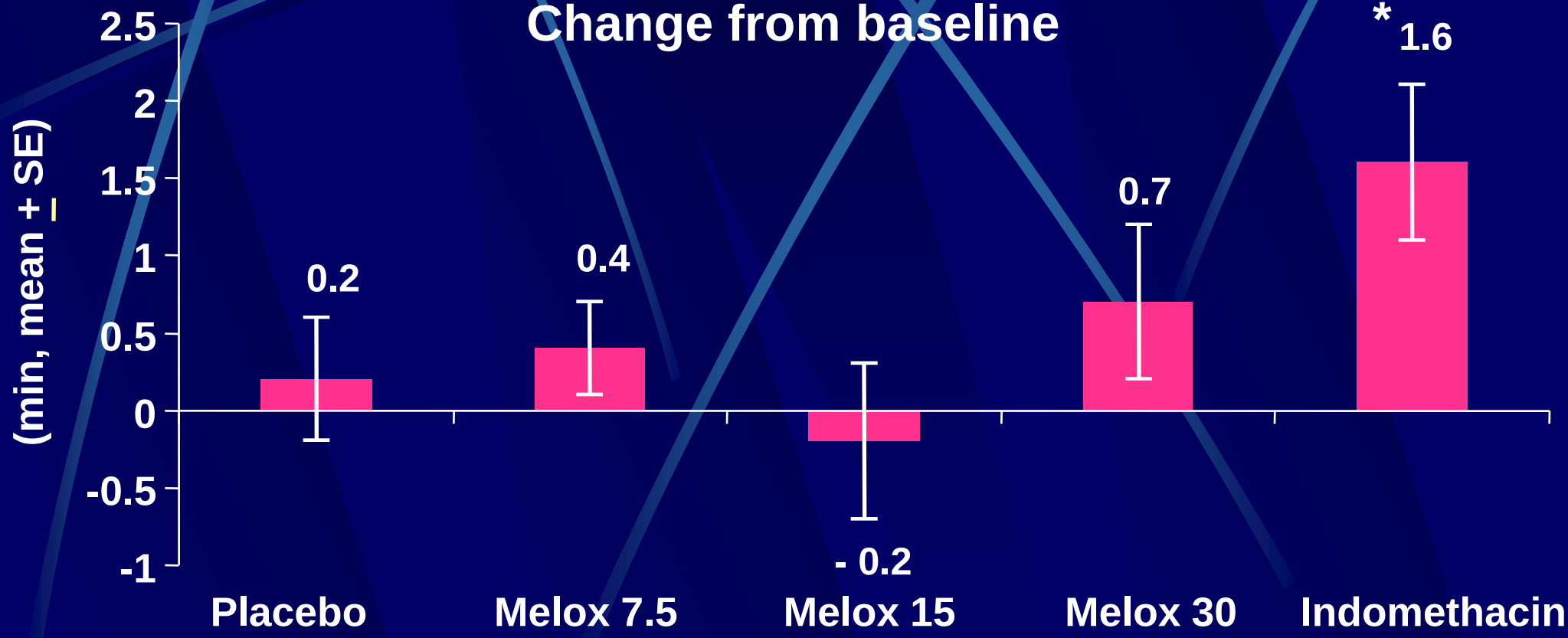
- Low risk of GI event at 7.5mg or 15mg
- No increased incidence of, or apparent association of:
  - MIs
  - Increase HTN
  - Peripheral Edema
  - Thromboemoblic events
  - Strokes
  - Cardiorenal effects
  - CHF or AMI compared to non-selective NSAIDs

Boulton-Jones JM et al. *Br J Clin Pharmacol.* 1997.
Türck D et al. *Eur J Clin Pharmacol.* 1996.
MOBIC® (meloxicam) U.S. Product Information. 1999.

Meloxicam Platelet Aggregation and Bleed Time

Meloxicam

Bleeding Time at Steady State

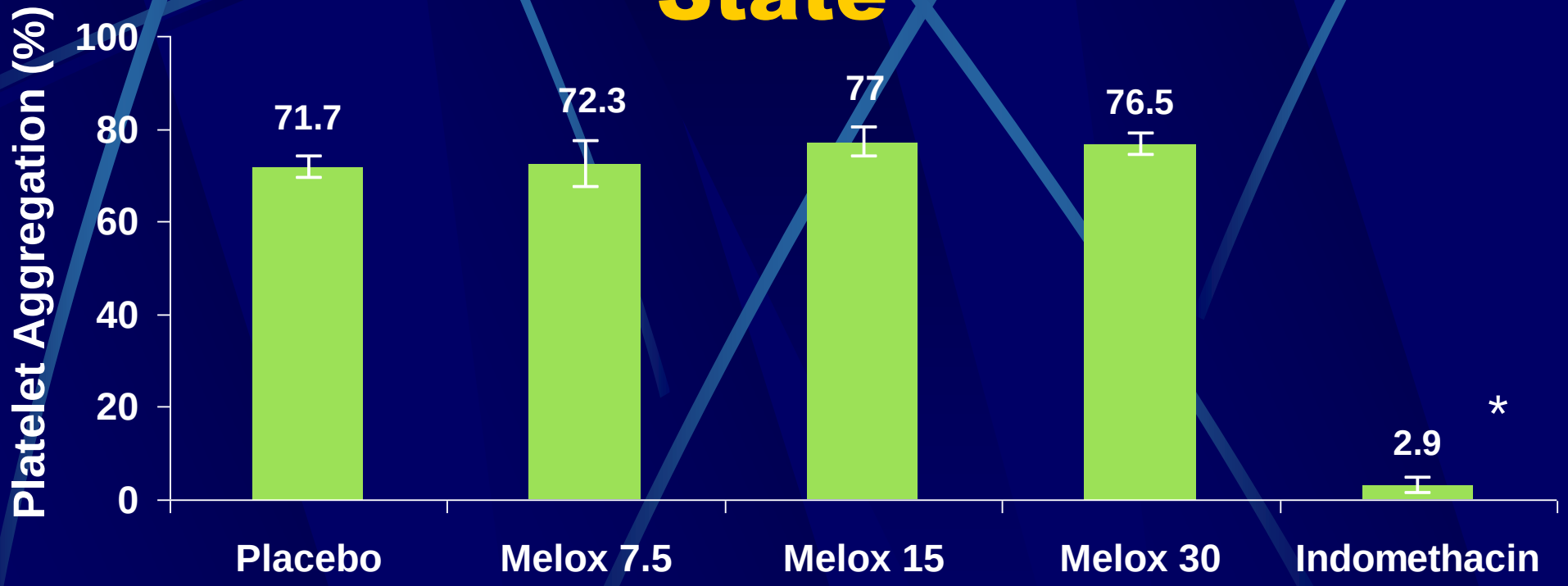


*$P < 0.05$ vs placebo

[1]Data on file, Study 107.236

Day 8, 6 Hours Post dose, Values are the means, not for the SE

Meloxicam Platelet Aggregation at Steady State



*$P < 0.05$ vs placebo

[1]Data on file, Study 107.236

Day 8, 6 Hours Post dose to arachidonic acid, Values are the means, not for the SE

Bleed Time and Platelet Aggregation Summary

- Meloxicam at higher than recommended doses had no effect on arachidonic acid-induced platelet aggregation and bleeding time

IMPROVE Trial

Impact of
Meloxicam on
Prescription
Regimens in
Osteoarthritis
Vs
Everyday Care

IMPROVE Trial: Objective

- To determine:

  the percent of successes or failures

  of meloxicam vs prescription NSAIDs in patients with OA in MCO's
- Success:
  - Satisfied with initial NSAID
  - Did not switch to another NSAID
  - Completed the study

IMPROVE Trial Study Design

- U.S, multicenter, blinded-randomized, open-label, parallel-group (N~1,200, ~ 600/arm)
- Patients aged >18 years
- Diagnosis of OA of the hip, knee, hand, or spine
- Willing to change NSAID therapy or
- Requiring
  - initiation of an NSAID or
  - change to a different NSAID
- Randomized to either meloxicam or any other prescription NSAID

IMPROVE Trial: Patient Disposition

	Meloxicam	Usual Care
Rand & Treated (N)	662	647
Completed	91%	88.6%
Withdrew from study		
AE	2.6%	3.4%
Administrative	4.4%	6.3%
LOE	0.9%	0.2%
Other	1.2%	1.5%

ITT patient= randomized+took at least 1 dose of medication + at least one post-dose efficacy evaluation

IMPROVE Trial
Trial Demographics

	Meloxicam (N=662)	Usual Care (N=647)
Female	66%	69%
Age		
18-40 yrs	2%	3%
41-50 yrs	12%	12%
51-60 yrs	23%	22%
61-70 yrs	31%	30%
71-80 yrs	28%	26%
>80 yrs	4%	7%
Mean Duration of OA	9.5	9.7

IMPROVE Trial
POB and Ulcer History

History	Meloxicam (N=662)	Usual Care (N=647)
Perforation	0.2%	0.2%
Obstruction	0%	0%
Ulcer	7%	7%
Bleeding	1%	2%

IMPROVE Trial: Most Frequently Prescribed Initial UC NSAID

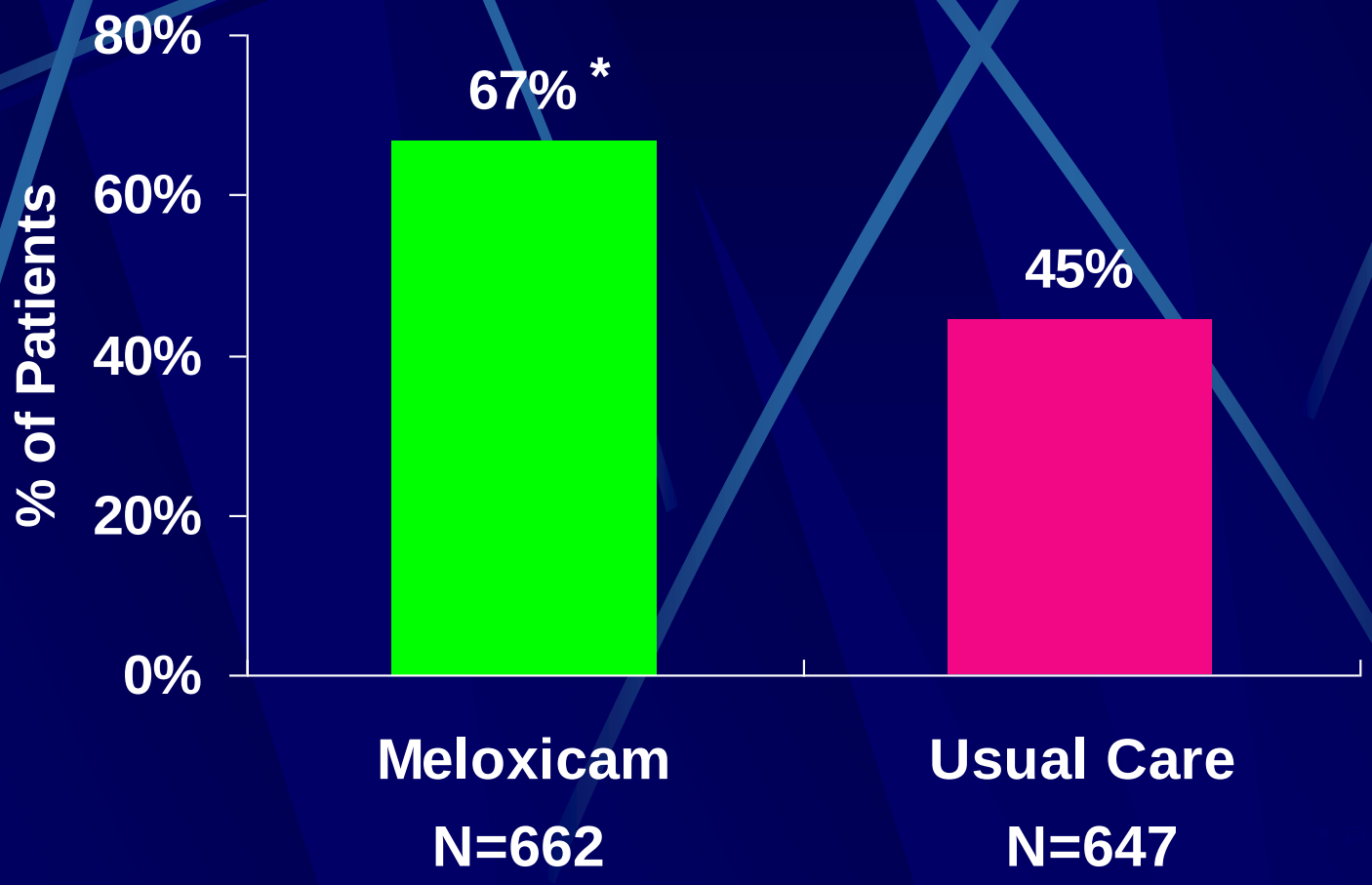
NSAID	N	% of Total UC
VIOXX	151	23%
CELEBREX	79	12%
NAPROXEN	71	11%
DICLOFENAC	66	10%
PIROXICAM	58	9%
NABUMETONE	46	7%
ETODOLAC	38	6%
SULINDAC	35	5%
OXAPROZIN	34	5%
IBUPROFEN	18	3%
ARTHROTEC	13	2%

IMPROVE Trial
Non NSAID & Non Pharmacologic Tx

Therapy	Prior Use		During Study	
	Melox %	UC %	Melox %	UC %
Acetaminophen	23	25	15	11
Top/Inj Steroid	19	20	5	5
Non Narc. Analgesic	14	15	7	7
Non-Pharm Tx	10	9	5	5
Glucosamine	8	7	7	6
Glu/Chon Combo	7	6	5	5
Narcotic Analgesic	5	5	4	5
Acet with Codeine	4	5	2	2
Chondroitin	3	3	4	2
Hyaluronic Acid	3	2	1	1
Local Anesthetic	2	3	2	1

Study Conducted: 10/98-5/00

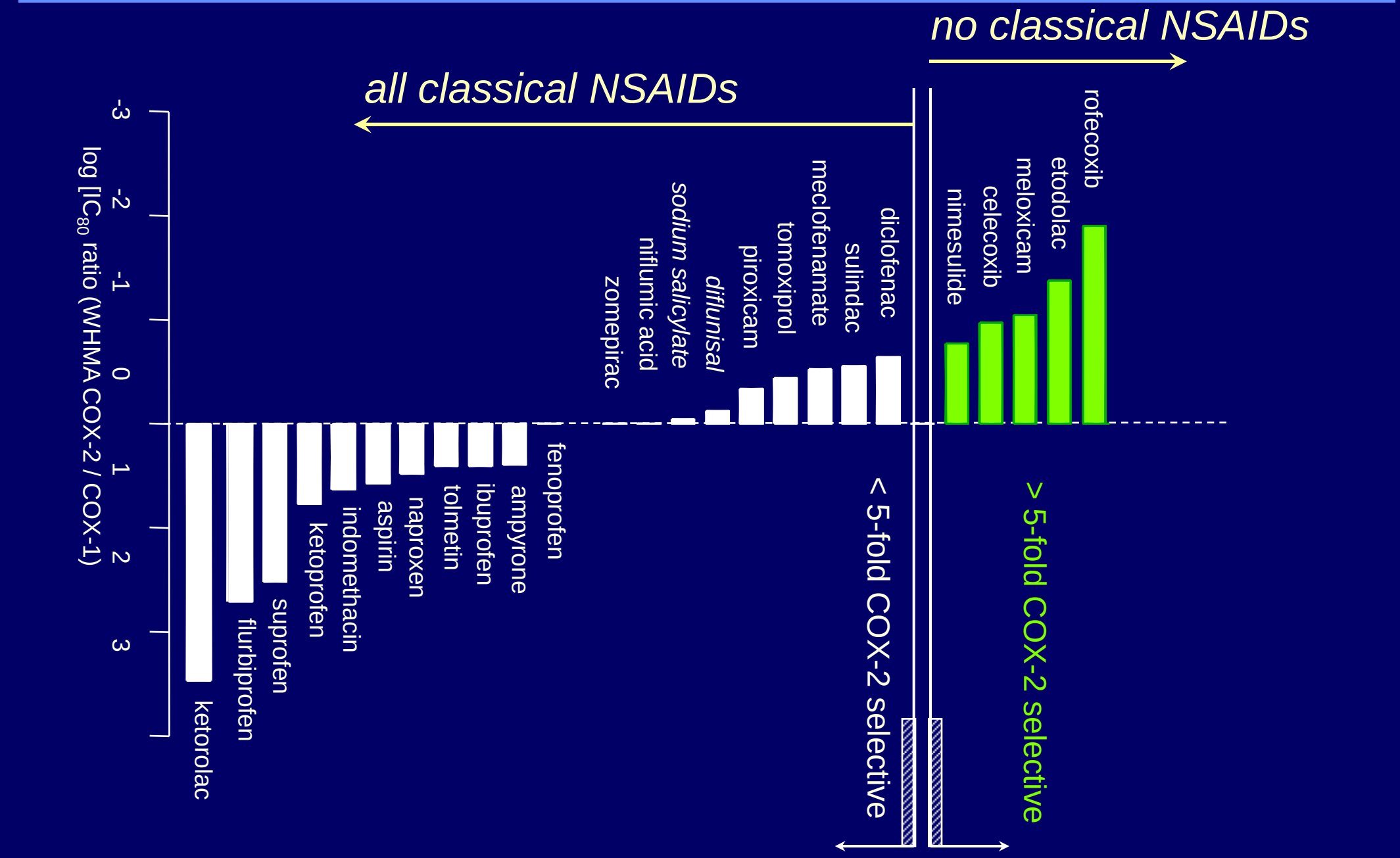
IMPROVE Trial Successes

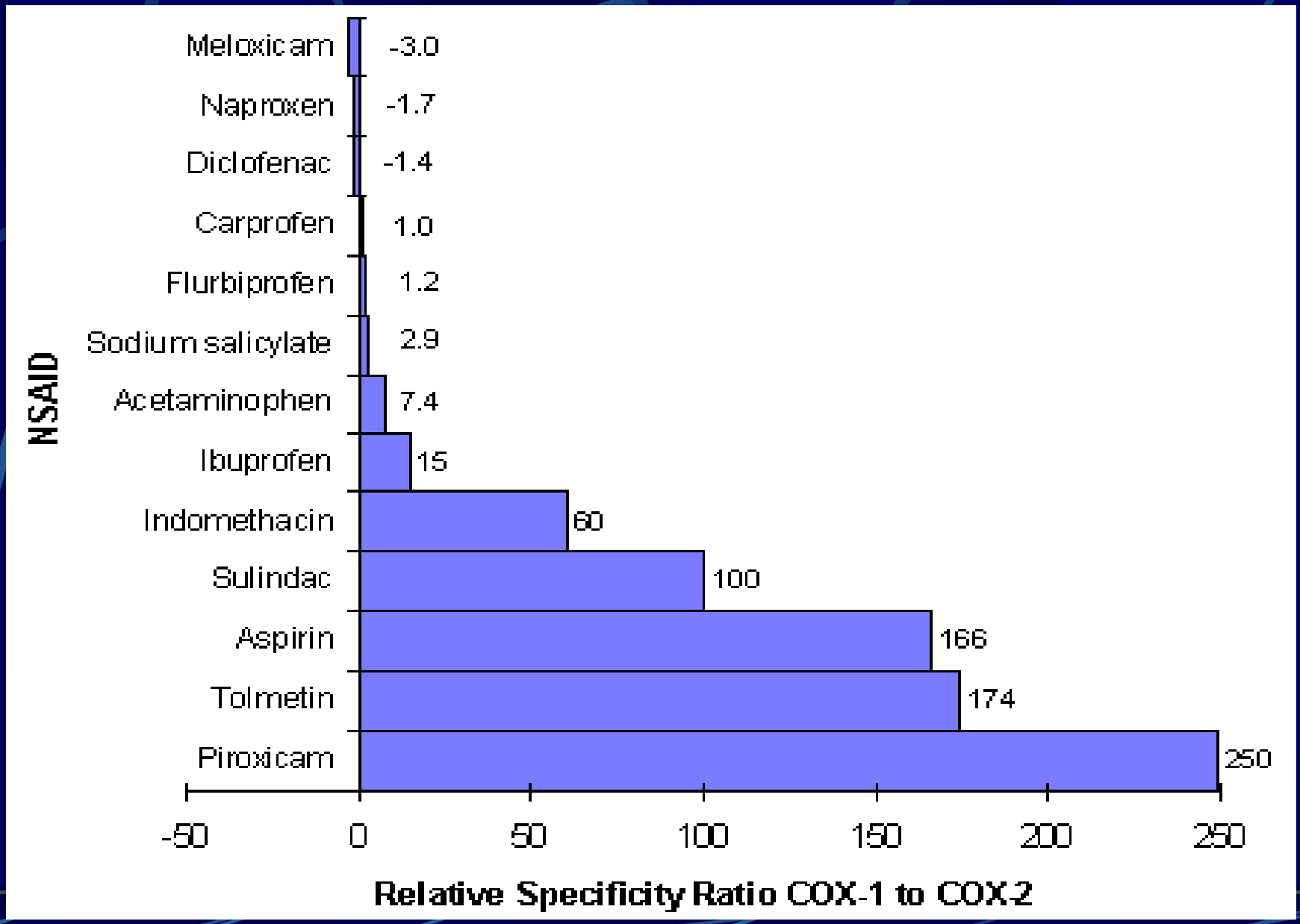


Success: Completed the study and never switched, or completed study but no longer needed an NSAID during the trial for Tx of their OA

COX-1 Sparing Effects of NSAIDs

The Range of COX Selectivities




Meloxicam
-3.0
Naproxen
-1.7
Diclofenac
-1.4
Carprofen
1.0
Flurbiprofen
1.2
Sodium salicylate
2.9
Acetaminophen
7.4
Ibuprofen
15
Indomethacin
60
Sulindac
100
Aspirin
166
Tolmetin
174
Piroxicam
250
NSAID
-50
0
50
100
150
200
250
Relative Specificity Ratio COX-1 to COX2

- Hence Meloxicam is Cox-2 selective and not specific

Hankey GJ. et.al

Stroke 34(11)2736-40 Nov. 2003

- "emerging data from animal, experimental, and clinical data suggest that COX –2 is atherogenic and thrombogenic and selective COX-2 inhibition may be cardio-protective"

- Hence the "**BALANCE**" concept

Mobic® (meloxicam) tablets Safety Information

- The starting and maintenance dose for Mobic is 7.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 15 mg once daily.
- Mobic is contraindicated in patients with known hypersensitivity to meloxicam. It should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.
- Higher doses of Mobic (22.5 mg and greater) have been associated with an increased risk of serious GI events; therefore, the daily dose of Mobic should not exceed 15 mg.
- The most common GI side effects (≥3%) observed during clinical trials associated with use of Mobic are diarrhea, dyspepsia and nausea, although these effects occurred in less than 5% of patients.

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