Presentation to 2005 Health Canada Expert Advisory Panel on COX-2 Inhibitors

Introduction

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Executive Director, Merck Frosst, Canada

Presentation to 2005 Health Canada Expert Advisory Panel on COX-2 Inhibitors

Review of Rofecoxib Safety

Speaker: Ned S. Braunstein, MD

Senior Director, Merck Research Labs

Outline of Merck Rofecoxib Presentation

- Overview
- Review of Rofecoxib Safety: GI
- Review of Rofecoxib Safety: Renovascular/CHF
- Review of Rofecoxib Safety: Thrombotic CV
- Implications of the Data

Overview: Key GI Observations with Rofecoxib

- Demonstrated reduction in clinical upper GI events vs. non-selective NSAIDs
  - Reduction vs. naproxen in VIGOR (outcomes study)
  - Consistent reduction vs. each of naproxen, ibuprofen, diclofenac
    - Pooled analysis of 20 OA/RA studies
- More upper GI events with rofecoxib than placebo
- Reduced incidence of lower GI events vs. naproxen in VIGOR

Overview: Key Renovascular and Thrombotic CV Safety Observations with Rofecoxib

- Renovascular effects (fluid retention/CHF, HTN) consistent with NSAID profile
- Clinical data on thrombotic CV events for rofecoxib show:
  - Increased risk relative to placebo
    - Seen with long-term use in APPROVe
  - Rates similar to non-naproxen NSAIDs
    - Long-term data limited
  - Increased risk compared to naproxen
    - Apparent after relatively short-term use

Overview: Key Public Health Questions

- What is risk/benefit of selective COX-2 inhibitors?
  - Relative to placebo
  - Relative to ibuprofen/diclofenac
  - Relative to naproxen
- Can we identify factors associated with observed increased risk for thrombotic CV events with these drugs?
- Is observed increased CV risk a class effect of COX-2 inhibition?
  - How big is the class?
  - What are long-term CV effects of traditional NSAIDs?

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- Review of Rofecoxib Safety: GI
  - VIGOR
  - Pooled analysis of OA and RA Studies
- Review of Rofecoxib Safety: Renovascular/CHF
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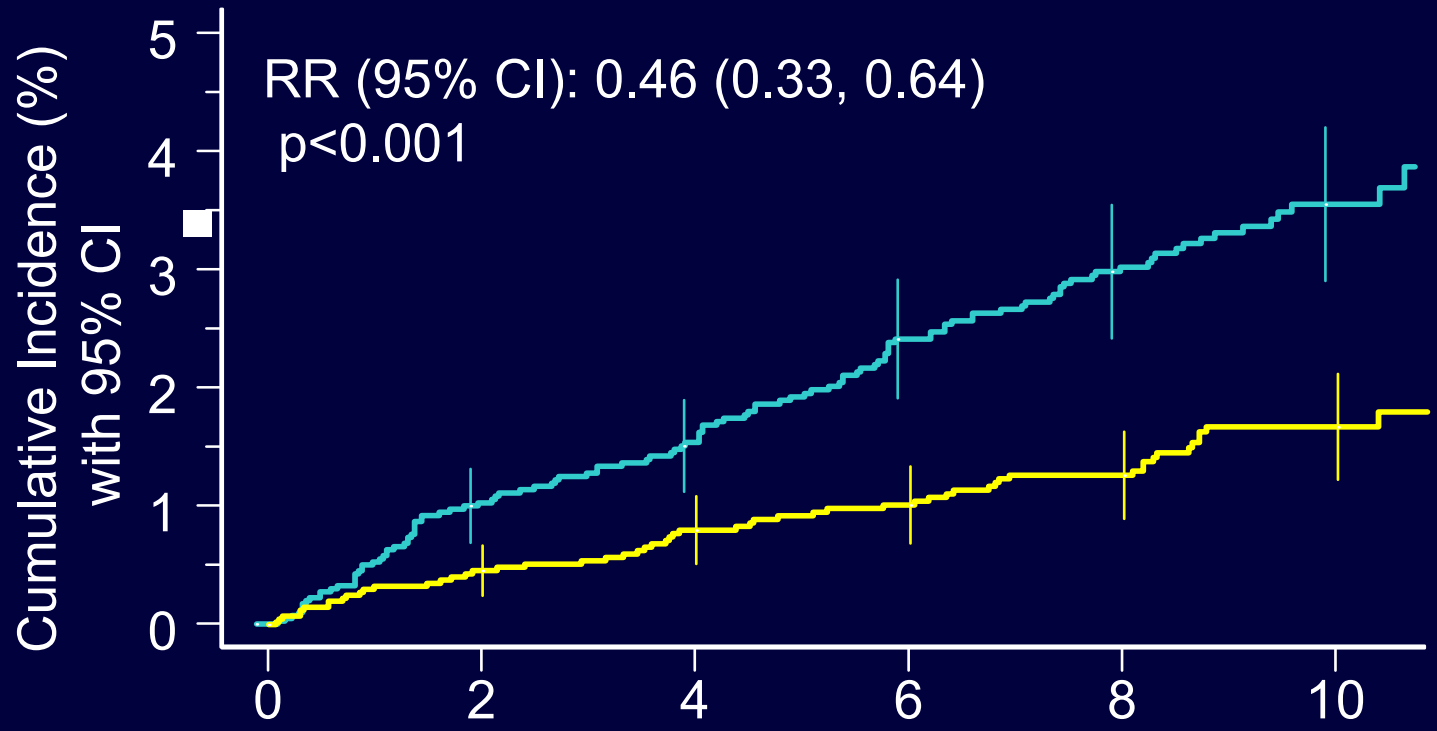
VIOXX GI Outcomes Research Study (VIGOR)

- 8076 rheumatoid arthritis (RA) patients:
  - Rofecoxib 50 mg QD
    - 2 to 4 times recommended chronic dose
    - Provides rigorous test of GI safety
  - Naproxen 500 mg BID
    - Extend GI findings to additional NSAID
    - Most common NSAID regimen for RA
- Exclusion Criteria
  - Patients using aspirin
    - Confounds test of COX-2 hypothesis

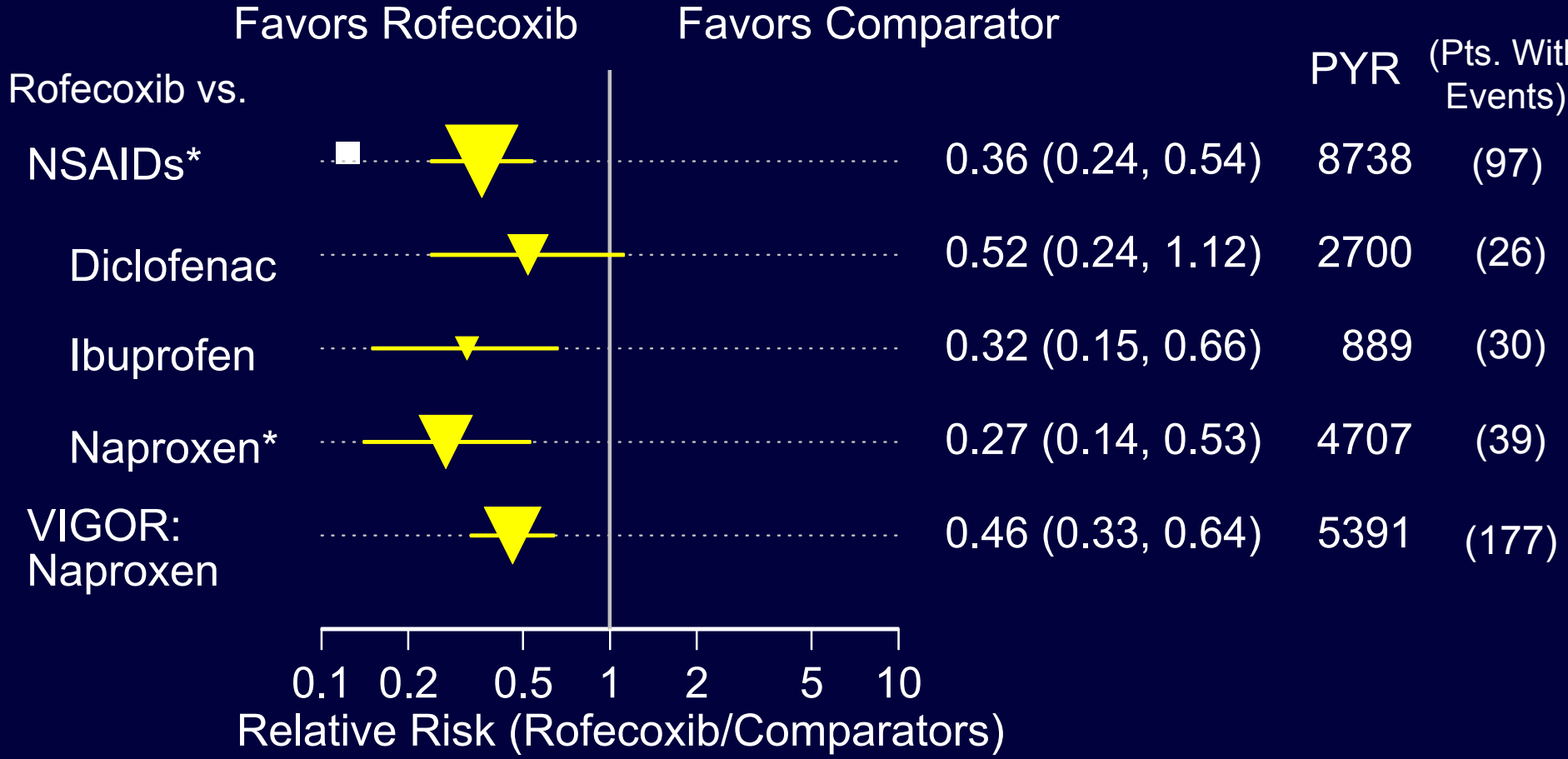
VIGOR Primary Endpoint
Time to Confirmed Clinical Upper GI Event



Patients at Risk							Pts. With Events
Rofecoxib 50 mg	4047	3641	3402	3180	2806	1073	56
Naproxen 1000 mg	4029	3644	3389	3163	2796	1071	121

Final Pooled Analysis Confirms and Broadens GI Safety Benefit for Rofecoxib (2003)

Confirmed Clinical Upper GI Events: Relative Risk with 95% CI



PYR = Patient-Years.
*Excludes VIGOR.

Summary: Rofecoxib GI Safety

- Demonstrated reduction in clinical upper GI events vs. non-selective NSAIDs
  - Reduction vs. naproxen in VIGOR (outcomes study)
  - Consistent reduction vs. each of naproxen, ibuprofen, diclofenac
    - Pooled analysis of 20 OA/RA studies
- Data in briefing package
  - Reduced incidence of lower GI events vs. naproxen in VIGOR
  - More upper GI events with rofecoxib than placebo

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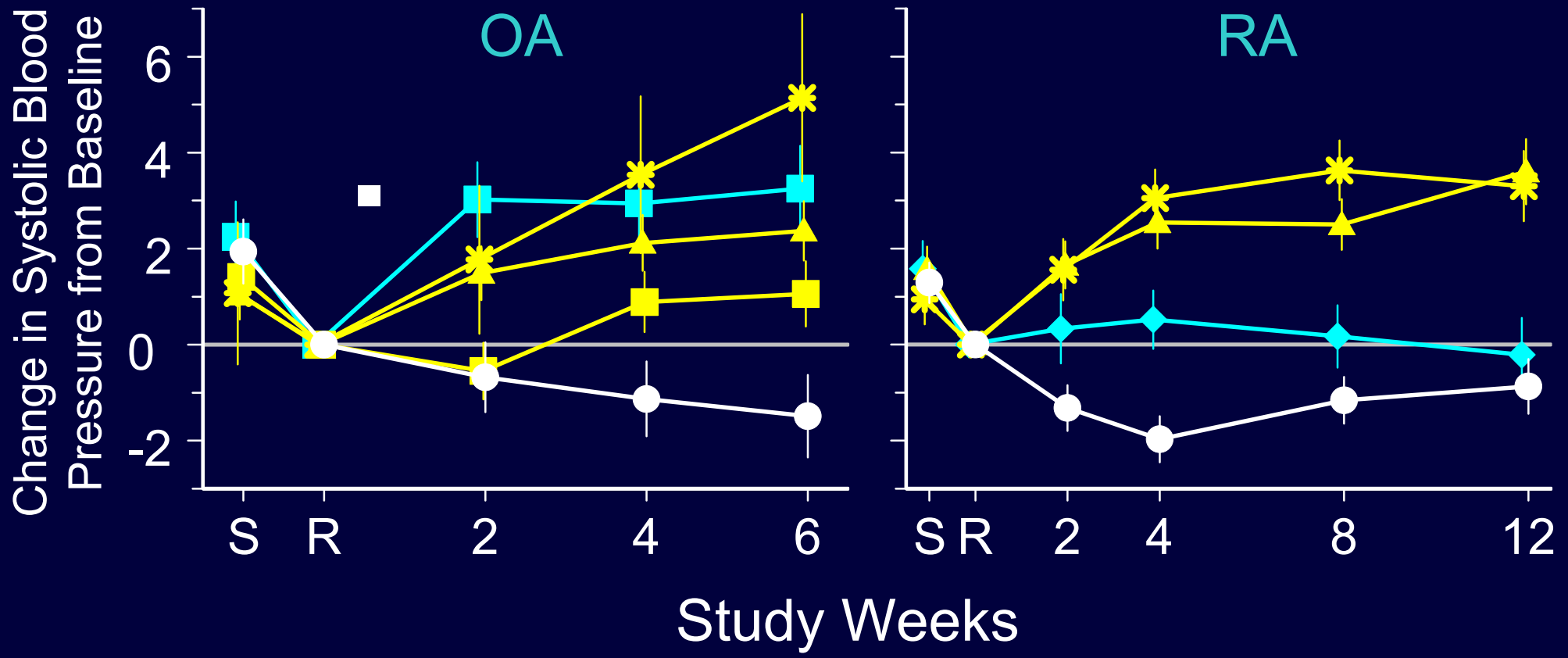
Systolic Blood Pressure: Change from Baseline in OA and RA IIb/III



Adverse Experiences of Congestive Heart Failure, Pulmonary Edema, or Cardiac Failure in Large Placebo-Controlled Studies

Study	Rofecoxib 25 mg n (%)	Placebo n (%)	p- value
APPROVe (N=2586)	17 (1.3)	4 (0.3)	0.004
Protocol 078 (N=1451)	16 (2.2)	19 (2.6)	>0.20
Protocol 091 (N=692)	11 (3.2)	5 (1.4)	>0.20

Summary: Rofecoxib Renovascular Safety

- Renovascular effects of NSAIDs (fluid retention/CHF, HTN) are mechanism-based and dose-dependent
  - Comparisons between NSAIDs (COXIBs) need to be performed at doses that provide similar levels of COX-2 inhibition
- Renovascular effects of rofecoxib are consistent with NSAID profile

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  - Final Data from randomized clinical trials before APPROVe
  - Design of Prospective Study of CV Outcomes
  - Final Data from APPROVe
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Rofecoxib Cardiovascular Safety
Historical Context

- 1998
  - Cardiovascular questions:
    - What is clinical importance of inhibiting systemic prostacyclin synthesis without inhibiting platelet thromboxane?
    - Can some NSAIDs, through their effects on COX-1, decrease the risk of thrombotic CV events?
    - Is there a clinical benefit to inhibiting COX-2 mediated inflammation in atherosclerotic plaques?

Rofecoxib Cardiovascular Safety
Historical Context

- 1998
  - Cardiovascular questions:
    - What is clinical importance of inhibiting systemic prostacyclin synthesis without inhibiting platelet thromboxane?
    - Can some NSAIDs, through their effects on COX-1, decrease the risk of thrombotic CV events?
    - Is there a clinical benefit to inhibiting COX-2 mediated inflammation in atherosclerotic plaques?
  - Phase III clinical studies completed and NDS submitted
    - Over 5000 patients with OA
    - CV risk similar on placebo & comparator NSAIDs
  - Merck initiated plan to adjudicate CV events in future COX-2 studies

Vascular Events Adjudication SOP

- Purpose
  - Standardize the evaluation of cardiovascular events
    - Predefined criteria
    - All source documentation collected
    - Blinded, external adjudication committees
  - Improve clarity by eliminating questionable events
- Pooled analysis of events planned across all studies
  - Increase precision

Rofecoxib Cardiovascular Safety
Historical Context

- 1999
  - VIGOR initiated: rofecoxib 50 mg v naproxen in RA patients
  - Rofecoxib approved for the treatment of OA and Acute pain
- 2000 - 2002
  - VIGOR data: more CV events with rofecoxib v naproxen
  - CV risk similar to placebo in Alzheimer Studies Interim Analyses
  - Rofecoxib pooled analysis
    - CV risk similar to placebo and non-naproxen NSAIDs
    - CV risk lower with naproxen
  - Monograph updated with VIGOR and Alzheimer's data
  - Merck initiates CV outcomes protocol to further study CV safety

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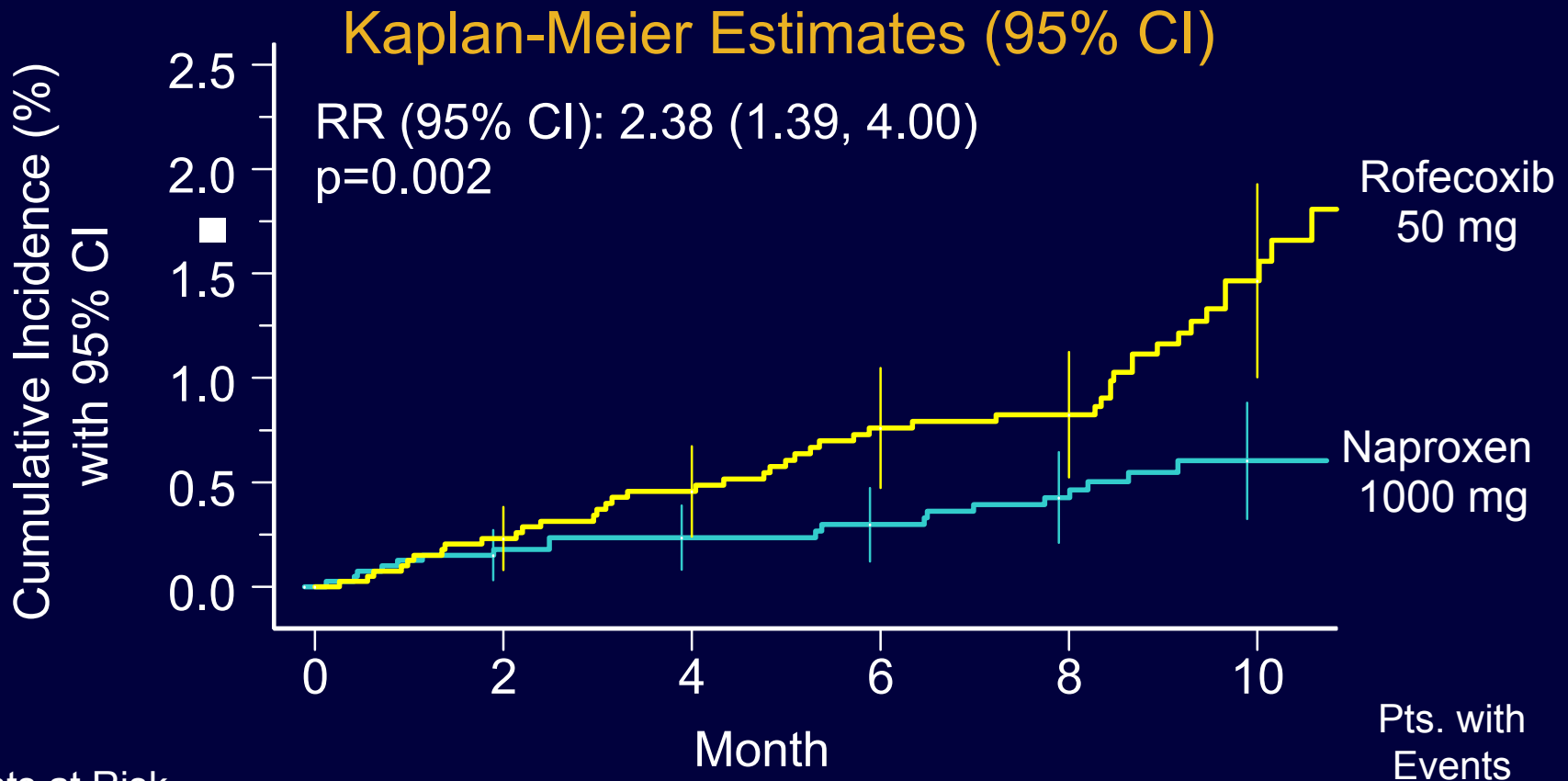
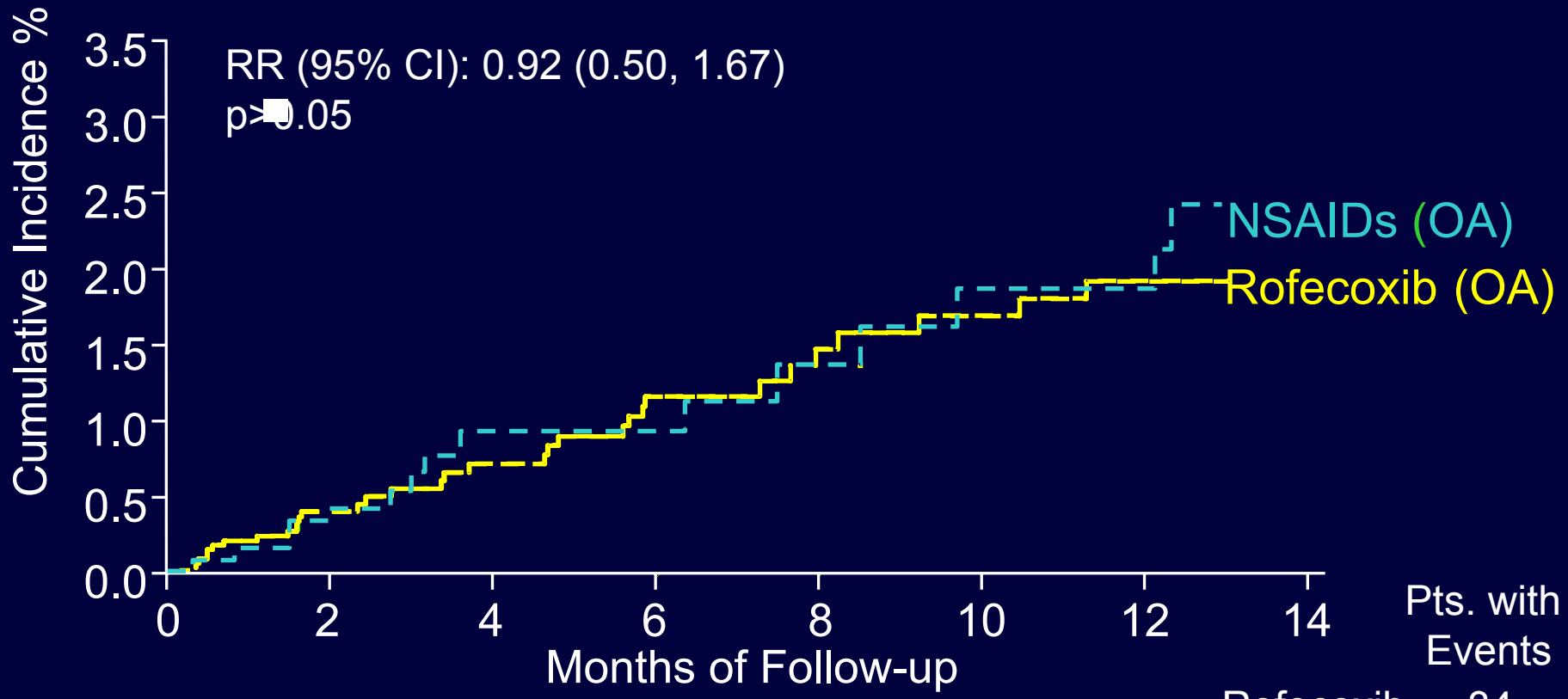
Confirmed Thrombotic CV Events
Rofecoxib vs. Naproxen: The VIGOR Study



Patients at Risk							Pts. with Events
Rofecoxib 50 mg	4047	3643	3405	3177	2806	1067	45
Naproxen 1000 mg	4029	3647	3395	3172	2798	1073	19

Ph IIb/III OA
Investigator-Reported Thrombotic CV Events
Rofecoxib vs. Non-Naproxen NSAIDs (NDS Data 1999)

Kaplan-Meier Estimates (95% CI)

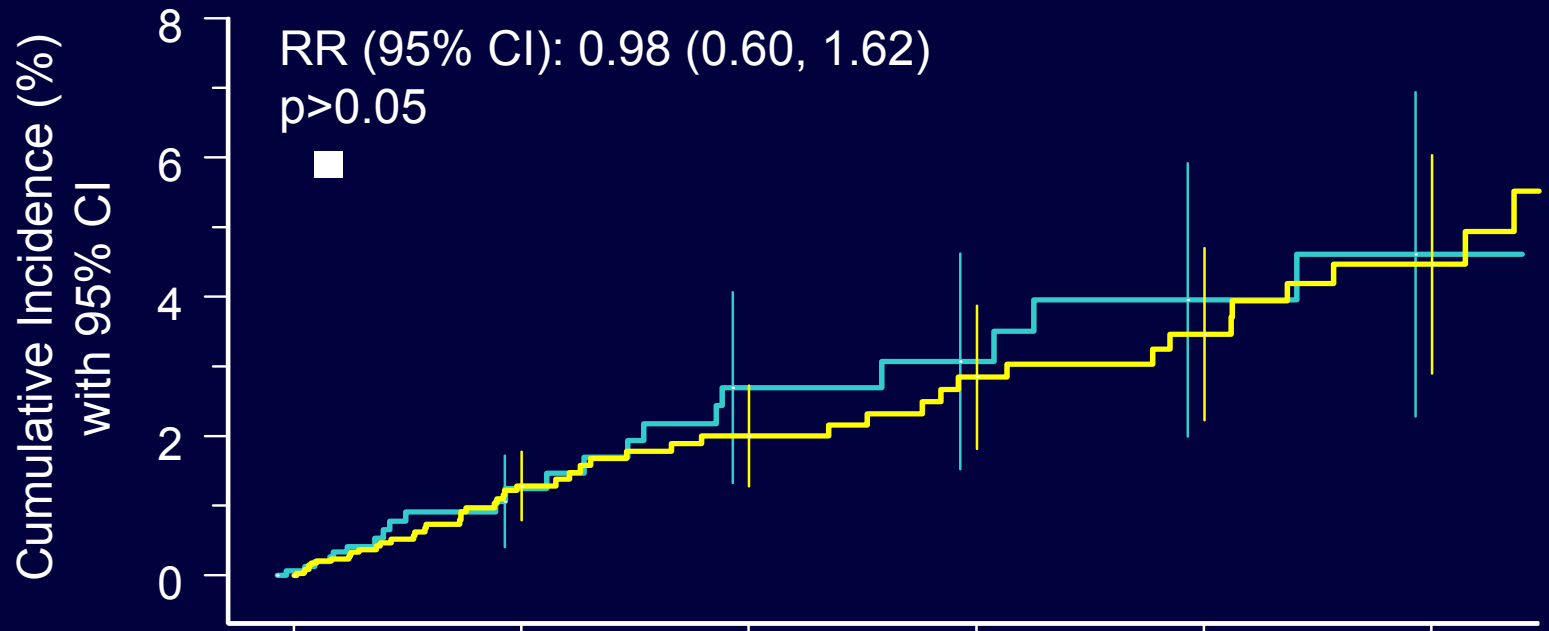


	Pts. with Events
Rofecoxib	34
Non-Naproxen NSAIDs†	16

† Ibuprofen, diclofenac, nabumetone.

Ph IIb/III OA
Investigator-Reported Thrombotic CV Events
Rofecoxib vs. Non-Naproxen NSAIDs (Final Data 2001)

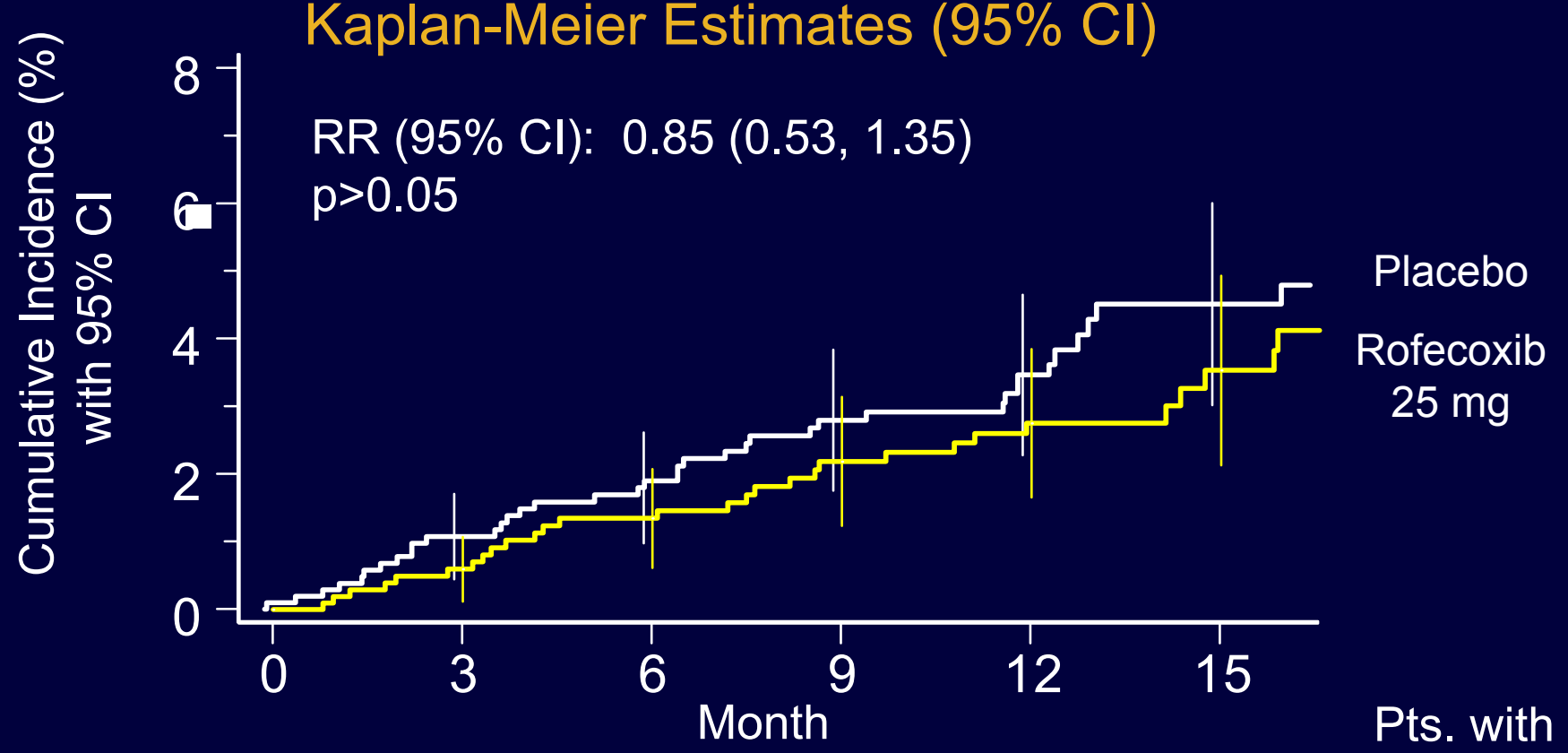
Kaplan-Meier Estimates (95% CI)



Patients at Risk						Pts. with Events
Rofecoxib	1245	849	534	448	261	50
Non-Naproxen NSAIDs†	541	368	237	184	105	22

† Ibuprofen, diclofenac, nabumetone.

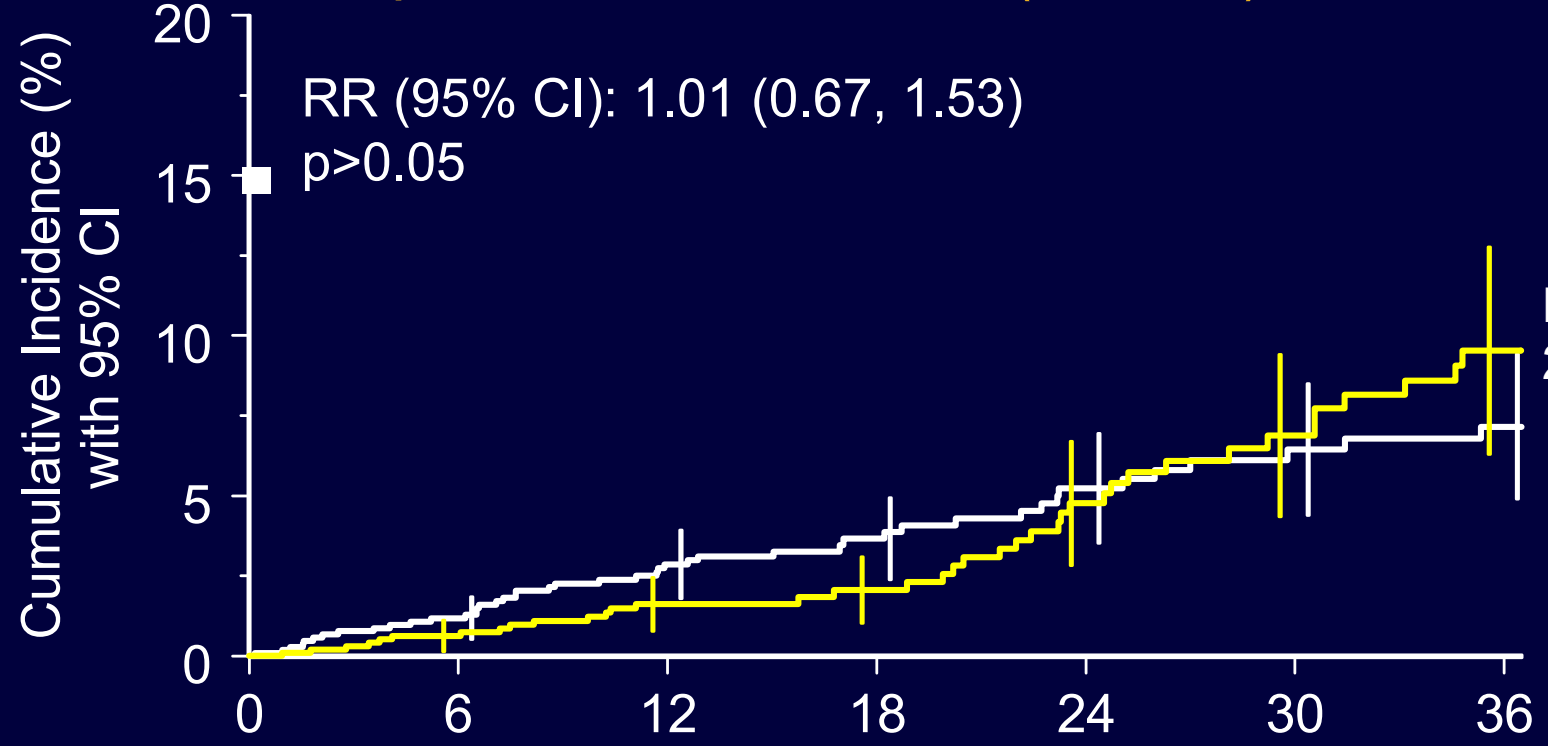
Alzheimer's Disease (PN 078 + 091)
Investigator-Reported Thrombotic CV Events
Rofecoxib vs. Placebo (Interim Data 2000)



Patients at Risk							Pts. with Events
Rofecoxib 25 mg	1041	947	879	769	640	359	32
Placebo	1050	991	930	816	693	376	40

Alzheimer's Disease (PN 078 + 091)
Confirmed Thrombotic CV Events
Rofecoxib vs. Placebo (Final Data 2003)

Kaplan-Meier Estimates (95% CI)

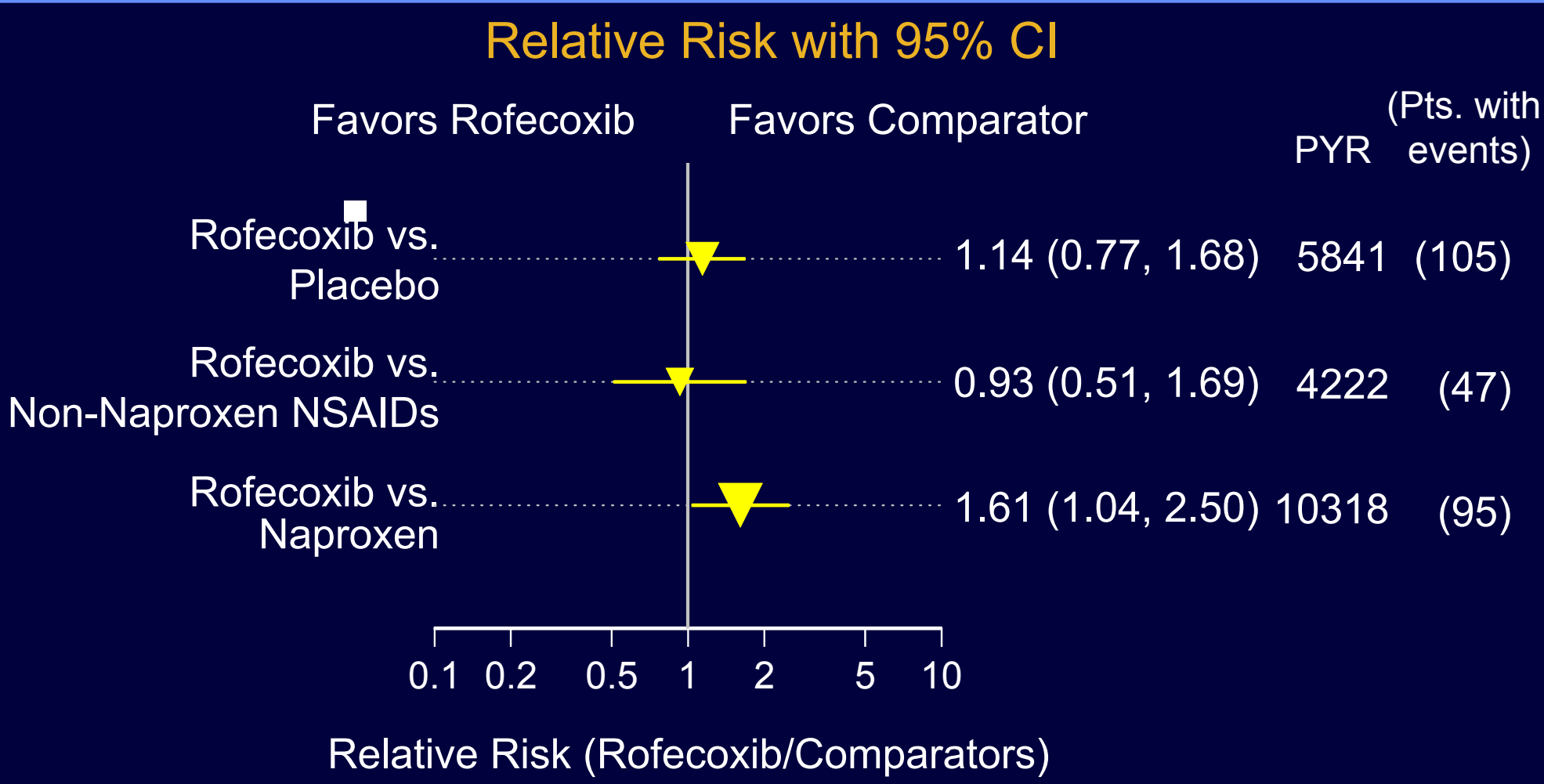


Patients at Risk								Pts. with Events
Rofecoxib 25 mg	1069	878	707	415	318	226	185	42
Placebo	1074	939	797	463	385	283	243	48

Cardiovascular Pooled Analysis

- Phase IIb to V (post-marketing) rofecoxib studies ≥4 weeks duration
- APTC combined endpoint (MI, CVA, vascular death)
  - Included studies not subject to adjudication
    - Reports of APTC events had high confirmation rates
  - Allowed comparison to published reports
- Pooled analysis of double-blinded patient-level data stratified by disease
- Included data on >32,000 patients and >19,000 patient-years

Pooled Analysis of APTC Combined Endpoint, Rofecoxib vs. Comparator Agents (2003)



PYR = Patient-Years.

Rofecoxib Safety Assessment (Pre-APPROVe)

- Thrombotic CV Data from rofecoxib randomized control trials:
  - CV event rates similar to placebo and non-naproxen NSAIDs
  - CV event rate higher than naproxen
    - Similar CV data with other COX-2 selective inhibitors
- Other data:
  - Observational epidemiology studies (10 presented or published)
    - Results mixed
  - Pre-clinical models
    - Applicability to humans uncertain
- Overall risk benefit favorable for rofecoxib
- CV outcomes study ongoing

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Rofecoxib Study of CV Outcomes (Oct-2002)

- Prospective combined analysis of 3 studies comparing rofecoxib 25 mg vs. placebo
  - APPROVe: Recurrent adenomatous colon polyps
  - VICTOR: Colon cancer mortality (Oxford University Study)
  - ViP: Incidence of prostate cancer in at-risk patients
- Separate protocol, analysis plan and safety monitoring board
- Approximately 25,000 patients
- Patients with broad spectrum CV risk
  - Aspirin users and non-users

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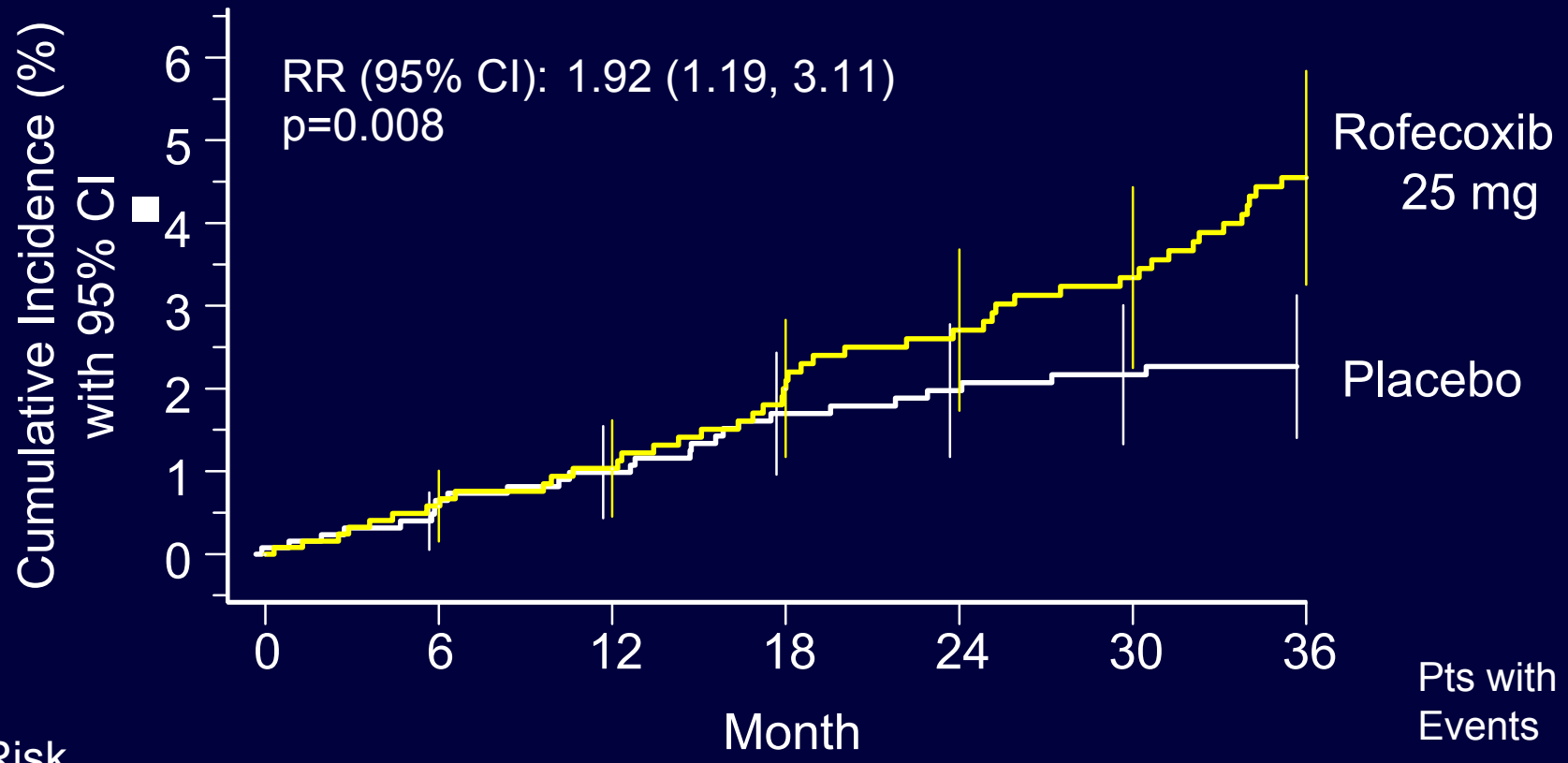
APPROVe Colon Polyp Prevention Study Design

- Rofecoxib 25 mg vs. placebo
  - Approximately 2600 patients
- 3-Year on-drug treatment period with 1-year off-drug period to assess rebound
- First patient screened in Dec-1999

APPROVe
Thrombotic CV Events Cumulative Incidence Over Time (Dec-2004)



Patients at Risk								Pts with Events
Rofecoxib 25 mg	1287	1129	1057	989	938	896	727	46
Placebo	1299	1195	1156	1079	1042	1001	835	26

Post-Hoc Exploratory Analyses of APPROVe (Dec-2004 Data)

- Many factors assessed in multiple analyses
  - Baseline factors (>10 factors)
    - (e.g., age, gender, individual CV risk factors, etc.)
  - Concomitant aspirin use
- Statistical approach: Tests for treatment-by-subgroup factor interaction, one subgroup factor at a time
- Test for interaction 0.05>p>0.10 in 2 subgroups
  - History diabetes; History symptomatic ASCVD
- Multiple subgroup testing
  - Results considered hypothesis generating

Blood Pressure Measurement Methodology in APPROVe

- BP measured once per visit
  - Every 4 months
- BP measurements not standardized across sites
  - Time of day and measurement technique varied
- Between-group difference in change from baseline in mean systolic and diastolic BP values (rofecoxib – placebo)
  - 4 mm Hg systolic
  - 2 mm Hg diastolic

APPROVe Exploratory Post-Hoc Analyses of Blood Pressure (Dec-2004 Data)

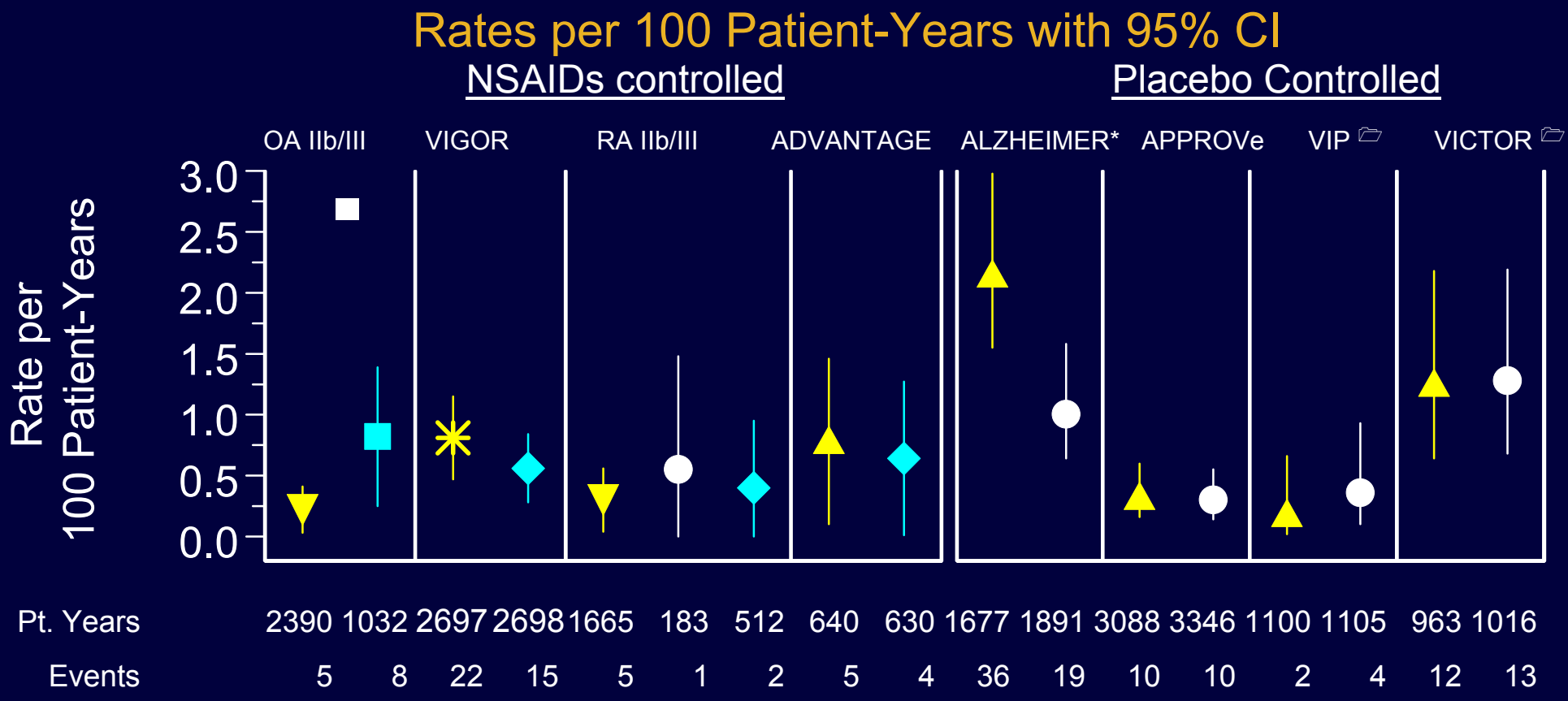
- Multiple BP analyses did not identify consistent patient subgroups or covariates associated with increased relative risk
  - Baseline BP
  - Change from baseline BP
  - On treatment BP
  - Hypertension reported as adverse experience
- One subgroup with increased relative risk
  - SBP ≥160 mm Hg
  - Similar trends not seen in other data sets

DBP = diastolic blood pressure.
SBP = systolic blood pressure.

Reasons for VIOXX™ Voluntary Withdrawal (30-Sep 2004)

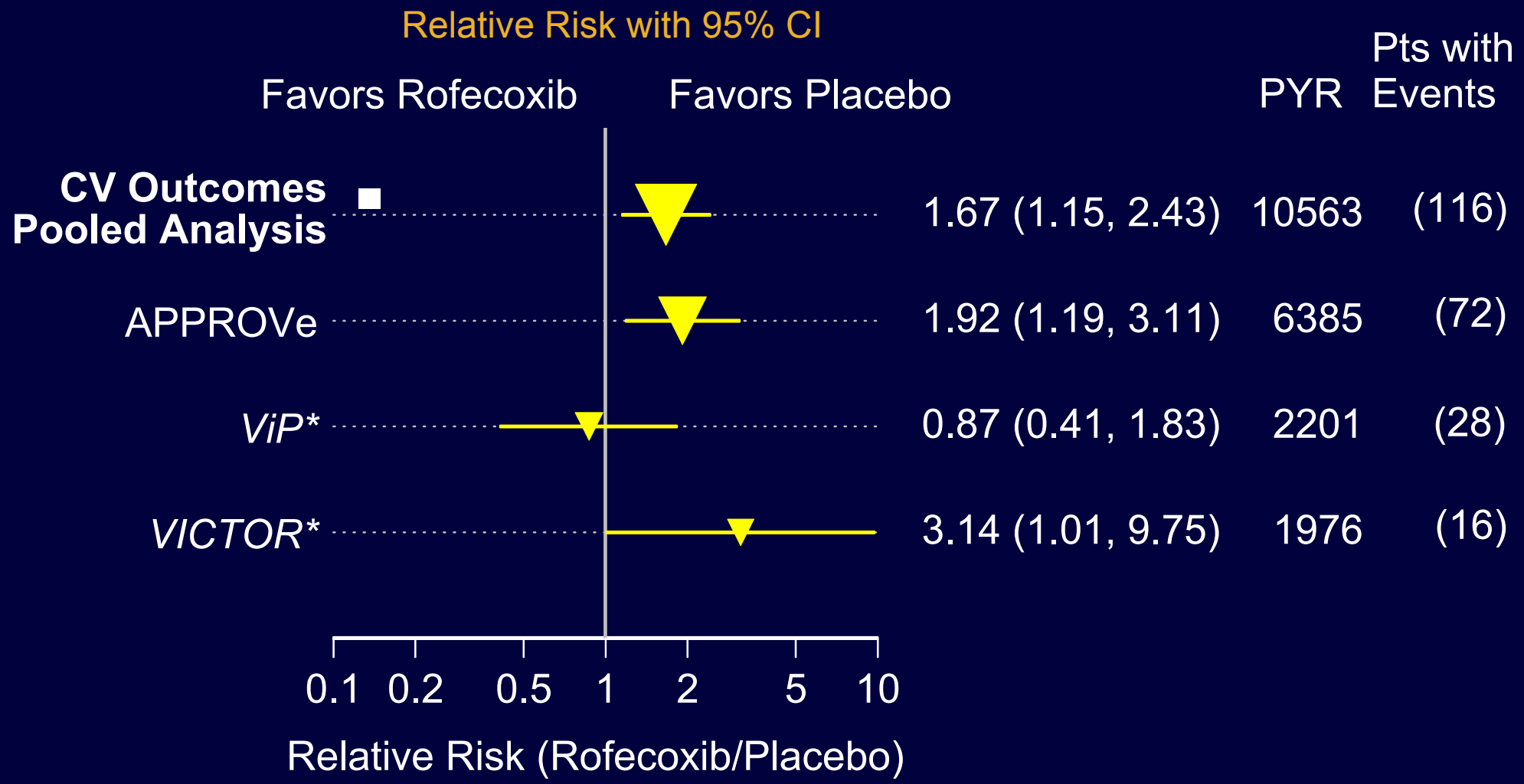
- APPROVe was first clinical trial with rofecoxib that showed an increased cardiovascular risk versus placebo
  - Risk similar to placebo over first approximately 18 months
  - Risk relative to placebo began to increase starting after approximately 18 months
- At that time, alternative therapies were available without evidence of a similar cardiovascular risk
- Merck believed voluntary withdrawal best served interest of patients

All-Cause Mortality in Rofecoxib Clinical Program: (Updated Feb-2005)



* On-drug population: Interim data as of Feb 2005

Pooled Analysis of Confirmed Thrombotic CV Events CV Outcomes Study (Interim Data Feb-2005)



*Interim data as of Feb 2005.

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Implications: Key Public Health Questions

- What is risk/benefit of selective COX-2 inhibitors for established indications?
  - Relative to ibuprofen/diclofenac
  - Relative to naproxen

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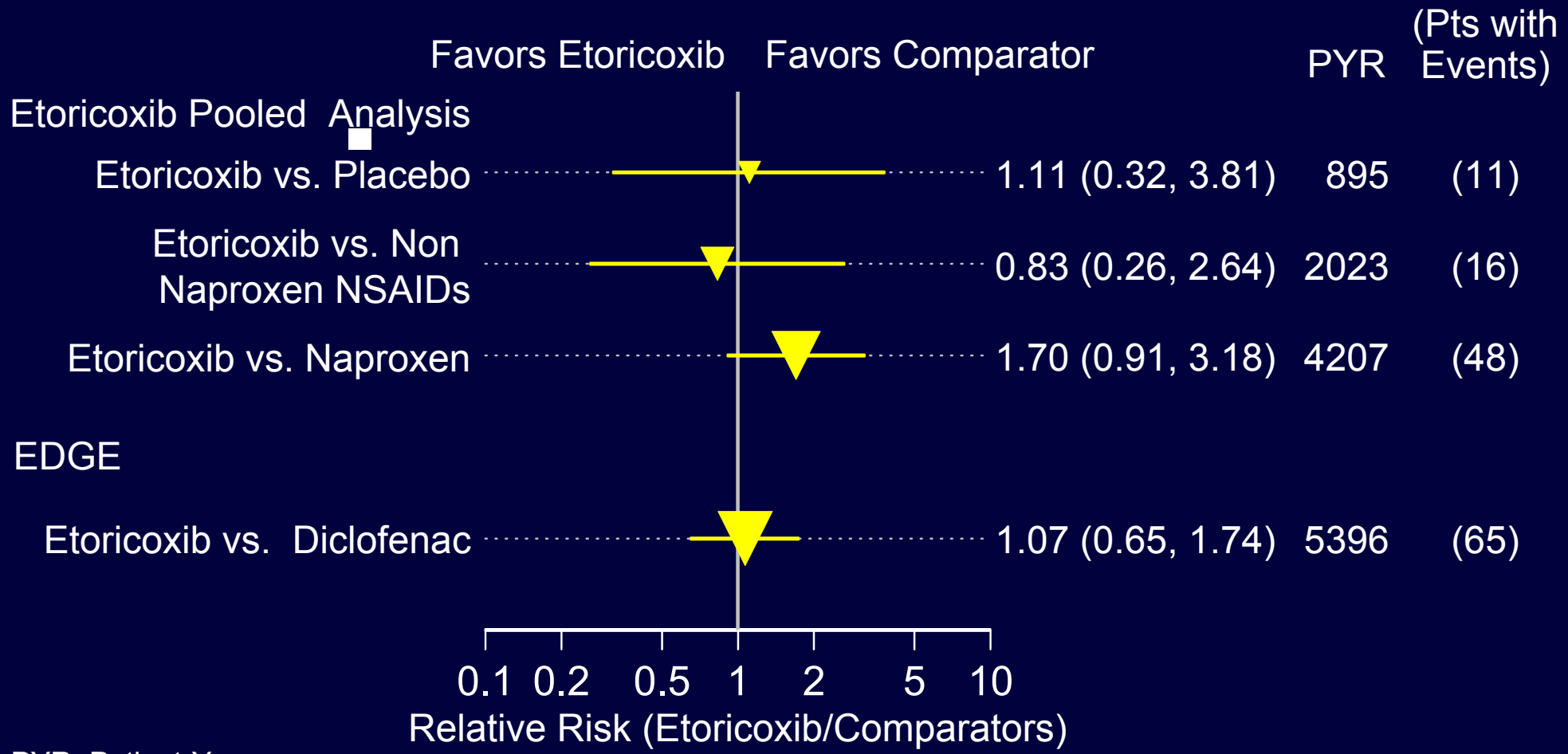
  - Relative to ibuprofen/diclofenac
  - Relative to naproxen
- Can we identify factors associated with observed increased risk for thrombotic CV events with these drugs?
  - Duration
  - Patient demographics
  - Dose

Implications: Key Public Health Questions

- What is risk/benefit of selective COX-2 inhibitors for established indications?
  - Relative to ibuprofen/diclofenac
  - Relative to naproxen
- Can we identify factors associated with observed increased risk for thrombotic CV events with these drugs?
  - Duration
  - Patient demographics
  - Dose
- Is observed increased CV risk a class effect of COX-2 inhibition?
  - How big is the class?
  - What are long-term CV effects of traditional NSAIDs?

Results of Etoricoxib Pooled Analysis, EDGE: No Difference Between Etoricoxib, Non-Naproxen NSAIDs

Confirmed Thrombotic CV Adverse Experiences: Relative Risk with 95% CI



PYR=Patient-Years.

Next Steps

- Ongoing assessment of rofecoxib thrombotic CV data
  - Examine additional factors for relationship in APPROVe
  - Patients in APPROVe being followed off-drug
- Scientific hypotheses for thrombotic CV findings being explored
- Efforts underway to analyze thrombotic CV data across drugs
- Comparative outcome studies needed to determine relative risk among agents in relevant populations
  - Etoricoxib vs. diclofenac in approximately 35,000 patients targeted to complete 2006

END OF CORE