INTERPRETATION OF STUDY FINDINGS:

PART II

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Framework

Framework for assessing statistical association and cause-effect relationships in clinical trials.

A. Is there a valid statistical association?

1. **Chance**
2. **Bias**
3. **Confounding**

B. If there is a valid statistical association, is it one of cause and effect? Positive criteria:

1. **Strength of association**
2. **Totality of evidence**
3. **Biologic credibility**
4. **Dose-response**

C. To whom can we generalize?

2nd Question: Is Valid Association Causal?

If after considering the alternative explanations of chance, bias and confounding, the observed association is felt to be valid, only then is the issue of causality to be considered.

Causality is an issue of judgment, not fact. No "test" for assessment of causality.

To assess causality, this judgment must be based on all available evidence. Positive criteria.

Positive Criteria for Causality

1. **Strength of the association:** the stronger the association, the more likely the association is to be causal. It minimizes the chance of unsuspected confounders. A weak association can be causal - but it is harder to prove.

2. **Totality of evidence, or consistency:** if other investigators studying different populations using different methodologies show similar results, strong support for causality.

Positive Criteria

3. **Biologic credibility:** **does the association "make sense"? If no biologic mechanism can be postulated, however, may merely be due to limits of current knowledge.**

4. **Dose-response:** **does level of risk or disease increase as dosage increases? Problems are that first, a dose-response relationship could be due to the effect of a confounder and second, a dose-response relationship may not be present if there is a threshold effect.**

CORONARY Trial

Is the observed beneficial association of off-pump vs off-pump on
1-year composite endpoint valid?

Chance:

12.1% vs. 13.3%: 288 vs 316 events. P=0.24: Chance cannot be ruled out as an explanation for the findings.

Correct interpretation: Abstract - "At 1 year, there was no significant difference in the rate of the primary composite outcome between off-pump and on-pump CABG".

No significant interactions - Presented hazard ratios for primary outcome in prespecified subgroups (Figure 2).

CORONARY Trial

Bias:

Quality of life and neurocognitive testing optional: initial participation rates low, and could not be done by phone for those not willing to come back.

Completers somewhat healthier than those who did not participate.

Sensitivity analyses suggested little difference between patients in the two groups.

CORONARY Trial

Confounding:

Demonstrated similar distributions between baseline and characteristics of treatment groups. Thus unknown confounders are also likely to be evenly distributed. Confounding unlikely explanation of the findings.

3rd Question - Generalizability

If the observed association is considered valid (internally validity), related issue is whether the findings are generalizable (external validity), i.e., to whom are they applicable.

Technically, study results are only applicable to the population in which study done. But want to make a judgment to broaden inference.

Validity trumps generalizability. Primary concern is validity, since you cannot generalize an invalid result. Watch that validity is not compromised in an effort to achieve generalizability.

CORONARY Trial

To whom can you generalize?

Did study in more diverse population than earlier trials.

Patients at higher surgical risk than previous trials (i.e., older, more patients known to have smaller coronary arteries (women, South Asian, East Asian), more patients with severe disease (i.e., more patients with 3-vessal disease)).

Diverse array of clinical settings.

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