Vascular Access Research

Dialysis Access Consortium Trials: A Good Start

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Two Concurrent DAC Trials

Fistula Trial
Clopidogrel for the Prevention of Early Thrombosis of AV Fistulas

Graft Trial
Dipyridamole and Aspirin (Aggrenox®) for the Prevention of AV Access Stenosis

Dialysis Access Consortium (DAC)

• NIH-funded multi-center consortium established in late 2000
• Charged with designing and conducting large multicenter clinical trials of interventions to improve vascular access outcomes

Fistula Trial Hypothesis
Platelet inhibition will prevent early fistula thrombosis and thereby allow a greater proportion of fistulas to successfully mature

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Anti-Platelet Agents Appeared Beneficial in Several Small Trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Rx / Control</th>
<th>Treatment</th>
<th>Duration</th>
<th>Thrombosis Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrassy</td>
<td>45/47</td>
<td>Aspirin</td>
<td>4 weeks</td>
<td>4%</td>
</tr>
<tr>
<td>Janicki</td>
<td>20/6</td>
<td>Sulfipyrazone</td>
<td>3 weeks</td>
<td>0%</td>
</tr>
<tr>
<td>Michie</td>
<td>7/5</td>
<td>Sulfipyrazone</td>
<td>3 months</td>
<td>29%</td>
</tr>
<tr>
<td>Grontoft</td>
<td>18/17</td>
<td>Ticlopidine</td>
<td>4 weeks</td>
<td>11%</td>
</tr>
<tr>
<td>Grontoft</td>
<td>129/131</td>
<td>Ticlopidine</td>
<td>4 weeks</td>
<td>12%</td>
</tr>
<tr>
<td>Fiskerstrand</td>
<td>6/9</td>
<td>Ticlopidine</td>
<td>1 month</td>
<td>6%</td>
</tr>
<tr>
<td>Janicki</td>
<td>11/15</td>
<td>Ticlopidine</td>
<td>3 weeks</td>
<td>9%</td>
</tr>
</tbody>
</table>

Kaufman JS, Seminars Dial 13:40, 2000
**DAC Fistula Trial Overview**

- **Fistula Creation**
  - Clopidogrel or Placebo
  - Randomization and start of study drug
  - **Patency Assessment Week 6**
  - **Suitability Ascertainment Month 5**

  - Clopidogrel
    - 300 mg loading dose
    - 75 mg daily dose

**Sample Size and Power for Patency Outcome**

- Trial designed to enroll 1284 subjects
- Provides 85% power to detect a 30% reduction in thrombosis at 6 weeks assuming:
  - Thrombosis rate of 25% in placebo group
  - 5% loss to follow-up
  - 3% treatment drop-out
  - 3% treatment drop-in

**Primary Outcome**

**Fistula patency at 6 weeks**

Presence of bruit throughout systole and diastole detectable along the vein at least 8 cm proximal to the AV anastomosis

**Secondary Outcome**

**Fistula suitability for dialysis**

- Ability to use the fistula for dialysis for 8 of 12 sessions during a four week period with a dialysis machine blood flow of ≥300 ml/min
- Ascertained during the 5th month following fistula creation, or during 1st month of dialysis if dialysis was initiated >4 months after surgery

**Sample Size and Power for Suitability Outcome**

1284 subjects provides 81% power to detect a 20% reduction in suitability failure assuming:

- Suitability failure rate of 40% in placebo group

**Nine Clinical Centers**

- Fistula surgeries at 27 hospitals
- Dialysis at 125 facilities
- Broad geographic distribution
- Urban and rural centers
- Academic and community practices
Enrollment Terminated Early (877 Subjects)

Thrombosis at 6 weeks
Clopidogrel 53 (12.2%)
Placebo 84 (19.5%)

Relative Risk 0.63
95% CI 0.46 – 0.97
P Value 0.018

Dember et al, JAMA 299:2164-71; 2008

But No Benefit of Clopidogrel on Suitability Outcome

Suitability Failure
Clopidogrel 236 (63%)
Placebo 215 (60%)

Relative Risk 1.06
95% CI 0.95 – 1.18
P Value 0.31

Dember et al, JAMA 299:2164-71; 2008

Trial Findings and Interpretation

• Clopidogrel reduced the risk of early fistula thrombosis but did not increase the proportion of fistulas that became suitable for use
• Thrombosis may be a manifestation, rather than cause, of maturation failure
• Findings do not support the routine use of clopidogrel to prevent early failure of new fistulas
• A high proportion of new fistulas do not mature adequately for use

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Trial Findings and Interpretation

Be cautious about relying on intermediate or surrogate outcomes

Previous Dipyridamole Trial

- 107 patients with AV graft randomized to dipyridamole, aspirin, dipyridamole/aspirin, or placebo
- In subset with new grafts (N=84), dipyridamole treatment associated with reduced rate of thrombosis (RR 0.35, p=0.02)

Sreedhara et al, Kidney Int 45:1477, 1994

Two Concurrent DAC Trials

- Fistula Trial
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- Graft Trial
  - Dipyridamole and Aspirin (Aggrenox\textsuperscript{®}) for the Prevention of AV Graft Stenosis

Overview of DAC Graft Trial

- Randomized, double-blind trial of ERDP/ASA vs placebo after graft placement
- Monthly flow monitoring with angiography triggered by specific criteria
- **Primary outcome:** Loss of primary unassisted patency
- **Secondary outcome:** Cumulative patency
- Study medication discontinued after primary outcome met

DAC Graft Trial Hypothesis

Extended release dipyridamole in the form of Aggrenox\textsuperscript{®} (ERDP/ASA) will inhibit stenosis and prolong primary unassisted patency of new grafts

Via inhibitory effect of dipyridamole on SMC proliferation

Loss of Primary Unassisted Patency

[Dixon et al, NEJM 360:2191-201; 2009](#)

**Graph:**
- % Loss of Patency vs Months
Loss of Primary Unassisted Patency

HR = 0.81
95% CI 0.65 - 0.97
P=0.02

Questions

• Is effect substantial enough to justify use?
• Was dipyridamole or aspirin responsible for effect?
• Would there have been a benefit on cumulative patency if drug were continued after first event?

How Much Benefit?

• Absolute difference of 5% in primary outcome at 1 year
• Median primary unassisted patency increased from 4.3 to 5.8 months with ERDP/ASA
• No difference in cumulative patency

Extraordinarily High Event Rate

77% failure rate at 1 year

Modest Effect......But

• First pharmacologic intervention shown in large clinical trial to have at least some benefit
• Suggests that this is a remediable problem
  – Better agents?
  – Local administration?
Overall Conclusions from DAC Trials

- Multicenter randomized trials of vascular access interventions can be performed successfully.
- Failure rates are high for both fistulas and grafts.
- New approaches to improve outcomes are needed.

Where Do We Go From Here?

Early Phase Trials of Promising Approaches

- NIH Hemodialysis Fistula Maturation (HFM) Study
  - Multicenter prospective cohort study (began May, 2010)
  - 600 subjects getting new fistulas
  - Pre-operative vascular function studies
    - FMD/NMD, PWV, venous capacitance
  - Intra-operative studies
    - Detailed surgical data
    - Vein tissue collection for histology and molecular analyses
  - Post-operative studies
    - Serial ultrasounds

Goals of HFM Study

- Identify pre-operative predictors of maturation
- Identify clinically useful early post-operative indicators of maturation failure
- Elucidate mechanisms underlying maturation failure and potential targets for interventions
- Identify surrogates for maturation that could facilitate evaluation of interventions
## Rationale for Outcomes

<table>
<thead>
<tr>
<th>Patency</th>
<th>Suitability</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinically important</td>
<td>• Clinically important</td>
</tr>
<tr>
<td>• Outcome closely related to biological effect of intervention</td>
<td></td>
</tr>
<tr>
<td>• Ascertainment highly feasible</td>
<td></td>
</tr>
<tr>
<td>• Supportive pilot data</td>
<td></td>
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</tbody>
</table>