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

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.
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

Cumulative Incidence (%)

Months of Follow-up

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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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