4th Seattle Symposium in Biostatistics

Identifying and Addressing Safety Signals In Clinical Trials

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Fleming TR. Identifying and Addressing Safety Signals in Clinical Trials. 2008; *NEJM* 359(13): 1400-1402.

Illustration: Cancer Risk with Vytorin in Slowing progression of Aortic-Valve Stenosis

SEAS Trial	N	CA. Incidence	CA. Deaths
Vytorin	944	101	37
Placebo	929	65	20
Relative Risk:		**1.55**	**1.78**
95% C.I.:		(**1.13**, 2.12)	(**1.03**. 3.11)

Challenge:

Interpreting safety signals from exploratory analyses

Class of Agents **and** **Example members**	***Safety Event*** **and** **Clinical Setting**	**Bkgd Rate /1K**	**Relative ↑ In Safety Risk, RR**	**Attrib Risk, #/1K PY**
Cox 2 inhibitors Celebrex, Vioxx, Bextra	*CV Death / Stroke / MI* RA, OA and Alzheimers	10	1.5	5
Long Acting β-Agonists Salmeterol, serevant	*Asthma-related Death* Severe Asthma	0.5	4	1.5
Anti-psychotics Ziprasidone	*QTc related CV Events* Schizophrenia	?	?	?
Tysabri	*Progressive Multifocal Leukoenceph* Multiple Sclerosis & Crohn's Disease	<0.001?	1000	1
Rotavirus Vaccine	*Intussusception* High Risk for Rotavirus	0.1	>10	>1
Muraglitazar Rosiglitazone	*CV Death / Stroke / MI* Type 2 Diabetes	20	1.5 - 2	10-20
Erythropoietin	*Thombosis, Death* Renal Disease, Oncology	?	1.1-1.15	?
ADHD Psychostimulants Adderall, Ritalin in Adults ADHD Drugs in Pediatrics	*CV Death / Stroke / MI* ADHD Adult Setting ADHDPediatric Setting	 10 0.12	 2.5 2.5	 15 0.2

Primary Goal

Identifying effective interventions
that are safe

⇒ An important objective:
Obtaining a Timely & *Reliable* Assessment
of Benefit-to-Risk

… Detecting **long** & short term risks…
… Detecting **rare** & frequent risks…

Enabling one to *rule out*
unacceptable increases in safety risks

Approaches to Pre- and Post-Marketing Evaluation of Safety

I Passive Surveillance Systems

II Active Surveillance Systems

III Large Randomized Clinical Trials

- ✓ Surveillance for new safety signals
- ✓ Exploration of existing signals

Passive Surveillance Systems

AERS:

(based on *voluntary* submission of MedWatch forms for serious AEs caregivers believe might be drug related)

+ Timely information
+ Uniformity of reporting procedure

– Not randomized; no comparator group
– Lack of denominator
– Voluntary submission $\Rightarrow$ underreporting

Active Surveillance Systems

Large Prospective Cohorts & Linked Databases:

+ Information on a defined population
+ Complete numerators & denominators
+ Fast & inexpensive

– Not randomized
– Confounder information often unavailable
– Outcome sensitivity
– Outcome specificity

… is stated event truly an event?

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Safety Assessments: Advantages provided by *Randomized* Prospective Cohorts

- Randomization removes systematically occurring imbalances in baseline characteristics
  - ~ Pts/caregivers don't start/stop treatments "at random"
  - ~ Known & recorded covariates are the "tip of iceburg"
- Need to conduct an ITT evaluation
  - $\Rightarrow$ Need ability to define a time 0 cohort
  - ~ Assess risk over specified time interval, even if intervention is stopped earlier in time
  - ~ Risk cannot be assumed to be independent of duration of exposure

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…Hypothesis Confirmation vs. Hypothesis Generation, keeping in mind "random high" type bias

Can Efficacy or Safety Signals Discovered in Exploratory Analyses Be Viewed to be Reliable Results?

- Criteria to be simultaneously satisfied:

✓ << P-values *(e.g., Tysabri & PML)*

✓ Biologically plausible effect

- *Ezetimibe blocks the absorption of phytosterols and other phytonutrients linked to protection against cancer, which provides some biologic plausibility that the drug could have an effect on the growth of cancer cells*

✓ Confirmed by external results

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- **IMPROVE-IT & SHARP Trials**

	N	CA. Incidence	CA. Deaths
Vytorin	10,391	313	97
Control	10,298	326	72
Relative Risk:		**0.96**	**1.34**
95% C.I.:		(**0.82**, 1.12)	(**0.98**, 1.84)

Interpreting the SEAS, IMPROVE-IT & SHARP Trials Regarding Cancer Risk with Vytorin

- ✓ *Peto et. al. (NEJM, 2008)*

"The available results from these 3 trials do not provide credible evidence of any adverse effect of ezetimibe on rates of cancer."

- ✓ However, safety is established by ruling out unacceptable increases in safety risks…

…i.e. by what you can say, not what you can't say…

Fleming (*NEJM*, 2008)

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Issues in interpreting the IMPROVE-IT & SHARP Trials Regarding Cancer Risk with Vytorin

- A relative increase of as much as 84% in cancer deaths with the use of Vytorin cannot be excluded
- IMPROVE-IT and SHARP are ongoing trials:
  - ✓ Reduced reliability of interim nature of data
  - ✓ The Integrity of these two trials can be disturbed by the release of interim data on safety or efficacy
  - ✓ Full access to peer-reviewed summaries of data from the two trials is required to address whether performance standards for safety trials have been met

Drazen / Wood

- An important safety signal has been identified for Vytorin …evidence of efficacy is limited to effects on biomarkers

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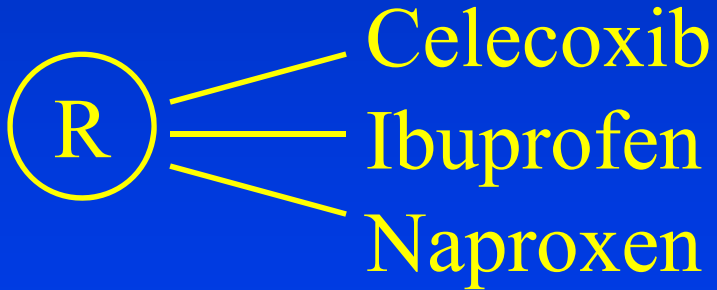
The PRECISION Trial: *Ruling out* Excess Rates of CV Death / Stroke / MI

Pain Medications in Patients with Osteoarthritis & Rheumatoid Arthritis With or at Hi Risk for CV Disease



PRECISION Trial

Using the Proportional Hazards Model
for the rate of "CV Death/Stroke/MI"

Naproxen : $\lambda_0(t)$ Celecoxib : $\lambda_1(t) = \lambda_0(t)r$

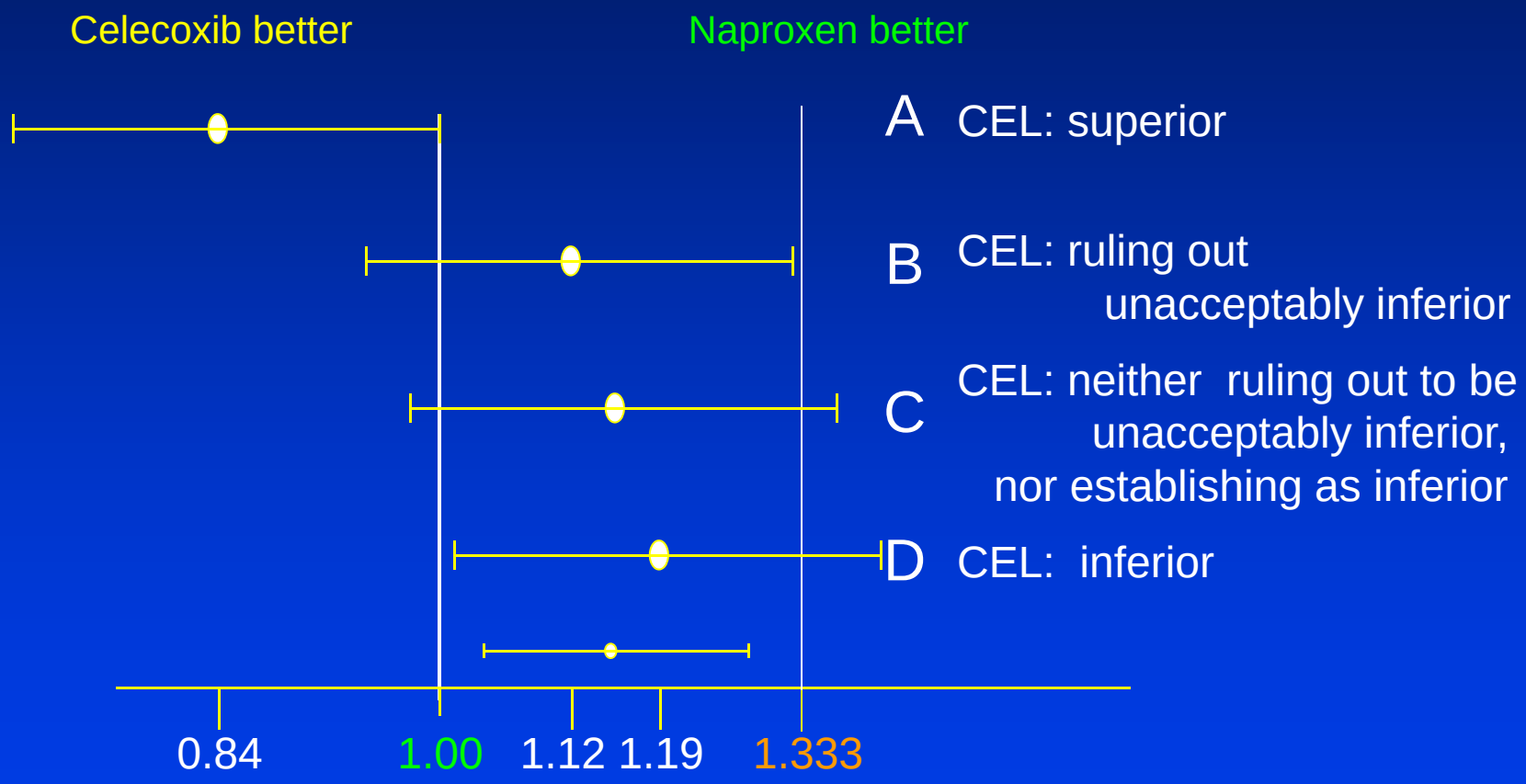
Note: With 10 events / 1000 p.y. in the control arm,
then $r = 1.333 \Rightarrow$ 3.33 add'l events / 1000 p.y.,
offsetting $\downarrow$ in GI ulceration & $\uparrow$ analgesic effects

Then $L = 508$ events are required, if one sets:

- ✓ $H_0 : r = 1.333$ & $H_1 : r = 1.00$
- ✓ (one-sided) 2.5% false positive error rate, and
- ✓ 10% false negative error rate (i.e., 90% power)

“CV Death / MI / Stroke” Events

Celecoxib compared with Naproxen



Based on analysis at L=508 Events

Performance Standards in Non-inferiority Safety Trials

- **Enrollment Rate**
  - ✓ need timely result
- **Target Population / Ineligibility Rate / Event Rate**
  - ✓ need to address settings where excess risk is most plausible
  - ✓ need sufficiently high risk to achieve targeted number of events
- **Adherence**
  - ✓ must at least match adherence in prior trials with safety signal
  - ✓ include frequency/timing of withdrawal from rand. treatment
- **Cross-ins**
  - ✓ minimize by: careful screening; educating caregivers & patients

  …*Very challenging in a post-marketing setting*…
- **Retention**
  - ✓ critical to maintaining integrity of randomization

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Consequences of Reliance on Surrogate Endpoints For Accelerated or Full Regulatory Approval

- Less reliable evidence regarding Efficacy
- Less reliable evidence regarding Safety

…The stronger the efficacy evidence , the greater the resilience regarding uncertainties about safety…

Recent Experiences:

- Tysabri : PML in Crohns Disease & Multiple Sclerosis
- Erythropoiesis Stimulating Agents :
  Chemo-Induced Anemia & Hemodialysis in CHF
- Muraglitazar & Rosiglitazone : Type 2 Diabetes
- Simvastatin/Ezetimibe (Vytorin) : Aortic Stenosis

Conclusions

An important objective:

Obtaining a Timely & *Reliable* Assessment of the Benefit-to-Risk Profile…

- ✓ …establishing substantial evidence of efficacy
- ✓ …enabling one to *rule out* unacceptable increases in safety risks

"Absence of Evidence
is not
Evidence of Absence"