Omega-3s and Heart Health
An Australian Perspective

Associate Professor David Colquhoun

7th November, 2013

University of Queensland, Greenslopes & Wesley Hospitals, Brisbane

www.coreresearchgroup.com
d.colquhoun@uq.edu.au

Slides prepared by David Colquhoun & Jenni Shields
Omega-3 and Heart Health
Australian Prospective

- Current recommendations of National Heart Foundation of Australia (NHFA)
- National Institute of Complementary Medicine (NICM)

Update on NHFA Omega-3 Working Group

Members: Chair – Paul Nestel, David Colquhoun, Peter Clifton, Rob Grenfell, Terry Mori, Manny Noakes, David Sullivan, Beth Thomas (NHFA), Melanie Chisholm (NHFA)
Health professionals should advise adult Australians with documented CHD to:

1. Consume about 1000 mg per day of combined DHA and EPA through a combination of the following:
   - two or three serves (150 g serve) of oily fish per week
   - fish oil capsules or liquid
   - food and drinks enriched with marine n-3 PUFA.
2. Consume at least 2 g per day of ALA.
3. Follow government advice on fish consumption regarding local safety issues.
4. Discuss healthy eating and concerns about nutrition with an Accredited Practising Dietitian or a doctor.

Health professionals should advise adult Australians with elevated triglycerides (TG) to take fish oil capsules or liquid and marine n-3 PUFA enriched foods and drink as first-line therapy by:

- starting with a dose of 1200 mg per day of DHA and EPA; and if appropriate
- increasing the dose to 4000 mg per day of DHA and EPA and checking their patient’s response every 3 to 4 weeks when the dose is changed, until target TG levels are reached.
NHFA Omega-3 Working Group formed mid 2013

Background: Since 2008 NHFA Position Statement there have been neutral intervention trials and at least 4 meta-analyses that reported little benefit of omega-3 supplementation.

- 2013 ESC actively disendorsed omega-3 for secondary prevention in 1 sentence and 2 references.
- 2013 AHA simply left out any reference to omega-3 in secondary prevention up-date
- 2013 NICE is considering disendorsing omega-3 EE post infarction (accepting submissions).
- Currently there is clinical equipoise. At last one large randomised outcome trial (4000 patients over 4 years 4 grams EPA/DHA vs placebo) has commenced.
OMEGA TRIAL

Chief Author/Investigator
Dr Jochen Senges

“The study was underpowered to show an effect because of the low rate of sudden cardiac death”

“It would be incorrect to say that omega-3 fatty acids are not effective” (Dr Senges)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration (months)</th>
<th>EPA/DHA dose</th>
<th>Major CVD CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008 Gissi-HF (n=6975)</td>
<td>47</td>
<td>1000mg as ethyl ester Omacor</td>
<td>CI (0.85-0.99) 9% reduction mortality P=0.04 8% mortality or hospital admission P=0.009</td>
</tr>
<tr>
<td>No problem:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 Alpha-Omega (n=4837)</td>
<td>41</td>
<td>376 mg in margarine</td>
<td>No benefit CI (0.7-1.2) *</td>
</tr>
<tr>
<td>Problem:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>? compliance / Dose too low</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 Omega (n=3851)</td>
<td>12</td>
<td>1000 mg as ethyl ester Omacor</td>
<td>No benefit CI (-0.3-3.6) *</td>
</tr>
<tr>
<td>Problem:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underpowered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 Su.FoL.OM3 (n=2501)</td>
<td>56</td>
<td>300 mg Maxepa</td>
<td>No benefit CI (0.79-1.47) *</td>
</tr>
<tr>
<td>Problem:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underpowered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011 Italian Post Bypass (n=2100)</td>
<td>36</td>
<td>2000 mg as ethyl ester Omacor</td>
<td>CI (0.36-0.73) 45% reduction mortality P=0.0002</td>
</tr>
<tr>
<td>Problem:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open label</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiologist preference for EPA/DHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012 Origin (n=12537)</td>
<td>84</td>
<td>1000 mg as ethyl ester Omacor</td>
<td>No benefit CVD CI (0.93-1.10) *</td>
</tr>
<tr>
<td>Problem:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>? compliance</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* wide confidence intervals (CI) which are consistent with the trials with positive results.
Evidence of ventricular fibrillation during 15 mins of myocardial ischaemia in rats

McLennan PL, Myocardial membrane fatty acids and the antiarrythmic actions of dietary fish oil in animal models. Lipids 36,S111-S114 (2001)
n-3 supplementation and induction VT

- 2 acute IVI studies in humans in EP lab
  - 1 hour after infusion
    - VT can no longer be induced in most patients

- 6 weeks oral 900mg of EPA & DHA (in triglyceride form) (Adelaide Study)
  - In 12 patients: 5 no longer inducible
  - 5 much greater stimulation needed (P=0.003)

In 14 controls: no difference in inducability.

(Adelaide Study) n-3 fatty acids and inducability of VT

Omega-3 index change
Supplement Group 3.7%→4.8% p=0.001
Control Group 3.6%→3.9% p=ns

Metcalf R, Sanders P, James M, Am J Cardiol 2008;101:758-761
NHFA Omega-3 Working Group 2013

AIM: To consider current recommendations and to grade recommendations and strength of evidence along NHMRC gradings.

- CHD primary and secondary
- HF (NHFA 2011 recommended 1 gram EPA/DHA)
- Atrial fibrillation
- ALA
- various preparations and clinical relevance
- relationship to other disorders including cancer.

PROGRESS: 2 teleconferences and one face-to-face (October 2013)
<table>
<thead>
<tr>
<th></th>
<th>Epidemiological</th>
<th>Animal studies</th>
<th>Surrogates</th>
<th>Clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>✔ ✔</td>
<td>✔</td>
<td>✔ ✔</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>SCD</td>
<td>✔ ✔</td>
<td>✔ ✔ ✔</td>
<td>✔</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔ ✔ ✔</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>No regression studies</td>
</tr>
<tr>
<td>Stroke</td>
<td>✔</td>
<td>?</td>
<td></td>
<td>No effect</td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
<td>✔ ✔ ✔</td>
<td>✔</td>
<td>✔</td>
</tr>
</tbody>
</table>

Side effects – Mild GI in < 5%; taste; nausea, diarrhoea
Polyunsaturated fatty acids (1000mg EPA&DHA) should be considered as a second-line agent for patients with CHF who remain symptomatic despite standard therapy.


1) GISSI-HF 2% absolute decrease in death over 3.9 years P = 0.04
   2% ARR death or CV admission P = 0.0009

2) Improves left ventricular function (similar to ACEI or β-blocker)

# Effects on high dose OMACOR on LV Function in Cardiomyopathy

**REF:** Nodari S. et al. JACC 2011 Vol 57, Feb.

## RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Active</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>1 year</td>
<td>Baseline</td>
</tr>
<tr>
<td>EF</td>
<td>37%</td>
<td>35% (↓ 5%)</td>
<td>36%</td>
</tr>
<tr>
<td>Hospitalisation rate for HF</td>
<td>30%</td>
<td></td>
<td>6% P=0.0002</td>
</tr>
<tr>
<td>TNF-α</td>
<td>No change</td>
<td></td>
<td>Decreased P&lt; 0.001</td>
</tr>
</tbody>
</table>
Members of Cardiovascular Research Priorities Expert Working Group 2010

Associate Professor David M Colquhoun (Chairman of the Working Group)
Cardiologist, Wesley & Greenslopes Private Hospitals, University of Queensland

Professor Alan Bensoussan
Executive Director, National Institute of Complementary Medicine

Dr Lesley Braun
Research Fellow, Prince Alfred Hospital

Kelvin Hill
Manager, Guidelines Programme, National Stroke Foundation

Professor Anthony Keech
Professor of Medicine, University of Sydney

Associate Professor Karam Kostner
Principal Research Fellow, School of Medicine, Mater Hospital

Professor Frank Rosenfeldt
Head, Cardiac Surgical Research Unit, Alfred Hospital & Baker Heart Institute

Professor Basil Roufogalis
Herbal Medicines Research & Education Centre, Faculty of Pharmacy, University of Sydney

Dr Ross Walker
Cardiologist

Professor Gerald Watts
School of Medicine, University of Western Australia
Cost effectiveness of complementary medicines

August 2010

Report by Access Economics Pty Limited for
The National Institute of Complementary Medicine
Fish oils as adjunctive treatment for prevention of heart disease among those who have had MI

Trials used in Analysis – GISSI-P
DART1

Assumptions: EPA/DHA $112.15/person/year

- Burden of disability weights were from Begg et al (2007)
- A second order Monte Carlo simulation was undertaken on the TreeAge decision Model
- Sensitivity analysis around treatment effect variables MI, Stroke, CHD death, all cause death

Access Economics report on Cost Effectiveness of complementary medicines for the National Institute of Complementary Medicine. August 2010
“Fish oils rich in omega-3 fatty acids are highly cost effective when used as an adjunctive treatment in people with a history of coronary heart disease, achieving reduced death and mortality. These findings are consistent with other international studies.”

Access Economics report on Cost Effectiveness of complementary medicines for the National Institute of Complementary Medicines. August 2010
Widespread belief of health benefits of omega-3 and in particular Krill oil (10x potent) among public.

CAM practitioners keen on omega-3 and Krill oil but paradoxically appear to be embracing coconut oil (influenced by Dr Mercola and advertising)

Medical practitioners disinterested or skeptical, worse since blitz advertising on TV
Concluding remarks

- The evidence base supporting omega-3 for primary and secondary prevention of CD has eroded. Await results of ongoing adequately powered clinical outcome trials.
- Evidence base for triglyceride lowering is secure
- Evidence base for role in heart failure is growing
- No role of omega-3 in atrial fibrillation
- Probable/possible role in other conditions and as rheumatoid and osteoarthritis, depression, schizophrenia.
- “It is the EPA/DHA Stupid”

Dose is far more important than vehicle!
(remember it all comes from algae)
The End