Transverse View Area Loss (TVAL): An informative angiographic outcome in below-knee lesions

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Disclosure

Speaker name: Mahmood Razavi MD

I have the following potential conflicts of interest to report:

- Consulting: Abbott, BSC, MDT, Philips, Terumo

- Employment in industry

- Stockholder of a healthcare company

- Owner of a healthcare company

- Research support: BD, BSC, Mercator, Philips, NIH

- I do not have any potential conflict of interest
Overview

- Improvements in clinical outcome of CLI pts is multifactorial & dependent on multiple variables
- Progress in endovascular revascularization of BTK arteries is incremental
- Sensitive & measurable indicators of incremental therapeutic effects are required
- In long, diffuse lesions, outcomes measures such as LLL or binary “patency” are inadequate to assess treatment success
Measuring Therapy Effect in Long BTK Lesions

- Total lesion length: 22 cm
- Proximal: diffuse disease
- Distal: 10-cm total occlusion
- Good revascularization result
- Good 6-month outcome
- Slight narrowing at proximal end (in largest part of vessel) results in high LLL: is this a failure?
TVAL: A Proposed Tool for Assessment of Therapeutic Effect in Long Lesions

• Defining Transverse View Area Loss (TVAL)
  – TVAL is the side-view lumen area that is lost from post-revascularization to follow up

**TRANSVERSE (SIDE) VIEW:**

\[
\text{Post-Revasc Lumen Area} = \text{Area Remaining} + \text{Area Lost}
\]

\[
\text{TVAL} = \text{Area Lost} \text{ as a % of } \text{Post Revasc Lumen Area} \text{ (red/initial blue)}
\]

TVAL is a 2-dimensional approximation of neointimal volume.
Example of TVAL Measurement

PRE REVASC:  
POST REVASC:  
6-MO F/U:
Example of TVAL Measurement

- **PRE REVASC:**
  - 28% gain in opacified area (relative to post)

- **POST REVASC:**
  - 3% loss in opacified area (relative to post)

- **6-MO F/U:**

**Graph:**
- Acute Gain, 28%
- Opacified Transverse Lumen Area (Pre), 72%
- Opacified Transverse Lumen Area (F/U), 97%
- TVAL, 3%

**Example of acute (procedural) transverse lumen area gain and 6-month area loss**
Correlation of TVAL to Traditional Endpoints

• LIMBO-ATX
  – 100 subjects randomized 1:1 to treatment (adventitial dexamethasone) or control (no adventitial delivery) after atherectomy with or without PTA
  – Below-the-knee lesions up to 25 cm in length
  – Rutherford 4-5
• TANGO-Low Dose Phase
  – 30 subjects randomized 2:1 to treatment (adventitial temsirolimus) or control (adventitial saline) after atherectomy and/or PTA
  – Below-the-knee lesions up to 25 cm in length
  – Rutherford 3-5
• 6-month follow-up angiographic endpoint in both studies
• Analysis of 6-month TVAL vs. 12-month outcomes pooled all subjects from LIMBO-ATX and TANGO-Low Dose Phase
Endpoints of TANGO & LIMBO-ATX

- **Primary Patency**
  - Freedom from CD-TLR
  - Freedom from DUS occlusion
  - Freedom from angiographic evidence of >95% narrowing
  - Freedom from major amputation due to ischemia

- **Sustained Clinical Benefit**
  - Sustained improvement of at least one Rutherford Category vs. pre-procedure baseline
  - Freedom from CD-TLR

- **TVAL is taken at 6 months or prior to 6-months if during a CD-TLR**
Correlation of TVAL to Clinical Endpoints: Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Subjects</th>
<th>Characteristic</th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>130</td>
<td>Rutherford 3</td>
<td>17 (13%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.6 ± 9.5</td>
<td>Rutherford 4</td>
<td>53 (41%)</td>
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<tr>
<td>Male</td>
<td>92 (71%)</td>
<td>Rutherford 5</td>
<td>55 (42%)</td>
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<tr>
<td>Black or African Descent</td>
<td>27 (21%)</td>
<td>Rutherford 6</td>
<td>5 (4%)</td>
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<tr>
<td>Caucasian</td>
<td>99 (77%)</td>
<td>ABI</td>
<td>0.84 ± 0.36</td>
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<tr>
<td>Obesity (BMI ≥ 30 kg/m²)</td>
<td>49 (38%)</td>
<td>Lesion Length (cm)</td>
<td>11.0 ± 7.1</td>
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<tr>
<td>CAD</td>
<td>77 (59%)</td>
<td>TASCII A</td>
<td>36 (28%)</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>87 (67%)</td>
<td>TASCII B</td>
<td>22 (17%)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>113 (87%)</td>
<td>TASCII C</td>
<td>29 (23%)</td>
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<tr>
<td>Hypertension</td>
<td>119 (92%)</td>
<td>TASCII D</td>
<td>41 (32%)</td>
</tr>
<tr>
<td>Tobacco Use (Current)</td>
<td>24 (18%)</td>
<td>Severe Calcification</td>
<td>14 (11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total Occlusion at Baseline</td>
<td>46 (35%)</td>
</tr>
</tbody>
</table>
Correlation of TVAL to Clinical Endpoints

6-month TVAL vs. 12-month Primary Patency in TANGO and LIMBO-ATX

- P<1e-11
- 55% not patent @12 mo
- 14% patent @ 12 mo

6-month TVAL vs. 12-month Sustained Clinical Benefit in TANGO and LIMBO-ATX

- P<0.01
- 48% no clinical benefit @ 12 mo
- 30% clinical benefit @ 12 mo
Correlation of 6-mo TVAL to 12-mo Patency

• ROC Curve for Predicting 12-mo Patency Given 6-mo %LLL (change in %DS from post to f/u)
  
  - With an area under ROC curve of 0.9-1.0, change in % diameter stenosis (post-revasc to 6-mo f/u) is an excellent predictor of 12-month patency.
  - This result seems obvious, since high %DS indicates loss of patency.

• ROC Curve for Predicting 12-mo Patency Given 6-mo TVAL
  
  - With area under ROC curve of 0.8-0.9, 6-month TVAL is a good predictor of 12-month patency.
  - This result indicates that the average neointimal volume at 6 months predicts long term loss of patency.
Correlation of 6-mo TVAL to 12-mo Clinical Endpoints

**ROC Curve for Predicting 12-mo Clinical Benefit Using 6-mo TVAL and Lesion Length**

- With an area under ROC curve of 0.7-0.8, 6-month TVAL is a fair predictor of 12-month clinical benefit.
- This result indicates the linkage between neointimal hyperplasia and clinical outcomes.

**Probability of 12-mo Clinical Benefit versus 6-mo TVAL**

- Measurable changes in 6-month TVAL correlate to meaningful changes in 12-month clinical benefit.
Conclusions

• There are statistically significant correlations between the quantitative vascular angiographic endpoint of 6-month TVAL and the 12-month endpoints of patency and clinical benefit
• Six-month TVAL is a fair predictor of 12-month clinical benefit
• Six-month TVAL is a good predictor of 12-month patency
• 6-month TVAL is a powerful tool to assess the biological response to therapy and can be key in determining programs to advance forward to pivotal studies
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