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Methodologic Lessons in the Rosiglitazone and Aprotinin Sagas

1. Debate between RCTs and observational studies is a false dichotomy
2. Using surrogate outcomes can be fraught with risk
3. Solutions



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Limitations of Pre-marketing RCTs

- Limited sample size
- Carefully selected subjects may not reflect real-life patients in whom drug will be used
- Study subjects may receive better care than real-life patients
- Drug use will follow label
- Short duration of treatment
- Short follow-up



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"Less than one in ten thousand—something like one in fourteen thousand—gets these side effects. Hardly anybody gets these side effects. They're extremely rare. You should be very proud."

Resulting “Opportunities”

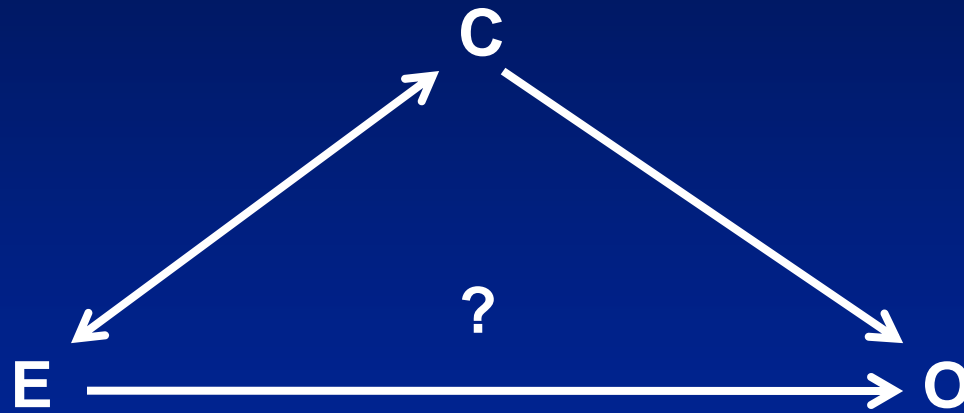
- 51% of drugs have label changes due to major safety issues discovered after marketing
- 20% of drugs get new “black box” warnings after marketing
- 4% of drugs are ultimately withdrawn for safety reasons



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Definition – A confounding variable is a variable other than a risk factor and outcome variable under study which is causally related to both of them

Confounding



Confounding by Indication

- Patients who are treated with a drug are inherently different from those who are not treated with the drug, in ways which relate to the outcome under study



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Issues

- Randomized trials cannot answer all questions, even in cardiology (!)
- Observational trials suffer from confounding by indication/selection bias/channeling
- Subject selection → issues in internal vs. external validity



Solution-1

- Differentiate bad science, from a bad design
- Disagreement between RCT and observational studies does not mean one is necessarily wrong → they are often addressing different questions
- Bridge between statistical sophistication and clinical understanding
- The question is, what is the question?



Solution-2

- **Both RCTs and observational studies have appropriate roles**
 - RCTs are generally preferable for studying beneficial effects
 - Observational studies are generally preferable for studying adverse effects



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Perils of Using Surrogate Outcomes

- Often needed to allow earlier marketing
- Mechanism does not always predict outcome



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General Solutions

- Use each design for its appropriate niche, only
- Register studies, regardless of design
- Consider use of large simple trials, as a hybrid
- When approving drugs based on surrogates, consider routinely requiring proper outcomes studies, to be launched along with the launch of the drug. Focus them on the outcomes that matter



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“Decisions usually involve risk.”

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