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

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**Manuscript available simultaneously online in *Circulation***
***http://circ.ahajournals.org***

# DISCLOSURES

No Disclosures

This research was funded entirely by the National Cancer Institute

# 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

[1]McGettigan JAMA 2006; [2]Graham et al. Lancet 2005; [3]Bresalier et al. NEJM 2005; [4]Solomon et al. NEJM 2005
[5]McAddam et al. PNAS 1999; [6]Fitzgerald NEJM 2001; [7]Fitgerald 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) trial[1]
  - 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

[1]Solomon et al Circulation 2006

# 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

Endpoint Definitions: Solomon et al. NEJM 2005

# 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 (%)

| | ADAPT | APC | CDME | MA27 | PreSAP | Cel/Sel | Total |
|---|---|---|---|---|---|---|---|
| # 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

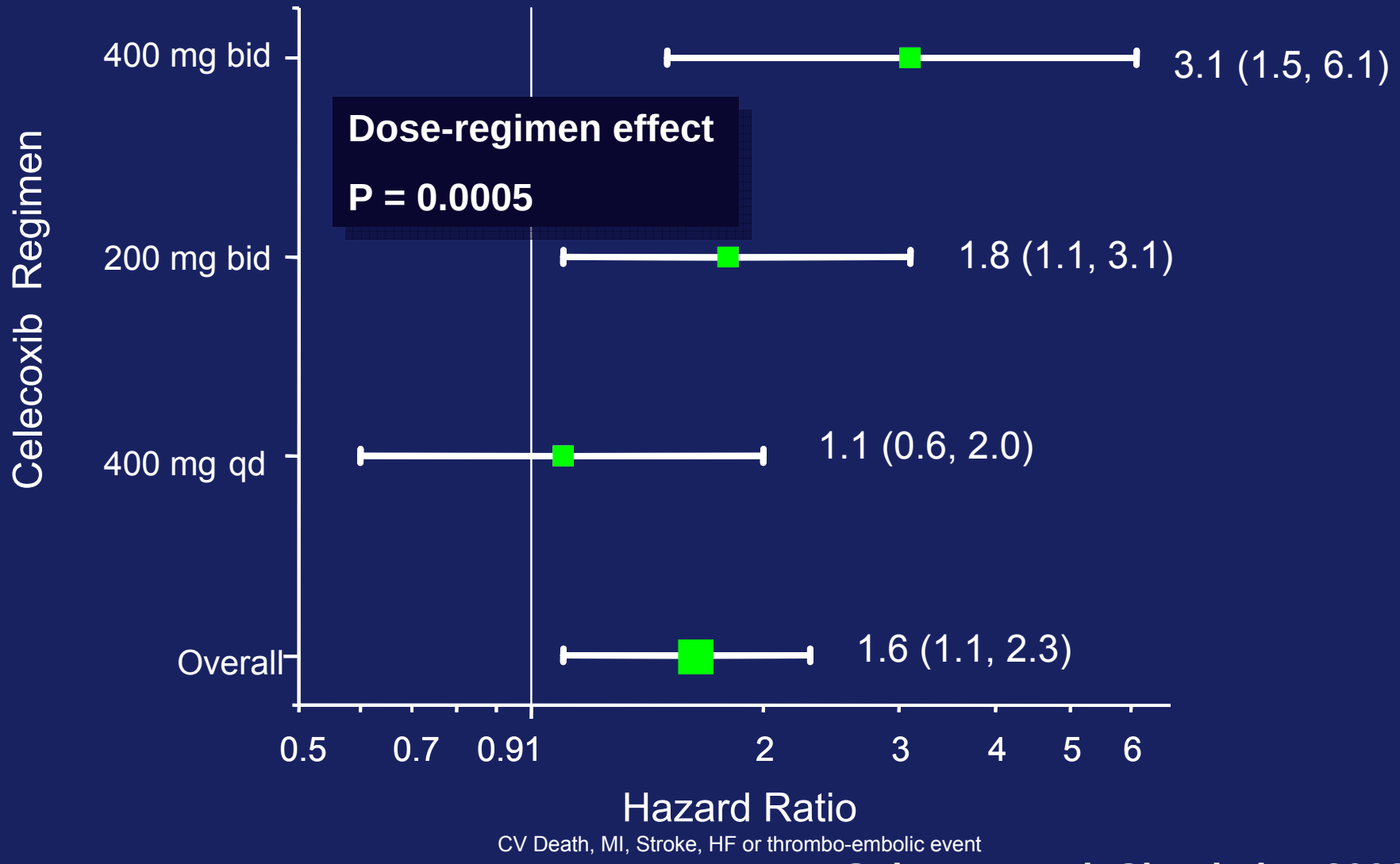
| | | Events (Event Rate per 1000/pt-yrs) | | Hazard Ratio |
|---|---|---|---|---|
| 400mg QD | | placebo | celecoxib | |
| | PreSAP | 12/628 (7.2) | 23/933 (9.4) | 1.3 (0.6, 2.5) |
| | Cel/Sel | 8/410 (11.8) | 7/414 (10.3) | 0.9 (0.3, 2.4) |
| **400mg QD Pooled** | | **20/1038 (8.6)** | **30/1347 (9.6)** | **1.1 (0.6, 2.0)** |
| 200mg BID | | | | |
| | 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)** |
| 400mg BID | | | | |
| | 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




**Solomon et al. Circulation 2008**

# 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**

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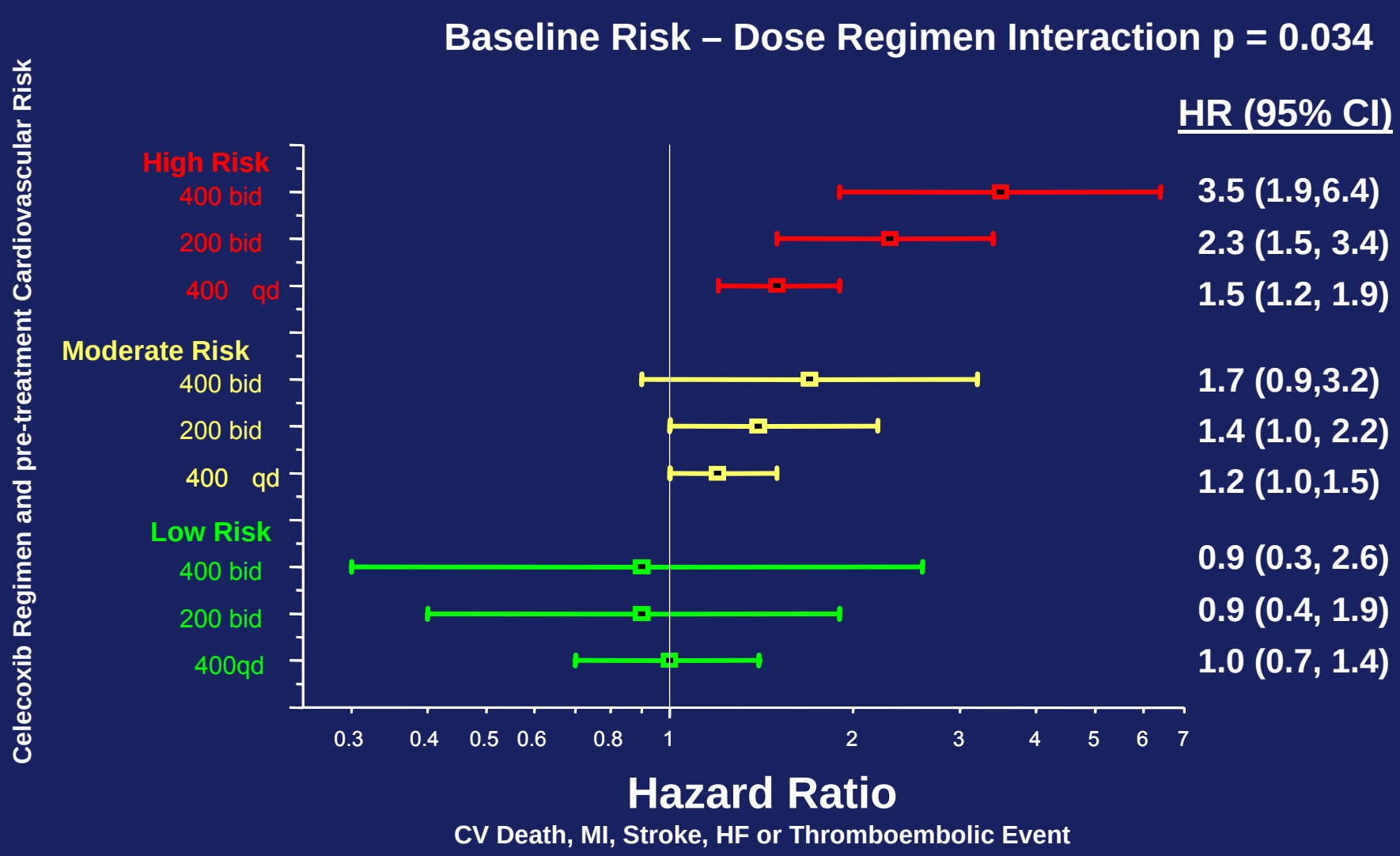
# Celecoxib Regimen and Baseline Cardiovascular Risk

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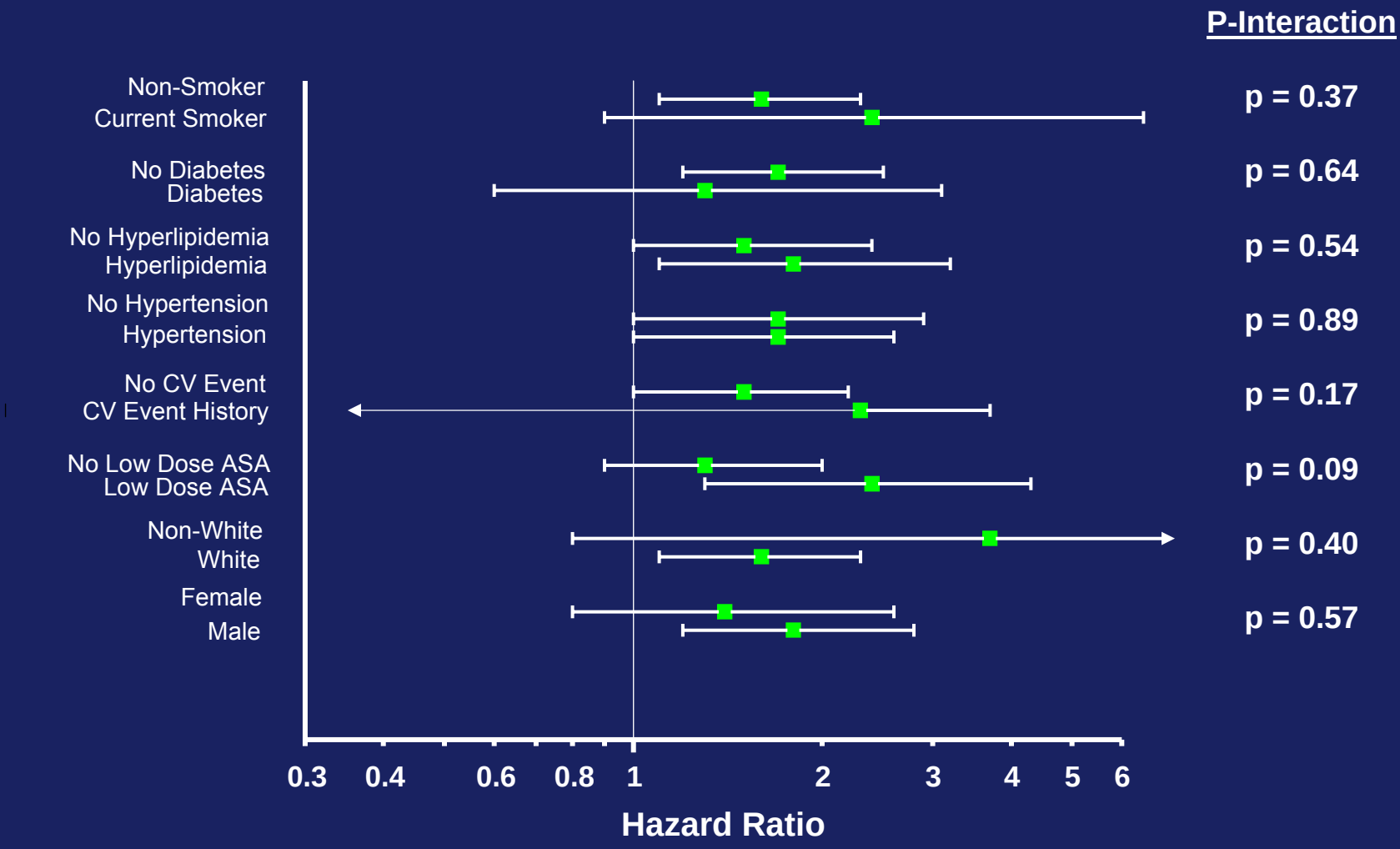
# Prespecified Subgroups

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# 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.

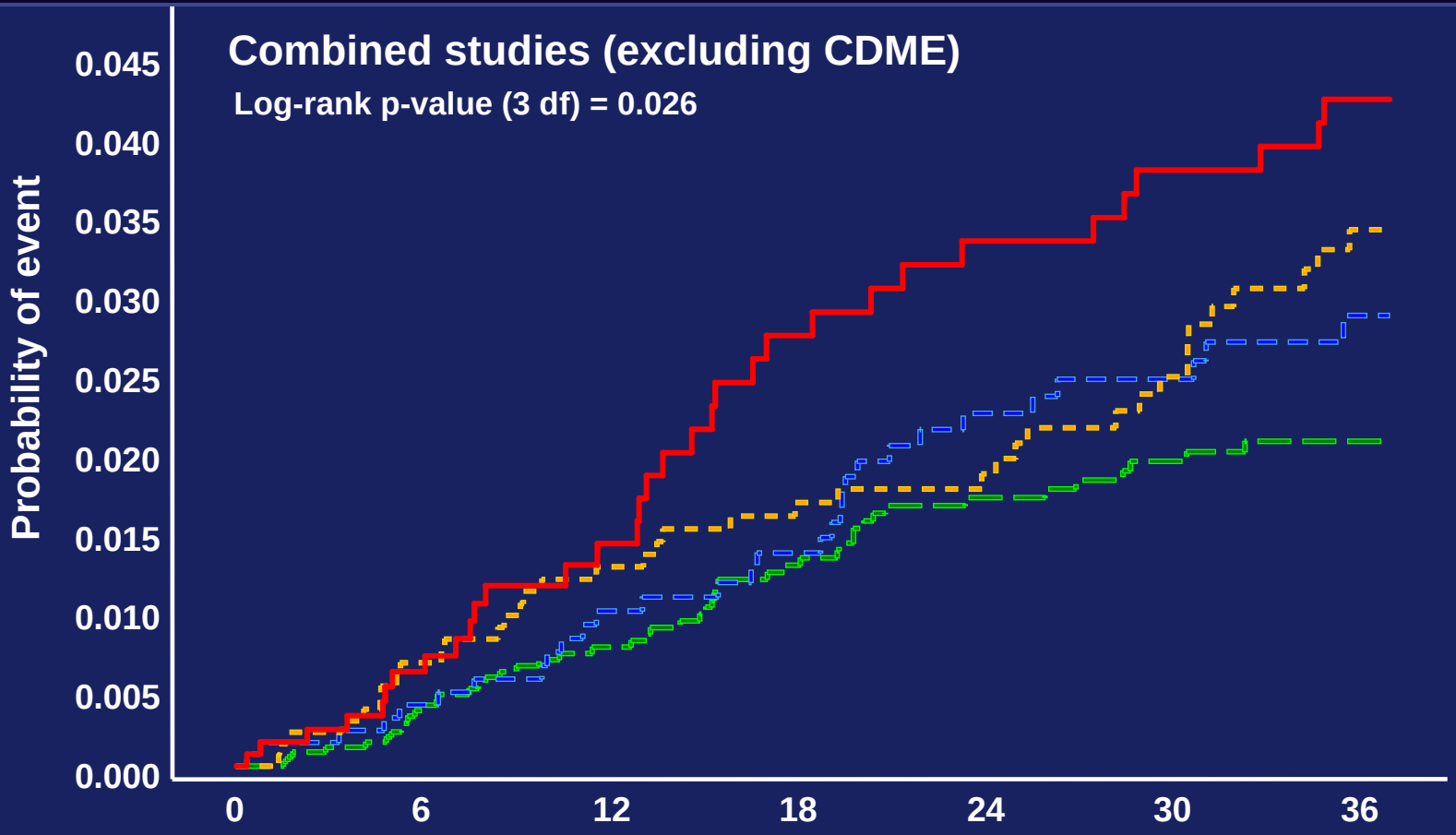
# Conclusions (1)

- 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.

# Composite KM Curves




| Sample size | | | | | | | |
|---|---|---|---|---|---|---|---|
| C 400 bid | 1489 | 990 | 714 | 654 | 648 | 645 | 641 |
| C 200 bid | 1411 | 1342 | 1258 | 1157 | 1033 | 894 | 768 |
| C 400 QD | 1347 | 1231 | 1134 | 1042 | 939 | 841 | 514 |
| Placebo | 3617 | 2943 | 2453 | 2168 | 1894 | 1598 | 1196 |