# Composite Endpoints In Clinical Trials

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#### What is a Composite Endpoint?

- Endpoint that combines several outcomes
  - Sub-components
- Components are typically directionally related (e.g. death/MI)
  - But may not be "equal" in severity and definitions can vary across trials
- May be related to the final outcome (death) but mechanisms can be different
  - Death/MI/bleeding
  - Death/MI/TVR

## **Composite Endpoints**

#### We need them

- Individual outcomes lack statistical power
- But this can be abused
- We sometimes dislike them
  - Components vary in their clinical importance
  - Treatment effect varies across components
- May actually lose power by using a composite endpoint!!!



#### **Composite Outcomes in Published CV Trials**

- 304 trials in 14 journals in 2000-2006
- 73% had composite as primary endpoint, median 3 components

death	98%
myocardial infarction	92%
reintervention	54%
stroke 32°	/o
angina	10%
hospitalization	12%
cardiac failure	9%



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#### Composite Endpoints: Take Care RITA 3 Trial





Fox K et al. Lancet 2002; 360(9335): 743-51

## **TYPHOON trial**

#### DES vs. BMS in primary PCI

#### primary endpoint: cardiac death, MI, TVR by 1 year

	sirolimus	control	
	(N=355)	(N=377 <b>)</b>	
primary	26	51	P=.004
cardiac death	7	5	
myocardial infarction	4	5	
TVR	20	48	



### 2 Primary Stent Endpoints (at 12 Months)

#### 1) Ischemia-driven TLR\*

#### and

2) Composite Safety MACE = All cause death, reinfarction, stent thrombosis (ARC definite or probable)\*\*, or stroke

#### Major Secondary Endpoint (at 13 Months)

#### **Binary angiographic restenosis**

\* Related to randomized stent lesions (whether study or non study stents were implanted); \*\* In randomized stent lesions with  $\geq 1$ stent implanted (whether study or non study stents)

### Primary Efficacy Endpoint: Ischemic TLR





### Primary Safety Endpoint: Safety MACE\*





\* Safety MACE = death, reinfarction, stroke, or stent thrombosis

Primary efficacy: target lesion revascularization at 1 year

Composite safety: death, reinfarction, stroke, stent thrombosis

	TAXUS stent	bare-metal stent	
TLR	(N=2257) 4.5%	(N=749) 7.5%	P=.002
Composite safety	8.1%	8.0%	P=.92

Separate re-intervention from major clinical concerns

Non-inferiority re safety, components "equally flat"



## SYNTAX: PCI vs. CABG

"SYNTAX fails to show non-inferiority for DES"

1800 patients with left main/3 vessel disease

**Primary Endpoint of MACCE:** 

Composite of death, stroke, MI repeat revascularisation



#### **MACCE to 12 Months**



#### Repeat Revascularization to 12 Months



## All-Cause Death/CVA/MI to 12 Months





#### All-Cause Death to 12 Months





**ITT** population

#### CVA to 12 Months



#### **Myocardial Infarction to 12 Months**







**ITT** population

## **SYNTAX Summary**

- Composite MACCE (death/MI/stroke/revasc) driven by greater repeat revascularization alone
  - Death/MI/Stroke rates virtually identical
- Composite death/MI/stroke had offsetting components
  - Higher MI with PCI
  - Higher stroke with CABG
- What about other differences not captured in the composite?



#### **PARTNER Endpoints**

- PRIMARY: All-cause mortality over the duration of the study
  - Superiority test (two-sided), 85% power to detect a difference,  $\alpha$  = 0.05, sample size = 350 total patients

- CO-PRIMARY: Hierarchical composite of all-cause mortality and repeat hospitalization
  - Non-parametric method described by Finkelstein and Schoenfeld (multiple pair-wise comparisons)
  - > 95% power to detect a difference,  $\alpha$  = 0.05

### Mortality or Repeat Hosp



### **Mortality or Repeat Hosp**



#### Finklestein & Schoenfeld Analysis (hierarchical multiple pair-wise comparison)

- Compare, at random, every TAVI patient with every Standard Rx patient; 179 x 179 (32,041) patient pairs, which did better?
- #1, compare "tim
  - 72% chance the second sec
  - If so, 63% cha
    37% chance the
- #2, if necessary,

17% chance

FS Method Produces a P-value < 0.0001

ent died first and

hospitalization"

at hosp first

 If so, 75% chance that Standard Rx patient had repeat hosp first and 25% chance that TAVI patient had repeat hosp first

#### **PARTNER: Win Ratio Analysis**

Compare every TAVI pt with Standard pt: Total no. of pairs: 179 x 179 = 32041

Death w TAVI 1st8498LOSEDeath w standard 1st14466WINHosp survivor w TAVI 1st1345LOSEHosp survivor w standard 1st3979WINNone of the above3753TIE

Win Ratio = Pairs with TAVI win / Total Number of pairs Win ratio for composite: 1.87 (95% CI 1.35-2.54)

### Weighting Components of Composites

- Endpoint Weights
  - Can discount less important outcomes (e.g. a TLR is worth some fraction of a non-fatal NQWMI)
- But from whose perspective?
- Outside of QOL / Cost-Effectiveness analyses, there is poor guidance on how to weigh endpoints
- Issues of interpretability



### Summary: Composite Endpoints

- Advantages
  - May provide gain in statistical power
  - Simple summary of several outcomes
- Disadvantages
  - Can be clinically difficult to interpret
  - May be a mixed bag of "hard" and "softer" outcomes
  - Combined outcomes of varying importance
    - Often no clear way to "weigh" these outcomes





- Composite primary endpoints are of value
  - When no single component dominates
  - Statistical power may be increased
  - Provides a global summary of treatment effect
- Composite primary endpoints have problems
  - What components to include?
  - Components vary in clinical importance
  - Treatment effect varies across components
  - Results often misinterpreted

