Utilities and Pitfalls of Composite and Surrogate Endpoints in Clinical Trials

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Common CV Clinical Endpoints

- Death (Cardiac, Non-Cardiac)
- Myocardial Infarction (Q-Wave, NQWMI)
- Stent Thrombosis (subcategories)
- Target Lesion Revascularization
- Target Vessel Revascularization

Surrogate Endpoints

- **What is a surrogate endpoint?**
  - An outcome measure which may occur sooner or with greater frequency than the "true" outcome of interest
  - Predictive of the "true" clinical endpoint
  - In the causal pathway

Treatment → Surrogate → Clinical Endpoint

Surrogate Endpoints in DES Studies

- Surrogates in DES Studies
  - Usually continuous variables that are objectively quantifiable and reproducible
- IVUS: Neointimal Volume
- Angiographic:
  - Late Lumen Loss
  - Percent Diameter Stenosis

Surrogate Endpoints

- Why use surrogate endpoints?
  - Reduce sample size with adequate power
    - fewer patients + shorter follow-up = reduced costs
  - Avoid/minimize randomizing patients to a therapy which might not provide benefit or possibly cause harm
  - Test new technologies and be able to anticipate their outcomes

Surrogate Endpoints

- How do I know if a surrogate is good enough to use in my clinical trial?

Statistical Criteria for Evaluating a Surrogate

- Access to patient level data from multiple well conducted trials is required
- Analysis of 11 trials evaluating DES v. BMS
  - TAXUS-IV, TAXUS-V, TAXUS-VI, SIRIUS, E-SIRIUS, C-SIRIUS, RAVEL, DELIVER, REALITY, ENDEAVOR II, ENDEAVOR III
- In-Segment and In-Stent Late Loss (LL) and %DS were evaluated

Statistical Criteria for Evaluating a Surrogate

1. Consistent evidence of treatment differences within each trial

Pocock, et al., JACC 2008; 51 p 23-32

1. Evidence of treatment difference

- *Z*-Scores for Treatment Difference

	TAX IV	TAX V	TAX VI	SIR-IUS	E-SIR-IUS	C-SIR-IUS	RA-VEL	DE-LIV-ER	RE-AL-ITY	END II	END III
In-Stent											
LL	11.6	10.5	10.6	18.7	14.5	8.2	13.7	3	7.4	9.2	8.3
%DS	12.5	10	10.5	18.5	14	8.1	11.9	2.7	3.3	8.5	6.5
In-Segment											
LL	8.9	7.3	7.2	13.1	11.1	5.8	9.8	2.3	4.5	7.7	4.4
%DS	9.4	6.2	8.2	13.3	11	6.8	7.2	2.3	2.5	7.3	3.4
TLR	4.7	4	3.6	7.1	6.1	3.1	3.8	1.3	1.1	4	1.1

Statistical Criteria for Evaluating a Surrogate

1. Consistent evidence of treatment differences within each trial
2. Strong relationship with clinical outcome

Pocock, et al., JACC 2008; 51 p 23-32

2. Relationship to clinical outcome

- c-statistics summarizing the strength of association to TLR in each trial

	In-Stent		In-Segment			In-Stent		In-Segment	
Trial	LL	%DS	LL	%DS	Trial	LL	%DS	LL	%DS
TAXUS-IV	0.9	0.94	0.92	0.97	RAVEL	0.98	0.93	0.91	0.95
TAXUS-V	0.88	0.9	0.91	0.95	DELIVER	0.85	0.86	0.86	0.91
TAXUS-VI	0.86	0.87	0.89	0.95	REALITY	0.9	0.93	0.93	0.98
SIRIUS	0.88	0.9	0.92	0.95	END. II	0.88	0.91	0.88	0.95
E-SIRIUS	0.94	0.95	0.92	0.95	END. III	0.77	0.8	0.93	0.95
C-SIRIUS	0.86	0.86	0.93	0.94	Averaged	0.88	0.9	0.91	0.95

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Pocock, et al., JACC 2008; 51 p 23-32

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Statistical Criteria for Evaluating a Surrogate

1. Consistent evidence of treatment differences within each trial
2. Strong relationship with clinical outcome
3. Treatment difference in clinical outcome statistically explained by the surrogate *within* each trial [Prentice criterion]

Pocock, et al., JACC 2008; 51 p 23-32

3. Treatment Differences explained within trial [Prentice criterion]

- Percent treatment effect explained* (largest 5 trials shown)

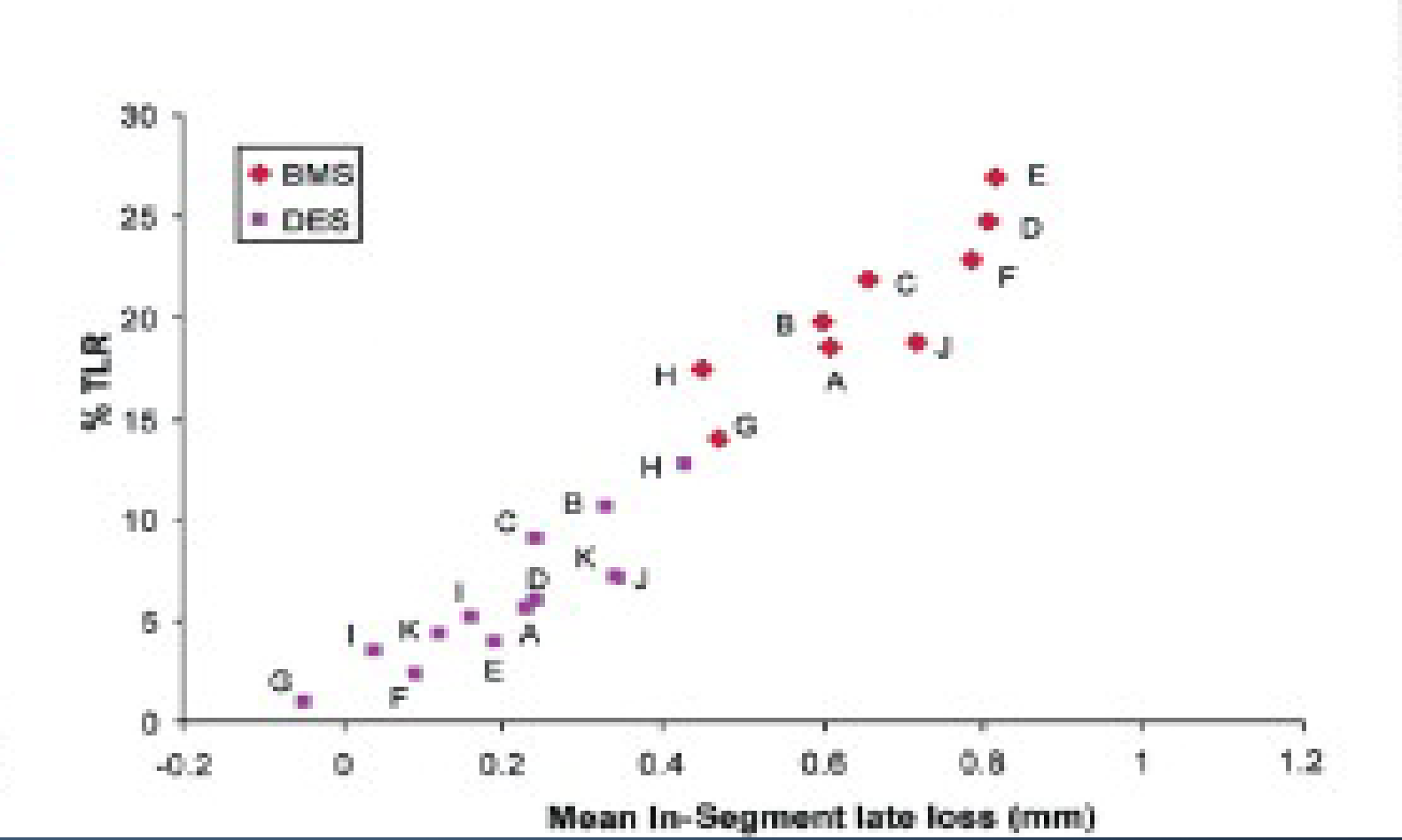
	In-Stent		In-Segment	
Trial	**LL**	**%DS**	**LL**	**%DS**
TAXUS-IV	98	138	83	83
TAXUS-V	101	94	82	47
TAXUS-VI	115	124	75	114
SIRIUS	132	142	91	103
ENDEAVOR II	100	119	82	107

* from logistic model for log odds of TLR after potential surrogate (e.g., LL) is added as predictor variable.

Statistical Criteria for Evaluating a Surrogate

1. Consistent evidence of treatment differences within 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]

4. Relating size of treatment effect across trials [Hughes criterion]



Pocock, et al., JACC 2008; 51 p 23-32

Example: XIENCE V

- SPIRIT III trial
- Primary endpoint: in-segment late loss at 8 months

	Xience V	Taxus	
N	669	332	
Mean Late Loss	0.14mm	0.26mm	P=0.003
Target Lesion Revasc.	3.4%	5.6%	P=0.12
1 year MACE	6.0%	10.3%	P=0.02

- Larger long term trials (and registries) underway to assess patient safety re death, MI, stent thrombosis

Stone, et al. JAMA 2008; 299 p 1903-1913

Surrogates

- Reduced trial size → more efficient progress
- LL and % DS both look good as surrogates for TLR in DES
- Use can speed up the regulatory process …

  IF the surrogate is acceptable to the regulatory agency

Surrogate Endpoints – Some Pitfalls

- May not predict clinical events in “real world”
- Surrogates for efficacy may not (and likely do not) predict safety
- Can lead to premature approval of potentially unsafe treatment
- Missing data issues: e.g. incomplete follow-up in angiographic endpoints may bias results

Composite Endpoints

- **What is a Composite Endpoint?**
  - Common in Cardiovascular Trials
  - Usually a group of clinical outcomes considered together to form a single endpoint
  - Generally weighted equally
  - Experiencing any of the individual outcomes → experiencing the composite

Composite Endpoints: Examples

- Examples of Composite Endpoints used in Cardiovascular Trials
  - Cardiac death/MI
  - Device-oriented (TLF): cardiac death/MI/TLR
  - TVF: cardiac death/MI/TVR
  - MACE: a mixed bag (and varies from study to study!)

Composite Endpoints

- Why use Composite Endpoints?
  - Gain in statistical power
  - Simple summary of several outcomes
  - Captures broader range of treatment experience
  - Multiple outcomes tested simultaneously without alpha “hit” for multiplicity
  - Avoids (some) issues of competing risks

Composite Endpoints

- Considerations
  - All components should be affected equally by treatment otherwise composite may be diluted
  - All components should be clinically relevant
  - All components should be defined as secondary and reported separately

Composite Endpoints

- In a review of 14 journals between 1 Jan 2000 and 1 Jan 2007
  - Of all cardiovascular trials (1231), 37% used composite endpoints
  - 98% of these included Mortality as a component
  - Typically 3 to 4 outcomes were included (based on the IQR)

Lim, et al. Ann Intern Med. 2008;149:612-617

Example: SYNTAX

"SYNTAX trial fails to show non-inferiority for DES" - Cardiovascular News, Sept 2008

- 1800 patients with left main/3 vessel disease comparing CABG vs. TAXUS
- MACCE = death/stroke/MI/Revascularizations
- 1-Year results were complex
- QOL results presented at ACC '09

Example: SYNTAX (1-year Results)

	CABG	TAXUS	
N Randomized	897	903	
MACCE (primary)	105 (12.4%)	159 (17.8%)	P=.002
Death	30 (3.5%)	39 (4.4%)	
Stroke	19 (2.2%)	5 (0.6%)	P=.003
MI	28 (3.3%)	43 (4.8%)	
Death/MI/Stroke	65 (7.7%)	68 (7.6%)	P=.98
Revascularization	50 (5.9%)	120 (13.5%)	P<.0001
PCI	40 (4.7%)	102 (11.4%)	
CABG	11 (1.3%)	25 (2.8%)	

Serruys, et al. N Engl J Med 2009; 360:961-972

Example: HORIZONS (30 day Results)

- **Evaluating efficacy and safety in composite endpoint**

	Heparin +IIb/IIIa	Bivalirudin alone	
N	1802	1800	
Major Bleed	8.3%	4.9%	P<0.001
MACE*	5.5%	5.4%	
Net Adverse Clinical Events	12.1%	9.2%	P=0.005
Death	3.1%	2.1%	P=0.047

* MACE = Death/MI/Stroke/TLR

Composite Endpoints: Some Pitfalls

- Survival analysis may count less severe outcomes over more severe (e.g. TLR vs. Mortality)

  Example: MACE = Death/MI/Stroke/TLR

  Patient A has TLR at 5 months but survives and feels well through end of trial (5 years)

  → Time to MACE = 5 months

  Patient B has no TLR, MI or Stroke, but dies at 9 months → Time to MACE = 9 months

Q: Is patient A really worse off than patient B?

Composite Endpoints: Some Pitfalls

- Can be misleading
  - MACE = Death/MI/Stroke/TLR
  - Why not

    MACE = TLR/MI/Death/Stroke?
  - Most important component listed first, but often has the lowest event rate (i.e. is the LEAST represented in the composite)

Composite Endpoints: Some Pitfalls

- All components tend to be treated equally
  - Can be weighted (but what are correct weights?)
- Some might presume that benefits relate to ALL components
- May dilute real treatment differences by including elements unaffected by treatment (impact on non-inferiority?)
- Can be difficult to interpret

CONCLUSIONS

- Both surrogates and composite endpoints are extremely useful for reducing sample sizes (increasing power)
- Both can get “better” treatments to patients faster
- But …
- Proceed with CAUTION!