# Swimming Upstream on Omega-3 Recommendations for Cardiovascular Health: Recent Research Finds Recommended Dosages May Not be Enough

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1

## Fish Oil /Omega-3 Lavie COI/Disclosures

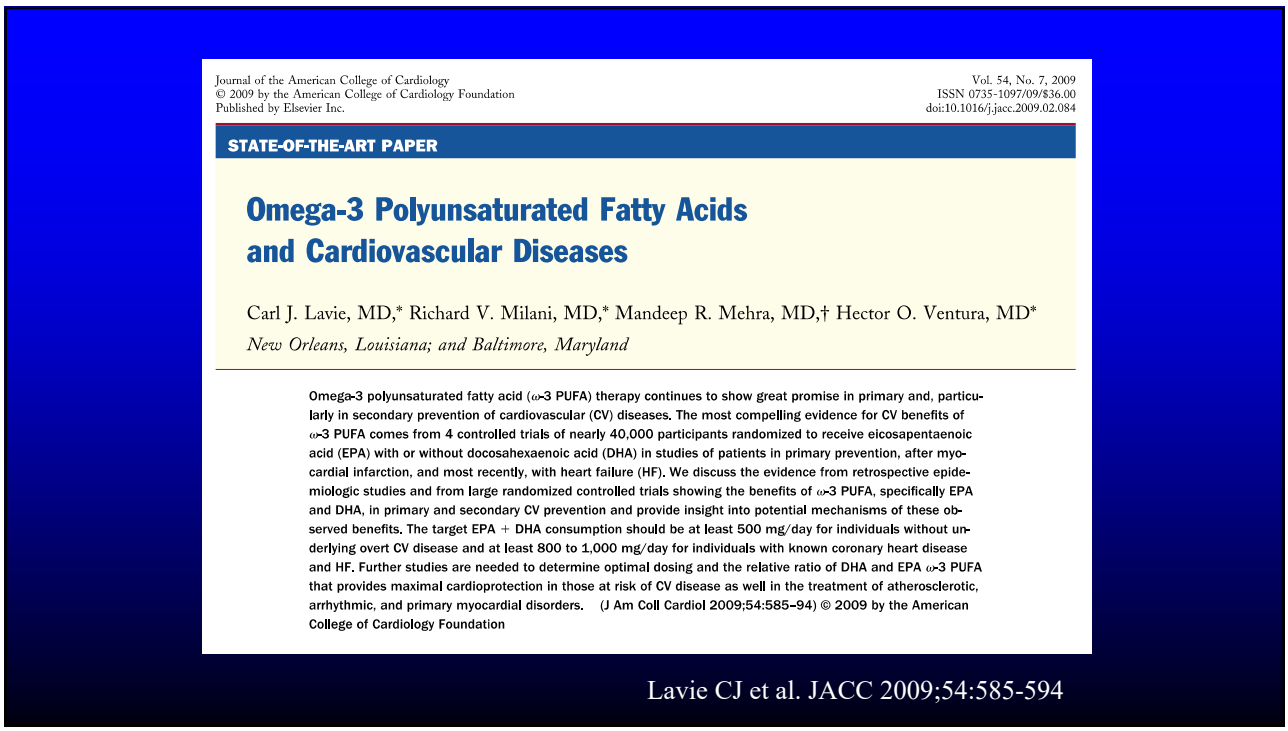
Speaker and Consultant for GOED and DSM and in the past for Amarin

2

# Omega-3 and CV Diseases- Learning Objectives

- Identify CVD outcomes related to Omega-3 /EPA and DHA intakes
- Translate Omega-3 Science into Clinical Practice , including assessments and interventions
- Distinguish between plant- and marine-based omega-3 and why the latter probably needs more emphasis than the former

3



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STATE-OF-THE-ART PAPER

# Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Diseases

Carl J. Lavie, MD,* Richard V. Milani, MD,* Mandeep R. Mehra, MD,† Hector O. Ventura, MD*
*New Orleans, Louisiana; and Baltimore, Maryland*

Omega-3 polyunsaturated fatty acid (ω-3 PUFA) therapy continues to show great promise in primary and, particularly in secondary prevention of cardiovascular (CV) diseases. The most compelling evidence for CV benefits of ω-3 PUFA comes from 4 controlled trials of nearly 40,000 participants randomized to receive eicosapentaenoic acid (EPA) with or without docosahexaenoic acid (DHA) in studies of patients in primary prevention, after myocardial infarction, and most recently, with heart failure (HF). We discuss the evidence from retrospective epidemiologic studies and from large randomized controlled trials showing the benefits of ω-3 PUFA, specifically EPA and DHA, in primary and secondary CV prevention and provide insight into potential mechanisms of these observed benefits. The target EPA + DHA consumption should be at least 500 mg/day for individuals without underlying overt CV disease and at least 800 to 1,000 mg/day for individuals with known coronary heart disease and HF. Further studies are needed to determine optimal dosing and the relative ratio of DHA and EPA ω-3 PUFA that provides maximal cardioprotection in those at risk of CV disease as well in the treatment of atherosclerotic, arrhythmic, and primary myocardial disorders. (J Am Coll Cardiol 2009;54:585–94) © 2009 by the American College of Cardiology Foundation

Lavie CJ et al. JACC 2009;54:585-594

4

# Fish Oil In Cardiovascular Prevention

**Fish oil is a *whale* of a story that not surprisingly gets *bigger* with every telling.**

Rogans JA. N Engl J Med 1987;316:626-627

5

6

# Daily Intake

| | Moderns | Foragers |
|---|---|---|
| Cholesterol | 200-300 mg | 500 mg |
| Fats | 30% | 35% |
| Saturated Fats | 14% | 7% |
| Omega-3 | 110 mg | 660 – 3000 mg |

7

# Norway: Exceptional Life Expectancy

8

# Omega-3 and CV Diseases

- Fish oil is obtained in human diet by eating oily fish (eg herring, mackerel, salmon, albacore tuna, sardines) or by fish oil supplements
- Fish do not naturally produce these oils, but they obtain them from micro-organisms

Lavie CJ et al. JACC 2009;54:585-594.

9

# Omega-3 and Cardiovascular Diseases

| Family* | Fatty Acids | Formula† | Source |
|---|---|---|---|
| I omega-9 | Oleic acid | C18:1 | Most vegetable oils (canola, olive); animal fats |
| II omega-6 | Linoleic acid | C18:2 | Many vegetable oils (corn, safflower, soybean) |
| | Arachidonic acid | C20:4 | Poultry, meats |
| III omega-3 | α-linolenic acid | C18:3 | Selected vegetable oil (flaxseed, canola) |
| | EPA | C20:5 | Marine oils and fish |
| | DHA | C22:6 | Marine oils and fish |
| IV saturated fats | Palmitic acid | C16:0 | Animal and vegetable fats |
| | Stearic acid | C18:0 | Butter, palm oil, kernel oil, coconut oil, and animal fats |

*The omega number refers to the position of the first double bond from the methyl end of the molecule. †The notation shows the total number of carbon atoms and total number of double bonds. Adapted with permission from Lavie et al. (2).
DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid.

Lavie CJ et al. JACC 2009;54:585-594.

# Omega-3 and CV Diseases

**Background:**

- **Sinclair in 1944 described the rarity of CHD in Greenland Eskimos, who ate a diet high in whale, seal and fish**
- **Bang and Dyerberg in the 70s described the diet and risk of MI in Greenland Eskimos compared with Danes**
- **Data from Japan, Holland, Norway and the US have extended this seminal work**

Lavie CJ et al. JACC 2009;54:585-594.

## Cardiovascular Diseases That May Benefit From Omega-3 Polyunsaturated Fatty Acids

- Post MI
- Hypercholesterolemia
- Heart Failure
- Hypertriglyceridemia
- Atherosclerosis
- Atrial Fibrillation
- Complex Ventricular Arrhythmias
- Hypertension

Lavie CJ et al. J Am Coll Cardiol 2009;54:585-594.

12

# Potential EPA and DHA Effects

- Anti-arrhythmic Effects
- Improvements in Autonomic Function
- Decreased Platelet Aggregation
- Vasodilation
- Decreased Blood Pressure
- Anti-inflammatory Effects
- Improvements in Endothelial Function
- Plaque Stabilization
- Reduced Atherosclerosis
- Reduced Free Fatty Acids and Triglycerides
- Up-regulate Adiponectin Synthesis
- Reduces Collagen Deposition

Lavie CJ et al. J Am Coll Cardiol 2009;54:585-594.

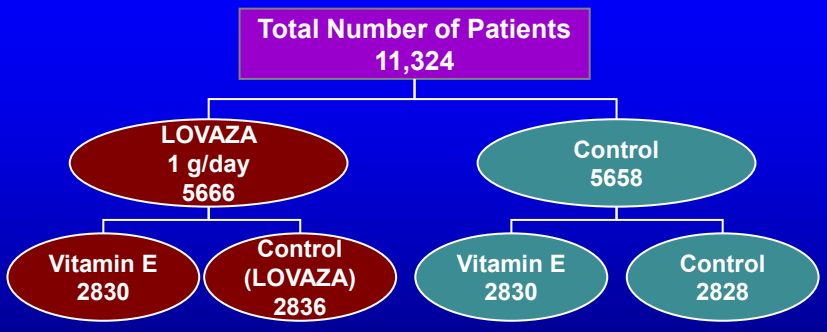
# Omega-3 and CVD – Trends in CHD

- DART
- GISSI – Prevenzione
- JELIS

Lavie CJ et al. JACC 2009;54:585-594.

14

# The GISSI-Prevenzione Trial: Post MI




» Hard endpoints. Duration: 3.5 years (start 1993). Patients post-MI within 3 months

- 172 centers in Italy involved, managed by the Mario Negri Institute
- The effect of LOVAZA on the risk of pancreatitis in patients with very high TG levels has not been evaluated. The effect of LOVAZA on cardiovascular mortality and morbidity in patients with very high TG levels has not been determined

GISSI=Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico;
MI=myocardial infarction.

GISSI-Prevenzione Investigators [published correction appears in *Lancet*. 2001;357:642]. *Lancet*. 1999;354:447-455.

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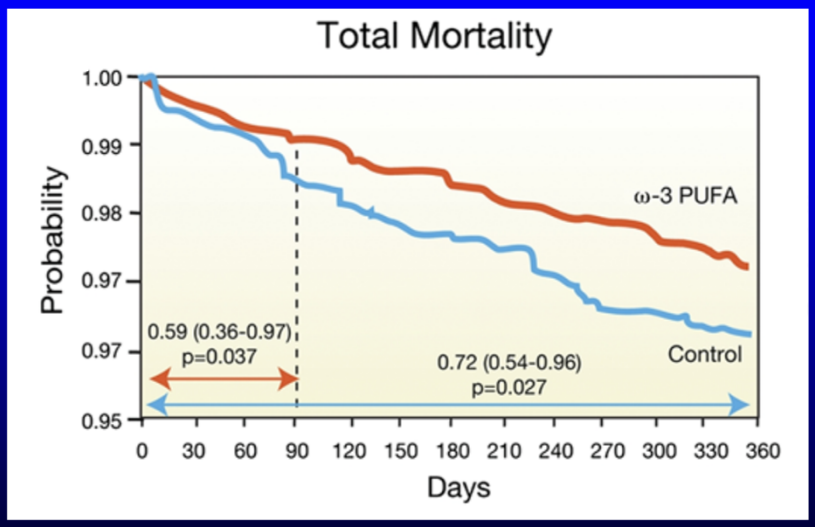
## Fish Oil and Post-MI Prognosis-The GISSI Prevenzione




Marchioli R et al. Circulation 2002;105:1897-1903.

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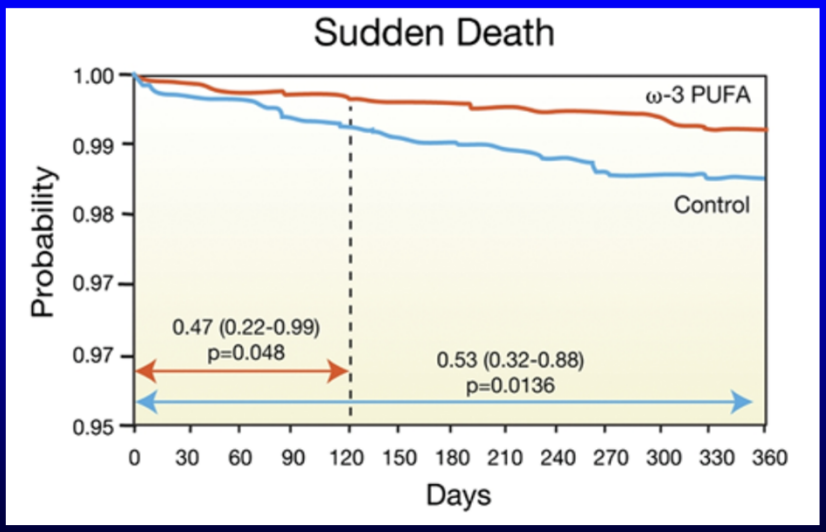
## Fish Oil and Post-MI Prognosis-The GISSI Prevenzione




Marchioli R et al. Circulation 2002;105:1897-1903.

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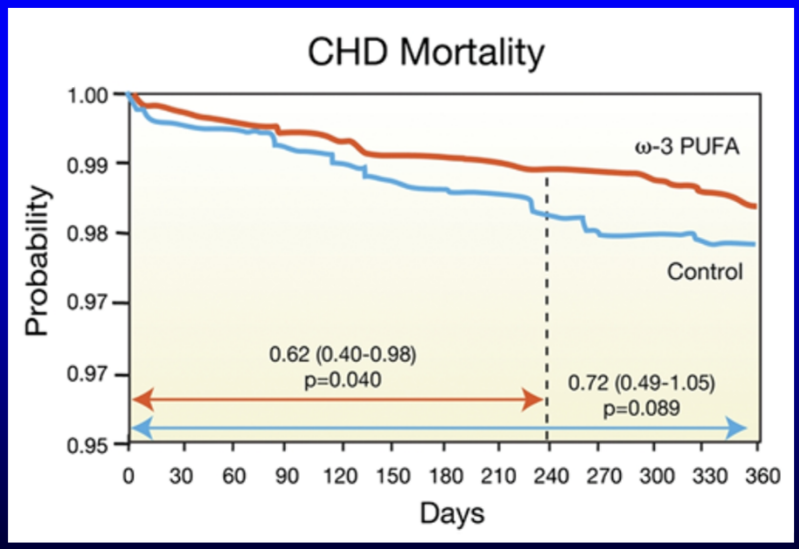
## Fish Oil and Post-MI Prognosis-The GISSI Prevenzione




Marchioli R et al. Circulation 2002;105:1897-1903.

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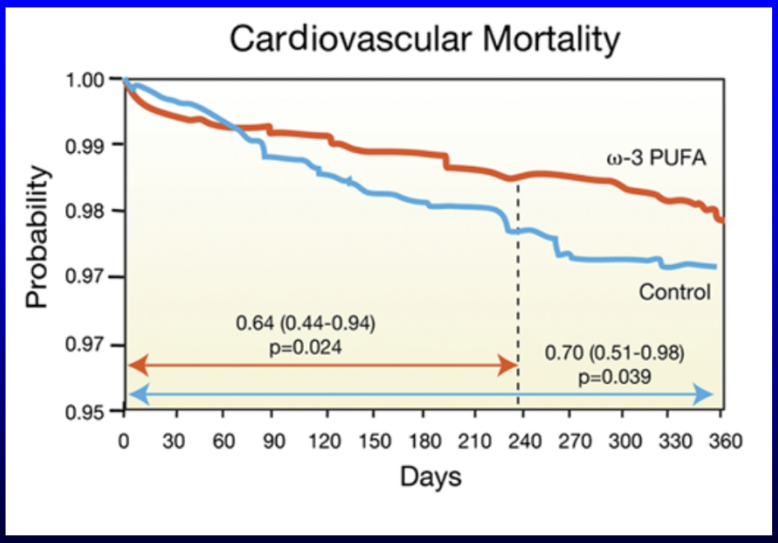
## Fish Oil and Post-MI Prognosis-The GISSI Prevenzione




Marchioli R et al. Circulation 2002;105:1897-1903.

19

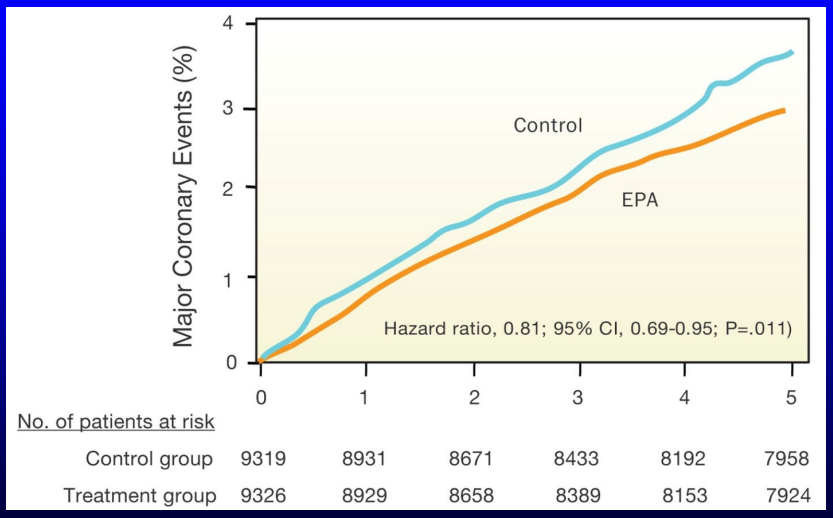
## Omega-3 and CVD - JELIS

- 18,645 patients (14,981 primary prevention and 3,664 secondary prevention)
- Statin alone or statin and EPA 1,800 mg/d
- EPA had 19% reduction in major CV events
- No reduction in SCD

Yokoyama M et al. Lancet 2007;369:1090-1098

20

# EPA in Primary Prevention




Yokoyama M et al. *Lancet* 2007;369:1090-1098.

21

# Japan EPA Lipid Intervention Study - JELIS

(Yokoyama et al. Lancet 2007;369:1090-98)

**18,645 Japanese (70% women, 61 yrs) randomized to statin alone or statin+EPA (1.8 g/d) and followed for 5 years**

Entire Cohort N=18,645 | 1[a] Prevention=14,981 | 2[a] Prevention=3,664

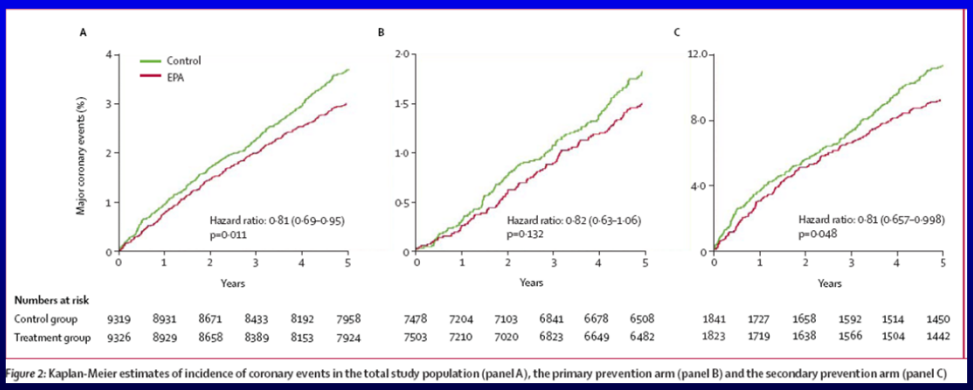



*Figure 2:* Kaplan-Meier estimates of incidence of coronary events in the total study population (panel A), the primary prevention arm (panel B) and the secondary prevention arm (panel C)

MCE = Major coronary events were considered to be sudden cardiac death, fatal and nonfatal MI, unstable AP, and angioplasty/stenting or CABG



22

# JELIS – EPA blood level and CHANGE in Risk

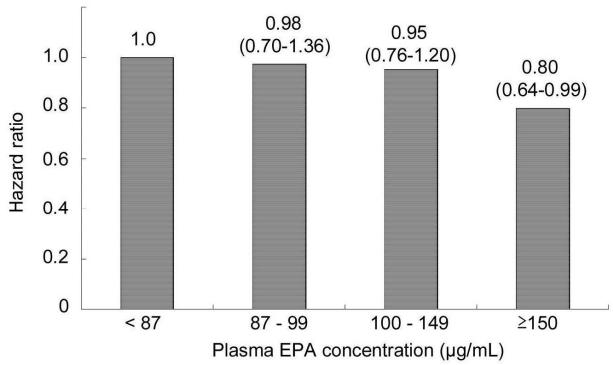



**Fig. 3.** Relationship between on-treatment EPA concentration and adjusted risk of major coronary events.

Itakura H et al. J Athero and Thrombo 2011;18:99-107

## Omega-3 and CHD

- Many other positive studies
- Negative studies, notably OMEGA trial and recent margarine study in NEJM
- Some studies were underpowered, underdosed or both

Lavie CJ et al. JACC 2009;54:585-594.

# Omega-3 and CVD – What About ALA?

- ALA is found in flaxseed, canola, olive oil, walnuts, other tree nuts, and in trace amounts in green leafy vegetables
- Humans typically convert <5% of ALA to EPA and much less to DHA
- Some studies with ALA have been positive, whereas many are negative
- Overall evidence is much less than for EPA and DHA

Lavie CJ et al. JACC 2009;54:585-594.

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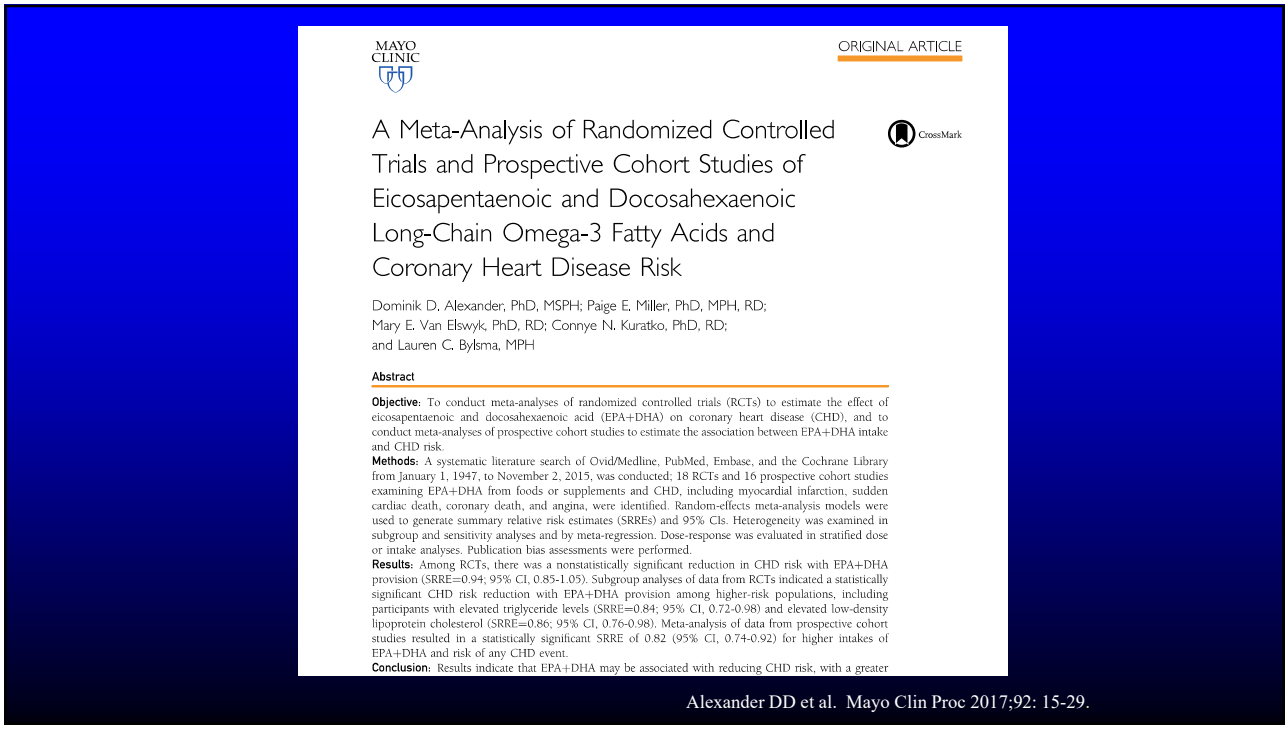


MAYO CLINIC

ORIGINAL ARTICLE

# A Meta-Analysis of Randomized Controlled Trials and Prospective Cohort Studies of Eicosapentaenoic and Docosahexaenoic Long-Chain Omega-3 Fatty Acids and Coronary Heart Disease Risk

Dominik D. Alexander, PhD, MSPH; Paige E. Miller, PhD, MPH, RD; Mary E. Van Elswyk, PhD, RD; Connye N. Kuratko, PhD, RD; and Lauren C. Bylsma, MPH

**Abstract**

**Objective:** To conduct meta-analyses of randomized controlled trials (RCTs) to estimate the effect of eicosapentaenoic and docosahexaenoic acid (EPA+DHA) on coronary heart disease (CHD), and to conduct meta-analyses of prospective cohort studies to estimate the association between EPA+DHA intake and CHD risk.

**Methods:** A systematic literature search of Ovid/Medline, PubMed, Embase, and the Cochrane Library from January 1, 1947, to November 2, 2015, was conducted; 18 RCTs and 16 prospective cohort studies examining EPA+DHA from foods or supplements and CHD, including myocardial infarction, sudden cardiac death, coronary death, and angina, were identified. Random-effects meta-analysis models were used to generate summary relative risk estimates (SRREs) and 95% CIs. Heterogeneity was examined in subgroup and sensitivity analyses and by meta-regression. Dose-response was evaluated in stratified dose or intake analyses. Publication bias assessments were performed.

**Results:** Among RCTs, there was a nonstatistically significant reduction in CHD risk with EPA+DHA provision (SRRE=0.94; 95% CI, 0.85-1.05). Subgroup analyses of data from RCTs indicated a statistically significant CHD risk reduction with EPA+DHA provision among higher-risk populations, including participants with elevated triglyceride levels (SRRE=0.84; 95% CI, 0.72-0.98) and elevated low-density lipoprotein cholesterol (SRRE=0.86; 95% CI, 0.76-0.98). Meta-analysis of data from prospective cohort studies resulted in a statistically significant SRRE of 0.82 (95% CI, 0.74-0.92) for higher intakes of EPA+DHA and risk of any CHD event.

**Conclusion:** Results indicate that EPA+DHA may be associated with reducing CHD risk, with a greater

Alexander DD et al. Mayo Clin Proc 2017;92: 15-29.

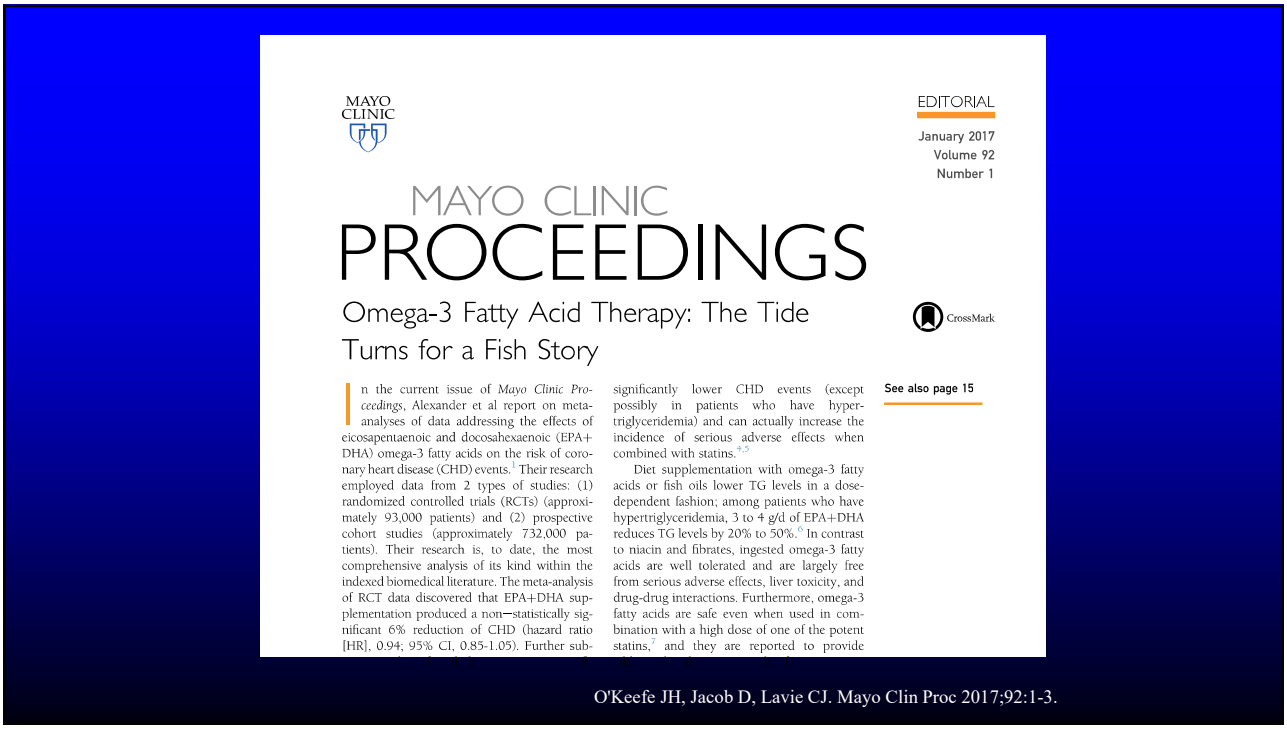
## Meta-Analysis to Estimate the Effect of EPA and DHA on Coronary Heart Disease (CHD)

- The meta-analysis used data from 18 randomized controlled trials (RCTs) and 17 prospective cohort studies, and is to date, the most comprehensive quantitative analysis of its kind, within peer reviewed literature.

- Findings:
  - A significant 18% risk reduction of CHD in the prospective cohort studies
  - Sub-group analysis of the RCTs in higher risk populations:
    - Reduced CHD risk by 16% in people with elevated blood levels of triglycerides (>150mg/dL)
    - Reduce CHD risk by 14% in people with elevated LDL-cholesterol (>130 mg/dL)

- The resulting coverage by media reached more than 100 million people and included stories on Time.com, Fox News and MSN and in countries as diverse as India, France, the UK, Romania, Qatar and Vietnam.

27



MAYO CLINIC

EDITORIAL

January 2017
Volume 92
Number 1

MAYO CLINIC
PROCEEDINGS

## Omega-3 Fatty Acid Therapy: The Tide Turns for a Fish Story

CrossMark

In the current issue of *Mayo Clinic Proceedings*, Alexander et al report on meta-analyses of data addressing the effects of eicosapentaenoic and docosahexaenoic (EPA+DHA) omega-3 fatty acids on the risk of coronary heart disease (CHD) events.[1] Their research employed data from 2 types of studies: (1) randomized controlled trials (RCTs) (approximately 93,000 patients) and (2) prospective cohort studies (approximately 732,000 patients). Their research is, to date, the most comprehensive analysis of its kind within the indexed biomedical literature. The meta-analysis of RCT data discovered that EPA+DHA supplementation produced a non–statistically significant 6% reduction of CHD (hazard ratio [HR], 0.94; 95% CI, 0.85-1.05). Further subsignificantly lower CHD events (except possibly in patients who have hypertriglyceridemia) and can actually increase the incidence of serious adverse effects when combined with statins.[4,5]

Diet supplementation with omega-3 fatty acids or fish oils lower TG levels in a dose-dependent fashion; among patients who have hypertriglyceridemia, 3 to 4 g/d of EPA+DHA reduces TG levels by 20% to 50%.[6] In contrast to niacin and fibrates, ingested omega-3 fatty acids are well tolerated and are largely free from serious adverse effects, liver toxicity, and drug-drug interactions. Furthermore, omega-3 fatty acids are safe even when used in combination with a high dose of one of the potent statins,[7] and they are reported to provide

See also page 15

O'Keefe JH, Jacob D, Lavie CJ. Mayo Clin Proc 2017;92:1-3.



28

Journal of Clinical Lipidology (2017) 11, 1152–1160

Journal of Clinical Lipidology

Original Articles

# Use of supplemental long-chain omega-3 fatty acids and risk for cardiac death: An updated meta-analysis and review of research gaps

**Kevin C. Maki, PhD, CLS, FNLA*, Orsolya M. Palacios, RD, PhD, Marjorie Bell, BS, Peter P. Toth, MD, PhD, FNLA**

*Midwest Biomedical Research, Center for Metabolic and Cardiovascular Health, Glen Ellyn, IL, USA (Drs Maki, Palacios, and Bell); CGH Medical Center, Sterling, IL, USA (Dr Toth); and Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins University School of Medicine, Baltimore, MD, USA (Dr Toth)*

**KEYWORDS:**
Omega-3 fatty acids;
Fish oil;
Eicosapentaenoic acid;
EPA;
Docosahexaenoic acid;
DHA;
Cardiac death;
Meta-analysis

**BACKGROUND:** Randomized controlled trials (RCTs) assessing use of long-chain omega-3 polyunsaturated fatty acids (LC-OM3), primarily eicosapentaenoic acid, and/or docosahexaenoic acid have shown mixed results.

**OBJECTIVE:** The objectives of the study were to update and further explore the available RCT data regarding LC-OM3 supplementation and risk for cardiac death and to propose testable hypotheses for the mixed results obtained in RCTs regarding supplemental LC-OM3 use and cardiac risk.

**METHODS:** A literature search was conducted using PubMed and Ovid/MEDLINE for RCTs assessing LC-OM3 supplements or pharmaceuticals with intervention periods of at least 6 months and reporting on the outcome of cardiac death. Meta-analysis was used to compare cumulative frequencies of cardiac death events between the LC-OM3 and control groups, including sensitivity and subset analyses.

**RESULTS:** Fourteen RCTs were identified for the primary analysis (71,899 subjects). In the LC-OM3 arms, 1613 cardiac deaths were recorded (4.48% of subjects), compared with 1746 cardiac deaths in the control groups (4.87% of subjects). The pooled relative risk estimate showed an 8.0% (95% confidence interval 1.6%, 13.9%, $P = .015$) lower risk in the LC-OM3 arms vs controls. Subset analyses showed numerically larger effects (12.9%–29.1% lower risks, all $P < .05$) in subsets of RCTs with eicosapentaenoic acid + docosahexaenoic acid dosages >1 g/d and higher risk samples (secondary prevention, baseline mean or median triglycerides ≥150 mg/dL, low-density lipoprotein cholesterol ≥130 mg/dL, statin use <40% of subjects). Heterogeneity was low ($I^2 \leq 15.5\%$, $P > .05$) for the primary and subset analyses.

**CONCLUSION:** LC-OM3 supplementation is associated with a modest reduction in cardiac death.


Maki KC et al.Journal of Clinical Lipidology 2017; 11: 1152–1160

29

## Omega-3 Reduces Cardiac Death

- 14 RCT's in close to 72,000 for cardiac death
- 8% reduction in cardiac mortality with omega-3
- 13-16% reductions in cardiac mortality in higher risk due to higher LDL, TGs, or lower use of statins

Maki KC et al. Journal of Clinical Lipidology 2017; 11: 1152-1160

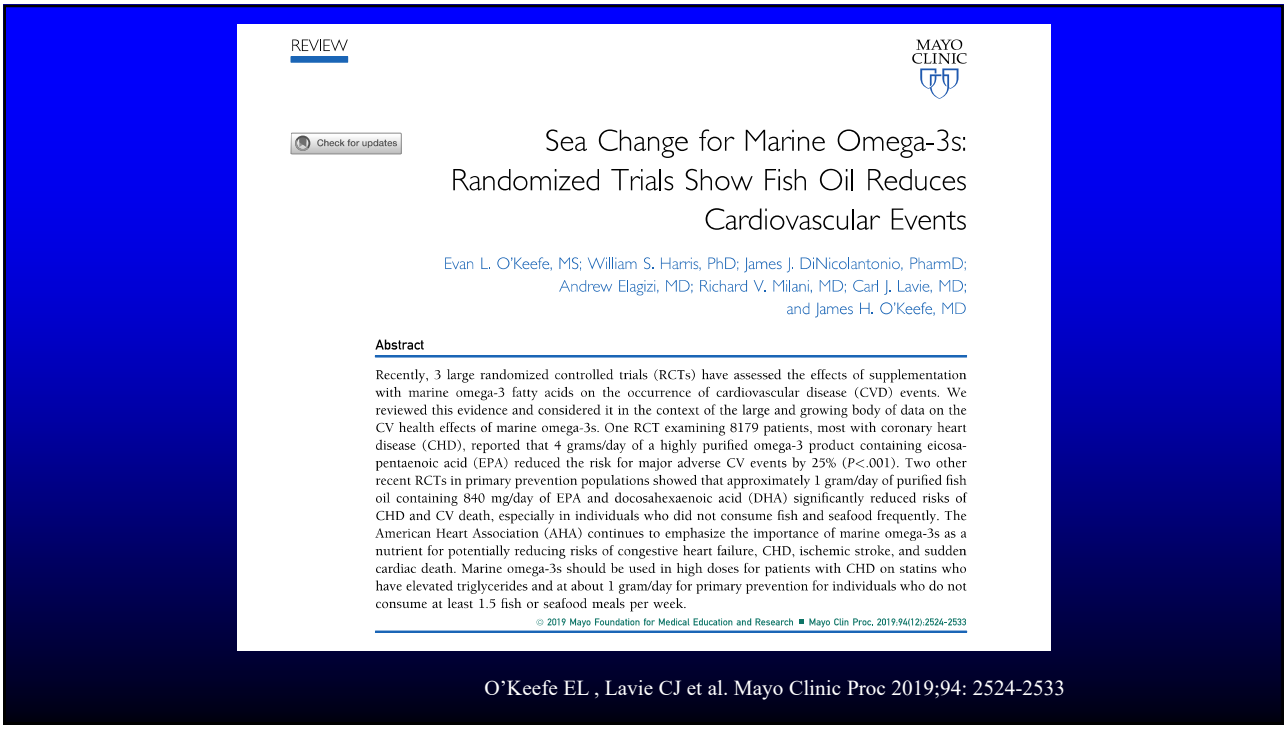
30

## Recent Major Omega-3 Meta-Analyses

- Abdelhamid et al Cochrane Analysis reported no significant effect
- Rizos et al in JAMA finds protective effect using usual p-value cut-off of 0.05, but dismisses it as "uncertain" using very conservative multiple hypothesis corrections and very strong p-value cut-points
- Maki et al finds a statistically significant effect

Lavie CJ et al. Submitted 2019

31



REVIEW

MAYO CLINIC

Check for updates

# Sea Change for Marine Omega-3s: Randomized Trials Show Fish Oil Reduces Cardiovascular Events

Evan L. O'Keefe, MS; William S. Harris, PhD; James J. DiNicolantonio, PharmD; Andrew Elagizi, MD; Richard V. Milani, MD; Carl J. Lavie, MD; and James H. O'Keefe, MD

**Abstract**

Recently, 3 large randomized controlled trials (RCTs) have assessed the effects of supplementation with marine omega-3 fatty acids on the occurrence of cardiovascular disease (CVD) events. We reviewed this evidence and considered it in the context of the large and growing body of data on the CV health effects of marine omega-3s. One RCT examining 8179 patients, most with coronary heart disease (CHD), reported that 4 grams/day of a highly purified omega-3 product containing eicosapentaenoic acid (EPA) reduced the risk for major adverse CV events by 25% ($P<.001$). Two other recent RCTs in primary prevention populations showed that approximately 1 gram/day of purified fish oil containing 840 mg/day of EPA and docosahexaenoic acid (DHA) significantly reduced risks of CHD and CV death, especially in individuals who did not consume fish and seafood frequently. The American Heart Association (AHA) continues to emphasize the importance of marine omega-3s as a nutrient for potentially reducing risks of congestive heart failure, CHD, ischemic stroke, and sudden cardiac death. Marine omega-3s should be used in high doses for patients with CHD on statins who have elevated triglycerides and at about 1 gram/day for primary prevention for individuals who do not consume at least 1.5 fish or seafood meals per week.

 ■ Mayo Clin Proc. 2019;94(12):2524-2533

O'Keefe EL , Lavie CJ et al. Mayo Clinic Proc 2019;94: 2524-2533

32

# Recent Major Omega-3 RCTs

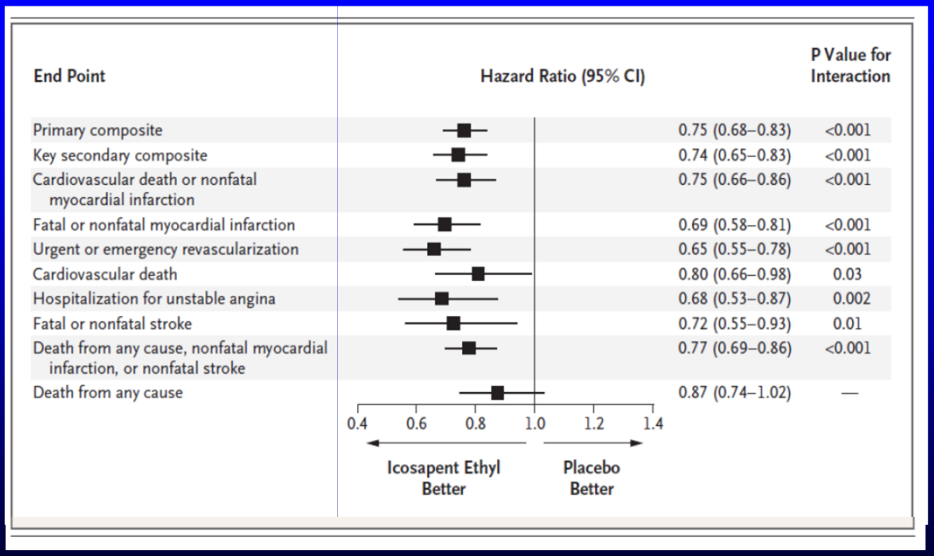
## NEJM

- REDUCE-IT-probably the strongest of all recent lipid trials with agents added to statins
- VITAL-reported as negative , but with some important CHD findings
- ASCEND-also reported as negative in a DM cohort but with some important vascular findings

O'Keefe EL, Lavie CJ et al. Mayo Clinic Proc 2019,;94:2524-2533

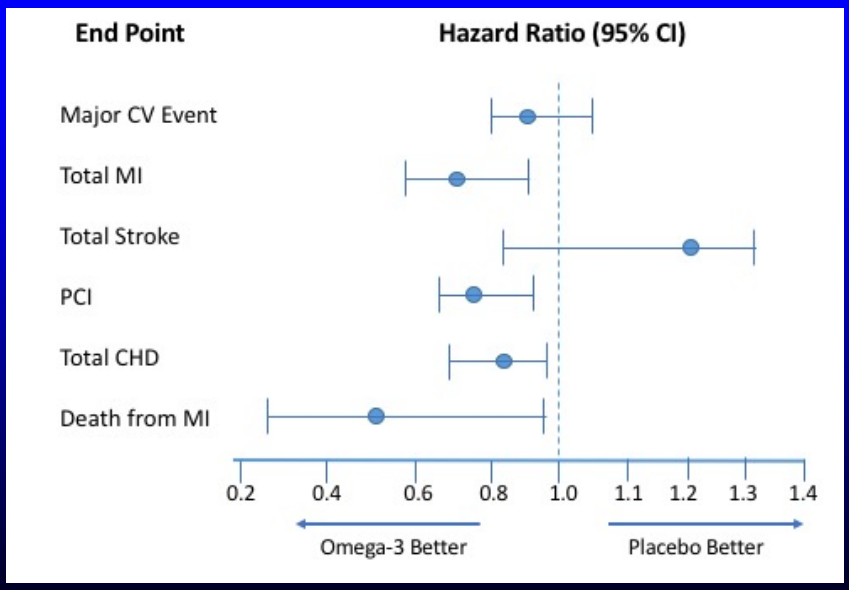
33

# Benefits of EPA in REDUCE-IT




Bhatt DL et al. NEJM 2018;380:11-22

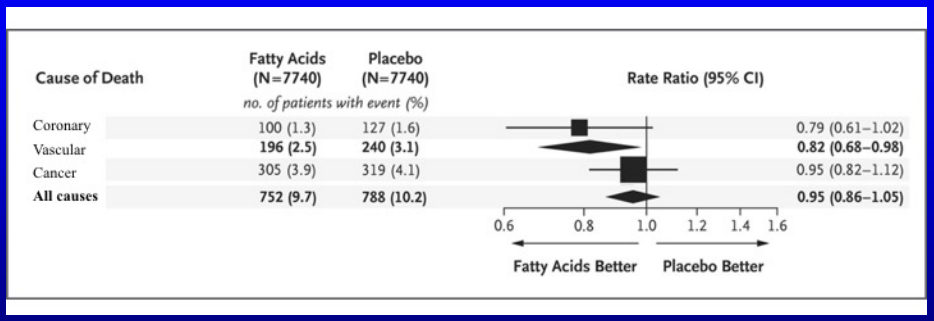
# Benefits of Omega-3 in VITAL




Manson JE et al. NEJM 2018; 380: 23-32

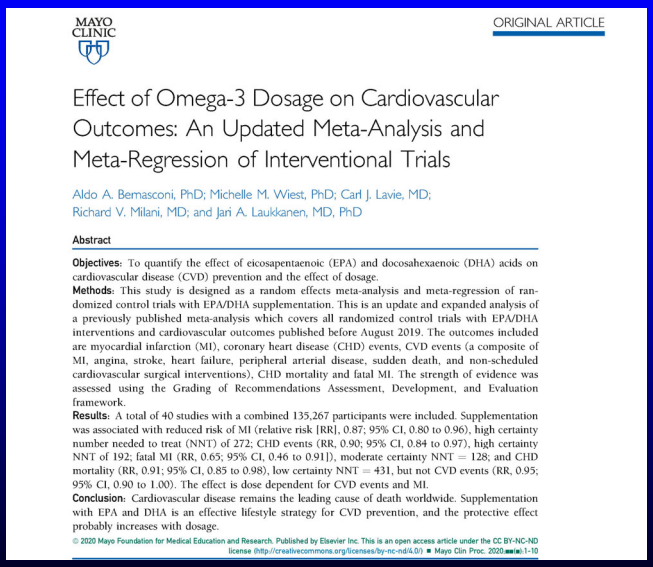
35

# Benefits of Omega-3 in ASCEND




Bowmam L et al. NEJM 2018; 379:1540-1550

# Omega-3 and Major Cardiovascular Outcomes



MAYO CLINIC

ORIGINAL ARTICLE

## Effect of Omega-3 Dosage on Cardiovascular Outcomes: An Updated Meta-Analysis and Meta-Regression of Interventional Trials

Aldo A. Bernasconi, PhD; Michelle M. Wiest, PhD; Carl J. Lavie, MD; Richard V. Milani, MD; and Jari A. Laukkanen, MD, PhD

**Abstract**

**Objectives:** To quantify the effect of eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids on cardiovascular disease (CVD) prevention and the effect of dosage.

**Methods:** This study is designed as a random effects meta-analysis and meta-regression of randomized control trials with EPA/DHA supplementation. This is an update and expanded analysis of a previously published meta-analysis which covers all randomized control trials with EPA/DHA interventions and cardiovascular outcomes published before August 2019. The outcomes included are myocardial infarction (MI), coronary heart disease (CHD) events, CVD events (a composite of MI, angina, stroke, heart failure, peripheral arterial disease, sudden death, and non-scheduled cardiovascular surgical interventions), CHD mortality and fatal MI. The strength of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation framework.

**Results:** A total of 40 studies with a combined 135,267 participants were included. Supplementation was associated with reduced risk of MI (relative risk [RR], 0.87; 95% CI, 0.80 to 0.96), high certainty number needed to treat (NNT) of 272; CHD events (RR, 0.90; 95% CI, 0.84 to 0.97), high certainty NNT of 192; fatal MI (RR, 0.65; 95% CI, 0.46 to 0.91]), moderate certainty NNT = 128; and CHD mortality (RR, 0.91; 95% CI, 0.85 to 0.98), low certainty NNT = 431, but not CVD events (RR, 0.95; 95% CI, 0.90 to 1.00). The effect is dose dependent for CVD events and MI.

**Conclusion:** Cardiovascular disease remains the leading cause of death worldwide. Supplementation with EPA and DHA is an effective lifestyle strategy for CVD prevention, and the protective effect probably increases with dosage.

 ■ Mayo Clin Proc. 2020;■(■):1-10

Benasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2021;96:304-313



37

# Meta-Analysis of Omega-3 RCTs of Supplements

- Updated additional studies since April 2017 after Abdelhamid et al and assessed Dosage Effects
- Only included RCTs of dietary supplements, not just dietary advice
- MI, CHD events, fatal MI, CHD death, CVD events
- 40 studies of 135,267 participants

Bernasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2021; 96:304-313

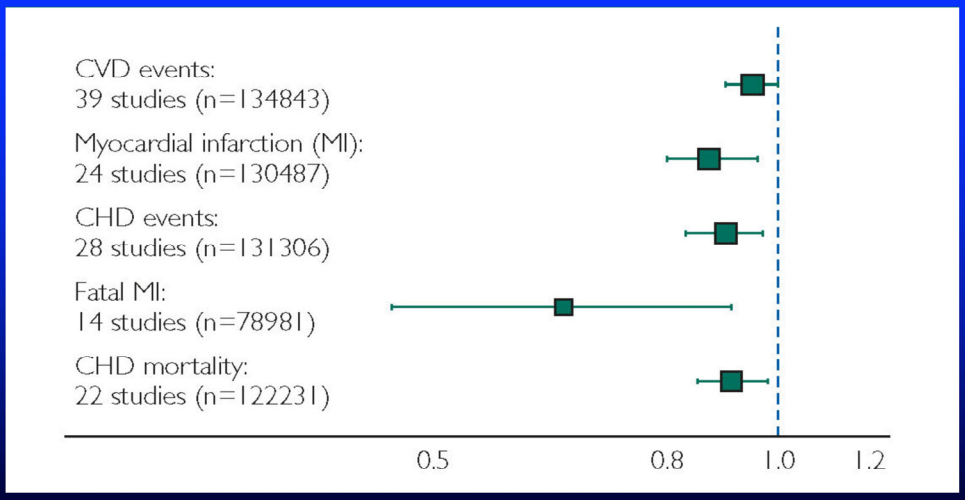
38

# Meta-Analysis of Omega-3 RCTs of Supplements

- Excluded DART studies which were dietary advice
- Dose varied from 400 mg/d EPA/DHA to 5500 mg/d
- Dose < 800 mg/d ( 5 studies, N=8036); 800-1200 mg/d (10 studies, N=94,936) and > 1200 mg/d (25 studies, N= 32,295)
- Mean Dosage 1221 mg

Bernasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2021; 96:304-313

# Omega-3 EPA/DHA and Major Cardiovascular Outcomes




Benasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2020; online Sept 17

# Meta-Analysis of Omega-3 RCTs of Supplements

- Major Reductions in Clinical Events
- 35 % reduced risk of Fatal MI ( NNT=128)
- 13% reduced risk of MI (NNT= 272)
- 10% reduced risk of CHD Events( NNT=192)
- 9 % reduced risk of Fatal CHD ( NNT=431)
- CVD events reduced 5% ( CI 0.90-1.00)

Bernasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2021;96:304-313

41

## Meta-Analysis of Omega-3 RCTs of Supplements Dosage Matters!

- **Dosage Matters!**
- **Assessed dose of EPA/DHA on major clinical events**
- **Generally increased CV Outcomes Reductions with higher EPA/DHA doasges**
- **Each additional 1g/d of EPA +DHA led to risk reductions for CVD events ( -5.8%), MI (-9.0 %).**

Bernasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2021;96: 304-313

# Omega-3 and Major Cardiovascular Outcomes

**TABLE 2. Meta-Regression Coefficients for Log-RR as a Linear Model With EPA+DHA Dosage as Predictor[a,b]**

| Outcome | Slope[c,d] | Intercept | Equivalent risk change per 1 g/day |
|---|---|---|---|
| CVD events | -6.0e-02 (-1.0e-01 to -1.6e-02)[e] | 2.4e-02 (-4.3e-02 to 9.0e-02) | -5.8% (-9.9% to -1.6%) |
| MI | -9.4e-02 (-1.5e-01 to -3.9e-02)[f] | 3.7e-03 (-9.8e-02 to 1.0e-01) | -9.0% (-13.9% to -3.8%) |
| CHD events | -5.5e-02 (-1.2e-01 to 6.4e-03) | -2.4e-02 (-1.3e-01 to 8.0e-02) | N/A |
| Fatal MI | 3.8e-01 (-3.1e-03 to 7.6e-01) | -8.6e-01 (-1.3e+00 to -4.2e-01)[f] | N/A |
| CHD mortality | 2.2e-02 (-2.0e-01 to 2.4e-01) | -1.2e-01 [-3.3e-01, 9.5e-02] | N/A |

[a]CHD = coronary heart disease; CVD = cardiovascular disease; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; MI = myocardial infarction; N/A = not applicable; RR = relative risk.
[b]Log-RR modeled as a function of daily EPA+DHA dosage, in g/day.
[c]For outcomes for which the slope is significantly non-zero, the change in risk for that outcome associated with each additional 1 g/day of EPA+DHA is reported.
[d]Estimates and 95% CIs are reported for slope and intercept.
[e]$P<.01$.
[f]$P<.001$.

Benasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2020; online Sept 17



43

# Meta-Analysis of Omega-3 RCTs of Supplements Older vs New Studies

- There is perception that the older Omega-3 Studies, like GISSI Prevencione , were more positive than recent studies
- Medical and Interventional Treatments now more effective
- But REDUCEIT, VITAL , ASCEND all had positive results
- We did not find any significant effect of year of publication on Omega-3's Benefits on CV Outcomes

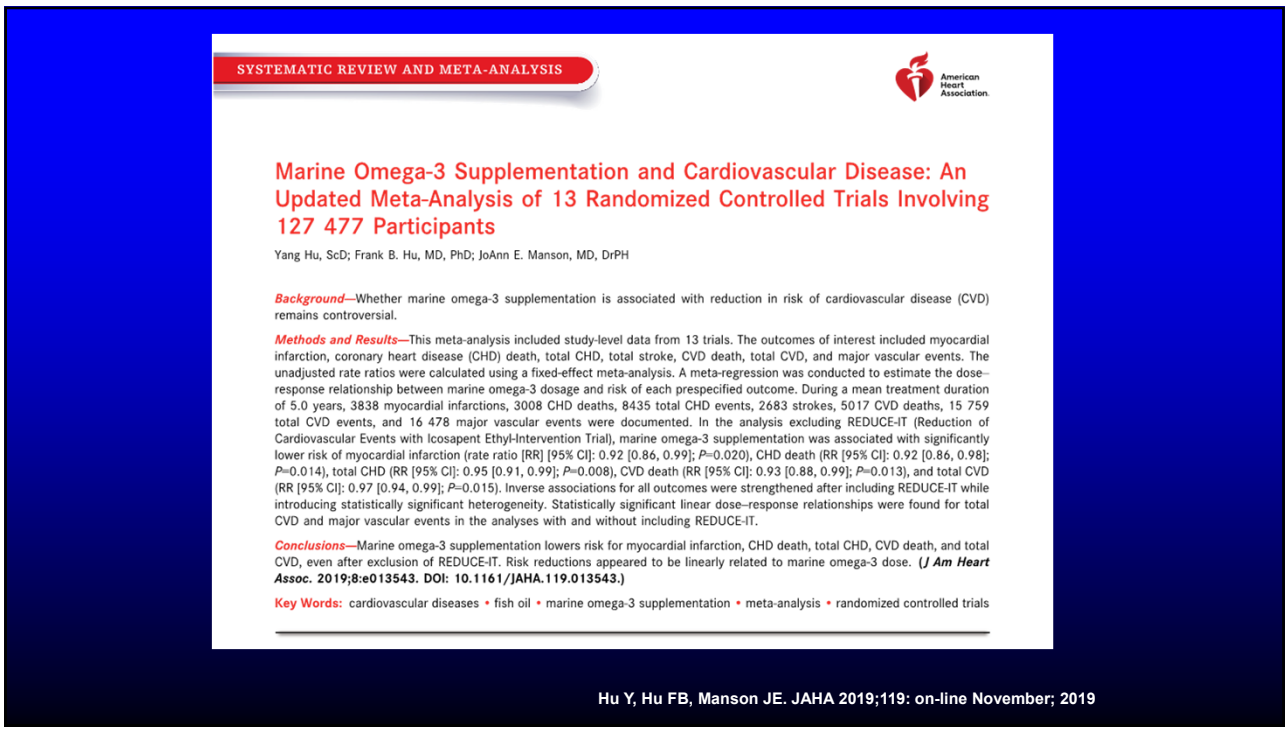
Bernasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2020;96: 304-313

# Meta-Analysis of Omega-3 RCTs of Supplements EPA vs EPA/DHA

- There is debate on whether EPA is more important than EPA/DHA
- EPA alone very positive in REDUCEIT and JELLIS
- We assessed EPA dosage vs EPA/DHA dosage on CV Outcomes
- We did not determine any significant advantage of total EPA vs the total EPA/DHA dosage on major CV Outcomes

Bernasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2020; 96: 304-313

45



SYSTEMATIC REVIEW AND META-ANALYSIS

American Heart Association.

# Marine Omega-3 Supplementation and Cardiovascular Disease: An Updated Meta-Analysis of 13 Randomized Controlled Trials Involving 127 477 Participants

Yang Hu, ScD; Frank B. Hu, MD, PhD; JoAnn E. Manson, MD, DrPH

***Background*—**Whether marine omega-3 supplementation is associated with reduction in risk of cardiovascular disease (CVD) remains controversial.

***Methods and Results*—**This meta-analysis included study-level data from 13 trials. The outcomes of interest included myocardial infarction, coronary heart disease (CHD) death, total CHD, total stroke, CVD death, total CVD, and major vascular events. The unadjusted rate ratios were calculated using a fixed-effect meta-analysis. A meta-regression was conducted to estimate the dose–response relationship between marine omega-3 dosage and risk of each prespecified outcome. During a mean treatment duration of 5.0 years, 3838 myocardial infarctions, 3008 CHD deaths, 8435 total CHD events, 2683 strokes, 5017 CVD deaths, 15 759 total CVD events, and 16 478 major vascular events were documented. In the analysis excluding REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial), marine omega-3 supplementation was associated with significantly lower risk of myocardial infarction (rate ratio [RR] [95% CI]: 0.92 [0.86, 0.99]; *P*=0.020), CHD death (RR [95% CI]: 0.92 [0.86, 0.98]; *P*=0.014), total CHD (RR [95% CI]: 0.95 [0.91, 0.99]; *P*=0.008), CVD death (RR [95% CI]: 0.93 [0.88, 0.99]; *P*=0.013), and total CVD (RR [95% CI]: 0.97 [0.94, 0.99]; *P*=0.015). Inverse associations for all outcomes were strengthened after including REDUCE-IT while introducing statistically significant heterogeneity. Statistically significant linear dose–response relationships were found for total CVD and major vascular events in the analyses with and without including REDUCE-IT.

***Conclusions*—**Marine omega-3 supplementation lowers risk for myocardial infarction, CHD death, total CHD, CVD death, and total CVD, even after exclusion of REDUCE-IT. Risk reductions appeared to be linearly related to marine omega-3 dose. (***J Am Heart Assoc.* **2019;8:e013543. DOI: 10.1161/JAHA.119.013543.)**

**Key Words:** cardiovascular diseases • fish oil • marine omega-3 supplementation • meta-analysis • randomized controlled trials

**Hu Y, Hu FB, Manson JE. JAHA 2019;119: on-line November; 2019**



46

# JAHA Omega-3 Meta-Analysis

**Table.** Baseline Characteristics of RCTs Investigating Effects of Marine Omega-3 Supplementation and CVDs

| Study | Year | Sample Size | Mean Age, y | Marine Omega-3 Dose, mg/d | Mean Follow-up Duration, y | Male, No. (%) | BMI, kg/m$^2$ | Diabetes Mellitus, No. (%) | Cholesterol-Lowering Drug Use, No. (%) |
|---|---|---|---|---|---|---|---|---|---|
| GISSI-P[16] | 1999 | 11 334 | 59.4 | 866 | 3.5 | 9658 (85.2) | 26.5 | 2139 (18.9) | NA |
| JELIS[17] | 2007 | 18 645 | 61.0 | 1800 | 4.6 | 5859 (31.4) | 24.0 | 3040 (16.3) | 18 645 (100.0) |
| GISSI-HF[22] | 2008 | 6975 | 67.0 | 866 | 3.9* | 5459 (78.3) | 27.0 | 1974 (28.3) | NA |
| DOIT[12] | 2010 | 563 | 70.0 | 1320 | 3.0 | 563 (100) | NA | 46 (8.2) | NA |
| SU.FOL.OM3[13] | 2010 | 2501 | 61.0* | 600 | 4.2 | 1987 (79.4) | 27.2 | 440 (17.9) | 2079 (83.1) |
| Alpha Omega[14] | 2010 | 4837 | 69.0 | 376 | 3.4* | 3783 (78.2) | 27.8 | 1014 (21.0) | 4122 (85.2) |
| OMEGA[15] | 2010 | 3818 | 64.0* | 850 | 1.0 | 2841 (74.4) | 27.5 | 948 (27.0) | 3566 (94.2) |
| ORIGIN[19] | 2012 | 12 536 | 63.5 | 840 | 6.2* | 8150 (65.0) | 29.8 | 11 081 (88.4) | 6739 (53.8) |
| R&P[20] | 2013 | 12 505 | 64.0 | 866 | 5.0 | 7687 (61.5) | 29.4 | 7494 (59.9) | 12 505 (100.0) |
| AREDS-2[21] | 2014 | 4203 | 74.0 | 1000 | 4.8* | 1816 (43.2) | NA | 546 (13.0) | 1866 (44.4) |
| VITAL[10] | 2018 | 25 871 | 67.1 | 840 | 5.3* | 12 786 (49.4) | 28.1 | 3549 (13.7) | 9524 (37.5) |
| ASCEND[9] | 2018 | 15 480 | 63.3 | 840 | 7.4 | 9684 (62.6) | 30.8 | 14 569 (94.1) | 11 653 (75.3) |
| REDUCE-IT[11] | 2018 | 8179 | 64.0* | 4000 | 4.9* | 5822 (71.2) | 30.8 | 3389 (41.4) | 8145 (100)† |
| Total | NA | 127 477 | 64.3 | NA | 5.0 | 76 095 (59.7) | 28.0 | 50 229 (39.4) | 78,844 (72.6) |

Hu Y, Hu FB, Manson JE. JAHA 2019;119: on-line November; 2019

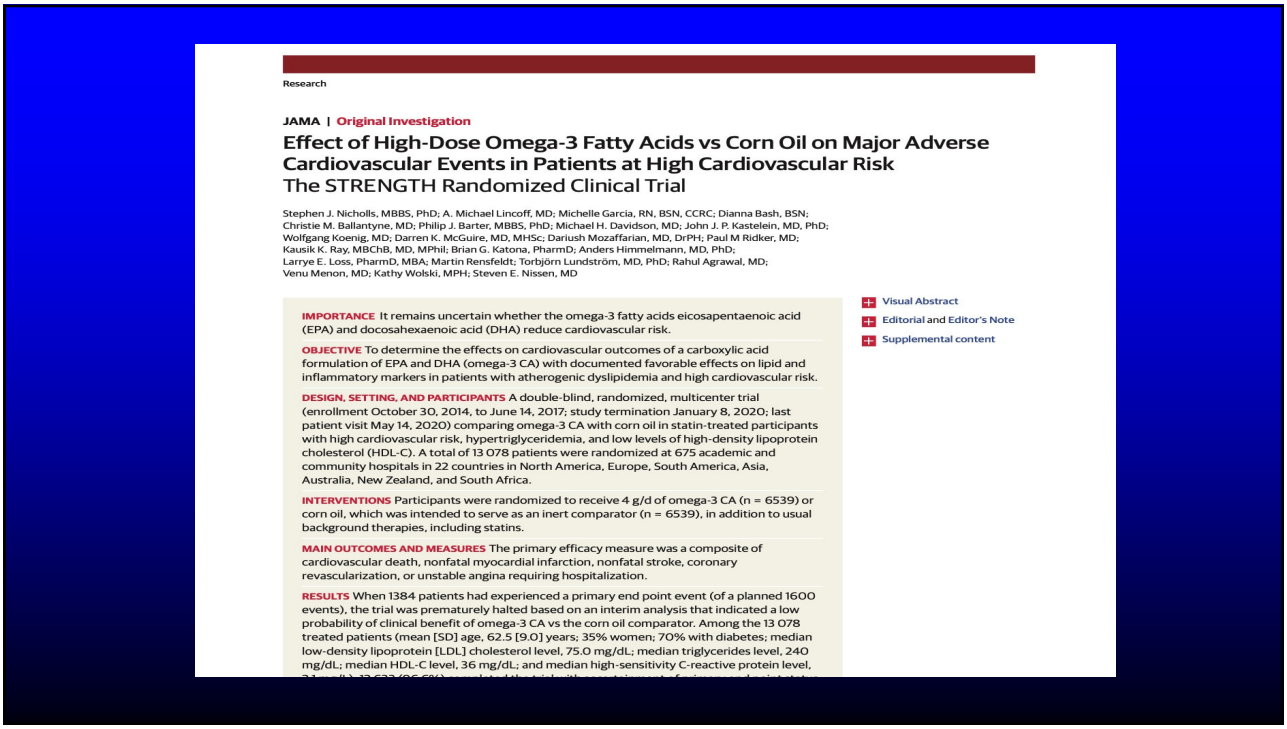


47

# JAHA Meta-Analysis of 13 Omega-3 RCTs

- RCTs with N> 1000;dose at least 840 mg EPA/DHA;at least 2 year follow-up
- 13 trials, N=127,977
- Added ASCEND,VITAL,REDUCE-IT
- 8% lower MI, 8 % lower CHD death ,5% lower total CHD, 7% lower total CVD death, 3% lower total CVD
- Benefit greater with higher dose

Hu Y, Hu FB, Manson JE. JAHA 2019; 119: online November



Research

JAMA | Original Investigation

# Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk
## The STRENGTH Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; A. Michael Lincoff, MD; Michelle Garcia, RN, BSN, CCRC; Dianna Bash, BSN; Christie M. Ballantyne, MD; Philip J. Barter, MBBS, PhD; Michael H. Davidson, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Darren K. McGuire, MD, MHSc; Dariush Mozaffarian, MD, DrPH; Paul M Ridker, MD; Kausik K. Ray, MBChB, MD, MPhil; Brian G. Katona, PharmD; Anders Himmelmann, MD, PhD; Larrye E. Loss, PharmD, MBA; Martin Rensfeldt; Torbjörn Lundström, MD, PhD; Rahul Agrawal, MD; Venu Menon, MD; Kathy Wolski, MPH; Steven E. Nissen, MD

**IMPORTANCE** It remains uncertain whether the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce cardiovascular risk.

**OBJECTIVE** To determine the effects on cardiovascular outcomes of a carboxylic acid formulation of EPA and DHA (omega-3 CA) with documented favorable effects on lipid and inflammatory markers in patients with atherogenic dyslipidemia and high cardiovascular risk.

**DESIGN, SETTING, AND PARTICIPANTS** A double-blind, randomized, multicenter trial (enrollment October 30, 2014, to June 14, 2017; study termination January 8, 2020; last patient visit May 14, 2020) comparing omega-3 CA with corn oil in statin-treated participants with high cardiovascular risk, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C). A total of 13 078 patients were randomized at 675 academic and community hospitals in 22 countries in North America, Europe, South America, Asia, Australia, New Zealand, and South Africa.

**INTERVENTIONS** Participants were randomized to receive 4 g/d of omega-3 CA (n = 6539) or corn oil, which was intended to serve as an inert comparator (n = 6539), in addition to usual background therapies, including statins.

**MAIN OUTCOMES AND MEASURES** The primary efficacy measure was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization.

**RESULTS** When 1384 patients had experienced a primary end point event (of a planned 1600 events), the trial was prematurely halted based on an interim analysis that indicated a low probability of clinical benefit of omega-3 CA vs the corn oil comparator. Among the 13 078 treated patients (mean [SD] age, 62.5 [9.0] years; 35% women; 70% with diabetes; median low-density lipoprotein [LDL] cholesterol level, 75.0 mg/dL; median triglycerides level, 240 mg/dL; median HDL-C level, 36 mg/dL; and median high-sensitivity C-reactive protein level,

Visual Abstract
Editorial and Editor's Note
Supplemental content



49

# Effects of n-3 Fatty Acid Supplements in Elderly Patients after Myocardial Infarction: A Randomized Controlled Trial

**Running Title:** *Kalstad & Myhre, et al.; Omega-3 in Elderly with Recent AMI*

Are Annesønn Kalstad, MD[1,2*]; Peder Langeland Myhre, MD, PhD[2,3*];
Kristian Laake MD, PhD[1]; Sjur Hansen Tveit, MD[2,3]; Erik Berg Schmidt, MD PhD[4];
Paal Smith P, MD PhD[2,3]; Dennis Winston Trygve Nilsen, MD PhD[6,7];
Arnljot Tveit, MD, PhD[2,5]; Morten Wang Fagerland, PhD[8]; Svein Solheim, MD PhD[1];
Ingebjørg Seljeflot, PhD[1,2**]; Harald Arnesen, MD PhD[1,2**];
on behalf of the OMEMI investigators

50

# Updated Meta-Analysis of Omega-3 RCTs of Supplements
## EPA vs EPA/DHA

- Added STRENGTH and OMEMI; 42 studies; N=149,359
- Only CVD events and CHD Events changed
- CVD Events now reduced 4% ; p=0.05
- CHD events reduced 9%; p< 0.05
- Each 1 g/d EPA/DHA reduced MI by an additional 9 %

Bernasconi AA, Lavie CJ, et al. Mayo Clin Proc 2021, Submitted

51

# Updated Meta-Analysis of Omega-3 RCTs of Supplements
## EPA vs EPA/DHA

- Added STRENGTH and OMEMI; 42 studies; N=149,359
- Reduced Fatal MI 35%
- Reduced MI 13%
- Reduced both CHD events and CHD mortality 9%
- Borderline 4% reduction in CVD events
- Still VERY SIGNIFICANT Omega-3 Benefits

Bernasconi AA, Lavie CJ, et al. Mayo Clin Proc 2021, Submitted

52

## Fish Oil/Omega-3 in Heart Failure

**Less than 1 gram helped a little-**

**Higher Dosage Needed???**

53

# Cardiovascular Health Study

- Population-based study ~5,000 men and women
- Followed for over 12 yrs
- Consumption of broiled/baked fish
- Associated with a lower incidence of congestive HF

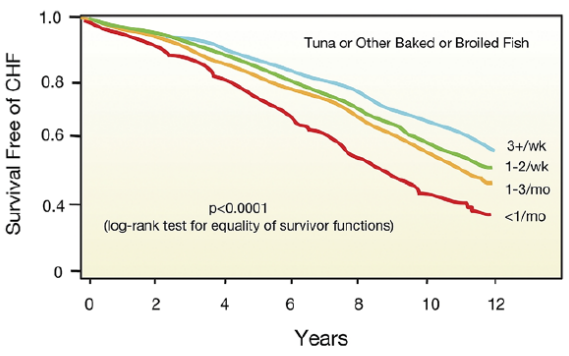



**Figure 3** Fish Intake and CHF

Survival free of congestive heart failure (CHF) according to consumption of tuna or other fish that are high in eicosapentaenoic acid and docosahexaenoic acid. Reprinted, with permission, from Mozaffarian et al. (41).

**Mozaffarian D et al. JACC 2005;45:2015-2021**

## Atherosclerosis Risk in Community Study

- 3,500 pts
- Followed for 14 years
- Inverse relationship between intake of PUFA and incidence of HF in women, but not in men.

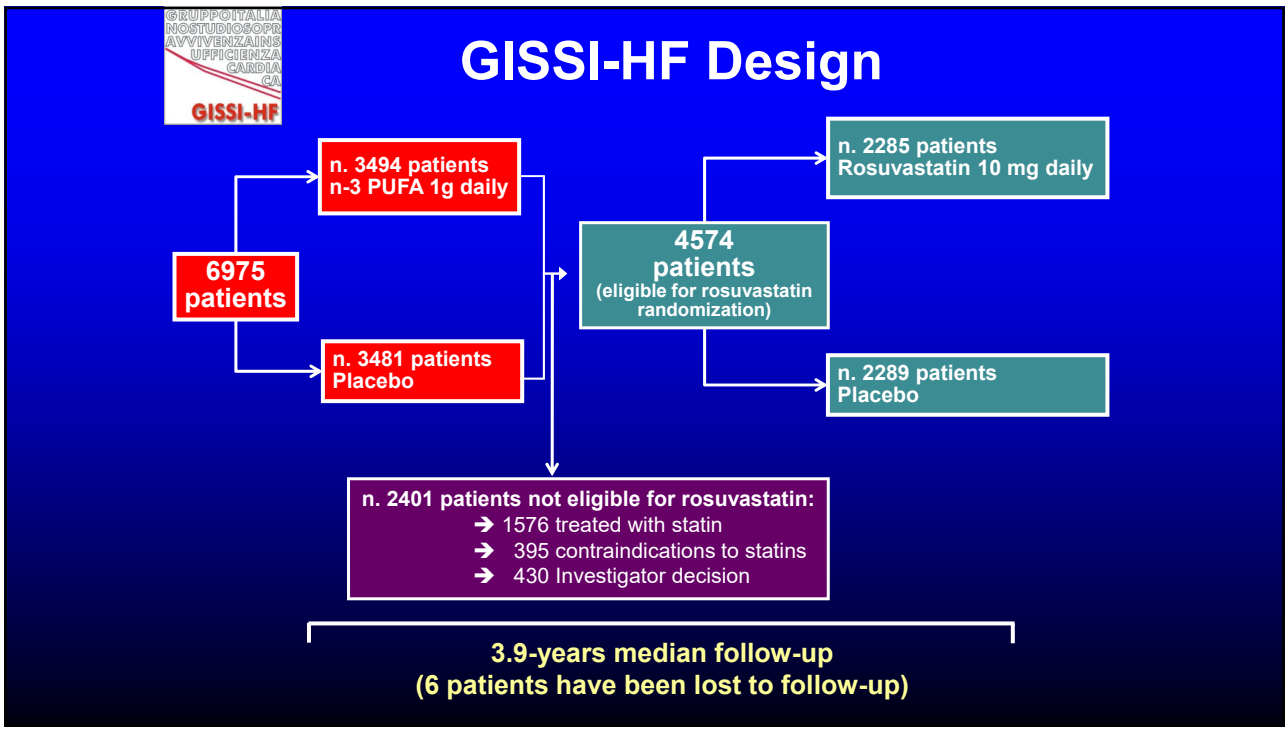
## Japanese Epidemiological Study

- Largest prospective, observational study
- 60,000 men and women
- Followed for 13 years
- Inverse association between omega-3 consumption and CV mortality, including HF mortality

55

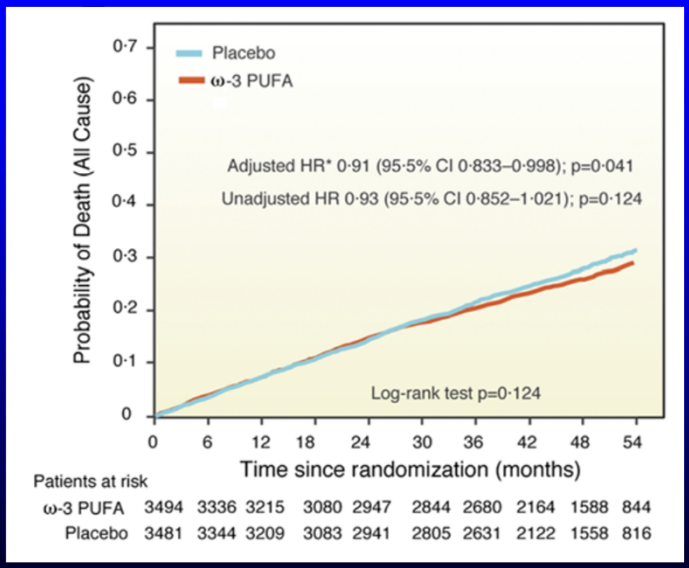

Articles
Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial
GISSI-HF investigators*
Lancet 2008; 372:
*Members listed at end of paper
Correspondence to:
GISSI-HF Coordinating Centre,
ANMCO Research Centre,
Via La Marmora 34,
50121 Florence, Italy
gissihf@anmco.it

56


GISSI-HF
GISSI-HF Design
n. 3494 patients
n-3 PUFA 1g daily
6975
patients
n. 3481 patients
Placebo
4574
patients
(eligible for rosuvastatin
randomization)
n. 2285 patients
Rosuvastatin 10 mg daily
n. 2289 patients
Placebo
n. 2401 patients not eligible for rosuvastatin:
➔ 1576 treated with statin
➔ 395 contraindications to statins
➔ 430 Investigator decision
3.9-years median follow-up
(6 patients have been lost to follow-up)

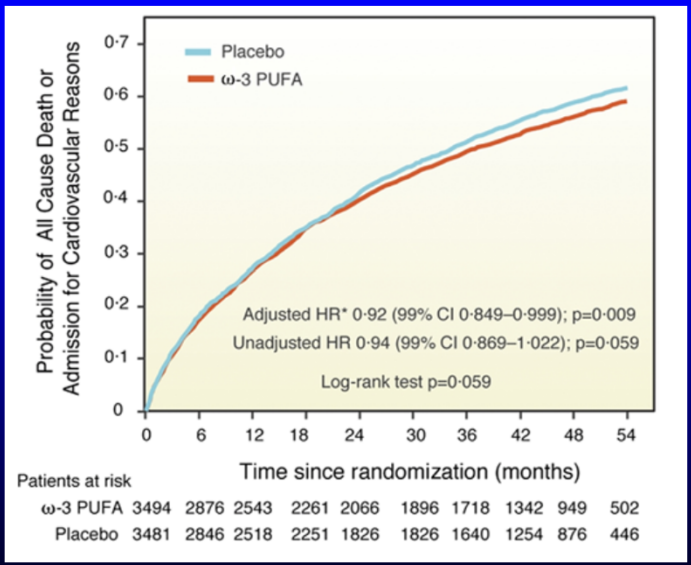
57

# Fish Intake and HF Survival-GISSI-HF




GISSI-HF. Lancet 2008;372:1223-1230

# Fish Intake and HF Survival-GISSI-HF



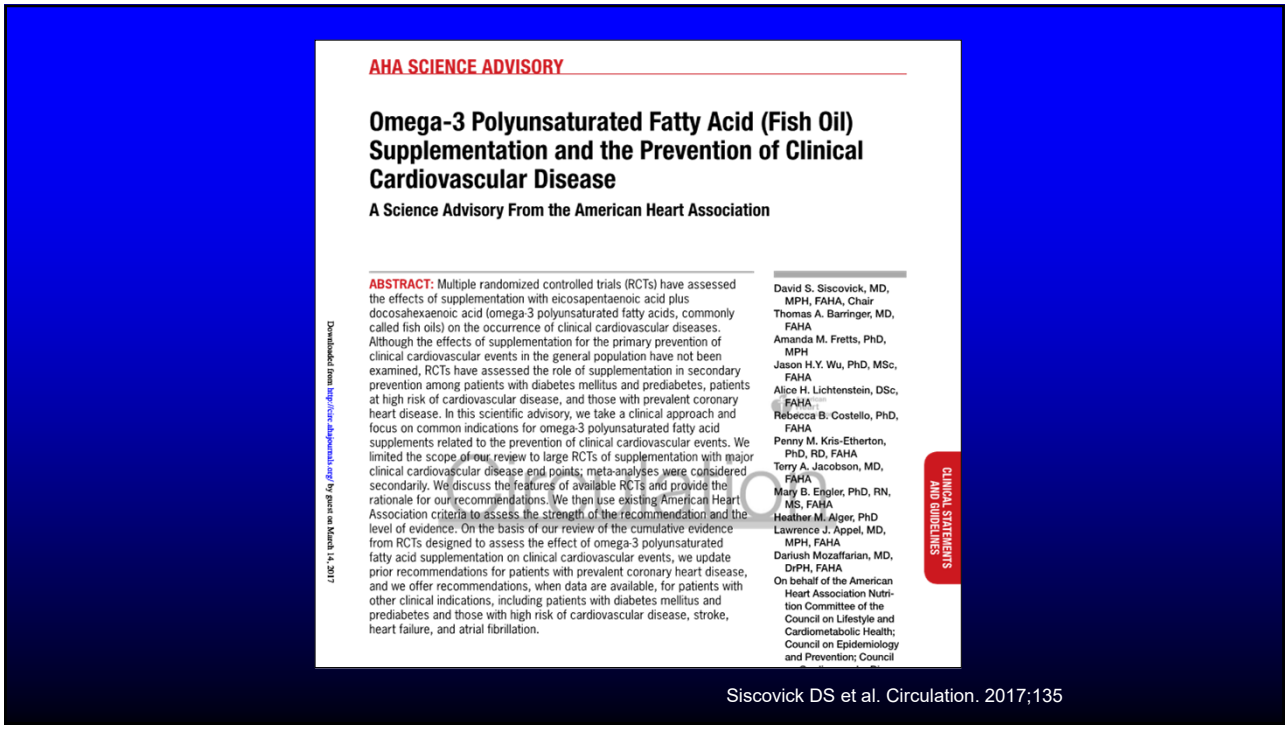

GISSI-HF. Lancet 2008;372:1223-1230

## Omega-3 and HF-GISSI-HF

"Although these benefits seem to be only modest, they translate into 56 patients needing to be treated for 4 years to avoid 1 death or hospital CV admission. Importantly, this therapy is safe, inexpensive, and well-tolerated."

Lavie CJ et al. JACC 2009;54:585-594.
GISSI-HF. Lancet 2008;372:1223-1230

60



AHA SCIENCE ADVISORY

# Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease

## A Science Advisory From the American Heart Association

**ABSTRACT:** Multiple randomized controlled trials (RCTs) have assessed the effects of supplementation with eicosapentaenoic acid plus docosahexaenoic acid (omega-3 polyunsaturated fatty acids, commonly called fish oils) on the occurrence of clinical cardiovascular diseases. Although the effects of supplementation for the primary prevention of clinical cardiovascular events in the general population have not been examined, RCTs have assessed the role of supplementation in secondary prevention among patients with diabetes mellitus and prediabetes, patients at high risk of cardiovascular disease, and those with prevalent coronary heart disease. In this scientific advisory, we take a clinical approach and focus on common indications for omega-3 polyunsaturated fatty acid supplements related to the prevention of clinical cardiovascular events. We limited the scope of our review to large RCTs of supplementation with major clinical cardiovascular disease end points; meta-analyses were considered secondarily. We discuss the features of available RCTs and provide the rationale for our recommendations. We then use existing American Heart Association criteria to assess the strength of the recommendation and the level of evidence. On the basis of our review of the cumulative evidence from RCTs designed to assess the effect of omega-3 polyunsaturated fatty acid supplementation on clinical cardiovascular events, we update prior recommendations for patients with prevalent coronary heart disease, and we offer recommendations, when data are available, for patients with other clinical indications, including patients with diabetes mellitus and prediabetes and those with high risk of cardiovascular disease, stroke, heart failure, and atrial fibrillation.

David S. Siscovick, MD, MPH, FAHA, Chair
Thomas A. Barringer, MD, FAHA
Amanda M. Fretts, PhD, MPH
Jason H.Y. Wu, PhD, MSc, FAHA
Alice H. Lichtenstein, DSc, FAHA
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Mary B. Engler, PhD, RN, MS, FAHA
Heather M. Alger, PhD
Lawrence J. Appel, MD, MPH, FAHA
Dariush Mozaffarian, MD, DrPH, FAHA
On behalf of the American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council

CLINICAL STATEMENTS AND GUIDELINES



Siscovick DS et al. Circulation. 2017;135

61

JACC: HEART FAILURE
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PUBLISHED BY ELSEVIER

VOL. ■, NO. ■, 2019

# Predicting Risk for Incident Heart Failure With Omega-3 Fatty Acids

## From MESA

Robert C. Block, MD,[a,b] Linxi Liu, MS,[a] David M. Herrington, MD,[c] Shue Huang, MS,[d] Michael Y. Tsai, PhD,[e] Timothy D. O'Connell, PhD,[f] Gregory C. Shearer, PhD[d]

ABSTRACT

**OBJECTIVES** The aim of this study was to determine if plasma eicosapentaenoic acid (EPA) abundance (%EPA) is associated with reduced hazard for primary heart failure (HF) events in the MESA (Multi-Ethnic Study of Atherosclerosis) trial.

**BACKGROUND** Clinical trials suggest that omega-3 polyunsaturated fatty acids (ω3 PUFAs) prevent sudden death in coronary heart disease and HF, but this is controversial. In mice, the authors demonstrated that the ω3 PUFA EPA prevents contractile dysfunction and fibrosis in an HF model, but whether this extends to humans is unclear.

**METHODS** In the MESA cohort, the authors tested if plasma phospholipid EPA predicts primary HF incidence, including HF with reduced ejection fraction (EF) (EF <45%) and HF with preserved EF (EF ≥45%) using Cox proportional hazards modeling.

**RESULTS** A total of 6,562 participants 45 to 84 years of age had EPA measured at baseline (1,794 black, 794 Chinese, 1,442 Hispanic, and 2,532 white; 52% women). Over a median follow-up period of 13.0 years, 292 HF events occurred: 128 HF with reduced EF, 110 HF with preserved EF, and 54 with unknown EF status. %EPA in HF-free participants was 0.76% (0.75% to 0.77%) but was lower in participants with HF at 0.69% (0.64% to 0.74%) ($p = 0.005$). Log %EPA was associated with lower HF incidence (hazard ratio: 0.73 [95% confidence interval: 0.60 to 0.91] per log-unit difference in %EPA; $p = 0.001$). Adjusting for age, sex, race, body mass index, smoking, diabetes mellitus, blood pressure, lipids and lipid-lowering drugs, albuminuria, and the lead fatty acid for each cluster did not change this relationship. Sensitivity analyses showed no dependence on HF type.

**CONCLUSIONS** Higher plasma EPA was significantly associated with reduced risk for HF, with both reduced and preserved EF. (Multi-Ethnic Study of Atherosclerosis [MESA]; NCT00005487) (J Am Coll Cardiol HF 2019;■:■–■)


Block RC et al. JACC-HF 2019; in press



62

# Omega-3 Levels Predict Development of Heart Failure

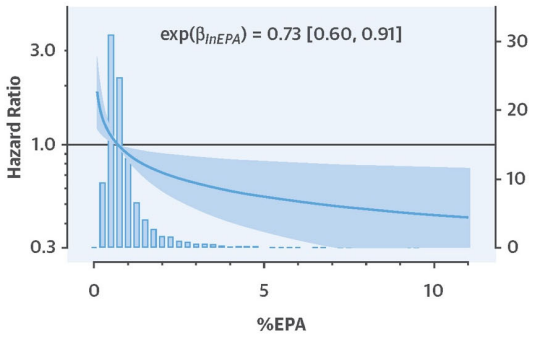
- 6,562 participants in MESA
- Over 13 years, 292 HF events ( 128 HFrEF, 110 HFpEF, and 54 HF with unknown LVEF)
- Higher EPA was associated with reduced HF
- Similar data with DHA and EPA/DHA

Block RC et al.JACC-HF 2019 on-line head of print.

63

**CENTRAL ILLUSTRATION** Eicosapentaenoic Acid Predict Hazard for All Heart Failure

## Higher EPA Levels are Associated with Reduced HF Incidence, But Most Participants have Levels Associated with High Risk

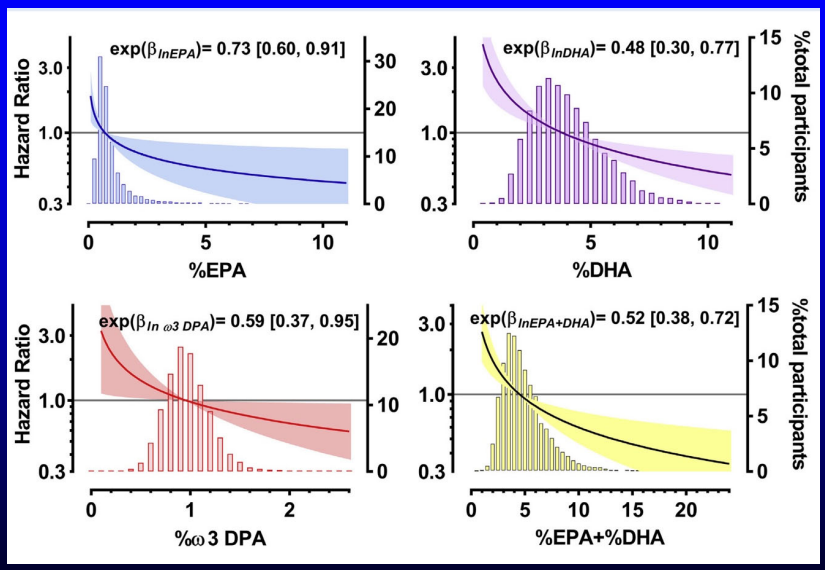



Block, R.C. et al. J Am Coll Cardiol HF. 2019;■(■):■-■.

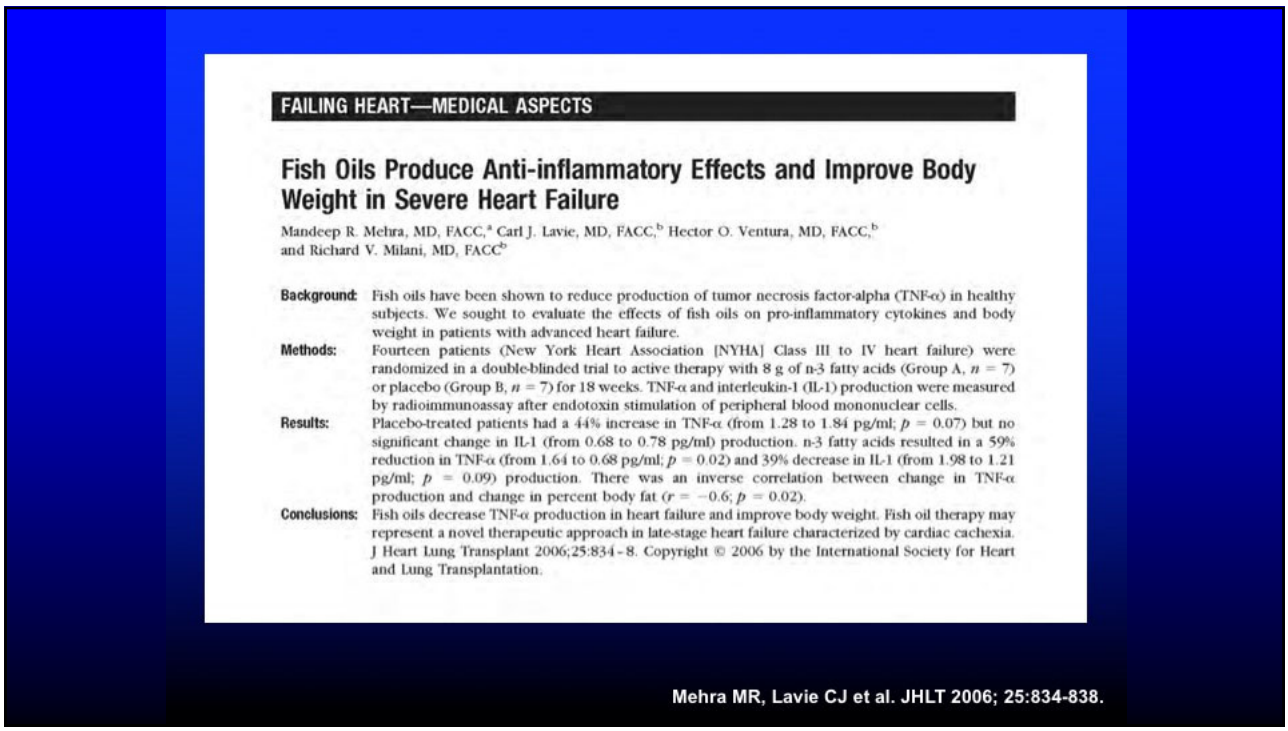
Block RC et al. JACC-HF 2019; in press

64

# Omega-3 Levels and HF




Block RC et al. JACC-HF 2019; in press


FAILING HEART—MEDICAL ASPECTS
Fish Oils Produce Anti-inflammatory Effects and Improve Body Weight in Severe Heart Failure
Mandeep R. Mehra, MD, FACC,[a] Carl J. Lavie, MD, FACC,[b] Hector O. Ventura, MD, FACC,[b] and Richard V. Milani, MD, FACC[b]
Background: Fish oils have been shown to reduce production of tumor necrosis factor-alpha (TNF-α) in healthy subjects. We sought to evaluate the effects of fish oils on pro-inflammatory cytokines and body weight in patients with advanced heart failure.
Methods: Fourteen patients (New York Heart Association [NYHA] Class III to IV heart failure) were randomized in a double-blinded trial to active therapy with 8 g of n-3 fatty acids (Group A, n = 7) or placebo (Group B, n = 7) for 18 weeks. TNF-α and interleukin-1 (IL-1) production were measured by radioimmunoassay after endotoxin stimulation of peripheral blood mononuclear cells.
Results: Placebo-treated patients had a 44% increase in TNF-α (from 1.28 to 1.84 pg/ml; p = 0.07) but no significant change in IL-1 (from 0.68 to 0.78 pg/ml) production. n-3 fatty acids resulted in a 59% reduction in TNF-α (from 1.64 to 0.68 pg/ml; p = 0.02) and 39% decrease in IL-1 (from 1.98 to 1.21 pg/ml; p = 0.09) production. There was an inverse correlation between change in TNF-α production and change in percent body fat (r = −0.6; p = 0.02).
Conclusions: Fish oils decrease TNF-α production in heart failure and improve body weight. Fish oil therapy may represent a novel therapeutic approach in late-stage heart failure characterized by cardiac cachexia. J Heart Lung Transplant 2006;25:834–8. Copyright © 2006 by the International Society for Heart and Lung Transplantation.
Mehra MR, Lavie CJ et al. JHLT 2006; 25:834-838.

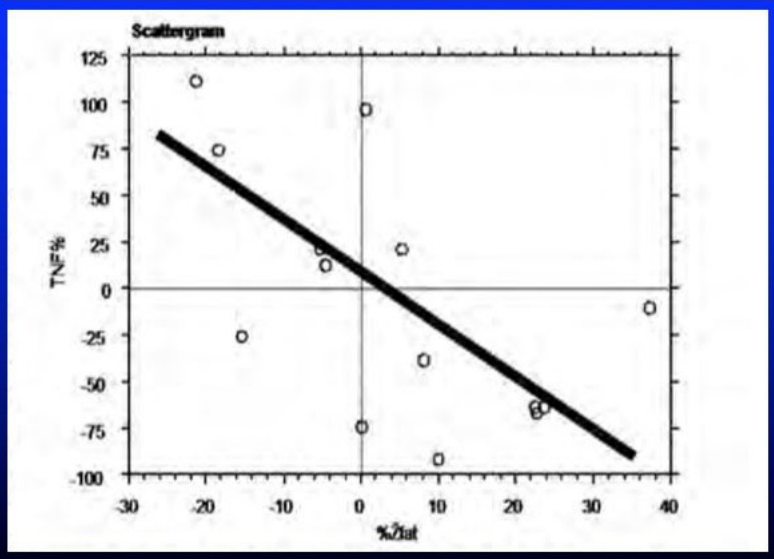
66

# High Dose Omega-3 in Severe Systolic HF

- 14 patients with NYHA Class III-IV systolic HF
- Double-blinded RCT of 8g omega-3 vs placebo
- Placebo 44% increase in TNF and NC in IL-1
- Omega-3 had 59% reduction in TNF and 39% decrease in IL-1
- Inverse correlation between TNF production and change in % Body Fat
- High dose omega-3 benefits advanced HF, especially with cachexia

Mehra MR, Lavie CJ et al. JHLT 2006; 25:834-838.

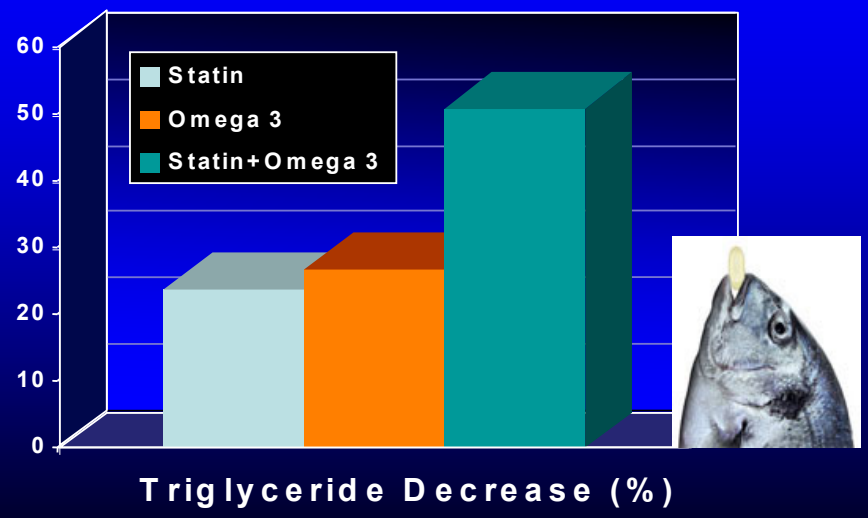
## High Dose Omega-3 Improves Body Composition and Reduces TNF in Advanced HF




Mehra MR, Lavie CJ et al. JHLT 2006; 25:834-838.

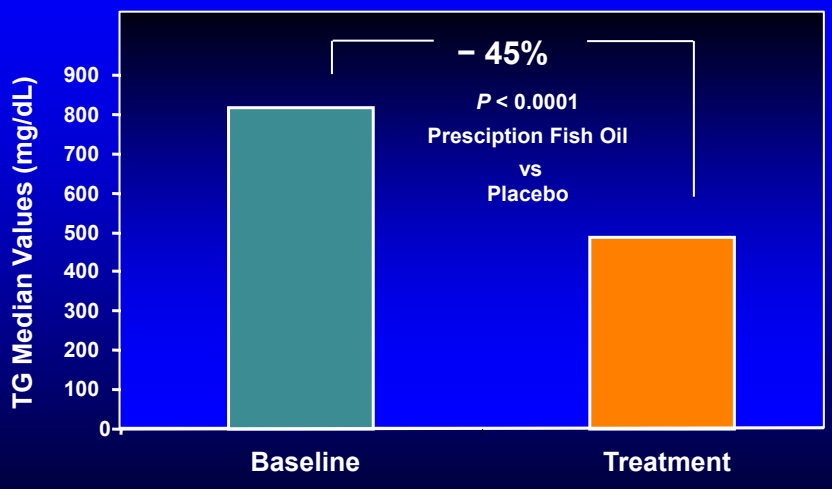
# Omega 3 for Triglyceride Rx

*Heart* 2001;85:544-548




69

# Omega-3 4 grams/day Reduces Triglycerides 45%

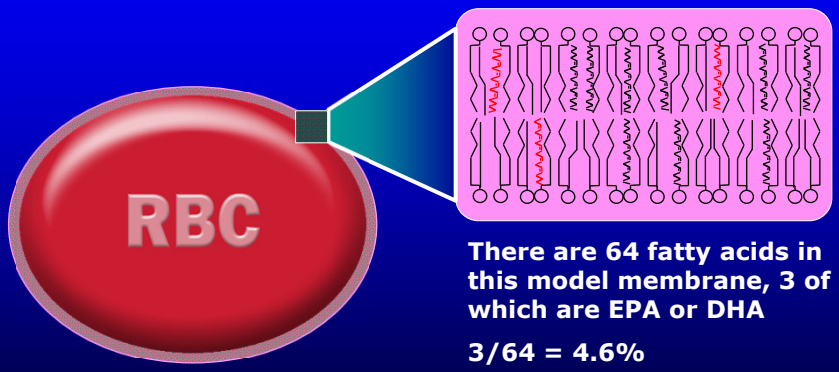



Stalenhoef AFH, de Graaf JD, Wittekoek ME, et al. The effect of concentrated n-3 fatty acids versus gemfibrozil on plasma lipoproteins, low density lipoprotein heterogeneity and oxidizability in patients with hypertriglyceridemia.

*Atherosclerosis.* 2000;153:129-138.

# HS-Omega-3 Index

**A measure of the amount of EPA+DHA in red blood cell membranes expressed as the percent of total fatty acids**




**There are 64 fatty acids in this model membrane, 3 of which are EPA or DHA**

**3/64 = 4.6%**

**HS-Omega-3 Index = 4.6%**

Harris WS and von Schacky. *Prev Med* 2004;39:212-220.

71

# Proposed HS-Omega-3 Index Risk Zones

## Relative Risk for Death from CHD

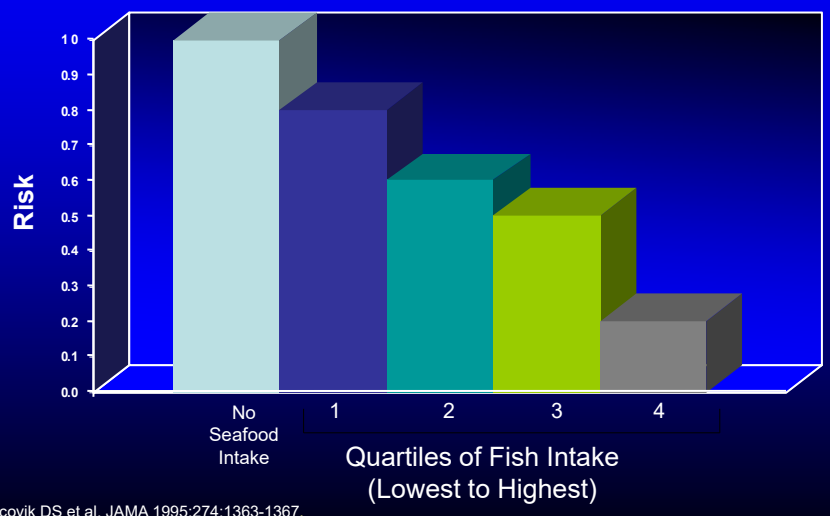

**Percent of EPA+DHA in RBC**

Harris WS and von Schacky. *Prev Med* 2004;39:212-220.

Itomura, *in vivo* 2008;22:131-136.

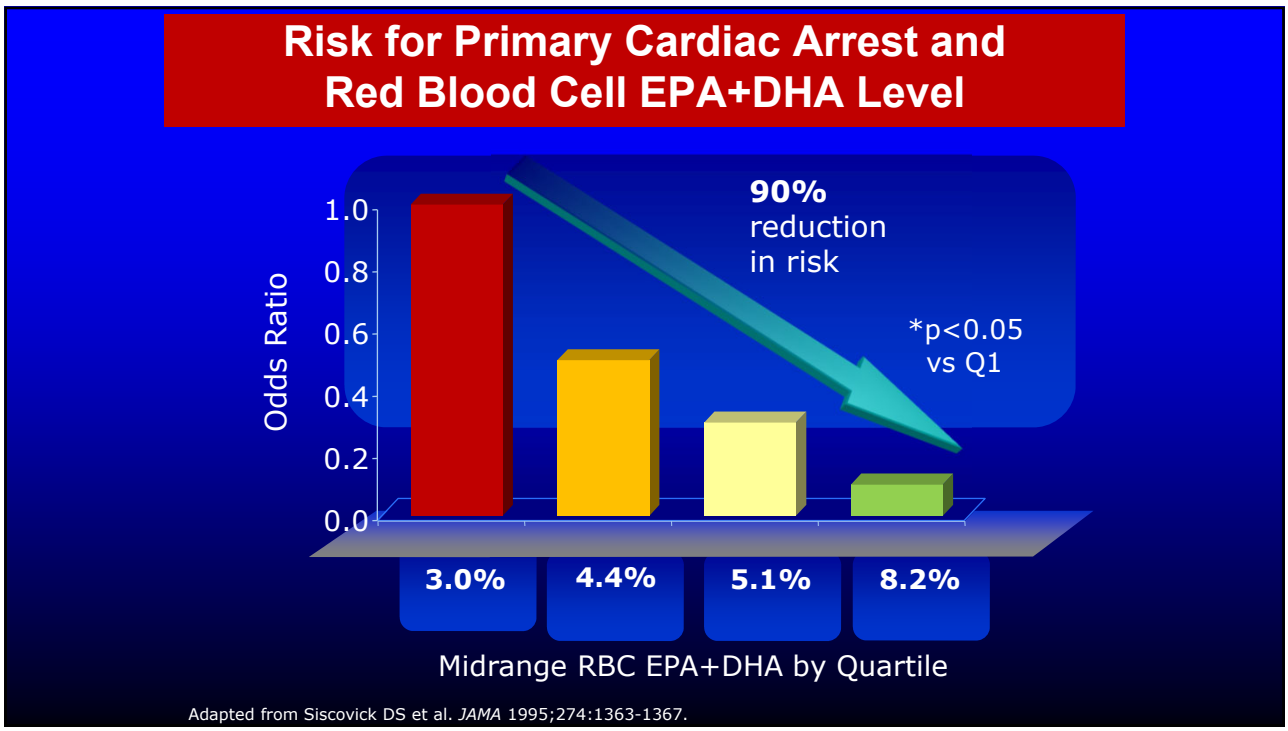
72

# Risk of Primary Cardiac Arrest with Dietary Intake of n-3 Fatty Acids

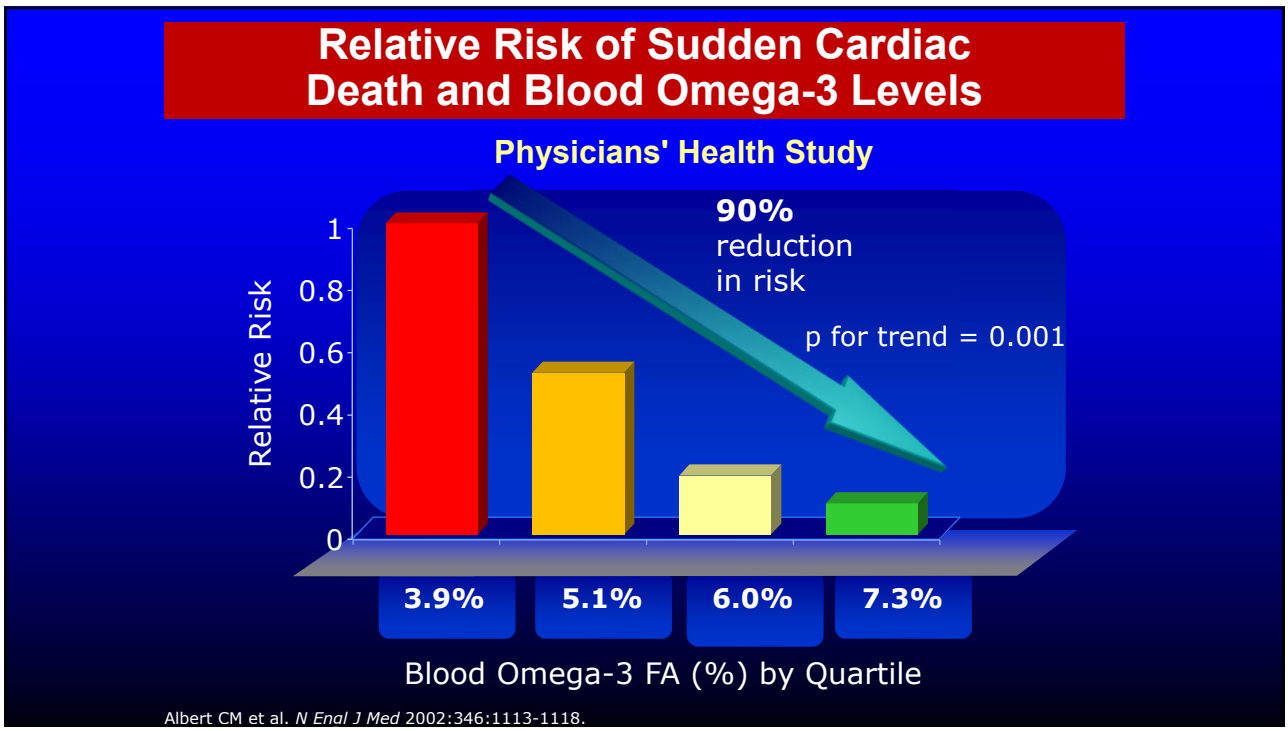



Siscovik DS et al. JAMA 1995;274:1363-1367.

73

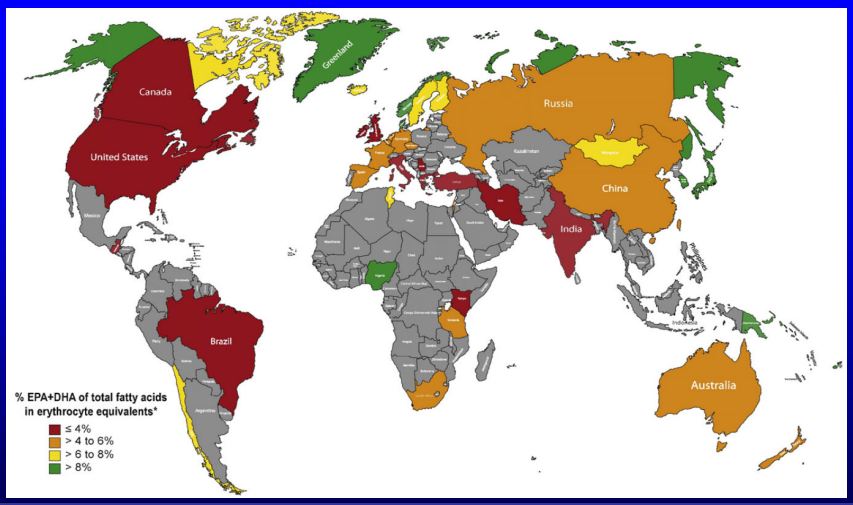

Risk for Primary Cardiac Arrest and Red Blood Cell EPA+DHA Level
90% reduction in risk
*p<0.05 vs Q1
Odds Ratio
1.0
0.8
0.6
0.4
0.2
0.0
3.0%
4.4%
5.1%
8.2%
Midrange RBC EPA+DHA by Quartile
Adapted from Siscovick DS et al. JAMA 1995;274:1363-1367.

74


Relative Risk of Sudden Cardiac Death and Blood Omega-3 Levels
Physicians' Health Study
90% reduction in risk
p for trend = 0.001
Relative Risk
1
0.8
0.6
0.4
0.2
0
3.9%
5.1%
6.0%
7.3%
Blood Omega-3 FA (%) by Quartile
Albert CM et al. N Engl J Med 2002:346:1113-1118.

75

# Global map




Regions with high EPA and DHA blood levels (>8%) include the Sea of Japan, Scandinavia, and areas with indigenous populations or populations not fully adapted to Westernized food habits. Very low blood levels (≤4%) were observed in North America, Central and South America, Europe, the Middle East, Southeast Asia, and Africa.

The review reveals considerable variability in global blood levels of EPA and DHA and the very low to low range of EPA and DHA for most of the world increases may have implications on the global risk for chronic disease.

# Global survey of the omega-3s in the blood stream of healthy adults


- Systematic review of published literature reporting blood levels of the omega-3s, (EPA and DHA), in healthy adults in order to create a global overview.
- Papers published in 1980 or later were considered; a total of 298 studies met all inclusion criteria.
- First systematic review to examine blood levels of omega-3s (specifically EPA and DHA) on a global scale. The review reveals considerable variability in blood levels of EPA and DHA, and suggests that EPA and DHA blood levels are in the very low to low range for most of the globe.
- The paper was published by Stark et al., 20 May 2016 in Progress in Lipid Research
  http://authors.elsevier.com/sd/article/S0163782715300333

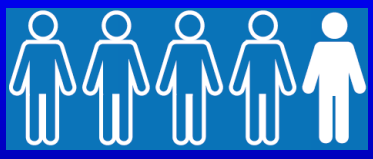
77

# Key outcomes:

- Blood levels of EPA and DHA vary across the globe, with most of the countries and regions of the world having levels that are considered low to very low.
- The low and very low bloods levels observed are associated with an increased risk in cardiovascular related mortality based on previous observational studies. It is also likely that decreased blood levels of EPA and DHA may increase the risk of cognitive decline with normal aging.
- More data on blood levels of EPA and DHA is needed for large regions of the globe, particularly for developing countries.
- Efforts to establish reference ranges in blood levels of fatty acids are needed and this data would complement existing information on dietary intake. Given the challenges of fatty acid analyses and reporting, standardized approaches and the development of a global systematic database is needed.


1. Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, et al. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. JAMA : the journal of the American Medical Association. 1995;274:1363-7.
2. Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. The New England journal of medicine. 2002;346:1113-8.

- 4 in 5 Americans don't consume the recommended amount of fish[3] and have inadequate omega-3 status[4]



- Almost all Americans have omega-3 levels below those associated with decreased risk of sudden cardiac death[4]




79

## The only naturally rich food source of long chain Omega 3 fatty acids is fatty (“oily”) fish

80

# Fish Content of EPA and DHA

| Type | DHA (g/100 g) | EPA (g/100 g) | DHA and EPA (g/100 g) | Ratio DHA/EPA |
|---|---|---|---|---|
| Tuna | | | | |
| Bluefin | 1.141 | 0.363 | 1.504 | 3.1:1.0 |
| Light, canned in water | 0.223 | 0.047 | 0.270 | 4.8:1.0 |
| Albacore, canned in water | 0.629 | 0.233 | 0.862 | 2.7:1.0 |
| Salmon | | | | |
| Atlantic, farmed | 1.457 | 0.690 | 2.147 | 2.1:1.0 |
| Atlantic, wild | 1.429 | 0.411 | 1.840 | 3.5:1.0 |
| Chinook | 0.727 | 1.010 | 1.737 | 1.0:1.4 |
| Sockeye | 0.700 | 0.530 | 1.230 | 1.3:1.0 |
| Mackerel, Atlantic | 0.699 | 0.504 | 1.203 | 1.4:1.0 |
| Herring, Atlantic | 1.105 | 0.909 | 2.014 | 1.2:1.0 |

Lavie CJ et al. JACC 2009;54:585-594.

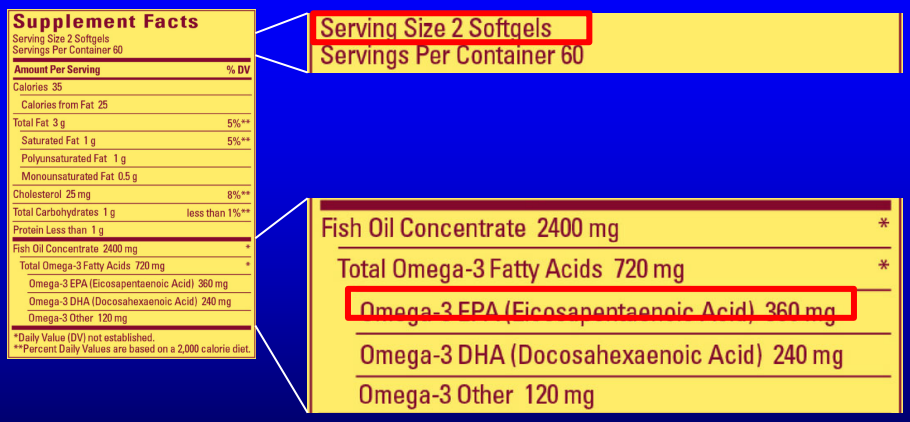
81

# Fish Content of EPA and DHA

| Type | DHA (g/100 g) | EPA (g/100 g) | DHA and EPA (g/100 g) | Ratio DHA/EPA |
|---|---|---|---|---|
| Trout | | | | |
| Rainbow, farmed | 0.820 | 0.334 | 1.154 | 2.5:1.0 |
| Rainbow, wild | 0.520 | 0.468 | 9.988 | 1.1:1.0 |
| Halibut | 0.374 | 0.091 | 0.465 | 4.1:1.0 |
| Cod | 0.154 | 0.004 | 0.158 | 38.5:1.0 |
| Haddock | 0.162 | 0.076 | 0.238 | 2.1:1.0 |
| Catfish | | | | |
| Channel, farmed | 0.128 | 0.049 | 0.177 | 2.6:1.0 |
| Channel, wild | 0.137 | 0.100 | 0.237 | 1.4:1.0 |
| Swordfish | 0.681 | 0.087 | 0.768 | 7.8:1.0 |
| Grouper | 0.213 | 0.035 | 0.248 | 6.1:1.0 |
| Shrimp | 0.144 | 0.171 | 0.315 | 1.0:1.2 |

Lavie CJ et al. JACC 2009;54:585-594.

# EPA+DHA in dietary supplements




**Total EPA+DHA content = 300 mg per 1 softgel**
**= 600 mg per 2 softgels**

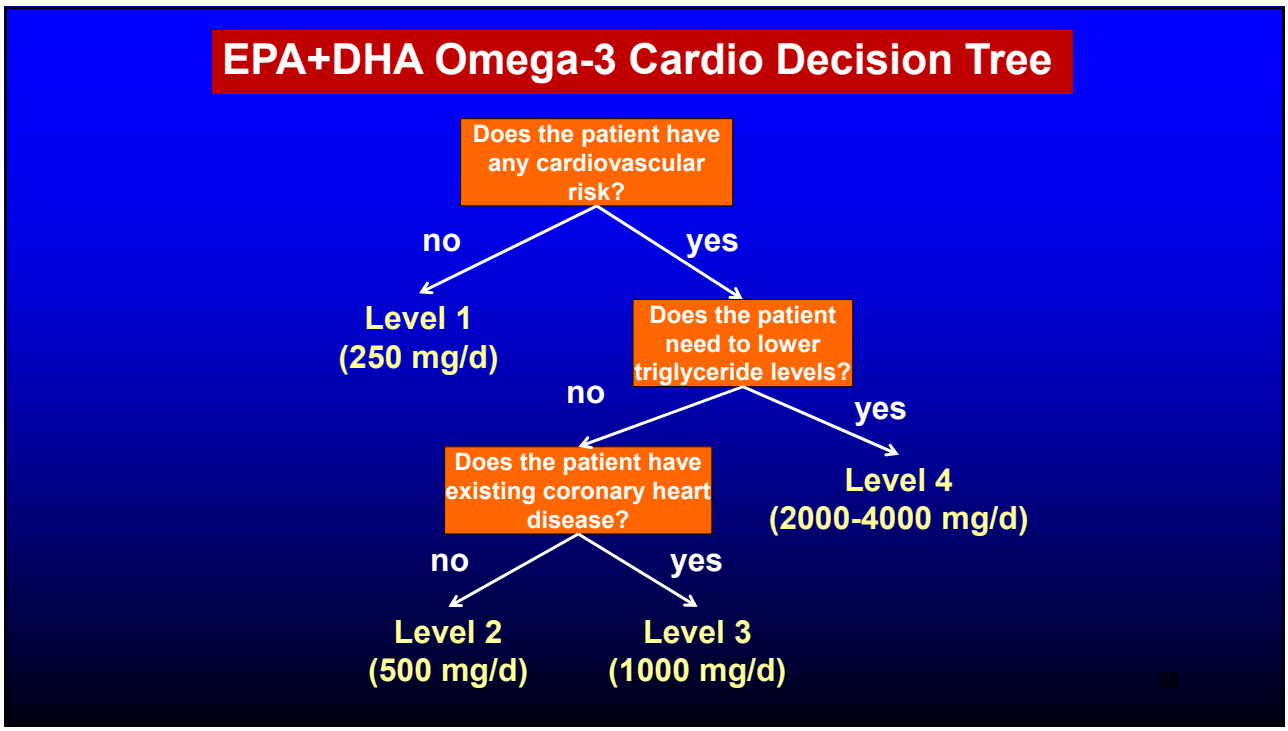
83

# EPA+DHA in dietary supplements


**Total EPA+DHA content = 935 mg per 1 softgel**

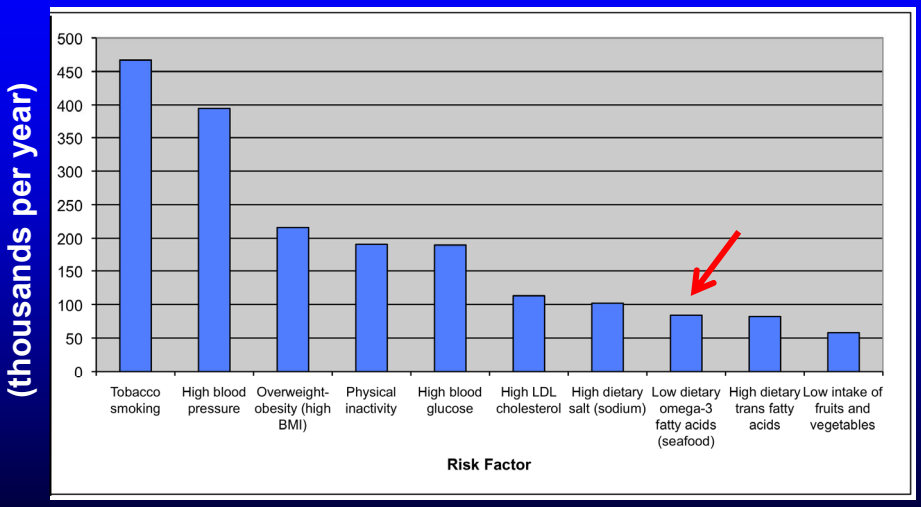
**4 Softgels = Approx. 4000 mg/day**

84


EPA+DHA Omega-3 Cardio Decision Tree
Does the patient have any cardiovascular risk?
no
yes
Level 1 (250 mg/d)
Does the patient need to lower triglyceride levels?
no
yes
Does the patient have existing coronary heart disease?
Level 4 (2000-4000 mg/d)
no
yes
Level 2 (500 mg/d)
Level 3 (1000 mg/d)
85

85

# Preventative Health Care in the U.S.




Ref: PLoS Med., 6(4), (2009).



86

# FISH OIL
# IN CARDIOVASCULAR PREVENTION

## RECOMMENDATIONS

- 2 - 3 fatty fish meals per week
- Supplements - 1 g EPA/DHA daily

Alaswad K, Lavie CJ ,Milani RV, et al. The Ochsner Journal 2002;4:83-90

87

# Target Omega 3 Intake: EPA+DHA

- 1° Prevention: 500 mg/d
- 2° Prevention: 1000 mg/d
- Triglyceride Rx: 3,000 to 6,000 mg/d

88

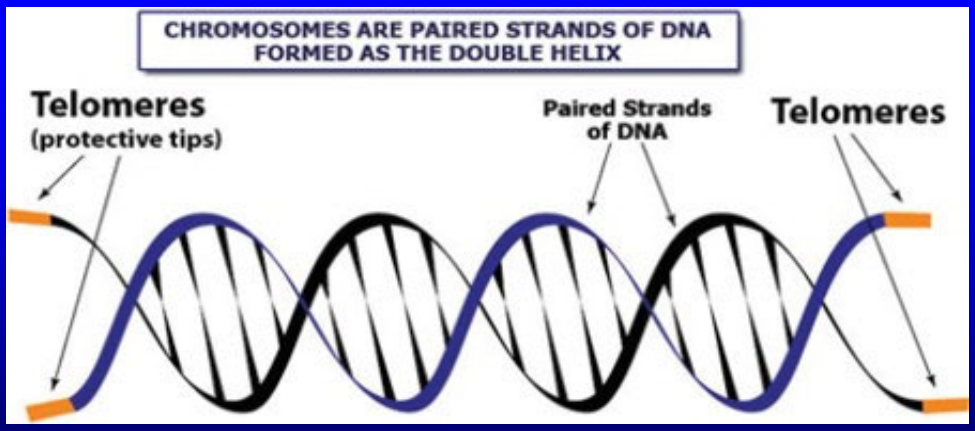
# Safety of Omega-3

- Prolonged bleeding times with "hyper-Eskimo" doses (eg over 20 g/d)
- No increased bleeding with up to 7g EPA/DHA
- Concern about mercury and other contaminants
- FDA advised children and pregnant or nursing women to avoid fish with high mercury (eg swordfish, tile fish, big mackerel, and shark)
- Salmon, sardines, trout, oysters, herring are quite low in mercury

Lavie CJ et al. JACC 2009;54:585-594.

89

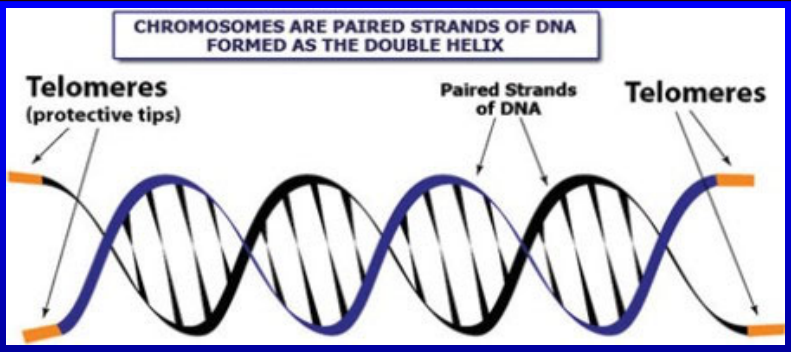
# Telomeres




- Telomeres : biological clock
- Reflects physiological age/health more accurately than chronological age
- Longer telomeres = healthier cells, better longevity

90

# Telomeres

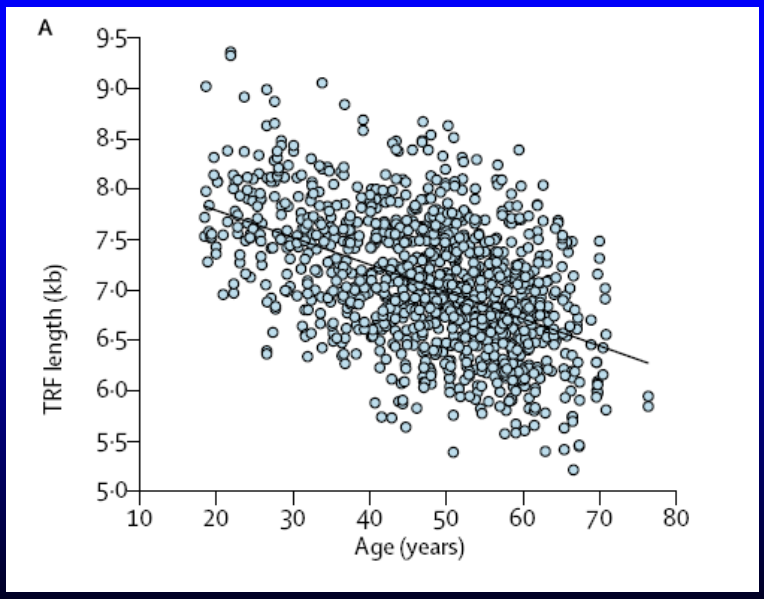



**Shorter telomeres predispose to:**

- Atherosclerosis, stroke, MI, CHF
- Alzheimer's Disease
- Cancer
- Death
- Diabetes

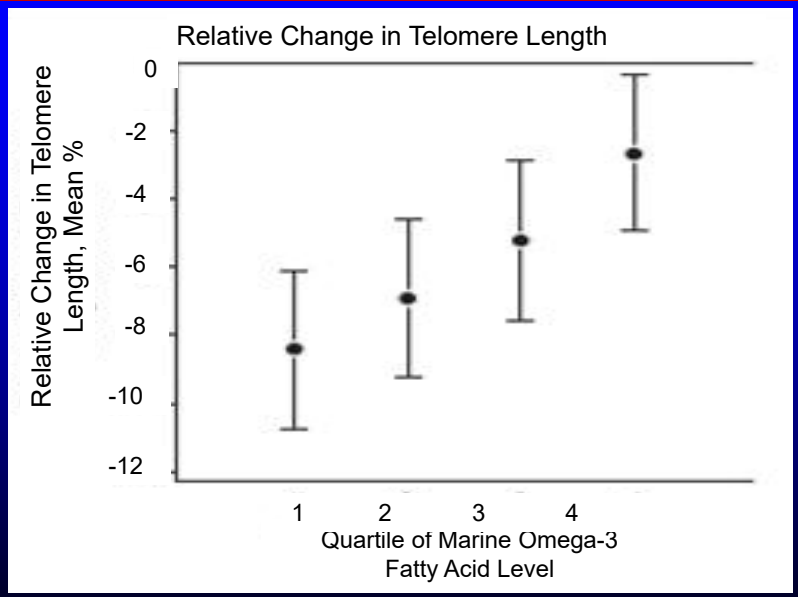
91

## Relation between telomere length and age




92

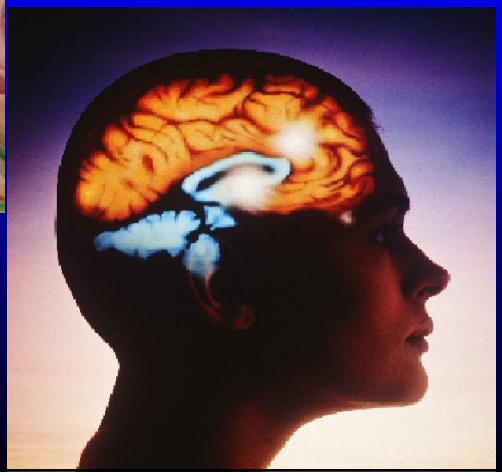
# Omega-3 Reduces Telomere Shortening




Farzanheh-Far R etal;JAMA 2010;303(3):250-257

93

# Omega 3: Brain and Eye Health



94

# Omega-3 and Dosing in Preventive Cardiology

- The Evidence for Omega-3's Clinical Benefits are strong, especially at doses close to 1 gram EPA/DHA daily
- Dose Matters , and doses over 1 g per day of EPA/DHA seem to have even greater benefits
- For higher risk patients , achieving doses of over 1 g/d, especially in the 1.5-2 g/d levels of EPA/DHA, may be preferred
- JELIS/REDUCE-IT doses of 2-4 g/d may be ideal, realizing these studies were just pure EPA

95

## Omega-3 and Future Directions-

- None of the major studies or meta-analyses, including our own, adequately assessed omega-3 in heart failure
- Additional Omega-3 studies are needed in both HF reduced ejection fraction and HF preserved ejection fraction
- Potentially, 2 or 4 g/d or even higher doses could be beneficial in different classes of HF
- Additional studies are needed to determine the relative effects of EPA vs DHA and combinations in different disease states

96

## Summary /Take Home Points

- Prevention in CVD is a realistic opportunity
- Diet is a modifiable risk factor that can be influenced by the individual with clinician guidance
- There is robust evidence for omega-3 benefits in cardiovascular health
- Omega-3 intake and status is in the very low to low range for most of the globe, including for the United States
- Supplementation with Omega-3s, a low-cost and low toxicity therapy, especially higher doses, provides substantial benefits for the individual and society
- Omega-3 intake via regular fish consumption and/or supplements should be part of prevention strategies

97

# Omega-3 Major References

- Many references are on each slide
- O'keefe EL et al. Mayo Clinic Proc 2019;94: 2524-2533
- Bernasconi AA et al. Mayo Clinic Proceedings 2021; 96: 304-313
- Farukhi ZM et al. MCP 2021; 96: 277-279
- Elagizi A et al. Nutrients 2021; online Open Access, ahead of print

98

# Fish Oil In Cardiovascular Prevention

"Fish oil is a whale of a story that not surprisingly gets bigger with every telling."

Rogans JA. N Engl J Med 1987;316:626-627

99

# Swimming Upstream on Omega-3 Recommendations for Cardiovascular Health: Recent Research Finds Recommended Dosages May Not be Enough

**Carl J. Lavie, MD, FACC, FACP, FCCP**

Medical Co-Director, Cardiac Rehabilitation and Prevention
Director, Exercise Laboratories

Ochsner Heart and Vascular Institute
New Orleans, Louisiana

100