Selective COX-2 inhibitor Non Steroidal Anti-Inflammatory Drugs Expert Advisory Panel and Public Forum

Gastrointestinal and Cardiovascular Safety of Lumiracoxib, Ibuprofen, and Naproxen

Ottawa, June 9, 2005

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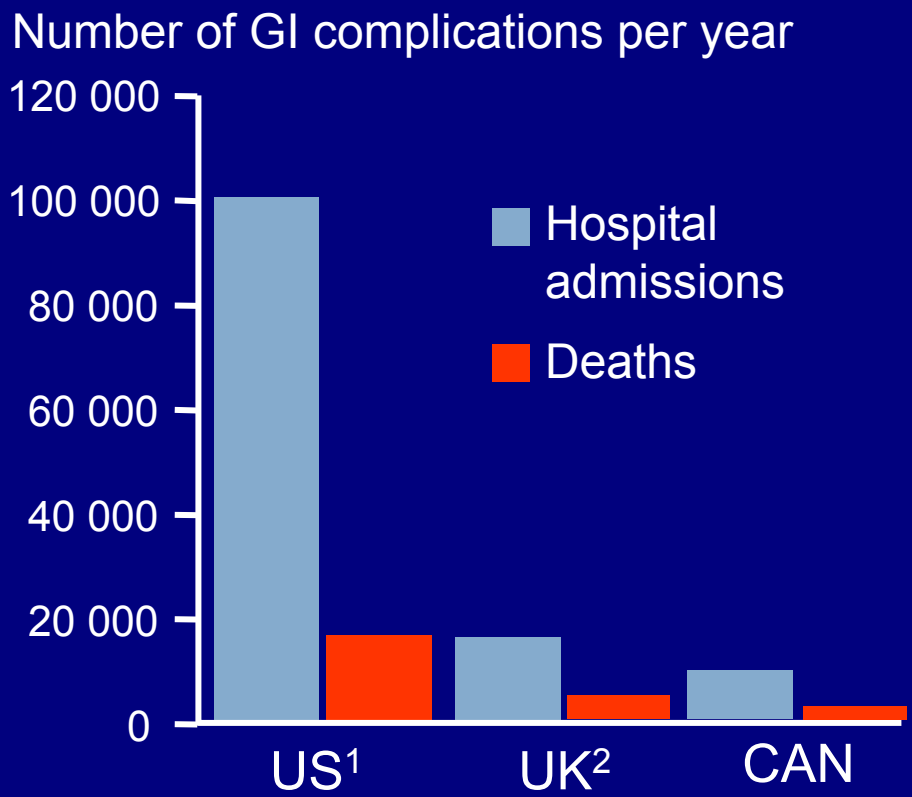
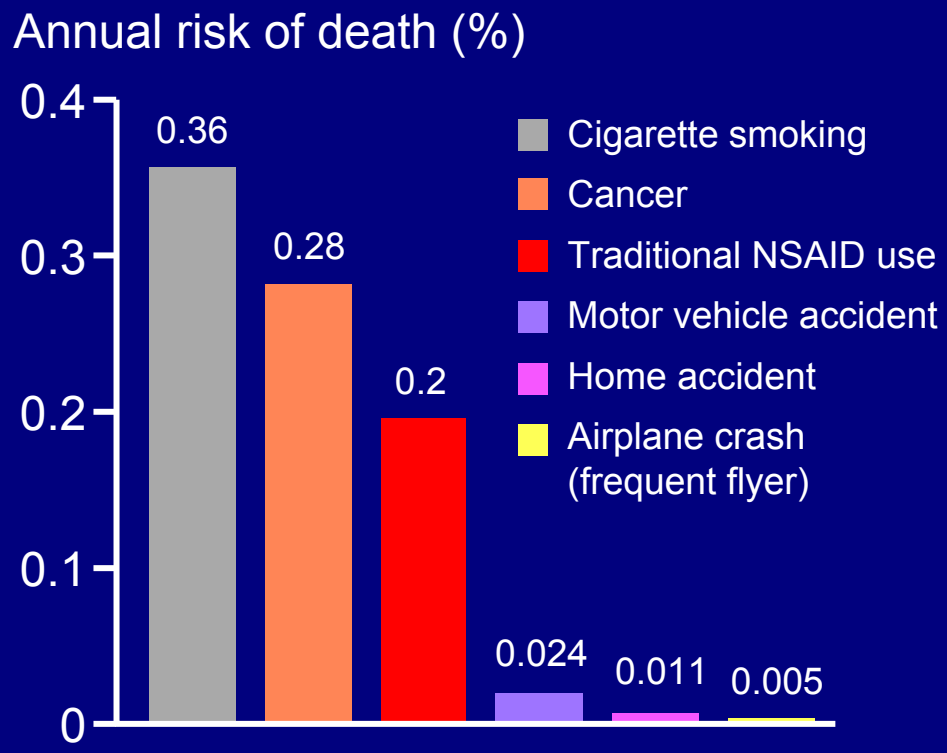
Vice President Drug Regulatory Affairs
Novartis Pharmaceuticals Canada Inc.

Traditional NSAIDs used for OA are associated with serious GI ulcer complications, including death

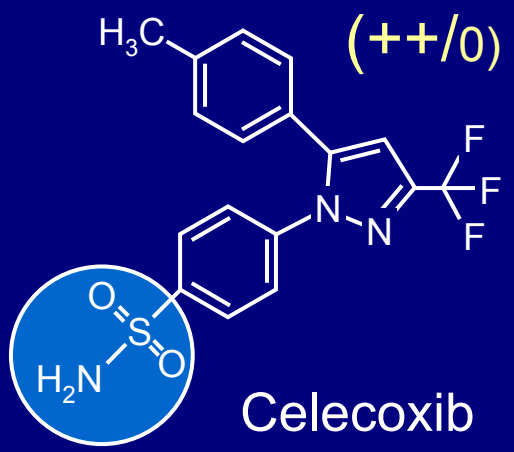




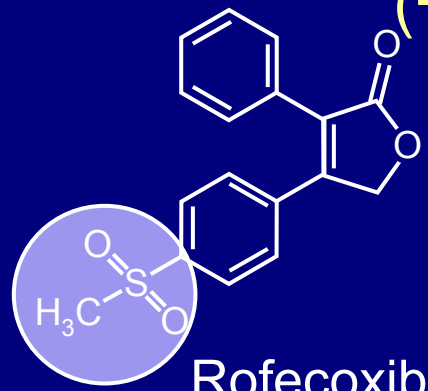
1. Singh G, *et al*. J Rheumatol 1999;26 (Suppl.56):18-24.
2. Blower AL, *et al*. Aliment Pharmacol Ther 1997;11:283-291.

Fries J, *et al*. 1991; Wilson R, Crouch E. 1987.

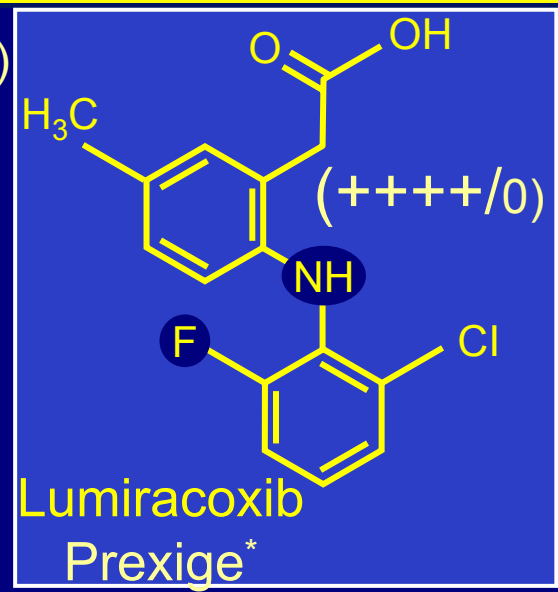
Chemical structures of COX-2 selective inhibitors (COX-2/COX-1 selectivity)



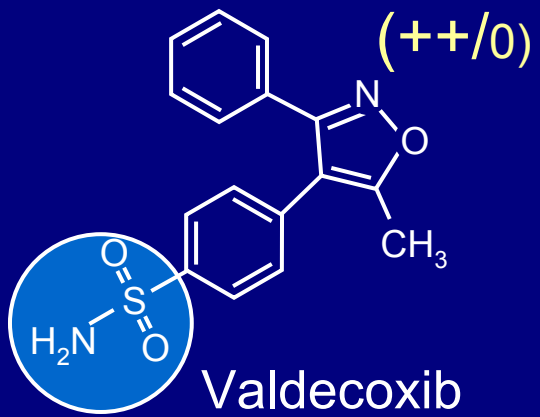
Celecoxib
Celebrex®



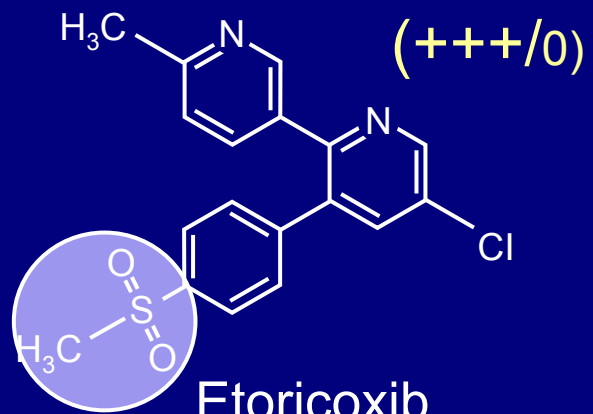
Rofecoxib
Vioxx®



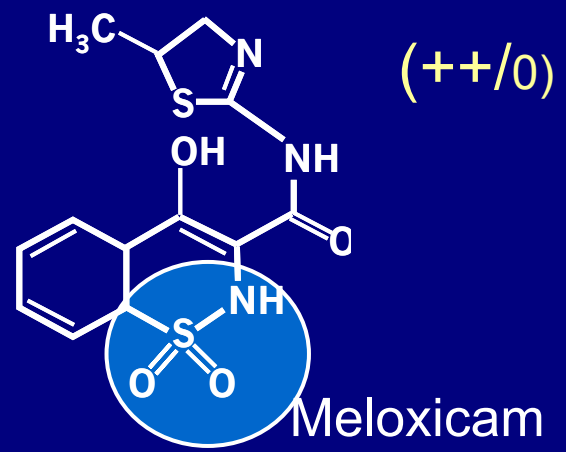
Lumiracoxib
Prexige*



Valdecoxib
Bextra®



Etoricoxib
Arcoxia®



Meloxicam
Mobic®

Prexige and its Distinct Characteristics

- highly selective COX-2 inhibitor with a structure very different from the other COX-2 selective inhibitors available (contains no sulfur)
- persists within the inflamed tissue compartment, an effect not observed with the other COX-2 selective inhibitors.
- rapidly absorbed in healthy subjects, reaching peak plasma concentrations 1–4 hours after dosing and a mean half-life (T½) of 3-6 hours.
- associated with significantly fewer symptomatic ulcers and prespecified GI AEs than traditional NSAIDs.
- favorable blood pressure profile, measured by significantly smaller changes from baseline in systolic and diastolic blood pressure compared with NSAIDs.

Key points

- Each NSAID/COX-2 selective inhibitor has a benefit-risk profile that must be considered individually
- Novartis development program provides clinically informative safety data for lumiracoxib, ibuprofen and naproxen
- Safety profile of lumiracoxib differs from non-selective NSAIDs and other COX-2 selective inhibitors

Presentation overview

- Presentation of the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)
  - Largest (18,325 patients) GI outcomes study conducted in OA patients
  - Compared lumiracoxib to naproxen and ibuprofen
  - Lumiracoxib dose is 4x the recommended chronic OA dose
- Presentation of comprehensive meta-analysis of CV safety
  - Includes all completed randomized controlled clinical trials of lumiracoxib with durations ≥ 1 week (22 trials; 33,933 patients)
- Definitive GI benefit in non-aspirin population
- No significant CV risk in meta-analysis of all lumiracoxib studies >1 week

Participants

- Presentation:
  - Patrice Matchaba, MD
    Global Medical Director, lumiracoxib program,
    Novartis Pharmaceuticals

TARGET
Unique design principles

- TARGET was powered to investigate upper GI ulcer complications – 'COX-2 promise'
- Increase in study size (>18 000) to include patients on low-dose aspirin
  - CLASS and VIGOR each had 8000 patients
  - Stratification of patients by low-dose aspirin use (24%)
  - CLASS (no aspirin stratification) and VIGOR (no aspirin)
- Fixed–term design (12 months) in order to increase power
  - CLASS (minimum 6 months) and VIGOR (median 9 months)
- Inclusion of two NSAIDs: naproxen and ibuprofen: not all NSAIDs have the same GI and CV profile
- Prospective expert adjudication committees

TARGET Study

Objective:

- Compare lumiracoxib 400 mg od (4 times OA dose) to NSAIDs (naproxen and ibuprofen at maximum label doses)
  - GI ulcer complications
  - CV events
  - renal, hepatic, and overall safety

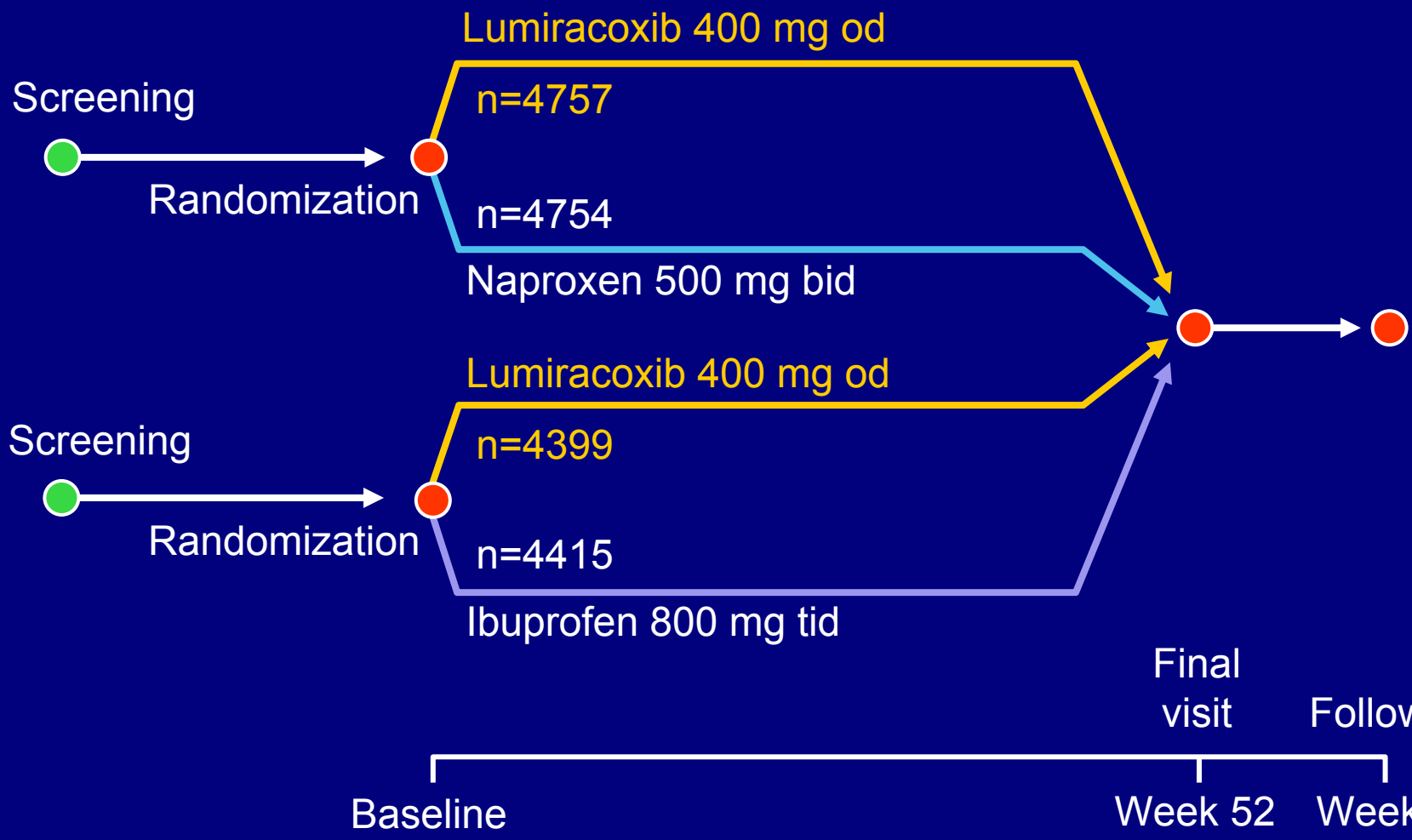
Key inclusion criteria

- Patients ≥50 years with primary OA
- Patients at high risk for CHD requiring aspirin (75–100 mg)

Key GI exclusion criterion

- Active GI ulceration within the previous 30 days, bleeding of the upper GI tract in the previous year, or history of gastroduodenal perforations or obstructions

TARGET
Study design



Hawkey C, *et al*. 2004.

Major endpoints were prospectively defined and adjudicated by independent external committees

3 independent safety committees (GI, CV and hepatic)

Cardiovascular endpoints adjudicated:

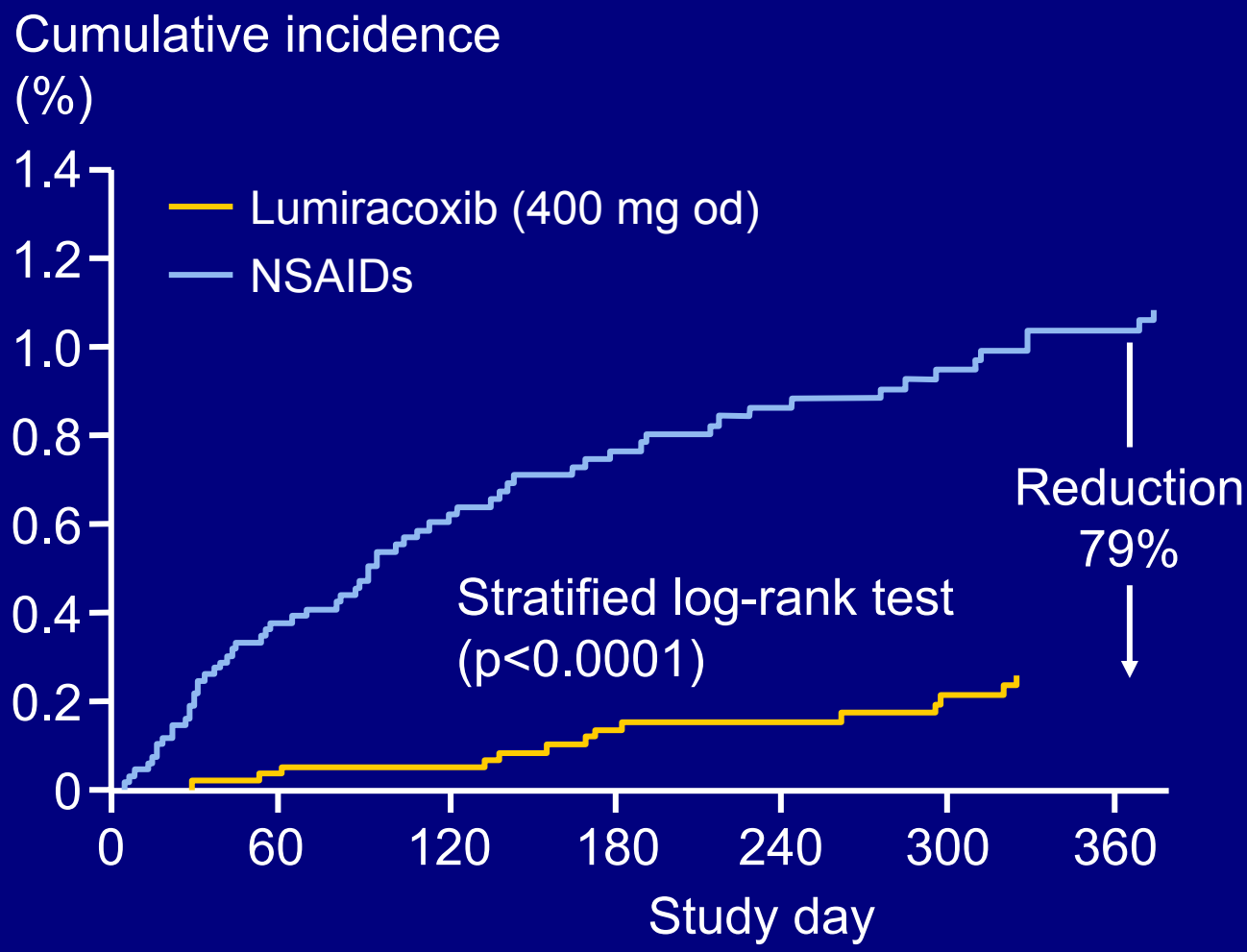
- Coronary events: MI (silent and clinical), unstable angina, cardiac arrest, cardiovascular death
- Cerebrovascular events: stroke (ischemic and hemorrhagic), TIA
- Deep vein thrombosis
- Pulmonary embolism

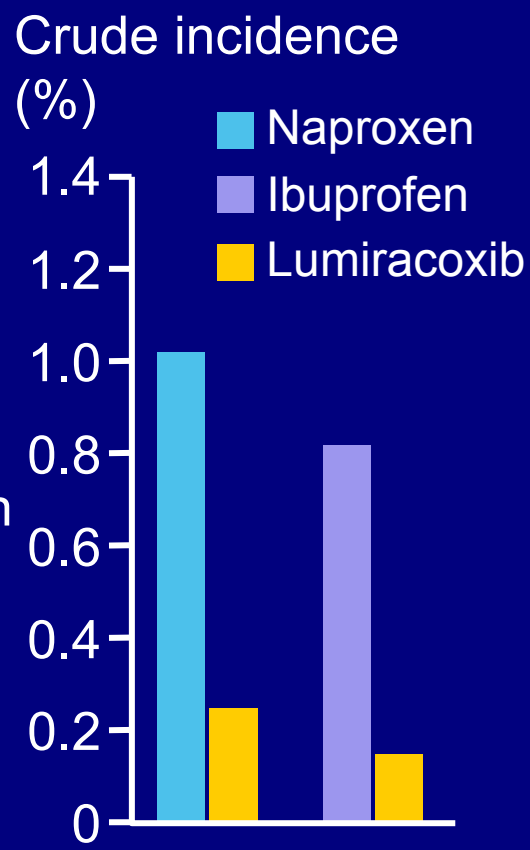
Patient demographics

- Mean age 63 years; 76% female
- 24% aspirin use (per stratification)
- 12% at high CV risk
  (CV history or as defined by Framingham criteria)
- Many patients had comorbidities
  - 45% had hypertension
  - 20% had dyslipidemia
  - 8% had diabetes
- More than 60% completed 12 months of treatment

Schnitzer T, *et al*. 2004.

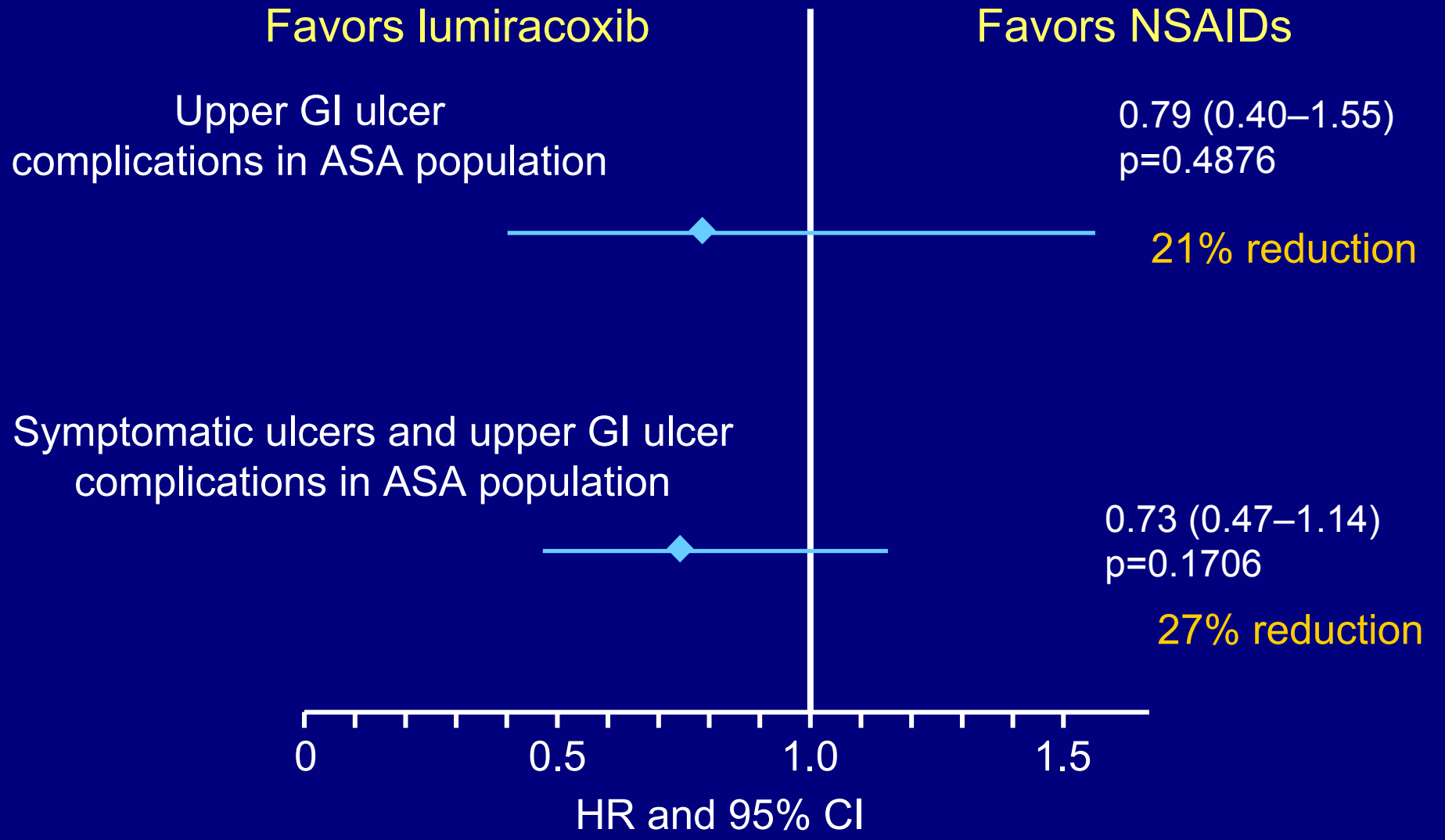
Fewer ulcer complications with lumiracoxib compared to NSAIDs (non-ASA population)





Schnitzer T, *et al*. 2004.

Consistent trend towards benefit in ASA population



Relative risk of upper GI ulcer complications in patients with at least one GI risk factor*

	Number of subjects at risk	Number (%) of subjects with events	RR	95% CI	p value
Overall population					
Lumiracoxib	6629	23 (0.35)			
NSAIDs	6687	75 (1.12)			
Lumiracoxib vs NSAIDs			0.31	0.19–0.49	<0.0001
Study 0117					
Lumiracoxib	3582	16 (0.45)			
Naproxen	3549	45 (1.27)			
Lumiracoxib vs naproxen			0.35	0.20–0.62	0.0002
Study 2332					
Lumiracoxib	3047	7 (0.23)			
Ibuprofen	3138	30 (0.96)			
Lumiracoxib vs ibuprofen			0.24	0.11–0.55	0.0002

*Age >65 years or use of low-dose aspirin or history of GI ulcer or bleed, or *h. pylori* positive

Summary of GI data

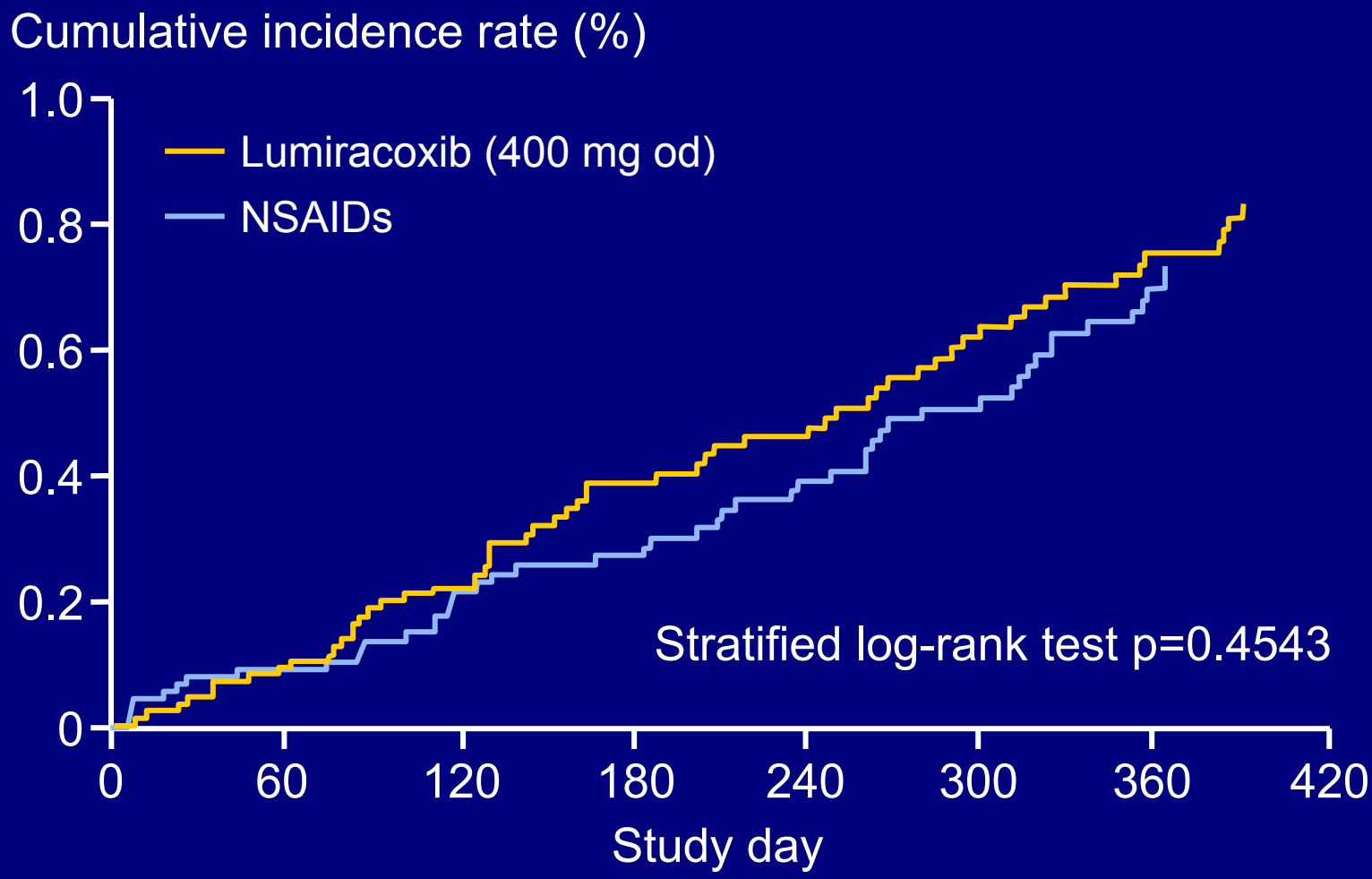
- Definitive GI benefit for patients taking lumiracoxib compared with naproxen and ibuprofen
  - in the population not taking low-dose aspirin
  - in the high GI risk population
  - in the overall population
- Consistent trend towards benefit in the population taking low-dose aspirin

APTC endpoint components

- Anti-Platelet Trialist Collaboration endpoint: Suspected cases blindly adjudicated by CV Safety Committee as confirmed or probable
  - non-fatal MI, including silent MI (ECG-detected)
  - non-fatal stroke (ischemic or hemorrhagic)
  - CV death

BMJ. 308:81-106.

No difference in cumulative rate of APTC endpoint between lumiracoxib and NSAIDs in overall population



Farkouh M, *et al*. 2004.

Patient demographics
Differences in CV baseline risk between substudies

	Study 0117		Study 2332	
	Lumiracoxib n=4741	Naproxen n=4730	Lumiracoxib n=4376	Ibuprofen n=4397
	n (%)	n (%)	n (%)	n (%)
Low-dose aspirin	1198 (25)	1199 (25)	978 (22)	970 (22)
High CV risk or CV history	657 (14)	643 (14)	484 (11)	423 (10)
Systolic/diastolic BP: SBP >140 mmHg or DBP >90 mmHg	2088 (44)	2100 (44)	1642 (38)	1592 (36)

High CV risk or CV history is defined as patients at high cardiovascular risk defined by the Framingham risk-assessment equations, or patients with a history of CV events.

No significant difference between lumiracoxib and ibuprofen in APTC endpoint

	Number of subjects at risk	Number (%) of subjects with events	Cox proportional hazards model		
			Hazard ratio	95% CI for hazard ratio	p value
Overall population					
Lumiracoxib	4376	19 (0.43)			
Ibuprofen	4397	23 (0.52)			
Lumiracoxib vs ibuprofen			0.76	0.41–1.40	0.3775
Non-aspirin population					
Lumiracoxib	3401	13 (0.38)			
Ibuprofen	3431	13 (0.38)			
Lumiracoxib vs ibuprofen			0.94	0.44–2.04	0.8842
Aspirin population					
Lumiracoxib	975	6 (0.62)			
Ibuprofen	966	10 (1.04)			
Lumiracoxib vs ibuprofen			0.56	0.20–1.54	0.2603

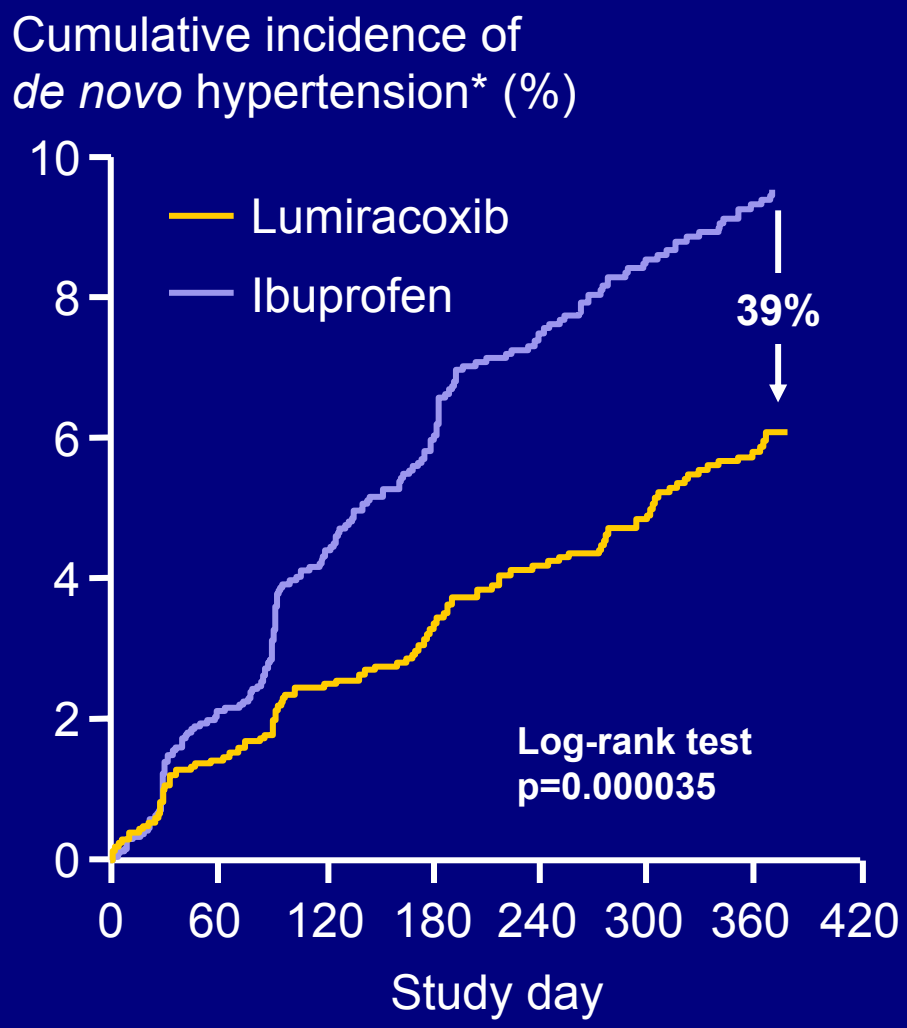
No significant difference between lumiracoxib and ibuprofen in confirmed or probable MIs (clinical and silent)

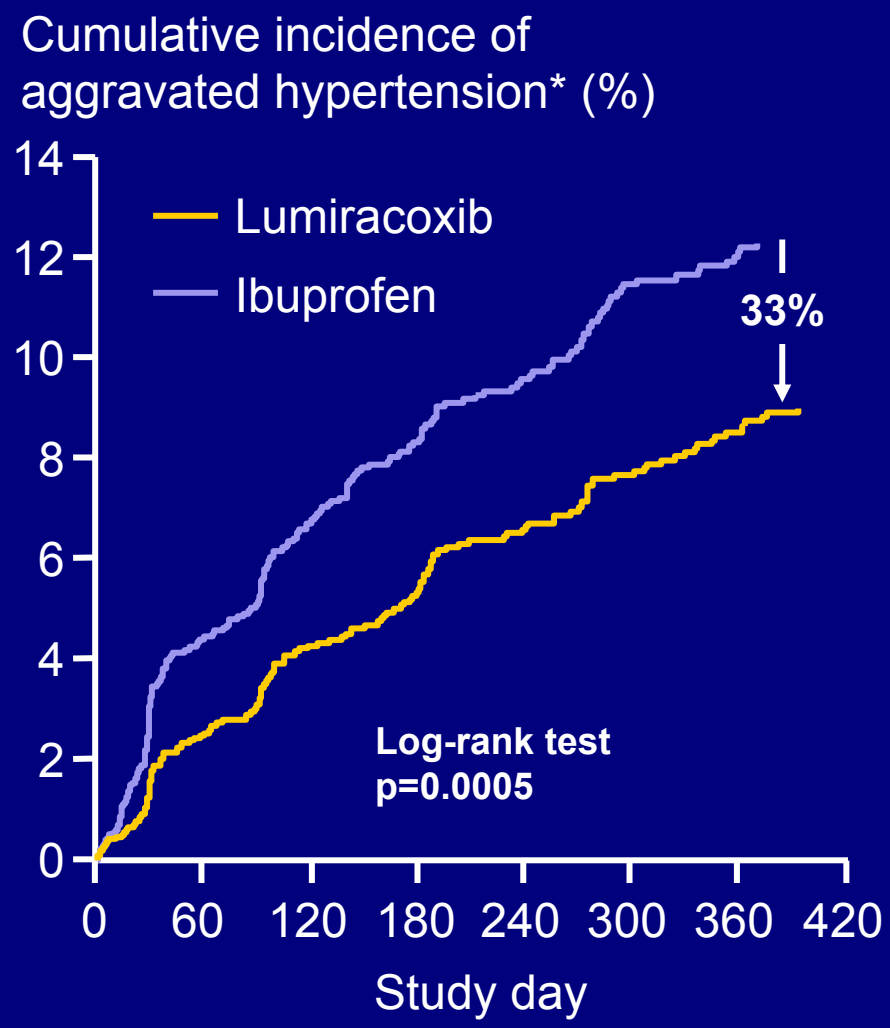
	Number of subjects at risk	Number (%) of subjects with event	Cox proportional hazards model		
			Hazard ratio	95% CI for hazard ratio	p value
Overall population					
Lumiracoxib	4376	5 (0.11)			
Ibuprofen	4397	7 (0.16)			
Lumiracoxib vs ibuprofen			0.66	0.21–2.09	0.4833
Non-aspirin population					
Lumiracoxib	3401	4 (0.12)			
Ibuprofen	3431	5 (0.15)			
Lumiracoxib vs ibuprofen			0.75	0.20–2.79	0.6669
Aspirin population					
Lumiracoxib	975	1 (0.10)			
Ibuprofen	966	2 (0.21)			
Lumiracoxib vs ibuprofen			0.47	0.04–3.93	0.5328

No significant difference in confirmed or probable ischemic or hemorrhagic stroke between lumiracoxib and ibuprofen

	Number of subjects at risk	Number (%) of subjects with event	Cox proportional hazards model		
			Hazard ratio	95% CI for hazard ratio	p value
Overall population					
Lumiracoxib	4376	8 (0.18)			
Ibuprofen	4397	9 (0.20)			
Lumiracoxib vs ibuprofen			0.82	0.32–2.13	0.6844
Non-aspirin population					
Lumiracoxib	3401	6 (0.18)			
Ibuprofen	3431	5 (0.15)			
Lumiracoxib vs ibuprofen			1.16	0.35–3.79	0.8109
Aspirin population					
Lumiracoxib	975	2 (0.21)			
Ibuprofen	966	4 (0.41)			
Lumiracoxib vs ibuprofen			0.47	0.09–2.56	0.3812

Lower incidence of hypertension with lumiracoxib vs ibuprofen

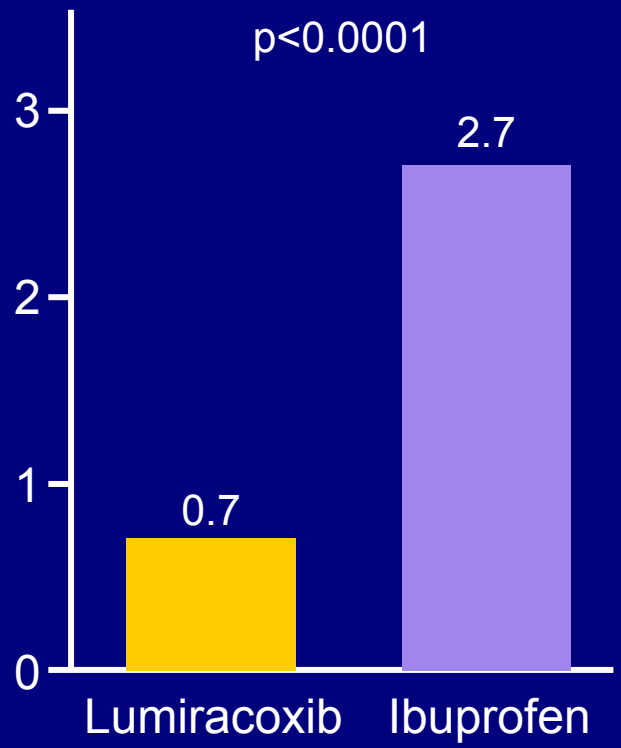




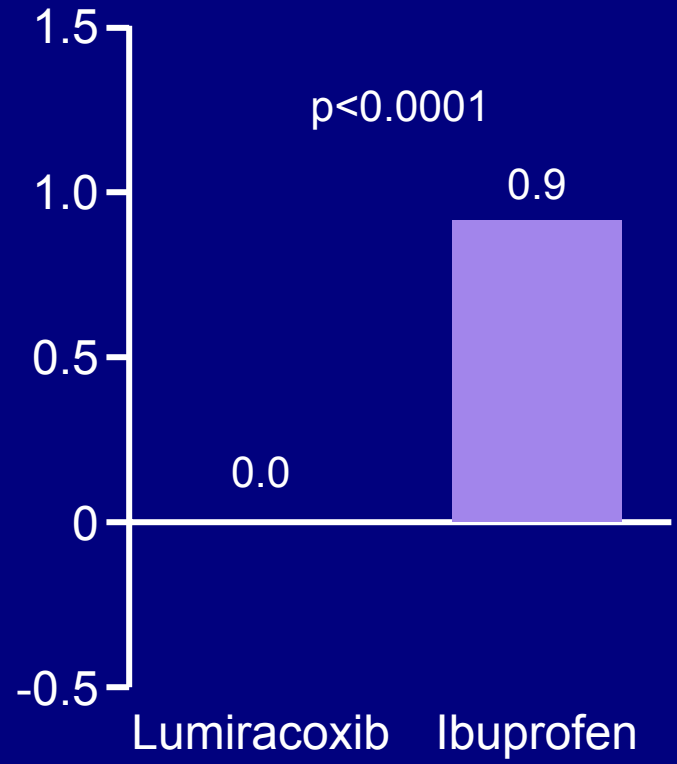
***based on the AE preferred terms**

Significantly larger increases in blood pressure with ibuprofen

Change in systolic blood pressure (least-square means, mmHg)

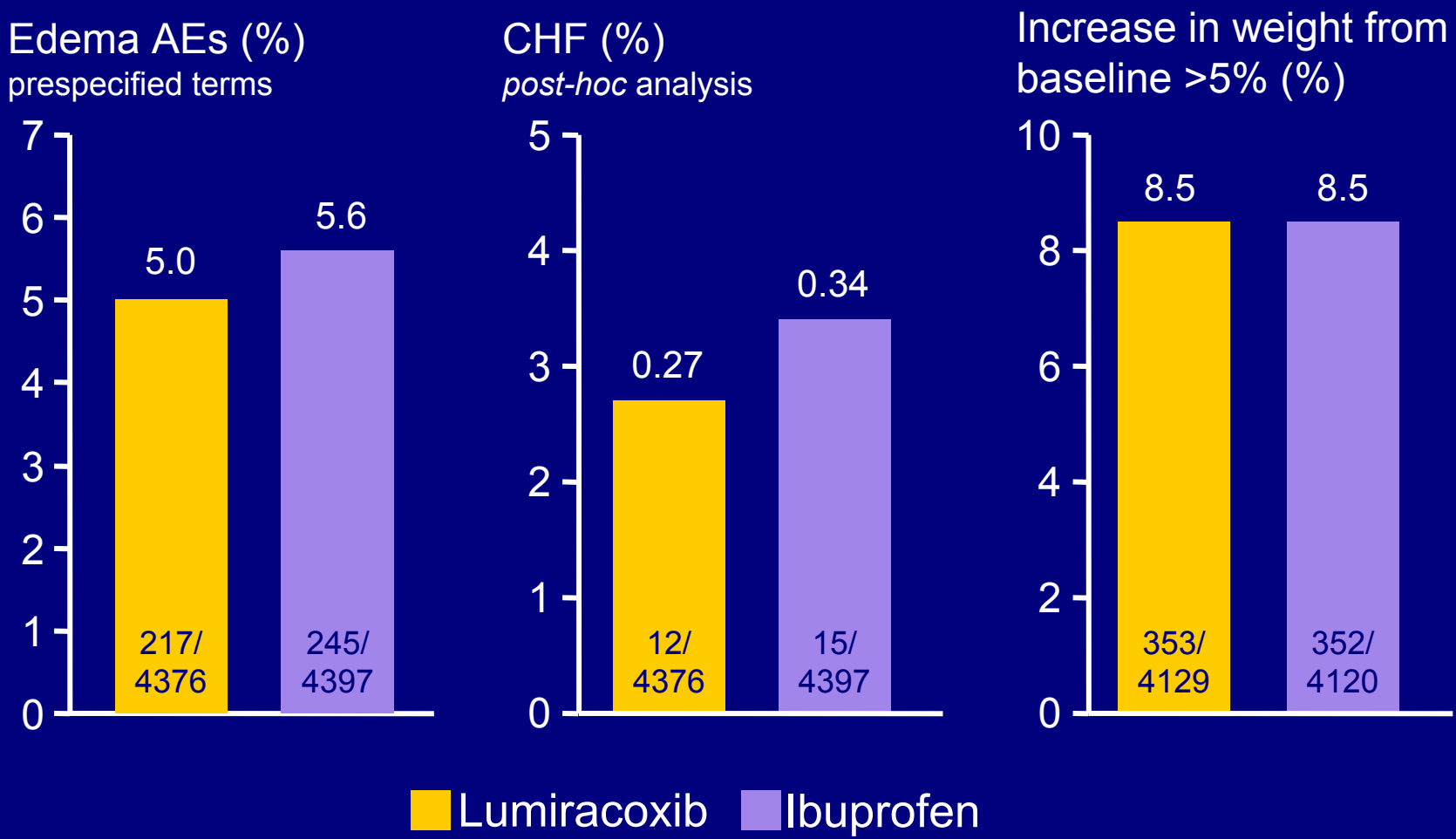


Change in diastolic blood pressure (least-square means, mmHg)

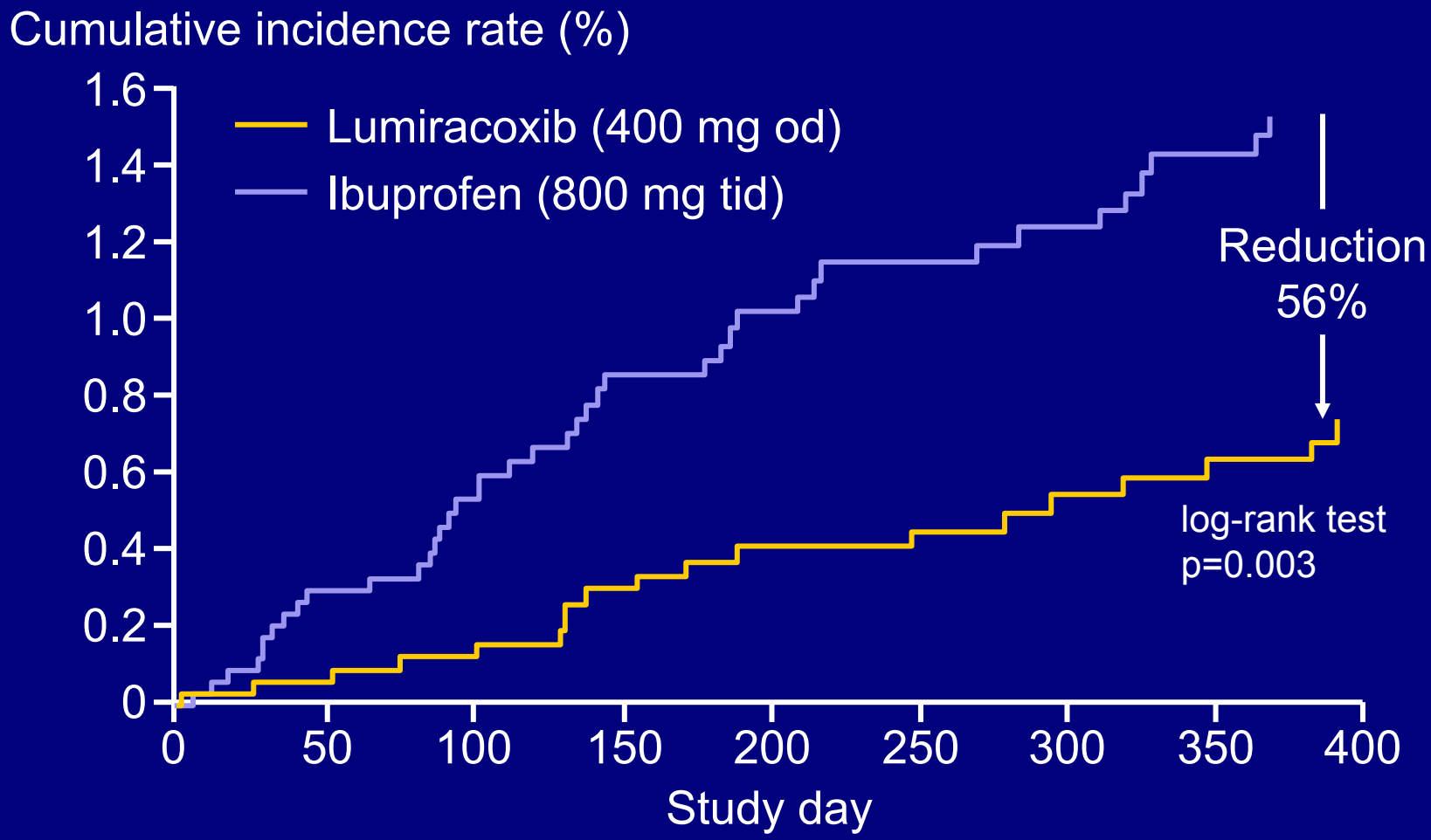


Farkouh M, *et al*. 2004

Incidence of edema, congestive heart failure and weight gain of lumiracoxib vs ibuprofen



Combined GI and CV endpoint significantly favors lumiracoxib vs ibuprofen (non-aspirin population)



Summary of lumiracoxib vs ibuprofen CV data

- Lumiracoxib not different from ibuprofen for APTC, MI, and stroke in the non-aspirin population
- Non-significant increase in APTC events with ibuprofen in the low-dose aspirin population
- Lumiracoxib has significantly smaller BP increases compared with ibuprofen
- No increase in edema, CHF, weight gain with lumiracoxib
- Combined GI and APTC safety endpoint significantly favors lumiracoxib

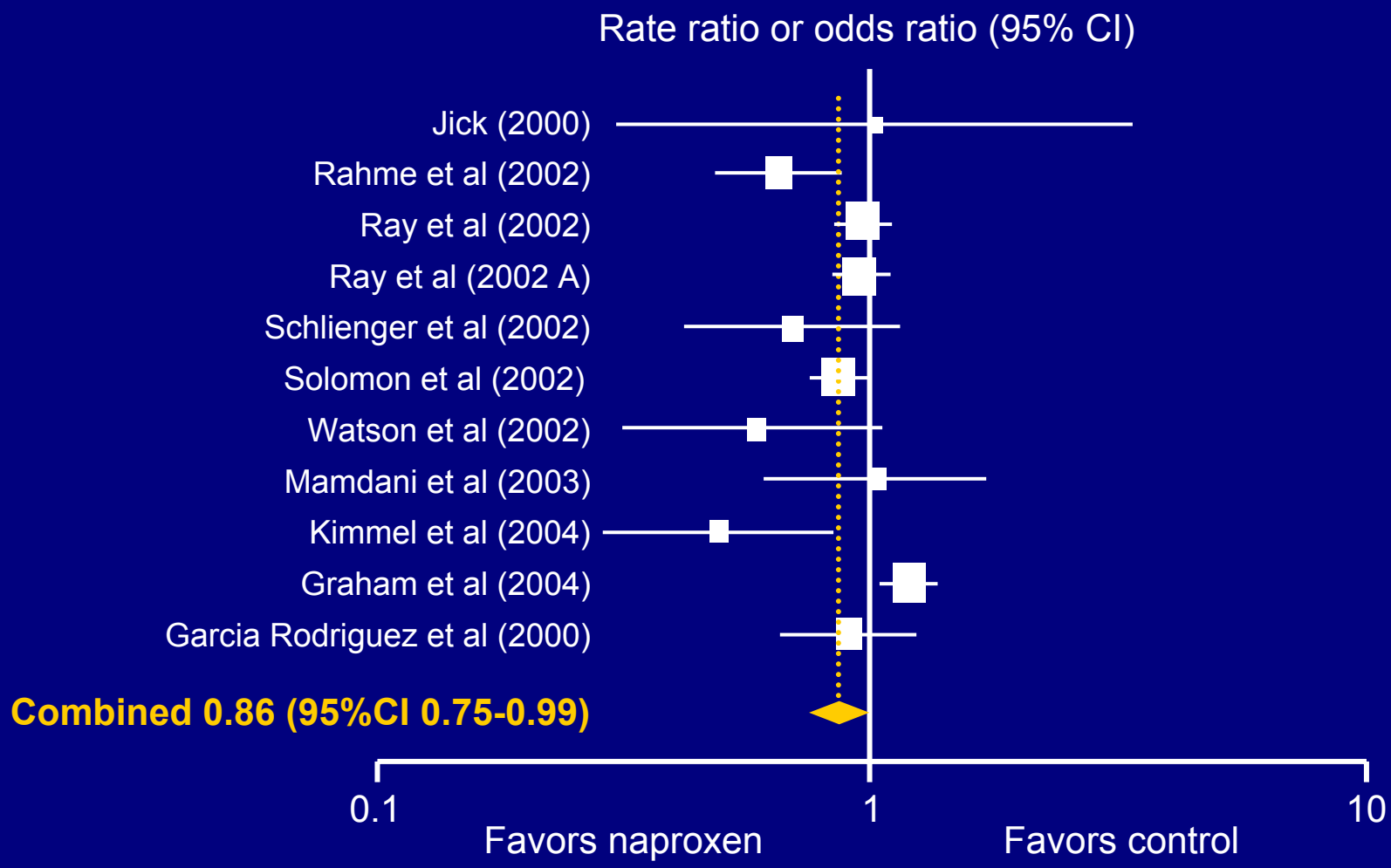
No statistically significant difference between lumiracoxib and naproxen in APTC endpoint

Contrast	Number of subjects at risk	Number (%) of subjects with events	Cox proportional hazards model		
			Hazard ratio	95% CI for hazard ratio	p value
Overall population					
Lumiracoxib	4741	40 (0.84)			
Naproxen	4730	27 (0.57)			
Lumiracoxib vs naproxen			1.46	0.89–2.37	0.1313
Non-aspirin population					
Lumiracoxib	3549	22 (0.62)			
Naproxen	3537	14 (0.40)			
Lumiracoxib vs naproxen			1.49	0.76–2.92	0.2417
Aspirin population					
Lumiracoxib	1192	18 (1.51)			
Naproxen	1193	13 (1.09)			
Lumiracoxib vs naproxen			1.42	0.70–2.90	0.3368

No statistically significant difference between lumiracoxib and naproxen in confirmed or probable MIs (clinical and silent)

Contrast	Number of subjects at risk	Number (%) of subjects with event	Cox proportional hazards model		
			Hazard ratio	95% CI for hazard ratio	p-value
Overall population					
Lumiracoxib	4741	18 (0.38)			
Naproxen	4730	10 (0.21)			
Lumiracoxib vs naproxen			1.77	0.82–3.84	0.1471
Non-aspirin population					
Lumiracoxib	3549	10 (0.28)			
Naproxen	3537	4 (0.11)			
Lumiracoxib vs naproxen			2.37	0.74–7.55	0.1454
Aspirin population					
Lumiracoxib	1192	8 (0.67)			
Naproxen	1193	6 (0.50)			
Lumiracoxib vs naproxen			1.36	0.47–3.93	0.5658

Naproxen has an effect on MI risk
Meta-analysis of observational studies
(Jüni et al. *Lancet* 2004)



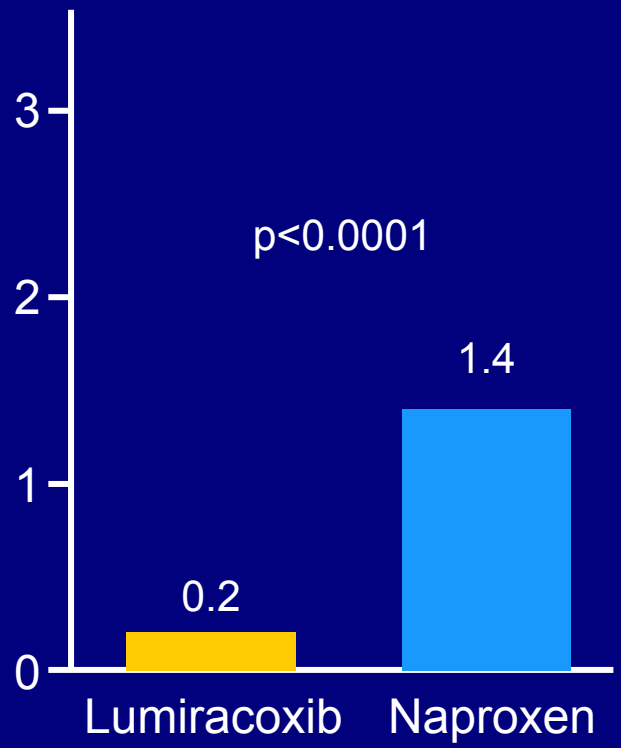
Jüni *et al*. Lancet. 2004.

No significant difference between lumiracoxib and naproxen in confirmed or probable ischemic or hemorrhagic stroke

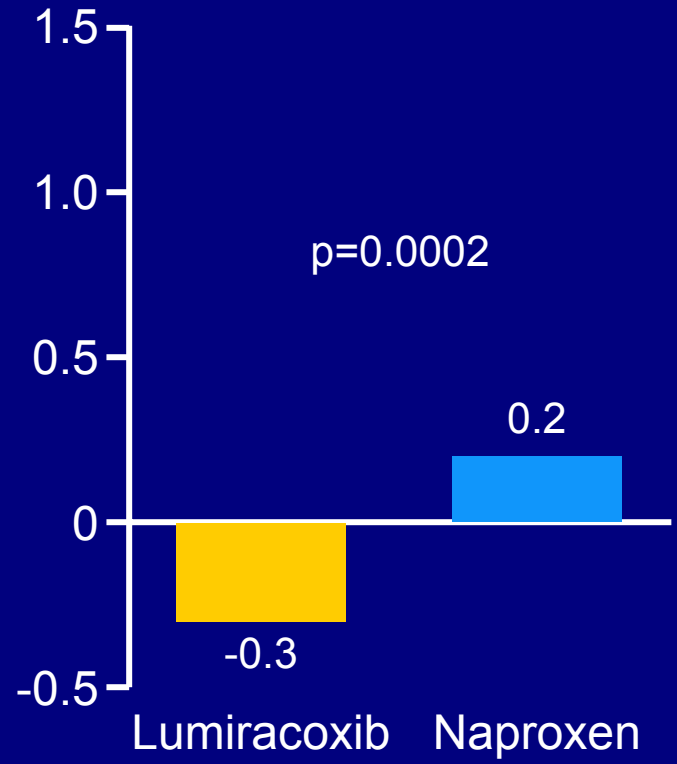
	Number of subjects at risk	Number (%) of subjects with event	Cox proportional hazards model		
			Hazard ratio	95% CI for hazard ratio	p value
Overall population					
Lumiracoxib	4741	16 (0.49)			
Naproxen	4730	12 (0.28)			
Lumiracoxib vs naproxen			1.11	0.62–2.79	0.4669
Non-aspirin population					
Lumiracoxib	3549	7 (0.20)			
Naproxen	3537	6 (0.17)			
Lumiracoxib vs naproxen			1.12	0.38–3.33	0.8421
Aspirin population					
Lumiracoxib	1192	9 (0.76)			
Naproxen	1193	6 (0.50)			
Lumiracoxib vs naproxen			1.53	0.55–4.31	0.4172

Significantly larger increases in blood pressure with naproxen

Change in systolic blood pressure (least-square means, mmHg)



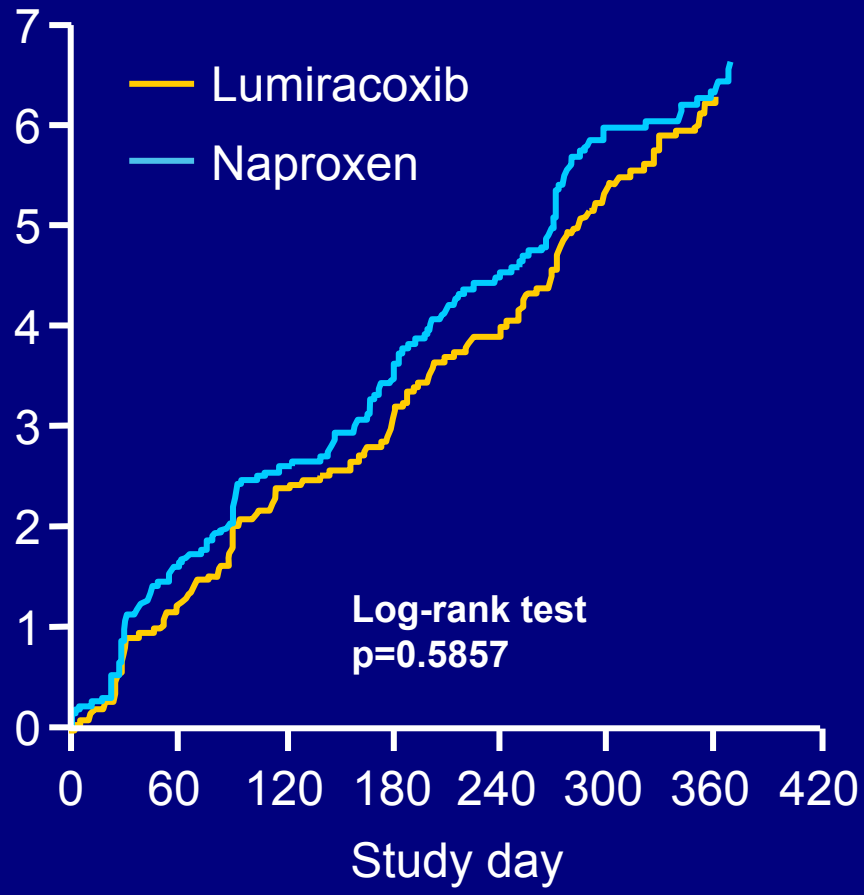
Change in diastolic blood pressure (least-square means, mmHg)



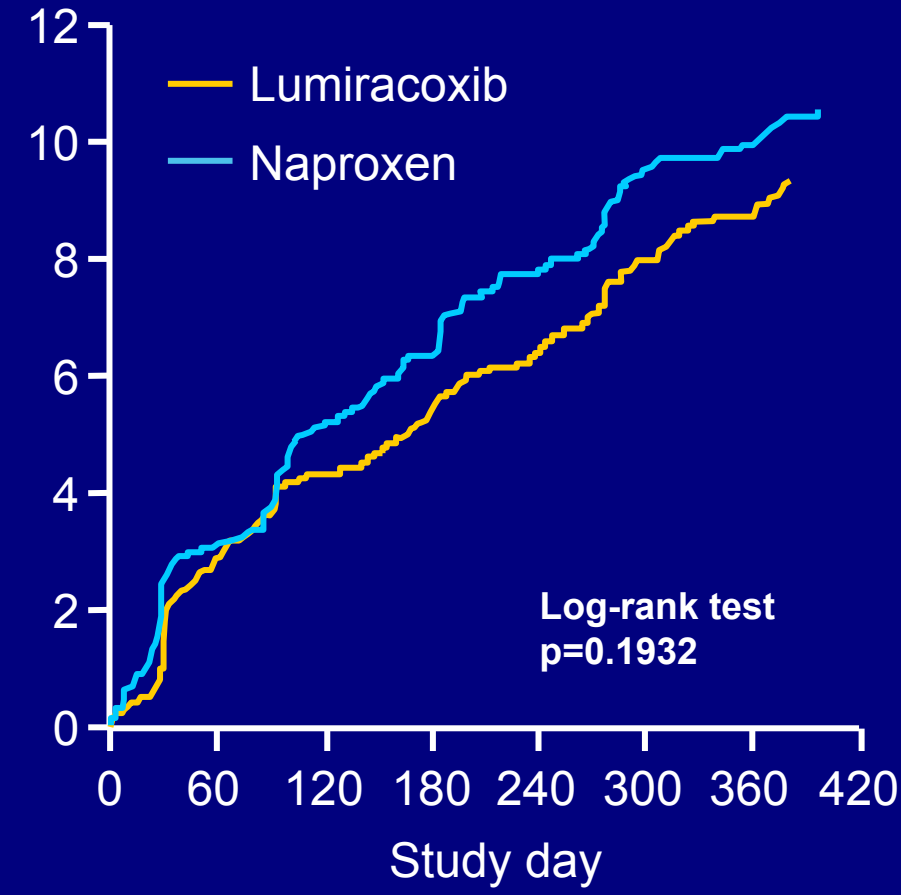
Farkouh M, *et al*. 2004

Incidence of hypertension with lumiracoxib vs naproxen

Cumulative incidence of *de novo* hypertension* (%)

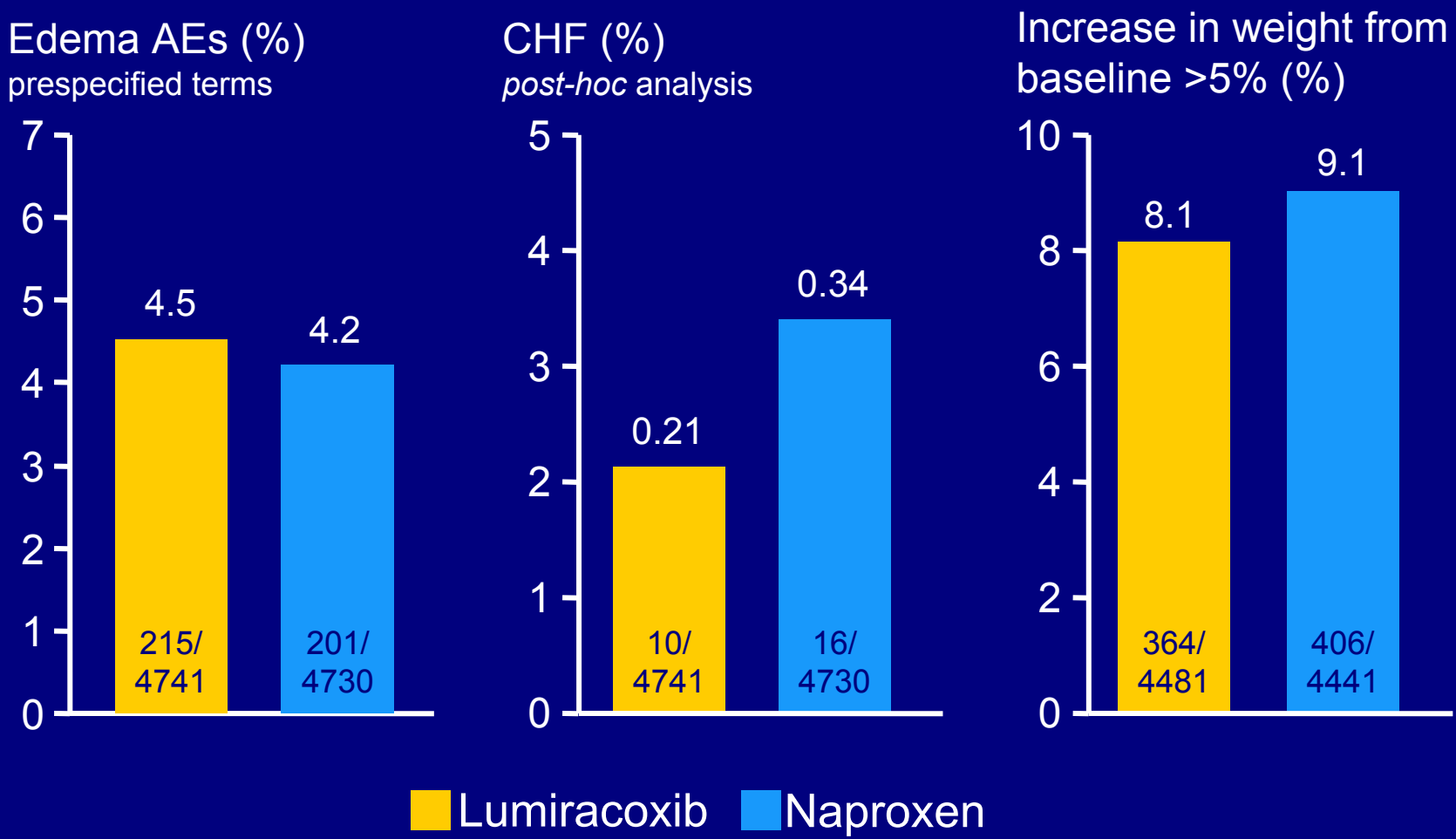


Cumulative incidence of aggravated hypertension* (%)

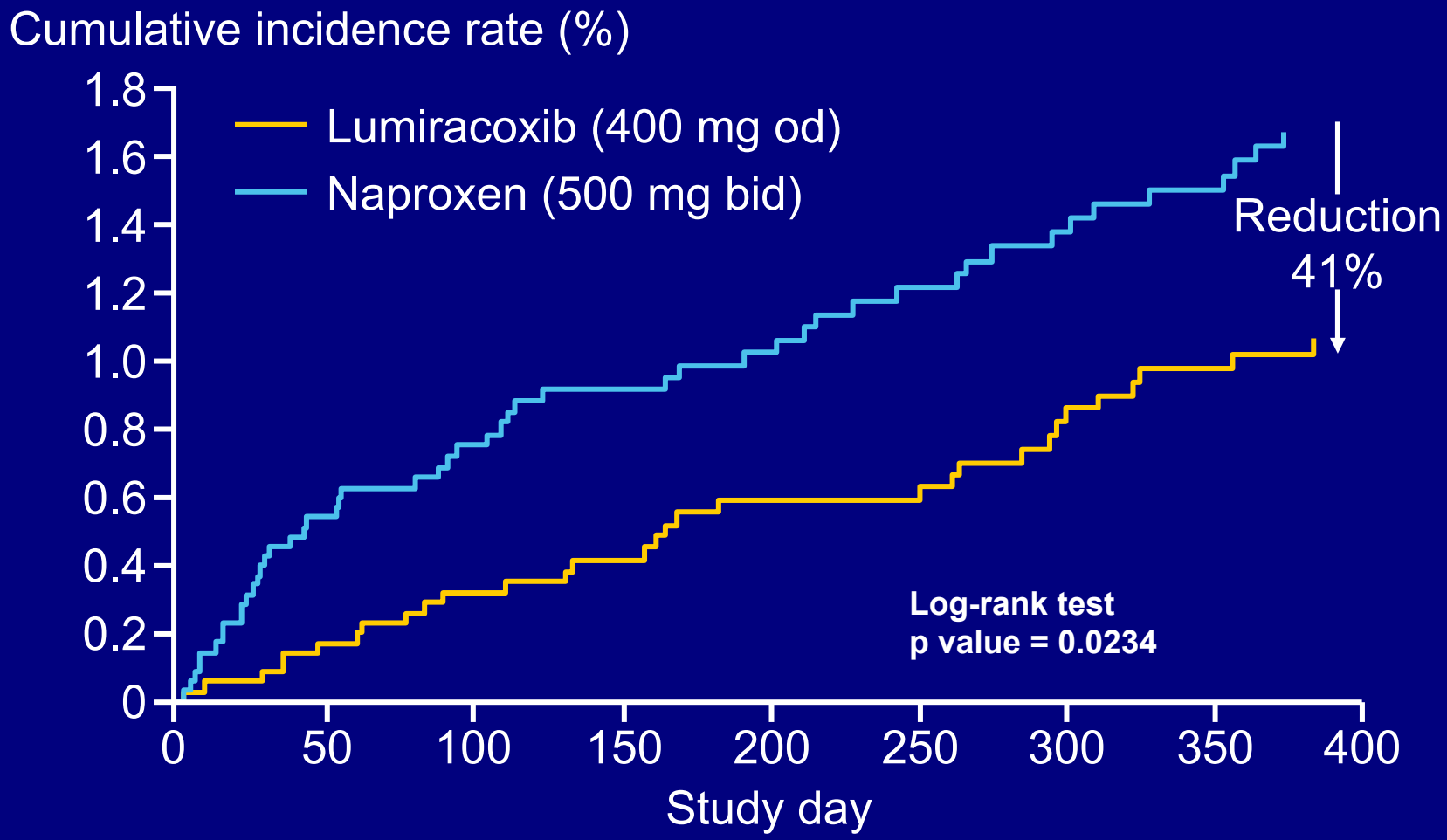


*based on the AE preferred terms

Incidence of edema, congestive heart failure, and weight gain of lumiracoxib vs naproxen



Combined GI and CV endpoint favors lumiracoxib vs naproxen (non-aspirin population)



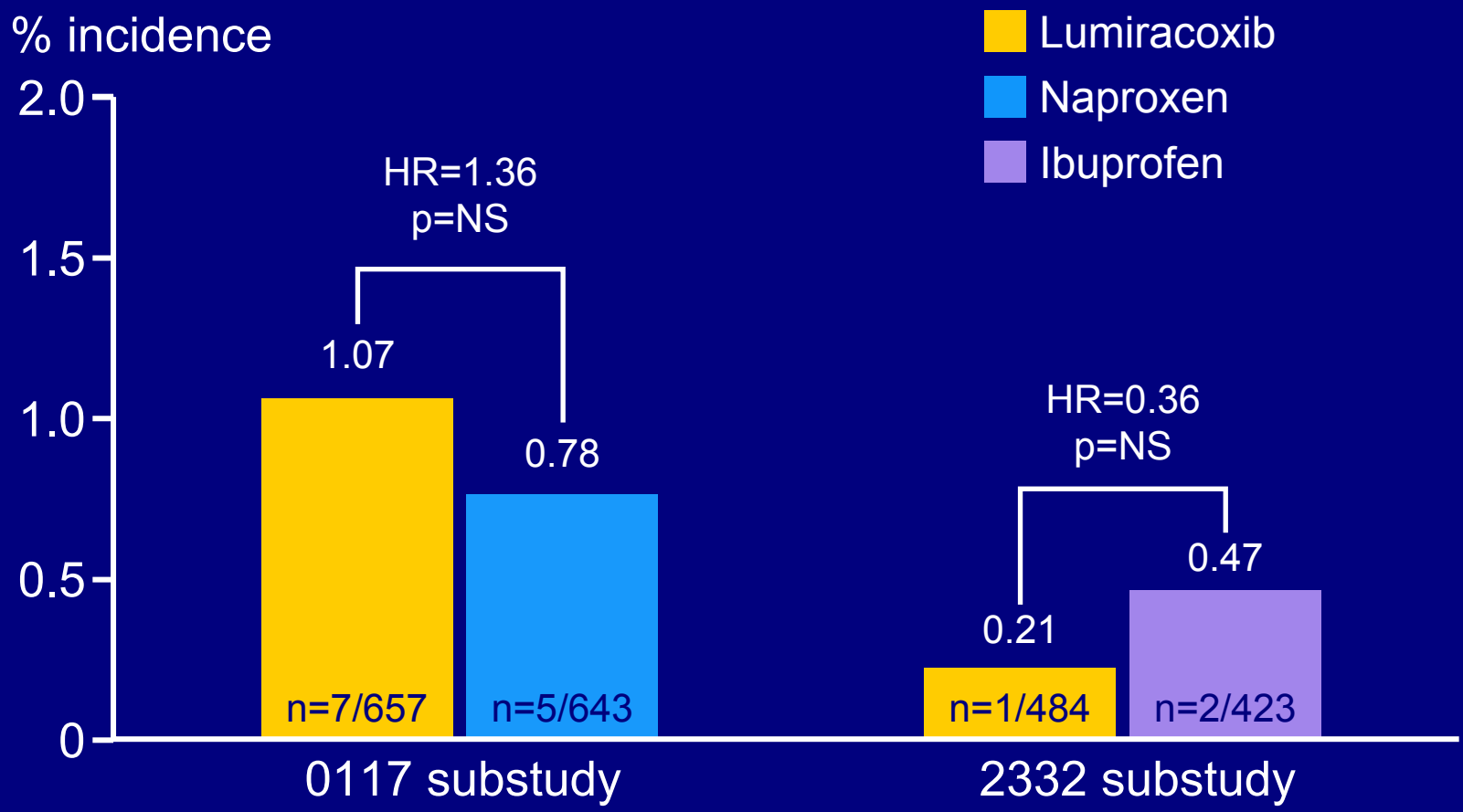
Summary of lumiracoxib vs naproxen CV data

- No significant difference in APTC endpoint between lumiracoxib and naproxen
- Numerically more MIs in the lumiracoxib group compared to naproxen in the non-aspirin population
- MIs similar in aspirin population
- Significantly lower mean BP increase with lumiracoxib compared to naproxen
- No increase in edema, CHF, weight gain with lumiracoxib
- Combined GI and APTC safety endpoint in the non-aspirin population significantly favors lumiracoxib

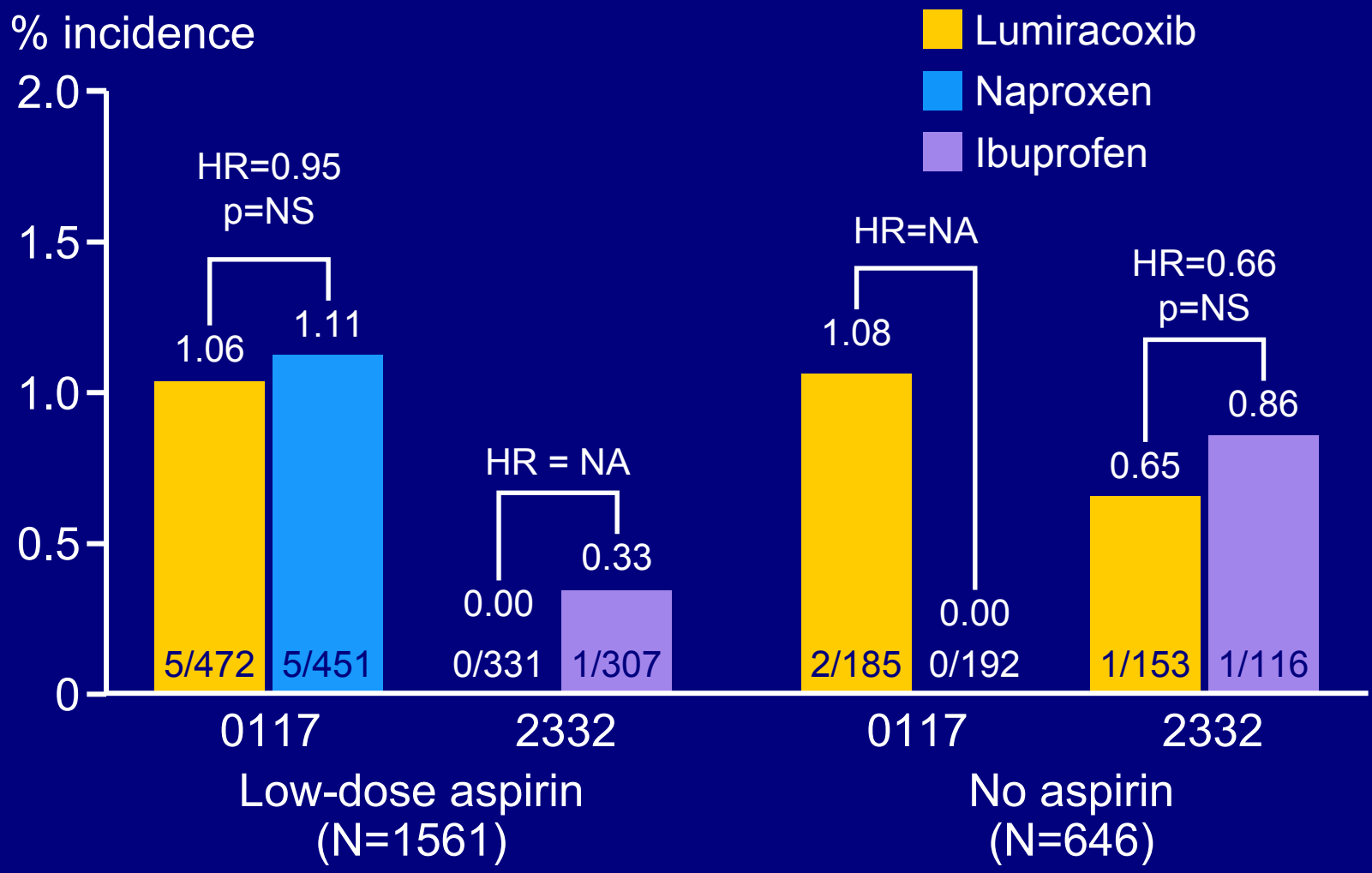
TARGET included patients with high CV risk

	Lumiracoxib (n=9117) n (%)	NSAIDs (n=9127) n (%)
History of CV disease	981 (10.8)	899 (9.8)
Coronary artery disease	683 (7.5)	624 (6.8)
MI	150 (1.6)	138 (1.5)
Cerebrovascular disease	177 (1.9)	172 (1.9)
Peripheral artery disease	151 (1.7)	145 (1.5)
High-risk Framingham score	160 (1.8)	167 (1.8)
Total high CV risk	1141 (12.5)	1066 (11.7)

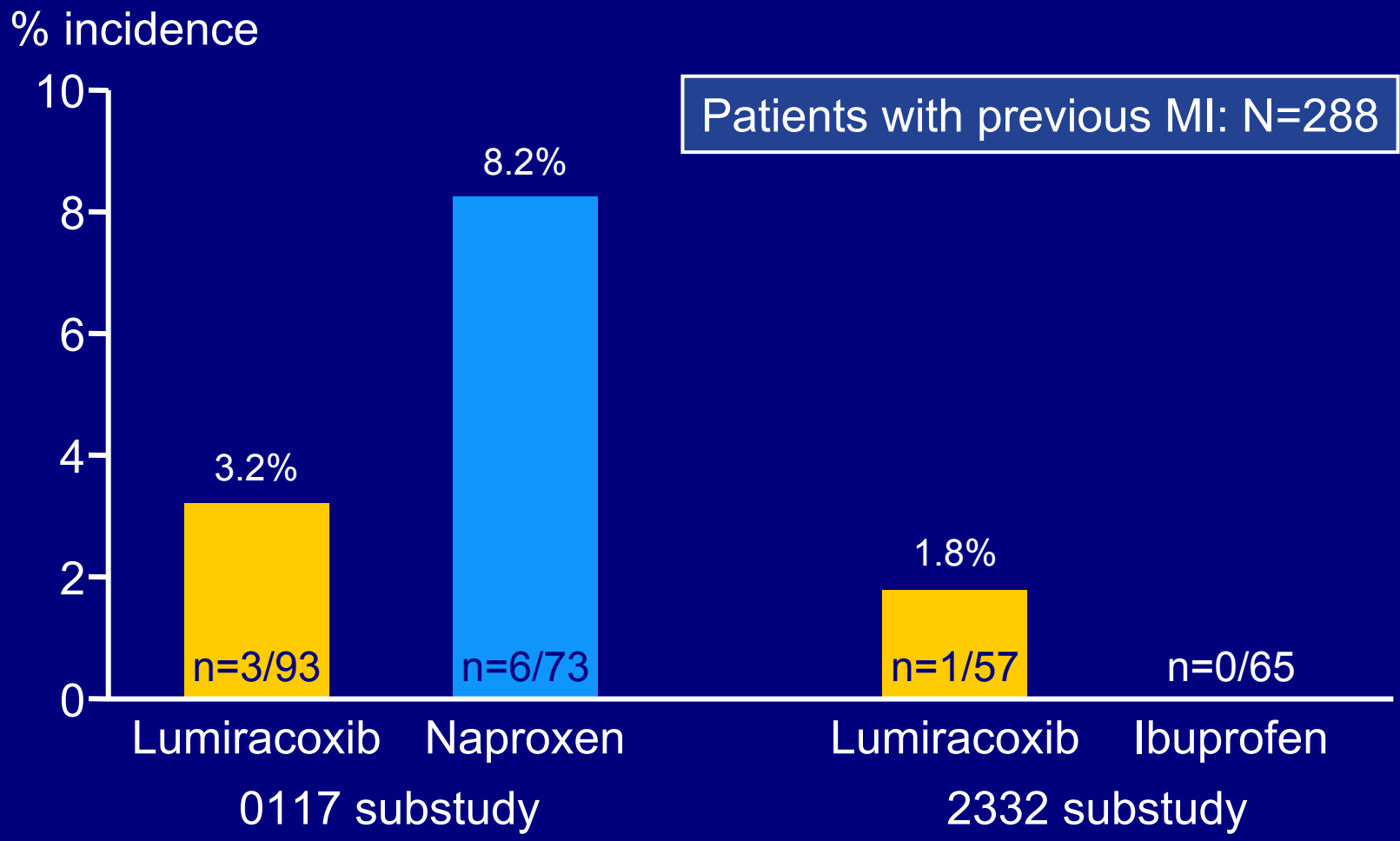
No significant difference in MIs in 2207 patients with high CV risk or CCV history (overall population)



No significant difference in MIs in patients with high CV risk or CCV history (aspirin and non-aspirin populations)



Patients on lumiracoxib with previous MI do not have a higher risk of APTC events



Cardiovascular safety

Meta-analysis data

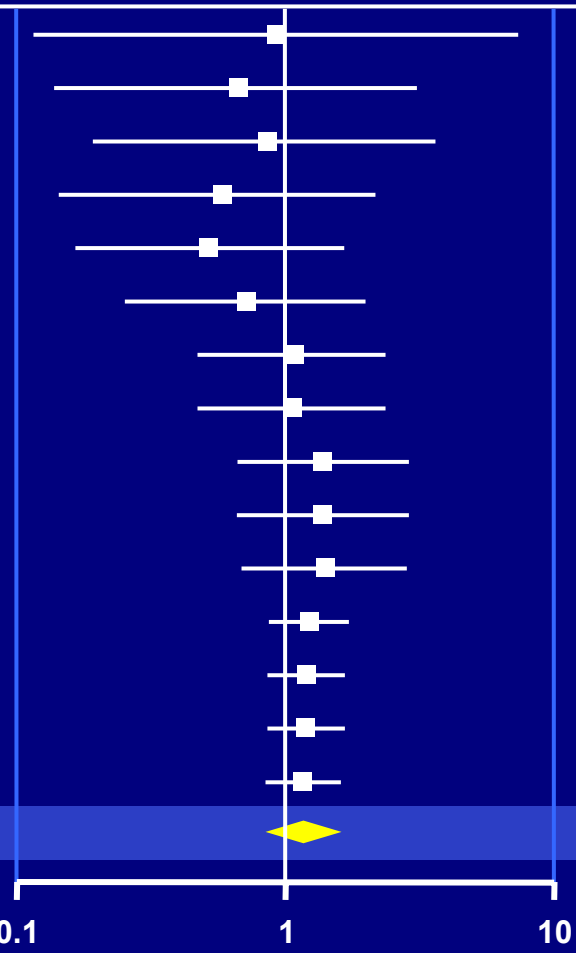
CV meta-analysis population reflects high level of long-term exposure

	Number of patients in meta-analysis	Patient-year exposure	% of patient-years exposure
*Total in 22 RCTs >1 week	34 668	18 621	100
Patients in 1 year RCTs	22 781	16 527	89
Patients externally adjudicated	23 194	15 679	84
Patients contributed by TARGET†	18 244	13 506	74

* Lumiracoxib doses 100–1200 mg.
† Lumiracoxib dose in TARGET 400 mg od.

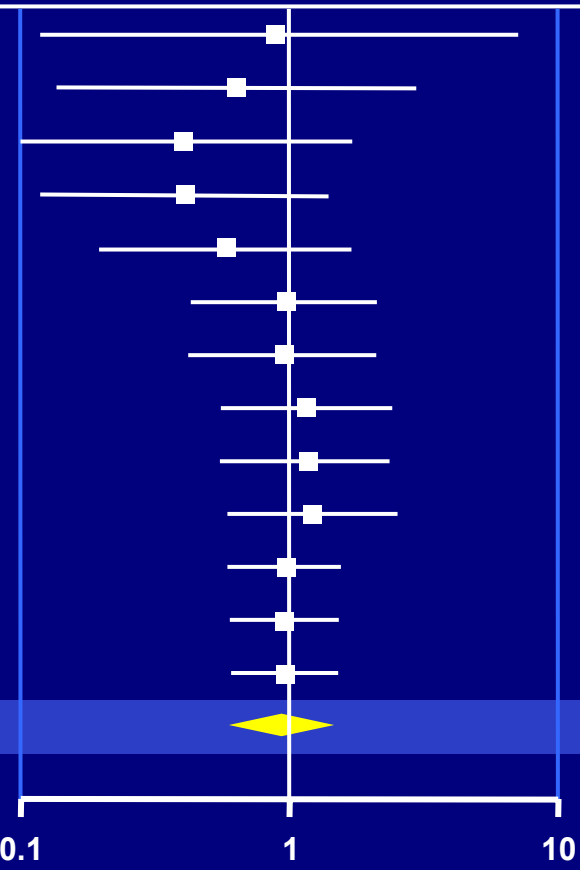
Cumulative meta-analysis of APTC in randomized trials comparing lumiracoxib with all controls

Year	Cumulative patients	Cumulative events	RR	95% CI
2001	3772	4	0.90	0.12–7.05
	4814	7	0.65	0.14 to 3.07
	4934	8	0.85	0.20 to 3.56
	6173	10	0.57	0.15 to 2.10
2002	6684	14	0.52	0.17 to 1.63
	8284	16	0.70	0.25 to 1.95
	9348	27	1.04	0.47 to 2.28
	9942	27	1.03	0.47 to 2.27
	11066	34	1.36	0.66 to 2.79
2003	11474	34	1.36	0.66 to 2.79
	12625	36	1.37	0.68 to 2.75
2004	30869	145	1.20	0.86 to 1.68
	32553	149	1.19	0.86 to 1.66
	34104	151	1.19	0.86 to 1.66
	34362	156	1.16	0.84 to 1.60
Total	34668		1.12	0.82 to 1.55



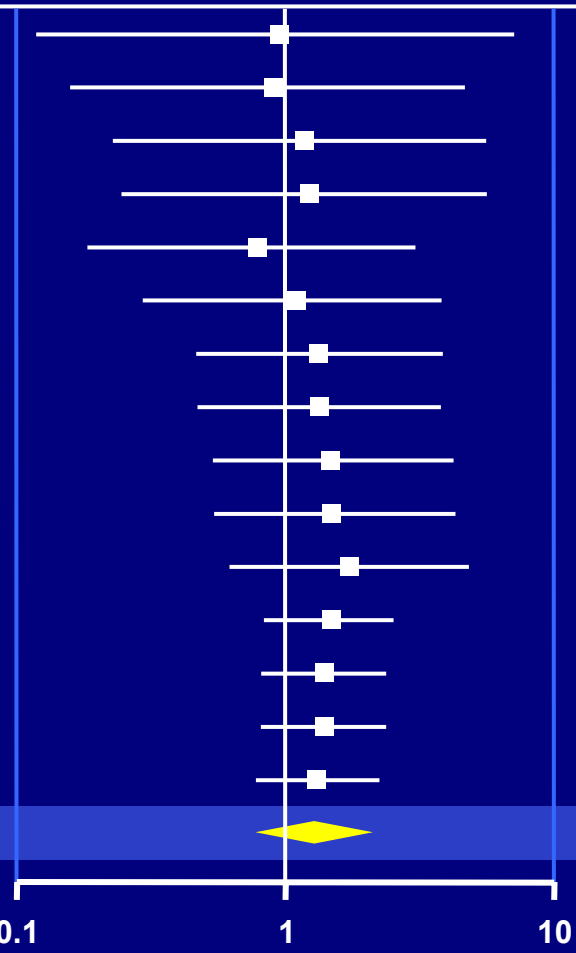
Cumulative meta-analysis of APTC in randomized trials comparing lumiracoxib with all controls excluding naproxen

Year	Cumulative patients	Cumulative events	RR	95% CI
2001	3772	4	0.90	0.12–7.05
	4814	7	0.65	0.14–3.07
	6053	9	0.41	0.10–1.71
2002	6564	13	0.42	0.12–1.42
	8164	15	0.59	0.20–1.73
	9228	26	0.98	0.44–2.17
	9822	26	0.97	0.44–2.15
	10667	33	1.19	0.57–2.46
2003	11075	33	1.19	0.57–2.46
	11998	34	1.26	0.61–2.59
2004	20771	76	0.98	0.61–1.55
	22455	80	0.98	0.62–1.54
	24006	82	0.98	0.63–1.53
Total	24312		0.94	0.61–1.45



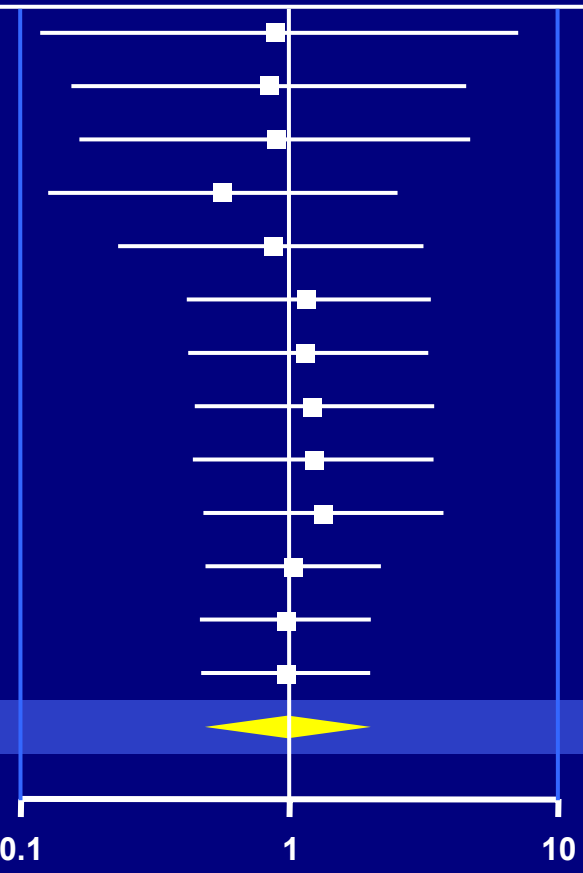
Cumulative meta-analysis of MI in randomized trials comparing lumiracoxib with all controls

Year	Cumulative patients	Cumulative events	RR	95% CI
2001	3772	4	0.90	0.12–7.05
	4814	6	0.87	0.16–4.60
	4934	7	1.13	0.24–5.35
	6173	7	1.18	0.25–5.54
2002	6684	9	0.75	0.19–2.95
	8284	11	1.06	0.31–3.63
	9348	17	1.31	0.47–3.63
	9942	17	1.30	0.47–3.61
	11066	18	1.48	0.54–4.04
2003	11474	18	1.48	0.54–4.05
	12625	19	1.68	0.62–4.53
2004	30869	59	1.42	0.83–2.44
	32553	60	1.37	0.81–2.33
	34104	60	1.37	0.81–2.33
	34362	63	1.29	0.77–2.16
Total	34668		1.28	0.78–2.12



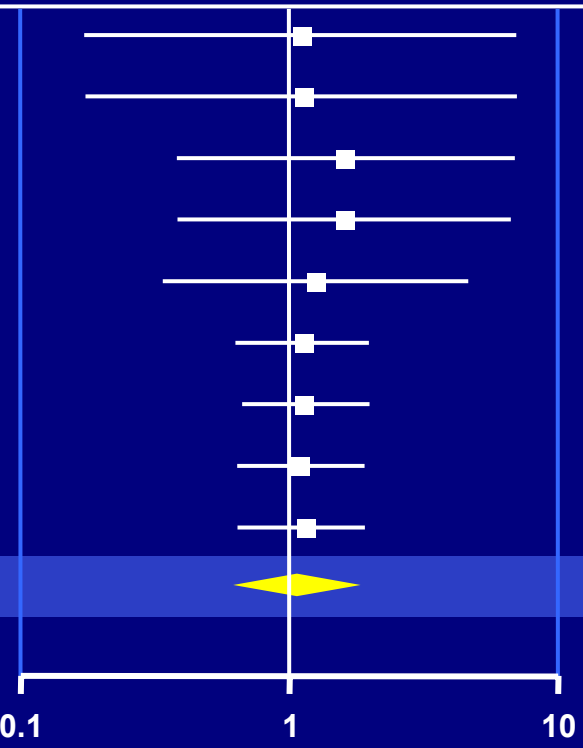
Cumulative meta-analysis of MI in randomized trials comparing lumiracoxib with all controls excluding naproxen

Year	Cumulative patients	Cumulative events	RR	95% CI
2001	3772	4	0.90	0.12–7.05
	4814	6	0.87	0.16–4.60
	6053	6	0.91	0.17–4.80
2002	6564	8	0.58	0.13–2.54
	8164	10	0.88	0.24–3.19
	9228	16	1.19	0.42–3.37
	9822	16	1.18	0.42–3.34
	10667	17	1.24	0.45–3.43
2003	11075	17	1.24	0.45–3.43
	11998	18	1.37	0.50–3.74
2004	20771	30	1.06	0.50–2.22
	22455	31	0.99	0.48–2.05
	24006	31	1.00	0.48–2.06
Total	24312		1.01	0.50–2.02



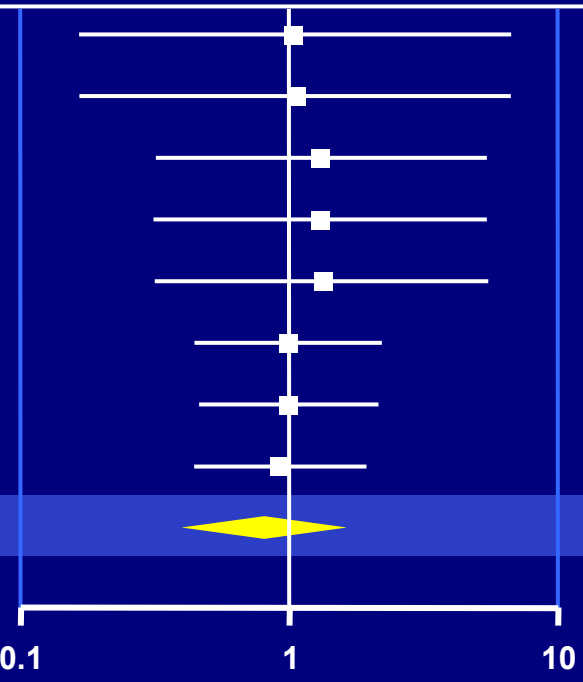
Cumulative meta-analysis of stroke in randomized trials comparing lumiracoxib with all controls

Year	Cumulative patients	Cumulative events	RR	95% CI
2002	9348	5	1.07	0.17–6.71
	9942	5	1.07	0.17–6.66
	11066	9	1.56	0.37–6.51
2003	11474	9	1.56	0.37–6.51
	12625	10	1.21	0.33–4.46
2004	30869	55	1.11	0.64–1.91
	32553	57	1.10	0.65–1.88
	34104	58	1.06	0.63–1.80
	34362	59	1.09	0.65–1.84
Total	34668	62	1.02	0.61–1.71



Cumulative meta-analysis of stroke in randomized trials comparing lumiracoxib with all controls excluding naproxen

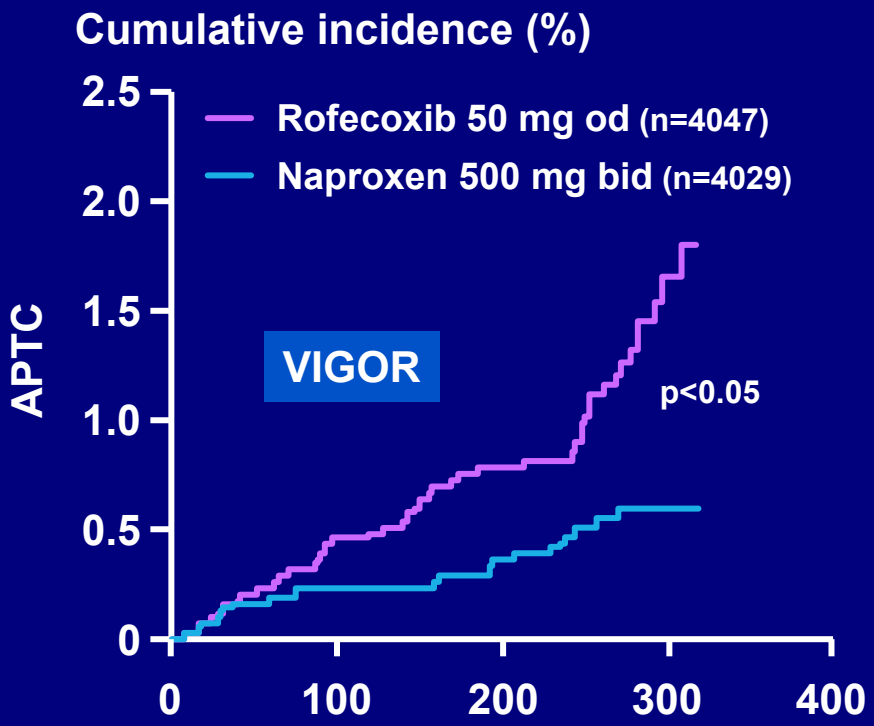
Year	Cumulative patients	Cumulative events	RR	95% CI
2002	9228	5	1.07	0.17–6.72
	9822	5	1.07	0.17–6.67
	10667	9	1.32	0.32–5.52
2003	11075	9	1.33	0.32–5.53
	11998	9	1.34	0.32–5.58
2004	20771	26	1.00	0.45–2.21
	22455	28	1.00	0.46–2.13
	24006	29	0.93	0.44–1.95
Total	24312	32	0.84	0.41–1.70



Rofecoxib and lumiracoxib have different profiles*

Rofecoxib

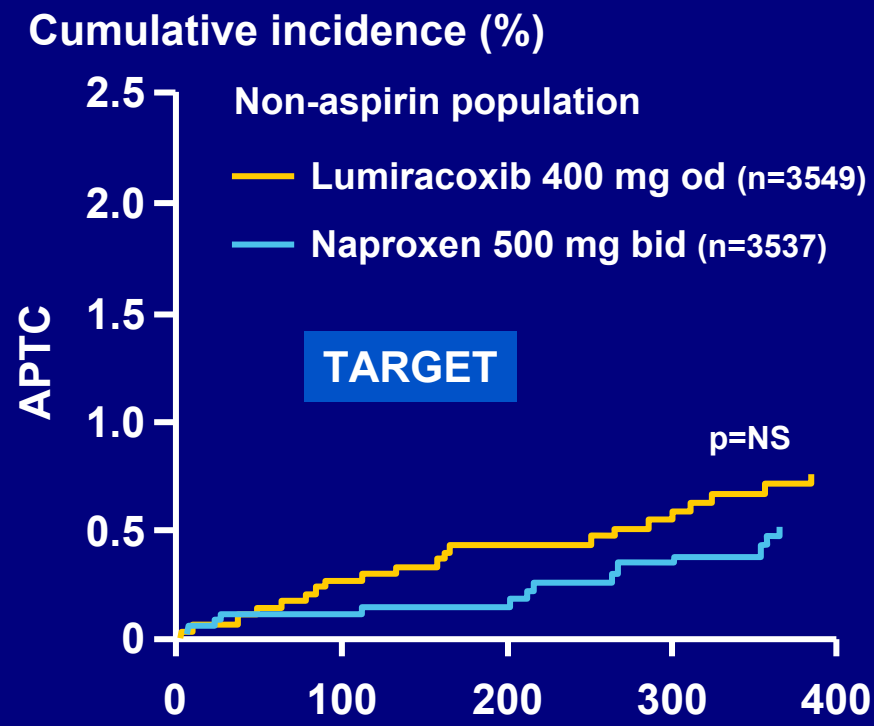
Half life	17 hours
Structure	sulphone



Rofecoxib vs naproxen:	Significant increase in BP Increase in edema and CHF

Lumiracoxib

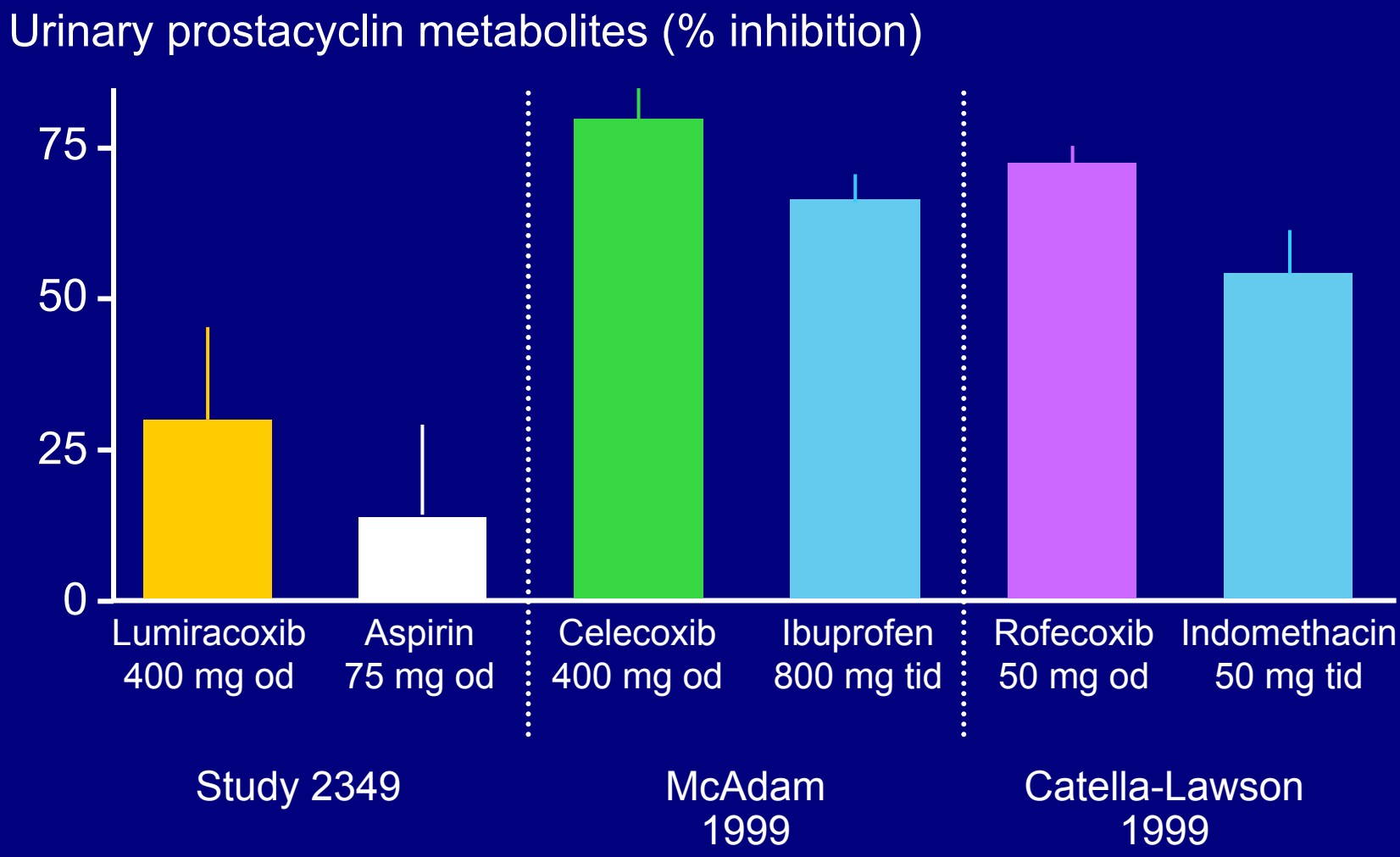
Half life	4 hours
Structure	carboxylic acid, no sulphur



Lumiracoxib vs naproxen:	Significantly lower BP change No difference in edema or CHF

*Not head-to-head comparison.

Lumiracoxib differs from NSAIDs and other coxibs*



*Not head-to-head comparison.

Lumiracoxib conclusions

- At 400 mg qd (4x chronic dose), definitive GI benefit in non-ASA population; consistent positive trend in ASA population
- No significant increase in CV events vs NSAIDs
- Superior blood pressure profile compared with both ibuprofen and naproxen
- No increase in edema, CHF, weight gain with lumiracoxib
- Combined GI and CV endpoint in non-aspirin population significantly favors lumiracoxib
- No significant CV risk in meta-analysis of all lumiracoxib studies >1 week

Overall Conclusions

- The presented data addresses all Health Canada's questions and in particular, Question 4 as well as Questions 5 and 6.
- Lumiracoxib with its distinct molecular structure and distinct pharmacologic properties need to be considered in a population suffering of arthritis,
  - inadequately treated with the current NSAIDs,
  - suffering of GI complications related to NSAIDs use
  - or allergic to sulphur containing COX-2 inhibitors.