Importance of Trial Design and Other Factors in Evaluating the Differing Results with DEBs (or DCBs)

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  - Proteon
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  - www.vivapvd.com

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Conflict of Interest …and potential source of BIAS

International Co-PI for LEVANT 2
Major role in design of the trial…
…so I may be biased about this subject!!!
(Important to recognize such biases when delivering scientific information!)

“Every system is perfectly designed to get the results it gets.”
- Professor Paul Batalden, Dartmouth College

“Every TRIAL is perfectly designed to get the results it gets.”

Treatment Comparisons - Basic Scientific Principles

• Randomized, controlled, blinded comparisons represent highest level of evidence
• Injection of bias - known or inadvertent – at any point in conduct of a scientific trial can influence and confound results
• Unintended bias impacts results both in obvious ways, and in ways that are subtle or unrecognized

Levels of evidence produced according to trial design

“comparison of two different randomized trials” is not on this pyramid
Treatment Comparisons - Basic Scientific Principles

- Post-hoc comparisons of trial results must be undertaken with extreme caution and healthy skepticism
- Potential pitfalls
  - Different trial construct and parameters
  - Difference in blinding techniques or rigor
  - Different populations of patients
  - Different operators and expertise
  - Different instructions to investigators
  - Different timeframes for intervention/measurement

Other Factors which may affect results

- Choice of Investigators
  - Level of Experience
  - Judgement and bias
- Site Location (US/OUS)
- Treatment location
- Lesion characteristics
- Etc...

Many of the differences b/n trials are subtle and difficult to illuminate!

Two Recently Approved DCB’s in US

Levant 2 Randomized
  - Followed by Real World Global Registry

INPACT SFA I&II
  - Followed by Real World Global Registry

LEVANT 2 Study Flow

Test Arm
  - Dilatation with Lutonix Drug Coated Balloon
  - Randomized 2:1

Control Arm
  - Dilatation with Standard PTA

Treatment per standard practice
  - 30 day follow-up for safety

12 Month Follow-up
  - Successful Pre-Dilatation
  - OR >70% residual stenosis

IN.PACT SFA Trial

Combined two trials, different time-frames

IN.PACT SFA I
  - 150 subjects enrolled at 13 EU sites Sep 2010 - Apr 2011

IN.PACT SFA II
  - 181 subjects enrolled at 44 US sites Apr 2012 - Jan 2013

- Independent and blinded Duplex Ultrasound Core Lab [1]
- Angiographic Core Lab [2]
- Clinical Events Committee [3]
- Independent Data Safety Monitoring Board [3]
- External monitoring with 100% source data verification
- Subjects followed up to 5 years

1. VasCore DUS Core Laboratory, Boston, MA, US
2. SynvaCor Angiographic Core Laboratory, Springfield, IL, US
3. CEC and DSMB services provided by HCRI, Boston, MA, US
Levant 2 RESULTS
Primary Patency at 12 months
Kaplan-Meier “Time to Event Curve”

Levant 2 and IN.PACT SFA

- Similar trial design, but some differences…
- Similar class effect of DCB over PTA
- Both had “drop-off” after 12 months
- Better patency for Control patients in Levant 2… What is up with such high POBA patency?? Perhaps related to trial procedures, case selection, and technique?
- Lower TLR for IN.PACT….Explanations?

Levant 2: Extensive Blinding Steps Taken to Reduce Bias

Baseline Angiographic Characteristics (ITT) and Other Trial Parameters…differences
Could Lack of Blinding Result in More Reinterventions for PTA than DCB?

<table>
<thead>
<tr>
<th>Patients with Binary Restenosis by DUS who had TLR</th>
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<tbody>
<tr>
<td>LEVANT 2 (12 mo)</td>
</tr>
<tr>
<td># of Patients</td>
</tr>
<tr>
<td># of Binary Restenosis</td>
</tr>
<tr>
<td>% of Binary restenosis patients with a reintervention (95% CI)</td>
</tr>
<tr>
<td>% Difference (DCB vs PTA)</td>
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</tbody>
</table>

Results are reported in different studies with different protocols and different patient populations. Not intended for head to head comparisons.

Could Lack of Blinding Result in More Reinterventions for PTA than DCB?

Different deployment techniques?

Levant 2 investigators were encouraged not to overdilate or overstretch... but may have "under-delivered" drug as a result.

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Conclusion

- Important differences exist b/n current DCB trial designs
- Trial design can certainly influence outcome and confounds comparison b/n trials
- Consistency and rigor is important across trials to enable comparison
- Results between these two (and other DCB/s) are similar and both confirm a "class effect"
- Real World TLR is generally similar, based on post-approval studies
- Physician-scientists should be more involved in trial design!

Conclusion

- Must be cautious comparing trial results for DCB’s
- Way to determine differences will be ultimately be direct RCT between DCB’s. New DCB’s may be forced to compare to previously approved devices. Blinding will be important in all studies, to compare apples to apples.