

**Cardiovascular Risk of Celecoxib
in
6 Randomized Placebo-controlled Trials:
The Cross Trial Safety Analysis**

Scott D. Solomon, MD, Janet Wittes, PhD,
Ernest Hawk, MD, MPH for the Celecoxib
Cross Trials Safety Analysis Investigators

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DISCLOSURES

No Disclosures

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Background

- Observational studies and randomized controlled trials have reported increased cardiovascular risk associated with cyclooxygenase-2 (cox-2) inhibitors (coxibs) ^{1,2,3,4}
- Strong biologic basis for this risk supported by abundant basic research^{5,6,7}
- Most clinical studies compared coxibs with active comparators in short-term arthritis trials

¹McGettigan JAMA 2006; ²Graham et al. Lancet 2005; ³Bresalier et al. NEJM 2005; ⁴Solomon et al. NEJM 2005
⁵McAddam et al. PNAS 1999; ⁶Fitzgerald NEJM 2001; ⁷Fitzgerald et al. NEJM 2004

Background

- In December 2004, interim results from the Adenoma Prevention with Celecoxib (APC) trial results led to stopping drug in that trial and in 5 other long-term trials comparing celecoxib to placebo:
 - The Prevention of Sporadic Adenomatous Polyps (PreSAP) trial¹
 - The Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)²
 - The MA-27 Breast Cancer Trial,
 - The Celecoxib Diabetic Macular Edema (CDME) trial
 - The Celecoxib/Selenium Trial.
- FDA hearing resulted in Black Box Warning.
- Celecoxib is the only available cox-2 inhibitor in US.

¹ Arber et al. NEJM 2006; ² ADAPT Invest. PLOS 2006

Low Event Rates Lead to Challenges in Risk Assessment with Coxibs

- Low precision of the estimates
- Inability to test observational and RCT data suggesting
 - coxib-associated CV risk may be dose related
 - dose and interval may be important in CV risk.¹
- Inability to assess whether CV risk associated with celecoxib varies by baseline CV risk

Objective

- To understand more fully the cardiovascular risk profile associated with long-term use of celecoxib
 - NCI commissioned and funded analysis of long-term placebo controlled trials

Selection of Studies

- Randomized, double-blind, placebo-controlled trials
- Planned follow-up of at least 3 years
- Source documentation available for adjudication
- 4 trials + APC and PreSAP fulfilled these criteria:
 - ADAPT
 - MA-27
 - CDME
 - Celecoxib/Selenium Trial

Methodology

- Each study submitted patient-level data:
 - Baseline data
 - Outcomes
 - Adverse events
- A blinded adjudication team identified all potential cardiovascular events from broad list of SAEs and AEs
- Requested source documentation for all relevant events
- All potential cardiovascular events were adjudicated by two reviewers masked to treatment allocation
 - Categorized all deaths
 - Adjudicated all non-fatal events

Endpoints

- The following endpoints were adjudicated:
 - Death (cardiovascular or non-cardiovascular)
 - Myocardial Infarction
 - Stroke
 - Hospitalization for heart Failure
 - Thromboembolic event
 - Other cardiovascular
- Primary endpoint:
 - CV death, MI, stroke, heart failure or thromboembolic event

Statistical Analysis

- Intention-to-treat
- Time-to-event analyses for each study
 - Calculated incidence of each outcome, rate (per 1000 pt-yrs) by Rx group
 - Cox models and KM curves
- Pooled (meta) analysis:
 - Estimated hazard ratios calculated from the average of the log-hazard ratio for each individual trial weighted by the inverse of its variance
 - Sensitivity of method assessed by standard Mantel-Haenszel pooled odds ratios and Cox models stratified by study.
 - Analyses adjusted for baseline cardiovascular risk
- Pooled analyses assessed overall risk and dosing regimen-related risk

Dose and Baseline Risk

- Studies were grouped according to dose regimen:
 - 400mg once daily (2 studies)
 - 200mg twice daily (3 studies)
 - 400mg twice daily (2 studies)
- We tested for interaction between dose regimen and celecoxib risk
- We created a 3-category risk score using a modified Framingham Risk model conforming to the availability of data from these studies:
 - Low: No known risk factor
 - Moderate: One of following , age > 75, hypertension, hyperlipidemia, current smoker, low-dose ASA
 - High: Diabetes, prior CV disease, or ≥ 2 risk factors in “moderate” category
- We tested for interaction between baseline risk and celecoxib-related risk.

Placebo-Controlled Trials

Study	N	Sponsor	Disease being Studied	Celecoxib Dose	Planned follow-up time
APC	2035	NCI and Pfizer	Colorectal polyps	Celecoxib 200mg BID, celecoxib 400mg BID, or placebo	3+ Years
PreSAP	1561	Pfizer	Colorectal Polyps	Celecoxib 400mg QD or placebo	3+ Years
MA27	1635	NCI, NCI Canada, & Pfizer	Breast Cancer Recurrence	celecoxib 400 mg BID or placebo	3+ Years
ADAPT	1809	NIA	Alzheimer's disease and cognitive decline	Celecoxib 200mg BID or Naproxen sodium 220 mg BID, or placebo	Up to 7 years
CDME	86	NEI	Diabetic Retinopathy	Celecoxib 200mg BID or placebo	3+ Years
Cel/Sel	824	NCI	Colorectal polyps	Celecoxib 400 mg QD or placebo	3-5 Years

Baseline Characteristics (%)

	<i>ADAPT</i>	<i>APC</i>	<i>CDME</i>	<i>MA27</i>	<i>PreSAP</i>	<i>Cel/Sel</i>	<i>Total</i>
# enrolled	1809	2035	86	1635	1561	824	7950
Pt-Years	3530	6234	101	695	4141	1369	16070
Age, mean (SD)	75 ± 4	59 ± 10	59 ± 9	64 ± 9	60 ± 10	63 ± 9	64 ± 10
Male	54	68	62	0	66	68	50
White race	97	92	67	94	89	96	93
Diabetes	7.4	9.5	100	6.1	10	7.5	9.2
HTN or med	40	41	62	34	37	36	38
Hyperlipidemia or med	33	38	55	17	17	33	28
Current smoker	3	17	?	?	24	16	14
Low-dose ASA use	50	31	62	14	17	45	31
Prior CV event	13	14	1.2	7	13	14	12
Low CV risk	14	24	0	50	32	19	28
Moderate CV risk	26	29	0	23	31	31	27
High CV risk	59	47	100	27	37	51	45

Event Numbers, Rates and Hazard Ratios

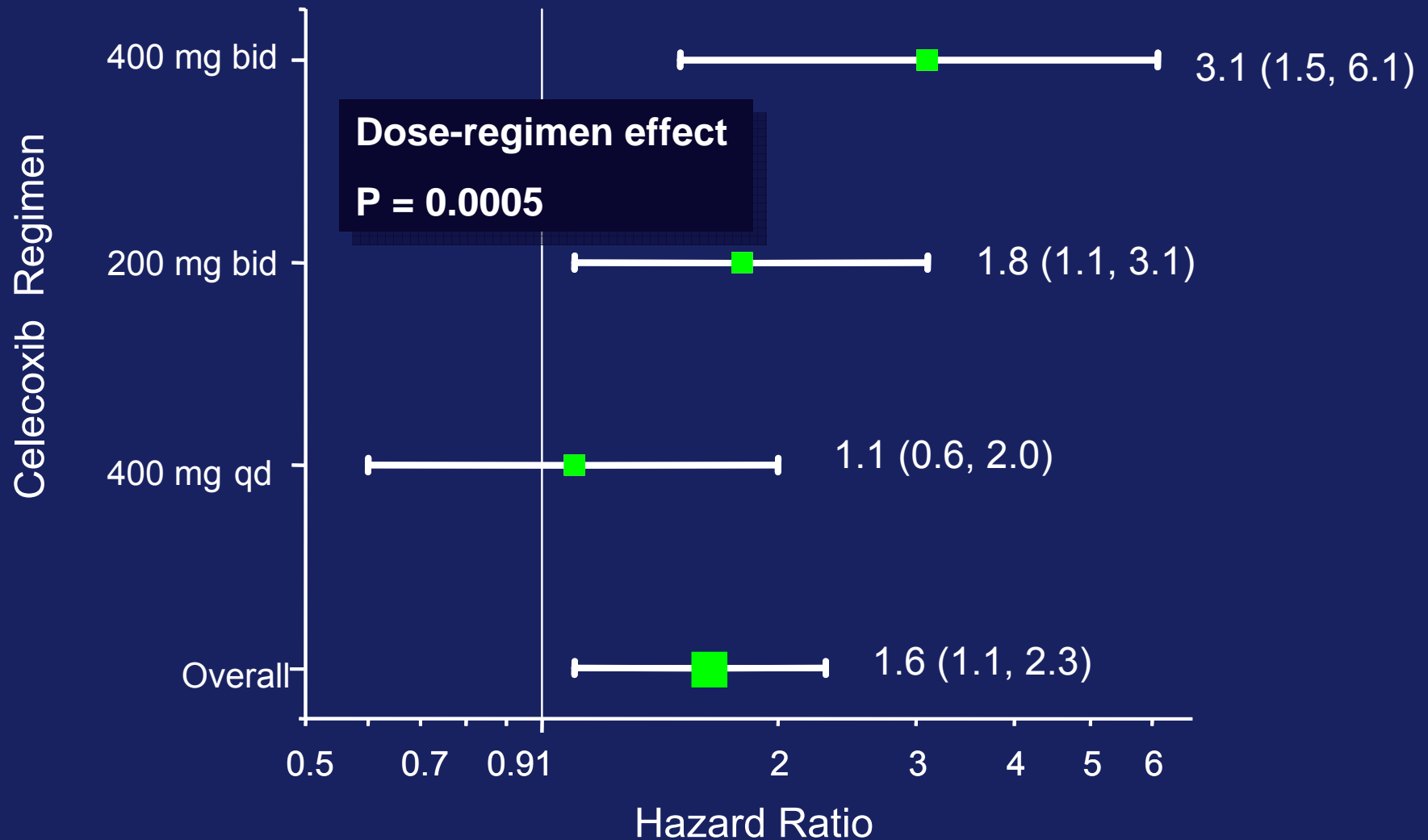
	<u>Events</u> (Event Rate per 1000/pt-yrs)		<u>Hazard Ratio</u>
	<u>placebo</u>	<u>celecoxib</u>	
<u>400mg QD</u>			
PreSAP	12/628 (7.2)	23/933 (9.4)	1.3 (0.6, 2.5)
Cel/Sel	8/410 (11.8)	7/414 (10.3)	0.9 (0.3, 2.4)
400mg QD Pooled	20/1038 (8.6)	30/1347 (9.6)	1.1 (0.6, 2.0)
<u>200mg BID</u>			
ADAPT	18/1083 (8.6)	18/725 (12.8)	1.5 (0.8, 2.9)
APC	8/679 (3.9)	20/685 (9.7)	2.5 (1.1, 5.7)
200mg BID Pooled	29/1809 (6.9)	38/1450 (10.8)	1.8 (1.1, 3.1)
<u>400mg BID</u>			
APC	8/679 (3.9)	27/671 (13.4)	3.6 (1.6, 8.0)
MA-27	3/817 (8.7)	6/818 (17.2)	1.8 (0.4, 7.3)
400mg BID pooled	11/1496 (4.6)	33/1489 (13.9)	3.1 (1.5, 6.1)

*CDME Not included in this table because of extremely low event rates

Solomon et al. Circulation 2008

Hazard Associated with Celecoxib at Various Doses

Stratified by Study and low-dose ASA use and Adjusted for Baseline CV Risk



CV Death, MI, Stroke, HF or thrombo-embolic event

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Composite Outcomes (Hazard ratio and 95% CI)

	400mg QD	200mg BID	400mg BID
CV Death	0.5 (0.2, 1.7)	1.8 (0.5, 6.2)	6.5 (0.8, 54)
+ MI	1.0 (0.5, 2.1)	2.1 (1.0, 4.1)	3.4 (1.2, 9.6)
+Stroke	1.0 (0.5, 1.9)	1.6 (0.9, 3.0)	2.9 (1.3, 6.6)
+ HF	1.1 (0.6, 2.1)	1.7 (1.0, 3.1)	2.7 (1.3, 5.6)
+ Embolic event	1.1 (0.6, 2.0)	1.8 (1.1, 3.1)	3.1 (1.5, 6.1)
Any CV Event	1.3 (0.9, 1.9)	1.4 (1.0, 1.8)	1.6 (1.1, 2.3)

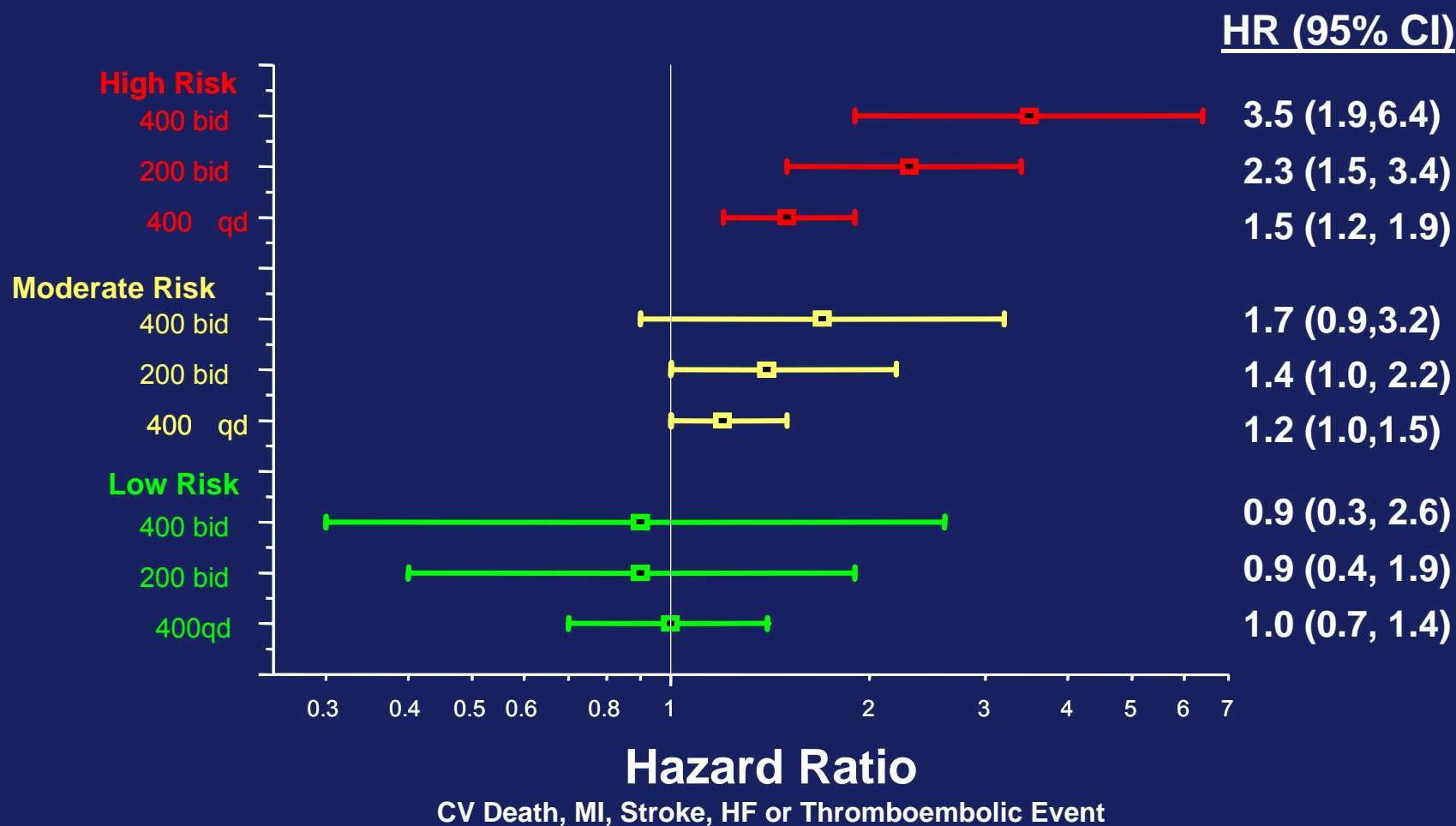
Stratified by study and baseline aspirin use and adjusted for baseline risk

Solomon et al. Circulation 2008

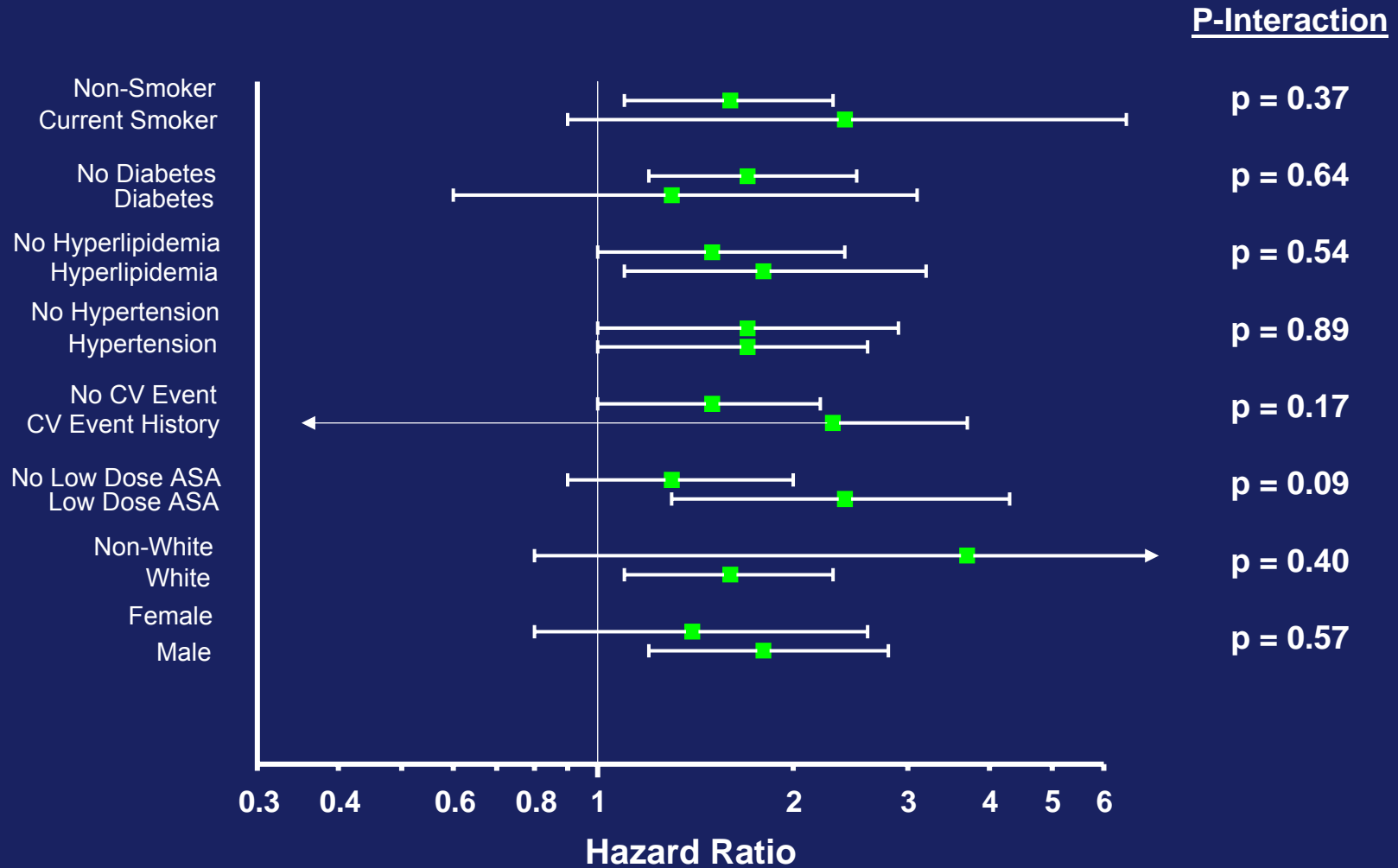
Celecoxib Regimen and Baseline Cardiovascular Risk

Baseline Risk – Dose Regimen Interaction $p = 0.034$

Celecoxib Regimen and pre-treatment Cardiovascular Risk



Prespecified Subgroups



Limitations and Caveats

- None of the trials included in this analysis was designed or powered with the intent of assessing cardiovascular risk.
- Doses tested higher than those typically used in osteoarthritis patients.
 - recommended doses in rheumatoid arthritis, acute pain and dysmenorrhea, FAP.
 - These data provide the strongest evidence of a dose-related risk
- While our data support differential risk based on dosing interval, wide confidence intervals suggest we cannot rigorously exclude hazard at the 400mg once daily dose.
- These data do not address the cardiovascular risk of doses lower than those tested or of other non-selective NSAIDs.

Conclusions (1)

- A pooled analysis of six randomized trials comparing celecoxib to placebo, with over 16,000 patient-years of follow-up, shows an overall increase in cardiovascular risk, with evidence for differences in risk based on the dose and dose-regimen of celecoxib.
- The data showed evidence of an interaction between baseline cardiovascular risk and the effect of celecoxib, suggesting that patients at highest baseline risk had an increased relative risk for celecoxib-related adverse cardiovascular events.

Conclusions (2)

- Our observation that baseline risk influences the cardiovascular risk associated with celecoxib may provide a measure of comfort in prescribing the drug in patients with very low baseline risk, and would argue for more caution in prescribing the drug in patients with higher baseline risk.
- Since celecoxib remains the only coxib available in the United States, and is the most commonly used coxib worldwide, these data should help guide rational clinical decisions regarding celecoxib use.