NIH studies on vascular access: What do we need to know?

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NIH clinic trials
1) 2008: Clopidogrel use for AVF patency
2) 2009: Dipyridamole+ASA use for AVG patency
3) 2011: ASA for AVG patency
4) 2011: Factor V Leiden genotype association with AVG patency
5) 2013: Hemodialysis Fistula Maturation Study

Study design
- Double-blinded, placebo controlled RCT
- Clopidogrel
  - Loading dose of 300mg on day #1
  - 75 mg po qd for 41 days, thereafter
- Randomized and study drug administered within 1 day of AVF creation
- Stratification by location of AVF and center
  - Forearm
  - Upper arm

Outcomes
1. Thrombosis 6 wks after AVF creation
2. Failure to attain suitability for HD

Primary outcome: AVF thrombosis

Effect of Clopidogrel on Early Failure of Arteriovenous Fistulas for Hemodialysis: A Randomized Controlled Trial

JAMA, May 14, 2008—Vol 299, No. 18

<table>
<thead>
<tr>
<th>Table 2. Fistula Thrombosis</th>
<th>No. (%) of Patients</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel b (n = 426a)</td>
<td>53 (12.2)</td>
<td>0.63 (0.46-0.87)</td>
</tr>
<tr>
<td>Placebo (n = 431)</td>
<td>84 (19.5)</td>
<td></td>
</tr>
<tr>
<td>By location:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm fistula</td>
<td>31 (12.0)</td>
<td>0.63 (0.36-0.77)</td>
</tr>
<tr>
<td>Upper arm fistula</td>
<td>22 (11.3)</td>
<td>0.69 (0.52-1.03)</td>
</tr>
</tbody>
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Clopidogrel associated with a significant reduction in AVF thrombosis (p=0.018)
Secondary outcome: AVF Suitability Failure

<table>
<thead>
<tr>
<th>AVF Suitability Failure</th>
<th>No. (%) of Patients</th>
<th>Relative Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel (n=268)</td>
<td>Placebo (n=273)</td>
</tr>
<tr>
<td>Suitability failure (p=patients)</td>
<td>236 (88.9)</td>
<td>222 (81.5)</td>
</tr>
<tr>
<td>By location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm veins</td>
<td>144 (86.9)</td>
<td>137 (84.1)</td>
</tr>
<tr>
<td>Upper arm veins</td>
<td>92 (85.3)</td>
<td>65 (82.4)</td>
</tr>
<tr>
<td>By failure reason</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVF abandoned with no expectation of durability</td>
<td>115 (89.9)</td>
<td>104 (95.9)</td>
</tr>
<tr>
<td>AVF not in use despite treatment with antibiotics</td>
<td>57 (84.5)</td>
<td>47 (72.6)</td>
</tr>
<tr>
<td>AVF in use during assessment period but failed to meet suitability criteria</td>
<td>66 (97.1)</td>
<td>41 (11.0)</td>
</tr>
</tbody>
</table>

No significant difference in AVF suitability

Conclusions

- Clopidogrel reduced the frequency of early thrombosis of new AVFs
- This was not accompanied by an increase in AVFs suitable for HD
- No increase in bleeding events
- Early patency is needed for AVF maturation, but is not sufficient
- Additional factors must be responsible for AVF maturation failure
  - Vascular anatomy
  - Vascular biology
  - Surgical technique
  - Hence the initiation of the HFMS

Methods

- RCT, double blinded, placebo controlled clinical trial
- 649 pts
- New AVGs
- EDRP/ASA 200mg/25mg BID
  - EDRP selected as shown to inhibit vascular smooth muscle proliferation
  - EDRP/ASA combo used as only form of EDRP available in US
- Pts on ASA for med indications were permitted to continue asa in either arm

OUTCOMES

- Primary:
  - Loss of primary unassisted AVG patency
    - First occurrence of AVG thrombosis
    - An access procedure performed to correct a stenosis of 50% or more
    - Another surgical modification of the AVG (infection)
- Secondary Outcomes
  - Cumulative AVG failure
    - Time from randomization to complete loss of the access site for HD
    - Death from any cause
    - Combined death from any cause or cumulative graft failure
Conclusions

- ERDP/ASA resulted in
  - a significant, but modest, decrease in the cumulative incidence of loss of primary unassisted AVG patency
    - In pts receiving a new AVG
      - Absolute reduction: 5%
    - A decrease in the incidence of clinically significant AVG stenosis (≥50%)
    - No increase in adverse events

Primary unassisted patency is prolonged for all groups receiving ASA

Secondary cohort analysis of DAC ERDA/ASA AVG trial

43% of pts on ASA at baseline
- 53% on 81 mg qd
- 38% on 325 mg qd
- >80% remained on ASA throughout the study

Comparison of patients taking ASA vs. not on ASA at baseline

Higher baseline dose of ASA is associated with prolonged unassisted AVG patency

HR=0.76, 95% CI=0.59-0.99, p=0.04
**Conclusions**

- ASA alone may modestly prolong primary unassisted patency of newly created AVGs
  - Dose dependent
  - No increase in adverse events

**Hemodialysis Fistula Maturation (HFM) Study**


*JASN 22:2011* [Abstract]

**HFM Study Objectives**

To identify pre-, intra-, and post-operative predictors and the underlying mechanisms of AVF maturation in the domains of:

- a) vascular anatomy
- b) vascular biology
- c) clinical patient-specific attributes
- d) processes of healthcare

Enrollment began May 2010
In Nov 2011: 250/600 patients enrolled
Expected completion: 2013

**Factor V Leiden Gene Polymorphism is Associated with AVG failure**

Michael Allen, Li Zhang, Ivan Mayo, Molly Bray, Jose Fernandez and the Dialysis Access Consortium

*JASN 22:2011* [Abstract]

354 DAC AVG study patients

MTHFR, HO-1, TGF-B1, ACE, NOS, Klotho (all non-significant)
Inclusion Criteria

1. Newly created single-stage AVF (w/ or w/o transposition)
2. On chronic dialysis, or expected to start within 3 months
3. Age:
   a. >18 years
   b. ≤80 years if not yet on chronic hemodialysis
4. Life expectancy ≥ 9 months

Key Protocol Features

1. Pre-operative vascular assessment
   a. Endothelial function (flow mediated dilation)
   b. Vascular stiffness (pulse wave velocity)
   c. Venous capacitance (plethysmography)
   d. Vascular anatomy (ultrasonographic mapping)
2. Documentation of intra-operative procedures
3. Post-op ultrasounds <2 day, 2, 6, ~26 weeks
4. Characterization of clinical AVF use
5. Collection of serum, plasma, DNA, and intraoperative vein tissue

Clinical Patient-Level Attributes

- Demographics
  - Cardiovascular risk factors
    - Diabetes
    - Blood pressure
    - Obesity
    - Smoking status
  - Prior vascular access placement
  - Other prior vascular procedures

Processes of Care

- Pre-operative evaluation
- Surgical practices
  - Intravenous heparin
  - Size of vein
  - Surgeon attributes
  - Anatomical site
- AVF cannulation practices
- AVF salvage procedures

Primary Outcome

Unassisted Clinical Maturation

Use of the AVF with two needles for 75% of dialysis sessions within a 4-week period AND either:
A. 4 consecutive sessions in which the mean blood pump speed ≥300 ml/min.
B. A measured spKt/V ≥1.4 or URR >70%

Follow-up continues until AVF abandonment

Secondary Outcomes

- Other Fistula Use
  - Assisted clinical maturation after a procedure to facilitate maturation
  - Successful cannulation
  - Abandonment
  - Central venous catheter use
- Fistula Complications
  - Stenosis, thrombosis, pseudoaneurysm, ischemic steal syndrome, bacteremia
- Fistula Procedures
  - Angioplasty, surgical revision, stenting, ligation/embolization of accessory veins
- Anatomic Maturation
  - Fistula blood flow and vessel diameter assessed by ultrasound
Funded HFM Ancillary Studies

1. Hemodynamics and Vascular Wall Biology
   Determine Arteriovenous Fistula Maturation (R01)
   - Dr. A Cheung

2. Real Time Nitric Oxide Measurements as a Determinant of AV Fistula Maturation (R21)
   - Dr. Roy-Chaudhury

3. Nitric Oxide in Hemodialysis AV Fistula Maturation (R21)
   - Dr. Cohen and Dember

4. Genomics (GLUE) (R01) grant
   - Dr. Moldawer

In conclusion...

- The HFM Study represents the largest nationally sponsored initiative to date
- It is designed to elucidate the set of predictors and mechanistic factors associated with AVF maturation failure
- Findings of the HFM study will likely guide the next wave of large scale clinical trials targeting improvement of clinical outcomes after AVF placement