Stent-grafts for Long-Segment SFA Disease: Better than the Alternatives…?

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SFA Treatment Overview: Longer Lesions
• Medical therapy – small population benefits
• Exercise – effective when supervised; not reimbursed
• PTA – limited effectiveness for lesions > 5 cm
• Surgery – invasive, higher initial morbidity
• BMS – more effective than PTA in moderate lesions
• Stent-grafts – shown to be beneficial in long lesions
• DES (Zilver PTX) – Just released in the US, registry results are impressive
• Previous DES (polymer-based, limus drug coatings) – no sustained difference from BMS
• Atherectomy and cyroplasty – little randomized data
• Paclitaxel-coated balloons – promising in simple lesions?
• Bioabsorbable Stents and BDES, in the distant future…

Disclosures:
• Research Support:
  – Cook, W.L. Gore, Bard,
• Honoraria:
  – Cordis, W.L. Gore Inc, Bard, Inc.
• Consultancies
  – Abbott Vascular, W.L. Gore, Control Medical Systems

BMS Have Been Proven in Moderate-Length Lesions Vs PTA
• 8 Nitinol stent trials have all had similar findings:
  – Claudicators make up the vast majority of patients treated
  – Moderate average lesion lengths of 6 to 11 cm
  – A significant patency benefit over PTA alone in 3 randomized trials
    • Approximate 60%-80% primary patency at 12 months
• But, ISR rates can be substantial
  – Over 50% at 2 yrs in some of these studies
    • More common with the treatment of longer lesions >10 cm
  – Therefore, in my mind: “Full Metal Jacket” of the FPA using BMS for lesions >15 cm is rarely indicated. Very little supporting data

**Zilver PTX DES Single-Arm Study**

- Prospective, non-randomized, Multinational study
  - One of the largest studies to date of endovascular treatment of SFA disease (787 patients, 900 lesions)
  - Average lesion length 10 cm
- Real-world patient population
  - Long lesions, in-stent restenosis, overlapping stents
- CEC and DSMB oversight with data monitoring
- Primary patency assessment
  - Duplex ultrasonography at 6 and 12 months
- Long-term clinical follow-up through 2 years
  - Bilateral ABI, Rutherford class, walking scores


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**Zilver PTX Effectiveness**

- Zilver PTX DES is an effective treatment for patients with complex disease:
  - 86.2% primary patency rate at 12 months
    - Diabetics: 86% patency through 12 months
    - >15 cm long lesions: 77% patency through 12 months
    - Tx of In-stent restenosis: 80% patency through 12 months
  - Freedom from TLR remains stable through 24 months
  - Sustained clinical benefit through 24 months
  - No comparative Data with stent-grafts, but clearly a useful technique in 10-20 cm lesions, maybe longer?


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**Stent-Grafts in the FPA: Primary Patency And Lesion Length (1401 Limbs, 21 Independent Studies)**

<table>
<thead>
<tr>
<th>First Author</th>
<th>Year</th>
<th>Journal/Conference</th>
<th># Limbs</th>
<th>Mean Lesion Length</th>
<th>Occlusions</th>
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**Non Heparin SG Literature Review**

- Over 1300 limbs have been reported in the FPA
  - Average lesion length: 16.5 cm
  - Substantially longer than other “endovascular technique trials”
  - In about 60%, total occlusions were treated as opposed to stenoses
  - Approximately 20% had ischemic limbs included
- Stent-graft primary patency:
  - 70% at 2 years
  - 62% at 4 years (More long-term data than other techniques)
- From a patency standpoint, stent-grafts are already a reasonable alternative for long FPA lesions
- Results appear improved with the “heparin bioactive surface”
**Vibrant Randomized Trial: BMS VS Stent-Grafts**

- Prospective multicenter trial of stent-grafts vs. Nitinol stents
  - SFA lesions >8 cm long, 151 patients randomized
  - 20 cm long, high complexity lesions (more realistic)
    - Dense calcifications, >55% occlusions
  - No difference in primary patency at one and three years
    - ≈55% primary patency at one year, poor in both groups at three yrs
  - No difference in clinical outcome at 3 years
    - 21% received stent-grafts for treatment of ISR in BMS
      - Cross-over complicated the comparison of clinical outcomes
  - RB Category, QOL, MAE, ALI were all the same statistically
  - Risk of ALI was actually lower with stent-grafts
    - Over 5% for BMS, 2.5% for stent-grafts at one year

  Ansel, et al Viva ’09, ’11

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**Heparin Stent-Graft (HSG) Endoprosthesis Description**

- Ultra-thin wall ePTFE tube
- Contoured proximal edge
- Unique, durable bonding film
- Heparin Bioactive Surface
- Polished nitinol support
- Lengths: 2.5, 5, 10, 15 cm
- Diameters: 5–8 mm

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**Failure Modes: SG Vs BMS**

- Edge stenosis is the main failure mode with Stent-grafts
  - Usually asymptomatic, but can lead to abrupt thrombosis
  - Need to detect through surveillance and revise when detected to avoid occlusions
- Diffuse ISR is the usual failure mode of long BMS,
  - Causes recurrent symptoms, much more difficult to treat

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**VIPER Trial**

- Heparin-bonded ePTFE stent-graft evaluation
- Prospective, single-arm multicenter trial, 11 centers, 119 pts
- Lesions >5 cm long with no length limit
- Primary endpoints: primary patency at 1 year, MAE 30 days
- Pt population, lesion characteristics identical to VIBRANT
  - Average lesion length 19 cm
  - 60% TASC II C and D lesions
  - 61% moderate to severe calcification
  - 13% were in patients CLI (Rutherford 4 or 5)
  - Often Excluded from BMS trials

  Saxon, et al., JVIR 2013;24:165-173
VIPER Core Lab Results

- Investigator measurement: mean diameter
  - Proximal to treated vessel = 5.5 ± 0.6 mm
  - Distal to the lesion was 5.3 ± 0.6 mm
- As assessed by the core laboratory:
  - Proximal to treated vessel = 4.5 ± 1.1 mm
  - Distal to the treated vessel = 4.7 ± 1.3 mm
- Investigators were dramatically over-estimating vessel size
VIPER: Effect of Device Sizing Proximally

Device over-sizing assessed by independent Core Lab

Possible Adverse Effects of Over-Sizing

- Vessel stretch at edge
  - Acute – rigorous PTA at device edge
  - Chronic – radial force of stent
- Turbulent flow at interface
- Poor wall apposition and/or graft infolding
- Lower flow velocity in graft
VIPER Trial: 1-Year Results

- 88% of pts were RB class 0 or 1
  - Mean improvement over baseline = 2.4
- ALI occurred in 2 pts (1.6%), no major amputations, AFS 96%
  - No 30 day mortality
  - 14 pts had revisions for surveillance detected stenoses
    - 50% were asymptomatic
  - Only 4 patients underwent a bypass due to HSG failure
- No adverse patency affect with DM, occlusions, fewer runoff vessels
  (1 vs 3), or history of smoking
- Patency was significantly worse in pts under 60
  - <60 yrs of age = 40% (n=27) vs those ≥60 yrs of age, 82% (n=92)
  - Younger pts appear more prone to edge stenosis and thrombosis
  - The same age affect has been seen with FPA bypass grafts

Population Based Study of Bypass Results

- Peri-operative Outcomes and AFS in lower ext bypass surgery in California hospitals, 1996-1999
  - If we look at FPA Bypass only from this study: Over 23,000 pts
  - Unclear how many were treated for CLI vs Claudication
  - 30 day Mortality 4.3%
  - At one year: limb salvage 90.7%, AFS 80.5%
- One can easily argue that SG appear to have lower morbidity and mortality with at least equal clinical success when compared to these population based surgical results

Feinglass et al, JVS 2009; 776-783
Dr Vartanian, et al, and I May Not Agree…

But… I worked with John Porter and Greg Moneta when I was at OHSU, and they taught me to be dogmatic and aggressive with my opinion. That is probably why most Vascular surgeons like me.

So, I mean no offense while I win this debate!

“Poor” UCSF Stent-Graft Results:
The Main Reason For Our Debate:

- “Risk Factors For Clinical Failure after SFA Stent-Grafts”
  - 87 limbs in 78 pts, retrospective review, single center
    - 45% were TASC II D lesions
    - 39% for CLI
    - 29% SG were used as a secondary intervention
    - 9% no patent runoff
  - Tough patient population
  - Primary patency: 57% by TLR
    - Relative poor patency results, similar to Vibrant
  - Despite the poor patency:
    - No in hospital mortality (30 day not reported)
    - No amputations at 1 year
    - Only 9% in-hospital morbidity (mostly minor issues)

UCSF Stent Graft Retrospective Results at One Year

- 28% MALE (thrombolysis, bypass or major amputation)
- The authors raised concerns about using HSG
  - High “failure rate”, need for lytics in pt pop of 55% claudicators
- But there were no amputations in a pt pop of 39% CLI
- Thrombolysis was used in 17%, bypass in 11% (10 pts)
  - 10.4% ALI rate (total of 9 limbs)
    - Substantially higher than other SG trials, VIPER
- But, 4 of these limbs were class 5 or 6 pre-procedure
- 5 were claudicators
  - 3 of these went on to bypass (similar to VIPER)
  - Bypass rate in claudicators was low, especially if primary bypass is the treatment being advocated

Objective Performance Criteria for CLI

<table>
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<tr>
<th>Outcome</th>
<th>Point (95% CI)</th>
<th>Efficacy OPC %</th>
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</thead>
<tbody>
<tr>
<td>MALE+POD</td>
<td>76.9% (74-78)</td>
<td>71%</td>
</tr>
<tr>
<td>AFS</td>
<td>76.5% (74-80)</td>
<td>71%</td>
</tr>
<tr>
<td>RAS</td>
<td>46.5% (42-51)</td>
<td>39%</td>
</tr>
<tr>
<td>RAO</td>
<td>61.3% (58-645)</td>
<td>55%</td>
</tr>
<tr>
<td>Limb Salvage</td>
<td>88.9% (87-91)</td>
<td>84%</td>
</tr>
<tr>
<td>Survival</td>
<td>85.7% (83-88)</td>
<td>80%</td>
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</table>

MALE+POD = major adverse limb event + post operative death
AFS = amputation free survival, RAS = any reintervention, amputation or stenosis
RAO = any reintervention or above ankle amputation

Major Adverse Coronary Event including death in the surgical “Standard of Care trials” was 6.2% at 30 days
Re-interpreting the UCSF Results

- Exceeded the OPC performance criteria in most ways that matter:
  - No in hospital mortality, likely low 30 day mortality
    - MACE, including death, in the surgical “Standard of Care trials” used to create the OPC data was 6.2% at 30 days
    - MACE is a standard way of looking at morbidity after vascular treatment, but it was left out of the OPC criteria, why?
  - No major amputations (OPC 84%), AFS 83% (OPC 71%)
  - Glass is half full, given that 39% of patients presented with CLI
- Moreover, I believe the low patency and high MALE rate in the UCSF data was very technique-dependent
  - I don’t think they new then what I Know now

Why Were the UCSF Results Relatively Poor?

- No Quantitative techniques were used to size the vessels
- Dilated to the device size, not the vessel size
  - Could have been “massively” over dilating the arteries
    - Poor results with the 5 mm devices, were they treating 3.5 mm vessels?
    - Likely caused a high incidence of edge stenosis, decreasing patency
- Poor patient follow-up and revision
  - Only 63% of patients had any duplex follow-up at all
  - In 8/10 pts treated with thrombolytics, Edge stenoses were detected
  - Many occlusions could have been avoided if adequate duplex surveillance and follow-up had occurred, decreasing MALE rate
- 9% had no patent tibial runoff
  - Excluded in other trials, affect not analyzed, could have led to occlusions

Poor 5 mm Device Patency
Is It Due to Pt Selection + lack of QVA?


VIPER: Primary Patency By Device Diameter

when multiple devices implanted, minimum device diameter used
Just Don’t Use the 5 mm Devices?
Primary Patency: VIPER vs VIBRANT

A 32% improvement in Primary Patency at the end of one year window
Vibrant had no 5 mm devices, no heparin surface, no contoured edge

VIASTAR: HSG VS BMS
- Multicenter, randomized study of 141 pts
- Lessons learned from VIPER were incorporated
- Heparin-bonded stent-grafts (HSG) Vs. Bare Metal Stent (BMS) for long FPA lesions
- 18 cm average Lesion Length (TASC B, C, D)
  - All lesions 10-35 cm in length
  - 74% chronic total occlusions
  - At least 1 vessel runoff (not done with no runoff)
- Rutherford-Becker 2-5
  - 6 excluded from each arm (lost to fu, refused)

Lammer, Presented VEITH Nov, 2012

VIASTAR

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<th>BMS</th>
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<td>Number of patients</td>
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<td>Mean lesion length</td>
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<td>C and D lesions</td>
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<td>50%</td>
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<tr>
<td>All AE</td>
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<tr>
<td>SAE</td>
<td>1 pt ALI, no amputations</td>
<td>1 pt ALI, no amputations</td>
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VIASTAR Results at One Year

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<tbody>
<tr>
<td>Primary Patency</td>
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<td>53% [P=.01]</td>
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<tr>
<td>&gt;20 cm primary patency</td>
<td>73%</td>
<td>33% [P&lt;.05]</td>
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<tr>
<td>&lt;20 cm primary patency</td>
<td>86%</td>
<td>63% [P&lt;.05]</td>
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<td>Secondary patency</td>
<td>90%</td>
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<td>Freedom from TLR</td>
<td>84%</td>
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<td>ABI</td>
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<td>TLR/Bypass</td>
<td>9 (7/2)</td>
<td>13 (12/1)</td>
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VBH, no difference in patency by TASC class
BMS patency very different by TASC class
No difference in the number of bypasses by treatment
VIASTAR One Year Results

• Walking impairment questionnaire showed markedly better walking distance in the VBH patient population

• TASC-adjusted Odds Ratio: Patients treated with BMS are 2.9x more likely to lose patency than those treated with HSG

Lammer, CIRSE 2012

Above Knee Bypass: Vein

UCSF Trial: Did They Use Best Practices?

1. Avoid excessive over-sizing, shoot for 5%
   - Could not have been done, no quantitative vessel sizing
2. Post-dilate to the native landing zone, not the device size, and do not PTA outside of the device
   - Clearly not done, they dilated to device size
3. Treat all of the disease, especially near the SFA origin
   - Doubt this was done due to concerns over collateral occlusion
4. Use duplex ultrasonography for follow-up and treat progressive disease to avoid occlusions
   - Clearly not done, and if it isn’t, other techniques may be preferred

Risk of ALI: Stent-Graft VS BMS

• US PMA, VIBRANT, VIASTAR randomized trials all showed no difference in safety between stent-grafts and PTA/Nitinol stents in moderate to long length lesions
  - Risk of ALI <3% in all for SG, <2% in VIPER/VIASTAR with HSG
  - Risk of ALI was Higher in Vibrant for BMS

• MAE rates are clearly higher with Surgery and Atherectomy
  - In the Definitive LE atherectomy trial, MAE = 7.6%, Garcia, VIVA 2012

• AE secondary to “Collateral occlusion” with SG is not a proven, evidence based reason to use other endovascular techniques over stent-grafts or a reason to leave disease uncovered

References:
Garcia, VIVA 2012
**Stent-graft 1-Year Results**

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<td>VIASTAR</td>
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- 2 patients with RB 5 and 6 pre treatment, failed both Viabahn and subsequent bypass and went on to amputation
- Amputation free survival was 86% at 28.5 months mean F/U

**What about HSG VS DES for long lesions?**

- No comparative data
- This is a question we need to answer with a new trial
- DES may have a major role to play and we must consider them as an alternative
- Personally, I will use PTX over a BMS in lesions >10 cm-20 cm, for restenosis, and more liberally than BMS in diabetics
- However, given the lack of comparative data in lesions >10 cm long, I will continue to use VBH for the majority of endovascular cases with lesions >15-20 cm in length
Cost-Effective Care =
Getting It Right the First Time

• What can we control?
  – Be more objective in our treatment algorithms to improve outcomes and cost effectiveness
  – QA (with some form of internal calibration) or IVUS is required for stent-grafts (callibrated wires, not a tape outside the pt)
  – Our “eye ball” is not accurate when trying to get optimal outcomes
  – Try to avoid treating patients with stent-grafts that don’t fit the IFU
  – Some patients are better treated with a bypass, a BMS, a DES or combination of therapies.

Health care needs to be individualized, randomized data doesn’t tell you how to do this…

When are Stent-Grafts the Preferred Treatment for Long FPA Lesions?

• Based on VIPER and Viastar, HSG are the preferred treatment right now in pts that often used to be bypass candidates. The ideal patient:
  – Long lesions >15 cm, preferably patients >60 yrs of age
  – Vessel landing zones >4-4.5 mm by quantitative means
  • Try for 5% device over-sizing, (<20%)
  • Cover all of the disease
  – Treat patients who will comply with a surveillance program
  – Expected 1-year primary patency: >80-85%
• Pharmacologic mediation of the healing response is still needed to further decrease the rate of Edge Stenosis
Conclusions

• Endovascular approaches have lower initial morbidity and mortality
• It is very unusual for a patient to need an amputation after a VBH occludes who didn't have CLI pre-treatment
• One yr Patency rates are at least equal to synthetic bypass and approach venous bypass when patients are carefully selected and carefully treated
• Randomized data shows significant benefit over BMS in long lesions
  – Other endovascular techniques have a major role to play
    • Especially DES now, and we hope DEBS in the future
  – Not all patients are a candidate for an endovascular approach
  – Venous bypass remains an excellent option, if conduit is available and the patients anatomy dictates
• One size does not fit all, but HSG are clearly appropriate if used with careful technique in the correct population. I rest my Case!