Drug Eluting Balloon for AVF Angioplasty: Does it work?

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Disclosure

I do not have any potential conflict of interest for this presentation
Kidney Dialysis Outcomes Quality Initiative (K-DOQI) Guidelines

- Stenosis within the dialysis circuit is the main cause of dysfunction / thrombosis of AVF / AVG
- PTA is the standard of care for the treatment of AVF / AVG stenosis
- 6 month primary patency ~ 50%
  - Repeated interventions required to maintain patency and function
  - 12 month secondary patency > 80%

Pre  POBA  Post
AVF / AVG Stenosis and Patency

• Neo intimal hyperplasia is the main pathologic basis for development of stenosis

• Numerous strategies to increase patency of AVF/AVGs have been explored
  – high pressure balloon angioplasty
  – cutting balloon angioplasty
  – bare metal stenting
  – cryoplasty
  – Stenting with covered stent / stent graft

• Only covered stents have been shown to increase patency in AVGs (Haskal et al, NEJM 2010)
Drug Eluting Balloon (DEB)

- Deposition of an anti proliferative drug onto the vessel wall without leaving a permanent scaffold
- Paclitaxel is the most common drug used in DEBs
  - highly lipophilic, is anti mitotic + anti proliferative
  - promotes tubulin polymerisation resulting in non-functioning microtubules which halts cell division and protein transport, hence inducing apoptosis
  - also inhibits smooth muscle migration into the intima
- DEBs have been shown to be effective in inhibiting neointimal hyperplasia for the treatment of coronary in-stent restenosis and in stenotic femoro-popliteal arterial disease

Scheller et al, NEJM 2006;335:2113-24
Tepe et al, Circulation 2015;3;131(5):495-502
PROSPECTIVE RANDOMISED TRIAL COMPARING DRUG ELUTING BALLOON ANGIOPLASTY VERSUS CONVENTIONAL PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY FOR THE TREATMENT OF DYSFUNCTIONAL HEMODIALYSIS ARTERIOVENOUS FISTULA OR ARTERIO-VENOUS GRAFT (DEBAPTA Trial)

Investigator Initiated Trial funded by National Medical Research Council Singapore (NMRC/1296/2011) Registered on clinicaltrials.gov (NCT01544907)
DEB Angioplasty vs PTA

• **Aim**
  – To determine the efficacy of DEB angioplasty compared to conventional PTA in AVF and AVG stenoses at 6 months

• **Material and Method**
  – Prospective RCT (Jan 2012 to Apr 2013)
  – Single centre, un-blinded
  – 119 patients (40 females : 79 males)
  – Mean age of 59.1 years
Study Design

Patient with malfunctioning AVF/AVGs eligible and agreed for the study

Diagnostic AVFistulogram / AVGraftogram

Meets inclusion criteria

1:1 RANDOMISATION

DEBA (x1min) after initial PTA (DEBA) arm (InPact)

Conventional balloon angioplasty (PTA) arm (Reef)

*Aspirin x 6 mths, Clopidogrel x1 mth post procedure

*6-mths follow up AVFistulogram / AVGraftogram
(i) Restenosis rates
(ii) Mean late luminal loss

6-mth: DEBA arm (n=59)
6-mth: PTA arm (n=60)

Include Icons/Medtronic balloons were used:
- Reef PTA balloon
- IN.PACT Admiral DEB

Inclusion Criteria
1. Upper limb or groin malfunctioning AVF/AVG
2. AVF/AVG >3 months old (matured)
3. Native vessel between 4-7mm diameter (corresponding to the sizes of the available DEBs)
4. Able to cross the lesion with guide wire
5. Platelet count >50x10^9 / L
6. PT/PTT <3 seconds above normal

Exclusion Criteria
1. Thrombosed AVF/AVG
2. Evidence of systemic infection or local infection associated with the AVF/AVG
3. Age <21 years
4. Pregnant
5. Uncorrectable coagulopathy (despite transfusion) or hypercoagulable state
6. Enrolled in another investigational study
7. Co-morbid conditions limiting ability to comply with follow up requirement
8. Life expectancy <6months
Study End Points & Definitions

• Primary end point
  – Lesion primary patency at 6 months
  – Restenosis rate at 6 month follow up angiogram

• Secondary Endpoints
  – Anatomical and clinical success
  – Lesion primary patency at 12 months
  – Circuit primary patency at 6 and 12 months

• Definitions
  – Lesion primary patency was defined as absence of any repeat intervention (either endovascular or surgical) of the target lesion from the index PTA for the follow-up period.
  – Restenosis rate was defined as the incidence of ≥50% diameter stenosis of the trial lesion at 6-mth follow-up angiogram.
  – Anatomical success was defined as <30% residual diameter stenosis measured immediately after PTA.
  – Clinical success was defined as one successful hemodialysis via the access post-PTA.
  – Circuit primary patency was defined as the time interval from the index PTA to the next access intervention anywhere in the circuit from the arterial inflow to the cavo-atrial junction.
Consort Diagram

Enrollment

Assessed for eligibility (n=583)

Excluded (n=488)
- Not meeting inclusion criteria (n=88)
- Declined to participate (n=312)
- Other reasons (n=58)

Randomized (n=125)

Allocation

DEBA arm (n=63)

Follow-Up

6-month AVFistulogram/AVGraftogram (n=47)
- Re-intervention prior to 6mth F/U: 9
- Declined 6mth F/U: 2
- Mortality: 1 (Day 42; procedure unrelated)

Withdrawn from the study (n=4)
- Intolerant to Aspirin: 1
- Voluntary withdrawal: 2
- Mortality 1wk post intervention from IHD: 1

PTA arm (n=62)

6-month AVFistulogram/AVGraftogram (n=36)
- Re-intervention prior to 6mth F/U: 20
- Declined 6mth F/U: 3
- Mortality: 1 (Day 159; procedure unrelated)

Withdrawn from the study (n=2)
- Intolerant to Aspirin: 1
- Voluntary withdrawal: 1

Analysis

Analysed (n=69)

Analysed (n=60)
## Demographic & Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>DEBA (n=59)</th>
<th>PTA (n= 60)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>59.0 ± 11.5</td>
<td>59.4 ± 8.80</td>
<td>0.838</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>39 (66.1)</td>
<td>40 (66.7)</td>
<td>0.948</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td>5 (8.5)</td>
<td>6 (10)</td>
<td>0.774</td>
</tr>
<tr>
<td>Hyperlipidaemia, no. (%)</td>
<td>40 (67.8)</td>
<td>38 (63.3)</td>
<td>0.608</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>55 (93.2)</td>
<td>55 (91.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Ischaemic Heart Disease, no. (%)</td>
<td>27 (45.8)</td>
<td>23 (38.3)</td>
<td>0.412</td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>37 (62.7)</td>
<td>34 (56.7)</td>
<td>0.502</td>
</tr>
<tr>
<td><strong>Age of Dialysis Access (mos)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>44.4 ± 58.6</td>
<td>47.3 ± 54.3</td>
<td>0.782</td>
</tr>
<tr>
<td>Range</td>
<td>0–168</td>
<td>3–288</td>
<td></td>
</tr>
<tr>
<td><strong>Side of Dialysis Access, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>44 (74.6)</td>
<td>46 (76.7)</td>
<td>0.791</td>
</tr>
<tr>
<td>Right</td>
<td>15 (25.4)</td>
<td>14 (23.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Site of Dialysis Access, no. (%)</strong></td>
<td></td>
<td></td>
<td>0.016 *</td>
</tr>
<tr>
<td>Arm</td>
<td>15 (25.4)</td>
<td>28 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Forearm</td>
<td>44 (74.6)</td>
<td>32 (53.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of Dialysis Access, no. (%)</strong></td>
<td></td>
<td></td>
<td>0.101</td>
</tr>
<tr>
<td>AVF</td>
<td>52 (88.1)</td>
<td>46 (76.7)</td>
<td></td>
</tr>
<tr>
<td>AVG</td>
<td>7 (11.9)</td>
<td>14 (23.3)</td>
<td></td>
</tr>
<tr>
<td>AVF/AVG Type, no. (%)</td>
<td></td>
<td></td>
<td>0.176</td>
</tr>
<tr>
<td>Radio-cephalic (RC)</td>
<td>40 (67.8)</td>
<td>30 (50)</td>
<td></td>
</tr>
<tr>
<td>Brachio-cephalic (BC)</td>
<td>10 (16.9)</td>
<td>18 (30)</td>
<td></td>
</tr>
<tr>
<td>Brachio-basilic (BB)</td>
<td>9 (15.3)</td>
<td>7 (11.7)</td>
<td></td>
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<tr>
<td>Brachio-brachialis (BBr)</td>
<td>0</td>
<td>2 (3.3)</td>
<td></td>
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<tr>
<td>Radio-basilic (RB)</td>
<td>0</td>
<td>1 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Brachial-jugular (BJ)</td>
<td>0</td>
<td>1 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Brachial-axillary (BAx)</td>
<td>0</td>
<td>1 (1.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Number of previous angioplastics</strong></td>
<td></td>
<td></td>
<td>0.563</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.80 ± 2.32</td>
<td>2.07 ± 2.74</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0–9</td>
<td>0–14</td>
<td></td>
</tr>
<tr>
<td><strong>Length of target lesion (cm)</strong></td>
<td></td>
<td></td>
<td>0.832</td>
</tr>
<tr>
<td>Median</td>
<td>2.6</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.2–6.3</td>
<td>0.5–8.1</td>
<td></td>
</tr>
<tr>
<td><strong>Anatomic success</strong></td>
<td>53 (89.8)</td>
<td>47 (78.3)</td>
<td>0.087</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th></th>
<th>DEBA</th>
<th>cPTA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anatomical success</td>
<td>89.9%</td>
<td>78.3%</td>
<td>0.132</td>
</tr>
<tr>
<td>Clinical success</td>
<td>100%</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>Restenosis rate (@ 6mths)</td>
<td>34%</td>
<td>62.9%</td>
<td>0.014</td>
</tr>
<tr>
<td>Late lumen loss</td>
<td>26.2%</td>
<td>32.5%</td>
<td>0.180</td>
</tr>
</tbody>
</table>

- **Anatomical success**: <30% residual diameter stenosis measured immediately after PTA
- **Clinical success**: one successful hemodialysis via the access post-PTA
- **Restenosis rate**: incidence of ≥50% diameter stenosis of trial lesion at 6mth FU angio
- **Late lumen loss**: difference between percentage stenosis after angioplasty and at 6 mths
Lesion Primary Patency @ 6 and 12 months

At 6 months,
- DEBA – 81%
- cPTA – 61%
  \( p = 0.027 \)

At 12 months,
- DEBA – 51%
- cPTA – 34%
  \( p = 0.044 \)
At 6 months, DEBA – 76%
cPTA – 56%
p = 0.048

At 12 months, DEBA – 45%
cPTA – 32%
p = 0.124 (NS)
No significant restenosis at 6 month follow up angiogram
Mild restenosis at treated segment with interval development of new adjacent stenosis

Pre 6x60mm DEB  Post DEBA  6 mth angio
Univariate & Multivariate Cox Regression Analysis for Predictors for Lesion Primary Patency

<table>
<thead>
<tr>
<th>Variables</th>
<th>DEBA</th>
<th>cPTA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (&gt;60 yrs/ &lt;60 yrs)</td>
<td>0.50 (0.23, 1.07)</td>
<td>0.074</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>0.67 (0.32, 1.42)</td>
<td>0.293</td>
</tr>
<tr>
<td>Smoking (Y/N)</td>
<td>0.79 (0.19, 3.31)</td>
<td>0.744</td>
</tr>
<tr>
<td>Types (AVF/AVG)</td>
<td>0.67 (0.23, 1.93)</td>
<td>0.459</td>
</tr>
<tr>
<td>Site (Forearm/Arm)</td>
<td>1.15 (0.47, 2.82)</td>
<td>0.767</td>
</tr>
<tr>
<td>Age of dialysis access (&gt;24 mos/ &lt;24 mos)</td>
<td>0.41 (0.19, 0.87)</td>
<td><strong>0.021</strong></td>
</tr>
<tr>
<td>No. of previous angioplasties (Y/N)</td>
<td>0.68 (0.33, 1.42)</td>
<td>0.304</td>
</tr>
<tr>
<td>Length of stenosis (cm)</td>
<td>0.87 (0.67, 1.11)</td>
<td>0.253</td>
</tr>
</tbody>
</table>

1 Variables included were significant at p ≤ 0.05 using forward selection approach.

2 24 months was the median for the cohort for age of dialysis access.
Complications

- No study related mortality
  - 1 death in each arm but not procedure related
- No bleeding complication from dual antiplatelet therapy
- 1 venous rupture at angioplasty site in cPTA arm successfully controlled with balloon tamponade
- 1 balloon rupture in DEBA arm with no sequelae
Summary of Results

• Our study showed that DEBA was significantly superior to cPTA in terms of
  – 6 and 12 month lesion primary patency
  – 6 month circuit primary patency
  – 6 month restenosis rate

• No statistical significance in
  – 12 month circuit primary patency (p = NS)
  – 6 month late lumen loss (p = NS)
# DEB Angioplasty for AVF/AVG Stenosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type</th>
<th>Study</th>
<th>Group</th>
<th>N</th>
<th>DEB</th>
<th>6m PP</th>
<th>12m PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katsanos</td>
<td>2012</td>
<td>AVF, AVG</td>
<td>RCT</td>
<td>DEB PTA</td>
<td>20</td>
<td>InPACT</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>Lai</td>
<td>2014</td>
<td>AVF</td>
<td>Prospective</td>
<td>DEB PTA</td>
<td>10</td>
<td>10</td>
<td>70%</td>
<td>0%</td>
</tr>
<tr>
<td>Patane</td>
<td>2014</td>
<td>AVF</td>
<td>Retrospective</td>
<td>DEB PTA</td>
<td>26</td>
<td>-</td>
<td>96%</td>
<td>91%</td>
</tr>
<tr>
<td>Kitrou</td>
<td>2015</td>
<td>AVF, AVG</td>
<td>RCT</td>
<td>DEB PTA</td>
<td>20</td>
<td>20</td>
<td>35%</td>
<td>5%</td>
</tr>
<tr>
<td>Verbeeck</td>
<td>2016</td>
<td>AVF</td>
<td>Observational</td>
<td>DEB PTA</td>
<td>41</td>
<td>-</td>
<td>81%</td>
<td>60%</td>
</tr>
<tr>
<td>Cildag</td>
<td>2016</td>
<td>AVF</td>
<td>Retrospective</td>
<td>DEB PTA</td>
<td>26</td>
<td>26</td>
<td>77%</td>
<td>65%</td>
</tr>
<tr>
<td>DEBAPTA Trial at SGH</td>
<td>2017</td>
<td>AVF, AVG</td>
<td>RCT</td>
<td>DEB PTA</td>
<td>59</td>
<td>60</td>
<td>81%</td>
<td>61%</td>
</tr>
</tbody>
</table>
Systematic Review of DEB Angioplasty for Dialysis AVF Stenosis

- 6 studies with 254 interventions in 162 patients
  - 2 RCTs and 4 cohort studies
- 6 months Target Lesion Primary Patency
  - 70% to 97% for DEBs
  - 0% to 26% for non-DEBs.
- No procedure-related major or minor complications
- CONCLUSIONS:
  - DEBs are safe with some benefit in terms of improved rate of restenosis. However, this body of evidence is small and clinically heterogeneous.
  - A large multicentre RCT is needed to clarify the role of DEBs in treatment of dialysis access stenosis.

Cost Effectiveness Analysis

- **Our study**
  - Cost of DEB vs cPTA balloon = SGD 2000 vs SGD 250
  - Mean patency of DEBA vs cPTA = 7.8 months vs 5.7 months
  - 12 month lesion primary patency = 51% vs 34%

- **Kitrou et al, Eur J Radiol. 2015 Mar;84(3):418-23.**
  - Median patency of DEB vs PTA was 0.64 yrs vs 0.36 yrs
  - 12 month lesion primary patency was 35% vs 5% (p<0.001)
  - Incremental Cost Effectiveness ratio (ICER) was 2198€ per primary patency year of dialysis access gained.
  - Incremental Net Benefit (INB) was 1068€ for a willingness-to-pay (WTP) threshold of 5000€ (corresponding acceptability probability >97%).
Conclusions

• DEBA significantly prolonged both 6-month and 12-month lesion primary patency and 6-month circuit primary patency in AVF and AVG stenosis, when compared to cPTA.

• However, the superior circuit primary patency was not sustained at 12 months.

• DEB does work for AVF/AVG stenosis but does the incremental patency of about 2 months justify the high cost of DEB (SGD 2000)? ie Is it cost effective?

• Further large scale trials are needed.
Acknowledgements

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  – Terence Teo (PI), Farah Irani, Apoorva Gogna, Ankur Patel, Too Chow Wei, Shaun Chan, Leong Sum, Nanda Kumar, Karthikeyan Damodharan, Sivanathan Chandra Mohan, Thijs Urlings, Zhuang Kun Da, Ravi Muli Jogi, Richard Lo, Tan Bien Soo

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  – Chong Tze Tec, Tan Seck Guan, Chng Siew Ping, Edward Choke, John Wang, Chng Jack Kian

• Renal Medicine
  – Tan Chieh Suai, Lina Choong, Majorie Foo

• Research Associates
  – Stella, Win Hlaing Hlaing, Pwint Mar Khin
Thank you for your attention!
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