Drug Regimen per protocol
Interference with ASA Antiplatelet Effect

A. Platelet cyclooxygenase-1
   - Catalytic site
   - Serine residue at position 529
   - Channel of access
   - Arachidonic acid
   - PGH₂
   - TxA₂
   - TxB₂ (urine)

B. With aspirin
   - Acetyl serine

C. With ibuprofen and aspirin
   - Ibuprofen
   - Aspirin

Dose-Dependent Pharmacodynamic Interaction

Catella-Lawson et al.
NEJM 2001;345:1809

Li et al.
PNAS 111: 16830, 2014
Variable NSAID Use, FU, + Ascertainment of Events

On NSAID | OFF NSAID | Another NSAID | Lost to FU | Event
---|---|---|---|---

1. E1

2. E2

3. E3 (69% Subjects DC Drug)

4. OA

5. E5

6. LTFU (27% Subjects)

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<th>ITT</th>
<th>On Rx</th>
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(X) (X)
Relative Risk of Events

Drug Regimen A : Drug Regimen B

Noninferiority

A Better

RR = 0.6 0.7 0.8 0.9 1.0 1.1 1.2 1.3 1.4

B Better

Challenges to Interpretation of Noninferiority in PRECISION

Exposed To Drug 59% of Time in Trial

Crossover
**Dose-Related Increase in Risk with Celecoxib**

- **Rate ratio (RR)**
  - (direct evidence)

  - **(a) Celecoxib**
    - 800mg daily: 2.96 (1.21 - 7.25)
    - 400mg daily: 1.29 (0.81 - 2.04)
    - 200mg daily: 0.95 (0.30 - 3.00)
    - 100mg daily: 1.36 (1.00 - 1.84)

  - Any dose: 1.36 (1.00 - 1.84) p=0.05

  - N about 1925 subjects
  - 41 comparisons

- **Favours coxib**
- **Favours placebo**

**Interaction of Celecoxib Dose and Baseline CV Risk**

- **CV Risk**
  - High Risk: 400 bid, 200 bid, 400 qd
  - Moderate Risk: 400 bid, 200 bid, 400 qd
  - Low Risk: 400 bid, 200 bid, 400 qd

  - N=7950 subjects
  - 6 RCTs

- **P=0.034**

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CNT Meta-Analysis
Lancet 382: 769, 2013
Supplementary Material

Solomon
Circ 117:2104, 2008
• Lowest Risk Patient
• Lowest Risk Drug
• Lowest Dose Needed
• Shortest Period of Time
Current Approach: Common Phenotype Average Response

Precision Medicine Approach

Urgent Clinical Need: Novel Analgesics and Other Therapeutics to Avoid CV Risk from all NSAIDs

OA  RA

Antman + Loscalzo
Nat Rev Card 2016