INTERPRETATION OF STUDY FINDINGS:

PART I

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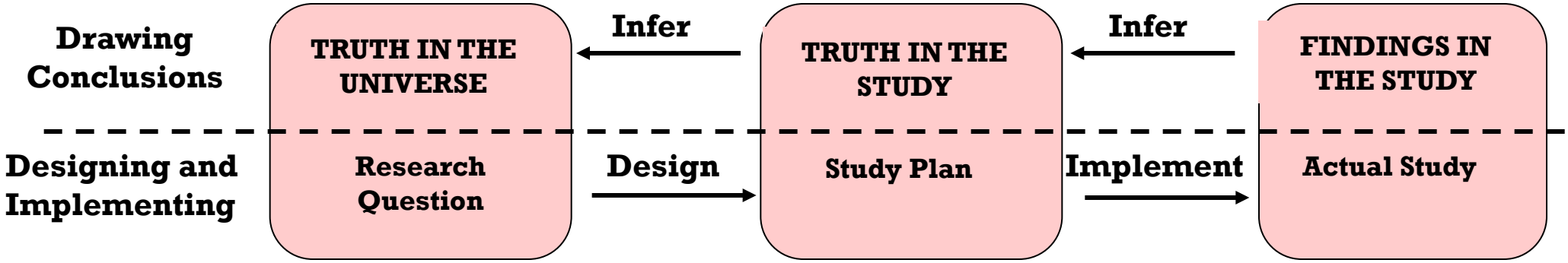


Source: Hulley SB, et al. Designing Clinical Research: 3rd Edition, Wolters Kluwer 2007.

The Problem

What we see in any type of analytic research design is a statistical association (relationship) between an exposure or intervention and the disease or outcome under study.

But what we are trying to do is evaluate whether that observed relationship is causal (i.e., does it play an essential role in the development of the disease).

If it does, an alteration in this exposure would lead to an alteration in risk of outcome. Goal of public health and clinical care.

How do we evaluate this?

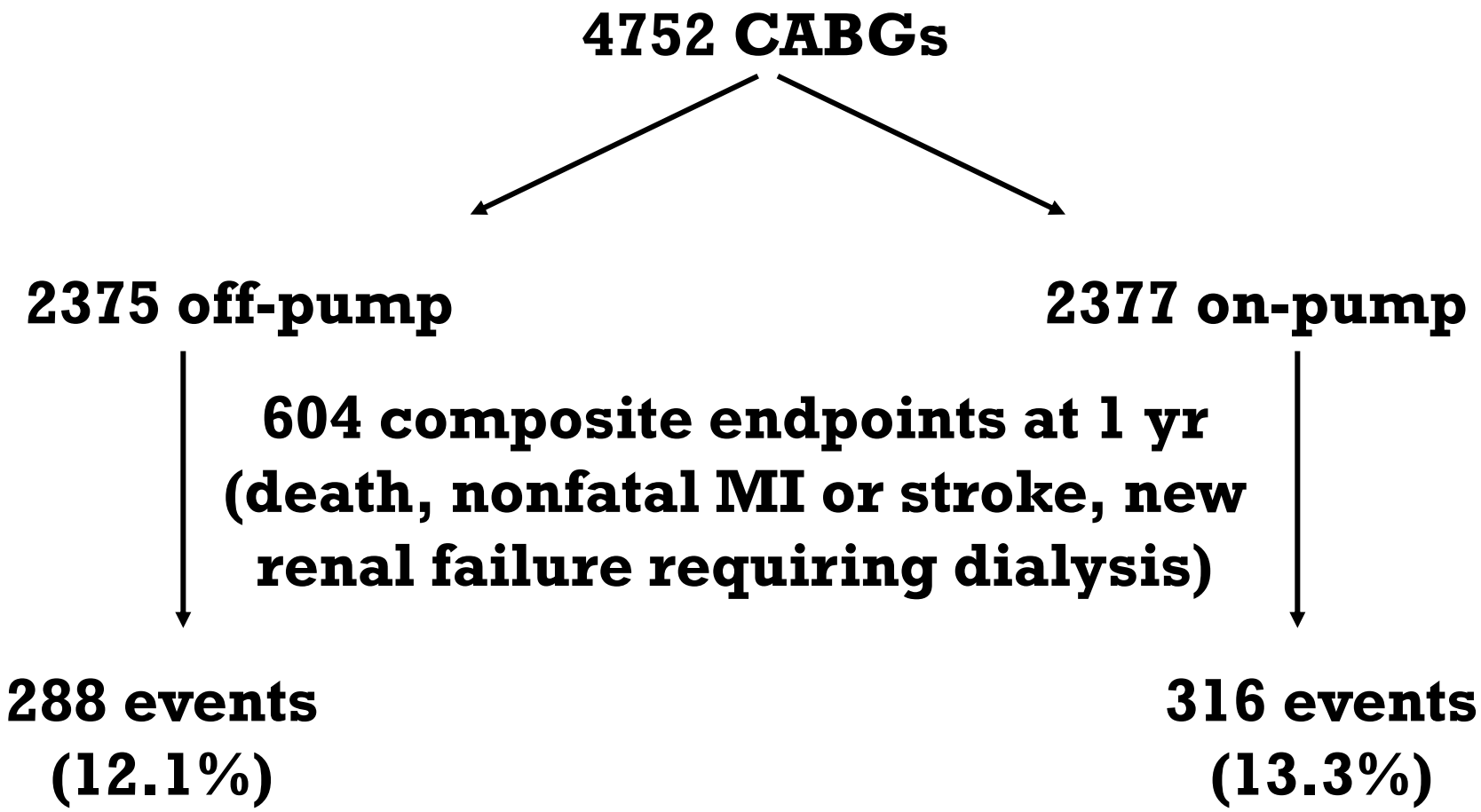
Goals of Session

Framework for assessing valid statistical association: evaluating the alternative explanations of chance, bias and confounding.

Framework for assessing causation: judgment using positive criteria.

Validity vs. generalizability.

How Do We Proceed? – CORONARY trial



HR = 0.91 (0.77-1.07); p = 0.24

CONCLUSION: There appears to be a beneficial association in these data between being off- vs on-pump and composite 1-year clinical endpoint. But can we say that it is having surgery off- pump itself that is causing the decrease in endpoint?

1st QUESTION: Is the observed reduction valid (i.e., is it a true estimate of the association between the exposure and the outcome)? Could it have been due to any alternative explanations?

2nd QUESTION: **If valid, is the observed association one of cause and effect?**

3rd QUESTION: **If valid, to whom is the finding generalizable?**

1st Question: Is the Association Valid

To determine if an association observed in a particular study is valid, need to rule out alternative explanations for the findings. We need to keep asking the question: "But what about? . . ."

Specifically, we need to consider the role of three alternative explanations:

- **Chance**
- **Bias**
- **Confounding**

Chance

Chance is always an explanation for our data, because we are trying to draw a conclusion about the outcomes of all people who had CABG surgery based on a sample.

Overriding principle: size of the sample on which we are basing conclusions will play a major role in the likelihood of chance being an explanation for our findings.

Bigger the sample, the more reliable the inference; smaller the sample, the greater the possibility of being misled.

Evaluation of the Role of Chance Involves 3 Steps

1. **Estimation of magnitude of effect or association (ex. relative, absolute).**

2. **Hypothesis testing: association due to chance? Is chance a reasonable alternative explanation?**

   p-value: probability that the observed association or one more extreme is due to chance alone, given that there is truly no association between the exposure and disease (i.e., H_0 is true).

3. **Estimation of the precision of the effect measure, i.e., calculation of the confidence interval (CI), or the range of values within which the true RR lies with a specified degree of confidence.**

Points to Remember

Subgroup analyses (effect modifiers, including compliers)

- **Hypothesis testing vs. hypothesis formulating?**
- **Hypothesis specified *a priori* (i.e., in the analysis protocol) vs *a posteriori* (i.e., after seeing the data, fishing expedition).**
- **Remember meaning of p=0.05: do 100 comparisons, 5 will be statistically significant by chance alone.**
- **Interpretation should be very different in these two circumstances.**

Points to Remember

- **The p-value/CI only evaluates the role of chance - it says absolutely nothing about the other alternative explanations of bias and confounding, or about causality.**
- **To state a conclusion regarding presence of causality based on a p-value <0.05 is totally incorrect.**
- **Moreover even if statistically significant, says nothing about its clinical or biologic importance.**

Bias

Any source of systematic error in the determination of the association between the exposure and disease.

May occur from the way participants are brought in to the study (selection bias) or the way information is obtained once they are in the study (observation bias).

The key word with respect to bias is the word "different".

Observation Bias

May result when there is a different level of accuracy or completeness of ascertainment of information between the study groups.

Recall bias: Differential recall of events.

Interviewer bias: Differential probing for or interpretation of information.

LTFU: Differential degree of follow-up.

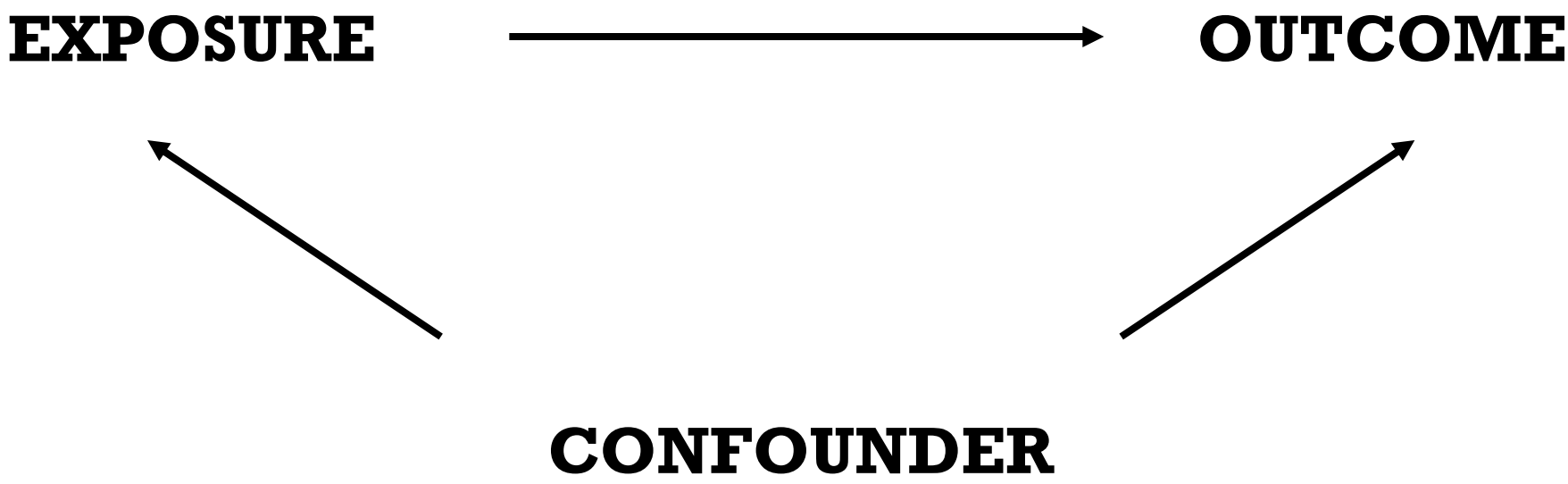
Example from CORONARY: bias in decision to do repeat revascularizations?

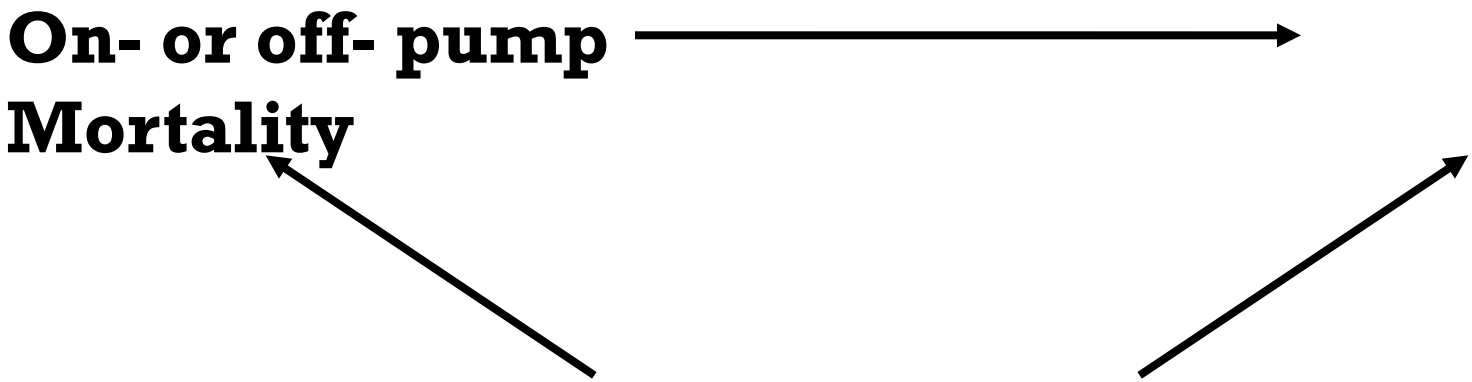
Confounding

A mixture of effects between the association under study and a third variable.

This third factor (the confounder) must be BOTH associated with the exposure under study and, independently of the exposure, be a cause or correlate of the cause of the outcome.

The confounder may be responsible in part or totally for the association seen in the data.


EXPOSURE
OUTCOME
CONFOUNDER


On- or off- pump
Mortality
Severity/location of heart disease
Obesity
COPD

Methods for Controlling Confounding

In an observational study, can control for known confounders, as long as you have collected information on them in the design phase of the study:

- **Control in the design: Restriction or matching.**
- **Control in the analysis: Stratification or multivariate analysis.**

Methods for Controlling Confounding

In a trial, randomization can control all confounders – known and unknown, measured and unmeasured or unmeasurable – as long as the sample size is large enough.

Unique strength of randomization if conducting a trial.

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?