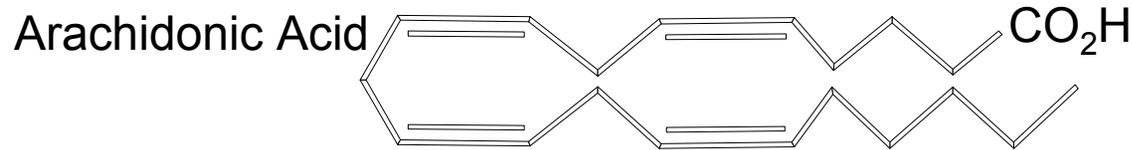

FDA Arthritis Advisory Committee
February 8, 2001

**VIOXX™ Gastrointestinal Outcomes Research Trial
(VIGOR)**

Bonnie Goldmann, M.D.
Regulatory Affairs
Merck Research Laboratories

Cyclooxygenases



**Protection of Gastric Mucosa
Platelet Function**

Renal Effects

Pain, Inflammation, Fever

Gastropathy and
Antithrombotic Effects

Effects on
Na⁺ Balance

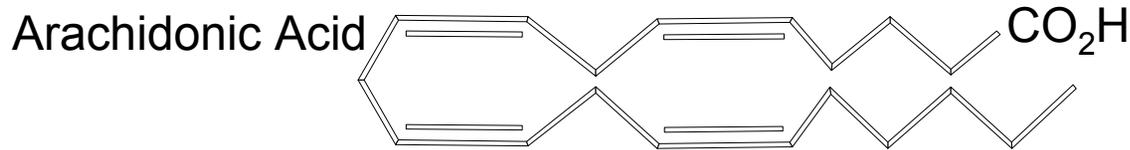
Anti-inflammatory and
Analgesic Effects

NSAID Gastropathy

- One of the most common serious drug-related adverse events are NSAID-related serious upper GI side effects
- Estimated to result in 103,000 hospitalizations and 16,500 deaths per year in the US*

*Wolfe, Lichtenstein, Singh, NEJM 340:1888-1899, [1999].

Cyclooxygenases



COX-1

Selective COX-2 Inhibitors

COX-2

Prostanoids

Prostanoids

Protection of Gastric Mucosa
Platelet Function

Renal Effects

Pain, Inflammation, Fever

Effects on
Na⁺ Balance

Anti-inflammatory and
Analgesic Effects

COX-2 Hypothesis

- Selective COX-2 inhibitor should demonstrate:
 - 1) Anti-inflammatory and analgesic efficacy similar to non-selective NSAIDs
 - 2) Significantly improved GI safety compared to non-selective NSAIDs
 - 3) Effects on renal sodium handling similar to non-selective NSAIDs
 - 4) No inhibitory effects on platelets

Rofecoxib Current Indications and Dosage

- For the relief of the signs and symptoms of osteoarthritis 12.5 to 25.0 mg daily
- For the management of acute pain in adults 50 mg daily
- For the treatment of primary dysmenorrhea

Post-Marketing Experience

- Available in 74 countries
- Approximately 13 million patients in the US; more than 24 million patients worldwide
- Estimated 4 million patient-years of exposure
- No significant, unexpected safety or tolerability issues raised in post-marketing surveillance

VIGOR

- 8076 rheumatoid arthritis patients; 301 centers, 22 countries
- Active controlled:
 - Rofecoxib 50 mg daily (2x max. chronic dose) vs.
 - Naproxen 1000 mg daily (most common RA dose)
- Median duration: 9 months
- Endpoints: clinically significant GI events

Major Conclusions of VIGOR

- Confirms that rofecoxib has a GI safety profile superior to non-selective NSAIDs
- Consistent with the general safety profile of rofecoxib as presented in the currently approved product circular

AGENDA

- COX-2 Selectivity
- Previous Clinical Safety Data

Alan Nies, M.D.

- VIGOR
- Related Clinical Data

Alise Reicin, M.D.

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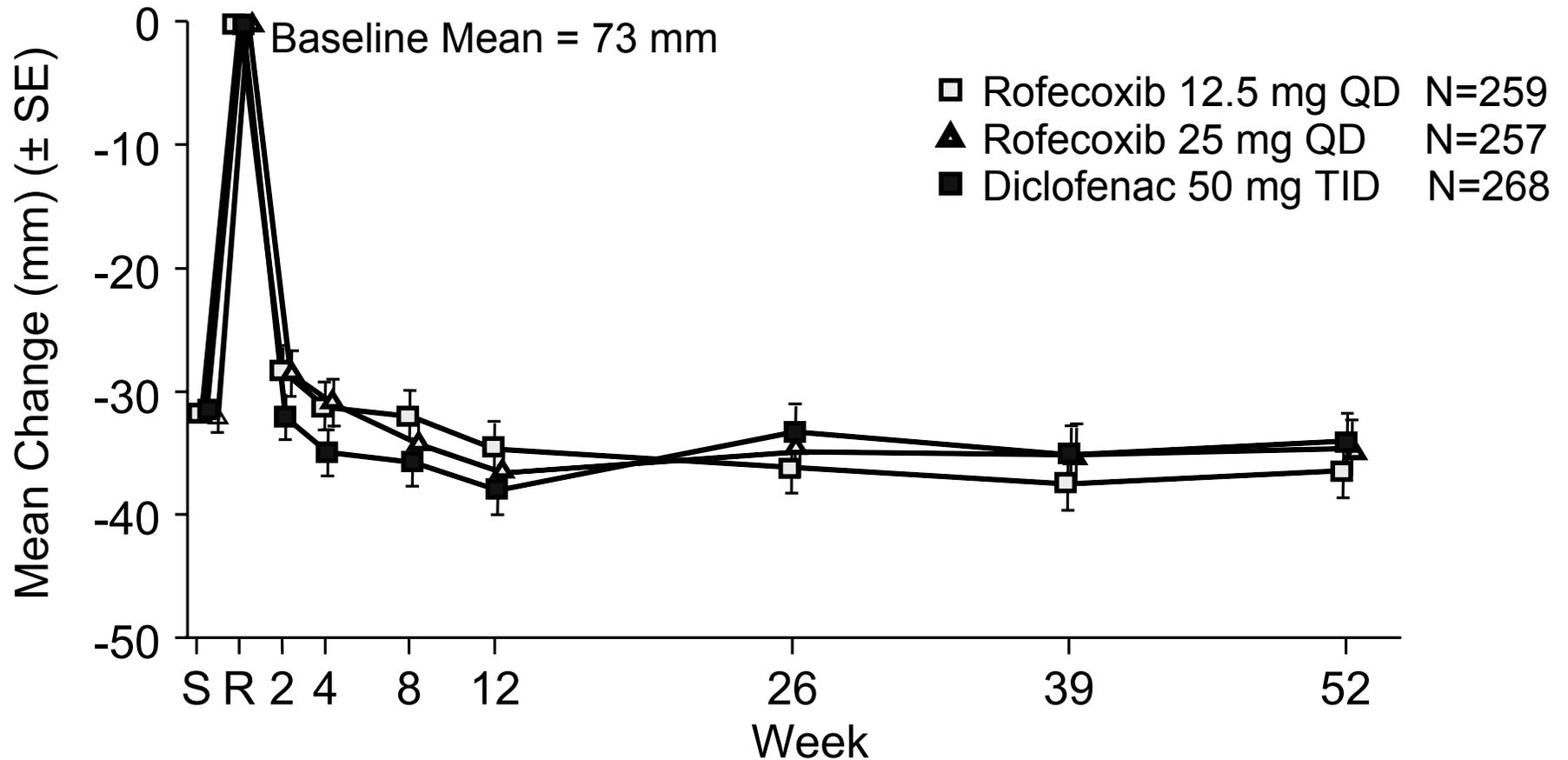
**Clinical Sciences
Merck Research Laboratories**

Rofecoxib Clinical Development

- Selectivity for COX-2
- Efficacy equivalent to NSAIDs
 - 12.5 mg and 25 mg for osteoarthritis
- Safety related to COX-2 inhibition
 - Gastrointestinal
 - Renal
 - Cardiovascular

Long Term Efficacy in Osteoarthritis Rofecoxib 12.5 mg & 25 mg Once Daily

OA Pain Walking on a Flat Surface



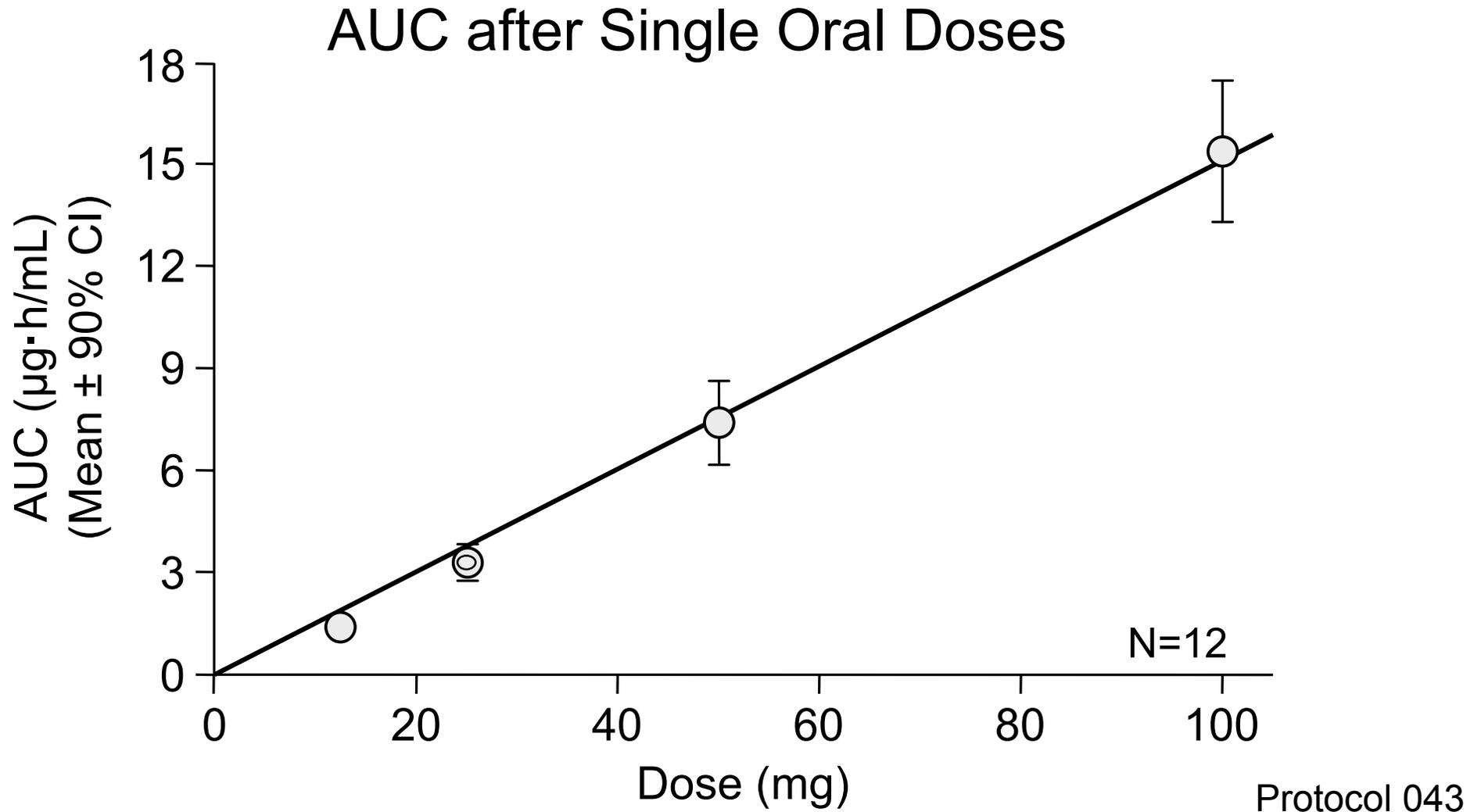
$p < 0.001$, all groups compared to baseline.

Last Observation Carried Forward

Rofecoxib COX Selectivity

- Defined clinically in subjects receiving rofecoxib
 - Assays of COX-1 and COX-2 activity in blood
 - no effect on COX-1 at any dose studied
 - dose-dependent inhibition of COX-2
 - similar to NSAIDs
 - Effects on bleeding time / platelet function
 - Assays of COX activity in gastric biopsies

Rofecoxib Pharmacokinetics Are Linear

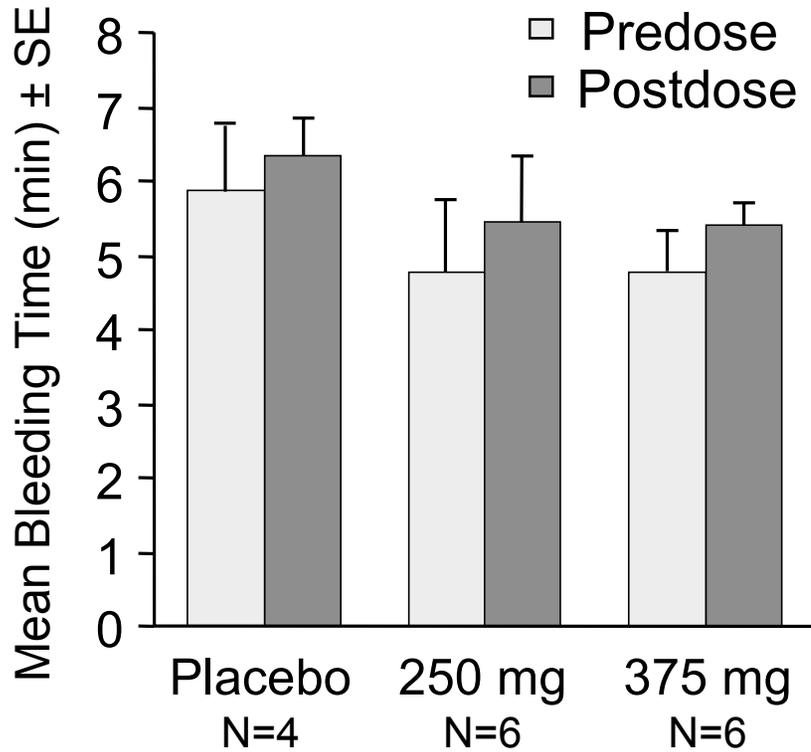


Rofecoxib COX Selectivity

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 - Effects on bleeding time / platelet function
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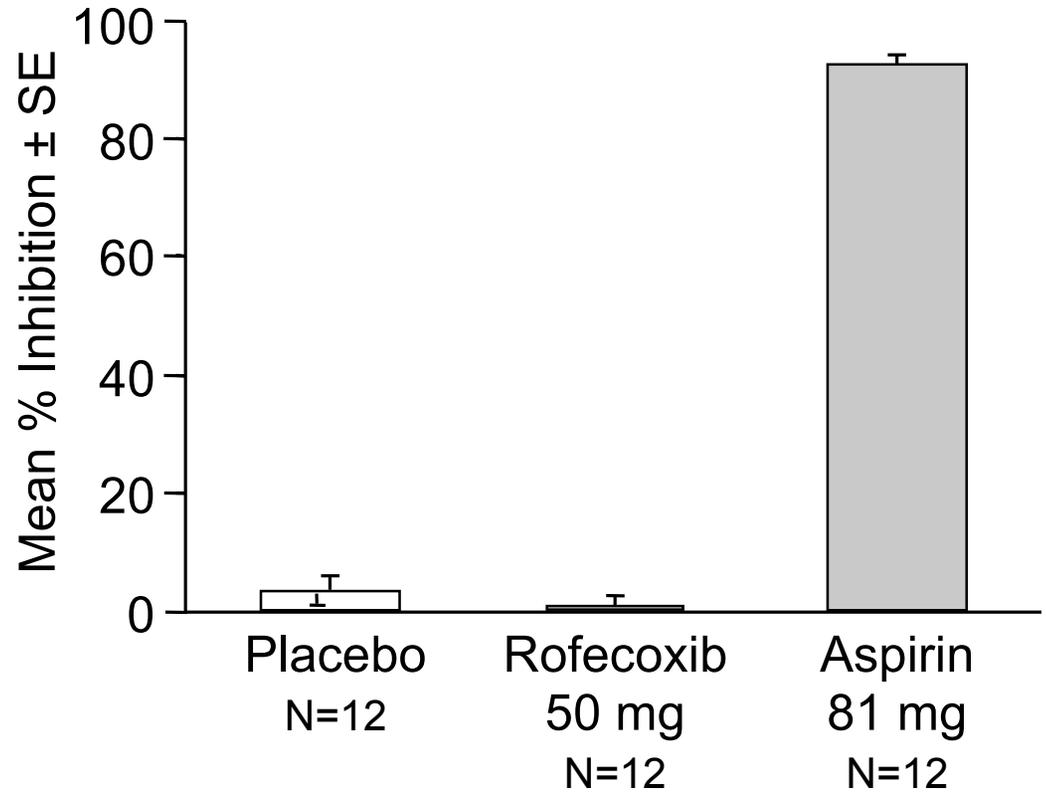
Rofecoxib Does Not Affect Bleeding Time or Platelet Aggregation

Bleeding Time



Protocols 005, 063

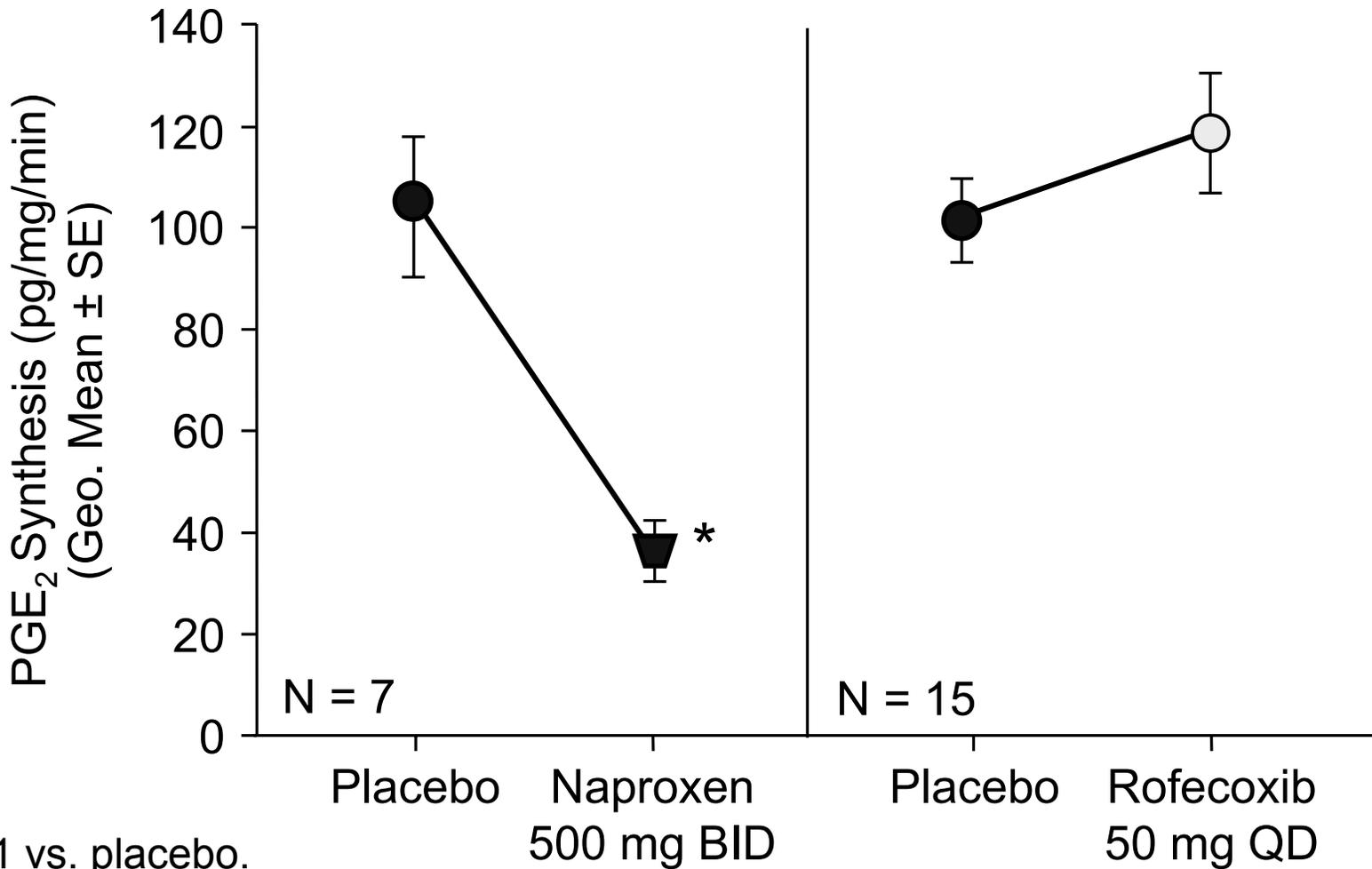
Platelet Aggregation (% Inhibition) (Arachidonic Acid 1mM)



Rofecoxib COX Selectivity

- Defined clinically in subjects receiving rofecoxib
 - Assays of COX-1 and COX-2 activity in blood
 - Effects on bleeding time / platelet function
 - Assays of COX activity in gastric biopsies

Effect of Rofecoxib 50 mg and Naproxen on *Ex vivo* PGE₂ Synthesis in Gastric Biopsy Samples



*p<0.001 vs. placebo.

Wight *et al.*, *Gastroenterology*, in press, 2001.

Protocol 092

Safety of Rofecoxib

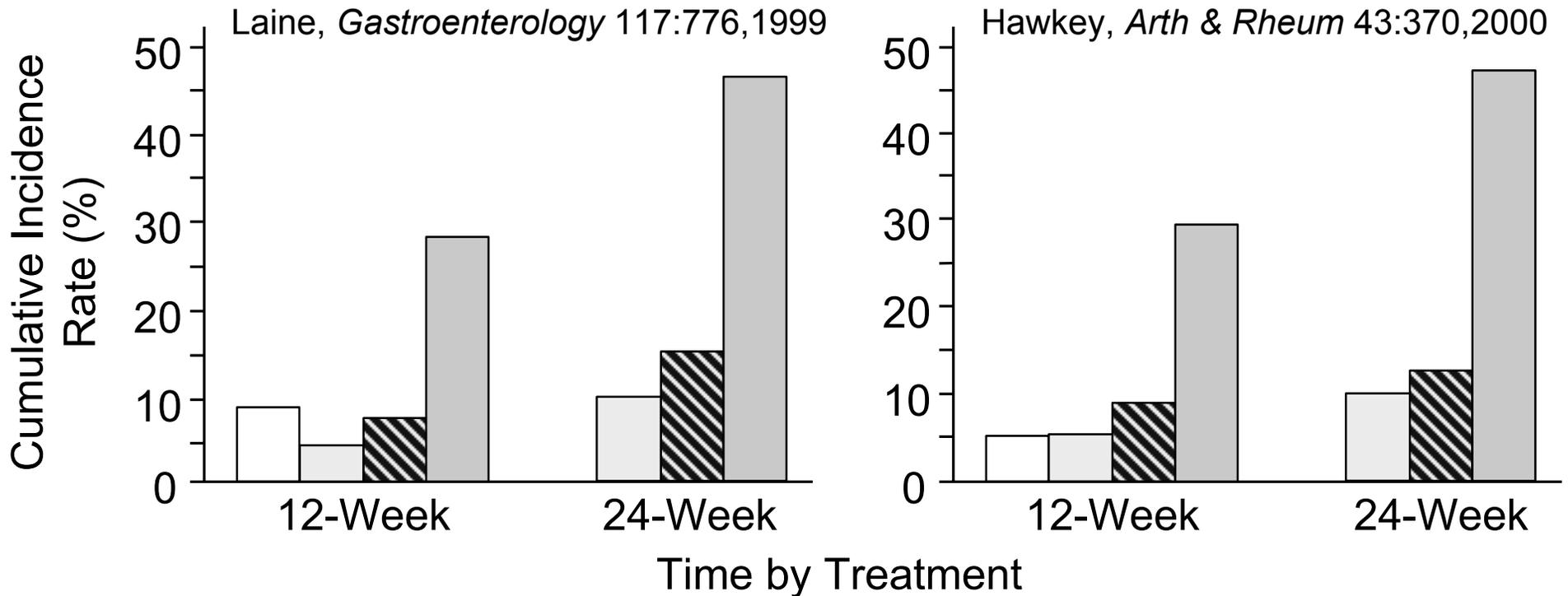
- Gastrointestinal Special Studies
- Renal
- Cardiovascular

Gastrointestinal Special Studies

- Endoscopic gastroduodenal erosion (normal subjects)
 - 250 mg superior to NSAID (aspirin and ibuprofen)
- Endoscopic gastroduodenal ulceration (OA patients)
 - 25 mg and 50 mg superior to ibuprofen 800 mg three times daily
- Special GI safety (normal subjects)
 - 25 mg and 50 mg superior to NSAID and similar to placebo
 - fecal red blood cell loss
 - intestinal permeability

Endoscopic Comparisons to Ibuprofen

Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 3 mm



□ Placebo N=158; 182
□ Rofecoxib 25 mg N=186; 187
▨ Rofecoxib 50 mg N=178; 182
■ Ibuprofen 2400 mg N=167; 187

$p < 0.001$ rofecoxib 25 mg, 50 mg, and placebo vs. ibuprofen.

Protocol 044 and 045

Gastrointestinal Special Studies

- Endoscopic gastroduodenal erosion (normal subjects)
 - 250 mg superior to NSAID
- Endoscopic gastroduodenal ulceration (OA patients)
 - 25 mg and 50 mg superior to ibuprofen 800 mg three times daily
- Special GI safety (normal subjects)
 - 25 mg and 50 mg superior to NSAID and similar to placebo
 - fecal red blood cell loss
 - intestinal permeability

Safety of Rofecoxib

- Gastrointestinal Special Studies
- Renal
- Cardiovascular

Prostaglandins and the Kidney

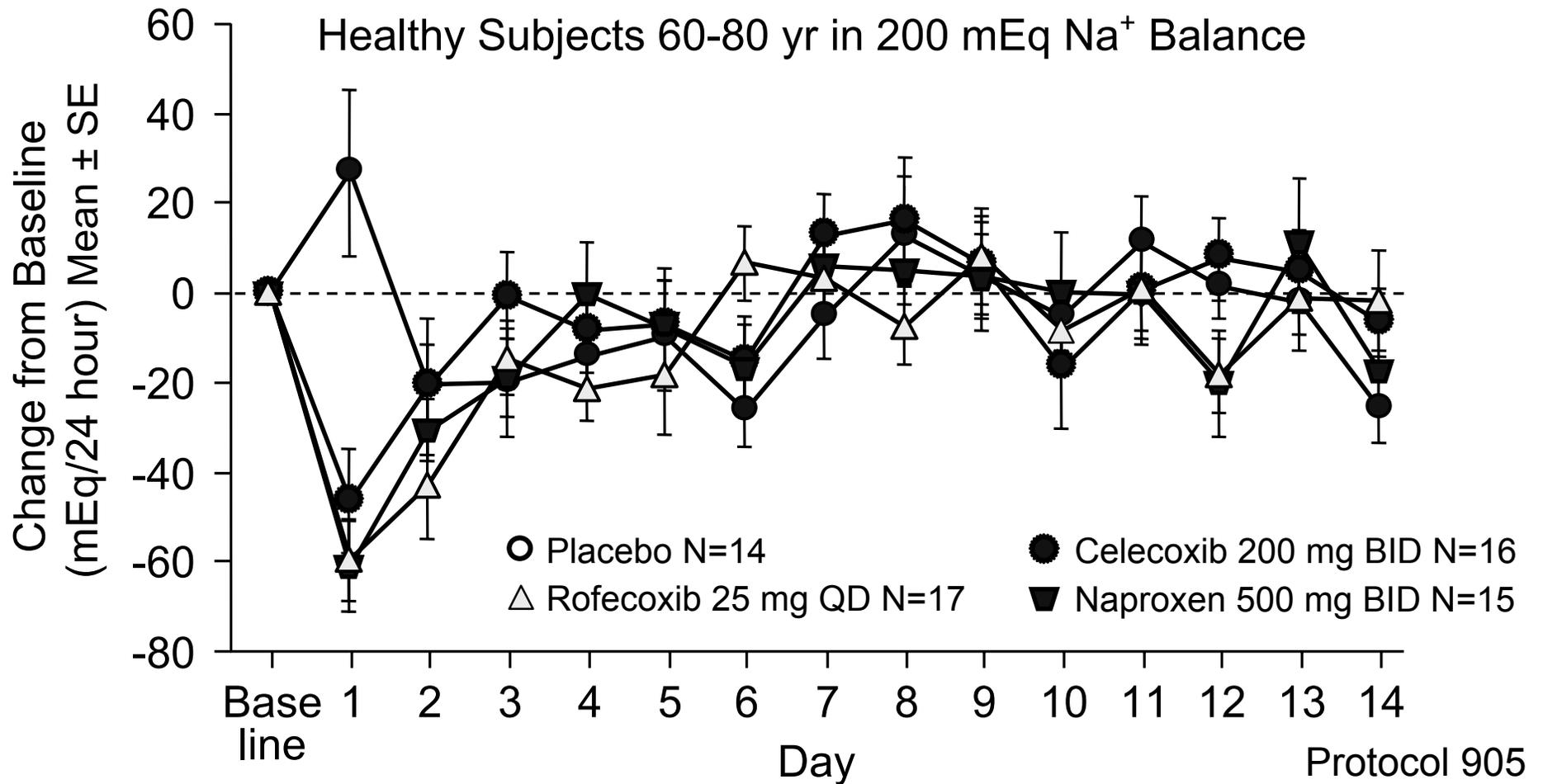
- Both COX-1 & COX-2 are present in the normal kidney
- Prostaglandins involved in renal physiology
 - Glomerular filtration rate
 - Renin secretion
 - Sodium, potassium and water homeostasis
- NSAIDs produce a small incidence of edema and hypertension

COX-2 Inhibitors and the Kidney

- COX-2 selective inhibitors are equivalent to non-selective NSAIDs in reducing urinary sodium excretion - Dose Related

Comparative Effects on Sodium

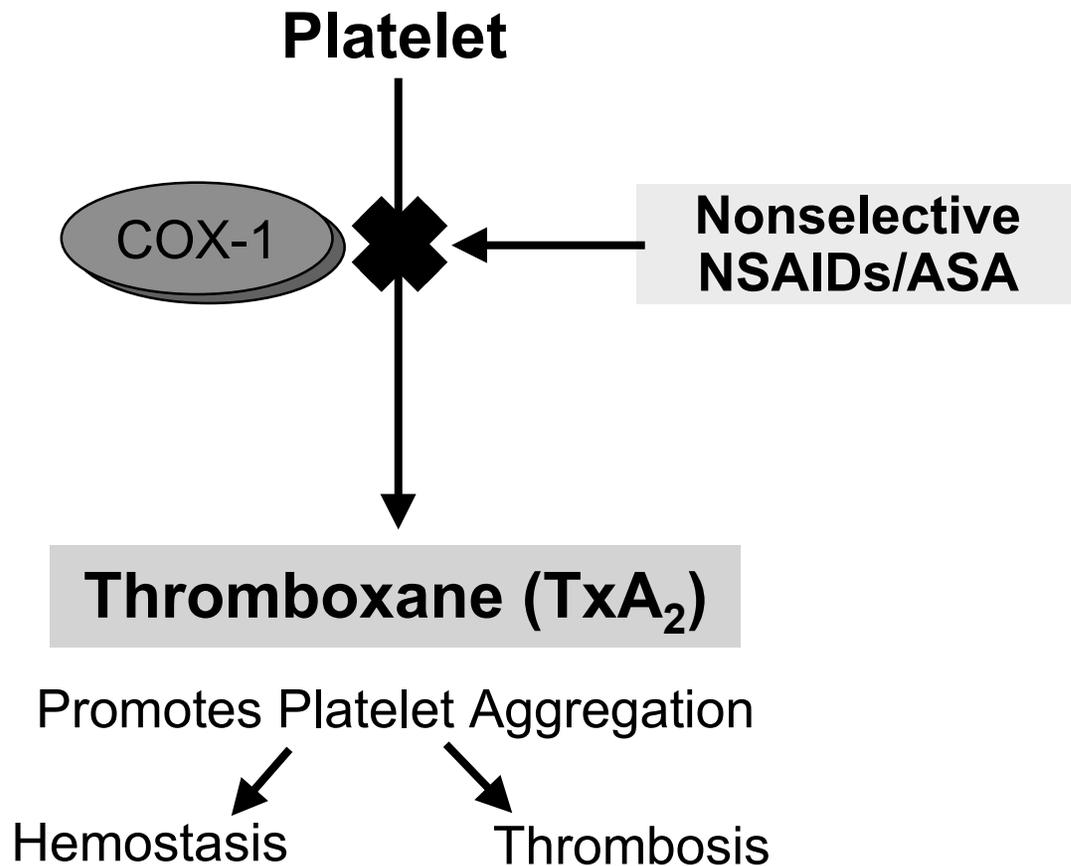
Change from Baseline Daily Urinary Sodium Excretion



Safety of Rofecoxib

- Gastrointestinal Special Studies
- Renal
- Cardiovascular
 - Platelet - Endothelium interactions

Effects of NSAIDs on Thromboxane

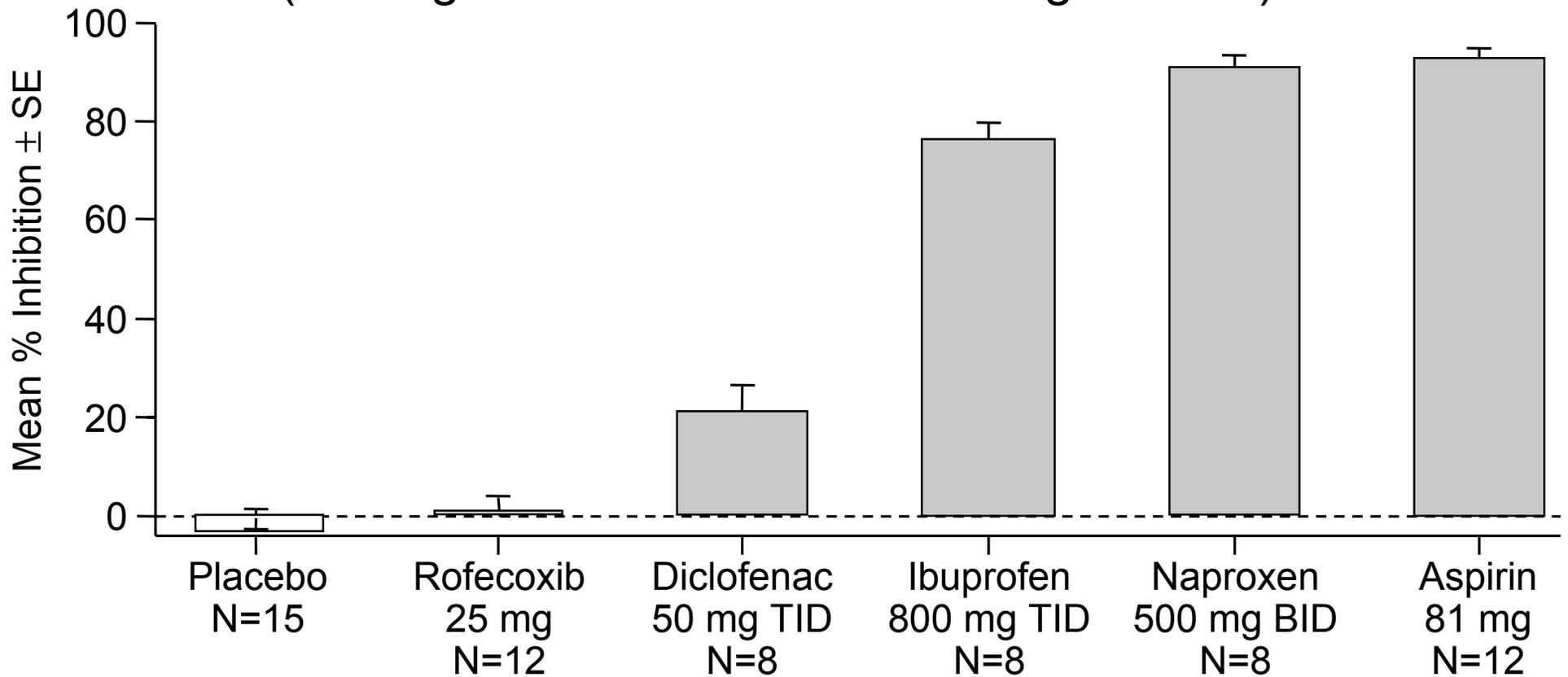


McAdam *et al.* *Proc. Natl. Acad. Sci. USA* . 1999;96:272.

Comparison of the Effect of Rofecoxib and NSAIDs on Platelet Aggregation

Platelet Aggregation

(Average % Inhibition Over Dosing Interval)

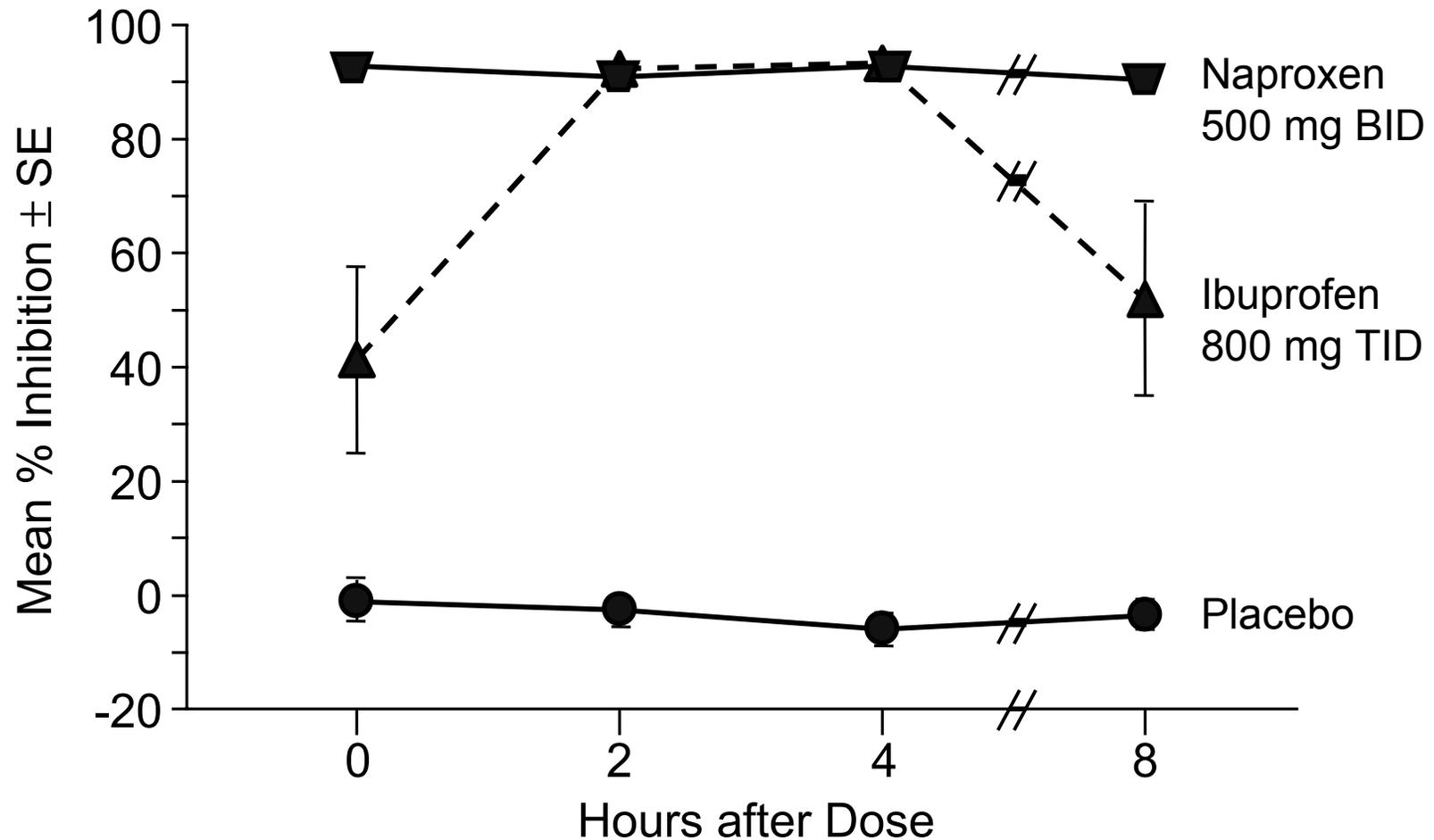


1mM arachidonic acid as agonist.

Protocol 061 & 063

Effect of NSAIDs on Platelet Aggregation

Steady State % Inhibition from Baseline During Dosing Interval



Comparison of Inhibitory Effect of Aspirin and Naproxen on Platelet Aggregation

	Aspirin 81 mg N=12	Naproxen 1000 mg N=8
Mean % inhibition* from baseline	92.1	93.0
Median	92.9	93.2
Minimum, maximum	84.1, 95.0	89.7, 96.4

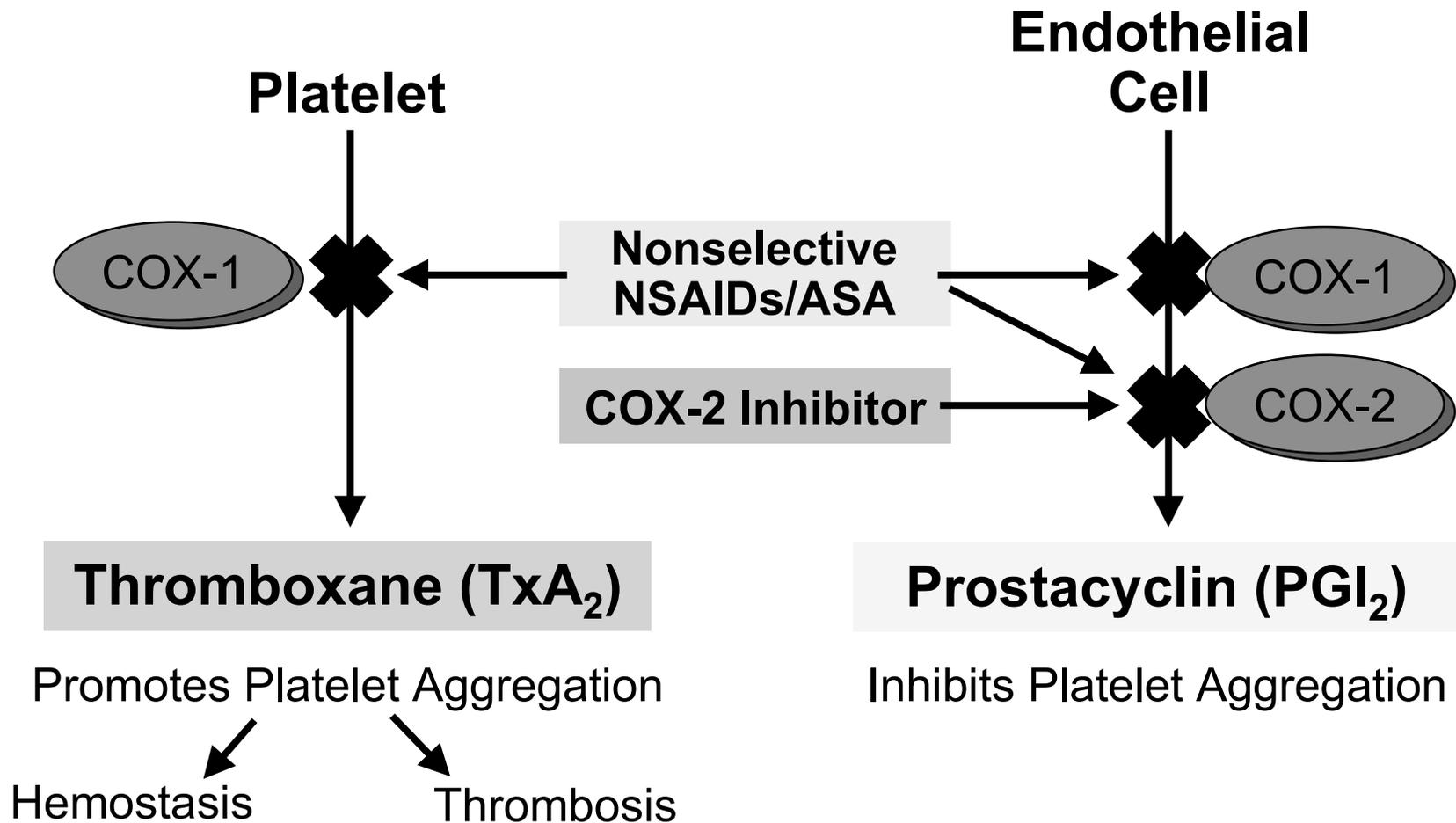
* Measured as percent light transmission using 1 mM arachidonic acid as an agonist.

Protocols 061, 063

COX-2 Cardiovascular Issues

- Can some NSAIDs, such as naproxen, have aspirin-like cardioprotective properties by potently inhibiting platelet aggregation?

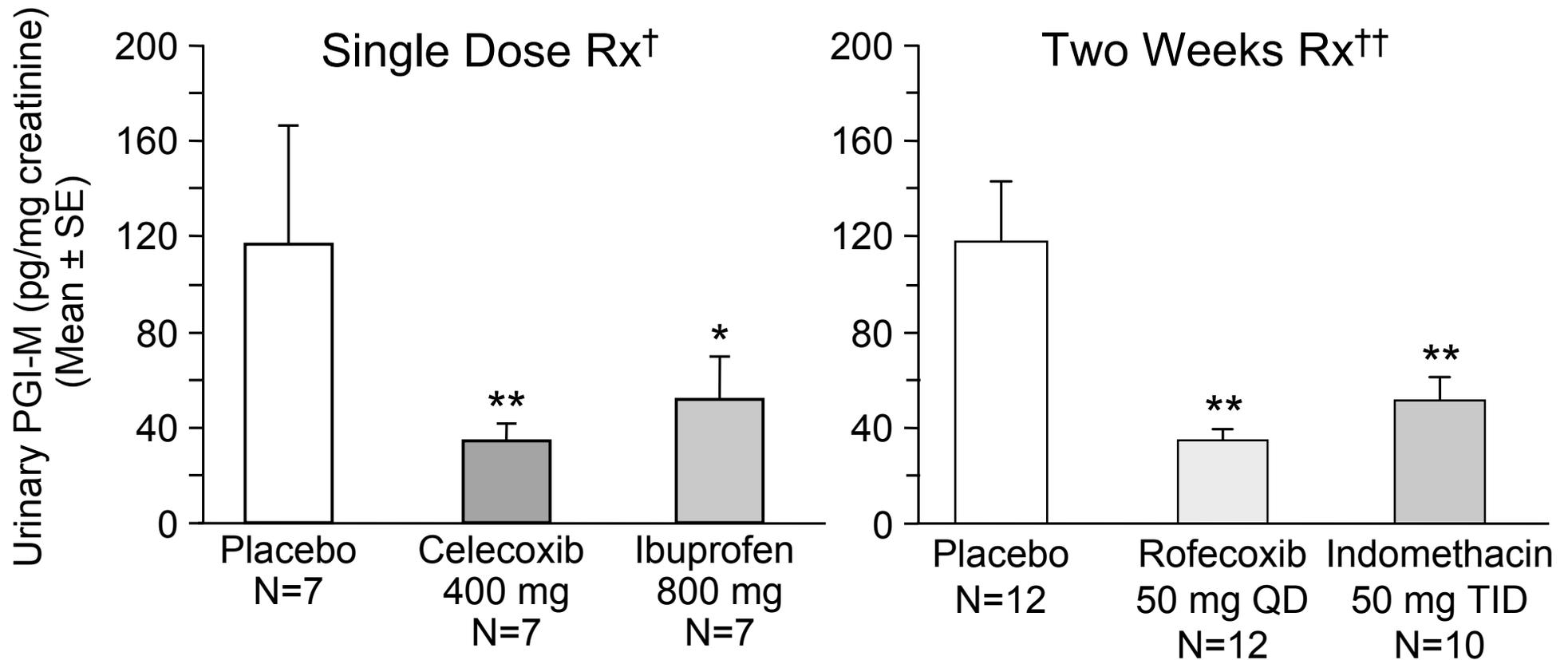
Effects of NSAIDs on Thromboxane and Prostacyclin



McAdam *et al.* *Proc. Natl. Acad. Sci. USA* . 1999;96:272.

Effect of Celecoxib & Rofecoxib on PGIM

Urinary 2,3 dinor-6-keto-PGF_{1α} (PGIM)



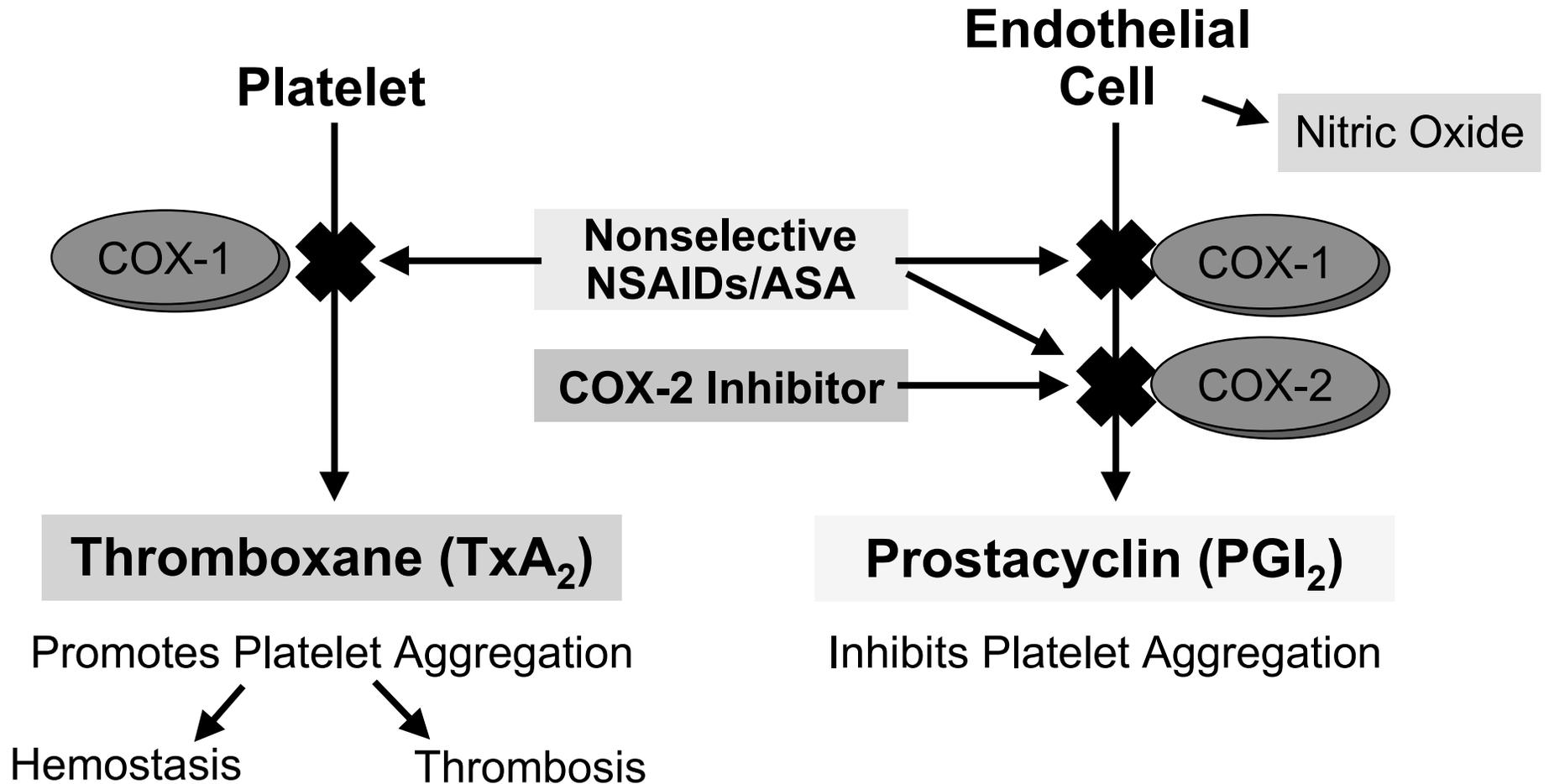
* p<0.05 vs. placebo.

**p<0.01 vs. placebo.

[†] *Proc. Natl. Acad. Sci. USA* 1999;96:272-277.

^{††} *J. Pharmacol. Exp. Ther.* 1999;289:735-741.

Effects of NSAIDs on Thromboxane and Prostacyclin



McAdam *et al. Proc. Natl. Acad Sci. USA* . 1999;96:272.

COX-2 Cardiovascular Issues

- By inhibiting platelet aggregation can some NSAIDs, such as naproxen, have aspirin-like cardioprotective properties?
- What is the clinical importance of inhibiting systemic prostacyclin synthesis without inhibiting platelet aggregation?

COX-2 Cardiovascular Issues

- We postulated that COX-2 inhibitors might alter the balance between the platelet and the endothelium
- We therefore examined our Phase IIb/III database. No evidence of excess cardiovascular events
 - Comparators: ibuprofen 800 mg TID; diclofenac 50 mg TID; placebo
- In 1998 we established a Standard Operating Procedure to capture and adjudicate cardiovascular events in all future COX-2 inhibitor studies - prior to VIGOR

Conclusions

- Rofecoxib is a COX-2 inhibitor without effects on COX-1 at and above the clinical doses
- Rofecoxib 12.5 mg and 25 mg once daily is equally effective to NSAIDs in osteoarthritis
- Rofecoxib effects on the gastrointestinal mucosa are significantly less than NSAIDs
- The renal effects of COX-2 inhibitors are similar to NSAIDs

Conclusions

- Platelet thromboxane production is variably reduced by NSAIDs but not by COX-2 inhibitors
- Systemic prostacyclin synthesis is reduced by both

The clinical effects of rofecoxib are a consequence of its selective inhibition of COX-2 and its lack of effect on COX-1. This supports the COX-2 hypothesis.

VIOXX™ Gastrointestinal Outcomes Research

VIGOR

Alise Reicin, M.D.
Clinical Research
Merck Research Laboratories

Overview

- Gastrointestinal Outcome Analyses
 - Rheumatoid Arthritis Outcome Study (VIGOR)
 - Phase IIb/III Osteoarthritis Analysis
- Demonstration of Efficacy in VIGOR
- General Safety
- Cardiovascular Safety
- Summary

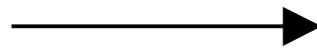
Clinical Upper GI Events

- Phase IIb/III GI Safety Studies demonstrated that rofecoxib's effects on the GI mucosa are significantly superior to NSAIDs
- The incidence of clinically significant upper GI events on rofecoxib compared with standard NSAIDs has been evaluated
 - In patients with RA (VIGOR)
 - In patients with OA (combined Phase IIb/III OA analysis)

Clinical Upper GI Endpoints

- Clinical upper GI events-
PUBs

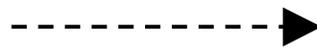
- Perforation
- Ulcer (symptomatic)
 - Obstruction
- Bleeding (upper GI)



Perforation



Obstruction



Major UGI bleeding*

- Complicated upper GI events

* ≥ 2 gm drop in hemoglobin, need for blood transfusion or hypotension.

Upper GI Event Case Review and Adjudication

- Blinded investigators evaluated and reported suspected clinical events
- Independent, blinded adjudication panel reviewed source documents
 - Classified events as:
 - confirmed or unconfirmed
 - complicated or uncomplicated
 - Based on prespecified, stringent case definitions

Overview

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VIGOR Organizational Structure

- 301 clinical centers in 22 countries
- Blinded Endpoint Adjudication Committee
- Blinded Steering Committee
 - Overall scientific and operational direction for the study
- Data Safety Monitoring Board
 - Reviewed interim safety analyses
 - Could request modifications to the protocol or termination of the study

VIGOR Objectives

- Compared to naproxen, rofecoxib at twice the maximum chronic dose will be associated with a reduced risk of:
 - Primary
 - confirmed clinical upper GI events
 - Secondary
 - confirmed complicated upper GI events
 - confirmed + unconfirmed clinical upper GI events
 - confirmed + unconfirmed complicated upper GI events
 - Exploratory
 - clinical GI bleeding (upper and lower GI tract)

VIGOR Study Design: Choice of Patient Population

- Rheumatoid arthritis versus osteoarthritis
 - Improved GI safety with rofecoxib demonstrated in patients with OA
 - potential ethical concerns
 - Patients with RA are routinely treated with chronic NSAIDs
 - Patients with RA are at high risk for NSAID related GI events
 - Extends Phase IIb/III GI safety results to another patient population

VIGOR Study Design: Choice of Comparator and Doses

- Naproxen 500 mg BID:
 - Most commonly prescribed NSAID and dose for the treatment of RA
- Rofecoxib 50 mg:
 - 2-4x OA dose
 - 2x anticipated RA dose
- Provides rigorous testing of the GI safety of rofecoxib

Study Design

- 8076 RA patients randomly assigned to:
 - Rofecoxib 50 mg QD
 - Naproxen 500 mg BID
- Randomization stratified by history of clinical upper GI events
- Washout of prior NSAIDs ≥ 3 days
- Return visits: 6 weeks, 4 months, every 4 months until study termination

VIGOR Study Duration

- Determined by time and cumulative number of endpoints
- Study terminated study based on the stopping guidelines
 - Study termination after a minimum of
 - 120 confirmed clinical upper GI events
and
 - 40 confirmed complicated events
and
 - 6 months had elapsed since the last patient was randomized

Patients: Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Rheumatoid arthritis
- Age ≥ 50 (≥ 40 if on chronic steroids)
- Require NSAIDs for at least 1 year

Exclusion Criteria

- Positive fecal occult blood test
- Patients using
 - Aspirin
 - Anticoagulants
 - Antiplatelet agents
 - Antiulcer medications (OTC doses of H₂-RAs allowed)

Patient Baseline Characteristics in VIGOR

<u>Characteristic</u>	<u>Rofecoxib N=4047</u>	<u>Naproxen N=4029</u>
Mean Age (Range)	58 (34 - 88)	58 (37 - 89)
Female	80%	80%
Prior upper GI event	8%	8%
Prior complicated upper GI event	2.5%	2.6%
Corticosteroid use	56%	56%
<i>H. pylori</i> seropositive	43%	43%

Patient Baseline Characteristics in VIGOR

<u>Characteristic</u>	<u>Rofecoxib N=4047</u>	<u>Naproxen N=4029</u>
Mean duration of RA (years)	11	11
Met ≥ 4 ACR criteria for RA	97%	97%
Methotrexate use	56%	56%
Other DMARD use	46%	45%

Patient Accounting

Total Screened - 9534

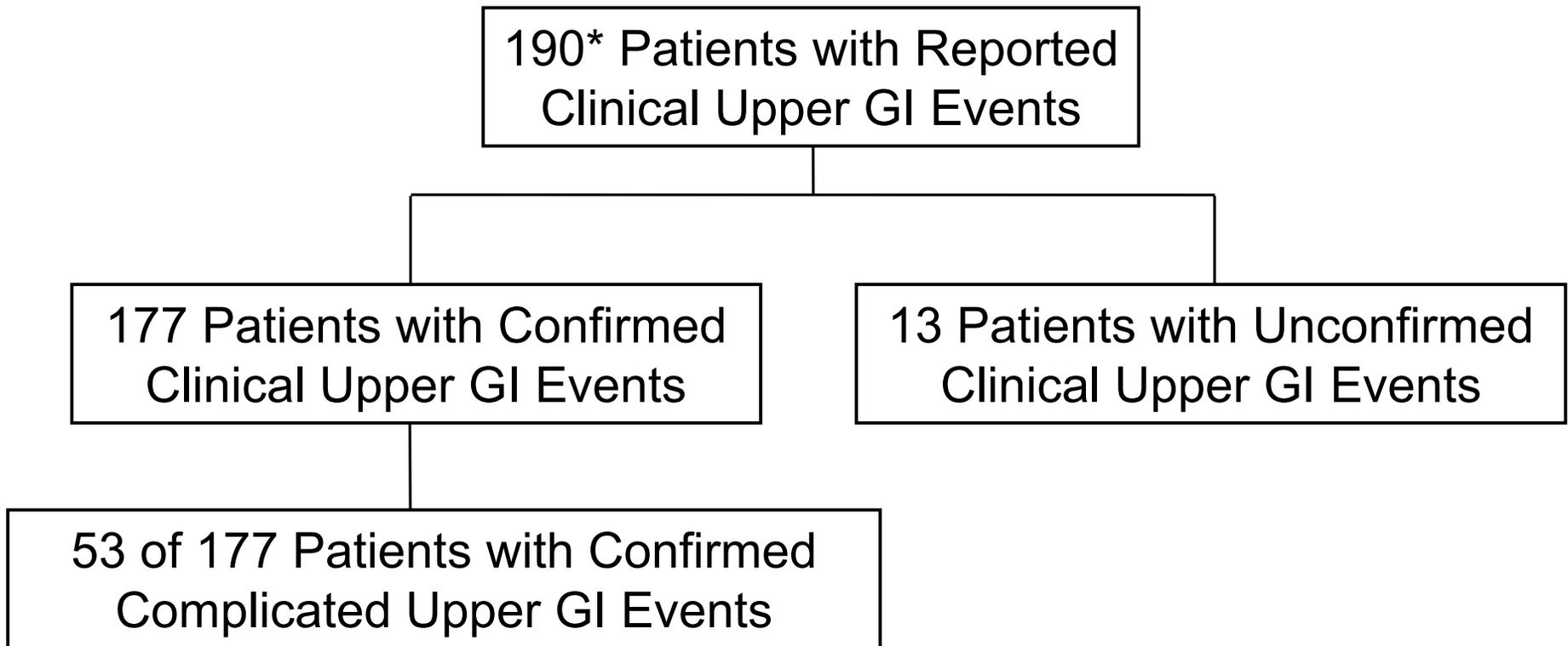
	<u>Rofecoxib</u>	<u>Naproxen</u>
Randomized	4047	4029
Completed study	2862 (71%)	2880 (71%)
Discon. due to AE	667 (16%)	648 (16%)
Discon. due to lack of efficacy	256 (6%)	263 (6%)
Withdrew consent	138 (3%)	130 (3%)
Protocol deviation	74 (2%)	58 (1%)
Other	50 (1%)	50 (1%)

Patient Accounting - Duration of Therapy

	<u>Rofecoxib N=4047</u>	<u>Naproxen N=4029</u>
Median follow-up (Range)	9 months (0.5-13)	9 months (0.5-13)
Patient-years	2699	2697

- All patients included in all analyses for entire duration of time on treatment + 14 days
 - Consistent with intention-to-treat principle

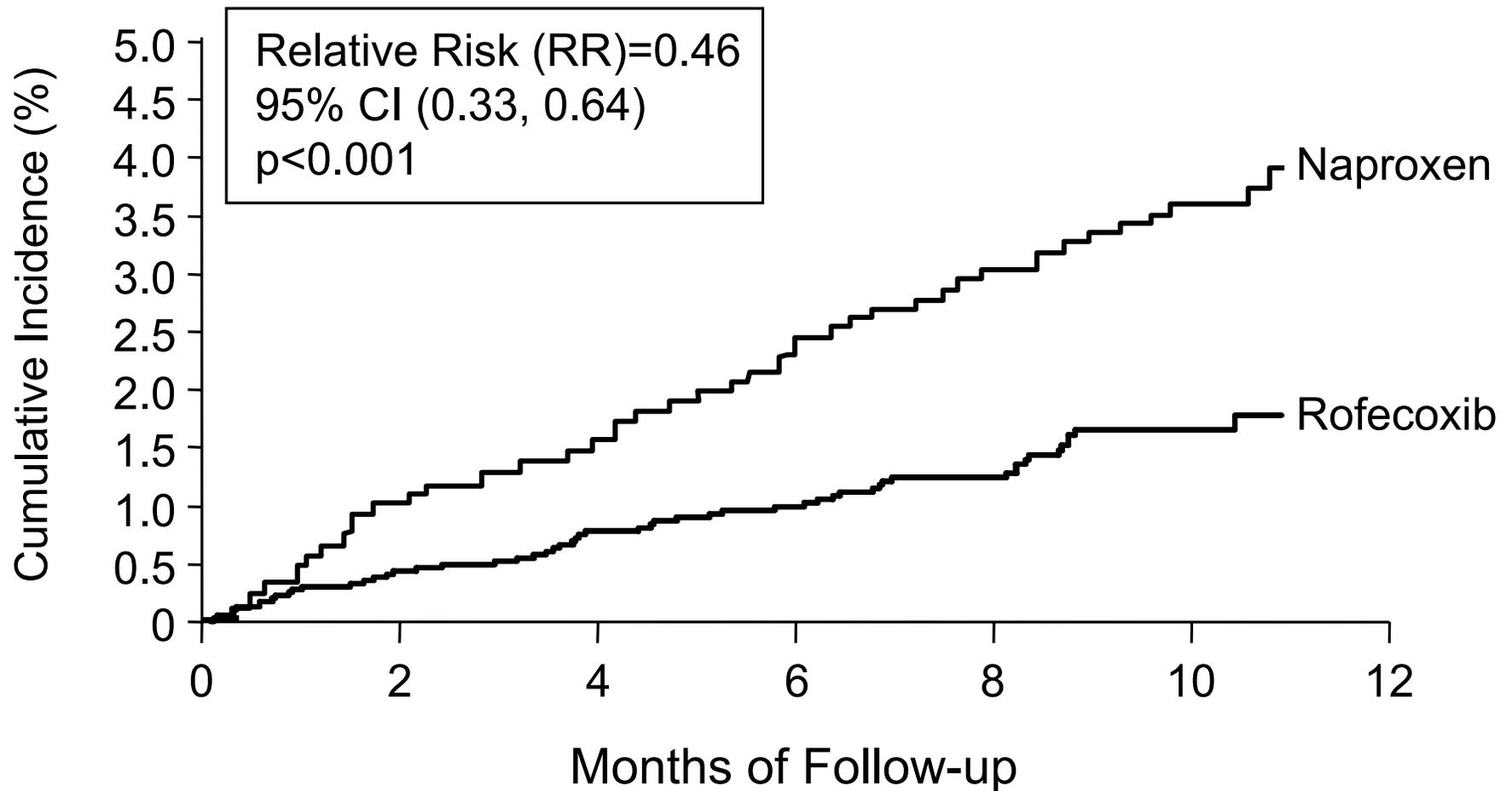
Patients with Upper GI Events



* Excludes one patient whose event was classified as not an upper GI event.

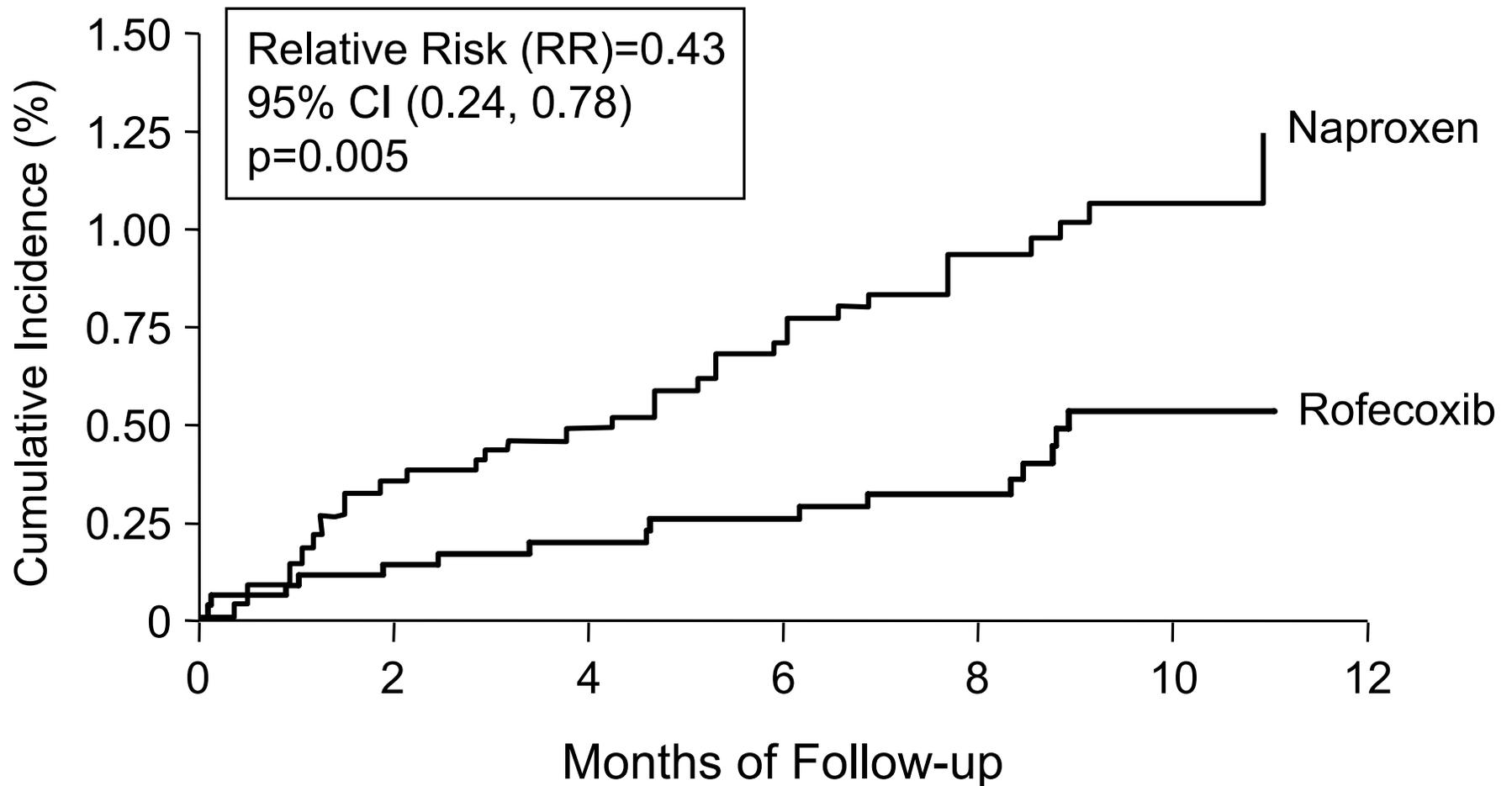
VIGOR Primary End Point

Time to Confirmed Clinical Upper GI Event

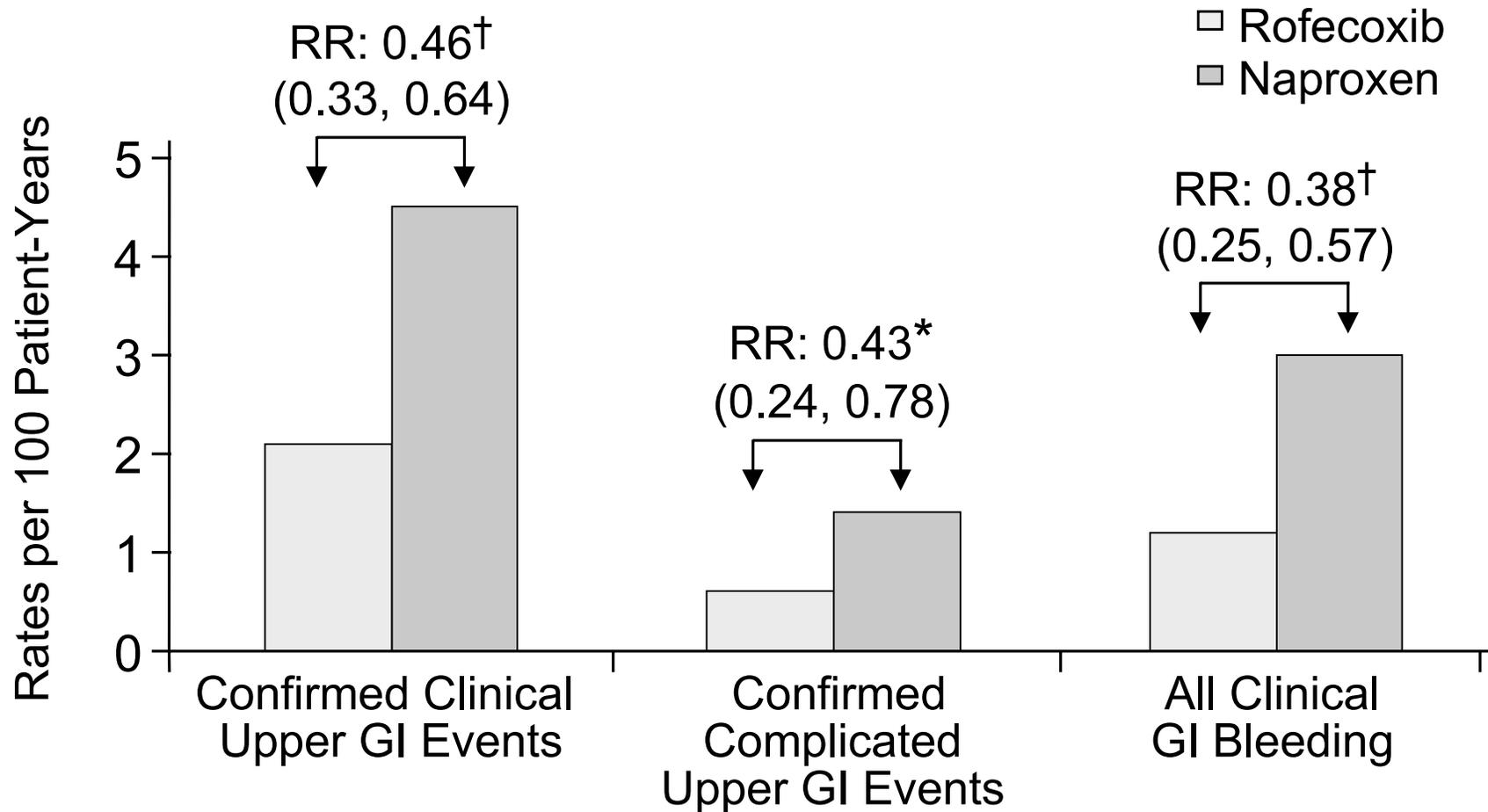


VIGOR Secondary End Point

Time to Confirmed Complicated Upper GI Event

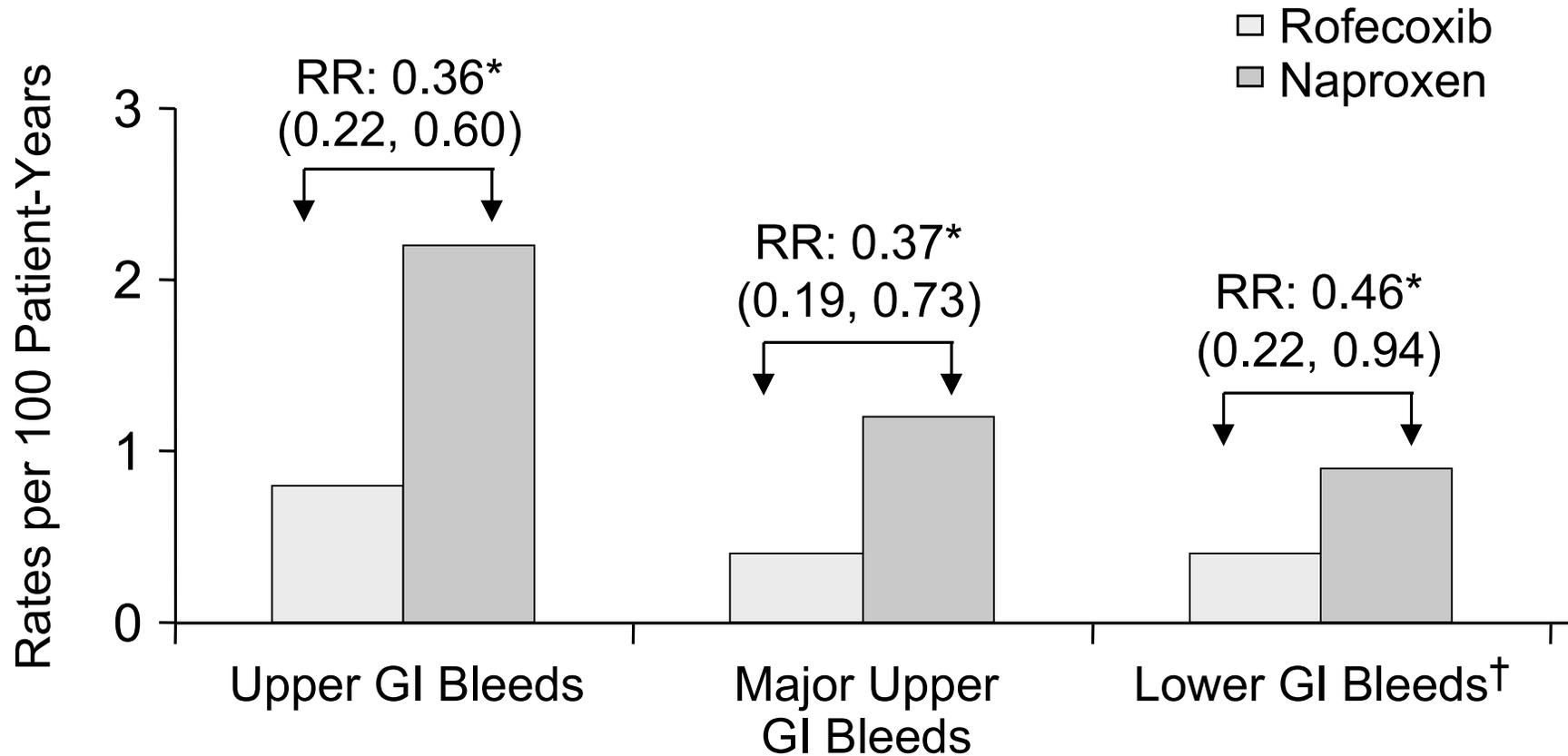


VIGOR - Summary of GI Endpoints



[†]p < 0.001. * p = 0.005. () = 95% CI.

VIGOR GI Bleed Analyses



*p<0.05.

() = 95% CI.

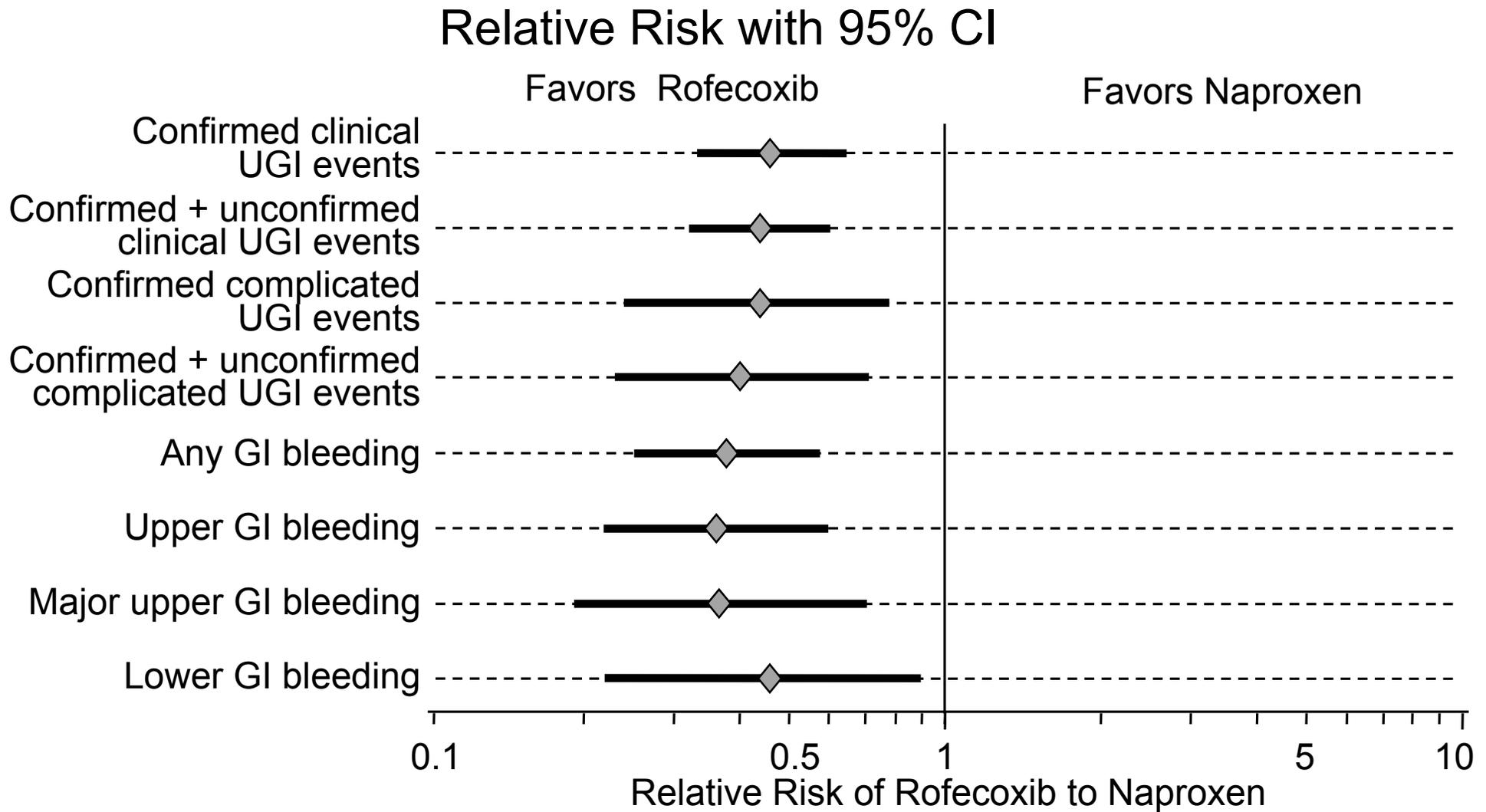
[†]Lower GI bleeds include all GI bleeds that were not of esophageal, gastric, or duodenal origin.

VIGOR - Types of Confirmed Upper GI Events

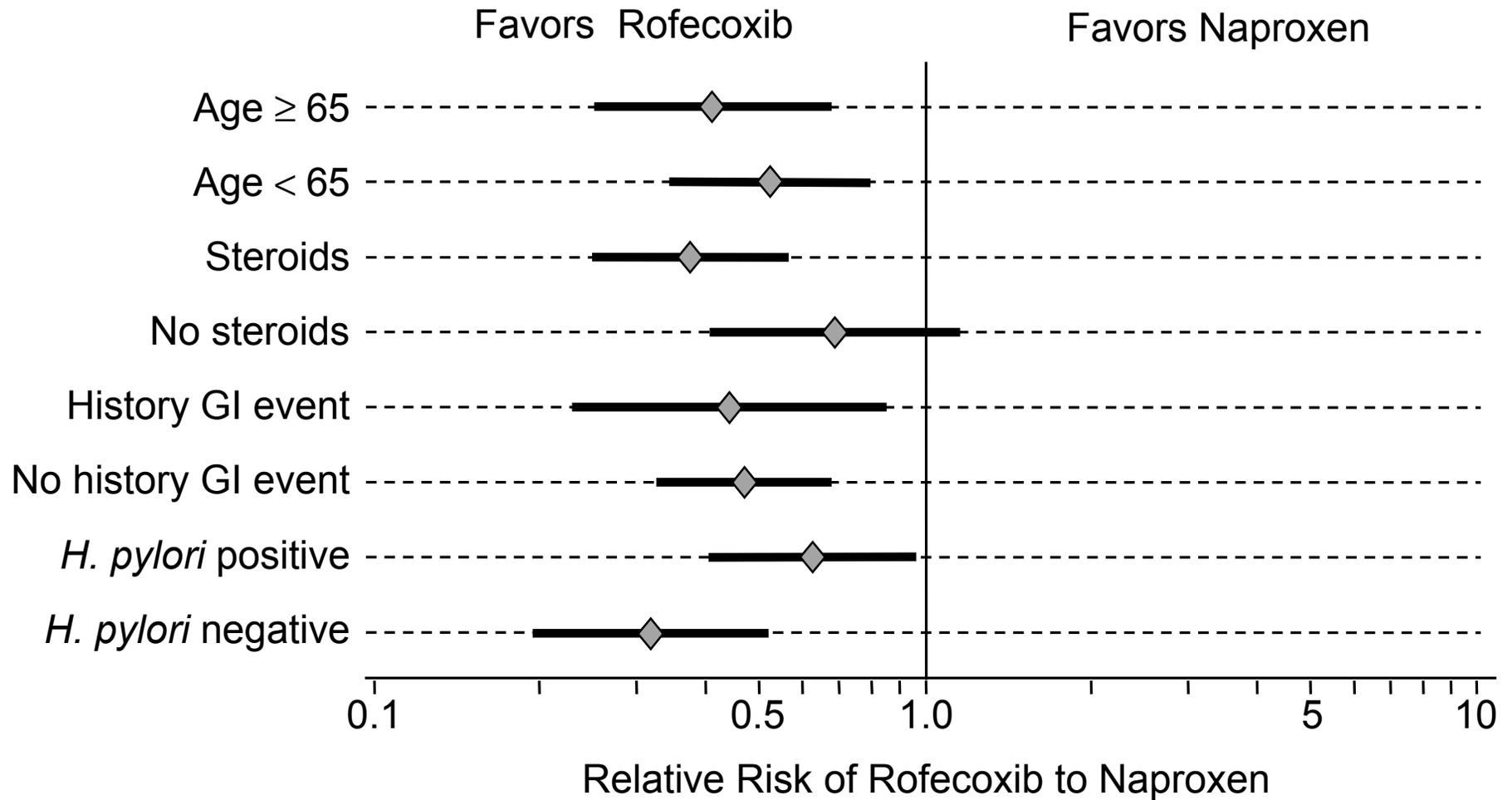
Primary Endpoint	Rofecoxib N=4047		Naproxen N=4029	
	n	%	n	%
Confirmed upper GI events	56	(1.4)	121	(3.0)
Symptomatic gastric ulcers	28	(0.7)	81	(2.0)
Symptomatic duodenal ulcers	27	(0.7)	39	(1.0)
Upper GI bleeds	14	(0.4)	35	(0.9)
Gastroduodenal perforations	3	(0.1)	4	(0.1)
Gastric outlet obstructions	1	(<0.1)	0	(0.0)

Patients may be counted in more than 1 row, but are counted once within a row.

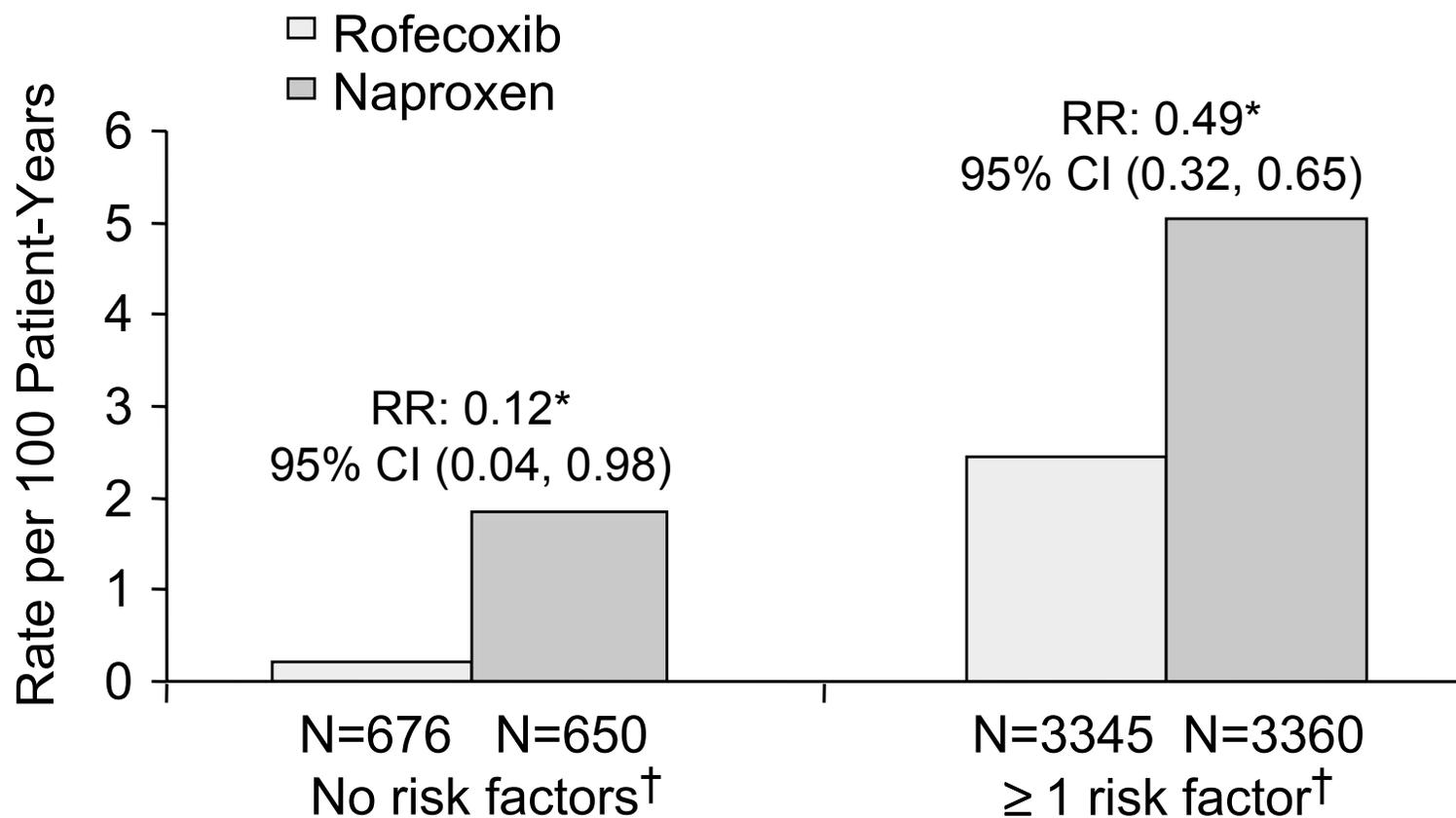
Consistency of Relative Risk in VIGOR: Rofecoxib vs. Naproxen



Relative Risk of Confirmed Upper GI Events in High and Low Risk Subgroups



Relative Risk of Confirmed Upper GI Events by Risk Category



* p<0.05.

[†]Risk factors: Age ≥ 65, *H. pylori* positive, Hx UGI event, use of corticosteroids.

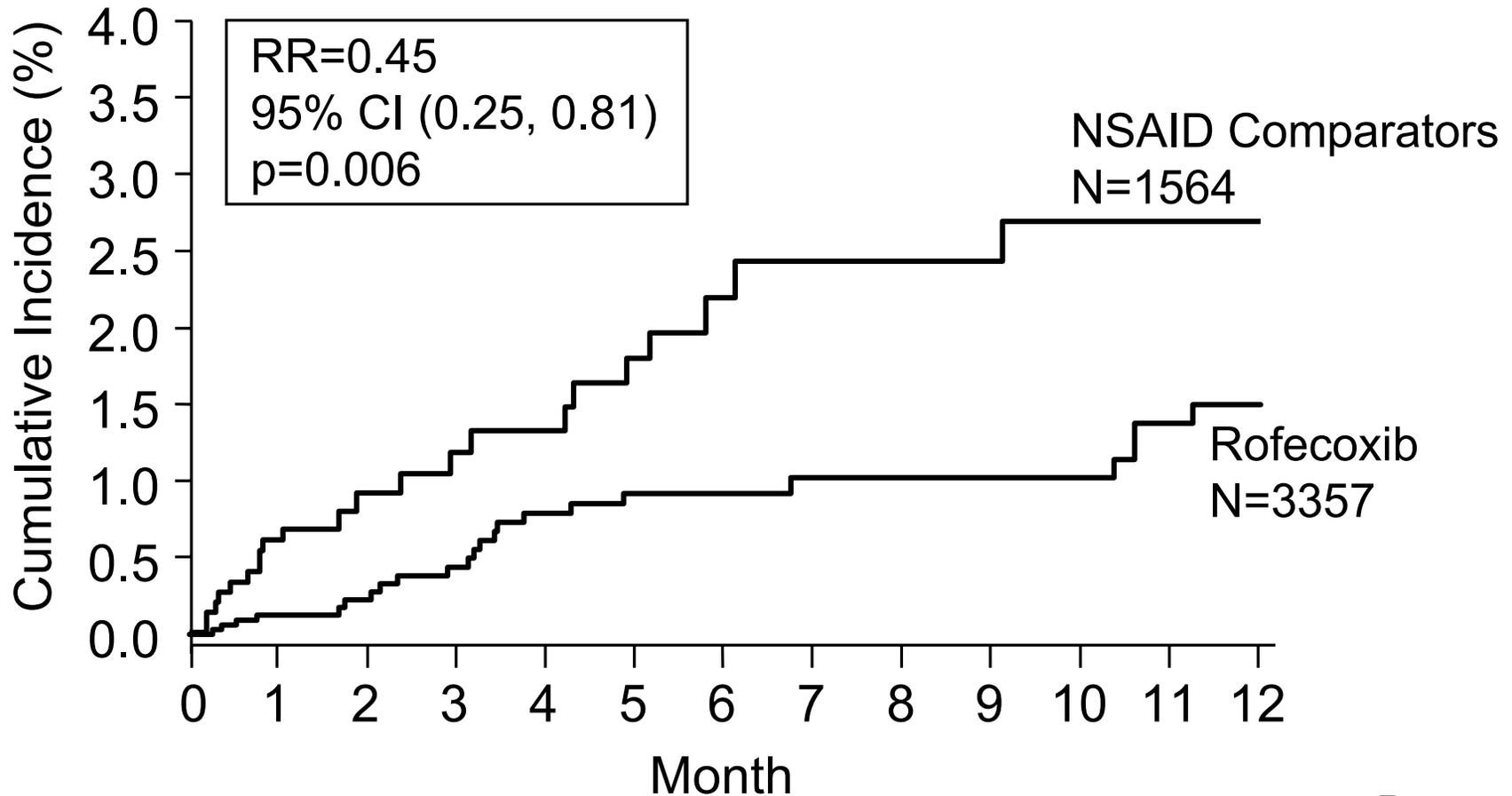
Overview

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Phase IIb/III OA Combined Analysis of Clinical Upper GI Events

- 5435 patients who received:
 - Rofecoxib 12.5 mg, 25 mg, 50 mg; mean dose = 24.7 (N=3357)
 - Diclofenac, ibuprofen, or nabumetone (N=1564)
 - Placebo (N=514): Up to 4 months
- Primary endpoint: Confirmed clinical upper GI events
- Secondary endpoint: Confirmed + unconfirmed clinical upper GI events
- GI endpoint adjudication process and committee were the same for the Phase IIb/III OA studies and the VIGOR study
- 55 reported upper GI events
 - 49 confirmed upper GI events; 6 unconfirmed events

Phase IIb/III OA Studies Primary Endpoint Confirmed Clinical Upper GI Events



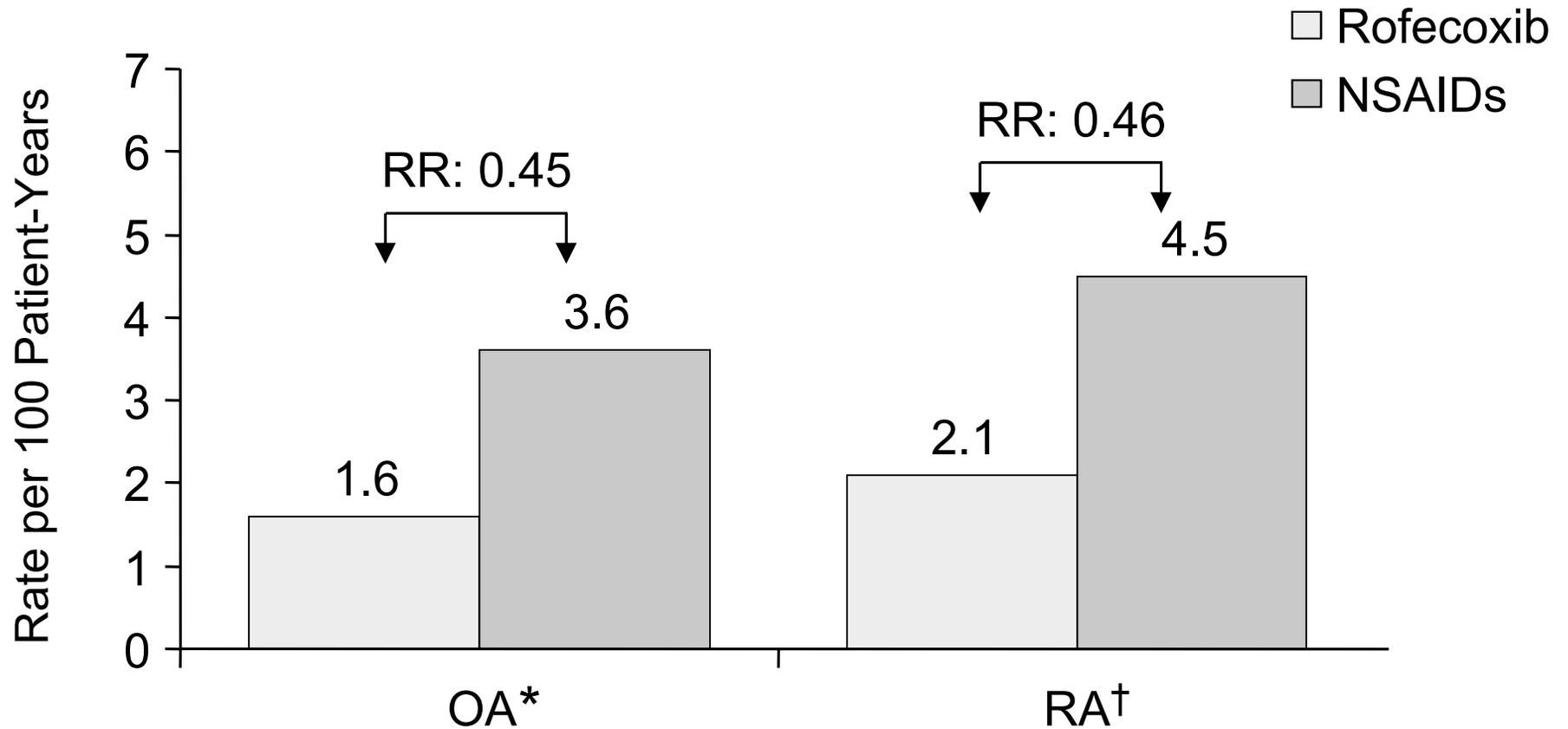
Protocol 069

Confirmed Clinical Upper GI Events in Placebo-Controlled Phase IIb/III Studies

4-Month Analysis: Confirmed Upper GI Events

<u>Treatment</u>	<u>N</u>	<u>No. of Events</u>	<u>No. of Patient-Years</u>	<u>Rate per 100 Patient-Years</u>
Placebo	514	4	112	3.6
Rofecoxib	1701	12	319	3.8
NSAIDs	847	14	139	10.1

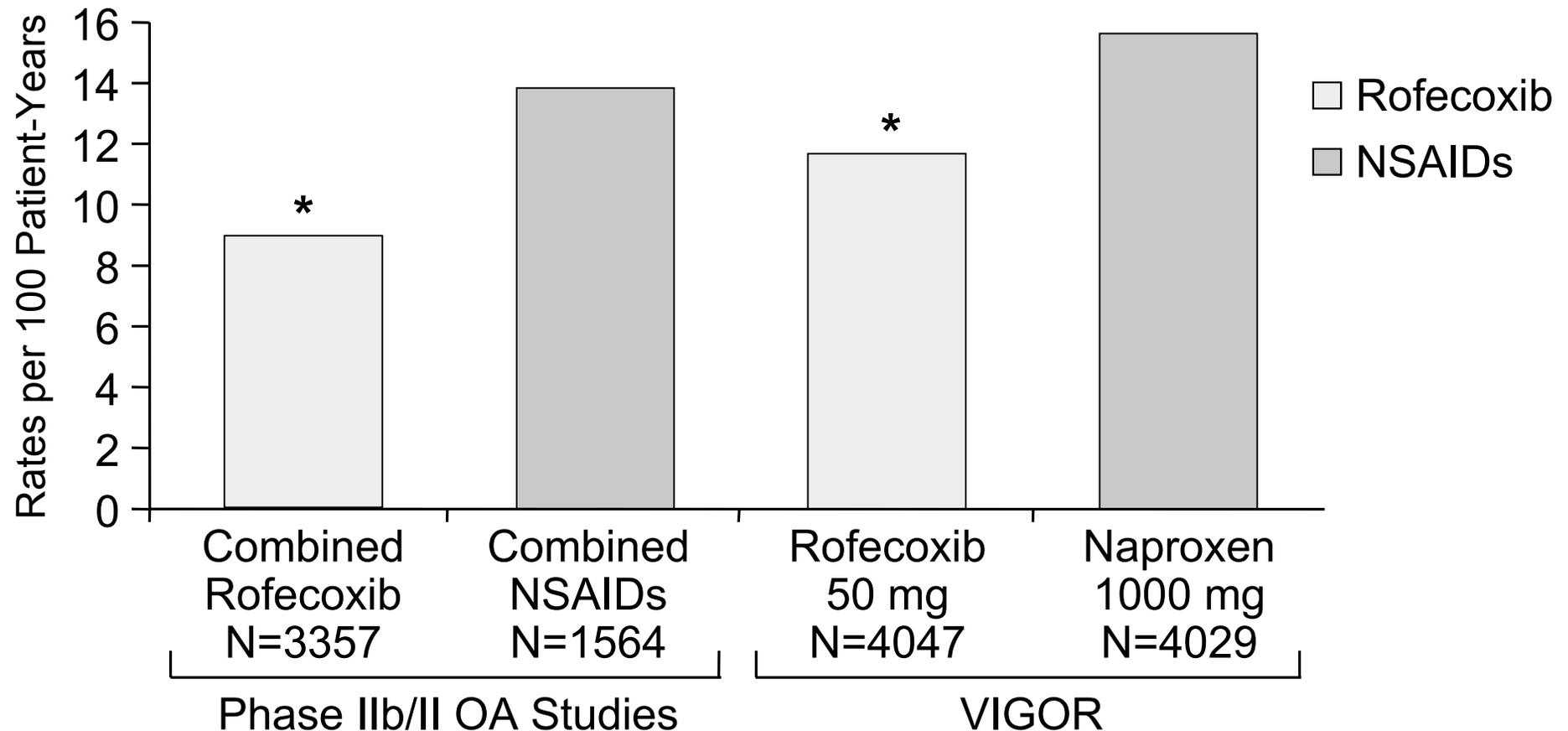
Confirmed Clinical Upper GI Events in Osteoarthritis and Rheumatoid Arthritis



* Phase IIb/III OA combined analysis.

† VIGOR.

Discontinuation Due to Gastrointestinal/Abdominal Adverse Experiences



* $p \leq 0.05$ vs. NSAID comparator.

Rofecoxib GI Safety Summary

- Rofecoxib significantly decreased the risk of clinically important GI events by 54-65%
 - Consistent and significant effects in all prespecified end points
 - Consistent effect in both high and low risk subgroups
- Improved GI safety demonstrated independently in both OA and RA
- These data warrant modification to the current rofecoxib label to distinguish the GI safety profile of rofecoxib compared with nonselective NSAIDs

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VIGOR Efficacy Objective

- Non-flare design
 - Maintenance of efficacy rather than improvements from baseline were anticipated
- To monitor disease activity during treatment with rofecoxib versus naproxen
 - Patient Global Assessment of Disease Activity
 - Investigator Global Assessment of Disease Activity
 - Discontinuation due to lack of efficacy
 - Modified Health Assessment Questionnaire (US only)

Monitoring of Disease Activity in VIGOR

Efficacy Endpoint	Average Change from Baseline	
	Rofecoxib N=4047	Naproxen N=4029
Patient Global Assessment of Disease Activity (0-4 Scale)	-0.5	-0.5
Investigator Global Assessment of Disease Activity (0-4 Scale)	-0.5	-0.5
Modified Health Assessment Questionnaire (0-3 Scale)	-0.1	-0.1
Discontinuation due to lack of efficacy	6.3%	6.5%

VIGOR Efficacy Summary

- Rofecoxib and naproxen provided similar efficacy in the treatment of RA in VIGOR
 - The GI safety comparison was done at similarly effective doses

Overview

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General Safety Phase IIb/III OA

- Safety profile in VIGOR similar to Phase IIb/III OA studies
 - Generally well tolerated
 - Superior GI tolerability compared with nonselective NSAIDs
 - Incidence of adverse experiences related to renal sodium handling
 - similar to NSAIDs within the clinical dose range
 - increased incidence with 50 mg (2x max. chronic dose)
 - Incidence of LFT abnormalities
 - low ~0.5%, similar to ibuprofen and less than diclofenac

VIGOR Clinical AE Summary

	Rofecoxib 50 mg N=4047 %	Naproxen 1000 mg N=4029 %	p-Value
Adverse experience (AE)	71.0	70.1	
Drug-related AE	34.5	36.1	NS [†]
Serious AE	9.3	7.8	<0.05
Serious drug-related AE	1.3	2.0	
Discon. due to AE	15.9	15.8	NS [†]
Discon. due to drug-related AE	11.3	12.9	

[†]p>0.05.

VIGOR Laboratory AE Summary

	Rofecoxib 50 mg N=4047 %	Naproxen 1000 mg N=4029 %	p-Value
Adverse experience (AE)	10.4	9.2	
Drug-related AE	4.8	4.3	NS [†]
Serious AE	<0.1	0.0	NS [†]
Discontinued due to AE	0.5	0.3	NS [†]

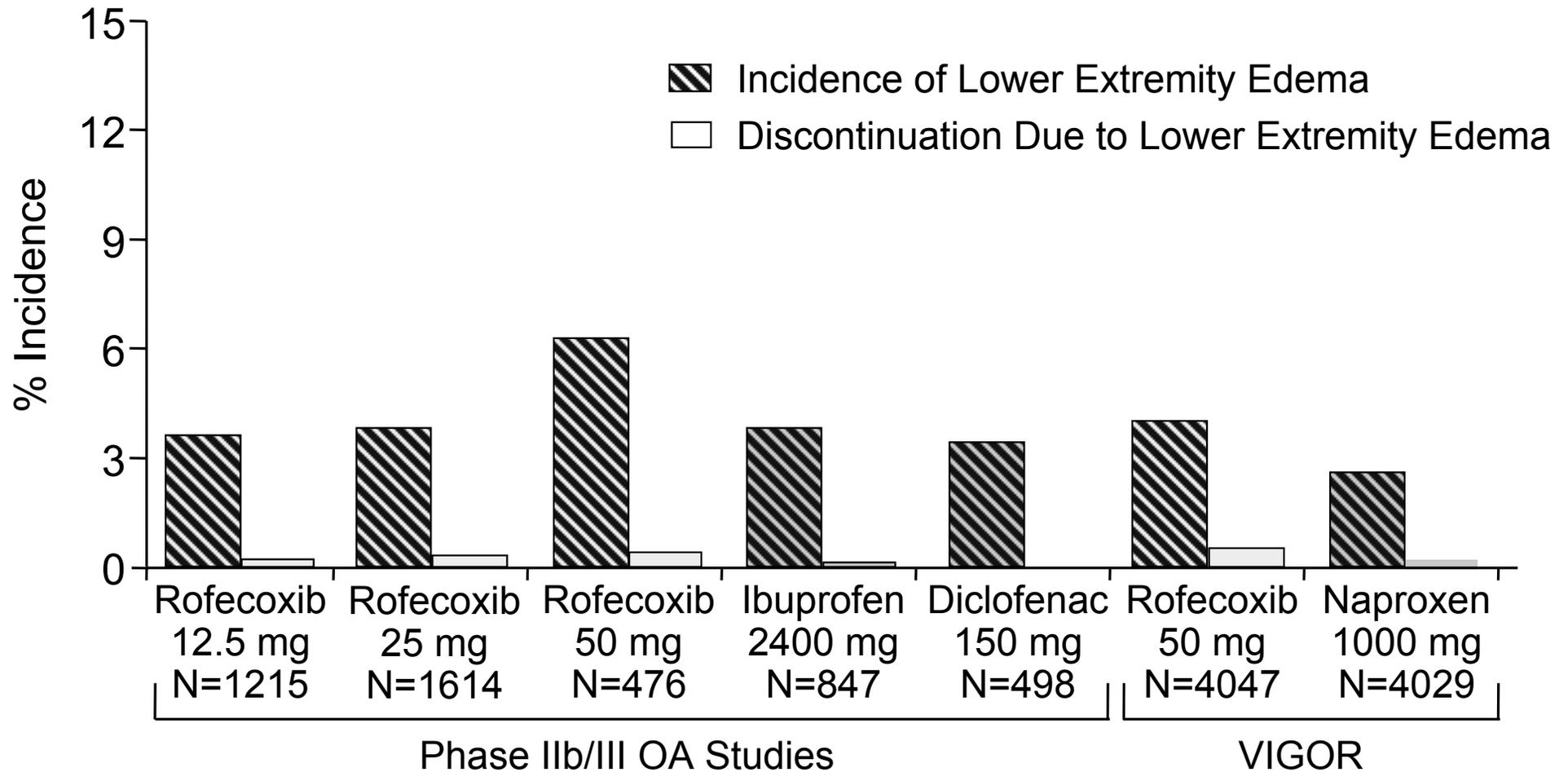
[†]p>0.05.

Summary of Prespecified Adverse Experiences in VIGOR

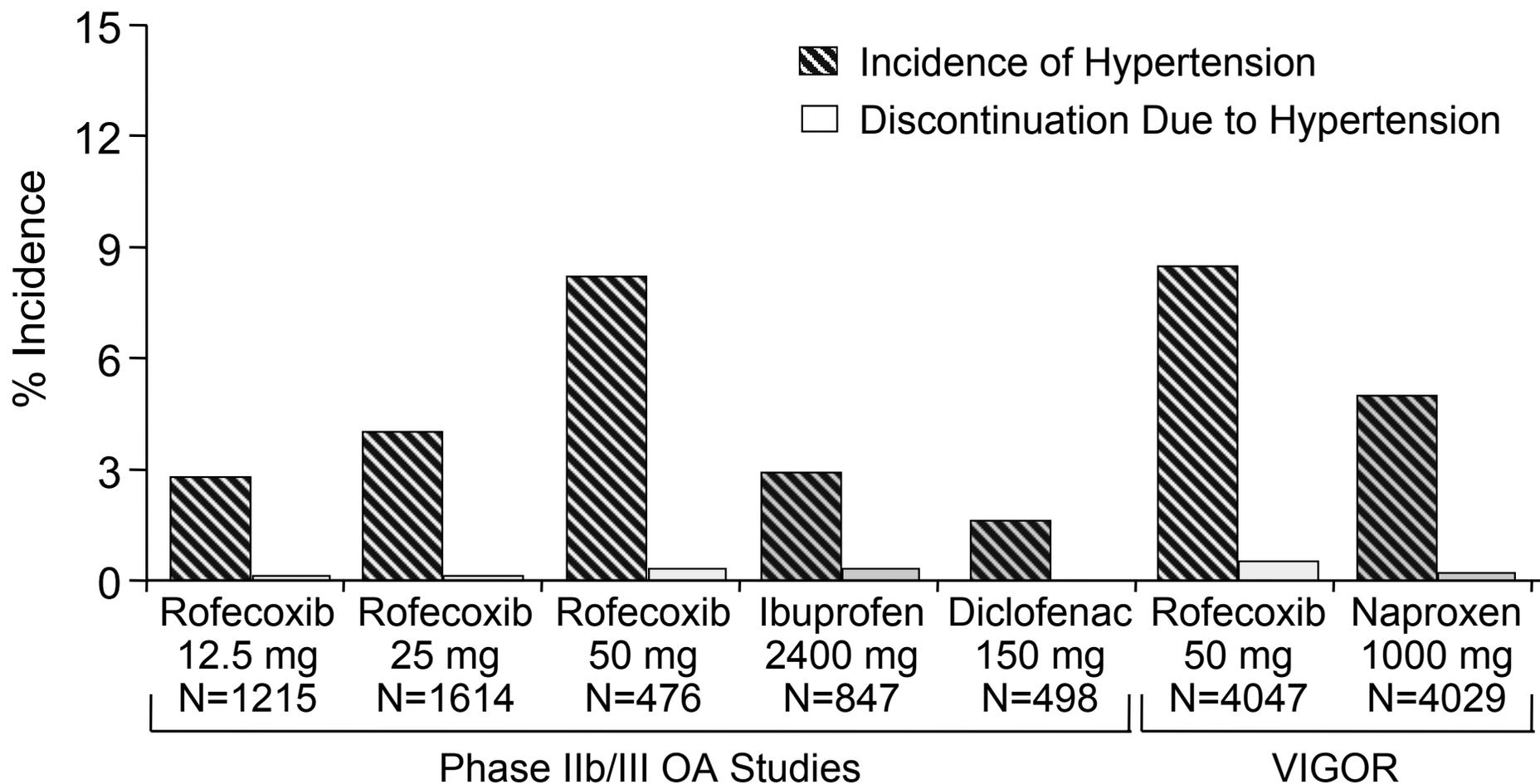
<u>Type of Adverse Experience (AE)</u>	<u>Rofecoxib 50 mg N=4047 %</u>	<u>Naproxen 1000 mg N=4029 %</u>
Discon. due to digestive system (including abdominal pain) AE	7.6	10.3*
Discon. due to edema-related AE	0.6	0.3
Discon. due to hypertension-related AE	0.7	0.1*
Congestive heart failure AE	0.5	0.2
Discon. due to renal-related AE	0.2	0.2
Discon. due to hepatic-related AE	0.2	0.1

* Indicates $p < 0.05$.

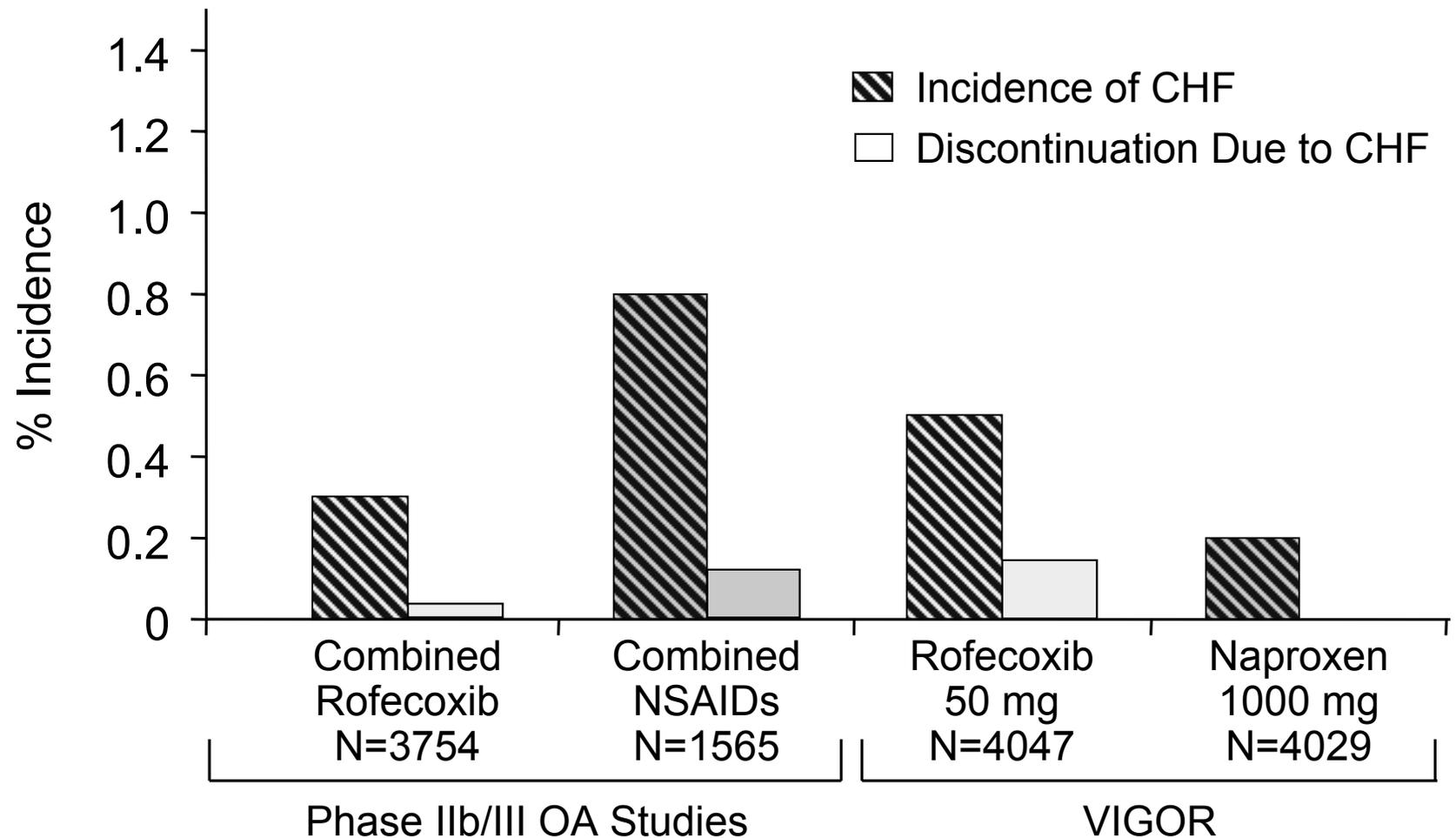
Lower Extremity Edema Incidence and Discontinuation Rate



Hypertension Incidence and Discontinuation Rate



Incidence of Congestive Heart Failure Adverse Experiences



Discontinuation Due to Renal and Hepatic Adverse Experiences

	Rofecoxib 50 mg N=4047 %	Naproxen 1000 mg N=4029 %
Renal AE*	0.2	0.2
Hepatic AE**	0.2	0.1

* Includes creatinine increased, BUN increased, renal failure and renal insufficiency.

**Includes ALT increased, AST increased, hepatic disorder, hepatic failure, hepatic function abnormality, hepatitis and jaundice.

Patients Exceeding Predefined Limits of Change for Serum Creatinine and Transaminases

% Patients with Increase on Consecutive Occasions*

	<u>Rofecoxib 50 mg N=3971</u>	<u>Naproxen 1000 mg N=3979</u>
Serum Creatinine Increase ≥ 0.5 mg/dL from Baseline and $>$ Normal	0.2%	0.2%
ALT ≥ 3 x ULN	0.2%	0.0%
AST ≥ 3 x ULN	0.1%	0.0%

*Or once and associated with discontinuation.

Rofecoxib General Safety Summary Phase IIb/III OA and VIGOR

- Generally well tolerated
- Superior GI tolerability compared with nonselective NSAIDs
- Incidence of renovascular adverse experiences
 - Similar to NSAIDs within the clinical dose range
 - Increased incidence with 50 mg
 - Discontinuations were rare
 - Increased creatinine is rare and similar to NSAIDs
- Incidence of LFT abnormalities
 - Similar to naproxen and ibuprofen and less than diclofenac

Overview

- Gastrointestinal Outcome Analyses
 - Rheumatoid Arthritis Outcome Study (VIGOR)
 - Phase IIb/III Osteoarthritis Analysis
- Demonstration of Efficacy in VIGOR
- General Safety
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Effects of NSAIDs and COX-2 Inhibitors on Thromboxane and Prostacyclin Synthesis

- Aspirin mediates near complete inhibition of platelet aggregation *throughout* its dosing interval
- All nonselective NSAIDs inhibit platelet aggregation
 - Most nonselective NSAIDs do not produce sustained inhibition of platelet aggregation
 - Naproxen inhibits platelet aggregation by ~ 90% throughout its dosing interval (similar to aspirin)
 - COX-2 selective inhibitors do not inhibit platelet aggregation
- Both nonselective NSAIDs and COX-2 inhibitors reduce the excretion of urinary metabolites of prostacyclin by 40-70%

The Role of COX-1 and COX-2 Inhibition on Thromboxane and Prostacyclin Synthesis

- By inhibiting platelet function, can some NSAIDs have aspirin-like cardioprotective properties?
 - Would differences be expected between NSAIDs based on the COX-1/COX-2 ratio and pharmacokinetics of the drugs?
- What are the clinical implications of inhibition of systemic prostacyclin synthesis without antiplatelet activity?

To address these issues

- SOP established after the completion of the Phase IIb/III OA studies and prior to VIGOR to capture and adjudicate cardiovascular events in all COX-2 inhibitor studies

Cardiovascular Thrombotic Endpoints

- Thrombotic serious cardiovascular events
 - Confirmed Thrombotic Cardiovascular Events
 - events confirmed by a blinded CV adjudication committee
 - Investigator Reported Thrombotic Cardiovascular Events
 - all serious events reported by the investigator
 - APTC Endpoint (Antiplatelet Trialists' Collaboration)*
 - cardiovascular and unknown cause of death (includes hemorrhagic deaths)
 - myocardial infarctions
 - cerebrovascular accident

*Collaborative overview of randomised trials of antiplatelet therapy--I. Antiplatelet Trialists' Collaboration. *BMJ*. 1994 Jan 8;308(6921):81-106.

Cardiovascular Safety Overview

- VIGOR cardiovascular results
- Cardiovascular safety in other rofecoxib studies
 - Phase IIb/III OA combined analysis
 - Alzheimer's and Mild Cognitive Impairment studies
- Meta-analysis of Phase IIb-V studies

The risk of sustaining a cardiovascular thrombotic event is similar on rofecoxib, placebo and nonselective NSAIDs without sustained antiplatelet activity.

VIGOR

Confirmed Thrombotic Cardiovascular Events

Patients with Events (Rates per 100 Patient-Years)

<u>Event Category</u>	<u>Rofecoxib N=4047</u>	<u>Naproxen N=4029</u>	<u>Relative Risk (95% CI)</u>
Confirmed CV events	45 (1.7)	19 (0.7)	0.42 (0.25, 0.72)
Cardiac events	28 (1.0)	10 (0.4)	0.36 (0.17, 0.74)
Cerebrovascular events	11 (0.4)	8 (0.3)	0.73 (0.29, 1.80)
Peripheral vascular events	6 (0.2)	1 (0.04)	0.17 (0.00, 1.37)

Lack of Association Between Hypertension Adverse Experiences and Confirmed Thrombotic CV Events

- Only 4 patients on rofecoxib reported a hypertension adverse experience prior to a thrombotic adverse experience
 - 1 deep vein thrombosis, 2 cerebrovascular accidents, 1 myocardial infarction
- Changes from baseline in blood pressure were similar in rofecoxib patients who had CV events compared with patients who did not have CV events

VIGOR Cardiovascular Summary

- Decreased incidence of serious thrombotic cardiovascular events on naproxen compared with rofecoxib
- Was the imbalance in cardiovascular events due to
 - A decrease in events on a platelet inhibiting NSAID?
 - An increase in events on a COX-2 selective inhibitor?

Cardiovascular Safety in Other Rofecoxib Studies

- VIGOR cardiovascular results
- Cardiovascular safety in other rofecoxib studies
 - Phase IIb/III OA combined analysis
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Phase IIb/III OA Studies

- Treatment groups
 - Rofecoxib
 - Combined NSAID group (diclofenac, ibuprofen and nabumetone)
 - Placebo
- Diclofenac, ibuprofen and nabumetone do not maintain >90% inhibition of platelet function (aggregation) throughout their dosing interval
 - Would not be effective anti-thrombotic agents

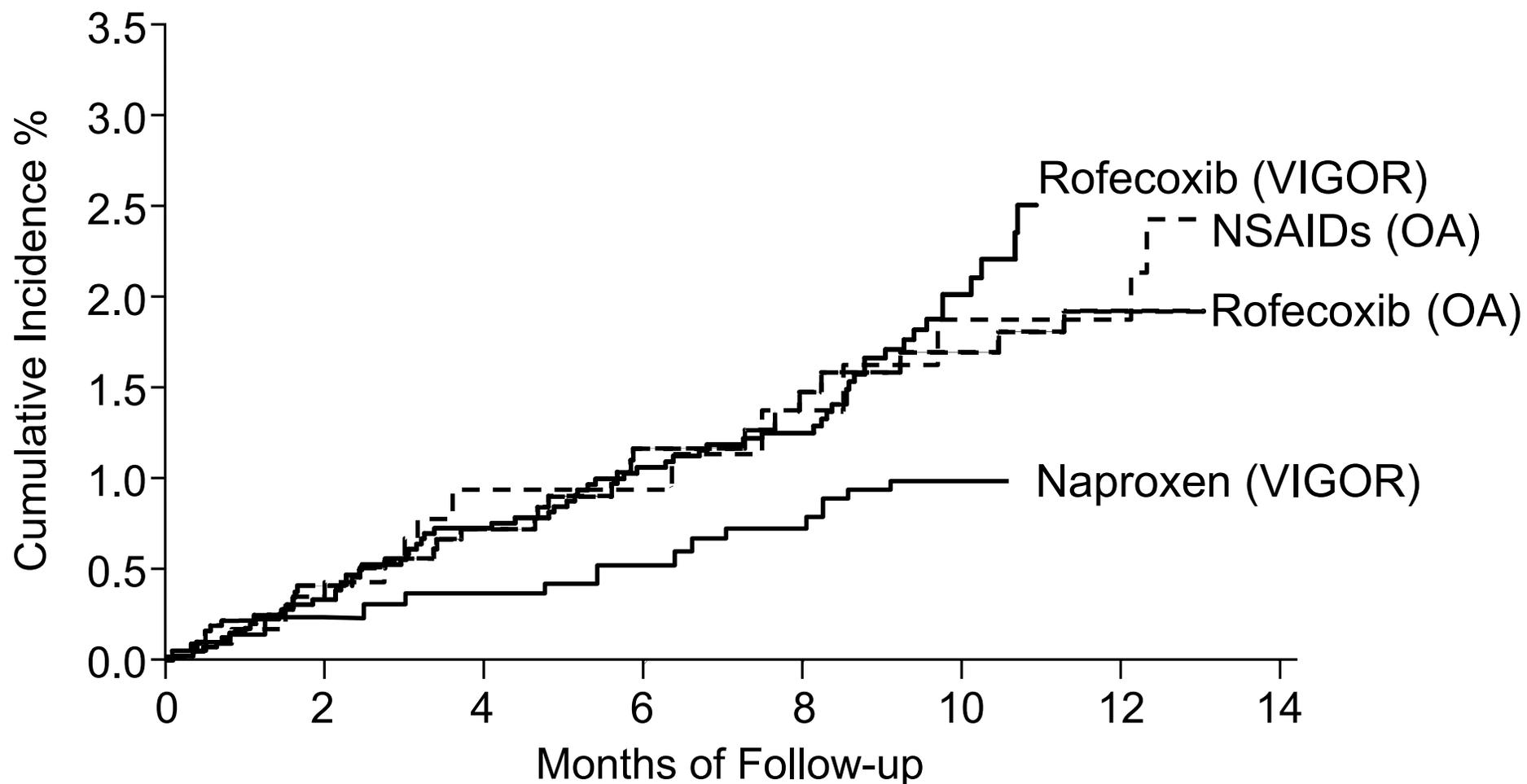
Investigator Reported Thrombotic Cardiovascular Events in Phase IIb/III OA Clinical Studies

Rates per 100 Patient-Years (Number of Events)

<u>Event</u>	<u>Rofecoxib N=3357</u>	<u>NSAIDs* N=1564</u>
Investigator-reported cardiovascular events	2.0 (34)	2.3 (16)
	<u>Rofecoxib N=1701</u>	<u>Placebo N=514</u>
Investigator-reported cardiovascular events	2.5 (9)	2.4 (3)

*Diclofenac, ibuprofen and nabumetone.

Investigator-Reported Thrombotic Cardiovascular Events in the VIGOR Study Compared with Phase IIb/III OA Study



Cardiovascular Safety in Other Rofecoxib Studies

- VIGOR cardiovascular results
- Cardiovascular safety in other rofecoxib studies
 - Phase IIb/III OA combined analysis
 - Alzheimer's and Mild Cognitive Impairment studies
- Meta-analysis of Phase IIb-V studies

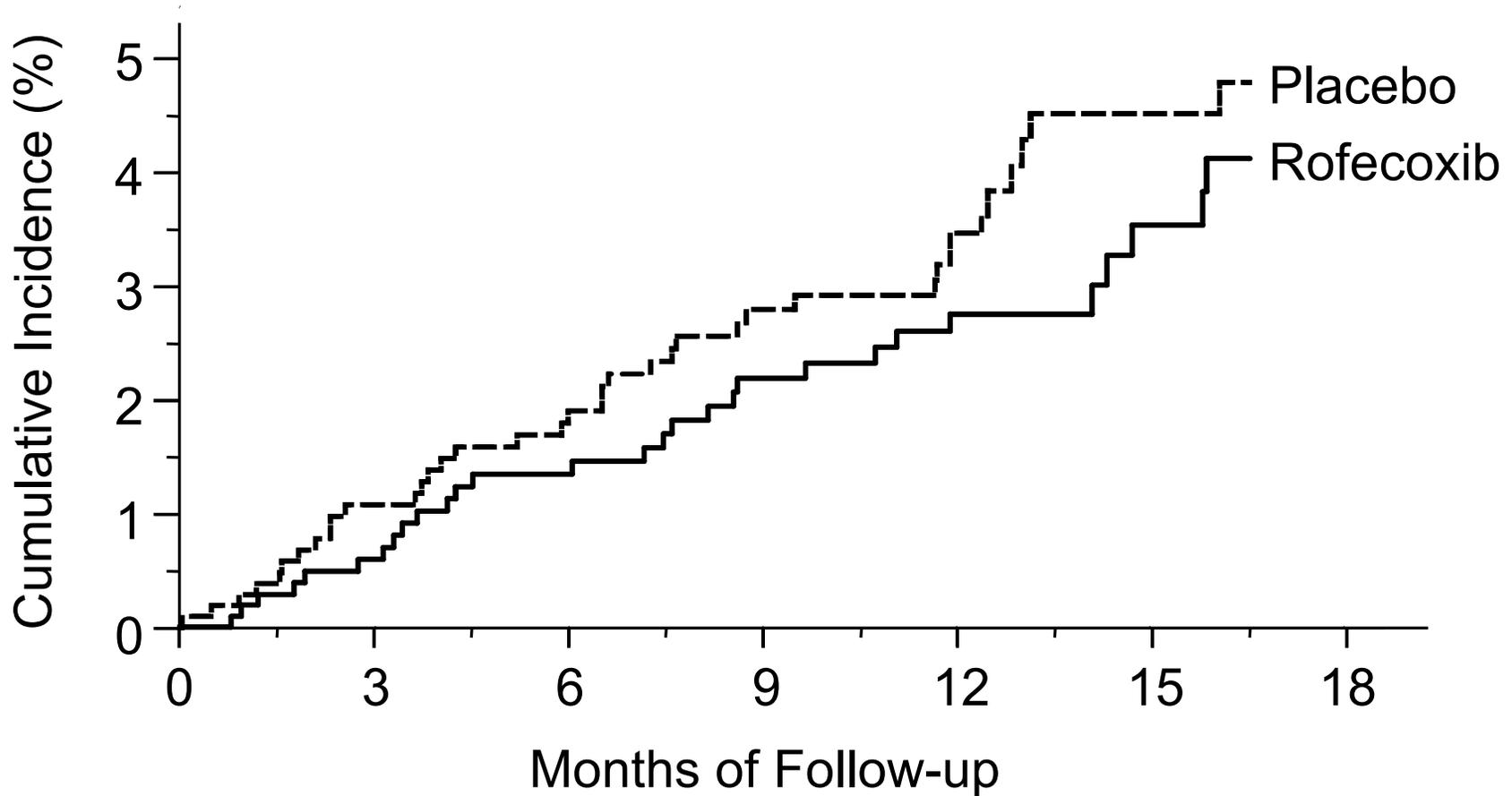
Alzheimer's Disease and Mild Cognitive Impairment Studies

- Combined analysis of two large placebo-controlled studies in patients with MCI and Alzheimer's
 - 25 mg rofecoxib vs. placebo
 - high-risk elderly patient population
- As of September, 2000:
 - >1000 patients and ~1200 patient-years in each treatment group
 - Median duration of therapy: 12.5 months

Investigator-Reported Thrombotic Cardiovascular Events in Alzheimer's and Mild Cognitive Impairment Studies

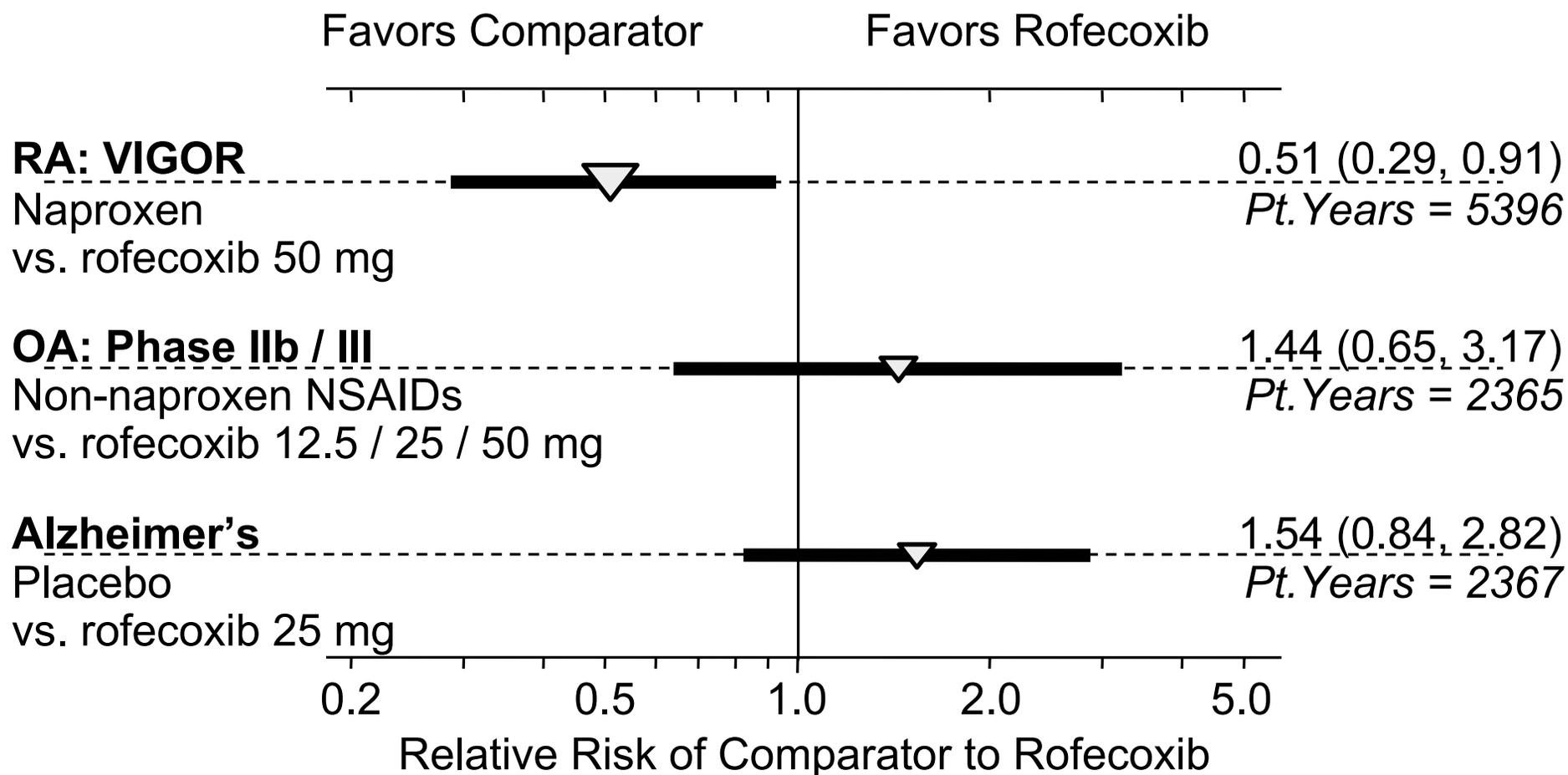
Rofecoxib N=1041		Placebo N=1050	
<u>No. of Events</u>	<u>Rates per 100 Patient-Years</u>	<u>No. of Events</u>	<u>Rates per 100 Patient-Years</u>
32	2.8	40	3.3

Investigator Reported Thrombotic Cardiovascular Events in the Alzheimer's Studies



Relative Risk of APTC Events in Rofecoxib Studies

Relative Risk of APTC Endpoint with 95% CI



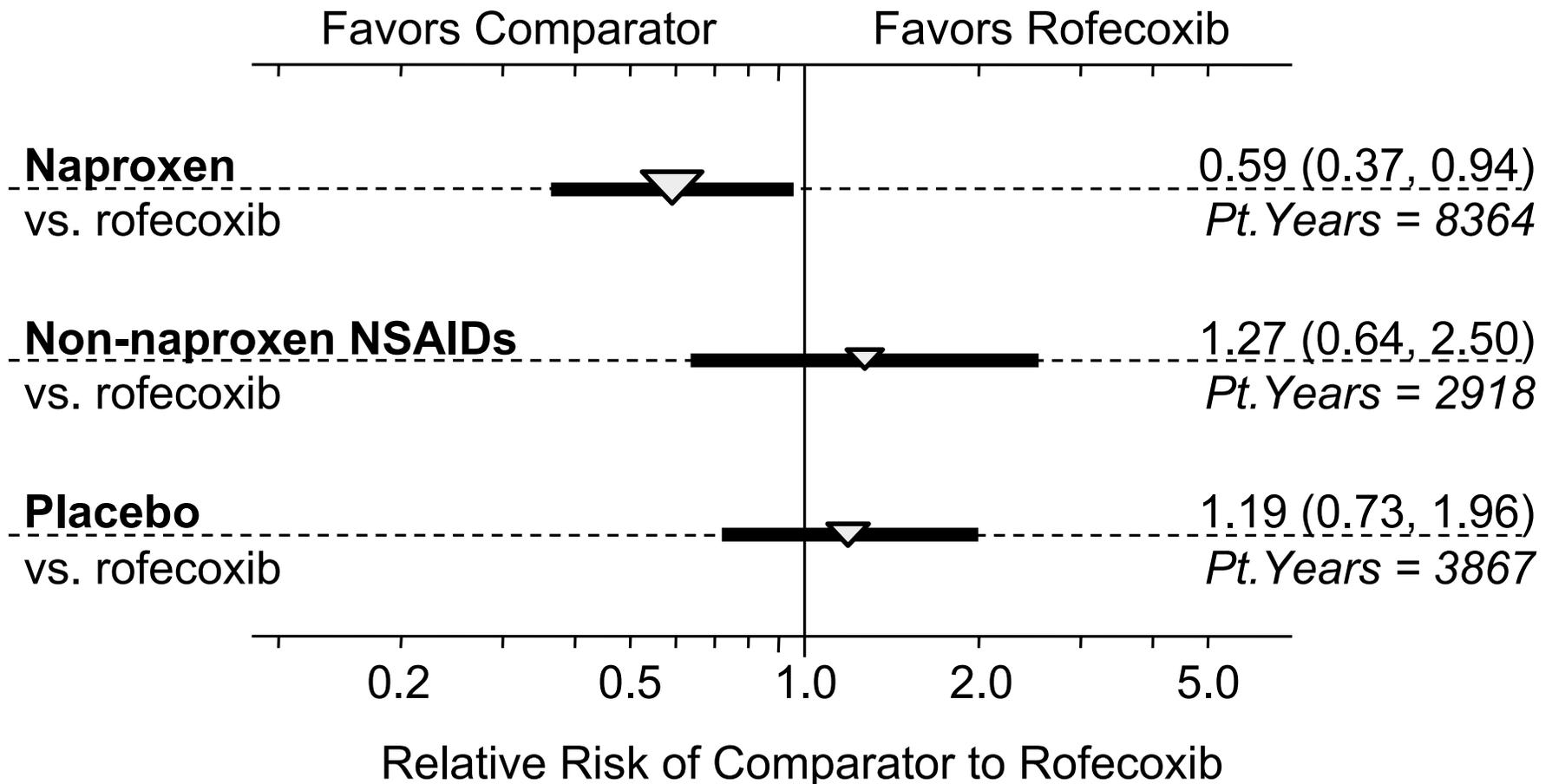
Cardiovascular Safety in Other Rofecoxib Studies

- Clinical pharmacology studies
- VIGOR cardiovascular results
- Cardiovascular safety in other rofecoxib studies
 - Phase IIb/III OA combined analysis
 - Alzheimer's and Mild Cognitive Impairment studies
- Meta-analysis of Phase IIb-V studies

Cardiovascular Meta-Analysis

- Phase IIb-V rofecoxib studies ≥ 4 weeks duration and completed by September 2000
 - Except Alzheimer's studies - interim data used
- APTC endpoint
- Includes data on >28,000 patients and >14,000 patient-years

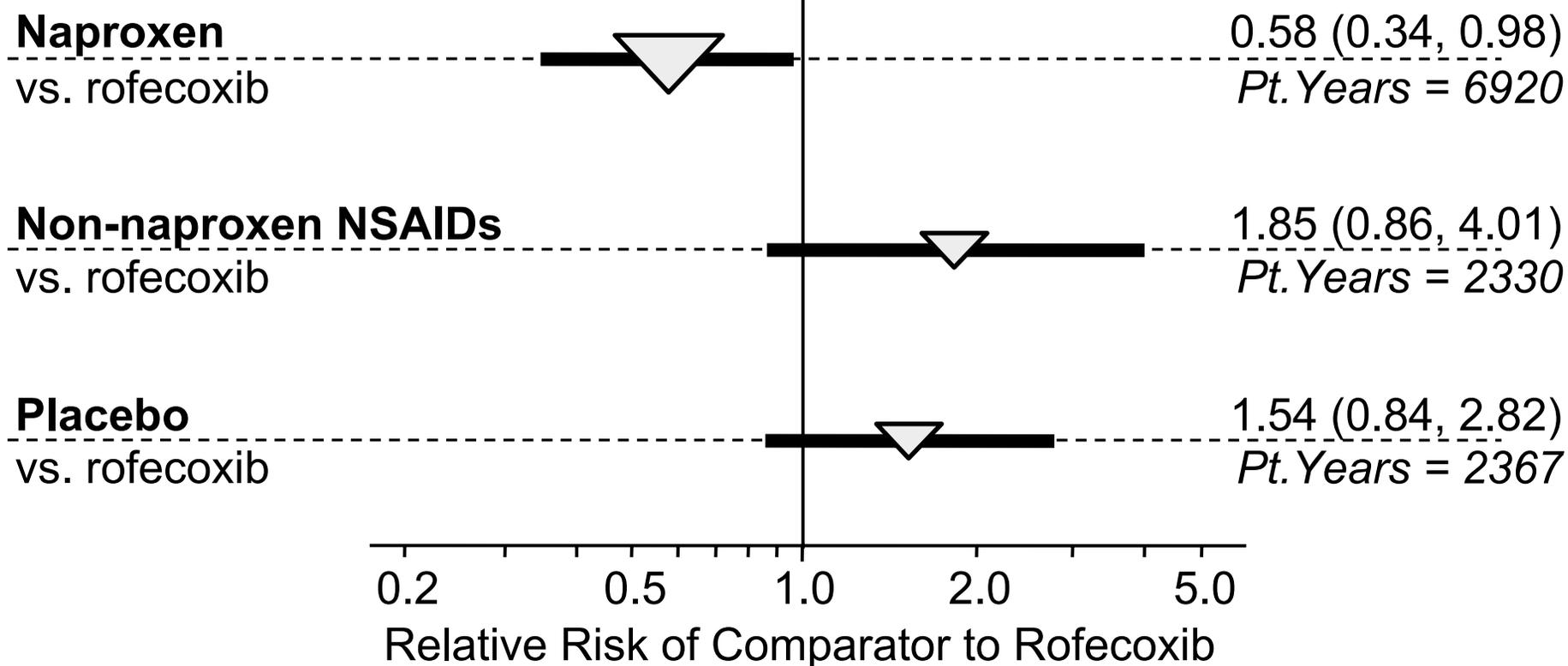
Relative Risk of an APTC Event in Patients Treated with Placebo or NSAIDs vs. Rofecoxib



Relative Risk of an APTC Event in Patients Treated with Placebo or NSAIDs vs. Rofecoxib

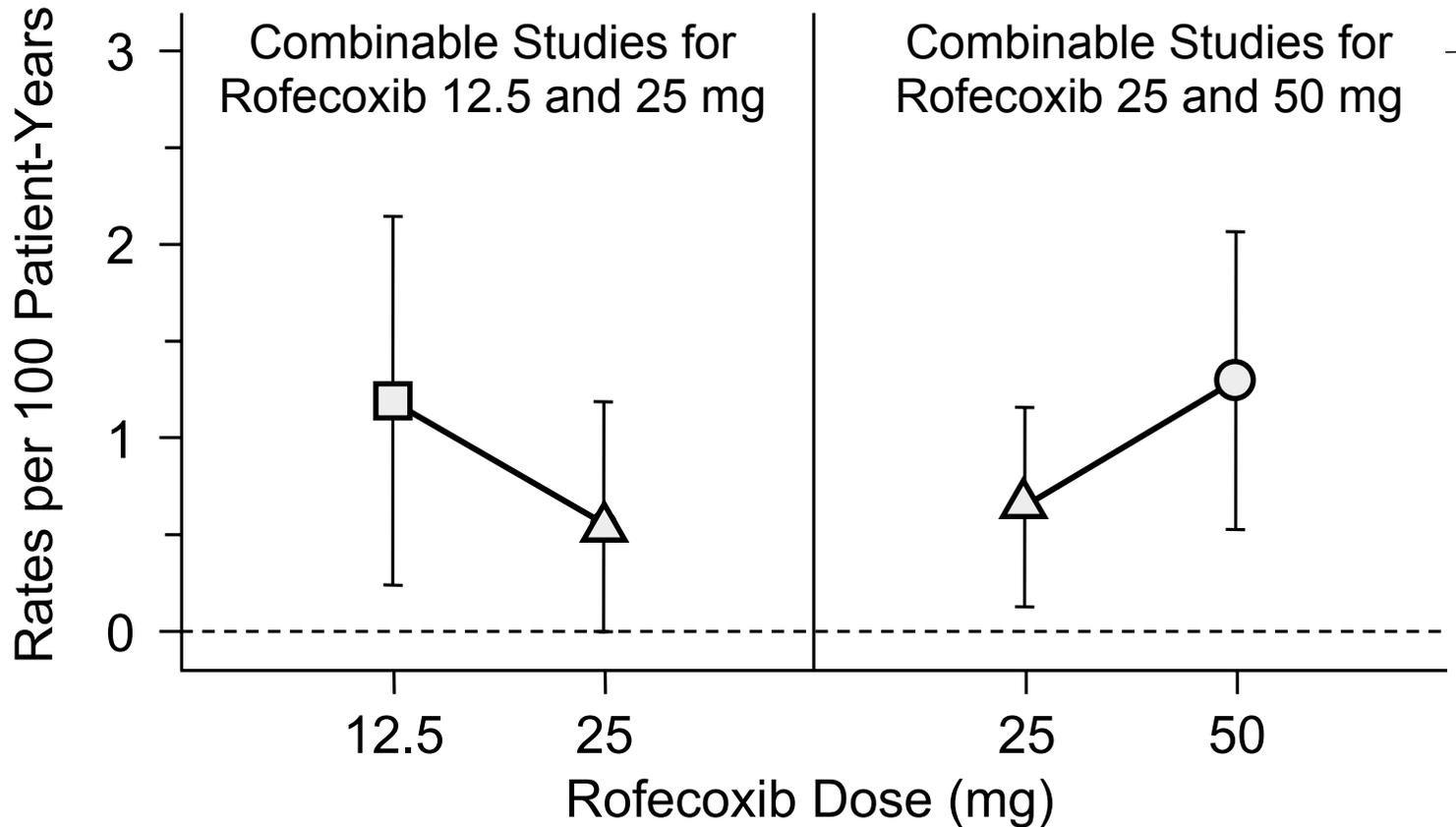
In Studies of at Least 6 Months Duration

Favors Comparator Favors Rofecoxib



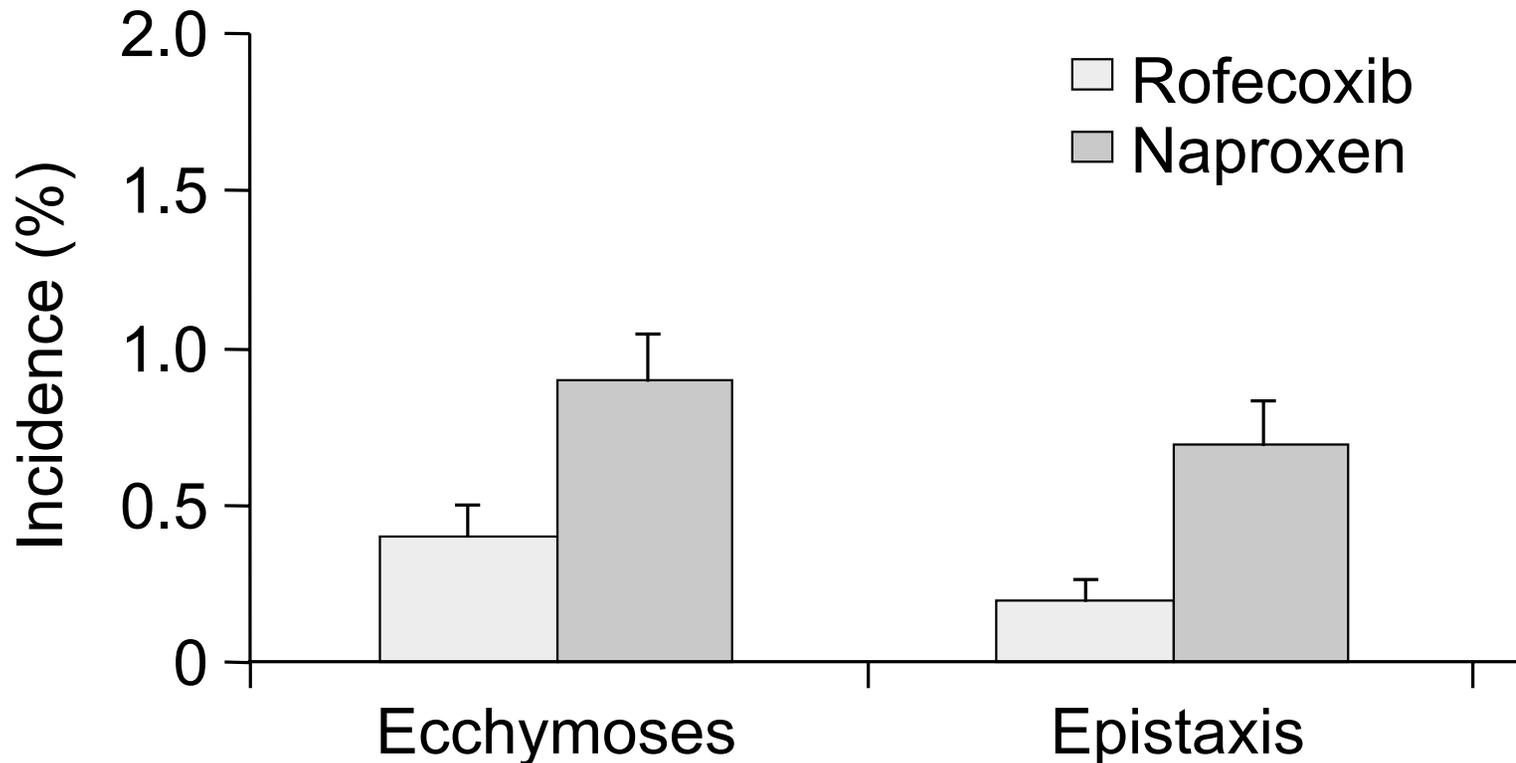
APTC Endpoint Stratified By Dose in Trials of 6 Months or Longer

Rates Per 100 Patient-Years with 95% CI



Bleeding Adverse Experiences of Non-GI Origin in VIGOR

Potentially Related to Antiplatelet Effects



Weight of Evidence for Cardioprotective Effect of Naproxen

- Preclinical pharmacology
 - Naproxen had antithrombotic efficacy similar to aspirin
- Clinical pharmacology
 - Aspirin-like inhibition of thromboxane synthesis and platelet aggregation
 - Aspirin-like increases in bleeding time
- Randomized clinical trials
 - Studies of indobufen and flurbiprofen show that non-selective NSAIDs that mediate potent, sustained antiplatelet effects are cardioprotective
 - Incidence of CV events comparable across all treatment arms, except naproxen, in large rofecoxib studies
 - Increased incidence of aspirin-like bleeding AEs in VIGOR
- Epidemiology
 - Lower CV risk in RA patients on naproxen in General Practice Database

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Overall Summary

- Rofecoxib is a COX-2 inhibitor without effects on COX-1 at and above the clinical doses
- Rofecoxib demonstrates analgesic and anti-inflammatory efficacy similar to nonselective NSAIDs in OA and acute pain
- Rofecoxib is associated with significantly fewer clinically important GI events compared with nonselective NSAIDs
 - Demonstrated independently in OA and RA
 - Consistent significant reductions in all endpoints
 - Consistent reductions in high and low risk subgroups
 - Consistent with endoscopic study results

General Safety Summary

- Rofecoxib is generally well tolerated in all patient populations studied
- The renal effects of COX-2 inhibitors are similar to nonselective NSAIDs and consistent with currently approved labeling
 - Discontinuations are rare
 - Differences between 50-mg rofecoxib and 1000-mg naproxen in mechanism-based, dose-dependent adverse events were consistent with the dose disparity
- Low incidence of transaminase elevations

Cardiovascular Safety Summary

- Risk of CV events on rofecoxib is similar to placebo and NSAIDs without sustained and nearly complete inhibition of platelet function
- Decreased CV events with naproxen in VIGOR consistent with its potent antiplatelet effects
- Cardiovascular results are consistent with rofecoxib's COX-2 selectivity and lack of antiplatelet activity

Overall Conclusions

- The COX-2 selective inhibitor rofecoxib has demonstrated
 - Efficacy similar to NSAIDs in OA and acute pain
 - Significantly improved GI safety compared to NSAIDs
 - Effects on renal sodium handling similar to NSAIDs
 - Risk for sustaining a thrombotic CV event is similar to placebo
- The COX-2 hypothesis has been confirmed and these data warrant modification to the current rofecoxib label to distinguish the GI safety profile of rofecoxib compared with nonselective NSAIDs