Health Canada Advisory Committee Meeting

9 June 2005

Dr. Gail Cawkwell, Pfizer Inc.

Cardiovascular Safety of Celecoxib

&

Benefit-Risk Assessment

Canadian Delegation

• Dr Todd Anderson	Cardiology
• Dr Algis Jovaisas	Rheumatology
• Ms. Sandra Knowles	Drug Safety Pharmacist
• Dr David Morgan	Gastroenterology
• Dr Yola Moride	Epidemiology
• Dr Mark Silverberg	Gastroenterology

Overall Conclusions

- Celecoxib presents a favorable benefit-risk for patients with the chronic inflammation and pain of arthritis compared with NSAIDs
- Celecoxib should remain a choice for Canadian patients, with appropriate warnings
- Celecoxib presents a favorable benefit-risk for patients with FAP and should remain a treatment for Canadian patients.

Overview

- Introduction
- GI Safety
- Celecoxib - CV safety
- FAP: Benefit-risk
- Conclusions

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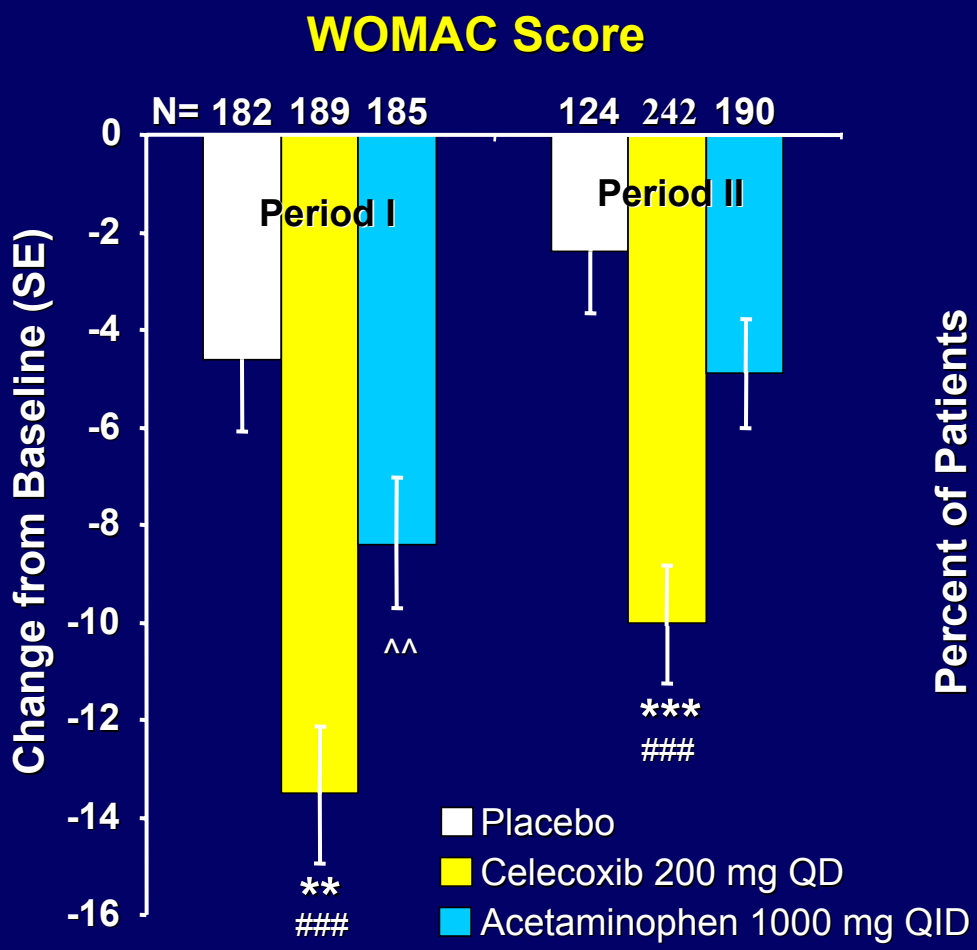
Escalating Prevalence of Burden of Arthritis

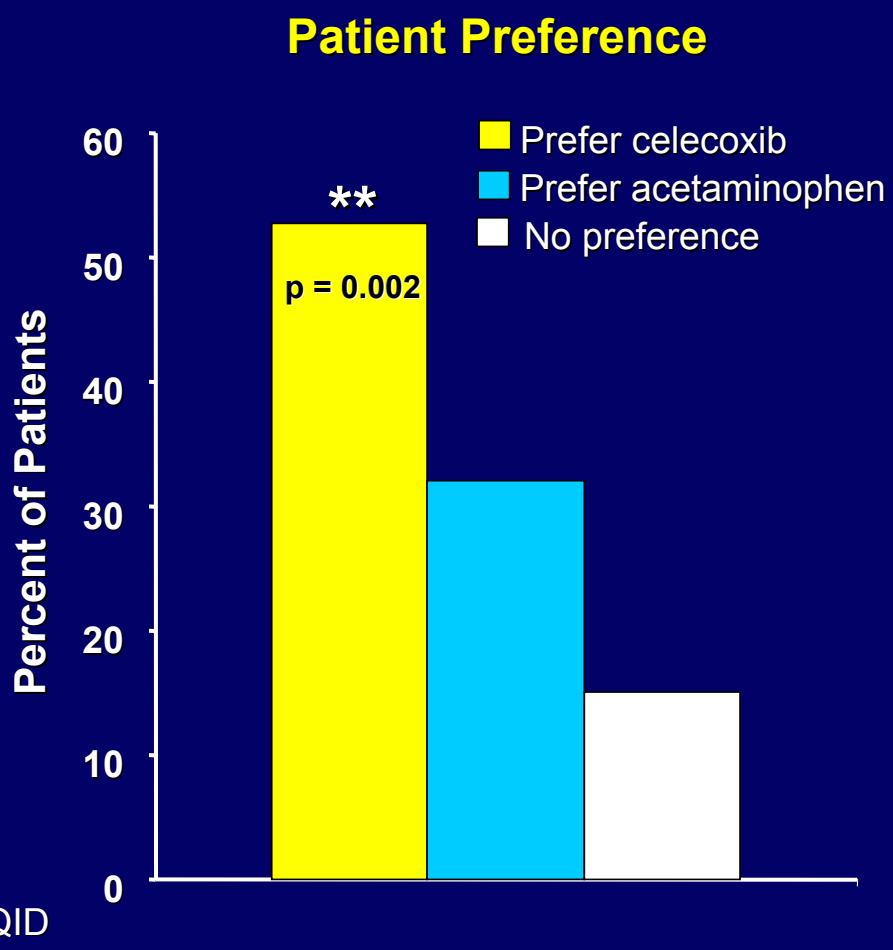
CANADA

- Arthritis affects ~ 17% of the Canadian population
- Arthritis affects > 4 million Canadians - 36.8% of all adults
- Prevalence is projected to increase by ~1 million / decade at least until the year 2031
- Between 1991 and 2031, disability due to arthritis projected to grow from 2.3% to 3.3%
- 39 Canadians per day becoming disabled by arthritis

Badley E *et al. Arthritis in Canada.* An Ongoing challenge. Ottawa: Health Canada; 2003
The Arthritis Society, www.arthritis.ca. Accessed October 12, 2001

PACES: WOMAC and Preference of Celecoxib vs. Acetaminophen



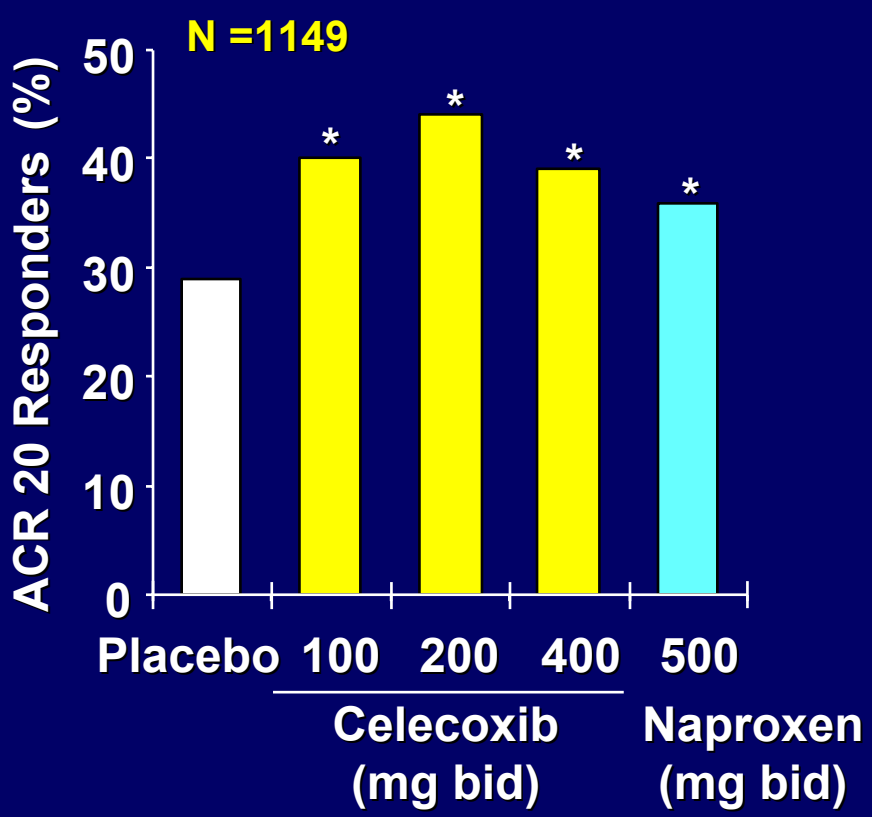


** Celecoxib vs acetaminophen: p < 0.01
*** Celecoxib vs acetaminophen: p < 0.001
Celecoxib vs placebo: p < 0.001
^^ Acetaminophen vs placebo: p < 0.05

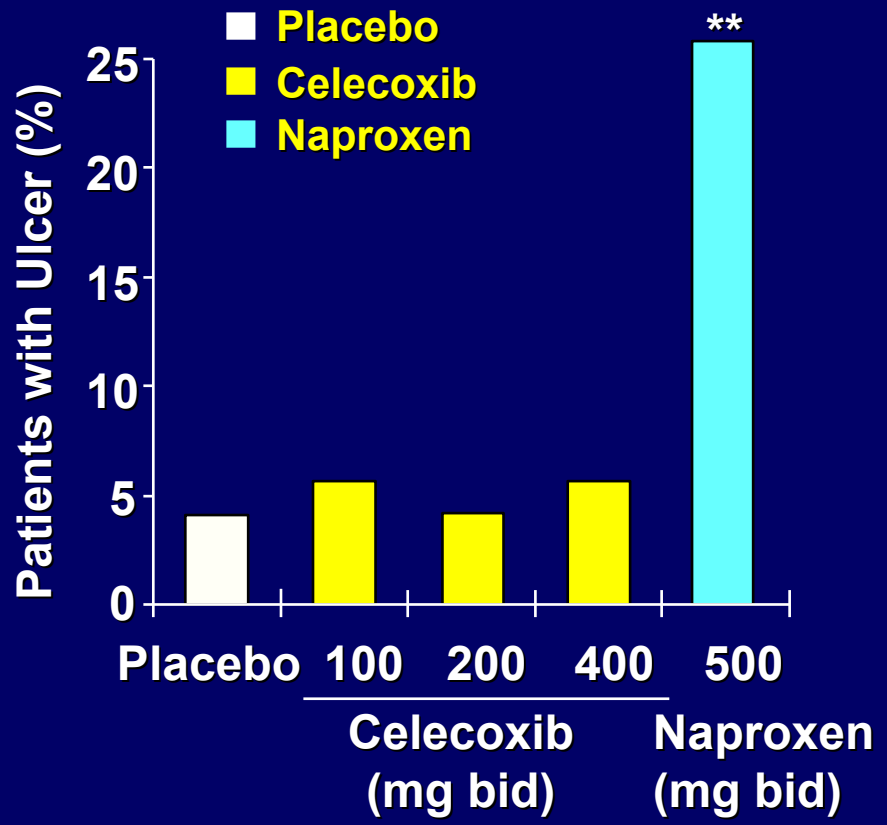
Pincus et al. Ann Rheum Dis 2004; 63:931-939

Clinical Effects of Celecoxib in RA

Efficacy



Upper GI Safety



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

*p <0.001 vs placebo **p <0.001 vs other treatments

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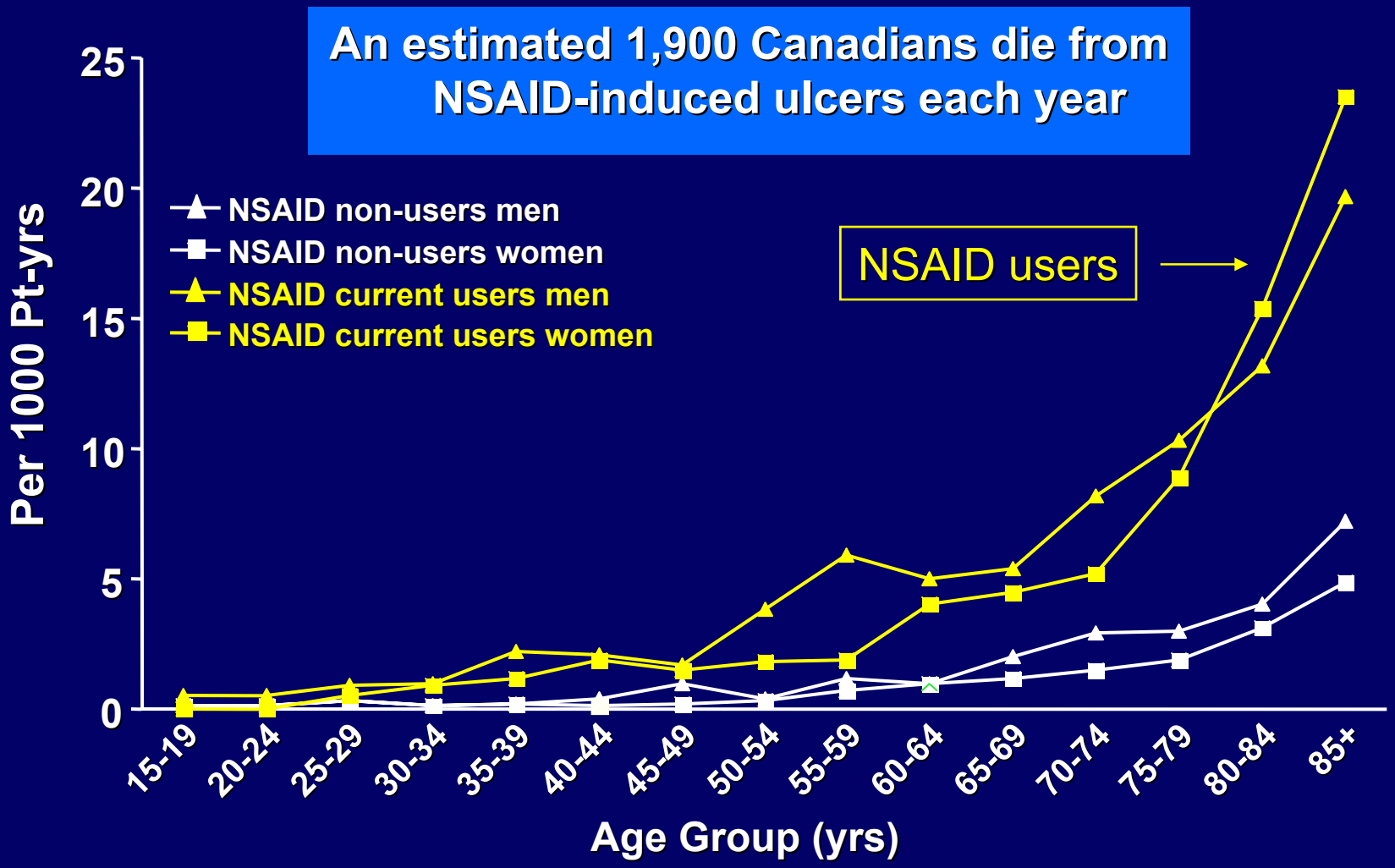
NSAIDs and Incidence of Hospitalization for GI Bleeding or Perforations

CANADA

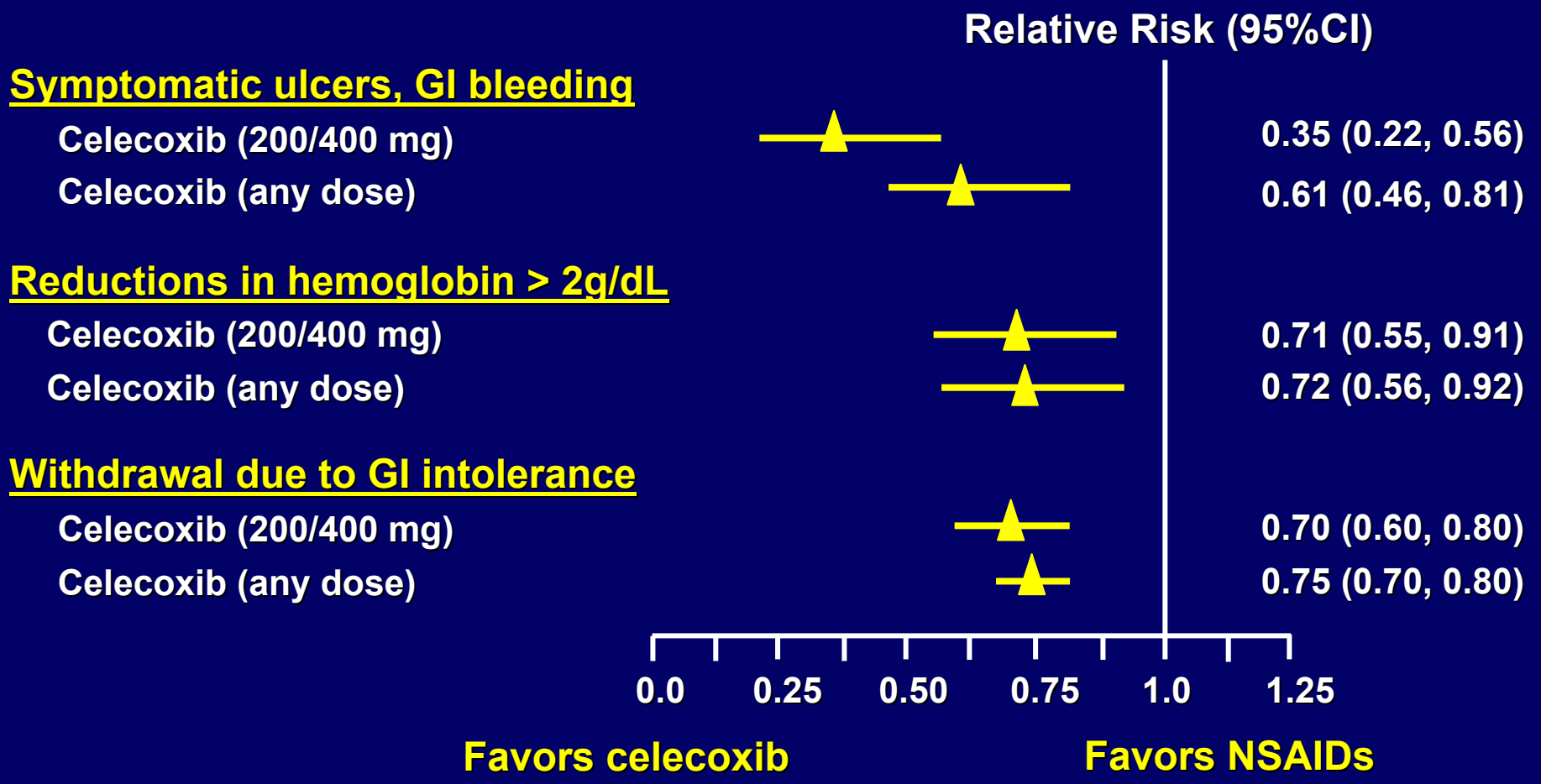


Perez-Gutthann et al. Epidemiology 1997;8:18-24
Anthroscope 1998 - The Arthritis Society (Canada)

GI Safety Profile of Celecoxib vs NSAIDs

Meta Analysis of Arthritis RCTs

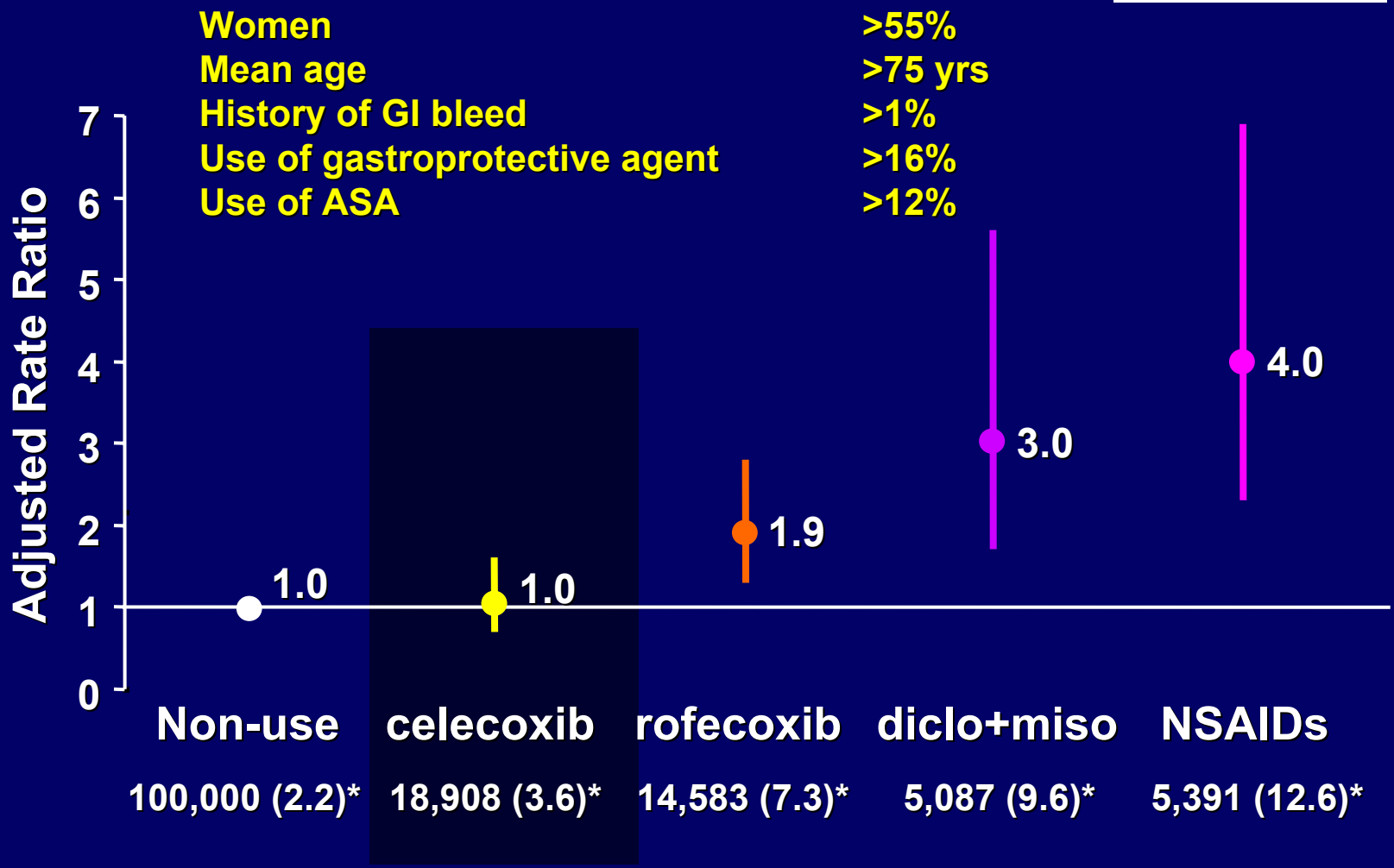
39,605 OA/RA patients; mean exposure ~7 mo



Moore et al. Arthritis Research & Therapy 2005; 7:R644-R665

Risk of Hospitalization for Upper GI Bleeding with Cox-2 Selective Inhibitors

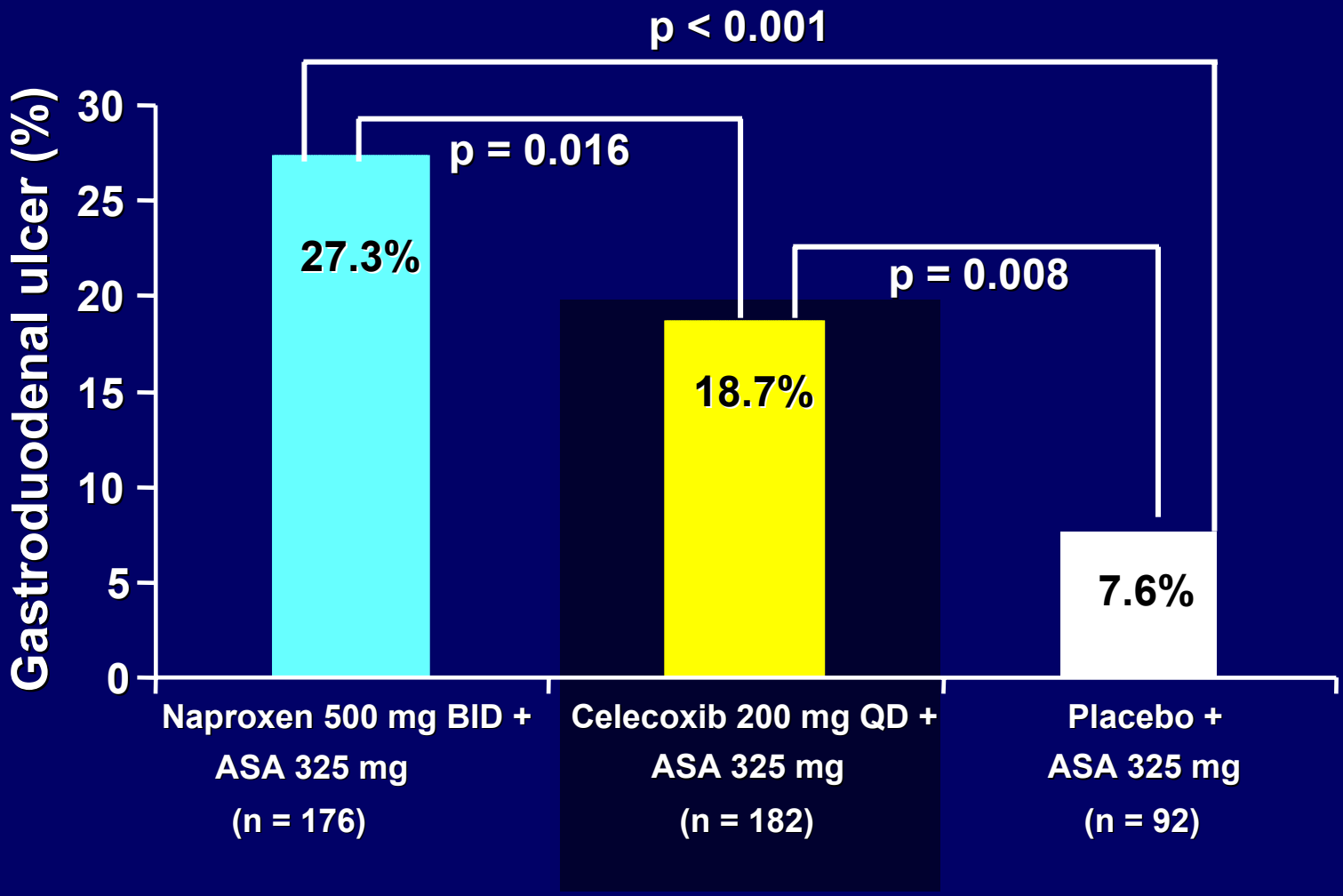
CANADA



*n (no. upper GI bleeds per 1000 person-yrs)

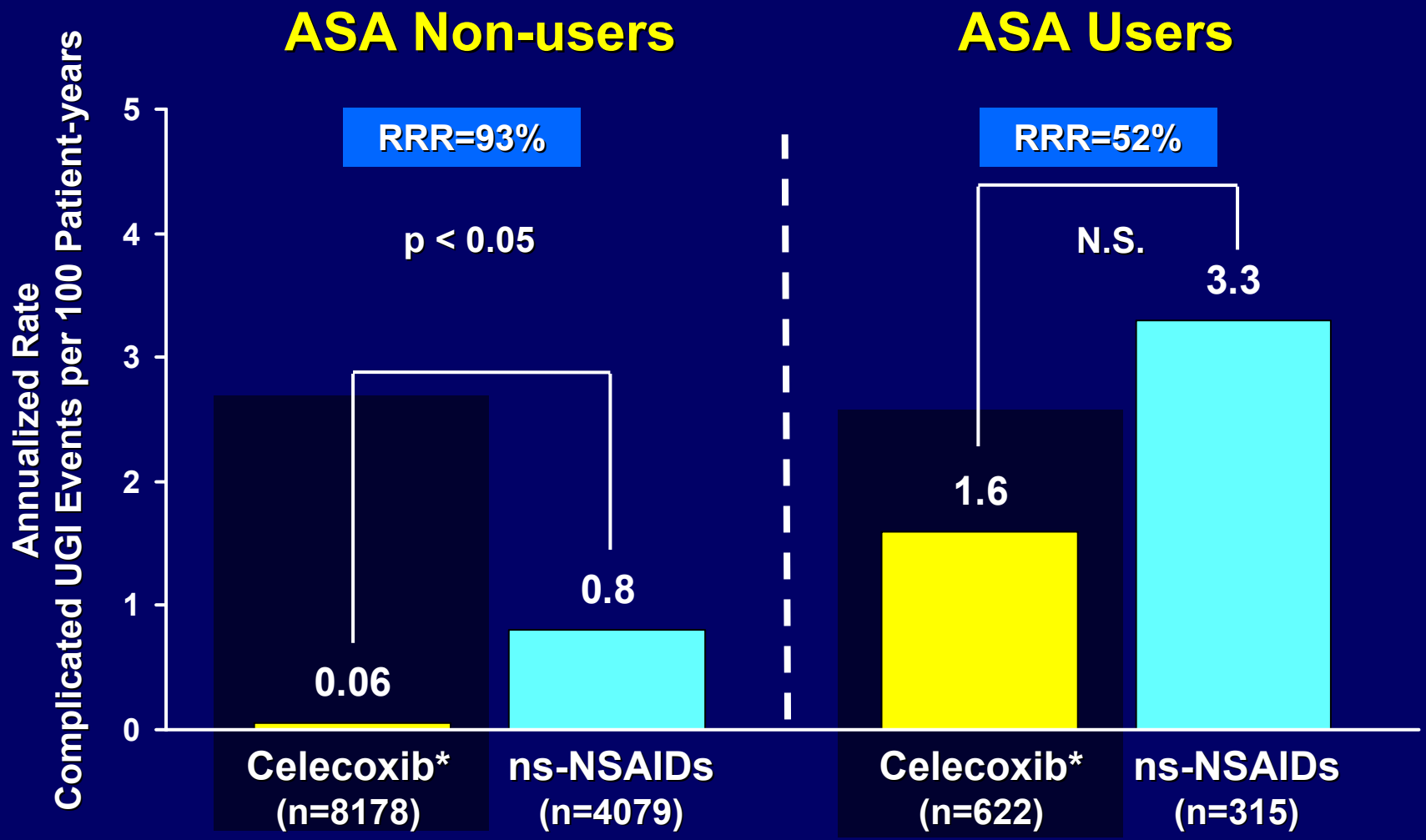
Mamdani et al. BMJ 2002;325(7365):624-7

Incidence of Gastroduodenal Ulcers in Healthy Elderly Subjects: Concomitant ASA Use



Clinical study report data on file

SUCCESS-1: Complicated UGI Events in Non-ASA and ASA Subgroups

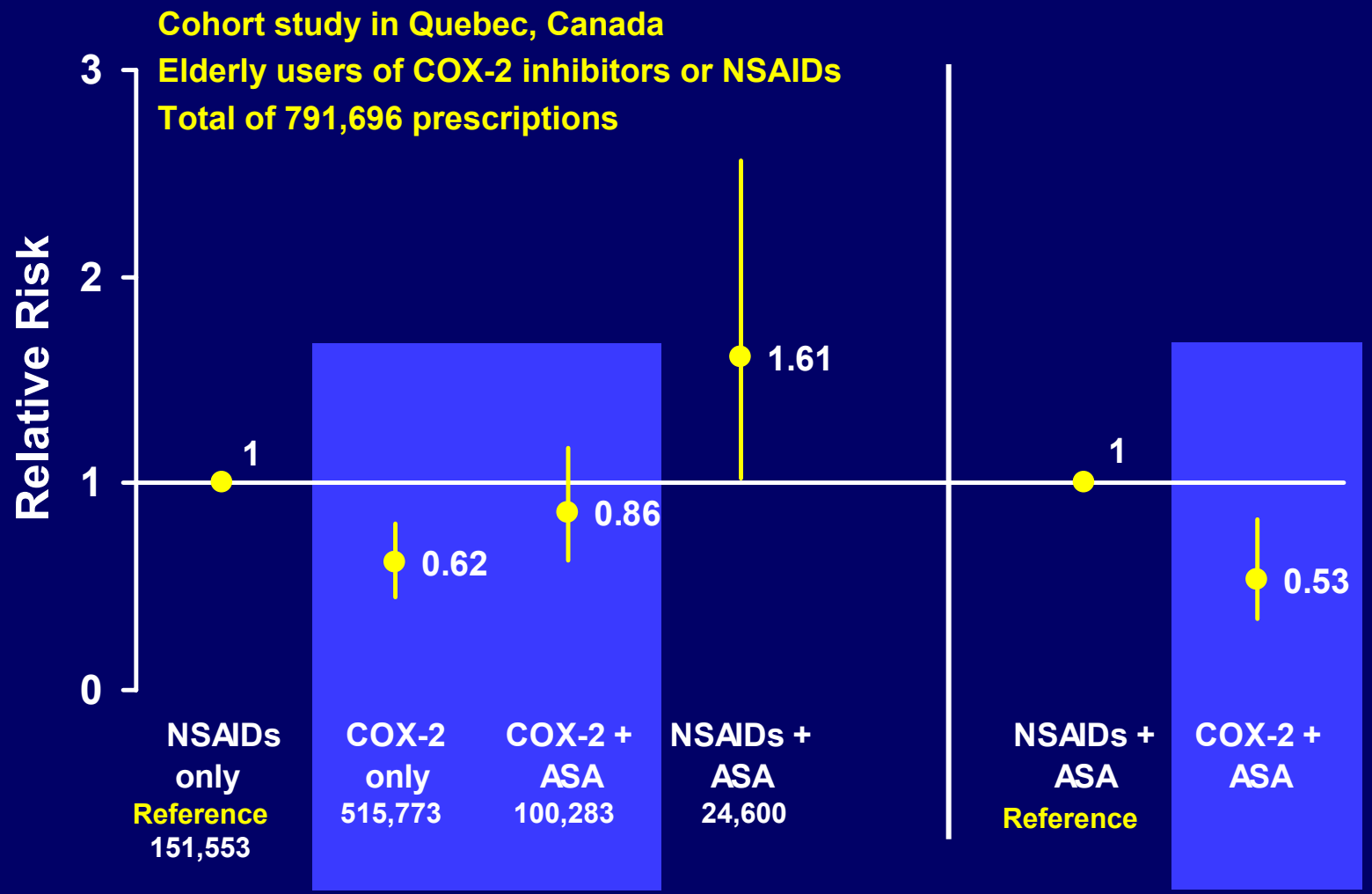


Singh G et al, in press Am J Med, 2005

* Celecoxib 200 mg/d to 400 mg/d

Risk of Upper GI Bleeding and Use of NSAIDs, COX-2 Selective Inhibitors and ASA

CANADA



Rahme E et al. Ann Rheum Dis 2004;63(S1):522s-523s
Rahme E et al. Pharmacoepidemiol Drug Saf 2004.13 (S1):233s-234s

GI Safety Benefit - Conclusions

- Medical need for improved GI safety is fulfilled with celecoxib
  - A favorable GI safety profile in contrast with NSAIDs
  - Differential GI benefit remains with concomitant ASA
  - Benefits are demonstrated in randomized controlled trials
  - Benefits are confirmed in the large, real-world setting of epidemiology studies

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Sporadic Adenoma Prevention Trials (SAP)

- Colorectal adenomas: precursors of colon cancer
- Over-expression of COX-2 (pre-cancer, cancer, metastatic disease)
- Two celecoxib SAP trials APC (005) & PreSAP (018)
  - 3 year placebo controlled randomized clinical trials
  - Hypothesis: celecoxib will reduce polyp recurrence by >35% in a high cancer-risk cohort with prior adenoma.

Setting allowed for first longer-term placebo comparison;
Celecoxib - agent of choice based on GI safety

Incidence of Hierarchical Cardiovascular Composite Endpoints in the APC Trial

Endpoint	Number of patients (%)			Rate/1000 patient-years		
	Placebo N=679	200 mg BID N=685	400 mg BID N=671	Placebo N=679	200 mg BID N=685	400 mg BID N=671
Death from CV causes	1 (0.1)	3 (0.4)	6 (0.9)	0.5	1.4	2.9
Death from CV causes or MI	4 (0.6)	12 (1.8)	15 (2.2)	1.9	5.8	7.4
Death from CV causes, MI, or stroke	**6 (0.9)**	**15 (2.2)**	**20 (3.0)**	**2.9**	**7.3**	**9.9**
Death from CV causes, MI, stroke, or heart failure	7 (1.0)	16 (2.3)	23 (3.4)	3.4	7.8	11.4
Death from CV causes, MI, stroke, heart failure, or angina	11 (1.6)	18 (2.6)	25 (3.7)	5.4	8.7	12.5
Death from CV causes, MI, stroke, heart failure, angina, or need for a CV procedure	17 (2.5)	26 (3.8)	31 (4.6)	8.4	12.7	15.5

Solomon SD, et al: N Engl J Med 352, 2005

Hazard Ratios for Hierarchical Cardiovascular Composite Endpoints in the APC Trial

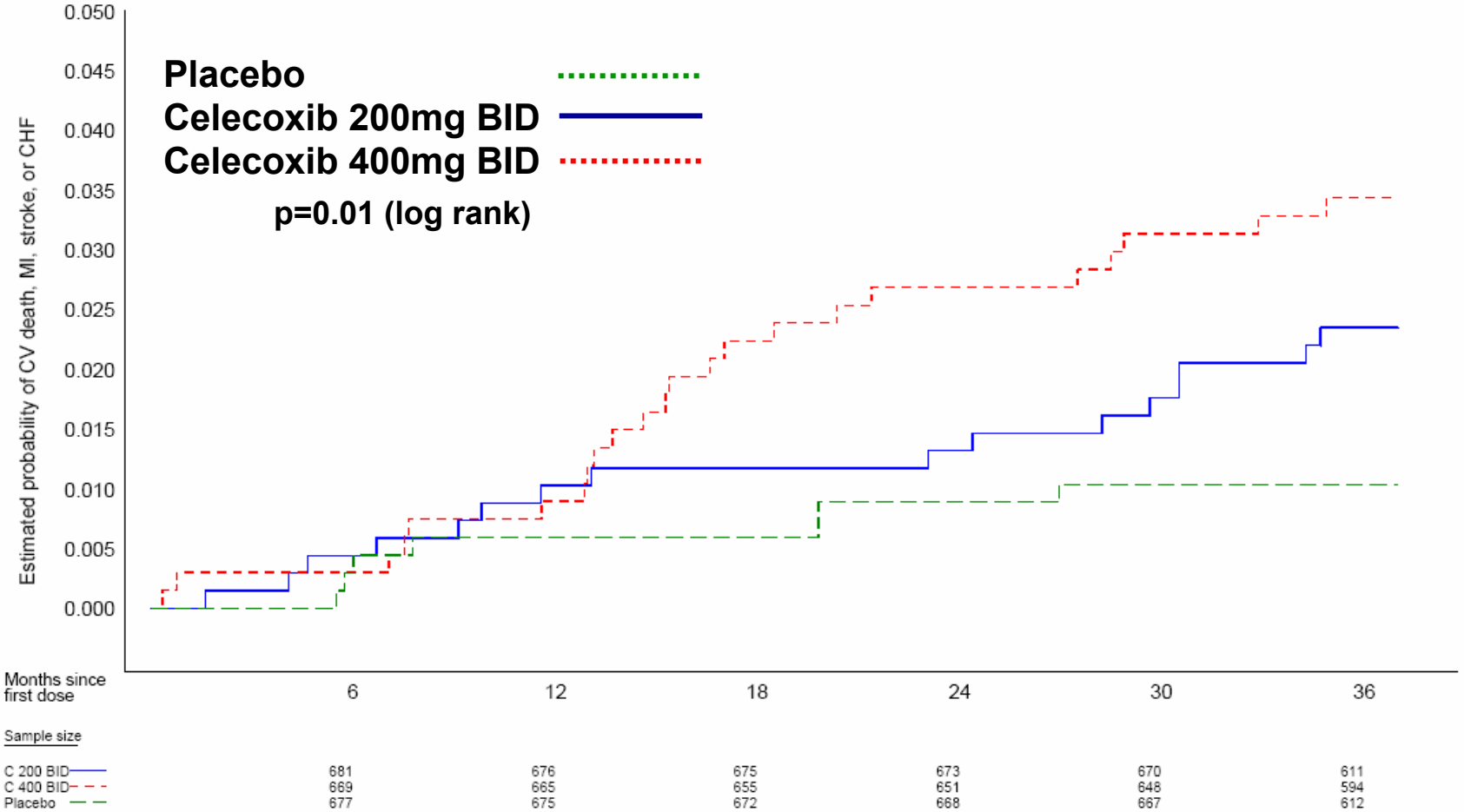
Endpoint	Hazard Ratio with 95% Confidence Interval*	
	200 mg BID N=685	400 mg BID N=671
Death from CV causes	3.0 (0.3-28.6)	6.1 (0.7-50.3)
Death from CV causes or MI	3.0 (1.0-9.3)	3.8 (1.3-11.5)
Death from CV causes, MI, or stroke	**2.5 (1.0-6.4)**	**3.4 (1.4-8.5)**
Death from CV causes, MI, stroke, or heart failure	2.3 (0.9-5.5)	3.4 (1.4-7.8)
Death from CV causes, MI, stroke, heart failure, or angina	1.6 (0.8-3.4)	2.3 (1.1-4.7)
Death from CV causes, MI, stroke, heart failure, angina, or need for a CV procedure	1.5 (0.8-2.8)	1.9 (1.0-3.3)

***Relative to placebo**

Solomon SD, et al: N Engl J Med 352, 2005

Kaplan-Meier Estimates of the Risk of Serious CV Events in the APC Trial by Treatment Arm

Serious CV events = Death from CV causes, MI, stroke, or heart failure



Solomon SD, et al: N Engl J Med 352, 2005

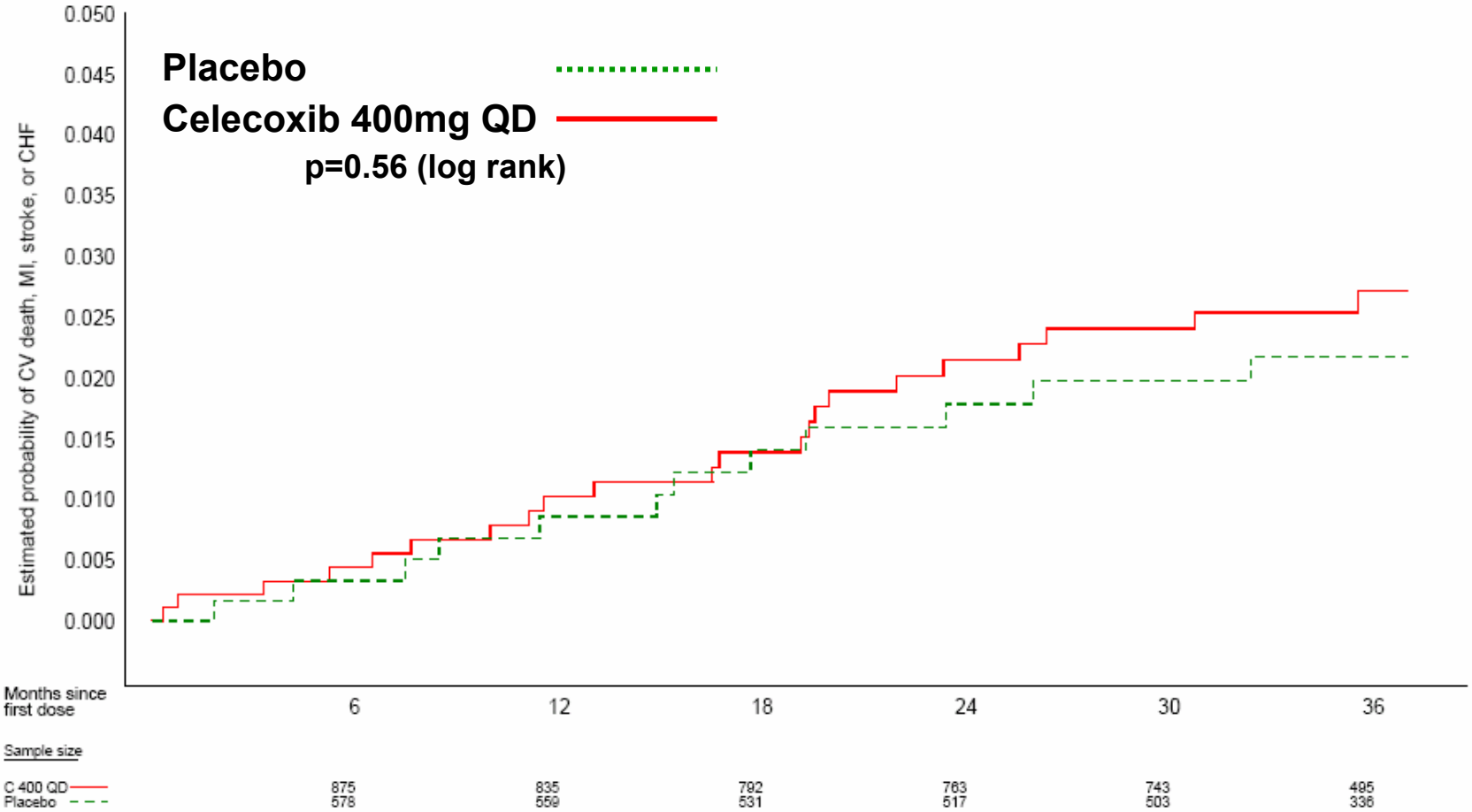
PreSAP Trial: Incidence & Hazard Ratio for Hierarchical CV Composite Endpoints

Endpoint	Number of patients (%)		Rate/1000 patient-years		Hazard Ratio with 95% Confidence Interval*
	Placebo N=628	400 mg QD N=933	Placebo N=628	400 mg QD N=933	
Death from CV causes	4 (0.6)	4 (0.4)	2.4	1.6	0.7 (0.2, 2.7)
Death from CV causes or MI	7 (1.1)	13 (1.4)	4.3	5.3	1.3 (0.5, 3.1)
Death from CV causes, MI, or stroke	**12 (1.9)**	**21 (2.3)**	**7.4**	**8.6**	**1.2 (0.6, 2.4)**
Death from CV causes, MI, stroke, or heart failure	12 (1.9)	22 (2.4)	7.4	9.1	1.2 (0.6, 2.5)
Death from CV causes, MI, stroke, heart failure, or angina	15 (2.4)	30 (3.2)	9.2	12.4	1.3 (0.7, 2.5)
Death from CV causes, MI, stroke, heart failure, angina, or need for a CV procedure	17 (2.7)	36 (3.9)	10.5	14.9	1.4 (0.8, 2.5)

***Relative to placebo**

Kaplan-Meier Estimates of the Risk of Serious CV Events in the PreSAP Trial by Treatment Arm

Serious CV events = Death from CV causes, MI, stroke, or heart failure



Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT)

- Randomized clinical trial of celecoxib 200 mg BID or naproxen 220 mg BID vs placebo
  - Elderly population (>70 yrs) at risk for AD (first degree relative with the disease)
  - Except for uncontrolled hypertension, no other restrictions for CV disease
  - Hypothesis: celecoxib will reduce the incidence of AD by >30% in a high risk cohort

First longer-term placebo-controlled trial with an NSAID

CV Safety of Chronic Celecoxib vs Placebo – Conclusions: 3 Longer-term Studies

- Alzheimer's Prevention:
  - CV events trended higher in patients treated with naproxen (220 mg BID) or celecoxib 200 mg BID compared to placebo
  - Naproxen showing greater numerical increase
- Adenomatous Polyp Prevention:
  - Two similar studies with conflicting results
    - No differences observed with continuous treatment of celecoxib up to 3 years in PreSAP
    - Increased rates vs placebo after ~1 year of continuous treatment in APC

3-Year Polyp Prevention Study with Low Dose ASA: Serious Adverse Events

Adverse Event	Placebo	ASA 81 mg	ASA 325 mg
	N=372	N=377	N=372
Myocardial infarction	1 (0.3)	2 (0.5)	5 (1.3)
Coronary revascularization	4 (1.1)	3 (0.8)	5 (1.3)
Stroke	0 (0.0)	2 (0.5)	5 (1.3)
Serious GI bleeding	3 (0.8)	2 (0.5)	4 (1.1)

n (percentage of patients)

Baron et al. NEJM 2003;348:891-899

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Cardiovascular Safety of Celecoxib:
Meta Analysis of RCTs

- 41 completed randomized controlled trials
- 44,308 treated patients (>91% OA/RA)
  - Celecoxib: 24,933
  - Placebo: 4,057
  - Active Comparator: 15,318
- Celecoxib: all studies had at least one ≥ 200 mg dose
  - Dose range: 50 – 800 mg daily
  - Focus: ≥ 200 mg total daily dose
- Predominant comparators – naproxen, ibuprofen, diclofenac
- Study duration – 2 wks to 1 yr

Celecoxib exposure		
≥ 3 months	n=11206	55% of patients
≥ 9 months	n=2472	12% of patients
≥ 1 yr	n= 803	4% of patients

Sources Available to Evaluate CV Safety of Celecoxib

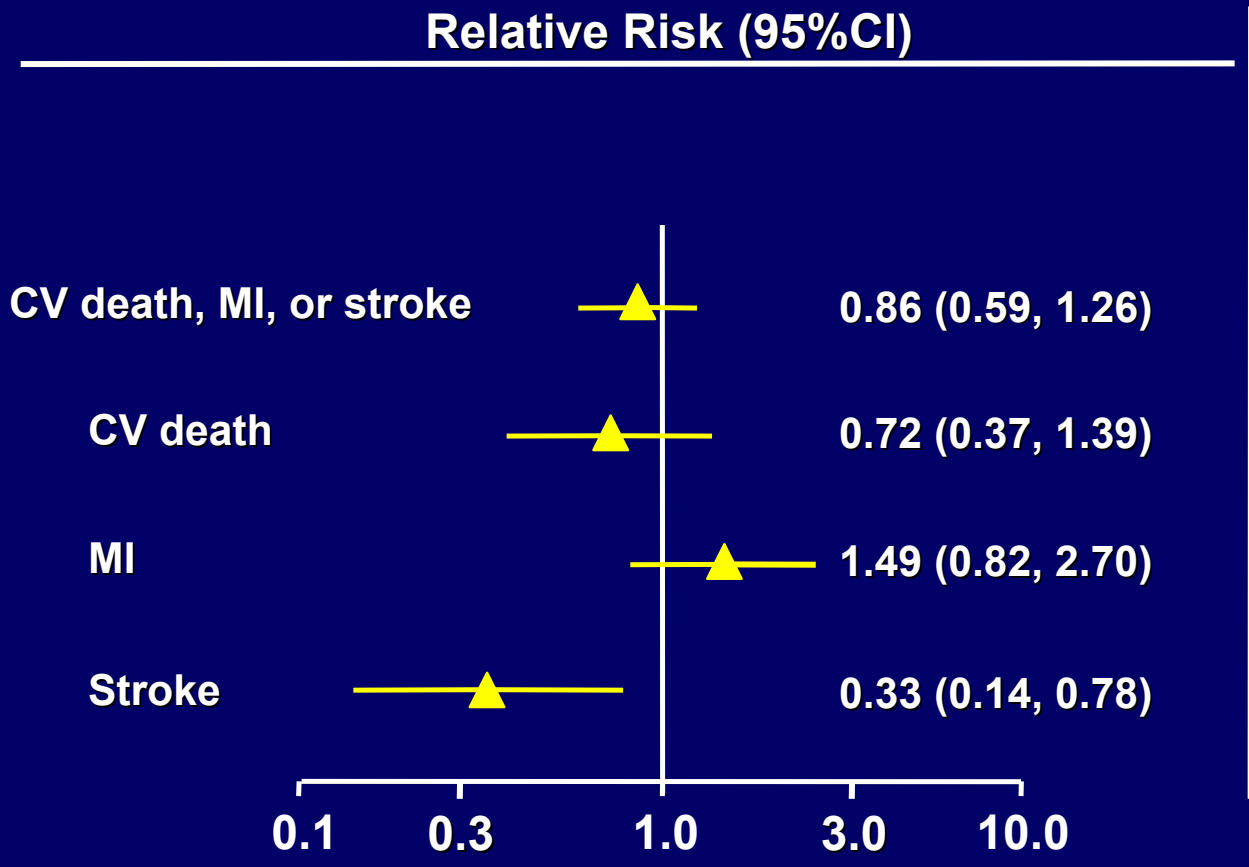
Study Description	APC[1]	Pre-SAP[2]	ADAPT	Meta-analysis of RCTs	
				vs. Placebo	vs. NSAIDs
Number of patients	2035	1561	2463	11519	33763
Study Period (yrs)*	2.8	2.6	1.6	0.16	0.30
Number APTC events	41	33	54	31	111
Baseline Characteristics					
Mean age (yrs)	60	61	75	59	60
Hx of hypertension	41%	39%	42%	46%	25%
Hx of CHD	n/a	2%	n/a	22%	10%
Diabetes	9%	21%	8%	19%	8%
Concomitant ASA	30%	16%	54%	13%	11%

*As of study drug stopping date , December 17, 2004

(1) Solomon et al, NEJM, 2005; 352:1071-1080 (2) CV Safety Review, April 12, 2005.

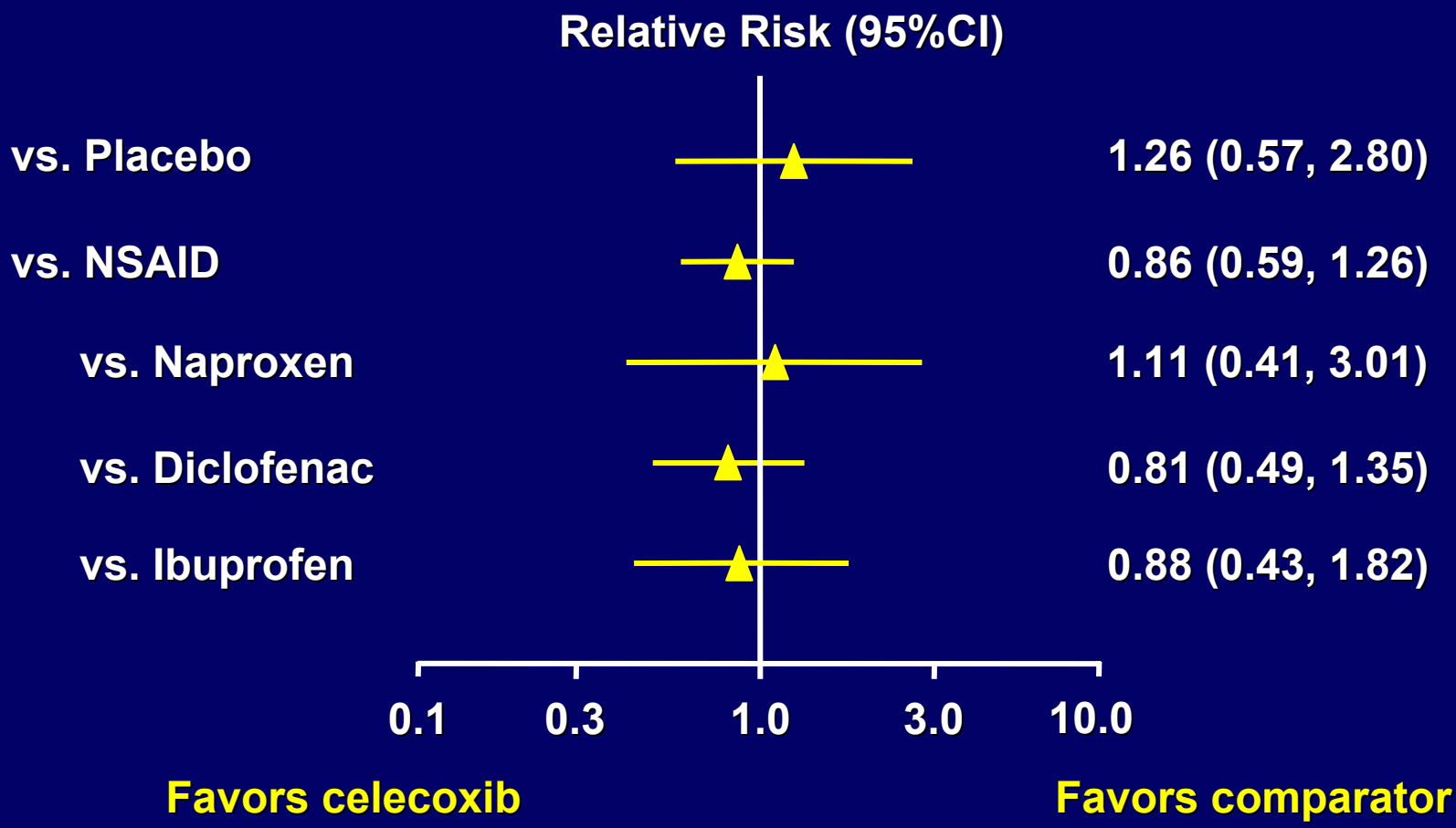
CV Death, MI and Stroke:

Celecoxib ≥ 200 mg daily dose vs. NSAIDs

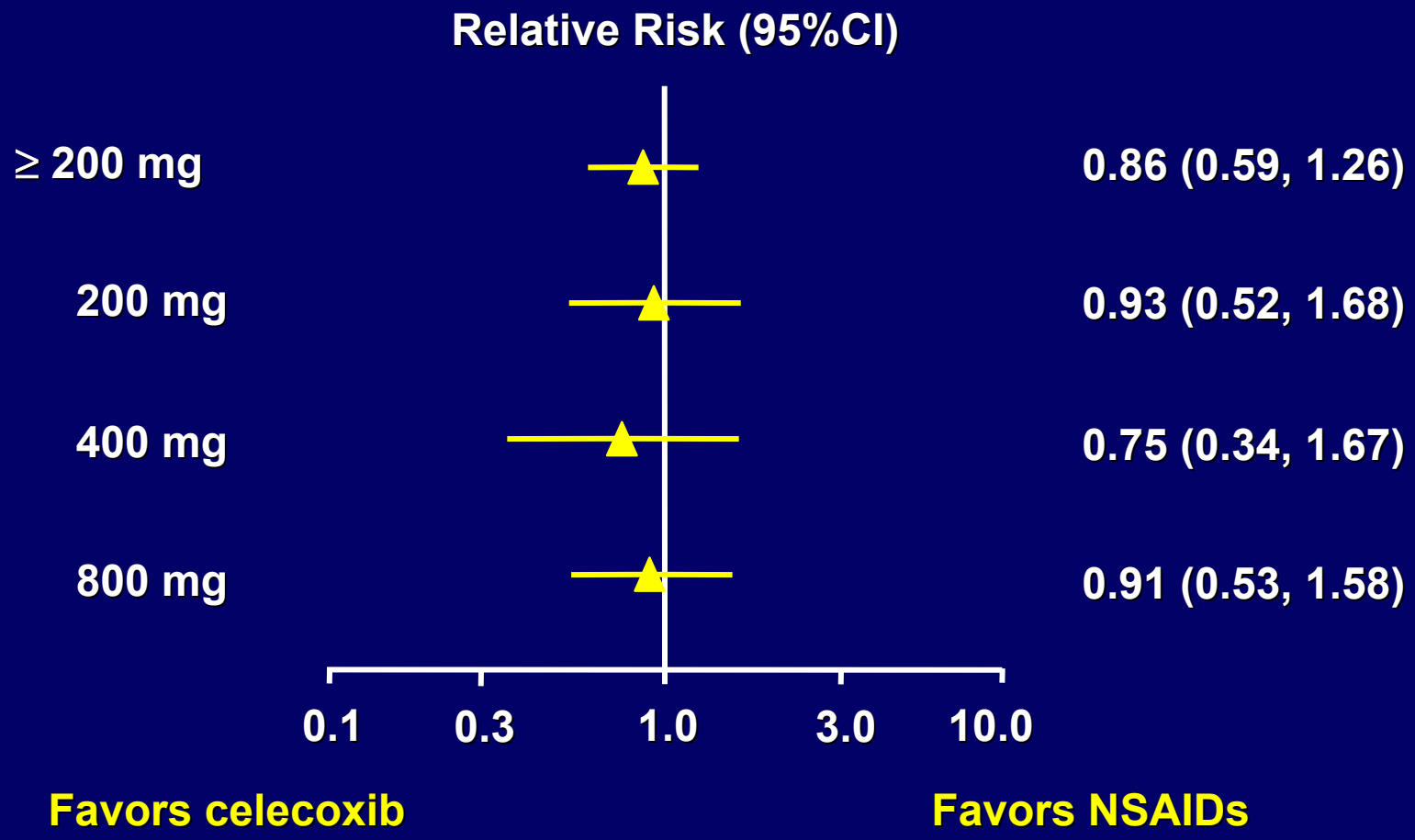


* Number of events (events per 100 patient-years)

CV Death, MI and Stroke:
Celecoxib ≥ 200 mg vs. Placebo and NSAIDs



CV Death, MI and Stroke:
Celecoxib vs. NSAIDs: By Dose



CV Safety in Randomized Clinical Trials: Conclusions

- No association for increased CV risk detected with use of celecoxib up to 1 yr compared to:
  - NSAIDs combined
  - naproxen, diclofenac or ibuprofen individually
- No dose-related increase in CV risk with celecoxib

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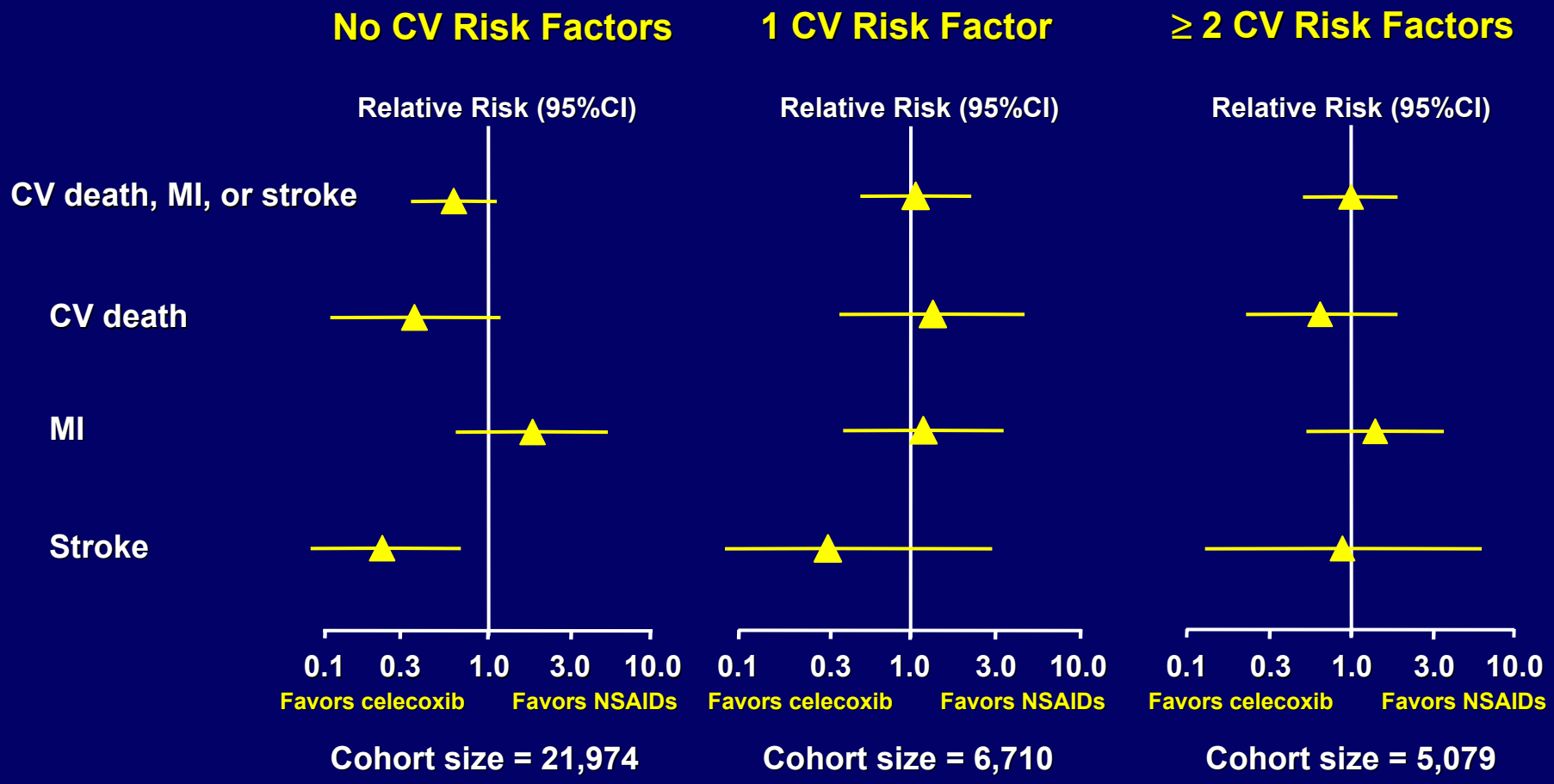
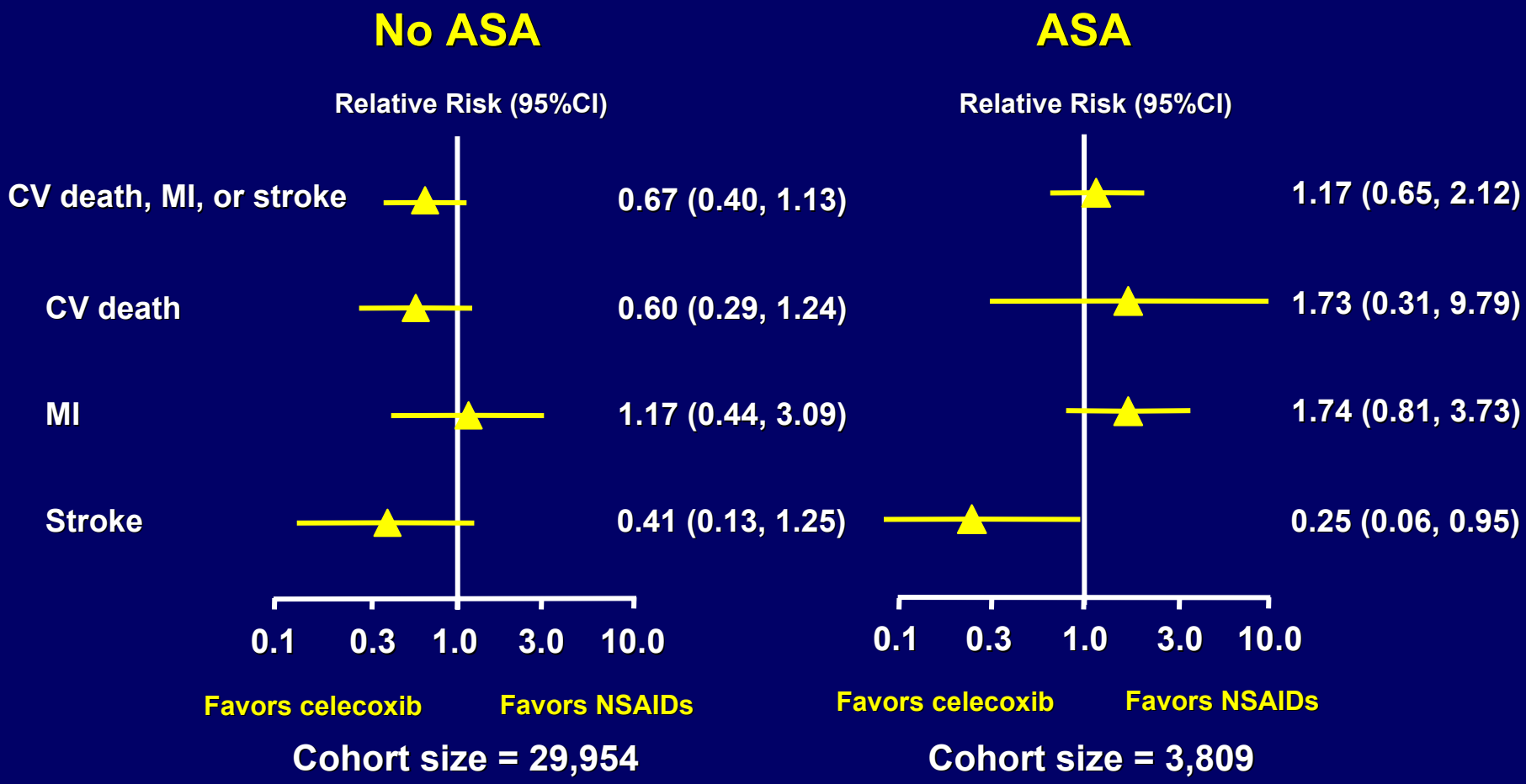
CV Death, MI and Stroke:
Celecoxib ≥ 200 mg vs. NSAIDs – By CV Risk Factors*



*Hypertension, diabetes, hyperlipidemia, coronary heart disease

CV Death, MI and Stroke:
Celecoxib ≥ 200 mg vs. NSAIDs – By ASA Use



Risk Factors - Conclusion

- The CV safety profile of celecoxib
  - comparable to NSAIDs
  - regardless of CV risk factors
  - whether based on medical history or use of low dose ASA

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COX-2 Selective Inhibitors and Risk of MI

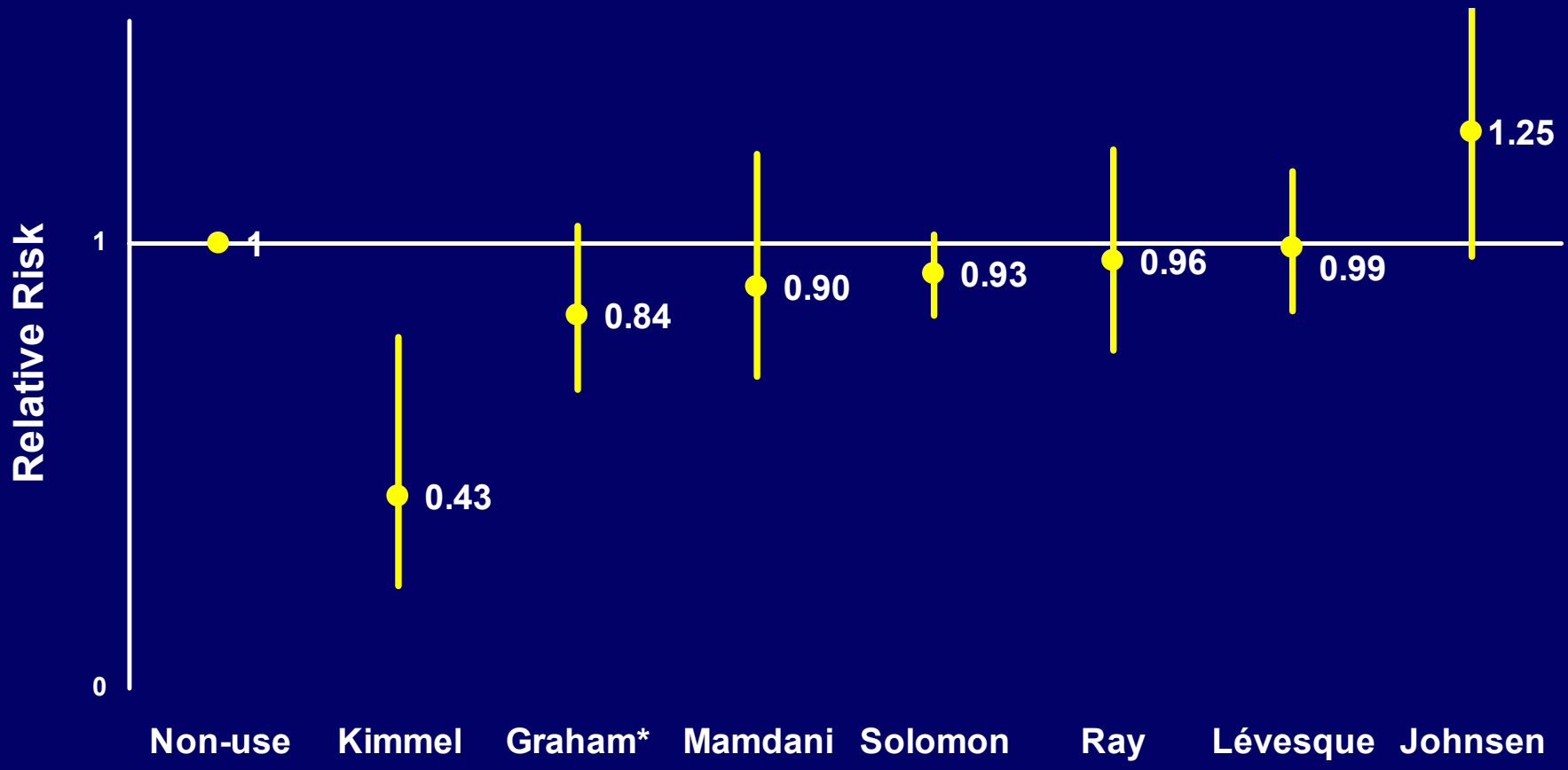
• Canada	Mamdani M et al.	Arch Intern Med 2003
• Canada	Lévesque LE et al.	Ann Intern Med 2005
• US	Ray WA et al.	Lancet 2002
• US	Solomon DH et al.	Circulation 2004
• US	Kimmel SE et al.	Ann Intern Med 2005
• US	Graham DJ et al.	Lancet 2005
• US	Shaya FT et al.	Arch Intern Med 2005
• Denmark	Johnsen SP et al.	Arch Intern Med 2005

Risk of MI and Use of Celecoxib
Published Epidemiological Studies

Population studied	2,311,937
Users of celecoxib	97,006
Person-years of use†	>12,647
Total number of events*	40,647
Events in celecoxib users	1,597

* Ray WA and Graham DJ include MI and CHD death; Kimmel SE non-fatal MI only
† Person-time of exposure to celecoxib not provided in studies of Graham DJ, Shaya FT, and Lévesque LE
Number of cases exposed to celecoxib not provided in Shaya FT
Published studies up to June 7, 2005

Risk of MI and Use of Celecoxib: Relative Risk Celecoxib vs Non-use/Remote Use*



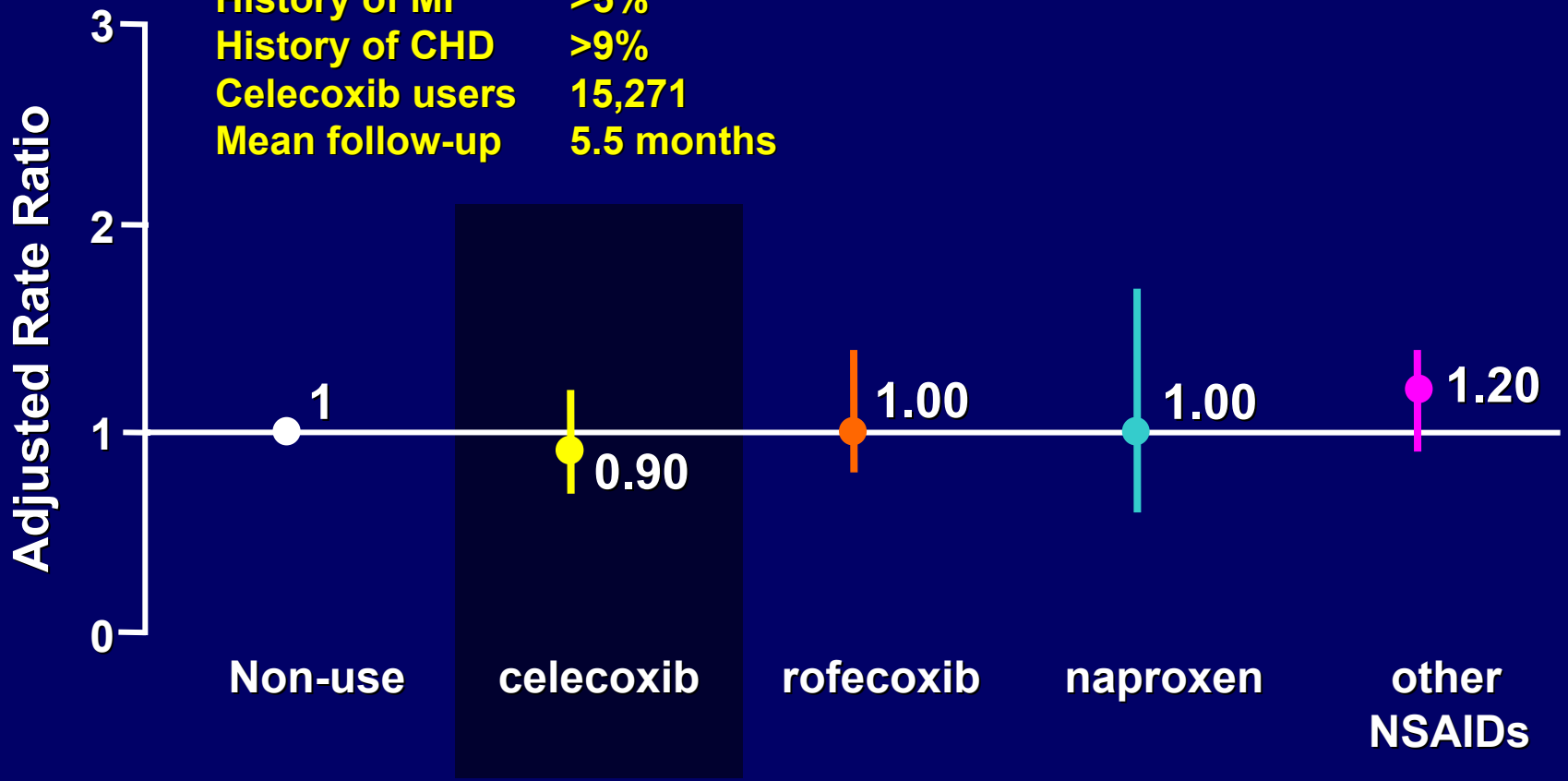
* Graham DJ: Reference group is remote use of NSAIDs

Relative Risk of MI:

Use of COX-2 Selective Inhibitors or NSAIDs vs. Non-use

CANADA

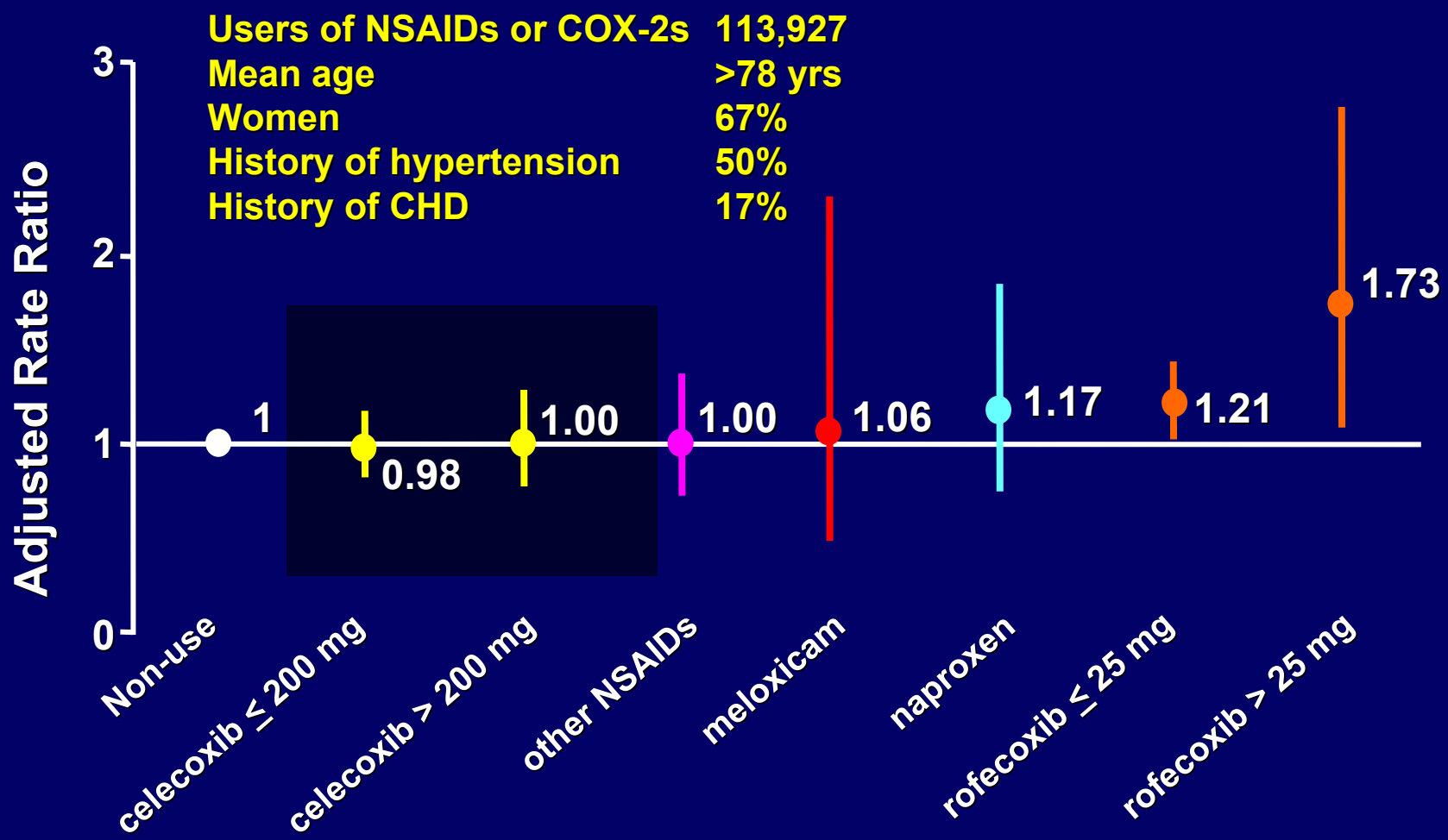
Mean age	>75 yrs
Women	>56%
History of MI	>5%
History of CHD	>9%
Celecoxib users	15,271
Mean follow-up	5.5 months



Mamdani et al. Arch Intern Med 2003;163:481-6

Relative Risk of MI:
Use of COX-2 Selective Inhibitors or NSAIDs vs. Non-use

CANADA

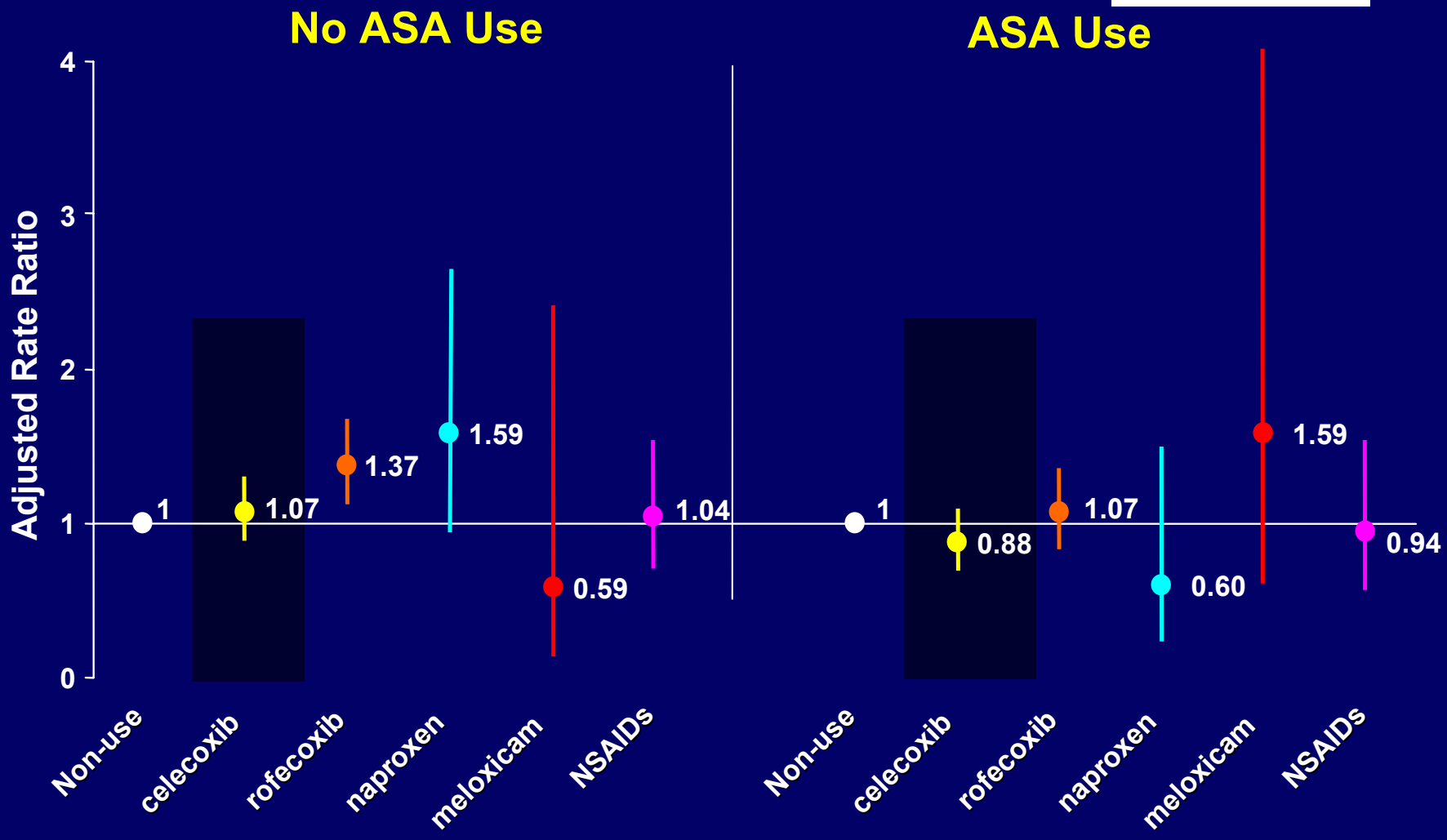


Lévesque et al. Ann Intern Med 2005;142:481-9

Risk of MI by ASA Use:

Relative Risk of COX-2 Selective Inhibitors vs. Non-use

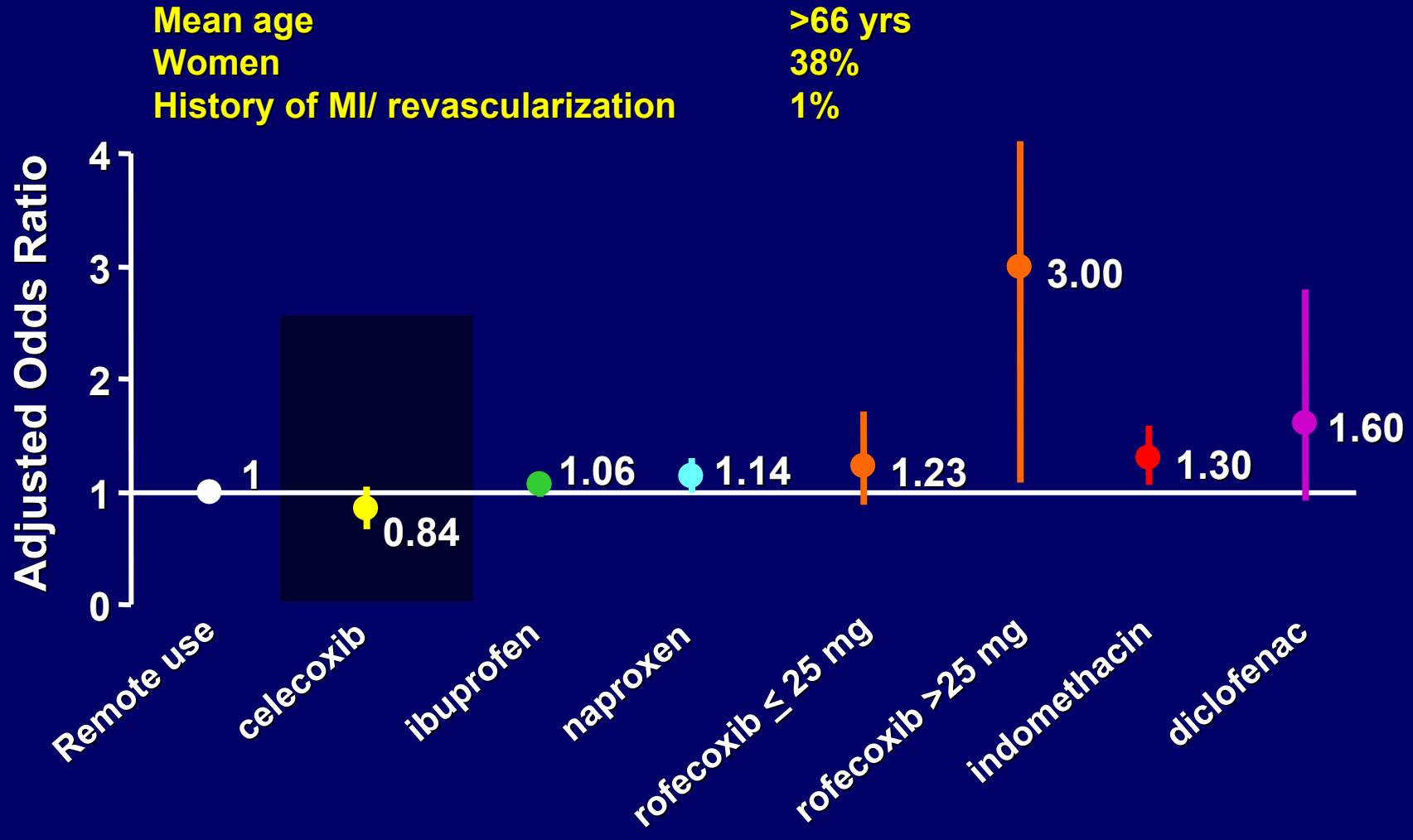
CANADA



Lévesque et al. Ann Intern Med 2005;142:481-9

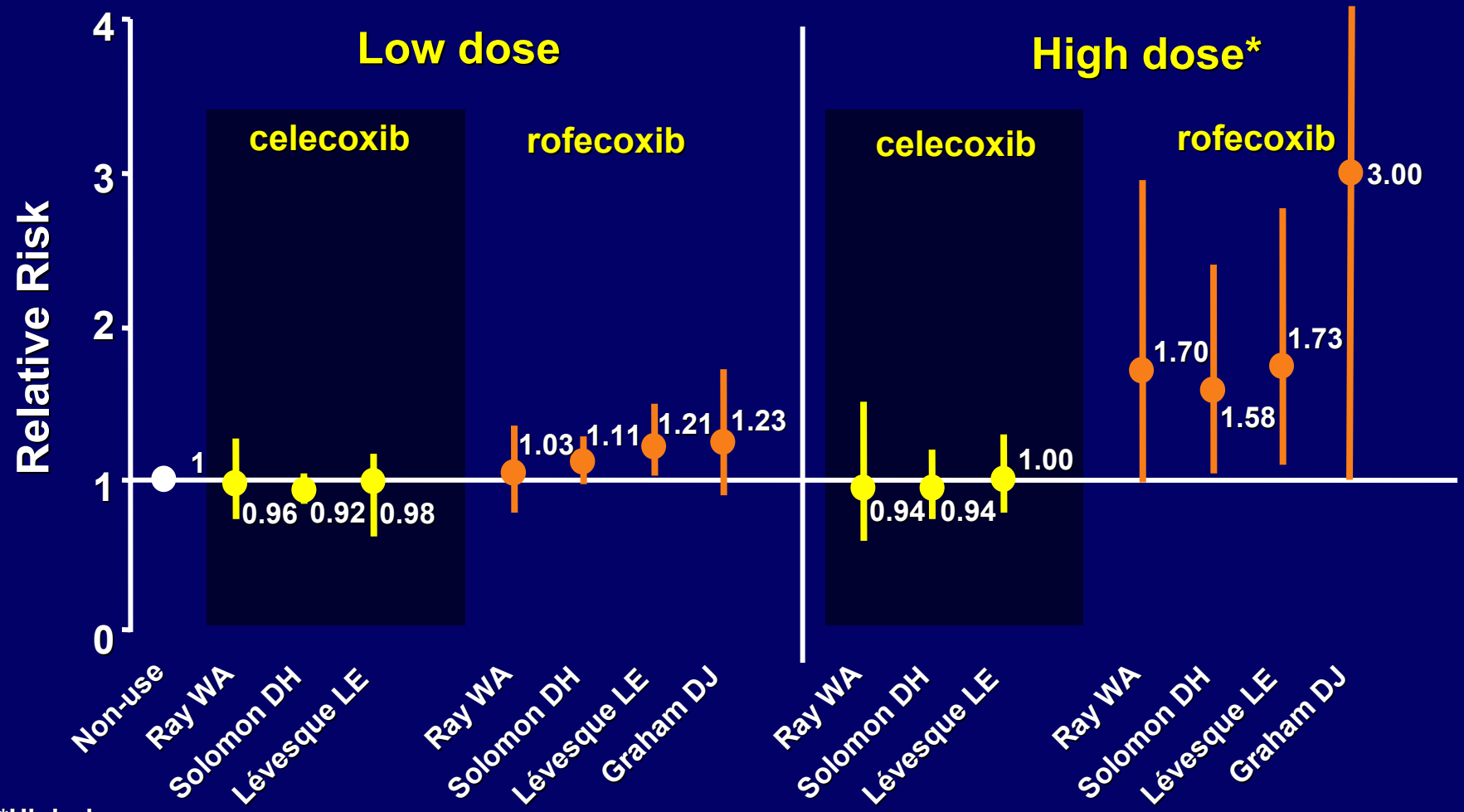
Relative Risk of MI/Coronary Death:

Use of COX-2 Selective Inhibitors or NSAIDs vs. Remote-use



Graham et al. Lancet 2005;365:475-81

Summary of MI Risk by Dose:
Relative Risk vs. Non-use/Remote Use



*High-dose:
rofecoxib >25 mg/day
celecoxib >200 mg/day in Solomon DH and Lévesque LE
celecoxib ≥ 300 mg/day in Ray WA

CV Epidemiology Studies - Conclusions

- The risk of MI with celecoxib, when prescribed in various real world settings, is
  - Consistent and similar to nonselective NSAIDs
  - Consistent and similar to non-use or remote use of NSAIDs
  - Celecoxib safety is consistent regardless of
    - dose
    - concomitant ASA usage

Benefit-Risk of Celecoxib in Arthritis - Conclusions

- In the currently approved arthritis indications, the benefit-risk of celecoxib remains positive relative to NSAIDs
  - Comparable efficacy
  - GI safety benefit
  - Comparable CV risk
- Shared uncertainty with NSAIDs regarding the CV safety beyond year of continuous treatment

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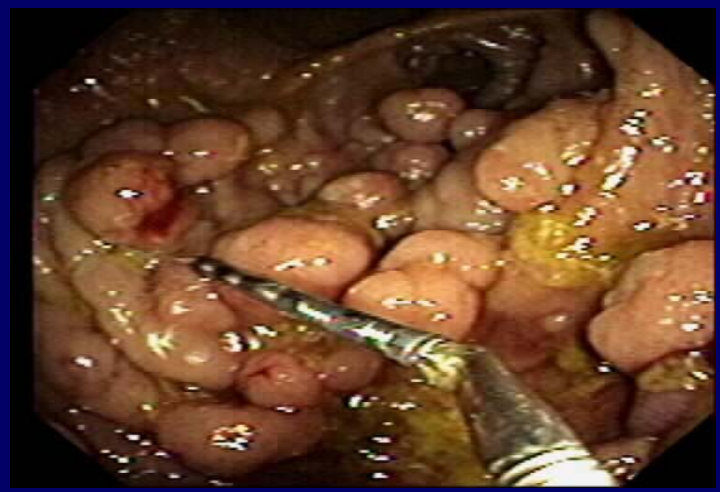
Familial Adenomatous Polyposis (FAP):
Celecoxib Approval- Background

- May 2002:
  - Health Canada granted a Notice of Compliance with Conditions for use of celecoxib 400 mg BID in FAP
- December 17, 2004:
  - The Data Safety Monitoring Board of a long-term celecoxib prevention trial (APC 005) in Sporadic Adenomatous Polyps (SAP) suspended study dosing due to an increased number of CV events in the celecoxib treatment arms, particularly with the 400 mg BID dose
- December 17, 2004:
  - Health Canada notified the manufacturer of celecoxib that the market authorization for the indication of prevention of recurrence of FAP was withdrawn due to CV concerns

Familial Adenomatous Polyposis (FAP)

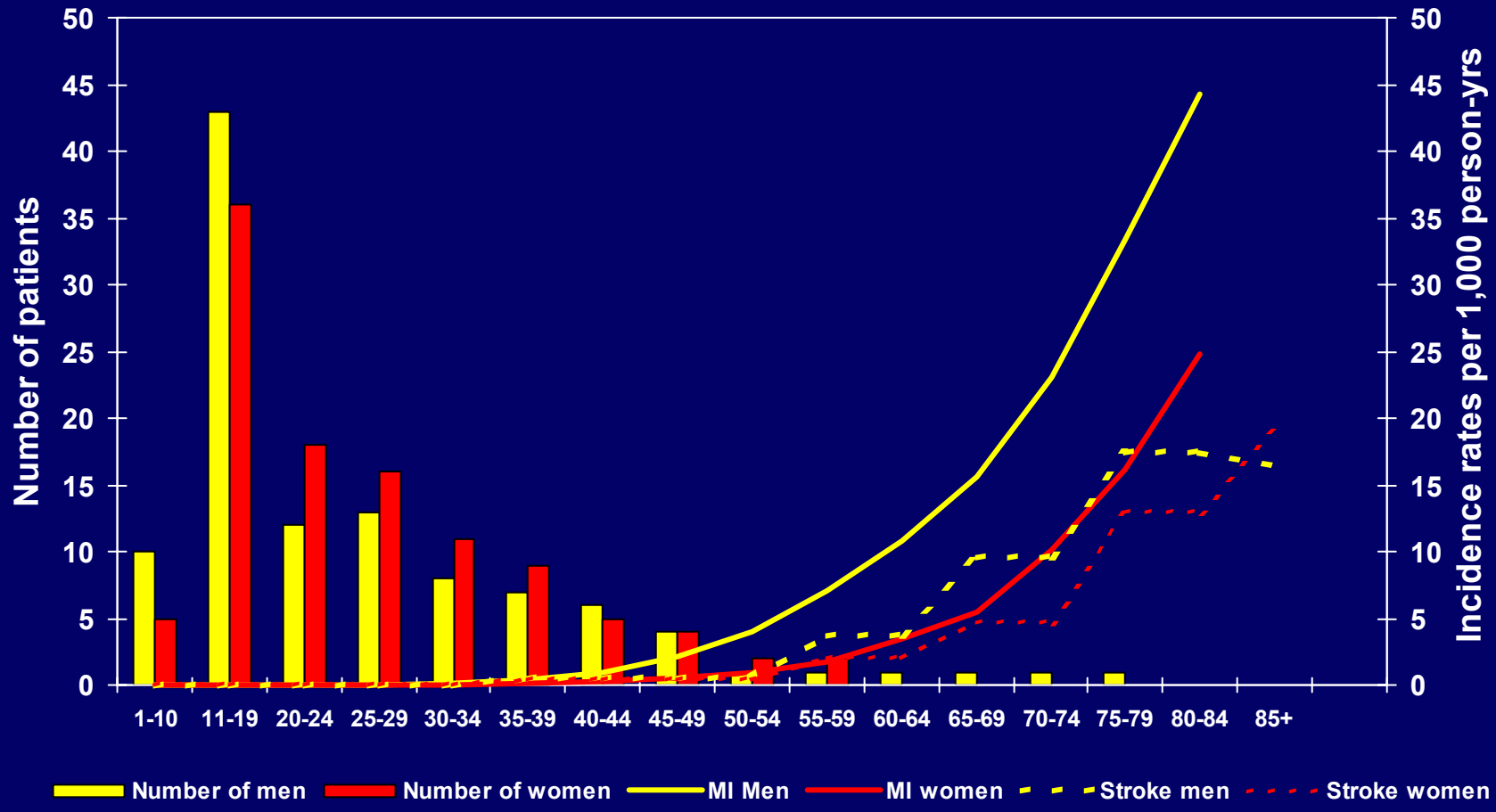
- Rare inherited disease starting in teenagers
  - Mean annual incidence rates: 0.9 to 1.9 per million*
  - Estimated annual incidence counts: 59§
  - Point prevalence rates: 26.3 to 46.5 per million*
  - Estimated prevalence counts: 1442 §
- > 100 pre-malignant colorectal adenomas
- 100% colorectal cancer risk if untreated
- Surgical prophylaxis reduced cancer risk, albeit with substantial morbidity



* Bülow S et al Gut 2003;52:742-746

§ Estimated from Bülow highest reported rates and 2001 Canadian population estimates

Age and Sex Distribution of FAP Patients at Diagnosis and Incidence Rates of MI and Stroke

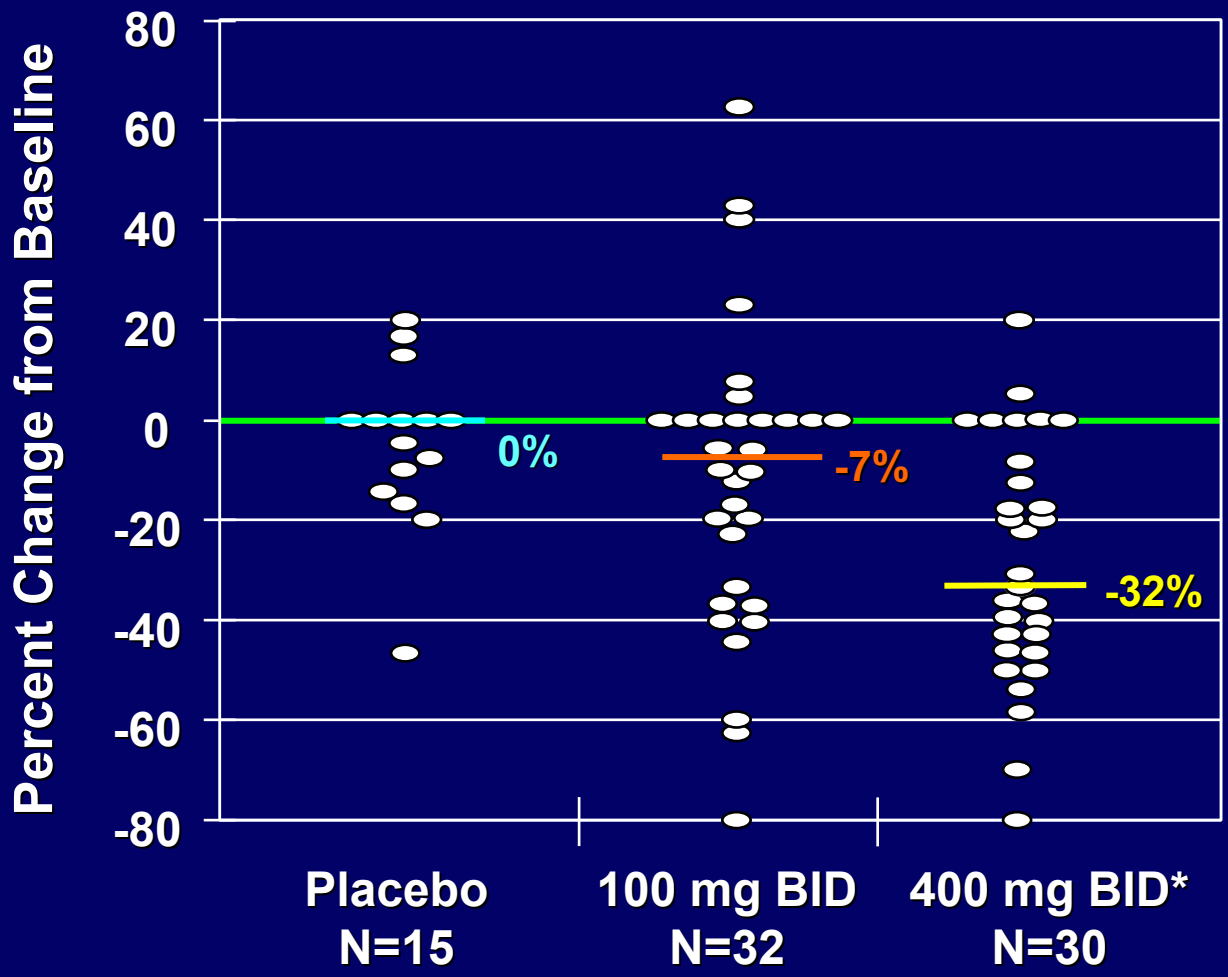


Hammar N et al Int. J Epidemiol 2001; 30: S30-S34 Johansson B, et al. Stroke 2000;31:481-486

Björk J et al Gastroenterol 1999; 34: 1230-1235

Colorectal Efficacy of Celecoxib in FAP Patients

Percent Change in Number of Colorectal Polyps



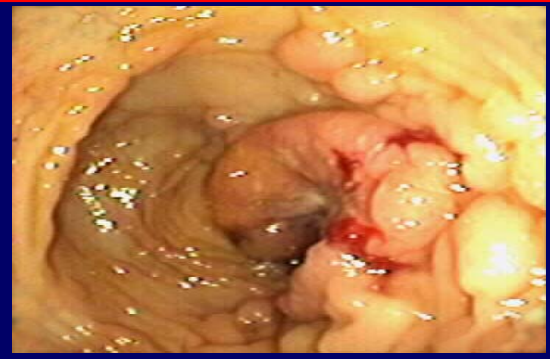
* p = 0.003 versus placebo

Bars represent median reductions in polyp numbers

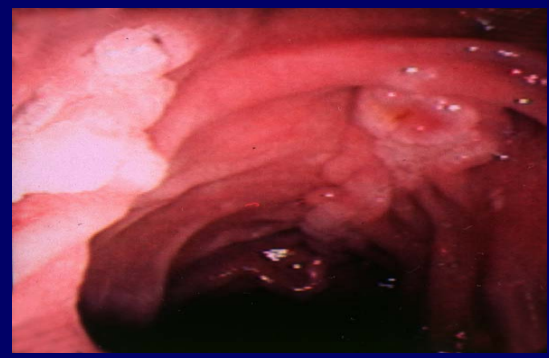
Steinbach, et al. NEJM, 2000

Celecoxib Offers Clinical Benefit for Patients with FAP

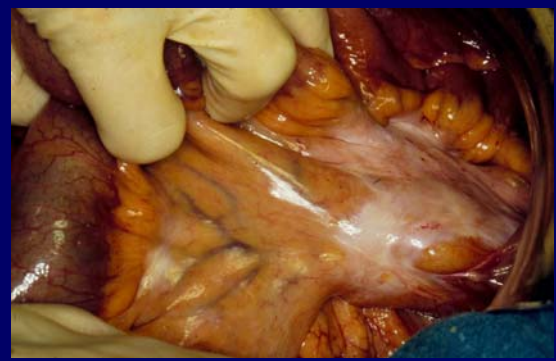
- Post-colectomy patients: prevent rectal adenomas to avoid proctectomy



- Duodenal adenoma patients: avoid Whipple procedure



- Other clinical situations restricting surgery e.g. desmoids, patient refusal



FAP Benefit-Risk: Conclusions

- Efficacy of celecoxib in this indication is demonstrated by significant polyp reduction
- CV risk is likely to be small in this young, low CV risk patient population
- Weighing the benefits against the risks for this indication, celecoxib should be available in Canada for treatment of FAP

Overview

- Introduction
- GI Safety
- Celecoxib - CV safety
- FAP: Benefit-risk
- Conclusions

Overall Conclusions

- Celecoxib presents a favorable benefit-risk for patients with the chronic inflammation and pain of arthritis compared with NSAIDs
- Celecoxib should remain a choice for patients with CV risk factors and CV histories, with appropriate warnings
- Pfizer is committed to research
  - to address important remaining questions on celecoxib benefits and risks
  - although more data exist for celecoxib than for most NSAID comparators
- Celecoxib presents a favorable benefit-risk for patients with FAP and should remain a treatment for Canadian patients