Types of Clinical Trials in Cardiology

Rationale for Trial Design: Size, Power, and Subgroup Analysis

Columbia University Medical Center
The Cardiovascular Research Foundation

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Basic Clinical Trial Designs

The importance of "Power" in Statistics

- Power Calculations are *critical* when designing studies
  - A RCT is not intrinsically better than an observational study if not adequately powered… in fact, it can be more misleading!
- Power is defined as the ability to be able to statistically detect a difference *when one is truly present*

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Statistical Power

- **Power is typically set at 80% (or higher)**
  - ***Thus, we accept a 1 in 5 possibility ("fall of the cards") that even if there is an actual difference between 2 stents, we will not be able to find a difference!!!***
  - ***1-power equals the "False Negative" rate***
- **When there is a lot riding on a trial, how much risk can you assume???**
  - **A 10% increase in power (to 90%) will increase sample size!!!**

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The Importance of Power Calculations

- If I flip a coin twice and it comes up heads once and tails once, does it definitively mean that the coin is fair (or has a 50/50 chance of heads)?

- On the other hand, if I flip a coin twice and it comes up heads twice, does that mean that it will never come up tails (or that it will come up heads twice as often)?

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The Importance of Power Calculations

- Underpowered studies:
  - When they are negative:
    - Can make two therapies seem similar when in fact differences might exist
  - Confidence intervals can help clarify the picture and determine how certain one can be with the results

Hypothetical Underpowered Trial

- DES A vs. DES B with 500 patients randomized (250 per group)
- 30 day rate of stent thrombosis:
  - 4 events (1.6%) for DES A
  - 4 events (1.6%) for DES B
- Does this mean there are truly no differences between DES A and DES B?

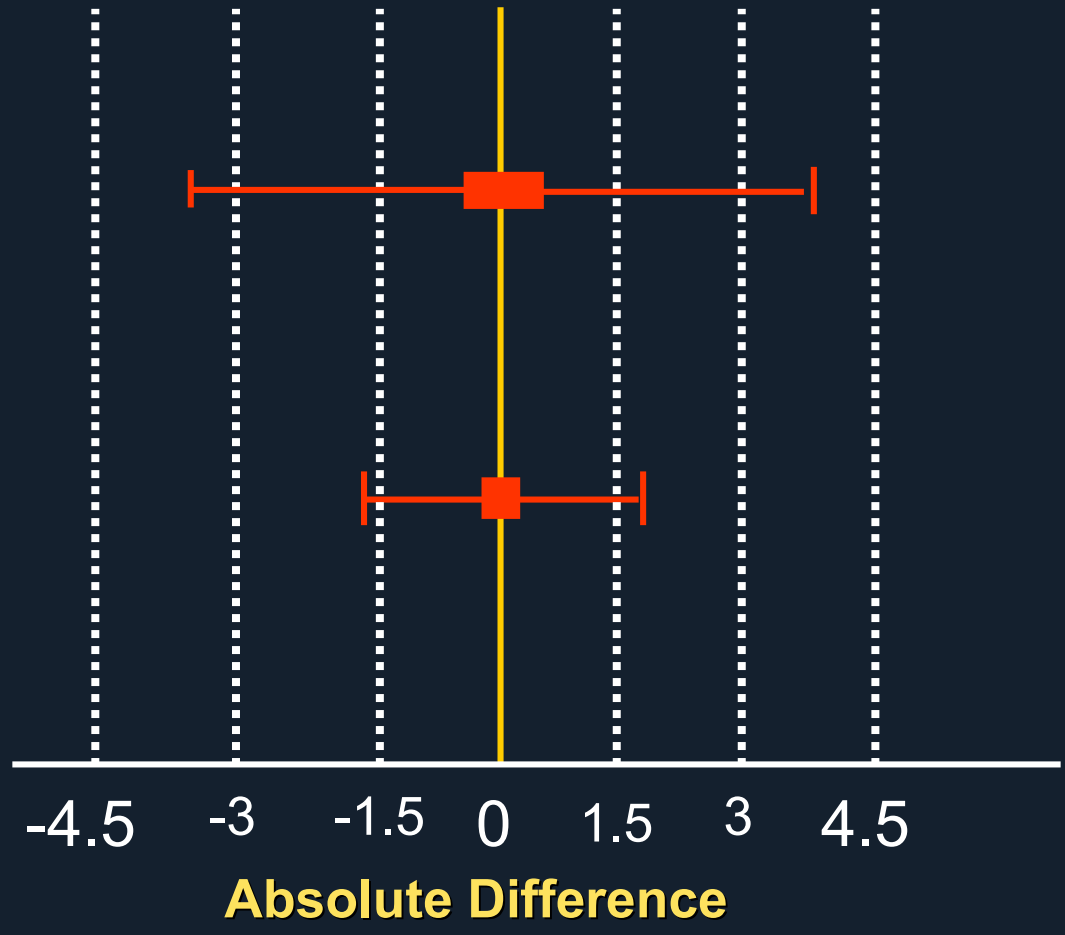
Confidence Intervals of Difference in ST rates between DES A and DES B

In this small trial:

Though there is no difference, we cannot exclude a truly larger difference!

In a larger trial (with 10X as many patients and the same event rates):

There might still be a difference, but we feel more certain of the rates!



Confidence intervals don't lie!

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The Importance of "Power" in Statistics

- Underpowered studies:
  - When they are "positive":
    - May only get published if results are statistically significant
    - Typically exaggerate treatment effects
    - Even when differences are "statistically significant", the absolute and relative differences are usually overstated

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Look at Number of Events Too

- Percentages alone can be very misleading – especially when sample size / events are low
- What if the rate of restenosis is 5% with DES A vs. 10% with DES B? This seems like a big difference, but might not be if there were not many overall patients in the study!

Baseline Rate	Total N	Number of Events	95% Confidence Interval
5%	20	1	[0.1%,24.9%]
5%	100	5	[1.6%,11.2%]
5%	1000	50	[3.7%,6.5%]

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Beware of "Relative Risk"

- For every relative risk increase (or reduction) the baseline risk will determine the absolute risk increase / the number needed to harm

Baseline Rate	Excess Rate (Relative Risk of 2)	Absolute Risk Increase	Number Needed to Harm
0.5%	1%	0.5%	200

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Relative vs. Absolute Risk

- Even if the relative risk were twice as great, it is important to consider not only relative risk, but *absolute risk* as well
  - If you sell one share of a $1 stock and it then doubles, are you as upset as if you sold one share of Berkshire Hathaway Series A at $134,100 and *it* then doubled?

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The Importance of Power Calculations

- An extreme example:
- Late stent thrombosis: 0 events with BMS vs. 5 events with DES (p=0.02)
  - The calculated relative risk is *infinite* – is this biologically plausible?
  - Do we think that the rate of late stent thrombosis is truly 0% with BMS?

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Alpha and the Magical <0.05 Threshold

- Researchers are trained to have an endorphin surge when they see the text "p<0.05"!!!
- But this is somewhat arbitrary… this just means that we accept that there is a 5% or less chance that the results observed (for example showing a difference between two stents) could be due to chance alone
  - Alpha is the "False positive" rate

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One-sided vs. Two-sided tests

- Statistical convention usually dictates that when we do a trial, we ask up front the question: "Is Stent A *different than* Stent B" rather than "Is Stent A *better than* Stent B"
  - This is a "two-sided" test (admits we are testing the possibility that A could be significantly worse as well)
  - We typically accept a 2.5% false positive error on either side; thus, the total error rate double this value (or $p<0.05$)
- But for non-inferiority tests, we are really testing if A is no worse than B, which *assumes directionality!*
  - This therefore utilizes a "one-sided" test (so we need a more strict threshold of $p<0.025$)

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Sample Size Calculations 101

- What do I need?
  - Baseline assumptions:
    - Event rate in treatment group
    - Event rate in control group
  - Other parameters
    - Balanced or Unbalanced Randomization (1:1 or other)
    - Superiority or Non-Inferiority Hypothesis
    - Power (usually 80% or greater)
    - Alpha (almost always 0.05 for two-sided, 0.025 one-sided)
  - A computer program to crunch the numbers

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Audience Poll

- As overall event rates go down, overall sample size goes…. **UP**
- As the difference between groups increases, sample size goes…. **DOWN**
- As randomization goes from balanced to unbalanced, overall sample size goes…. **UP**
- As power goes up, sample size goes.. **UP**
- As alpha goes down, sample size goes…. **UP**

Surrogate Endpoints in DES Studies

- Why use surrogate endpoints?
  - To reduce sample size and yet be adequately powered
  - To avoid minimize randomizing patients to a therapy which might not provide benefit or possibly cause harm
  - To test new technologies and be able to anticipate their outcomes

Statistical Criteria for Evaluating a Surrogate

1. Strong consistent evidence of treatment differences in each trial
2. Strong relationship with clinical outcome
3. Treatment difference in clinical outcome statistically explained by the surrogate *within* each trial
   [Prentice criterion]
4. Magnitude of treatment difference in clinical outcome clearly linked to magnitude of treatment difference in surrogate *across* trials
   [Hughes criterion]

Additional Key Considerations

- Access to patient level data from multiple well conducted trials is required
- Independent verification by FDA is necessary for FDA to accept results
- Demonstration of acceptable surrogacy for effectiveness does not necessarily imply the same for safety and vice versa

Additional Topics

- Subgroup Analyses
- Landmark Analyses
- Meta-Analysis

Subgroup Analyses

- Patients are not homogeneous and thus, response to treatment may well vary
  - Legitimate to explore in subgroup analyses
- BUT… trials are usually not large enough and lack power to detect subgroup effects
- Many possible subgroups
  - Watch for data dredging / false positives (1 in 20)
- *Do not rely on subgroup P-values; use interaction tests instead*

BARI Trial 10 Year Follow-up

	PTCA	CABG	P-value
All patients (N=1289)	29.0%	26.5%	0.18
Non-diabetics (N=1476)	22.7%	23.0%	Interaction test: p = 0.12
Diabetics (N=353)	54.5%	42.2%	

- Was the trial powered to detect differences within the diabetic subgroup – NO (68% power with this effect size!)
- *Interaction Test Definition:*
  - *Does the overall trial result (which was powered) vary by the diabetic status of the patients?*

NO!!!!

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The BARI Investigators
J Am Coll Cardiol 2007; 49(15):1600-6

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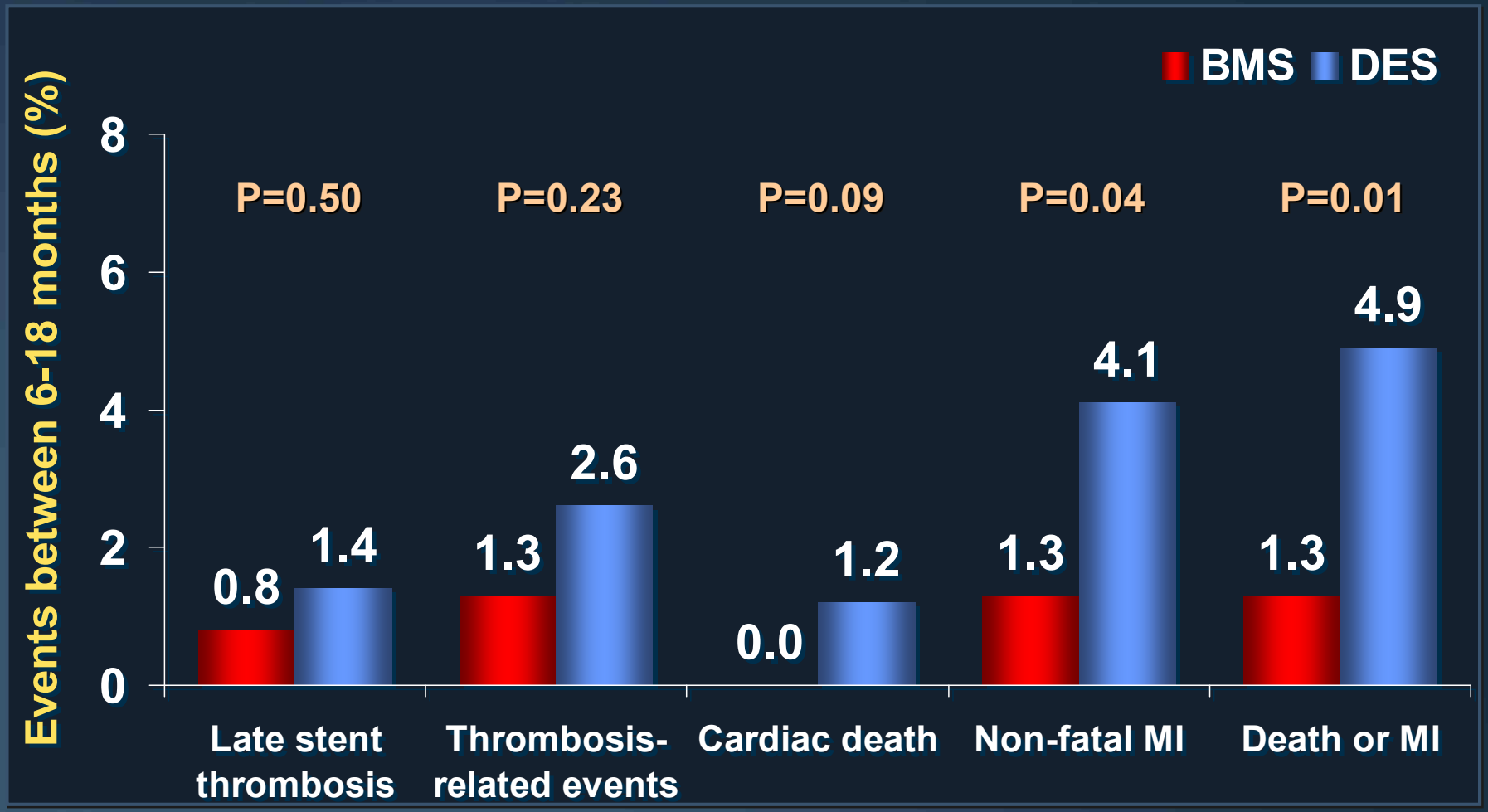
Landmark Analyses

- Despite the moniker, they are not (necessarily) "seminal" works
- Most studies assess patients from day of enrollment and assess all outcomes
  - "The landmark" refers to a timepoint from which data is analyzed
  - Earlier events are excluded in these analyses
    - Patients with earlier events are typically not included *unless data on repeated events is gathered/analyzed*
- **Landmark analysis-based information is useful, but selection bias can be a MAJOR issue, as groups are no longer truly "randomized"**

BASKET LATE Trial: 6-18 Mo MACE

N=743 (pts with early events excluded)



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Pfisterer M. ACC 2006

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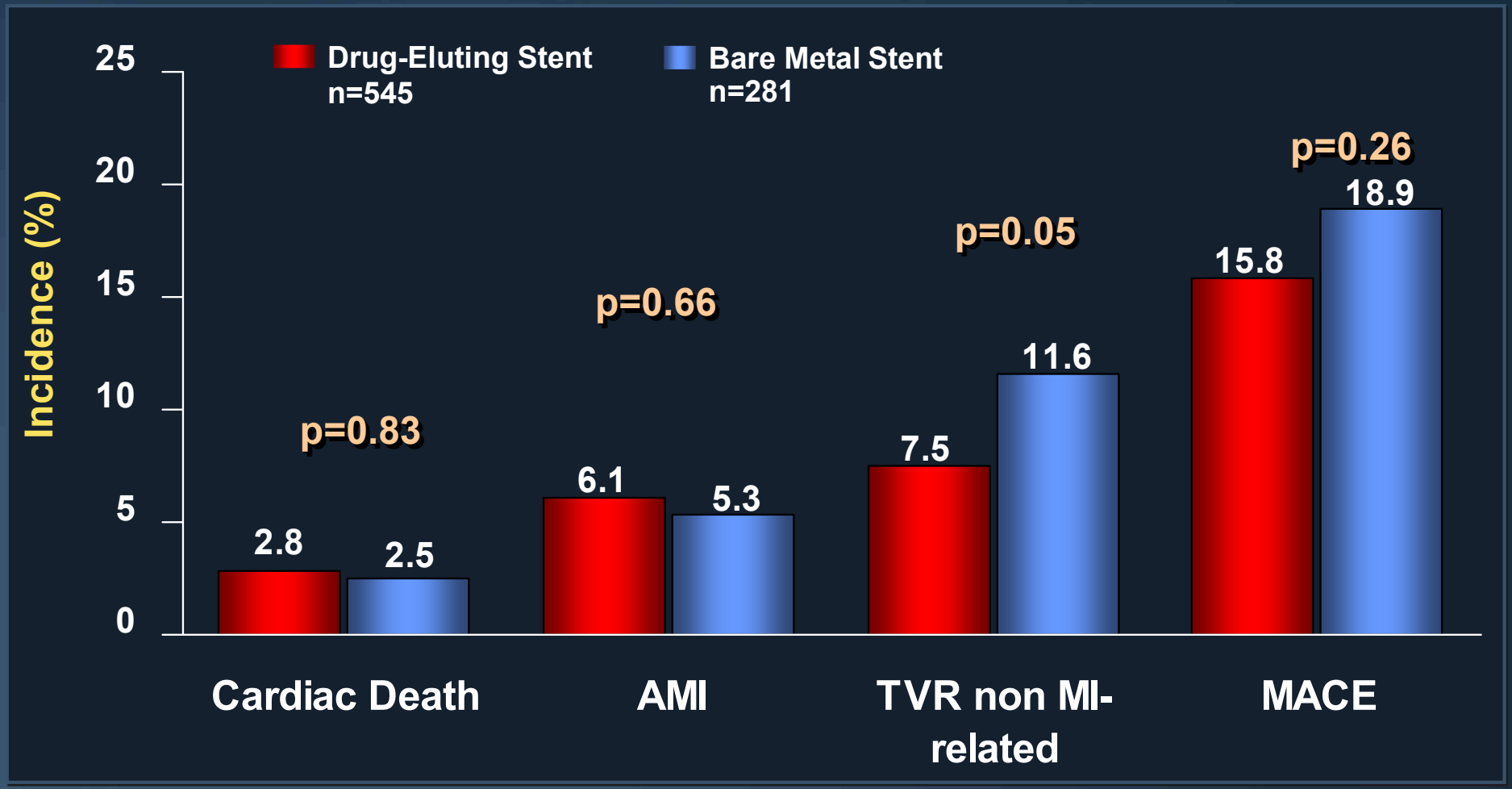
BASKET-LATE: DES vs. BMS

18 Month Clinical Outcomes



Kaiser C. World Congress of Cardiology 2006. Barcelona, Spain.

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Meta-Analysis

- A patient asks you: “Doc, what is better, DES or BMS?”
- You either:
  - Don’t know of any data (worst and less common scenario)
  - Know only the last study you read or the study that the last rep told you about (more common scenario)
  - Know all the data inside and out and can put them in a patient-specific context (less common unless your initials are GWS)
- Meta-Analysis aims to synthesize data *quantitatively*
  - But meta-analysis is only as strong as the studies that are included, and still requires a context to be applicable

The Need for Meta-analysis

- Any one study is too small and not generalizable
- Informal literature reviews too subjective

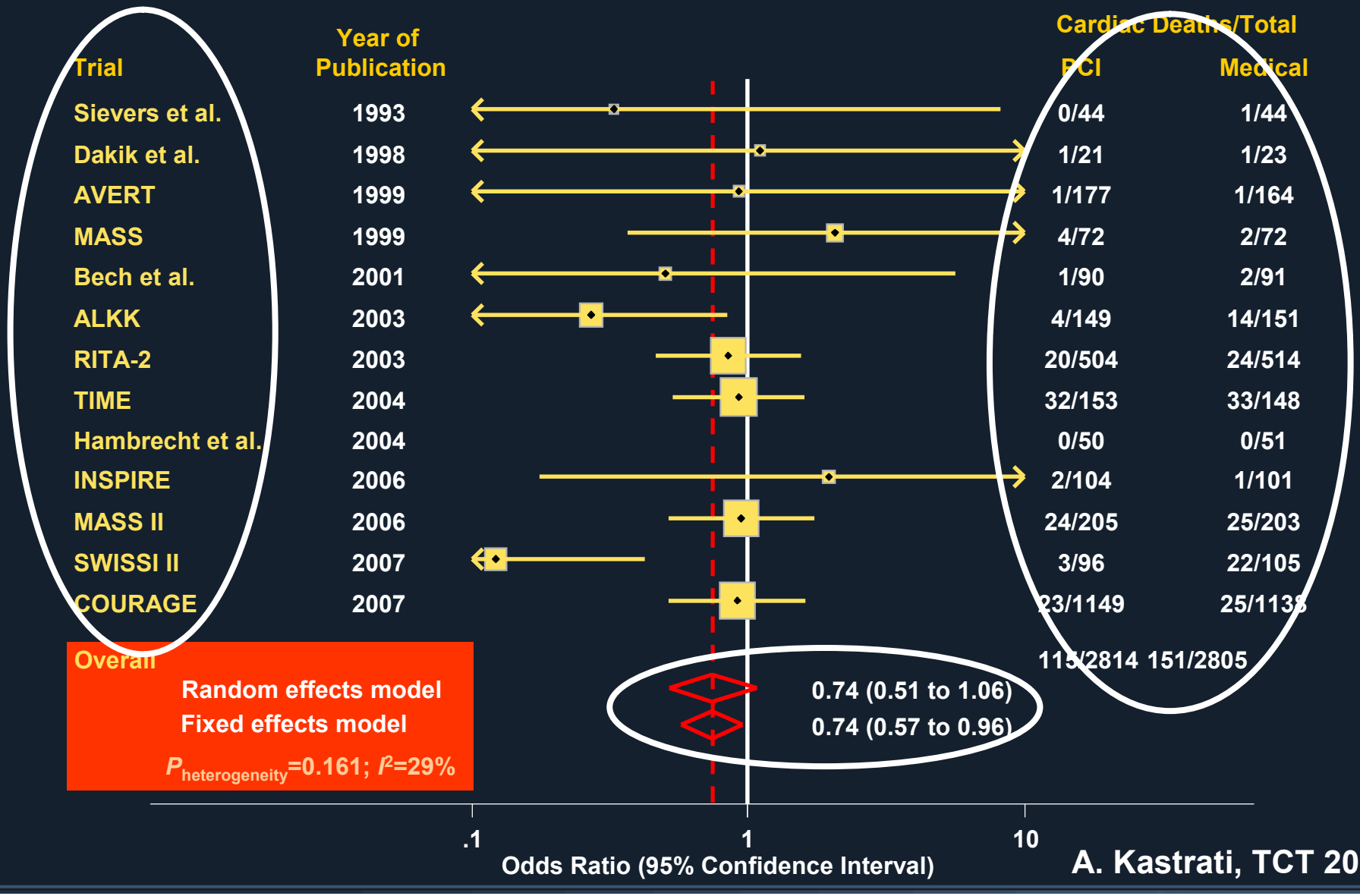
- Combining information from all the trials:
  1. Consistent objective data display
  2. Test of an overall (summary) hypothesis
  3. Estimate an average treatment effect
  4. Investigate if trials are consistent

A Sound Basis for Meta-analysis:

- Similarity of
  - treatments
  - patients
  - endpoints
- All studies included
- Unbiased and comparable study designs in included trials
- Clearly documented inclusion / exclusion criteria and methods
- Sensitivity Analyses

Meta-Analysis: How to Assess

PCI vs. Medical Treatment: Cardiac Death



A. Kastrati, TCT 2007

Conclusions

- Statistics are very powerful tools, but like any tool, they can be misused
- Incomplete understanding and inappropriate uses of statistics can lead to faulty conclusions and mass hysteria (DES thrombosis)
- Always put the data in a clinical perspective
  - The combination of great clinical skills with a knowledge of statistical methodology (and limitations) is a formidable one