Late Loss Is The Single Best Parameter For Estimating Stent-Based Restenosis Resistance

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Late Loss and DES

• Brief history of Late Loss
• Restenosis Endpoints
• Late Loss and Clinical Restenosis
• Late Loss Headroom
• Real Data on Late Loss and Clinical Restenosis
• Conclusion
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
**Human Proportional Injury Model**

Late loss (neointimal surrogate) is proportional to acute gain (injury surrogate)

**Loss Index:** Ratio of Loss-to-Gain

Late Loss

• Intuitive measure of coronary obstruction potential
  – Measured at the follow-up MLD
  – Best measurement of the principal physiological flow resistor
    • Flow is reduced by the $4^{th}$ order of reduction in the radius of the MLD
    • Not described by volume estimators
• It is the target of drug therapy
  – That is, we aim to reduce maximum late loss!
FIM Sirolimus: Angiographic Results

Is This Going to be a Good Stent?

What is the In-stent Late Loss?

Late Loss = 0.11 mm

In-lesion MLD
RAVEL: 6-Month QCA (n=238)
Late Loss

-0.1 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9

p<0.001 0.8 0.47

-0.01 -0.05

Sirolimus n=120
Control n=118

mm
<table>
<thead>
<tr>
<th>Events</th>
<th>Sirolimus % n=533</th>
<th>Control % n=525</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.9 (5)</td>
<td>0.6 (3)</td>
<td>0.726</td>
</tr>
<tr>
<td>MI (all)</td>
<td>2.8 (15)</td>
<td>3.2 (17)</td>
<td>0.723</td>
</tr>
<tr>
<td>Q-wave</td>
<td>0.8 (4)</td>
<td>0.4 (2)</td>
<td>0.687</td>
</tr>
<tr>
<td>Non Q-wave</td>
<td>2.1 (11)</td>
<td>2.9 (15)</td>
<td>0.433</td>
</tr>
<tr>
<td>TLR (clinically driven)</td>
<td>4.1 (22)</td>
<td>16.6 (87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TVR (non-TL)</td>
<td>3.2 (17)</td>
<td>4.8 (25)</td>
<td>0.210</td>
</tr>
<tr>
<td>MACE</td>
<td>7.1 (38)</td>
<td>18.9 (99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TVF (1st Endpoint)</td>
<td>8.6 (46)</td>
<td>21.0 (110)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Pivotal DES Trial Comparisons

TLR to 9 Months

<table>
<thead>
<tr>
<th>Device</th>
<th>Control</th>
<th>DES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endeavor</td>
<td>12.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Taxus</td>
<td>11.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Sirius</td>
<td>16.6</td>
<td>4.1</td>
</tr>
</tbody>
</table>

IS LL = 0.62
IS LL = 0.39
IS LL = 0.17
Late Loss and DES

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Restenosis Endpoints

• **Target Lesion Revascularization**
  – Best endpoint in a randomized Trial
  – Needs large sample size for stable Estimation
  – High level of influence by case-mix confounders renders it almost meaningless in comparison across trials.

• **Late Loss (In-stent version only)**
  – Stable and efficient estimate for any stent-type
  – Less influenced by case-mix confounders, and provides a “signature” value for any particular stent.
Restenosis Endpoints
The Noise Factor

• **Target Lesion Revascularization**
  - Affected by
    • Lesion length
    • Diabetes prevalence
    • Reference vessel size
    • Threshold for revascularization (50-70% renarrowing)
  - Estimates are wide ranging for BMS and DES

• **In-Stent Late Loss**
  - Affected by
    • Diabetes
    • Lesion length
  - Relatively more stable across trials
Risk and Restenosis

Some Contemporary Clinical Restenosis Rates

Recent BMS and DES Trials

Mauri L, Kuntz R submitted for publication
Recent BMS and DES Trials

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In-Stent Late Loss and TLR
Current DES and BMS Results

TLR (%) vs Mean Late Loss (mm)

- Cypher
- Taxus
- Endeavor
- BMS
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Late Loss Correlates with BAR in DES

Existing DES Trials
Points are all DES studies with Binary and LL reported (obviously time points etc vary between 6 and 12 months)
Late Loss is Monotonic (derived from 22 RCTS)

The higher the Late loss, the wider the standard deviation

This means that it is always better to have a lower late loss
In-Stent Late Loss Does Correlate with the Data!

Especially in the DES Late Loss Range

(L Mauri, R Kuntz, Circulation in press)
There is no Late Loss Threshold

- Biological effects are continuous
- In our 15 year BMS and DES experience, mean in-stent late loss ranges from 0.1 to 1.2
  - *The Lower The Better*
- Late Loss is Monotonic
  - There is never an advantage of having a higher late loss
- The real question is: What is the magnitude of the late loss effect on restenosis

*To see the real relationship of late loss and predicted BAR, we need some mathematical treatment*
Curvilinear Late Loss BAR Relationship
(L. Mauri, J Orav, R Kutz Circulation in press)

Mean Late Loss vs. Predicted Restenosis Rate

Binary Angiographic Restenosis (%) vs. Mean Late Loss (mm)
Follow-up Percent Diameter Stenosis

%DS is Correlated with In-Stent Late Loss

(22 Trials L Mauri, R Kuntz)
Risk and Restenosis

Late Loss and Clinical Restenosis

• Factors that put Late Loss into perspective
  – Threshold of late loss that leads to clinical revascularization
    • Thresholds are different across practices and countries
    • Lower for small vessels
  – Late Loss risk factors: diabetes and long lesions
    • Shift the late Loss curves to the right

Mauri L, Kuntz R submitted for publication
Frequency of Late Loss

In-stent Late Loss (mm)

Density (%)

Mean LL 0.2 mm
Mean LL 0.4 mm

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Frequency of Late Loss

Mean LL
- 0.6mm
- 1.0mm

In-stent Late Loss (mm)

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Density of Late Loss

Mauri L, Kuntz R submitted for publication
Density of Late Loss

mean late loss = 0.2mm

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Late Loss and TLR

Effect of mean reference vessel diameter

Threshold for TLR, if RVD = 2.8 mm
Threshold for TLR, if RVD = 3.5 mm

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Late Loss and TLR

Effect of small vessel stenting

Threshold for TLR
If RVD=2.2 mm

Threshold for TLR
If RVD=2.8 mm

Mauri L, Kuntz R submitted for publication
Density of Late Loss

Shift in Late loss Distributions

- Diabetics
- Long lesions

Small vessels

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Late Loss and TLR

Effect of High Risk Characteristics

Shift in Late loss Distributions

- Diabetics
- Long lesions
- Small vessels

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Late Loss Headroom

• Late Loss headroom is the space of extra late loss available for high risk restenosis case-mix cohorts
  – Headroom highest for low in-stent late loss stent systems
Late Loss Headroom

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Late Loss Headroom

Case-Mix 1

Headroom available, but not needed for this case-mix

Late Loss threshold for TLR

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Late Loss Headroom

Case-Mix 2

Late Loss threshold for TLR

Headroom allows for freedom for clinical restenosis

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Late Loss Headroom

• Late Loss headroom is the space of extra late loss available for high risk restenosis case-mix cohorts
  – Headroom highest for low in-stent late loss stent systems

• For low Late Loss stent systems, the headroom concept reduces the chance of high TLR over the wide range of case-mix risk
  – *Evident in real data from clinical trials*
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Late Loss and TLR Inter-Relationship in Clinical Trials

• For low risk cohort studies and randomized trials, TLR will be low over a wide range of In-Stent Late Loss values
  – *In such case-mixes, DES stents should be valued on secondary characteristics of safety, deliverability, coverage, etc.*

• For moderate to high risk cohort studies and randomized trials, high in-stent late loss values should predict higher TLR rates
Cypher vs. Taxus II

Angiographic Rest.

- Cypher: 14
- Taxus: 22

P = 0.19

Clinical Rest. (TVR)

- Cypher: 8
- Taxus: 19

P = 0.02
SIRTAX: Late Luminal Loss

Follow-up Angiography in 527 Patients With 714 Lesions
SIRTAX: Binary Restenosis

Follow-up Angiography in 527 Patients With 714 Lesions

<table>
<thead>
<tr>
<th></th>
<th>CYPHER (n=345)</th>
<th>TAXUS (n=369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-Stent % of Patients</td>
<td>3.2</td>
<td>7.6</td>
</tr>
<tr>
<td>P</td>
<td>0.013</td>
<td>0.020</td>
</tr>
<tr>
<td>In-Segment % of Patients</td>
<td>6.7</td>
<td>11.9</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.020</td>
</tr>
</tbody>
</table>
SIRTAX: 9 Month Outcomes

<table>
<thead>
<tr>
<th></th>
<th>CYPHER (n=503)</th>
<th>TAXUS (n=509)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, or TLR Primary Endpoint</td>
<td>6.2%</td>
<td>10.8%</td>
</tr>
<tr>
<td>TLR</td>
<td>4.8%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

P = 0.009
P = 0.025
Late Lumen Loss

**Late lumen loss (in-segment)**

\[ P = 0.002 \]

**Late lumen loss (in-stent)**

\[ P < 0.001 \]

Kastrati, A. ACC 05 LBCT Presentation
Restenosis

**Angiog. Restenosis**

- **CYPHER**: 6.9%
- **TAXUS**: 16.5%

**P=0.03**

**Clinical Restenosis (TLR)**

- **CYPHER**: 6.4%
- **TAXUS**: 12%

**P=0.13**

Kastrati, A. ACC 05 LBCT Presentation
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Late Loss and Restenosis

**TLR and Risk Concepts**

- Late Loss is a measure of the propensity for repeat revascularization.
- Late Loss “Head Room” is the extra space available for higher risk lesions to provide freedom from repeat revascularization.
  - *It’s always good to have low late loss.*
- Restenosis Risk is important to consider when interpreting the impact of late loss.
  - *Some trials have low risk patients, and BMSs do well.*
  - *Some trials have high risk patients, and low late loss is needed.*
Late Loss and Restenosis

**TLR and Risk Concepts**

- When given any parameter for a new DES, a low TLR may be reflective of low restenosis risk in the studied cohort, but late loss (in-stent) will give the best estimate of restenosis resistance over the wide range of restenosis risk.