Medical Device Surrogate Endpoints

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Medical Device Lifecycle (Class III)
Pathophysiology-Treatment Variables

- Pre-Market Pilot & Pivotal Evaluation
- Ideals, Design, Bench & Mfg Validation
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- Post-Market Studies & Surveillance
- Next Gen Improvements & Obsolescence

- Device Design
- Bench Measurement
- Pilot Pivotal Outcomes
- Device performance
- Real World Outcomes
- Rare AE Long-term Effects

- Narrow Patient Factors
- Clinical, Device Stress
- Broad Patient, Operator Factors
- Unknown Disease, Device Factors

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New Restenosis Concepts

Acute Gain
Late Loss
Net Gain

Kuntz, ...Baim
The importance of acute luminal diameter in determining restenosis
After coronary atherectomy or stenting. Circulation 1992;1827-1835
Curvilinear Late Loss BAR Relationship

(L. Mauri, J Orav, R Kuntz *Circulation* 2005)

**Mean Late Loss vs. Predicted Restenosis Rate**

- **Binary Angiographic Restenosis (%):** No Threshold

**No Threshold**

- **Mean Late Loss (mm):** 0.0, 0.2, 0.4, 0.6, 0.8, 1.0
- **Mean Late Loss (mm):** 0.0, 5.0, 10.0, 15.0, 20.0, 25.0, 30.0, 35.0, 40.0
In-Stent Late Loss and TLR

Current DES and BMS Results

![Graph showing in-stent late loss and TLR for various stents, including Cypher, Taxus, Endeavor, and BMS.](image)
Late Loss is Monotonic (derived from 22 RCTS)

The higher the Late loss, the wider the standard deviation

(L Mauri, R Kuntz, Circulation 2004)
In-Stent Late Loss Correlation with the Data
(L Mauri, R Kuntz, Circulation 2004)
Late Loss as a Surrogate Endpoint

Across individual patients in-stent late loss correlates with clinical restenosis:

\[ c \text{ statistic} = 0.915, \text{ SIRIUS} \]
\[ c \text{ statistic} = 0.918, \text{ TAXUS 4} \]

Not surprising, since LL and TLR are ascertained at the same time, and TLR is adjudicated based on the follow-up %DS (slight variation introduced by effect of RVD on %DS).

For true surrogacy, treatment-induced changes in the surrogate should reflect treatment-induced changes in the standard clinical endpoint.

Requires analysis across randomized trials of different treatments.
TLR Differences are related to LL Differences

(Regression Weighted by TLR Precision)

y = 0.1532x - 0.0116

$R^2 = 0.8298$

p<0.0005

32 Comparisons

17 BMS vs DES

3 DES vs DES

12 BMS vs BMS
Power: In-Stent Late Loss vs. BAR

Late Loss can be determined with certainty in as few as 50-100 subjects

TLR can be determined with certainty in >500 subjects

Assumptions:
- 35% treatment effect
- 200 subjects per arm
- $\alpha = 0.05$

Late Loss as a Surrogate for Coronary Stents

- LL is a good surrogate for BAR and TLR
- Value is in minor modifications and new design testing
- LL does not measure stent thrombosis, non-TLR revascularization, MI or death
- Few device surrogates are as simple or as well studied, still has limited applications
Medical Device Lifecycle (Class III)
Pathophysiology-Treatment Controls

Good method, describes practice, HA, representative sample, propensity control

Registry: Product Performance/Outcomes

Device Design → Bench Measurement → Pilot Pivotal Outcomes → Device performance → Real World Outcomes → Rare AE Long-term Effects

Spec δ
Narrow Patient Factors
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Medical Devices and Surrogates

- Validated surrogate endpoints for medical devices are rare, and implantable device durability and long-term effects are always problematic to study in the pre-approval space.
- The concept of surrogates could be extended to several device design elements such as computational bioengineering modeling.
- Product performance is another interesting endpoint (surrogate?), especially for prevention devices.
- The post approval space needs improved rigor with better observational statistical methods, and may be a valuable resource to balance pre- and post-approval burdens to keep pace with technology.