Special cardiac safety concerns

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Detecting safety signals in clinical trials

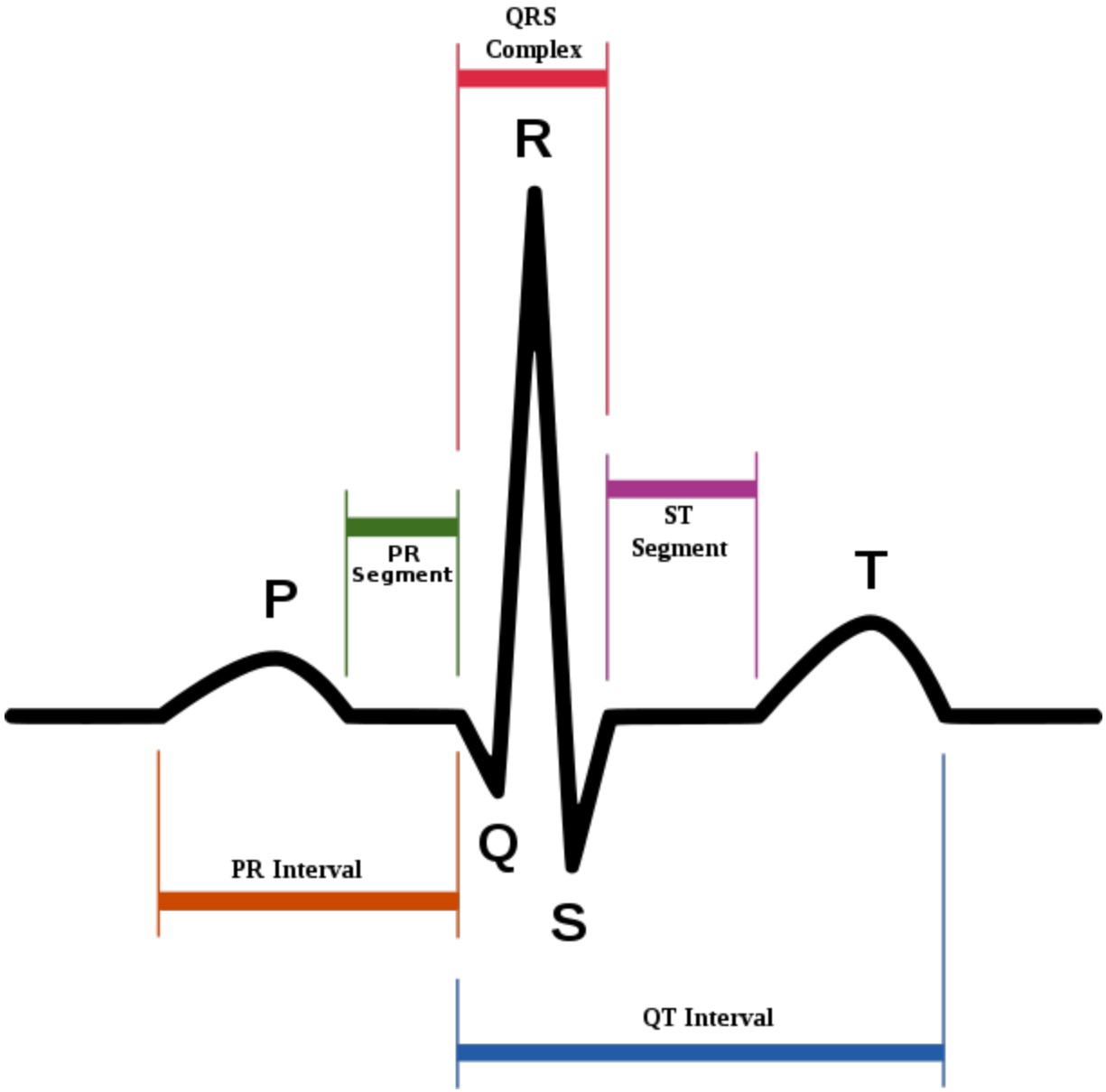
- *Common, drug-related*: can detect in controlled, clinical trials

- *Rare, severe, drug-related*: sometimes detected in clinical trials (e.g., Stevens-Johnson) or via
  - risk biomarkers (e.g., QT prolongation) or
  - epidemiologic studies (e.g., case-control)

- *Spontaneous events ↑ rate with drug*: single event usually ***not*** interpretable; detect via
  - large enough controlled trial
  - epidemiologic study (large hazard ratio)

This talk will focus on latter two scenarios.

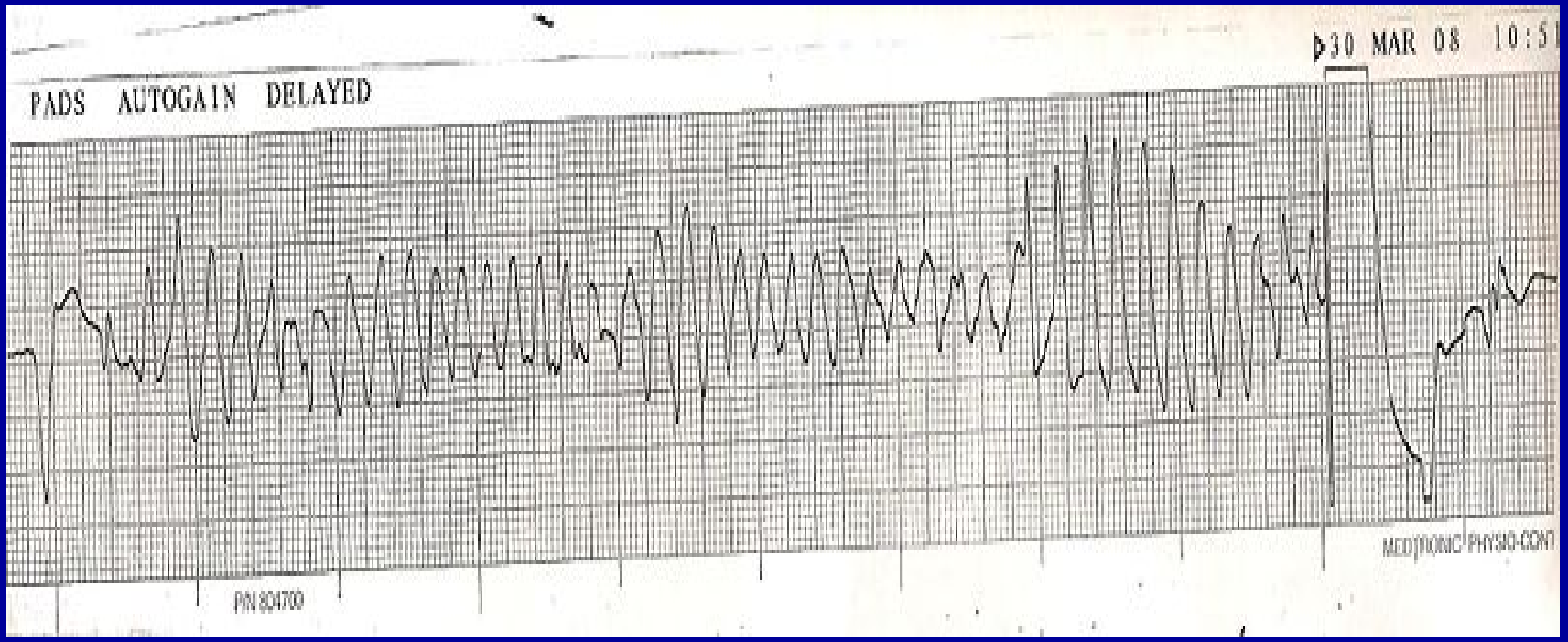
Case #1: QT Prolongation


QRS
Complex
R
PR
Segment
ST
Segment
P
T
Q
S
PR Interval
QT Interval

QT interval

- Varies with heart rate, autonomic tone, time of day
- Can be prolonged due to:
  - heart disease (e.g., congestive heart failure)
  - electrolyte abnormalities (e.g., hypokalemia)
  - drugs (e.g., quinidine).

Torsade de pointes: polymorphic ventricular tachycardia



Rare, but life-threatening. Might not be detected in a drug development program.

Background

- Certain antiarrhythmic drugs prolong QT
- Drug withdrawals due to QT risk (terfenadine, cisapride) for non-antiarrhythmic drugs

Current QT policy

- Most systemically available drugs need a "thorough QT" (TQT) study
- Threshold for potential clinical importance set very low (10 msec)
- "Negative study" → routine phase 3 monitoring
- Failure to rule out 10 ms → heightened phase 3 monitoring

TQT Study Characteristics

- Includes placebo and positive control
- Characterize QT effects of the drug under near “worst case” scenario
  - Exposure at supratherapeutic concentrations
  - ECG sampling at peak concentrations (drug/metabolites)
  - Sufficient duration of dosing/sampling to characterize effects

What if the study is positive?

- More intensive Phase 3 monitoring
- Might alter development (different dose, different target population, etc.)
- Look for benefits that might offset risk

Concerns about TQT studies

- QT studies difficult and expensive
- Relationship to risk (arrhythmia) not constant
- Unknown public health consequences of compounds removed from pharmaceutical pipeline
- **Interest in alternative approaches to assess proarrhythmic risk.**

Case #2: Drug-induced Valvulopathy

Weight loss

Appetite suppressants

- Fenfluramine (1973): approved for *short-term use*
  - racemic mixture*- increased serotonin, associated with depression
- Dexfenfluramine (1996)* thought to be "safer"
- Fen-Phen: never approved, widely used off-label for *long-term management*

*withdrawn in 1997

Case-control study in Europe: odds ratio **23.1** associated with use > 3 months.

The New England Journal of Medicine

VOLUME 335 AUGUST 29, 1996 NUMBER 9

APPETITE-SUPPRESSANT DRUGS AND THE RISK OF PRIMARY PULMONARY HYPERTENSION

LUCIEN ABENHAIM, M.D., YOLA MORIDE, PH.D., FRANÇOIS BRENOT, M.D.,* STUART RICH, M.D., JACQUES BENICHOU, M.D., XAVIER KURZ, M.D., TIM HIGENBOTTAM, M.D., CELIA OAKLEY, M.D., EMIL WOUTERS, M.D., MICHEL AUBIER, M.D., GÉRALD SIMONNEAU, M.D., AND BERNARD BÉGAUD, M.D., FOR THE INTERNATIONAL PRIMARY PULMONARY HYPERTENSION STUDY GROUP†

24 women, no prior heart disease, mean treatment duration 11 months.

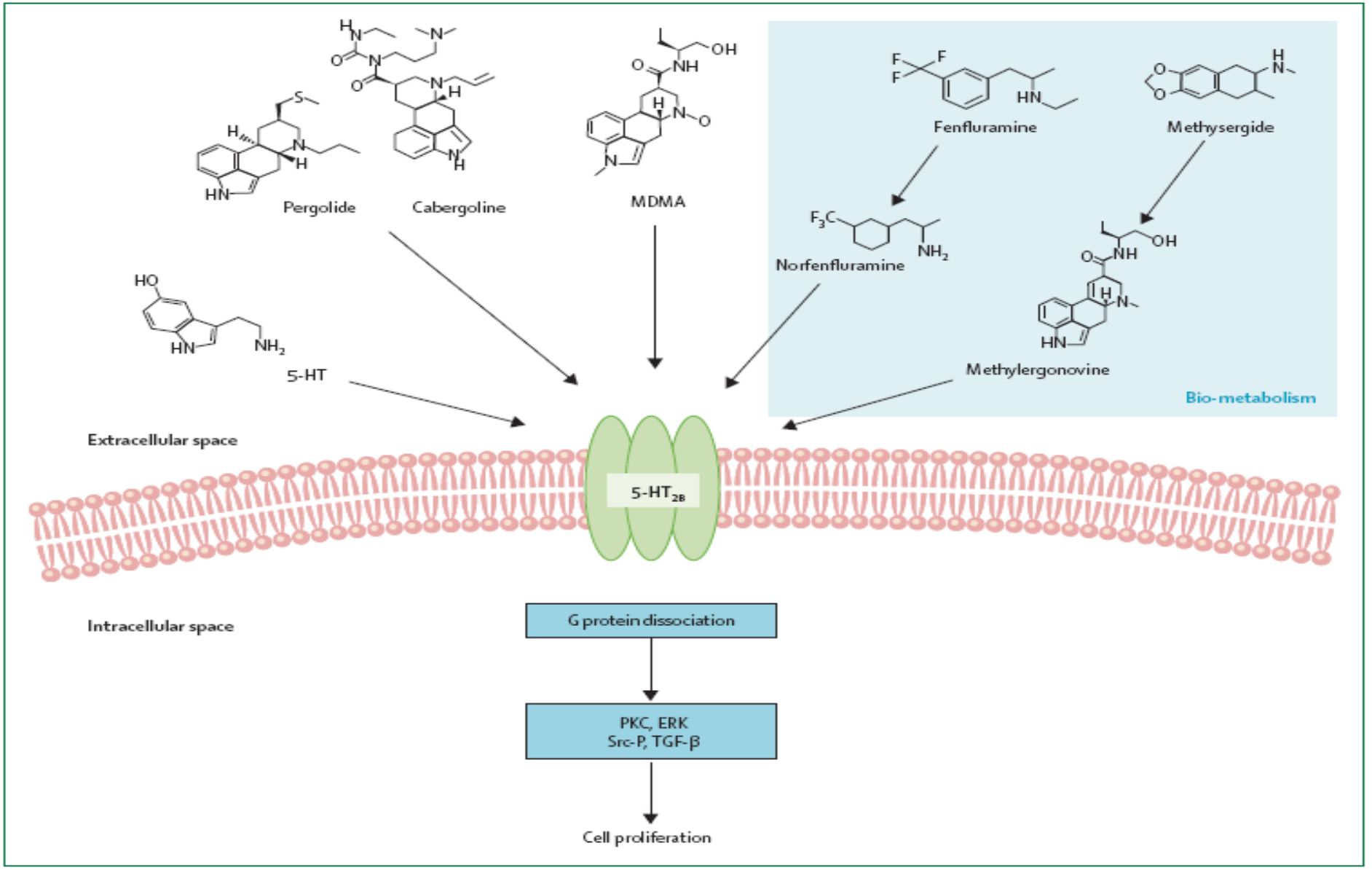
The New England Journal of Medicine

VOLUME 337 AUGUST 28, 1997 NUMBER 9

VALVULAR HEART DISEASE ASSOCIATED WITH FENFLURAMINE–PHENTERMINE

HEIDI M. CONNOLLY, M.D., JACK L. CRARY, M.D., MICHAEL D. MCGOON, M.D., DONALD D. HENSRUD, M.D., M.P.H., BROOKS S. EDWARDS, M.D., WILLIAM D. EDWARDS, M.D., AND HARTZELL V. SCHAFF, M.D.

Fenfluramine and dexfenfluramine voluntarily withdrawn on Sept. 15, 1997



Source: Bhattacharyya et. al. Lancet 2009; 374: 577-85

Case #3: Rofecoxib (Vioxx) and heart attacks

Rofecoxib (Vioxx)

- Originally approved (1999) for acute pain (up to 5 days), dysmenorrhea, and osteoarthritis (12.5 mg and 25 mg/day).
- Dose-related increase in hypertension and edema were observed
- No cardiovascular signal observed at approval.

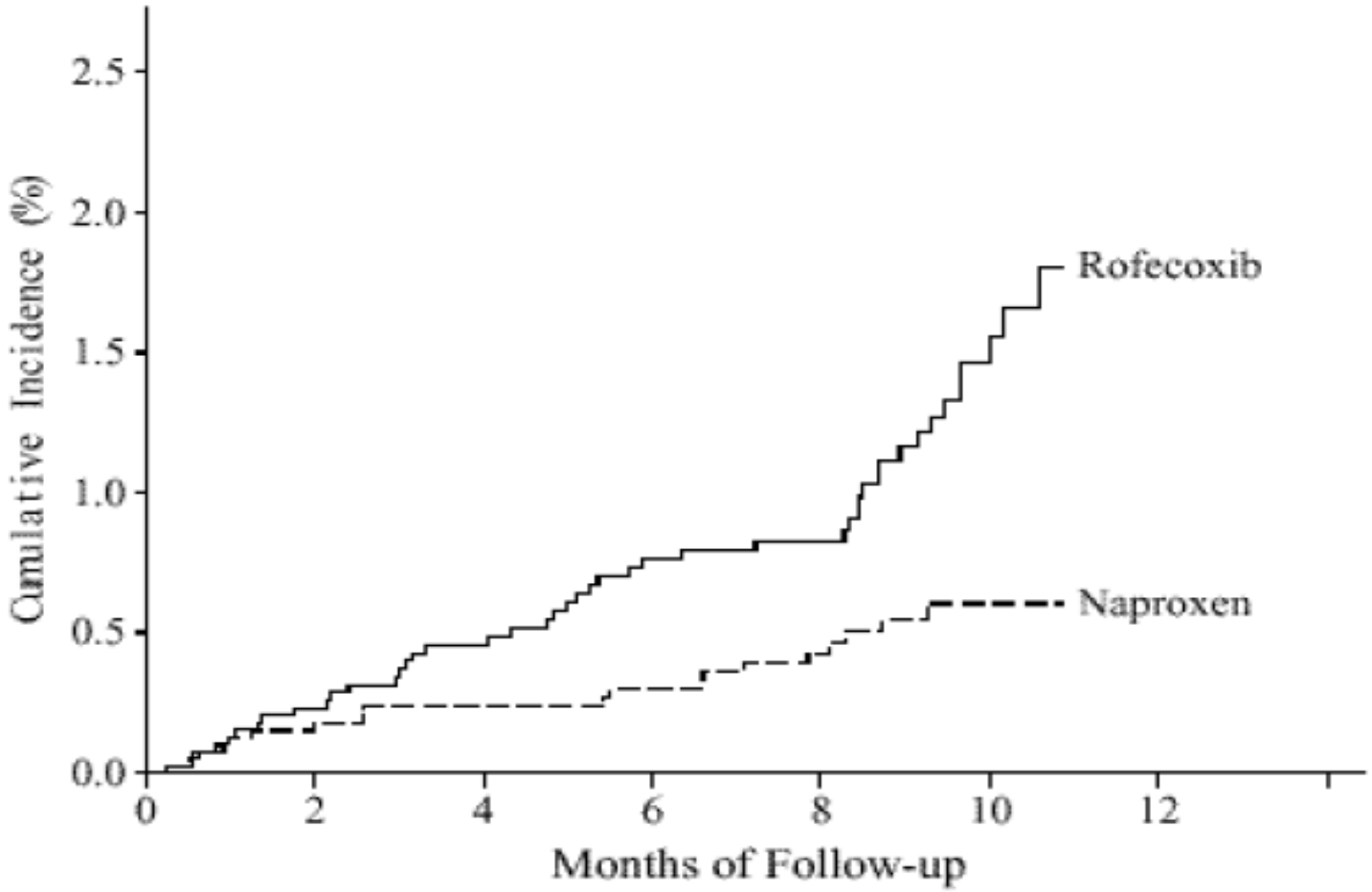
COX-2 inhibition

- Cyclooxygenase (COX): metabolize arachidonic acid to produce prostaglandins (PG)
- Promise of Cox 2 inhibition: analgesia with less gastrointestinal toxicity.

VIGOR study

- Randomized, large double-blind trial
- Vioxx 50 mg/day or Naproxen 500 mg twice/day –no placebo arm
- Primary endpoint was **GI events**
- Rheumatoid arthritis, mostly < 65 years

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Rheumatoid Arthritis Patients in the VIGOR Study Time-to-Event Plot (All Patients Randomized) Updated Application Data



at Risk						
Rofecoxib	n=4047	3643	3405	3177	2806	1067 531
Naproxen	n=4029	3647	3395	3172	2798	1073 514

APPROVe study

- Three-year, placebo-controlled study
- Primary endpoint prevention of colorectal polyps
- Terminated early—increased incidence of MI and stroke after 18 months of Vioxx.
- Vioxx withdrawn (2004)

Further evaluation of cardiovascular outcomes

- Guidance evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes (2008)
  - Integrated analyses of events in phase 2/3
  - Prespecified upper bound
- Adequately powered cardiovascular safety study (either pre- or post-approval).
- Expect further evolution in future

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  - epidemiologic studies (e.g., valvulopathy)

- *Spontaneous events ↑ rate with drug*: single event usually ***not*** interpretable; detect via
  - large enough controlled trial (e.g., Vioxx)

Thank you

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