Fish Oil to Increase Graft Patency

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Fish Oil: Basic Mechanisms

Benefits: ↓endothelial dysfunction, intimal hyperplasia, thrombosis

• ↓inflammatory cytokines, adhesion molecules
• ↓platelet aggregation, serum viscosity
• ↑release of NO, generation of PGI₂
• ↓endothelin-1
• ↓PDGF and smooth muscle proliferation
• Antioxidant effect in hemodialysis patients

Fish Oil

Omega-3 fatty acids
• Eicosapentanoic acid (EPA: 20:5n-3)
• Docosahexanoic acid (DHA: 22:6n-3)
• Anti-proliferative, anti-oxidant, vasodilatory effects

FISH Study

Primary Objective
• To compare the proportion of patients who experience a loss of native patency within 12 months after new graft creation in patients taking daily oral fish oil versus placebo supplementation

Secondary Outcomes
• Graft Outcomes:
  • The rate of and time to thrombosis, radiological or surgical intervention to maintain patency
  • Bleeding episodes
• Main Cardiovascular Outcomes:
  1) BP
  2) Cardiovascular Composite of: MI, CHF, Stroke, PVD

Inclusion/Exclusion Criteria

Includ[19]
• ESRD requiring a new synthetic graft
• Age ≥ 18 years
• Must be able to provide informed consent

Exclud[19]
• Surgical revision of a prior access e.g. a jump graft (i.e. must be new access)
• Major bleed within 1 month of study
• Malignant hypertension
• Receiving >2 antiplatelet agents or anticoagulants
• Ingestion of fish oil at randomization
BH1 suggest limiting the listing of exclusion criteria to the major ones for HD pts, for example, pregnancy could be removed, and the allergy ones - those are pretty standard. Consider others as well
Brenda Hemmelgarn, 11/7/2011

BH9 could reduce the number of words on the inclusion side, that is remove "for chronic HD", and the points in brackets for the consent - all fairly obvious
Brenda Hemmelgarn, 11/7/2011
FISH Study

Double blinded, multicentre RCT

- Intervention:
  - 1 gram soft gel capsule
  - 48% EPA (400 mg/cap), 25% DHA (200 mg/cap)
  - Steam deodorized and 1% peppermint flavored
  - vs. matching placebo
  - 4 x 1 gram caps/day x 12 months

Participating Sites

- Excluded prior to treatment: N=3
- 296 exclusions
  - 63 failed create
  - 85 other inclusion/exclusion
  - 74 deceased
  - Other

Results

- Hemodialysis graft required
- Stratify by Center
- Stratify by access history
- 1st Access
- > 1st Access
- Fish Oil
- Placebo

Compliance Testing

- Participant serum was collected at baseline and 3 months and sent to the University of Guelph, Ontario, for analysis
- A random 125 samples underwent gas-liquid chromatography to determine fatty acid composition (EPA) of total serum phospholipids
- Compliance was determined by EPA incorporation into cells

Statistical Analysis

- Intention to treat analysis
- Comparisons between groups of:
  - Proportions: Fisher’s exact test
  - Rates: exact binomial test
  - Quantitative values: Wilcoxon rank sum test or T-Test
  - Time to event: Kaplan-Meier survival curves

Patient Flow

- 497 assessed for eligibility
- 201 randomized
- Fish Oil: N=101
- Placebo: N=100
- Excluded prior to treatment: N=2
- Death
- Graft reaction
- Follow-up:
  - 83 – completed 12 months
  - 2 withdrew
  - 1 transferred
  - 8 died
- Analyzed N=99

- Fish Oil: N=101
- Placebo: N=100
- Excluded prior to treatment: N=2
- Withdraw consent
- Graft thrombosis before POD 7
- Failed create
- Follow-up:
  - 83 – completed 12 months
  - 2 withdraw
  - 1 transferred
  - 8 died
- Analyzed N=97
Slide 8

BH3  consider removing this slide - and just making this comment on the previous slide
Brenda Hemmelgarn, 11/7/2011

Slide 9

BH4  suggest just using the map - the text is too small for people to see anyway, and the purpose is to show that it is multi-centre, US and Canada, achieved quickly by your map
Brenda Hemmelgarn, 11/7/2011

Slide 10

BH5  remove this last line about STATA
Brenda Hemmelgarn, 11/7/2011
Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fish Oil (N=99)</th>
<th>Placebo (N=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr;range)</td>
<td>62.5 (28-88)</td>
<td>63.4 (27-87)</td>
</tr>
<tr>
<td>Male sex</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>Caucasian</td>
<td>64</td>
<td>59</td>
</tr>
<tr>
<td>ESRD Etiology: Diabetes</td>
<td>49</td>
<td>39</td>
</tr>
<tr>
<td>Comorbidities: Coronary heart disease</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>Congestive heart failure *</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Hemodialysis vintage (mean yrs)</td>
<td>2.76</td>
<td>2.84</td>
</tr>
<tr>
<td>Number prior accesses (mean)</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Graft location: Upper arm</td>
<td>34</td>
<td>43</td>
</tr>
<tr>
<td>Aspirin/Warfarin/Other anti-platelet</td>
<td>57/26/11</td>
<td>51/20/14</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>3.76 (145.4 mg/dL)</td>
<td>3.66 (141.5 mg/dL)</td>
</tr>
</tbody>
</table>

Compliance and Safety

- No difference in bleeding events
  - 9 in fish oil
  - 8 in placebo; (p=1.00)

Loss of Native Patency

- Primary Outcome: Proportion with Loss of Native Patency
  - 48 (48%) in fish oil group
  - 60 (62%) in placebo group
  - P=0.06

Clinically Important Endpoints

- Thromboosis
  - 50%

Mean Change in Systolic Blood Pressure

- RRR 41%

Interventions
BH13 Are you able to remove any of these, so not so busy? For example, is PVD necessary to include? Also graft location?
Brenda Hemmelgarn, 11/7/2011

BH14 would you be comfortable taking out the text (except for that about bleeding), and just speaking to the figure? would be nice and clear than
Brenda Hemmelgarn, 11/7/2011

BH16 suggest calling this "Change in Blood Pressure"
Brenda Hemmelgarn, 11/7/2011

BH17 don't think you need this text about baseline - you could comment that SBP and DBP were similar at baseline for the two groups
Brenda Hemmelgarn, 11/7/2011
**Blood Pressure**

- Reduction in the mean number of BP medications/patient
  - 1.69 (fish oil) \( P<0.001 \)
  - 0.61 (placebo)
- Proportion of patients who had at least 1 reduction in dose or frequency of BP meds
  - 64% (fish oil) \( P=0.004 \)
  - 42% (placebo)

**Cardiovascular Outcomes**

- Time to cardiovascular event
- RRR 59%
- \( P=0.02 \)
- Placebo

**Limitations**

- Enrolment goal not reached
- No difference in primary endpoint found
  - The choice of primary outcome measure as a proportion may not have been optimal

**Interpretation of FISH Study Result**

- Statistically “negative”
- Clinically “positive”
- What to do….
  - Look at trend
  - Why was it “negative”?
- Make your decision:
  - What does your patient have to gain or lose?

**Conclusions**

- Daily fish oil ingestion in hemodialysis patients with newly created grafts:
  - Prolongs the time to loss of native graft patency (unassisted primary patency)
  - Reduces the rate of thrombosis by half and reduces the frequency of needed radiological or surgical interventions to maintain patency
  - Improves blood pressure and cardiovascular events

**Acknowledgements**

- Study participants
- Site investigators and research personnel
- DSMB and steering committee
- Funding from:
  - Canadian Institutes of Health Research (CIHR)
  - Physicians Services Incorporated (PSI) Foundation
Lesson Learned: FISH Study

1) While the primary outcome was NOT statistically significant, secondary CLINICALLY RELEVANT endpoints were statistically significant

2) Choice of Endpoint is critically important

3) We should consider “non-traditional” endpoints

What is an Endpoint?

- Outcome + its measure
- E.g. Outcome = Thrombosis
- How can it be measured?
  - Proportion (yes/no) = binary= percentage (%)
  - Time to event=survival curves=Hazard ratio (HR)
  - Rate=frequency of event/unit e.g. number thrombosis/access-year
- What is most important to patient

What is a clinically important Endpoint

- Consider Hypothetical Non-Renal RCT
- Population: COPD or Lupus
- Intervention: RxA vs. Placebo
- Outcome:
  - Proportion (Yes/No) – Flare or Not
  - Time to flare
  - How many flares in a lifetime

Thank You: Participating Sites

**Canadian Sites**
- Beausejour Regional Health Authority
- Charles Lemoyne Hospital
- Credit Valley Hospital
- Foothills Hospital
- Grand River Hospital
- London Health Sciences Centre
- Oakville Trafalgar Hospital
- St. Michael’s Hospital
- Scarborough General Hospital
- Sunnybrook Health Sciences Centre
- University of Alberta
- University Health Network
- Toronto General Hospital

**US Sites**
- University of Alabama
- University of Texas Southwestern Medical Center
- University of Virginia

Back-up

Thank you
Study Definitions

**Thrombosis**
A blood clot found on follow-up radiological investigation in response to clinically important reduced graft flow/functioning that requires intervention, or a terminal clot that results in graft abandonment.

**Radiological or Surgical Intervention**
One that alters the anatomy or content of the graft (i.e. not an angiogram).

Radiology and surgery reports submitted and independently adjudicated; French reports were independently translated.

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**Study Definitions**

**Blood pressure**
- Pre dialysis recordings of systolic and diastolic values
- 3x in week and then averaged

**Major Bleed**
Requires either
- Blood transfusion (packed RBCs, fresh frozen plasma, other)
- Hospital admission to manage bleeding or its complications

**Cardiovascular Event**
- Myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, cardiac related death
- Required hospital admission and verification of records
- Followed strict definitions e.g. AHA criteria for MI, etc.

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**Study Definitions**

**Cardiac events**
- MI – 2/3:
  - Ischemic type chest pain/discomfort
  - Changes on serially obtained ECG
  - Rise and fall in serum cardiac markers
- CHF – 2/4:
  - Clinical S & S CHF
  - SOB resolved with diuresis or ultrafiltration
  - CXR evidence of CHF
  - No other obvious cause of SOB

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**Fish Oil: Basic Mechanisms**

Benefits: ↓endothelial dysfunction, intimal hyperplasia, thrombosis
- ↓inflammatory cytokines, adhesion molecules
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**FISH Study: Conclusions**

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