The Effect of Fish Oil On Cardiovascular Mortality
Resident Pharmacotherapy Rounds

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Learning Objectives

By the end of this presentation, participants will be able to:

- Understand the impact of cardiovascular disease on worldwide mortality.
- Explain the proposed benefits of fish oil
- List the approved indications for fish oil
- Identify the proposed effective doses of fish oil
- Review the major studies regarding fish oil and cardiovascular mortality
- Make an assessment of the likely effect of fish oil on cardiovascular mortality
Cardiovascular Disease and Mortality

Cardiovascular disease involves a wide range of conditions including but not limited to the following:
- Coronary heart disease (CHD)
- Cerebrovascular diseases
- Peripheral arterial disease (PAD)
- Rheumatic heart disease
- Congenital heart disease
- Deep vein thrombosis and pulmonary embolism

Contribution to Death and Typical Preventive Measures

Summary: Deaths (000s) by cause, in WHO Regions (a), estimates for 2008

<table>
<thead>
<tr>
<th>Cause</th>
<th>WORLD (b)</th>
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<tbody>
<tr>
<td>Population (000)</td>
<td>6 737 480</td>
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<tr>
<td></td>
<td>(000)</td>
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<tr>
<td>Cardiovascular diseases</td>
<td>17 327</td>
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<td>Rheumatic heart disease</td>
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<td>Hypertensive heart disease</td>
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<td>Ischaemic heart disease</td>
<td>7 254</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>6 152</td>
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<td>Inflammatory heart disease (h)</td>
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In 2008, cardiovascular disease led to 30.5% of deaths worldwide. Due to the large impact, novel therapies that have the potential to reduce cardiovascular mortality, such as fish oil, are met with eagerness. Below is a review of the disease states that have the most impact on cardiovascular mortality and the therapies used to control said mortality. The biggest contributors to cardiovascular death are ischemic heart disease (IHD), cerebrovascular disease and hypertensive heart disease.

Ischemic heart disease (IHD)
- IHD was responsible for 12.8% of deaths worldwide
- Typically characterized by reduced blood flow to the heart
- Involves:
  - Angina
  - Myocardial infarction
  - Heart Failure
- Preventive therapy includes
  - Nitroglycerin
  - Revascularization
  - Antiarrhythmics
  - Hypertension control
    - Beta blockers, calcium channel blockers, diuretics, renin-angiotension-aldosterone systems (RAAS) antagonists.
  - Cholesterol control
    - Statins, fibric acids, niacin.

Cerebrovascular disease
- In 2008, cerebrovascular disease was responsible for 10.8% of deaths worldwide
- Preventive therapy involves
  - Antiplatelet therapy
    - Aspirin, clopidogrel, dipyridamole
  - Anticoagulation
    - Warfarin, dabigatran
  - Hypertension control
  - Cholesterol control

Primarily via statins
- Hypertensive heart disease
  - Responsible for 2% of deaths worldwide in 2008
  - Therapy includes (as listed above):
    - Beta blockers, calcium channel blockers, diuretics, renin-angiotensin-aldosterone system (RAAS) antagonists
- This review aims to explore if fish oil also has a positive effect on decreasing the mortality associated with the above disease states

**What are Fish Oils?**

Fish oils involve a number of different types of oils derived from fish. In the terms of cardiovascular mortality, our interest is in those high in polyunsaturated fatty acids (PUFAs).

- Particulary omega-3 PUFAs

Polyunsaturated fatty acids\(^7\)

- PUFAs are long chain fatty acids whose structure contains multiple double bonds.

\[
\text{HO} \quad 1 \quad \alpha \quad 5 \quad 8 \quad 11 \quad 14 \quad 17 \quad 20
\]

- They are generally divided into omega-3 and omega-6 PUFAs
- Most PUFAs are produced by the body
  - However there are notable exceptions
  - These include:
    - Alpha-linoleic acid (ALA)
      - Omega-3 fatty acid
    - Linoleic acid (LA)
      - Omega-6 fatty acid
- ALA is converted in the body to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)
- Both LA metabolites and EPA are further metabolized to produce eicosanoids
  - Eicosanoids are structures involved both in promoting and mitigating inflammation.
  - They include prostaglandins, thromboxanes, leukotrienes etc.
o EPA derived eicosanoids decrease the excessive production of prostaglandins associated with:
  - Inflammation
  - Platelet aggregation
  - Vasoconstriction
o LA-derived eicosanoids, particularly 2-series prostaglandins, are thought to do the opposite
  • DHA is the major PUFA found in the brain
    o It is required to produce resolvins
      - These are compounds that respond to cerebral inflammation
      - Particularly in the decrease of inflammation due to ischemia.
  • Visual representations of EPA and DHA pathways and the related compounds are shown in appendices A and B

Sources of Fish Oil and EPA/DHA

PUFAs are naturally found in fatty or oily fish\(^6\)
  • These include:
    o Mackerel, tuna, salmon, sturgeon, mullet, bluefish, anchovy, sardines, trout, menhaden
  • These provide about 1 g omega-3 fatty acids per 3.5 oz fish.
Fish oil capsules are also a source
  • Available via prescription or over the counter
  • Dietary Supplements\(^9\)
  • At least 2900 products available
  • Not FDA approved
    o However a number are USP verified
  • At least 11 USP verified
    o USP verification\(^10\)
    o Conducted by USP-NF
    o Ensures that the product:
      - Includes the ingredients listed
      - Contains no or a minimum quantity of harmful products.
      - Will release in the body within a certain time.
      - Is made according to good manufacturing practices (GMP)
  • USP verified products are either 1g or 1.2g
    o Concentrations range:
      - 300 – 410mg EPA
      - 240 – 720mg DHA
• However most products include a maximum of 476mg DHA per capsule

• Prescription
  o Lovaza®
  o Omega-3-acid ethyl esters
  o 1 g capsule containing approximately:
    ▪ 465 mg EPA
    ▪ 375 mg DHA
  o FDA approved for lowering triglycerides
  o Recommended to be taken as 4 g per day
    ▪ Provides daily dose of 1.86g EPA and 1.5g DHA
  o Approval
    o Double blind randomized controlled trial (RCT)
    o Included a total of 84 patients
    o 42 received Lovaza® and 42 received placebo
    o Patients had baseline triglycerides (TG) between 500 and 2000 mg/dL
    o Patients were followed for 16 weeks
    o Showed a statistically significant 45% decrease in TG
    o Effect on cardiovascular (CV) mortality and morbidity not evaluated.

Benefit

• The benefit of fish oil is believed to be greater if they are purified to contain primarily omega-3-acid ethyl esters (or omega-3 PUFAs)
• Specifically due to EPA and DHA.
  o Increased amount of EPA and DHA in this ester compared to typical fish oils

FDA Indication

• Treatment of severe hypertriglyceridemia
  o Triglycerides (TG) greater than 500
  o And as an adjunct to diet

Proposed uses

• Hyperlipidemia
• Prevention of coronary arteriosclerosis due to hypertriglyceridemia
• Heart failure
• Migraine prophylaxis

Dose

• Lowering triglycerides
  o 4 grams daily
  o Single or two equally divided doses
• Decreasing cardiovascular mortality
Doses range, but the following doses have been studied
- 0.3 – 6g EPA
- 0.6 – 3.7g DHA

Mechanism of Action (MOA)\(^1,6\)
- Not clear, possibilities:
  - Anti-inflammatory action
    - Through the production of anti-inflammatory eicosanoids
  - Anticoagulant action
    - Certain studies have found a prolongation in bleeding time with fish oil use\(^9\)
  - Possible antiarrhythmic effects
- Triglyceride lowering
  - Inhibition of acyl CoA:1,2 diacylglycerol acyltransferase
  - Increased peroxisomal beta-oxidation in the liver
  - Diminish TG synthesis due to poor substrate

Adverse Effects
- **Rare**
- LDL increases have been observed
  - There has been much speculation as to whether this actually occurs.
  - Many of these studies have been done in patients with excessively high triglyceride levels.
  - LDL calculations are typically confounded by high triglyceride values
- Alanine amino transferase (ALT) and aspartate aminotransferase (AST) increases
  - In patients with known hepatic impairment, periodic ALT and AST monitoring is recommended.
- **Caution in Atrial Fibrillation and Flutter**
  - This caution is due to trial that saw a statistically nonsignificant increase in recurrent atrial fibrillation or flutter along with fish oil administration
  - Patients had been randomized to receive placebo or 8 grams Lovaza® per day for 7 days then 4 grams a day for 23 weeks.
  - Despite lack of statistical significance, caution is still recommended
- **Common**
- Eructation (belching)
- Dyspepsia
- Taste perversion
• The above side effects can be decreased by freezing the supplements or taking with food.

Drug Interactions
• Anticoagulants
  o Some studies have shown a prolongation of bleeding time.
  o Has not been outside of normal ranges.
  o However may recommend periodic monitoring of patients on other anticoagulants

Evidence for Fish Oil in Lowering Cardiovascular Mortality

Trials to be reviewed:
• DART (1989)
• GISSI Prevenzione (1999)
• DART-2 (2003)
• JELIS (2007)
• Rizos, et al (2012)

DART: Diet and Reinfarction Trial (1989)
  • Published in Lancet.
  • One of the early major trials that looked at fish oil
  • Primary endpoints
    o All cause mortality
    o Sudden cardiac death
    o Myocardial infarction
  • Selection
    o Non-diabetic men
    o Less than 70 years
    o Recovery from myocardial infarction (MI) within the previous 2 years.
  • Population
    o 2033 Welsh men post-MI
    o mean age 56.5
    o Diet high in omega-6 fatty acids
  • Intervention
    o Randomly allocated to receive advice or no advice on:
      • Increase in fatty fish intake
Fish Oil and Cardiovascular Mortality

KFuller

- At least 2 portions each week
  - 200 – 400 g.
  - Reduced fat intake with increase in polyunsaturated fat:saturated fat
    - Follow up occurred after 2 years.
- Compliance
  - Monitored by dietary questionnaires
  - Plasma fatty acid questionnaires
  - Satisfactory with fish and fiber
  - Less so with fat
- Results
  - Fish advice
    - 29% decrease in 2-year all cause mortality.
  - Other advice
    - No significant effects
- Conclusion
  - Fish oil use post-MI improves cardiovascular outcomes.
- Reception
  - A lot of fervor
  - First major trial to show that fish oil could have an effect on cardiovascular mortality.
- Points to Note
  - Non-diabetic patients
    - May not relate to our patient population
  - All men
    - Currently more women die of cardiovascular disease per year than men.
  - Diet high in omega-6 fatty acids
  - Overall
    - Results can be extrapolated to our patients based on diet.
    - Difficulty appears in terms of disease state and gender.
GISSI-Prevenzione (1999)

- Published in Lancet
- Purpose to assess the effect of vitamin e, n-3 polyunsaturated fatty acids (PUFA) or a combination thereof on CV mortality and morbidity
- Primary endpoints
  - Combined endpoint: death, non-fatal MI and stroke
- Selection
  - Enrolled between 1993 and 1995
  - 3 months or less post-MI
  - no history of heart failure (HF)
- Population
  - 11,324 Italian patients
  - Mediterranean diet
- Intervention
  - 4 groups, each with roughly 2800 patients.
  - 300 mg Vitamin E daily
    - roughly 447 IU
  - 1 g PUFA daily
  - Both
  - None
  - Followed for 3.5 years
- Results
  - Vitamin E had no benefit
  - PUFA
    - Decrease in primary endpoint.
    - Relative risk 10% CI (1, 18) two-way analysis
    - RR 15% [2,26] 4-way analysis
    - Death
      - 2-way RR 14% [3,24]
      - 4-way RR 20% [6,24]
    - Cardiovascular death
      - 2-way RR 17% [3,29]
      - 4-way RR 30% [13,44]
  - Combined
    - Similar results
    - RR 14% [1,26]
    - Fatal events RR 20% [5,33]
2-way or 4-way?

Conclusion
- Statistically significant
- Clinically important effect

Reception
- Issues with the trial
  - When taken in combination with results from the DART trial, people felt that fish oil probably lowered the risk of cardiovascular death.

Points to Note
- Really wide confidence interval.
- With that large a population, difficulty establishing difference can be suspect.
- Patients already exposed to "Mediterranean diet"
  - Results may be skewed or not externally valid if in a population whose diet may already provide a cardioprotective effect.
DART-2: Diet and Angina Randomized Trial

- Published in the European Journal of Clinical Nutrition
- Selection
  - Male
  - Under 70 years
  - Stable angina
- Population
  - 3114 Welsh men
  - Mean age 61.1
- Intervention
  - Randomized to four groups
  - Received advice on eating oily fish or fruits and vegetables both or none.
  - Advice
    - Fish
      - 2-3 servings of oily fish per week OR
      - Up to 3 g fish oil per day
    - Fruits and vegetables
      - 4-5 servings per day
  - Followed for 3 – 9 years.
- Results
  - Advise to eat oily fish or take fish oil
    - No effect on all-cause mortality
    - Significant (p=0.018) increase in sudden cardiac death.
    - Largely confined to group given advice to take fish oil capsules (what does that mean?)
  - Advice to eat more fruits and vegetables
    - No effect
    - Thought to be due to poor compliance
- Conclusion
  - Results contradictory with DART
- Points to Note
  - Different patient population
    - DART looked at patients post-MI, who are more susceptible to arrhythmias and sudden death.
    - DART-2 looked at patients with stable angina
    - Possible DART patients would have been at higher risk and effect of fish oil would have been more visible.
Nutritional supplements not necessarily same results as the foods from which they are derived.

**JELIS (2007)**

- Published in Lancet
- Yokoyama and colleagues
- **Purpose**
  - Efficacy of EPA in coronary prevention in patients with hypercholesterolemia who already consume fish.
- **Primary endpoint**
  - Any major coronary event
- **Selection**
  - Recruited 1996 – 1999
  - Men 40 – 75
  - Postmenopausal women over 75
- **Population**
  - 18,645 Japanese patients
  - Mean age 61 years
  - 69% women
  - Baseline disease states
    - Hypertension 36%
    - Diabetes 15%
    - Coronary artery disease (CAD) 20%
- **Intervention**
  - All patients received statin
    - Randomized to receive
      - Pravastatin 10 mg
      - Simvastatin 5 mg
    - Further randomization
      - Statin only
      - Statin plus 1800 mg EPA daily
  - Followed for 5 years.
- **Results**
  - Sudden cardiac death
    - No difference
  - Major coronary events
    - 18% reduction, p = 0.132
Subgroup with history of CAD
  - 19% reduction  p = 0.048

Unstable angina
  - 28% reduction,  p = 0.019
  - Seen only in patients being treated for secondary prevention

**Conclusion**
- EPA is promising for the prevention of major cardiac events.
- Effect greater on non-fatal events

**Points to Note**
- Concerns about population used
  - Results may not be externally valid when used in a population that consumes recommended daily amounts of fish at baseline.
- If useful, may be greater for secondary prevention.
Meta-analysis, Rizos, et al. (2012)


- Outcomes
  - All-cause mortality
  - Cardiac death
  - Sudden death
  - Myocardial infarction
  - Stroke

- Study Selection
  - Randomized controlled trials
    - Control using another diet or placebo.
  - Included open-label trials
    - Later conducted a sensitivity analysis excluding them.
  - Exclusion criteria
    - Treatment duration less than one year

- Methods
  - Data extraction performed by 2 authors
  - Screened independently by another.
  - Assessed studies for:
    - Selection bias
    - Randomization and allocation concealment
    - Blinding
    - Loss to follow-up and use of intention-to-treat principles
  - 3635 studies reviewed, 20 analyzed
  - 68,680 randomized patients

- Results
  - All cause mortality
    - No significant difference
  - Cardiac death
    - RR 0.91 [0.85,0.96]
  - Sudden death
    - Not significant
  - Myocardial infarction
    - Not significant
Summary

- Stroke
  - Not significant

Conclusion
- PUFA's not associated with decreased risk:
  - All-cause mortality
  - Cardiac death
  - Sudden death
  - Myocardial infarction
  - Stroke
- On both relative and absolute measures of reduction.

Review of Trials

Meta-Analysis

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<th>Outcome</th>
<th>Studies</th>
<th>Events</th>
<th>Participants</th>
<th>RR (95% CI)</th>
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<tbody>
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<td>All-cause mortality</td>
<td>17</td>
<td>63935</td>
<td>83279</td>
<td>0.96 (0.91-1.02)</td>
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Experimental Trials

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<th>Outcome</th>
<th>No. of Events</th>
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<td>All-cause mortality</td>
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<td>262</td>
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Interpretation
- If there is some benefit provided
  - Towards cardiac death
  - Marginal at best

Effect on clinical practice
- Providers might still continue to prescribe
- Best if prescribed to patients with high triglycerides

What would you tell your grandmother?
- There is a small chance taking fish oil daily may have a positive effect.
  - Especially if you have had a coronary event in the past.
- However by and large:
  - It is unlikely to help protect your heart.
References


Appendix A

Biologic action of certain omega-3 fatty acids
Appendix B
Involvement of resolvins in inflammation

Figure 1 While it reviews pain as well as inflammation, the below image gives good detail on resolvins and their role in inflammation.

INFLAMMATION, PAIN, AND RESOLVINS
Not all inflammation leads to pain. Despite widespread infection followed by fever, colds rarely cause pain. But when some cytokines and certain immune cells are active near pain-sensing nerves, they trigger receptors that convey pain sensations to the brain. Resolvins are naturally produced part-way into an inflammatory reaction, and help diminish inflammation as well as pain.

THE BASICS OF INFLAMMATORY PAIN
Upon injury or infection, inflammatory mediators such as prostaglandins are released by the damaged cells 1. These mediators cause nearby blood vessels to dilate and become porous, allowing immune cells to pass from the blood into the tissue 2. Neutrophils, one of the first immune responders, engulf and kill the invading microbes 3 and release more inflammatory cytokines, such as prostaglandins and TNF-α, amplifying the response 4. When the cellular damage occurs near a nerve cell, some of the inflammatory signals can trigger receptors on nerve endings, sending pain signals to the brain 5.

REDUCING INFLAMMATION AND PAIN
Several hours after initial inflammation, neutrophils begin to convert prostaglandins into lipoxins, resolvins, and protectins. Aspirin can speed this process by converting omega-3 fatty acids into these resolution factors. Together they block the penetration of additional neutrophils from the blood into the tissue 6, while attracting other immune cells, called macrophages, to clean up and remove the damaged tissue and dying neutrophils 7. The resolution mediators also block the production of additional inflammatory cytokines 8. Resolving factors reduce the pain signaled by the nerve endings by reducing the level of inflammatory cytokines and by indirectly inhibiting neuronal receptors that convey pain 9.