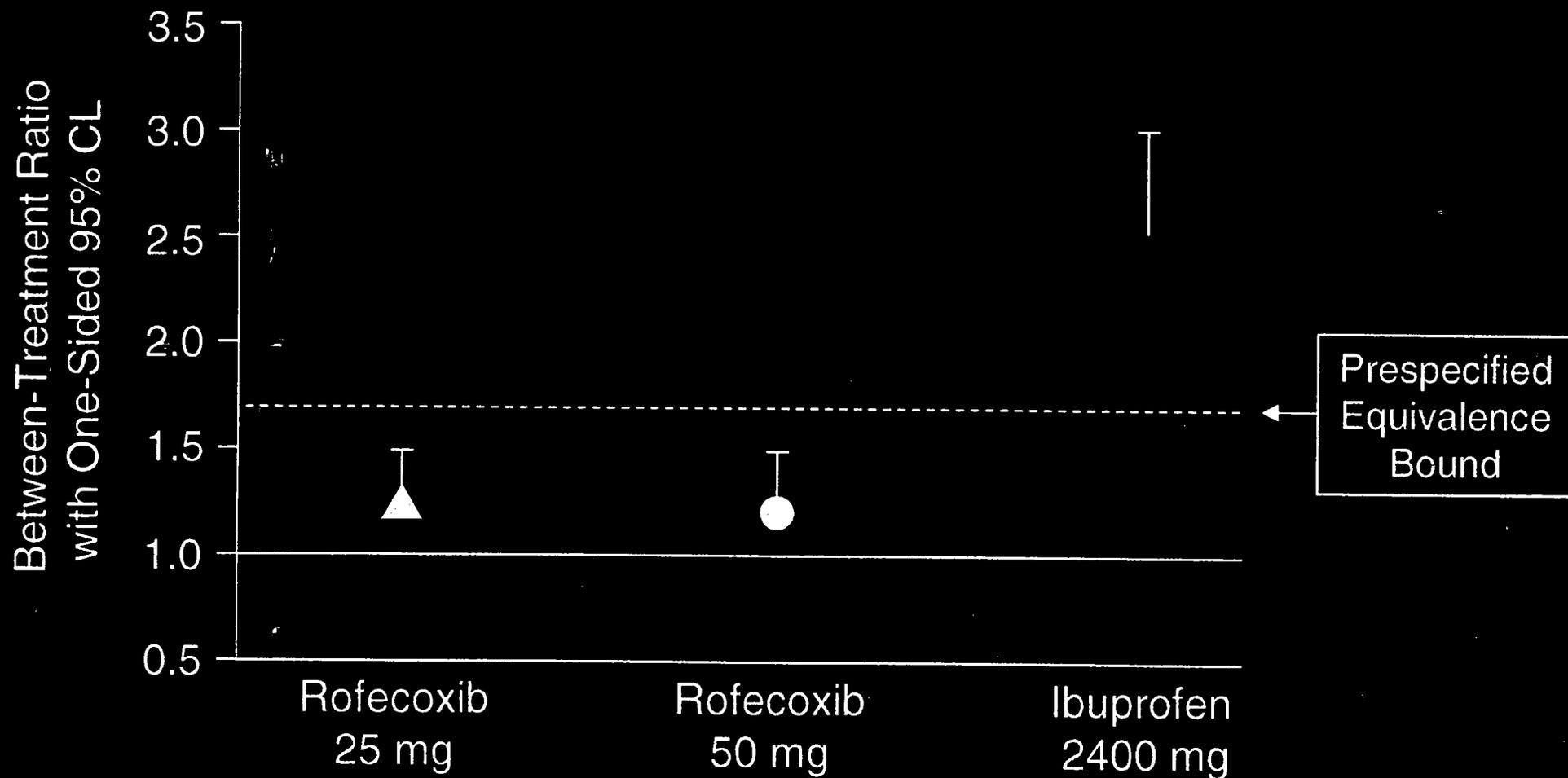


Fecal Red Blood Cell Loss

- Fecal excretion of ^{51}Cr , after re-infusing labeled red blood cells
- Rofecoxib 25 mg and 50 mg
 - Superior to ibuprofen 800 mg three times daily (statistically significant)
 - Statistically equivalent to placebo

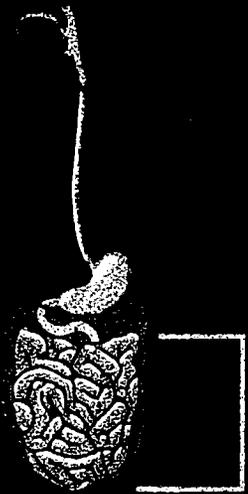


Fecal Red Blood Cell Loss Prespecified Comparison with Placebo

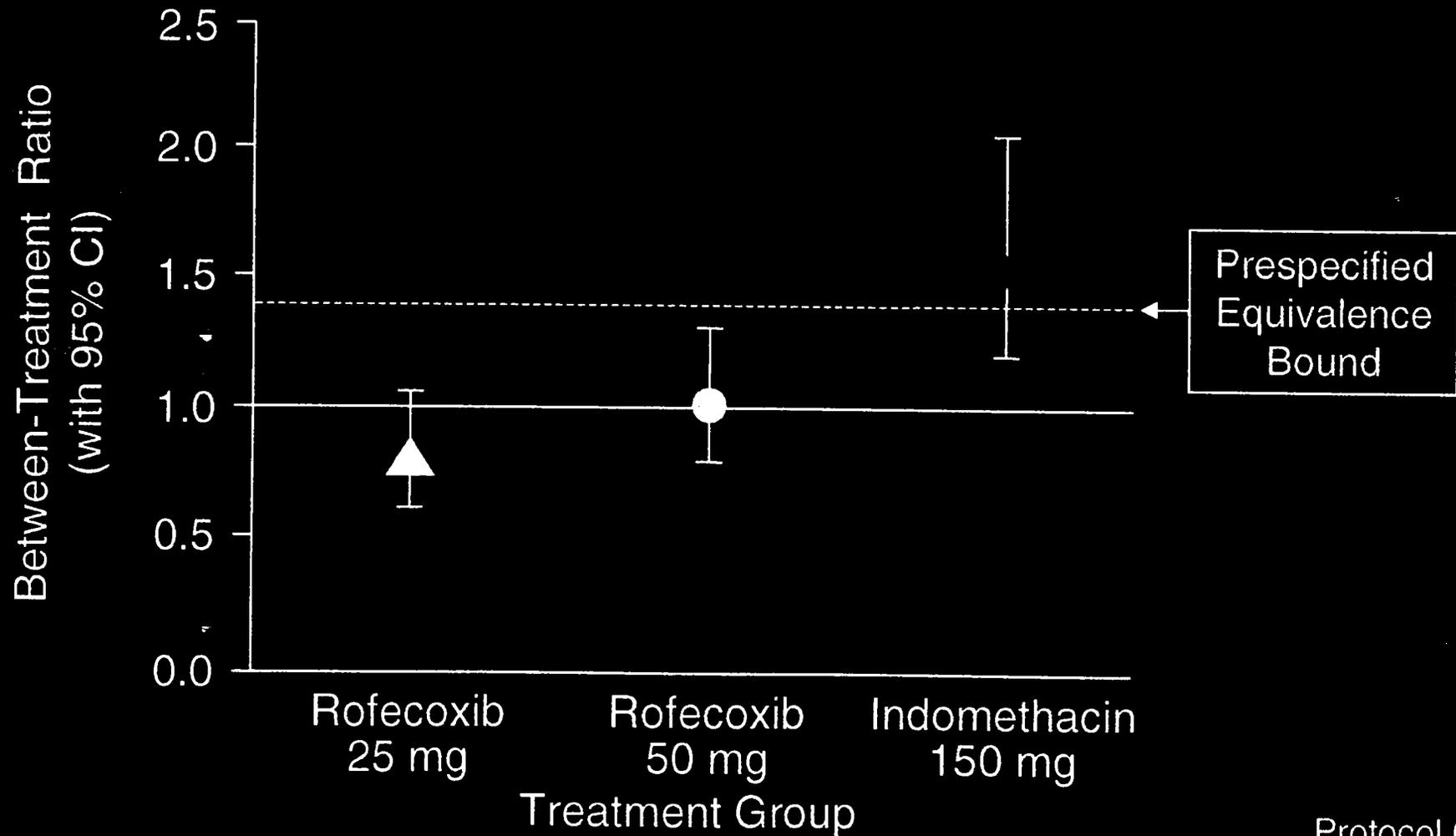


Intestinal Permeability Study

- Appearance of orally ingested marker substance in urine
- Rofecoxib 25 mg and 50 mg
 - Superior indomethacin (statistically significant)
 - Statistically equivalent to placebo



Intestinal Permeability Study Prespecified Comparison with Placebo



Overall Conclusions - GI Studies

- Endoscopic gastroduodenal erosion/ulceration
 - 250 mg superior to NSAID, numerically similar to placebo (healthy subjects)
- Endoscopic gastroduodenal ulceration
 - 25 mg and 50 mg superior to ibuprofen 800 mg three times daily (OA patients)
 - 25 mg statistically equivalent to placebo (OA patients)

Overall Conclusions - GI Studies (Cont'd)

- Special GI safety (healthy subjects)
 - 25 mg and 50 mg superior to NSAID, statistically equivalent to placebo
 - Fecal Red Blood Cell Loss
 - Intestinal Permeability

Rofecoxib GI Safety Program

Phase I/II Clinical Studies

Phase III Clinical Data

Phase III Clinical Data



Phase III Clinical Data

Phase III Clinical Data

Phase III Clinical Data



Combined GI, Efficacy Studies In OA Patients³

- Upper GI Symptoms
- Upper GI Clinical Events
(Prespecified Clinical Outcomes)

Combined Analysis of Osteoarthritis Trials

- Upper GI Symptoms

• *Medication-induced upper GI symptoms (MUGIS)*

• *Adverse events*

• *Adverse effects*

• *Population analysis*

• *Subgroup analysis*

• *Post hoc analysis of P-values*

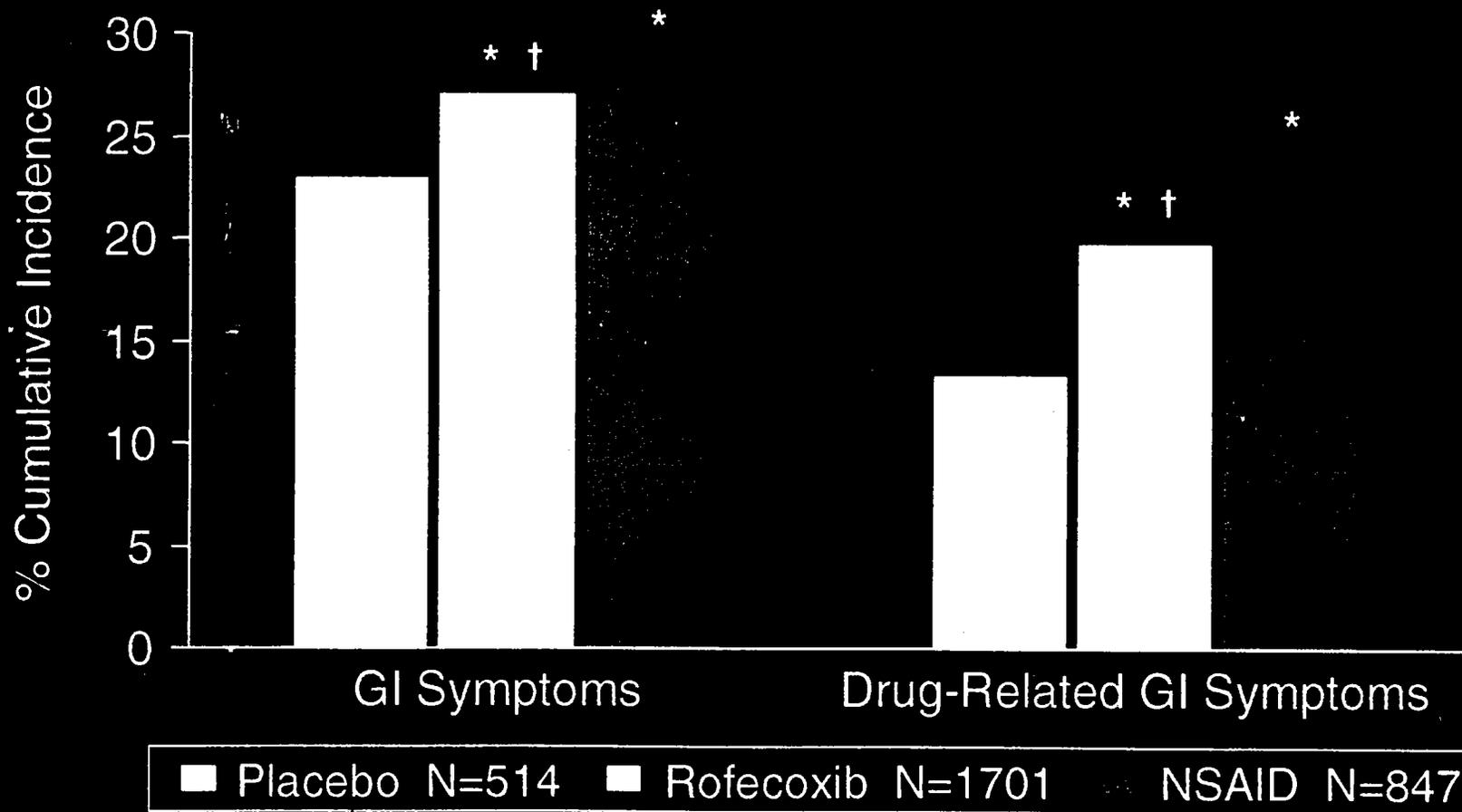
Studies Combined for Analysis

- All Phase IIb/III studies
 - Dose ranging, efficacy, endoscopy
- 5435 patients who received:
 - Rofecoxib 12.5 mg, 25 mg, 50 mg (N=3357)
 - Diclofenac, ibuprofen, or nabumetone (N=1564)
 - Placebo (N=514)

Up to 4 months

Predefined Analyses of Prespecified GI Symptoms

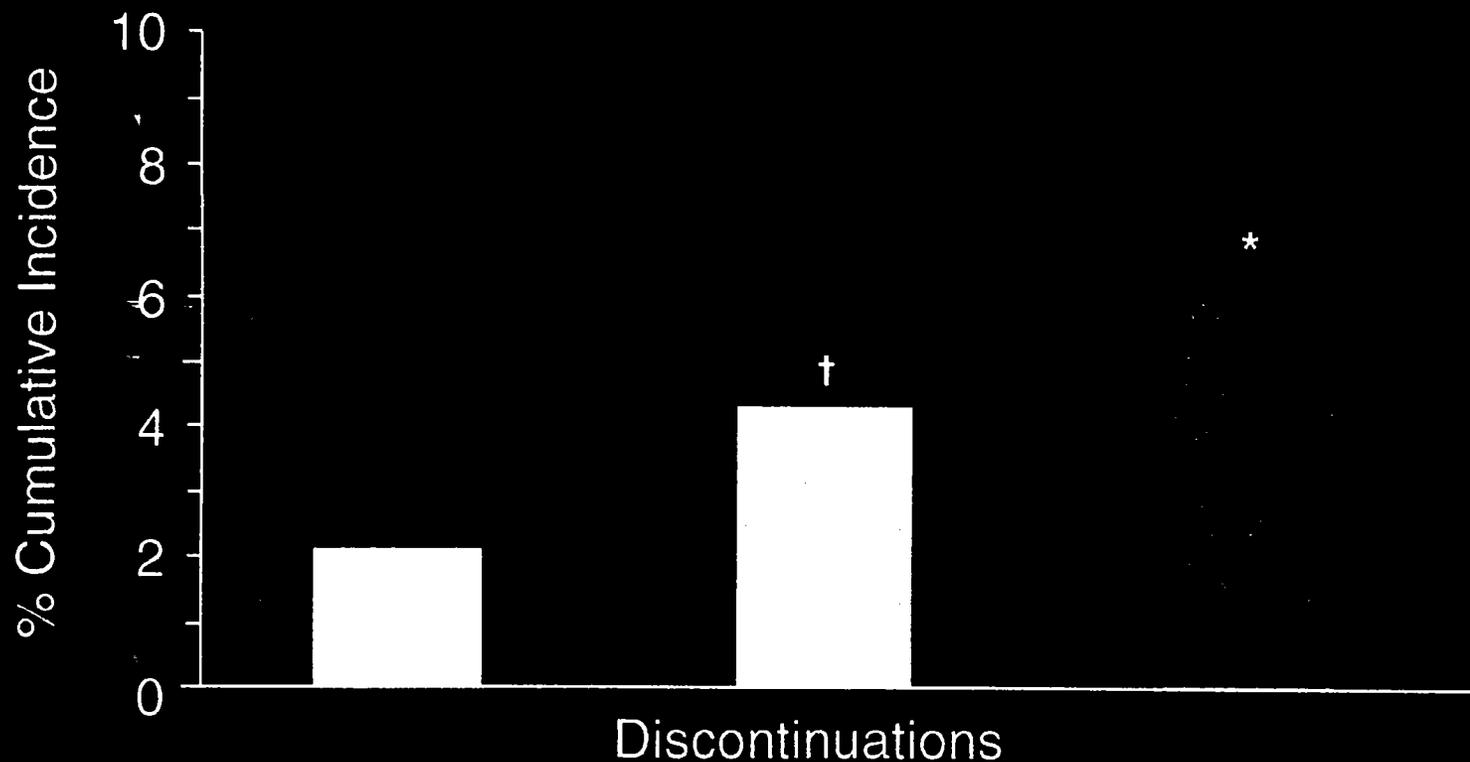
Acid Reflux, Dyspepsia, Epigastric Discomfort, Heartburn, Nausea, and Vomiting



* p < 0.05 compared to placebo. † p < 0.05 rofecoxib vs. NSAID.

Predefined Analyses of GI Symptoms Discontinuation Due to Any GI Adverse Events

Predefined Analyses of GI Symptoms Discontinuation Due to Any GI Adverse Events



■ Placebo N=514 ■ Rofecoxib N=1701 ■ NSAID N=847

* p < 0.05 compared to placebo. † p < 0.05 rofecoxib vs. NSAID.

Symptom Adverse Events and Mucosal Lesions

Acid Reflux, Dyspepsia, Epigastric Discomfort, Heartburn, Nausea, and Vomiting
+ Abdominal Pain

- Presence of symptom adverse event in week prior to endoscopy was a poor predictor of mucosal lesions
 - Gastroduodenal ulcers in endoscopy studies
Positive predictive value: 0.26
 - Esophageal score ≥ 2 in endoscopy studies
Positive predictive value: 0.10

Conclusions, Combined Analysis of Upper GI symptoms

- Predefined analyses of spontaneously reported upper GI symptom adverse events, discontinuation due to GI adverse events
 - Placebo < Rofecoxib < NSAIDs
- Presence of upper GI symptoms: poor predictor of mucosal lesions

Combined Analysis of Osteoarthritis Trials

• Upper GI Symptoms

- Perforations, ulcers, bleeds (PUBs)

• Intestines

• Pancreas

• Liver and gallbladder

• Kidneys and bladder

• Post hoc analyses of trials

Spectrum of NSAID-Induced Upper GI Injury

- Gastroduodenal ulcers (≥ 3 mm; ≥ 5 mm) detected during endoscopic surveillance
 - Endoscopy studies

“PUB”

- **Symptomatic clinical ulcers**
- **Ulcer complications: Perforations (rare), obstructions (rare), bleeding [“POB”]**

* Standard NSAID Warning

“Serious GI toxicity such as **bleeding, ulceration, and perforation** can occur at any time, with or without warning symptoms”

Combined Analysis of PUBs

- Primary hypothesis: Lower incidence of upper GI perforations, ulcers, and bleeds with rofecoxib vs. NSAID comparators
 - (PUBs = symptomatic ulcers + POBs)
- Primary endpoint: Confirmed cases only
 - Prespecified definitions
- Secondary endpoint: Investigator-reported cases

Combined Analysis of Osteoarthritis Trials

• Major GI Symptoms

- Perforations, ulcers, bleeds (PUBs)

- Database

- Handle

- Individual analyses

- Overall analysis

- Post hoc analyses of PUBs

PUB Case Review and Adjudication

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

Validity of Prespecified Combined Analysis of PUBs

- Biologically meaningful comparison: COX-2 inhibition versus non-specific NSAID
 - Small numbers of events expected within each protocol
- Predefined meta-analysis of all Phase IIB/III Osteoarthritis Trials (Same indication for treatment)
- Prespecified uniform case definition and uniform case adjudication by blinded external review committee
- Results not driven by any one protocol type
 - Omission of any one does not greatly alter the estimated common relative risk
 - Statistical criteria met for homogeneous effect (common relative risk) across protocol types

Combined Analysis of Osteoarthritis Trials

• Review of literature, 1980-1990 (1991)

• Objective

– Results

Predefined analyses

• Overall meta-analysis

• Subgroup analysis of RCTs

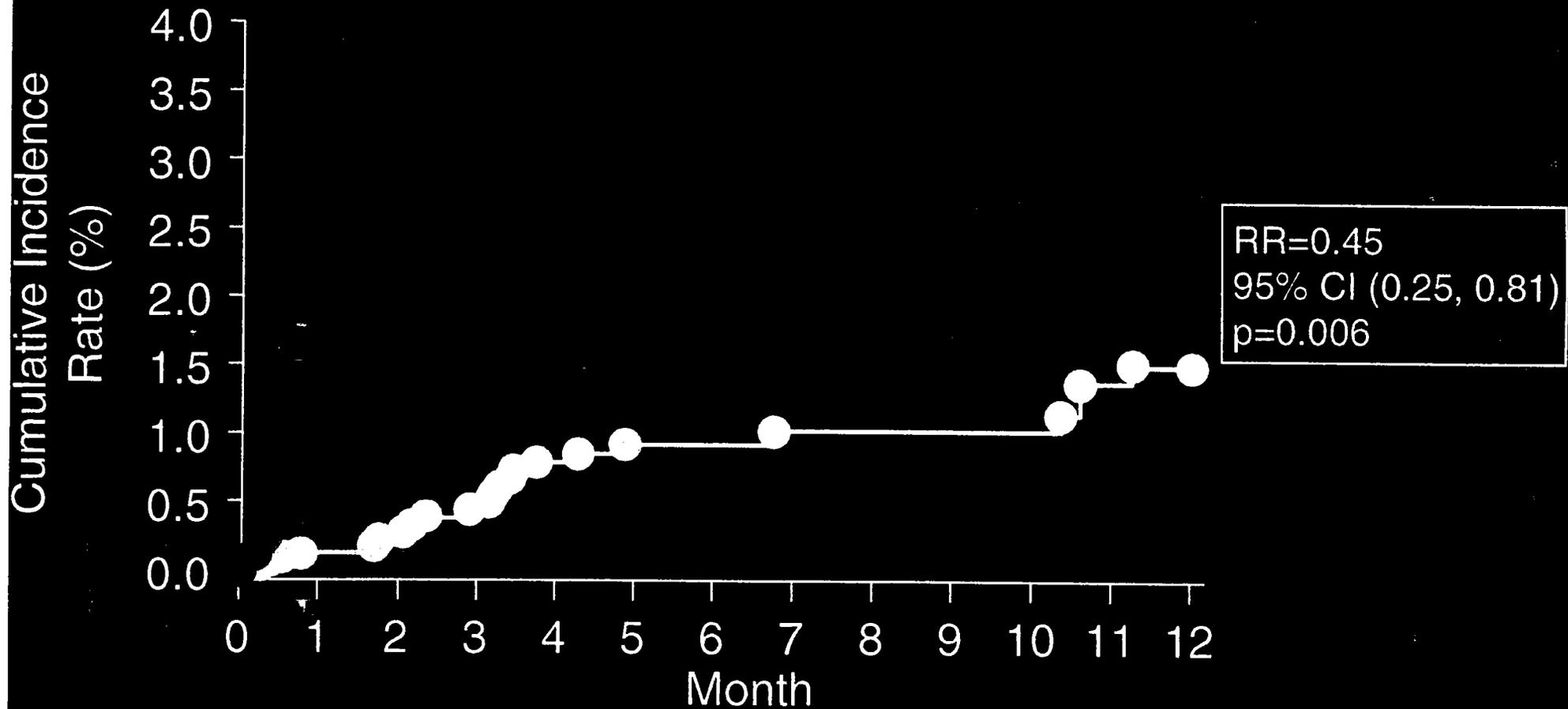
• Upper Extremities

Patients with Investigator-Reported PUBs

- 55 cases on treatment or within 14 days of discontinuation (prespecified)
 - 49 confirmed: primary endpoint
 - 39 symptomatic ulcers (2 with unconfirmed bleeds)
 - 0 perforations, 1 obstruction, 9 bleeds
 - 6 investigator-reported: secondary endpoint
 - Not confirmed by adjudication versus strict case definitions

All were bleeds

Confirmed Upper GI PUBs



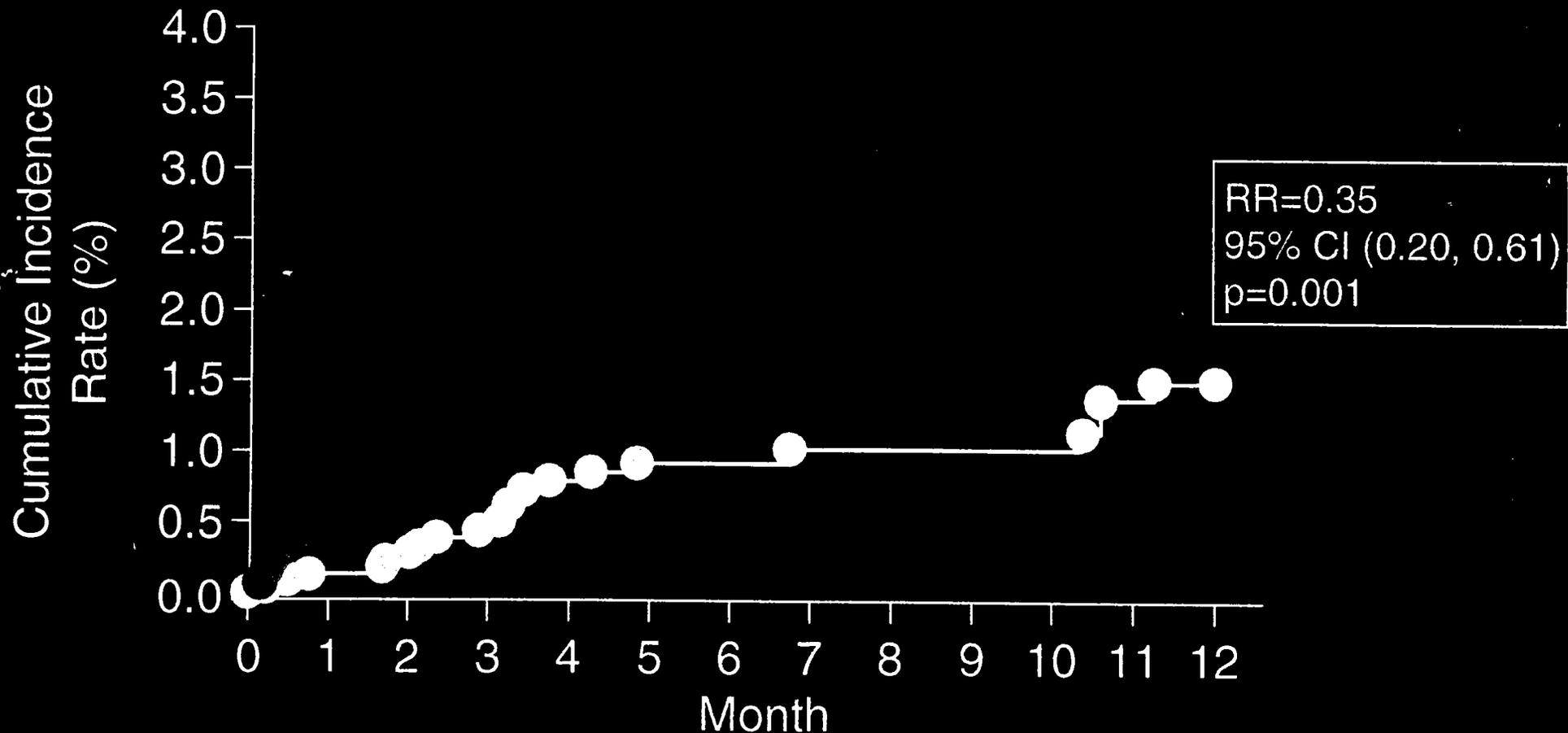
● Rofecoxib N=3357

○ NSAID Comparators N=1564

Protocol 069

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Investigator-Reported Upper GI PUBs



● Rofecoxib N=3357

● NSAID Comparators N=1564

Protocol 069

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PUBs in Placebo-Controlled Studies

<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