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Omega 3s and Cardiovascular Disease Prevention

Wednesday, February 4, 2026

Presented by
Carl J. Lavie, MD, FACC, FACP, FCCP

Moderator:
Lisa Diewald, MS, RDN, LDN
Associate Director
MacDonald Center for Nutrition Education and Research

Finding slides for today's webinar

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Continuing Professional Development Details

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- Villanova University M. Louise Fitzpatrick College of Nursing is accredited as a provider of nursing continuing professional development by the American Nurses Credentialing Center's Commission on Accreditation. This activity awards 1 contact hour for nursing professionals.

- This activity awards 1.0 CPEU in accordance with the Commission on Dietetic Registration's CPEU Prior Approval Program.

    - Level 2 activity
    - Suggested CDR Performance Indicators: 7.2.3, 9.1.5, 9.2.1, and 9.2.4
    - To receive CE credit, you must attend the entire program.

If you are an RD or RDN and have any questions or concerns about this continuing education activity, you may contact CDR directly at QualityCPE@eatright.org.

The Q&A Box is Open!

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- Questions are welcome!
- Please send through the Q&A Box during the presentation.
- Q&A session will follow the program.

Disclosures

Dr. Lavie served as a speaker and consultant for DSM Nutritional Products and GOED (related to omega-3) and with Amgen (unrelated to omega-3). The relevant financial relationships listed for this individual have been mitigated.

The Nurse Planner will monitor the program for any evidence of commercial bias.

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Carl J. Lavie, Jr.,MD,FACC,FACP,FCCP
Professor of Medicine
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Director, Exercise Laboratories
John Ochsner Heart and Vascular Institute

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Omega 3s and Cardiovascular Disease Prevention

Presented by
Carl J. Lavie, MD, FACC, FACP, FCCP

Omega-3 and Cardiovascular Disease Prevention- Update on the Overall Evidence

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

Medical Co-Director, Cardiac Rehabilitation and Prevention
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Ochsner Heart and Vascular Institute
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MEDICAL SCHOOL
THE UNIVERSITY OF QUEENSLAND
AUSTRALIA
Ochsner Health

Fish Oil /Omega-3 Lavie COI/Disclosures

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

Learning Objectives

- Cite specific CV health outcomes related to EPA and DHA Omega-3 intake;
- Identify resources for getting omega-3 levels checked and reasons why patients should have this information ;
- Provide accurate information for patients about how to increase omega-3 levels.

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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

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

Daily Intake

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

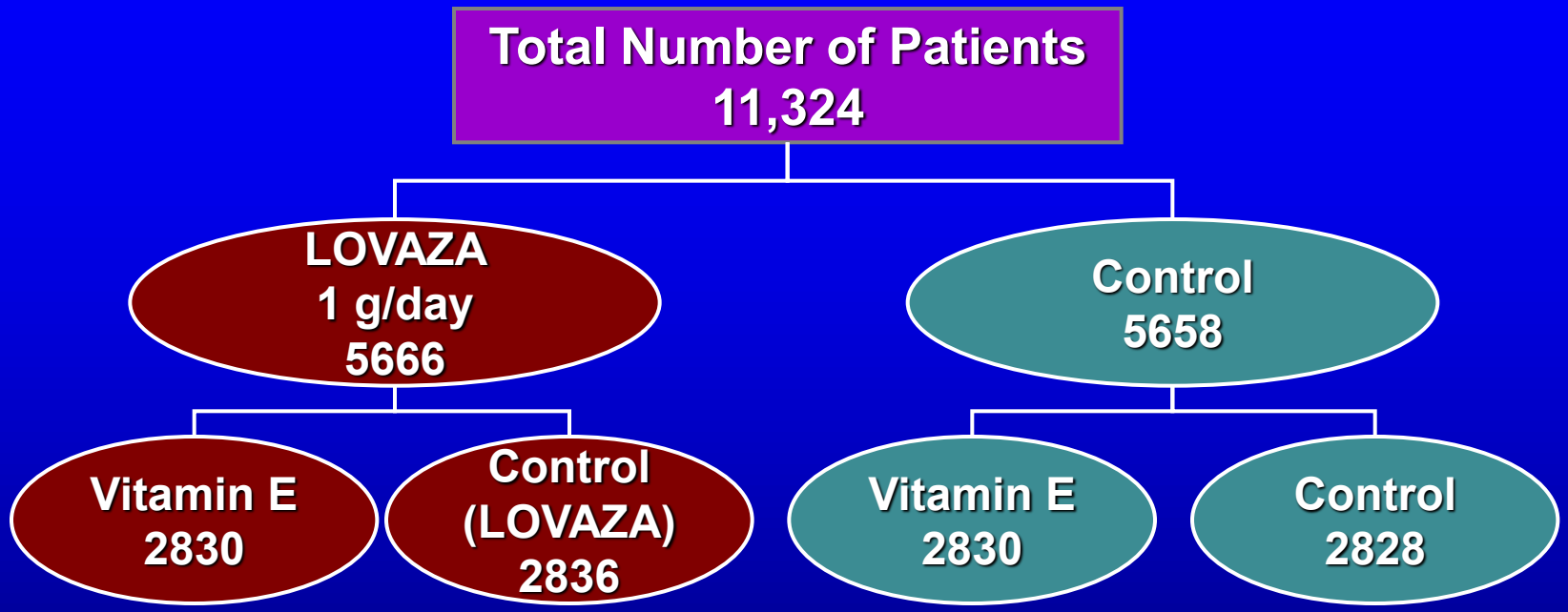
Norway: Exceptional Life Expectancy

Omega-3 and CVD – Trends in CHD

- DART
- GISSI – Prevenzione
- JELIS

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

The GISSI-Prevenzione Trial: Post MI



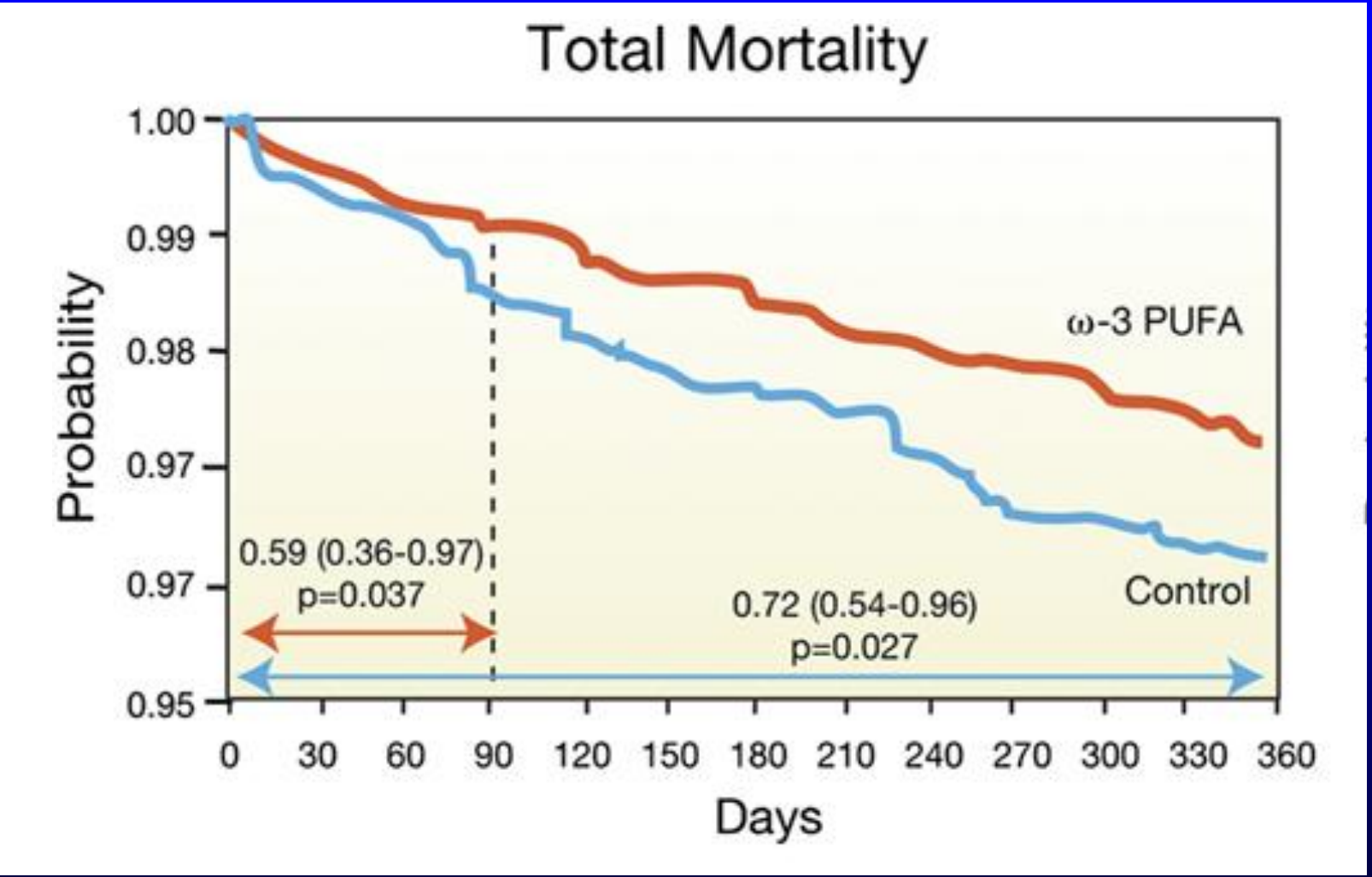
» Hard endpoints. Duration: 3.5 years (start 1993). Patients post-MI within 3 months

- 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.

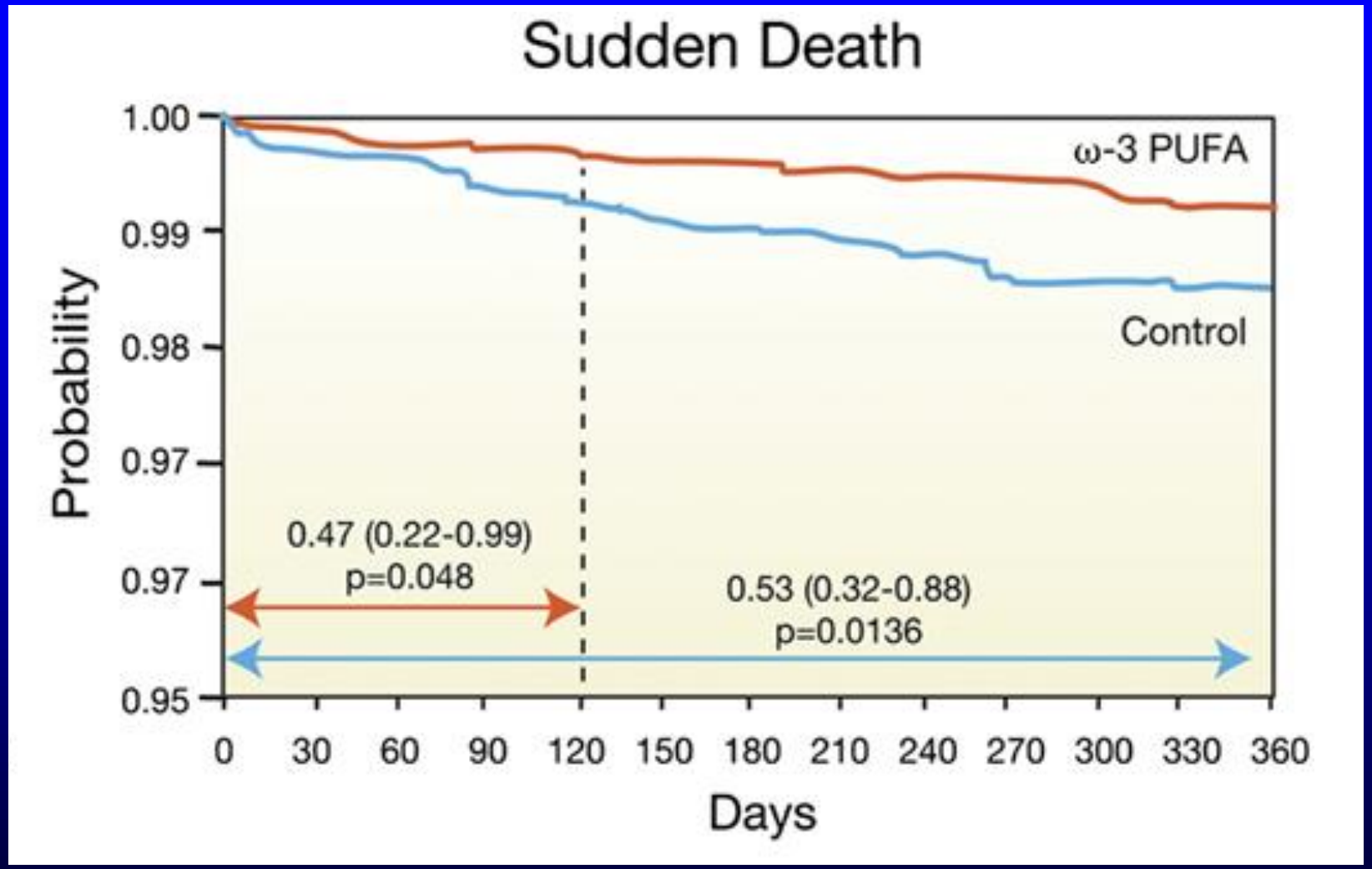
GISSI-Prevenzione Investigators [published correction appears in *Lancet*. 2001;357:642]. *Lancet*. 1999;354:447-455.

Fish Oil and Post-MI Prognosis-The GISSI Prevenzione



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

Fish Oil and Post-MI Prognosis-The GISSI Prevenzione



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

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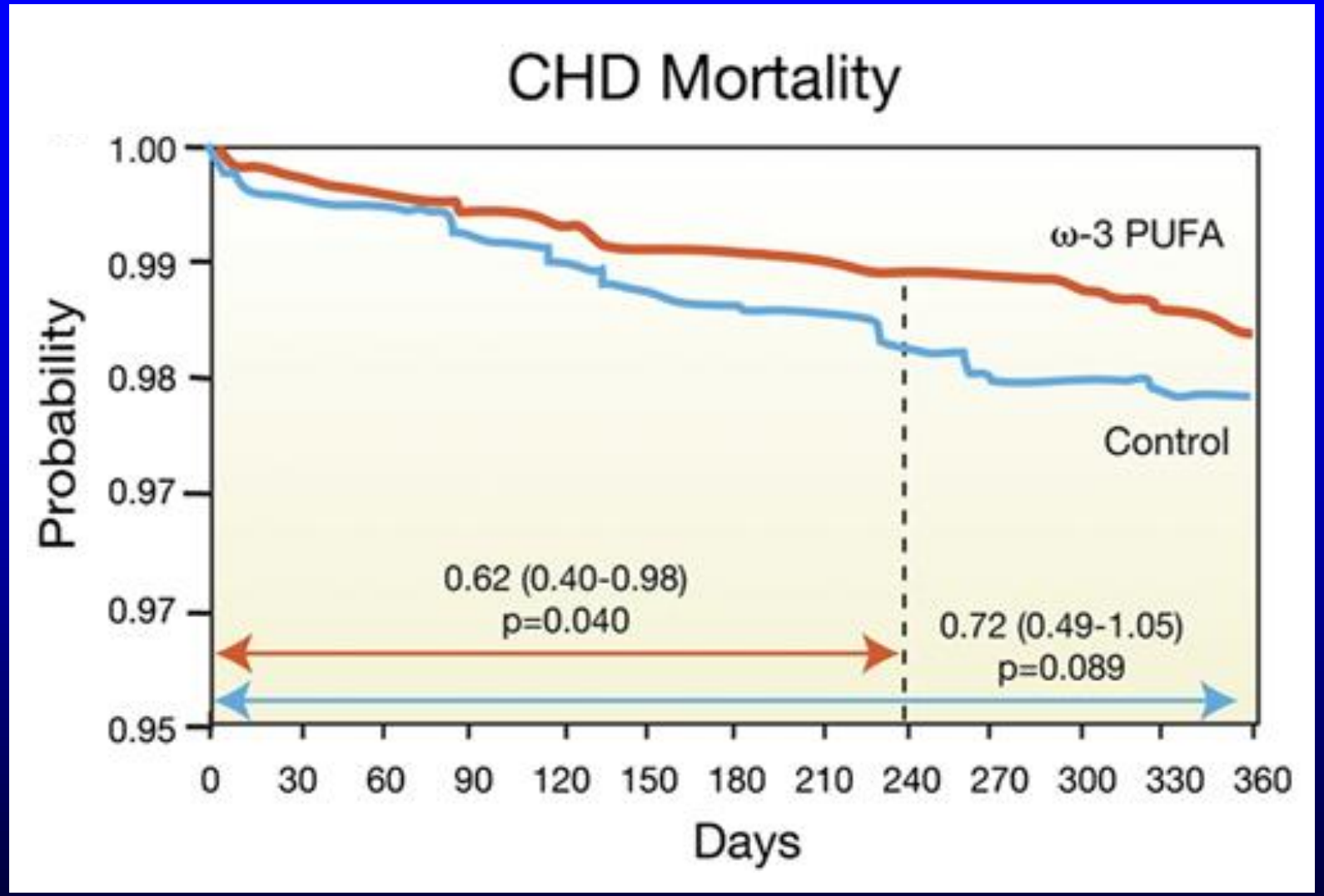
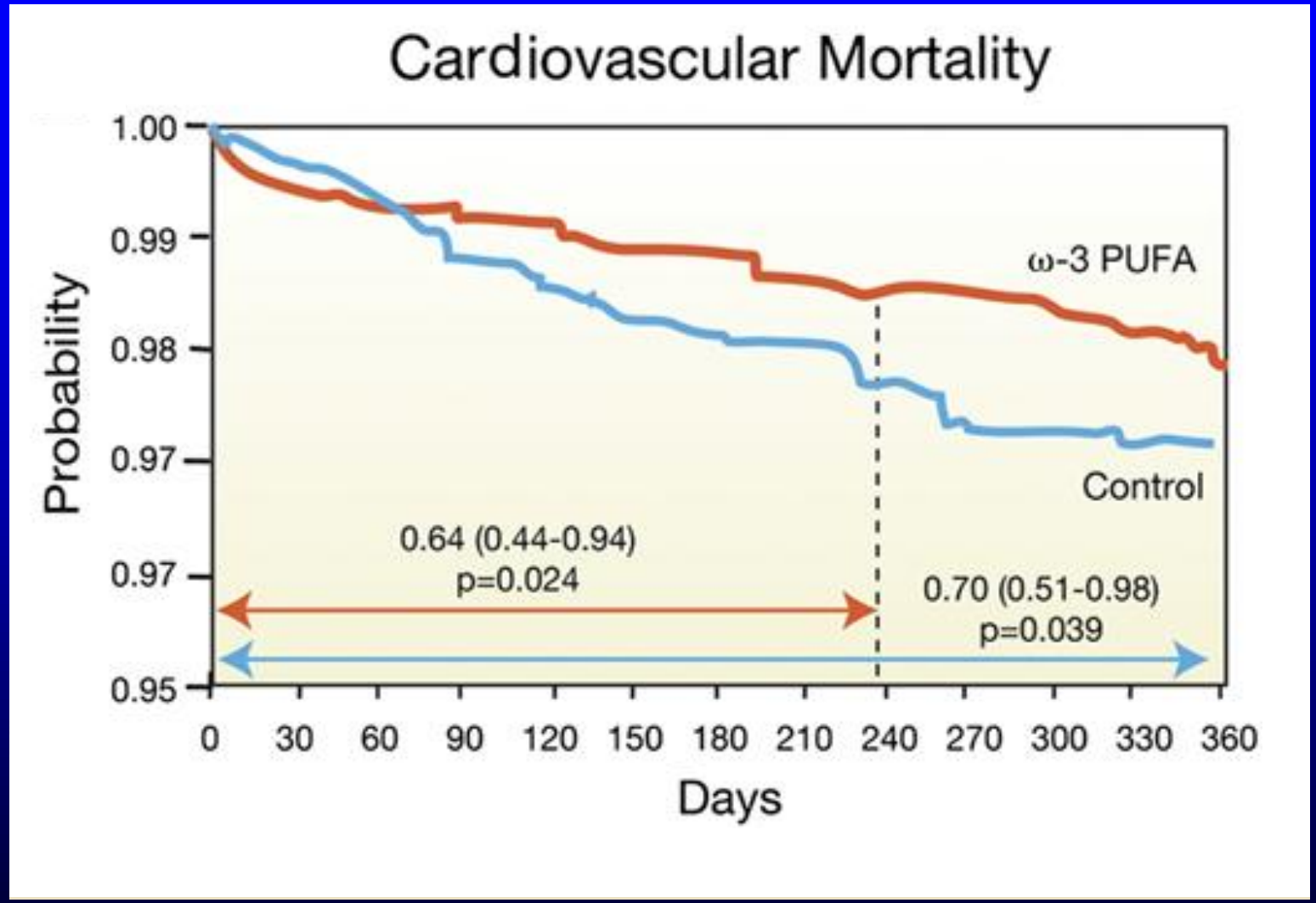


Marchioli R et al. Circulation 2002;105:1897-1903.

Fish Oil and Post-MI Prognosis-The GISSI Prevenzione



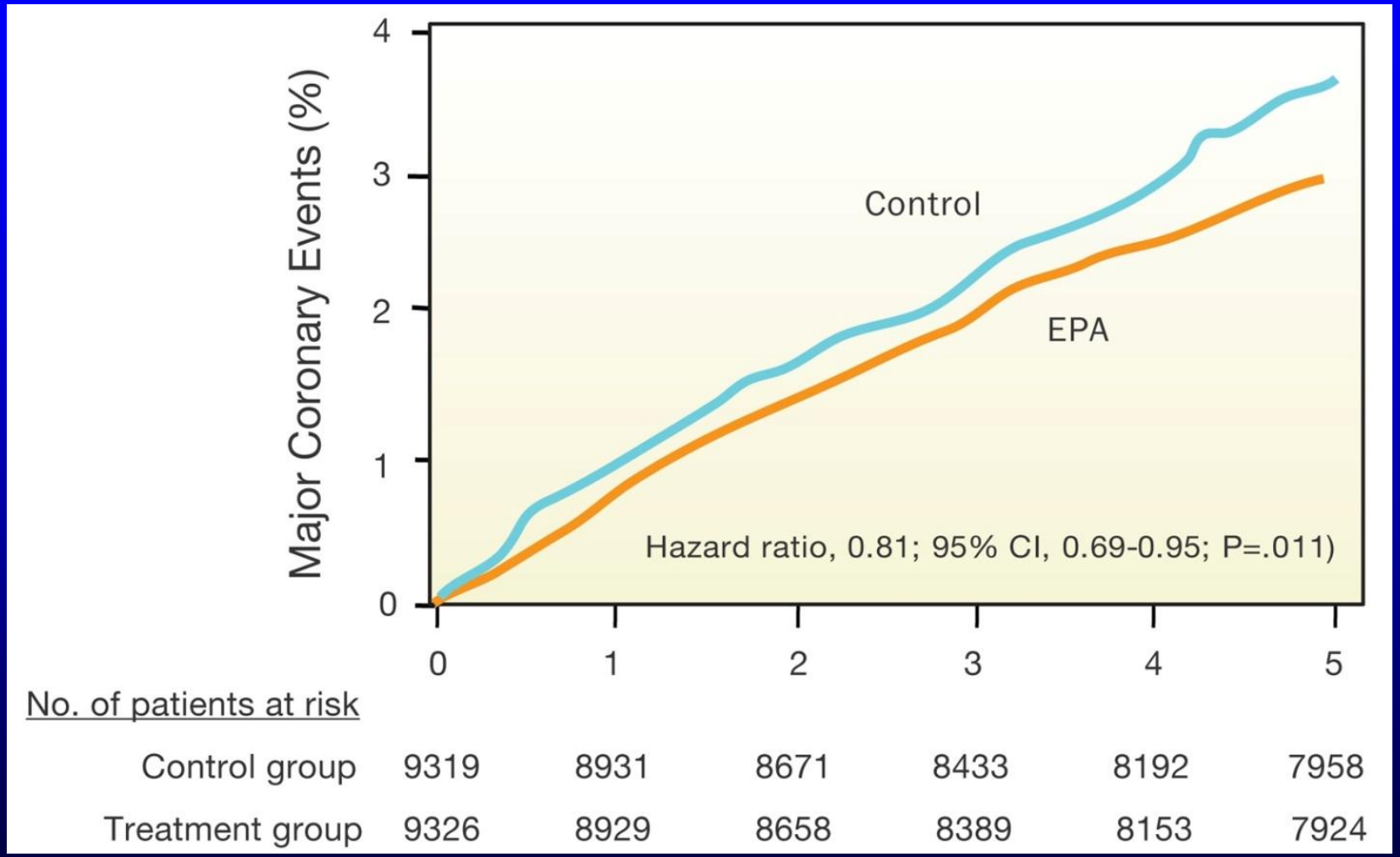
Marchioli R et al. Circulation 2002;105:1897-1903.

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

EPA in Primary Prevention



No. of patients at risk

Control group	9319	8931	8671	8433	8192	7958
Treatment group	9326	8929	8658	8389	8153	7924

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

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 | 1ª Prevention=14,981 | 2ª Prevention=3,664

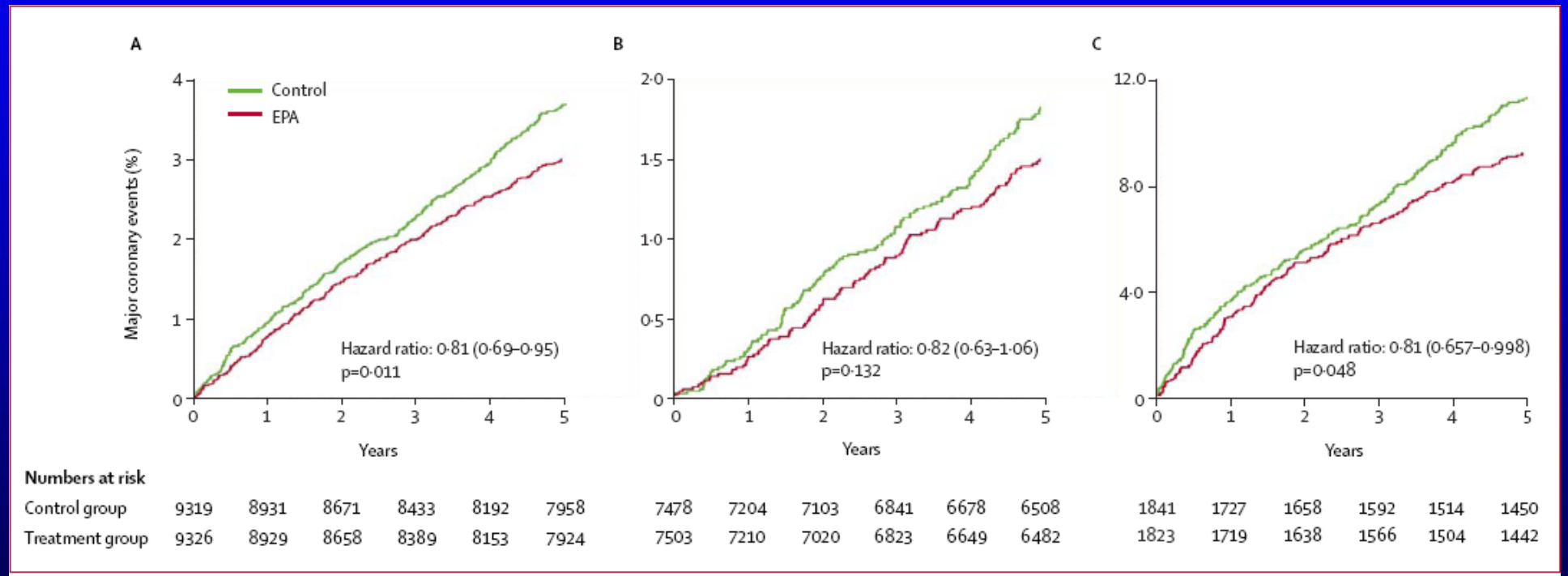


Figure 2: Kaplan-Meier estimates of incidence of coronary events in the total study population (panel A), the primary prevention arm (panel B) and the secondary prevention arm (panel C)

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

JELIS – EPA blood level and CHANGE in Risk

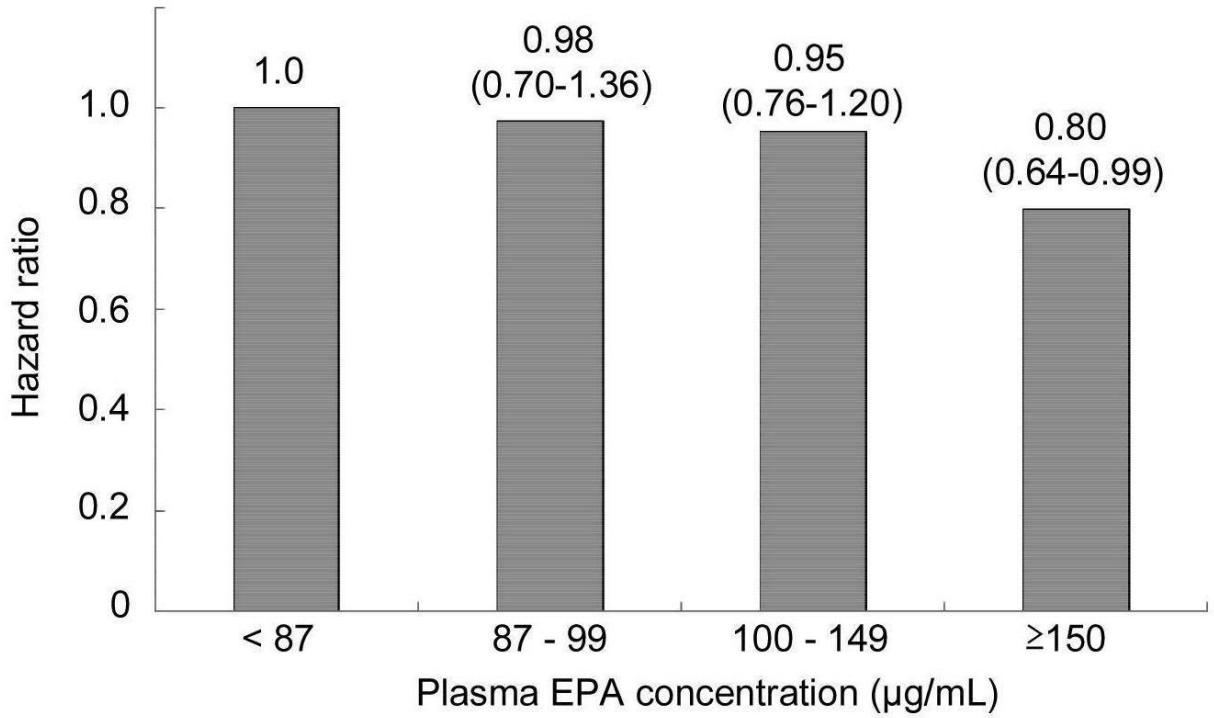


Fig. 3. Relationship between on-treatment EPA concentration and adjusted risk of major coronary events.

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

Omega-3 and 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.

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.

MAYO CLINIC

EDITORIAL

January 2017
Volume 92
Number 1

MAYO CLINIC
PROCEEDINGS

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

See also page 15

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 sub-

significantly 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

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

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.

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

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

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

Recent Major Omega-3 RCTs

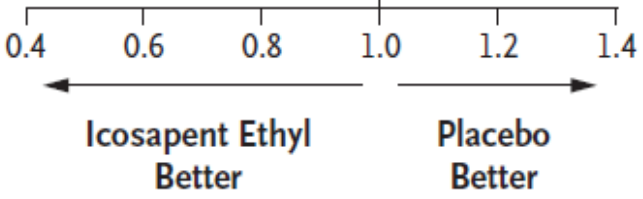
NEJM

- 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

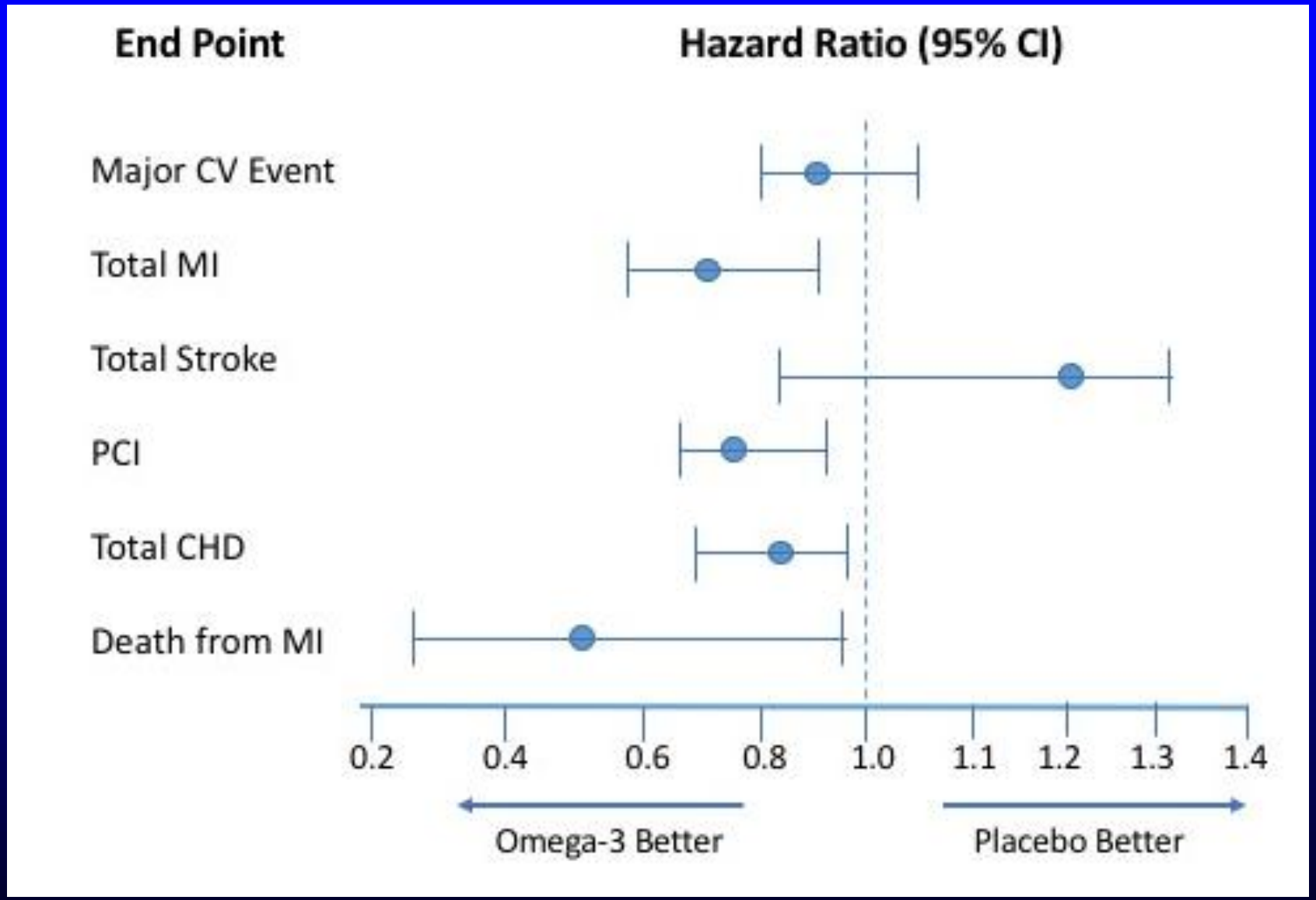
Benefits of EPA in REDUCE-IT

End Point	Hazard Ratio (95% CI)	P Value for Interaction
Primary composite	0.75 (0.68–0.83)	<0.001
Key secondary composite	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	0.65 (0.55–0.78)	<0.001
Cardiovascular death	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	0.77 (0.69–0.86)	<0.001
Death from any cause	0.87 (0.74–1.02)	—



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

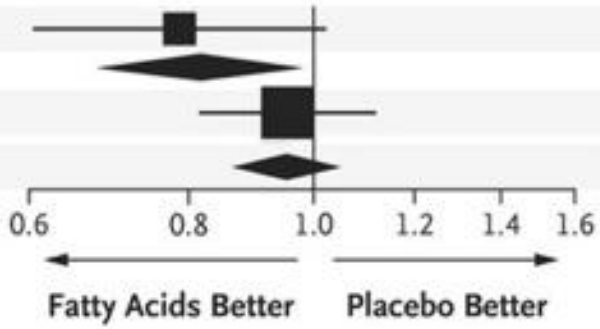
Benefits of Omega-3 in VITAL



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

Benefits of Omega-3 in ASCEND

Cause of Death	Fatty Acids (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)
	no. of patients with event (%)		
Coronary	100 (1.3)	127 (1.6)	0.79 (0.61–1.02)
Vascular	**196 (2.5)**	**240 (3.1)**	**0.82 (0.68–0.98)**
Cancer	305 (3.9)	319 (4.1)	0.95 (0.82–1.12)
All causes	**752 (9.7)**	**788 (10.2)**	**0.95 (0.86–1.05)**



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

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

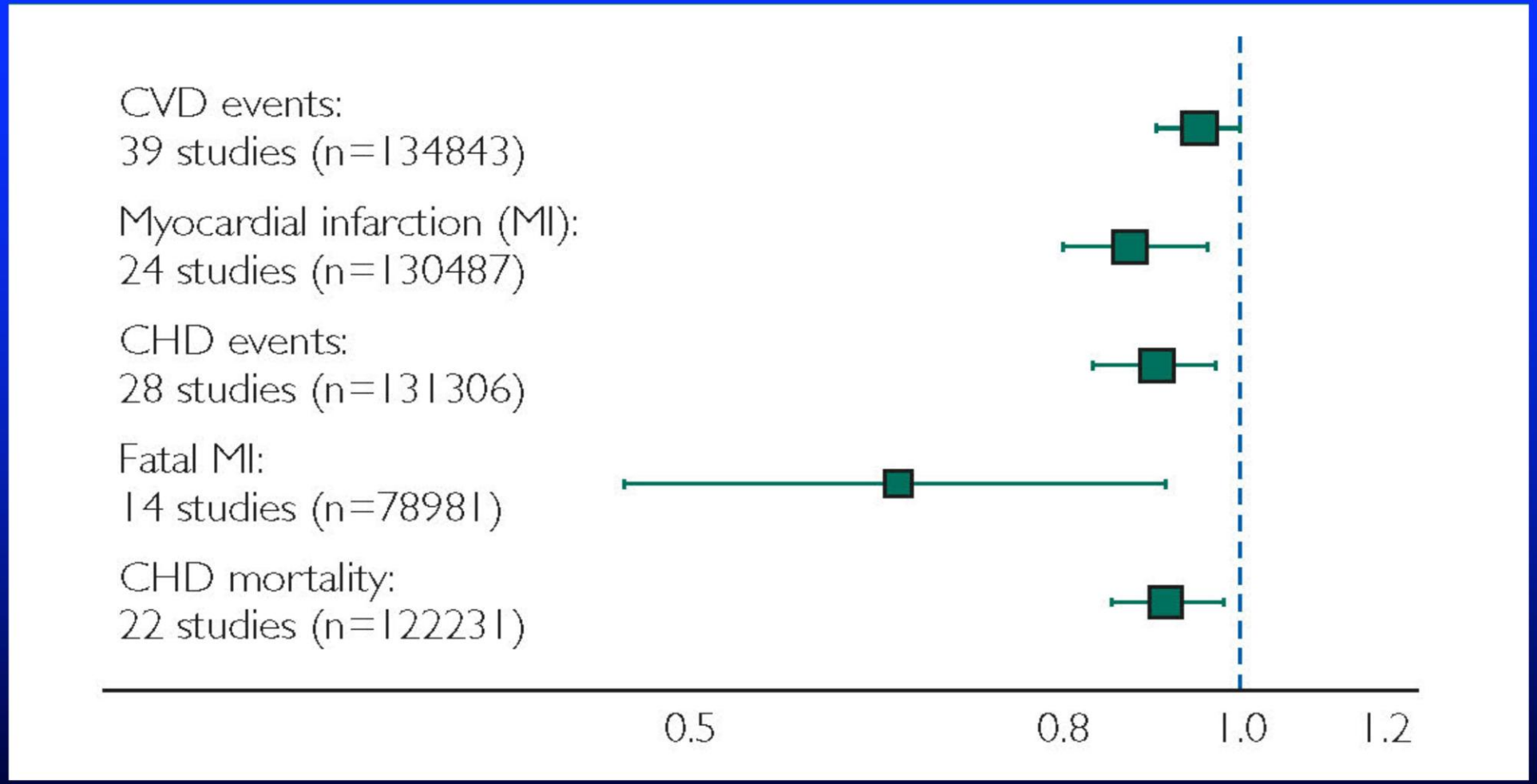
Bernasconi AA, Wiest MM, Lavie CJ, et al. Mayo Clin Proc 2021; 96:304-313

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

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

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

SYSTEMATIC REVIEW AND META-ANALYSIS

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

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

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

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, 2.1 mg/L), 12 633 (96.6%) completed the trial with ascertainment of primary end point status

Visual Abstract
Editorial and Editor's Note
Supplemental content

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

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;96: 1371-1372

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; 96: 1371-1372

Updated Meta-Analysis of Omega-3 RCTs of Supplements

EPA vs EPA/DHA

Omega-3 Benefits Remain Strong Post-STRENGTH

To The Editor: Eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids, the 2 main omega-3 long-chain polyunsaturated fatty acids of marine origin, have shown promise for the prevention of cardiovascular disease (CVD) outcomes in animal studies and epidemiologic studies.[1] Although several recent trials have shown benefits, as summarized in *Mayo Clinic Proceedings* in 2019,[2] 2 randomized control trials published in late 2020 showed neutral results. The situation is summarized thoughtfully in a recent editorial by Farukhi et al, published in *Mayo Clinic Proceedings,*[3] which cited our recent meta-analysis[6] on the subject. The authors observe that the results of these new trials (Outcomes Study to Assess Statin Residual Risk Reduction With Epa-Nova in High CV Risk Patients With Hypertriglyceridemia [STRENGTH][4] and Omega-3 Fatty Acids in Elderly With Myocardial Infarction [OMEMI][5]) need to be examined in the context of existing research. In particular, they suggest that it is necessary to update the results and review the conclusions of our meta-analysis.

Following their suggestion, with the addition of these new trials (both of which meet our inclusion criteria), our analysis now covers 42 studies with a combined 149,359 participants. As only results for CVD and coronary heart disease (CHD) outcomes were made available in the 2 new trials, our original results[6] for myocardial infarction (MI) relative risk (RR), 0.87; 95% confidence interval [CI], 0.80 to 0.96, high GRADE certainty, fatal MI RR, 0.65; 95% CI, 0.46 to 0.91, moderate certainty and CHD mortality RR, 0.91; 95% CI, 0.85 to 0.98, low certainty remain unchanged.

The newly published results change slightly the meta-analysis estimates, but not the conclusions, for CVD events and CHD events. For CVD events, the pooled estimate is now RR, 0.96; 95% CI, 0.91 to 1.00 (changed from RR, 0.95; 95% CI, 0.90 to 1.00). For CHD events: RR, 0.91; 95% CI, 0.85 to 0.97 (changed from RR, 0.90; 95% CI, 0.84 to 0.97). These results are summarized in the Figure.

The effect remains dose dependent for MI; an additional 1 g/d in EPA and DHA is associated with a 9% reduction in MI but no longer for CVD events. None of the other conclusions is changed; the effect remains independent of the year of publication, the population baseline risk, or whether the long-chain polyunsaturated fatty acids agent consisted of only EPA or a combination of EPA and DHA.

Although we believe that understanding why a high-dosage trial, such as STRENGTH, failed to find an effect will require more research, the totality of the evidence, including now 42 studies involving almost 150,000 participants, shows statistically significant reductions in fatal MI (−35%), MI (−13%), CHD events, and CHD mortality (both −9%). This is still consistent with the conclusion that EPA and DHA intake is an effective lifestyle intervention for protection against CVD.

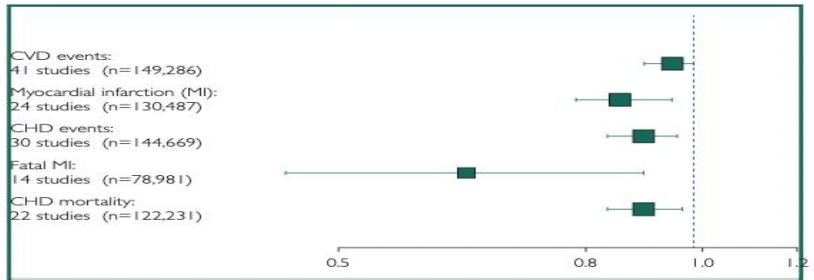


FIGURE. Pooled results from meta-analysis. The figure shows the pooled estimate of relative risk and 95% confidence interval, as well as the number of studies and combined number of participants. CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.

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print & web 4C/FPO

Bernasconoi A, Lavie C et al. MCP 2021; 96: 1371-1372

Fish Oil/Omega-3 in Heart Failure

Less than 1 gram helped a little-

Higher Dosage Needed???

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

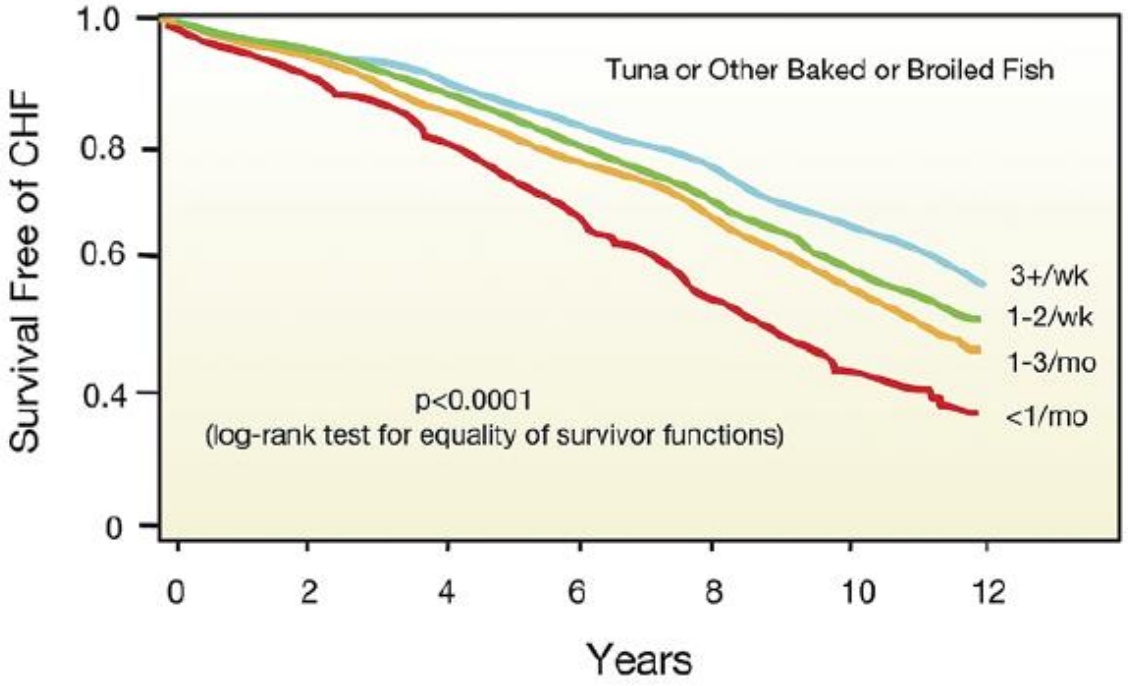

Figure 3 **Fish Intake and CHF**

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

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

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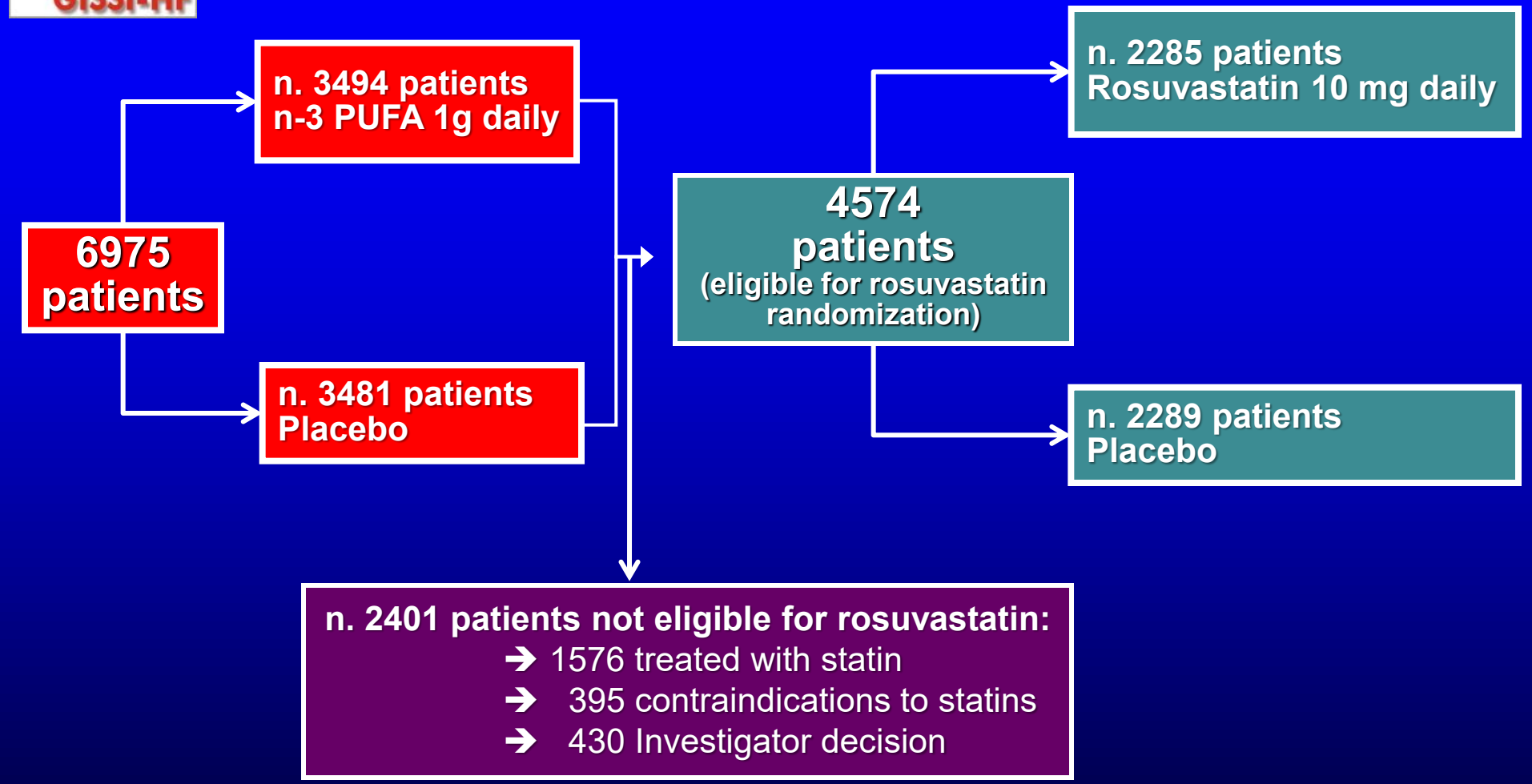
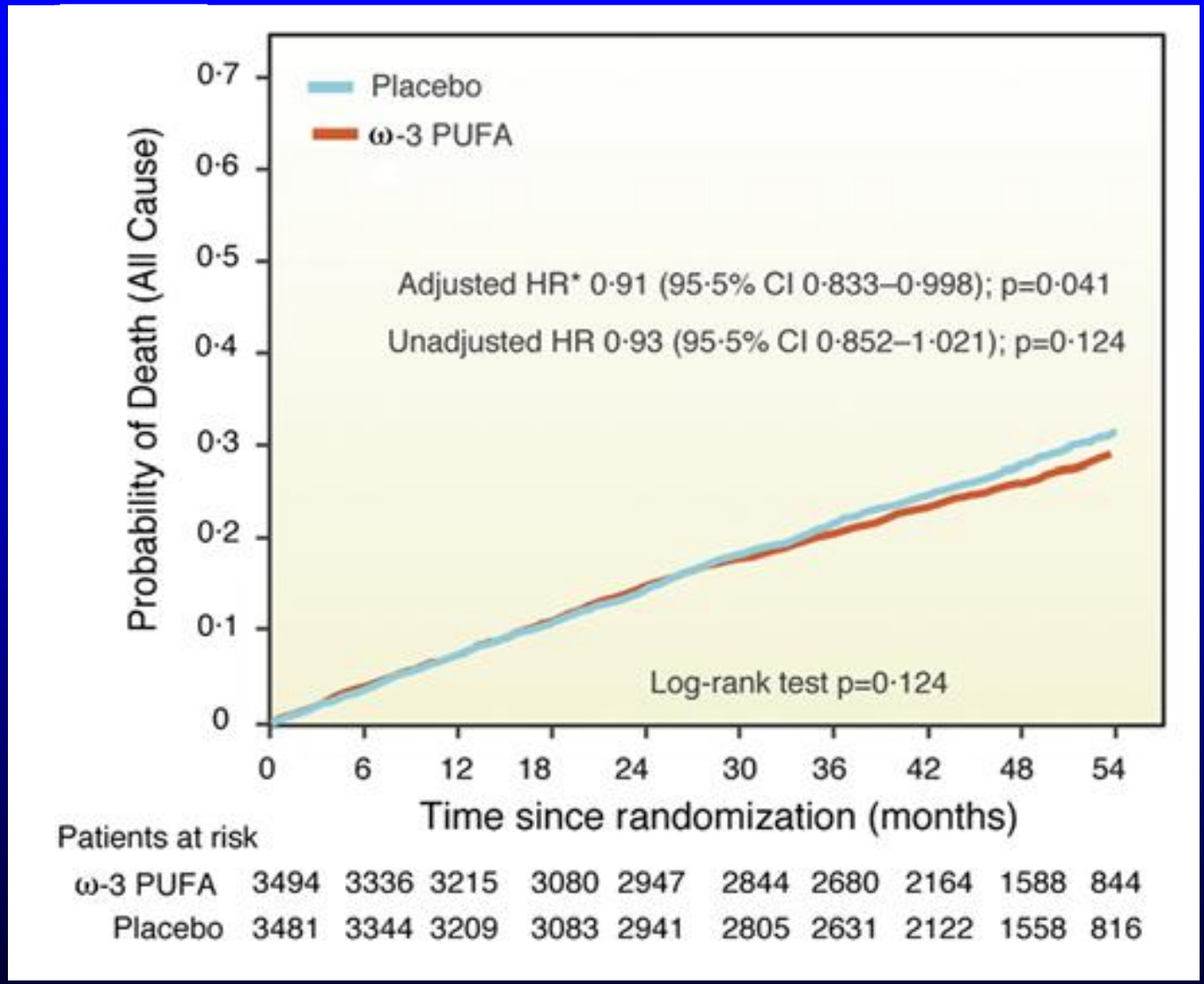
GISSI-HF Design

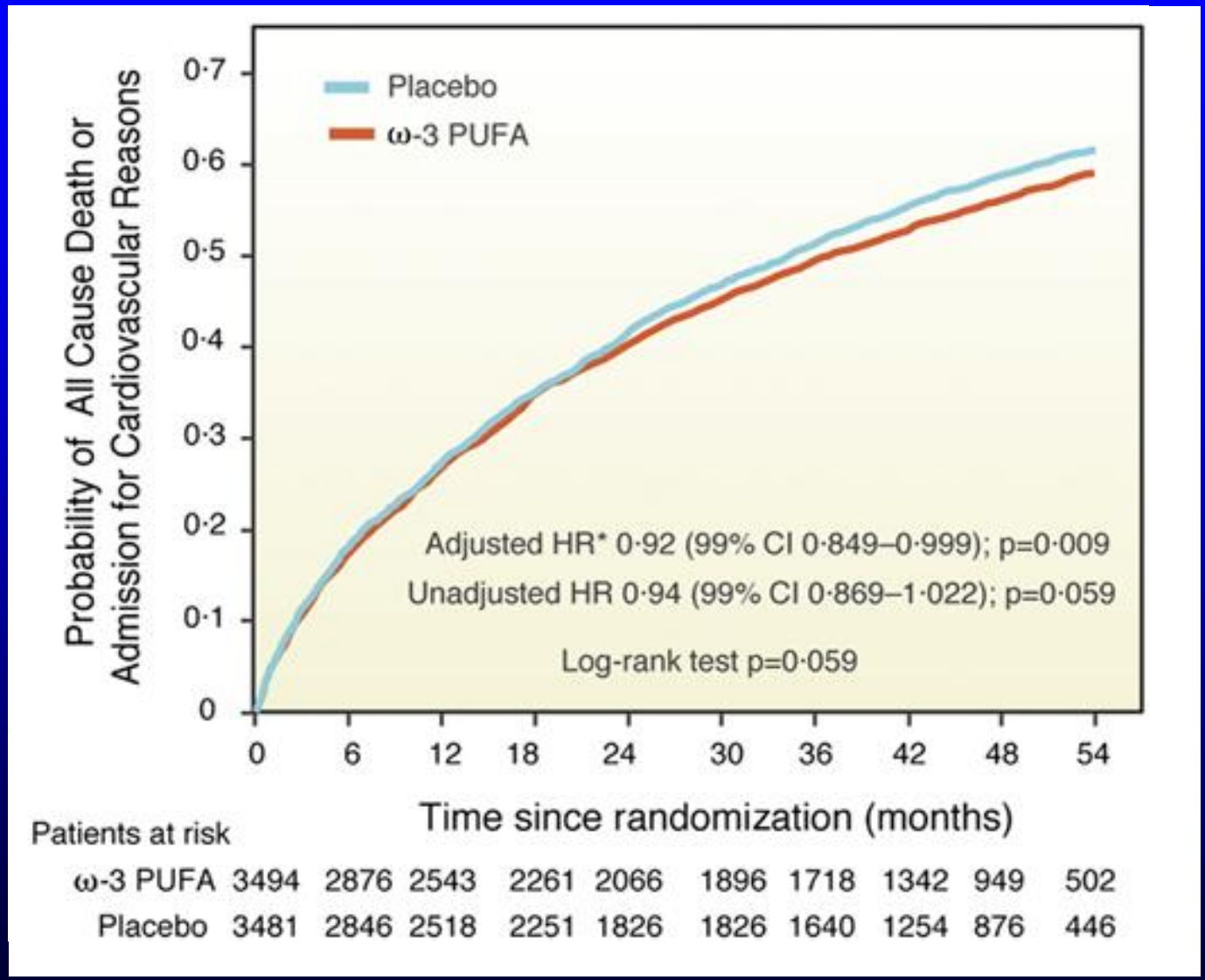


Fish Intake and HF Survival-GISSI-HF



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

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.

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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

JACC: HEART FAILURE
VOL. ■, NO. ■, 2019

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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

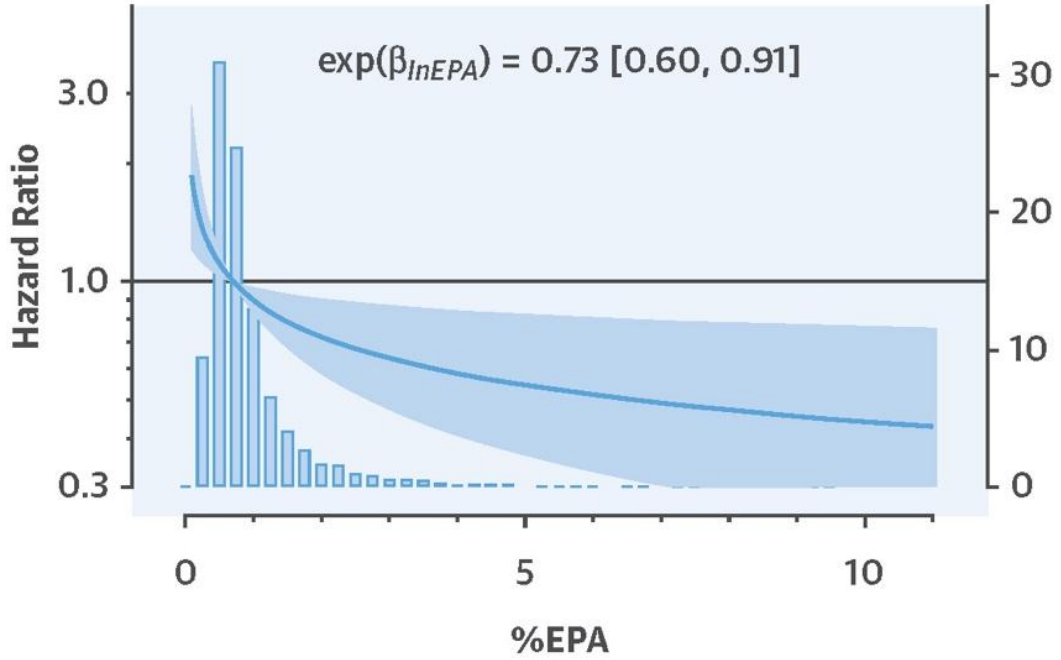
Omega-3 Levels Predict Development of Heart Failure

- 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.

CENTRAL ILLUSTRATION Eicosapentaenoic Acid Predict Hazard for All Heart Failure

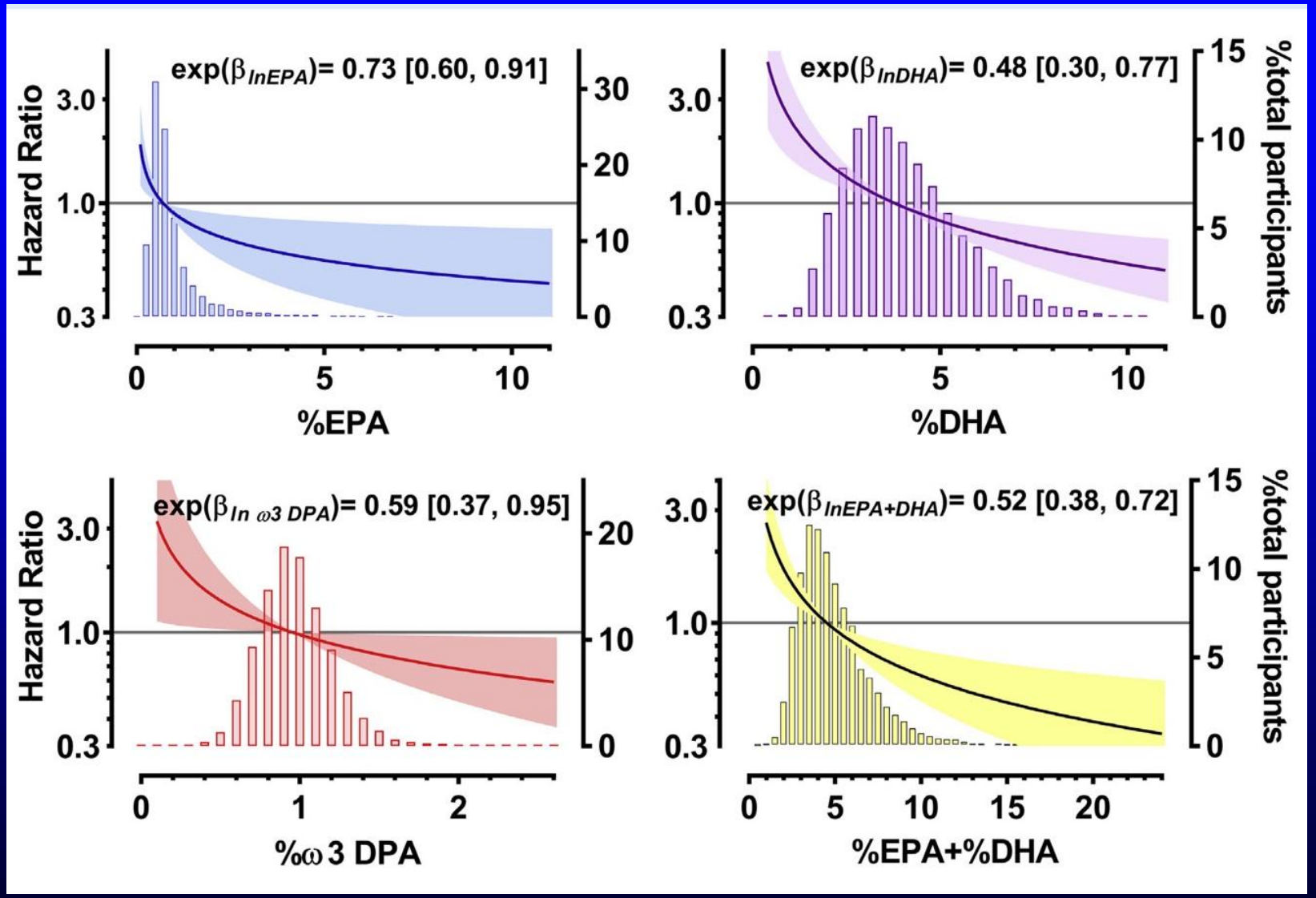
Higher EPA Levels are Associated with Reduced HF Incidence, But Most Participants have Levels Associated with High Risk



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

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

Omega-3 Levels and HF



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

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.

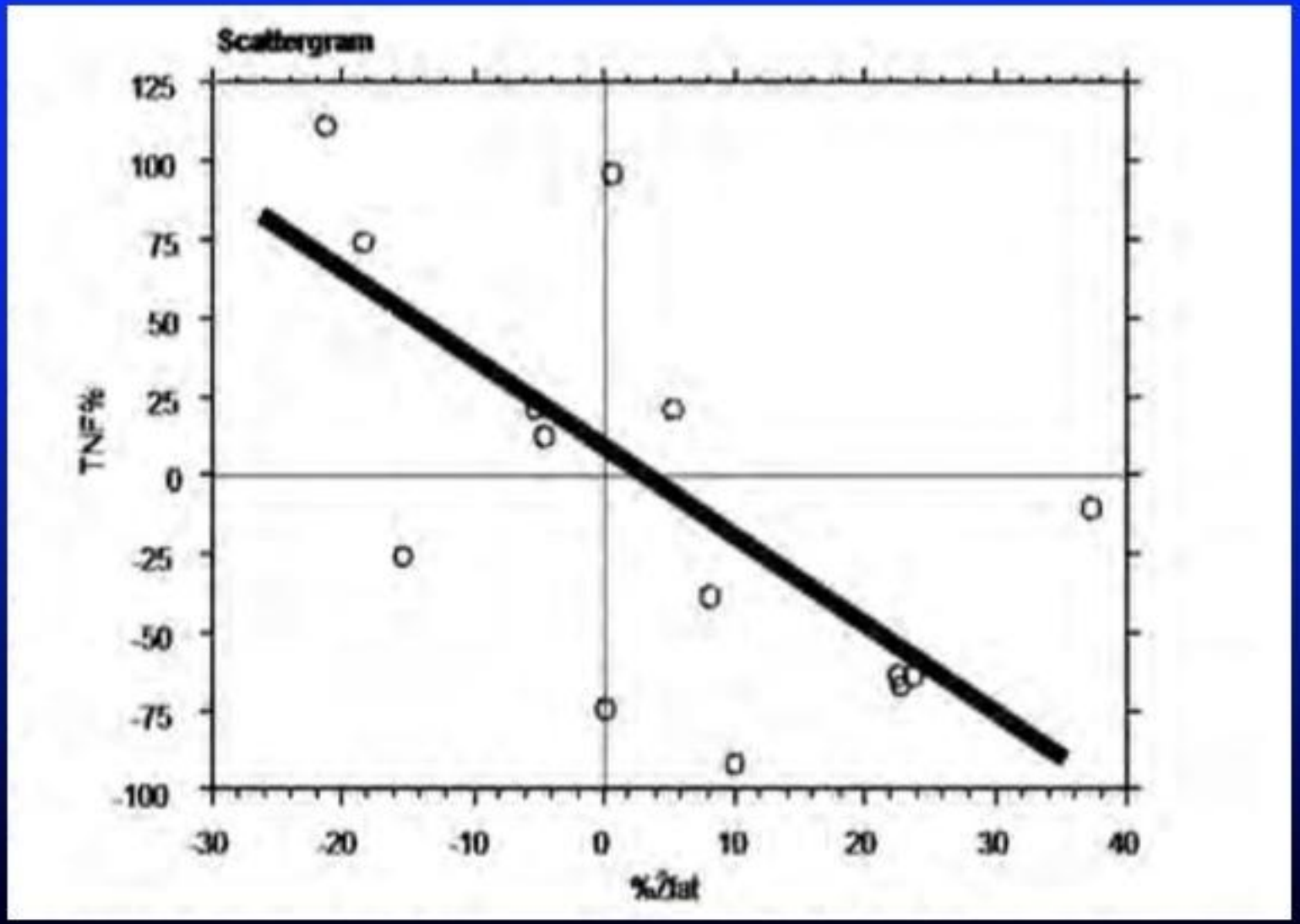
Mehra MR, Lavie CJ et al. JHLT 2006; 25:834-838.

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.

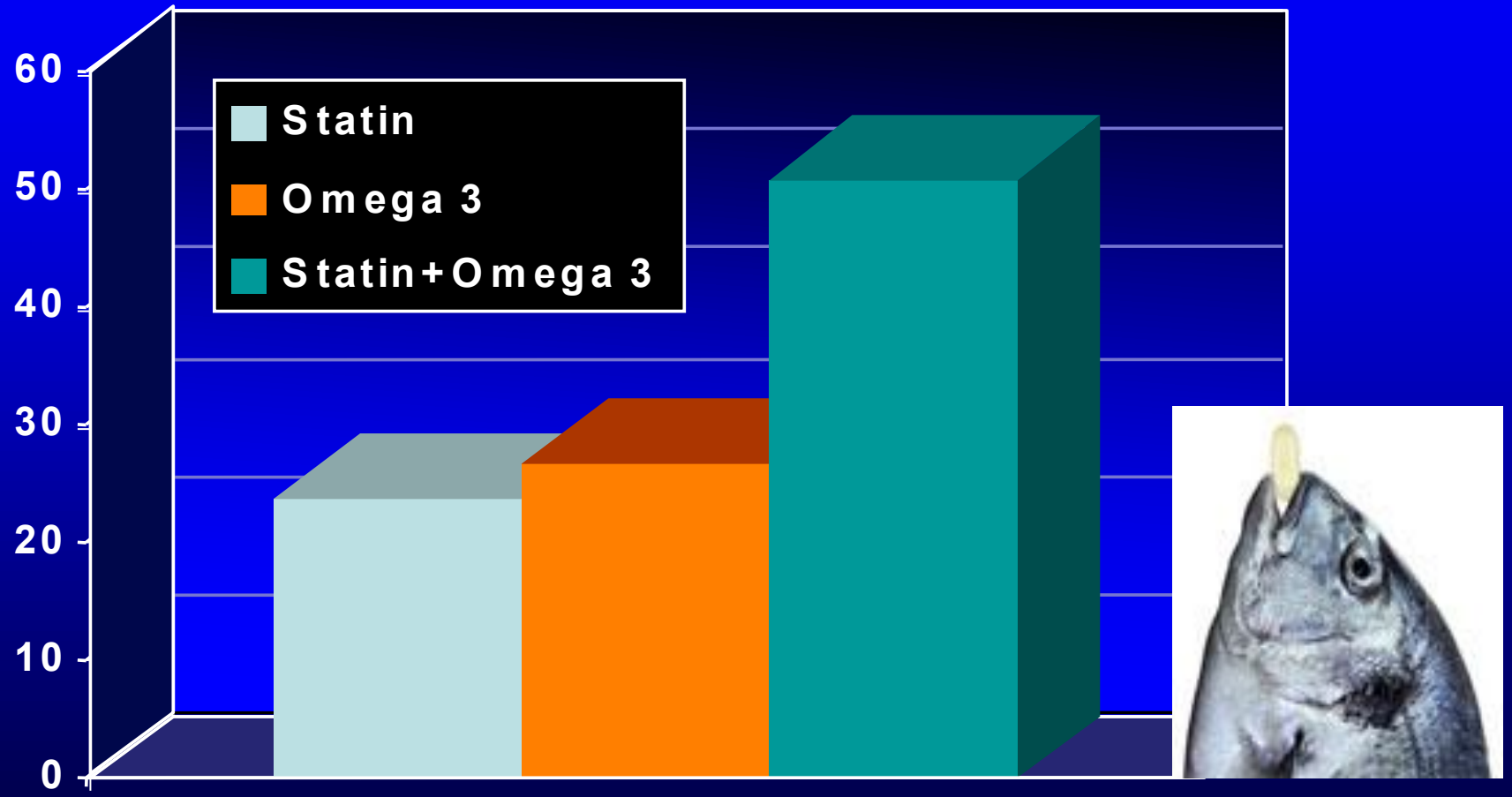
High Dose Omega-3 Improves Body Composition and Reduces TNF in Advanced HF



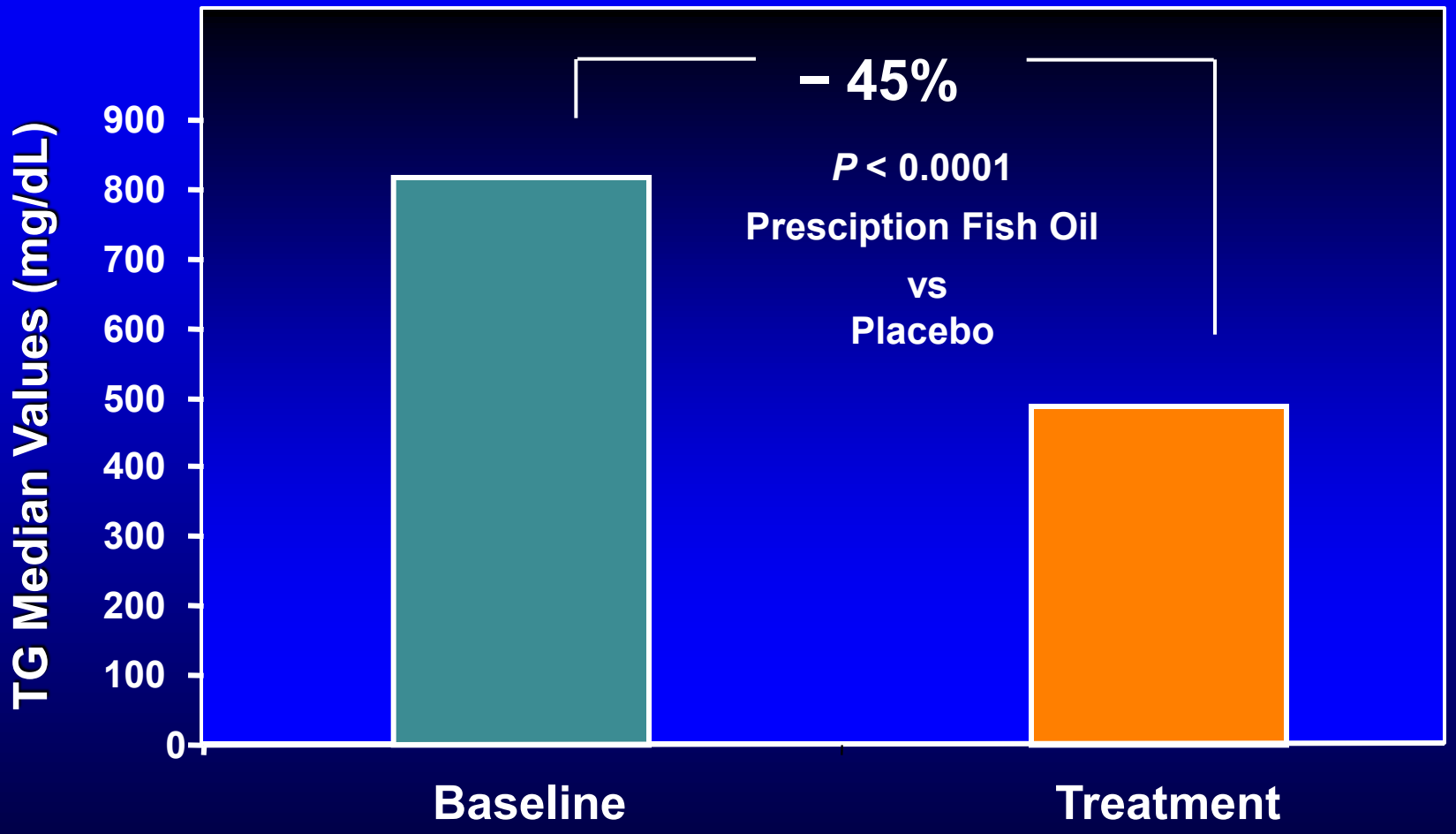
Mehra MR, Lavie CJ et al. JHLT 2006; 25:834-838.

Omega 3 for Triglyceride Rx

Heart 2001;85:544-548



Omega-3 4 grams/day Reduces Triglycerides 45%

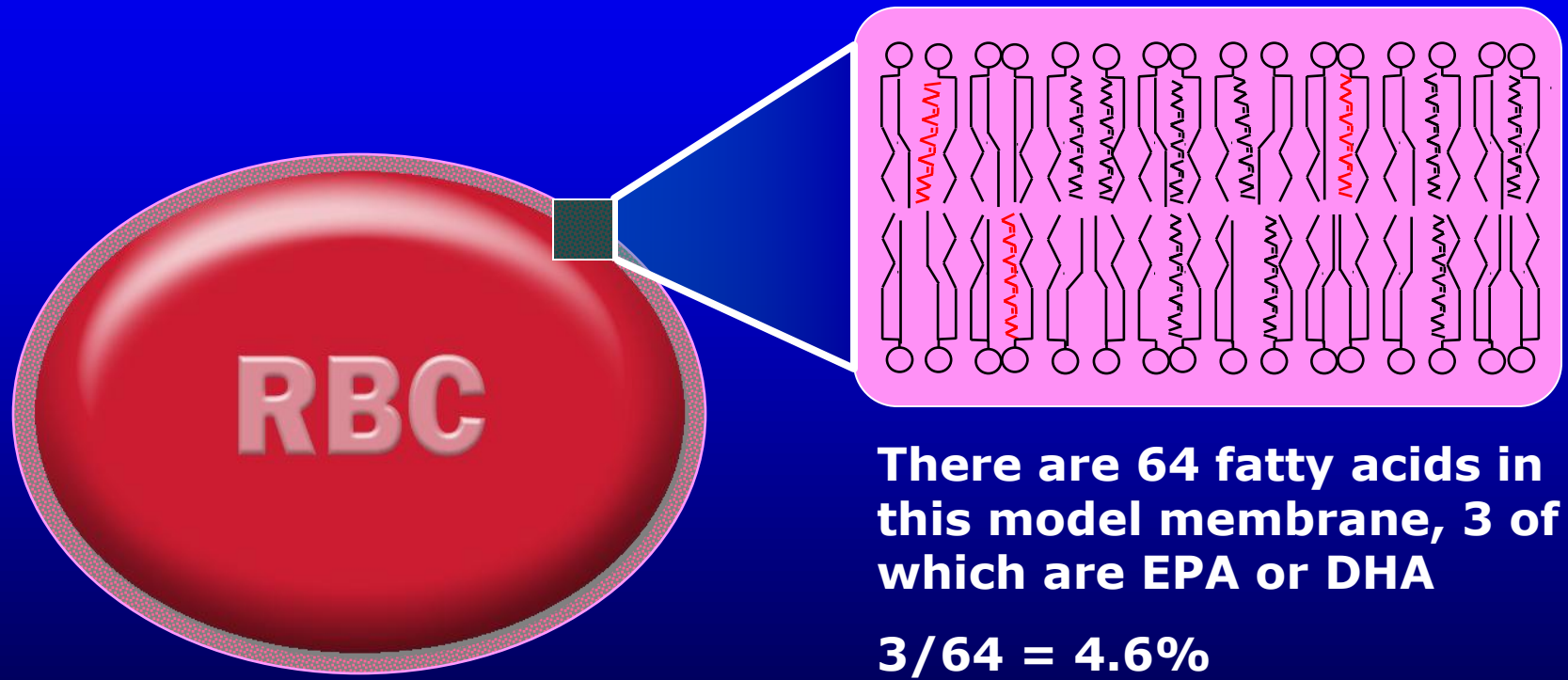


Stalenhoef AFH, de Graaf JD, Wittekoek ME, et al. The effect of concentrated n-3 fatty acids versus gemfibrozil on plasma lipoproteins, low density lipoprotein heterogeneity and oxidizability in patients with hypertriglyceridemia.

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

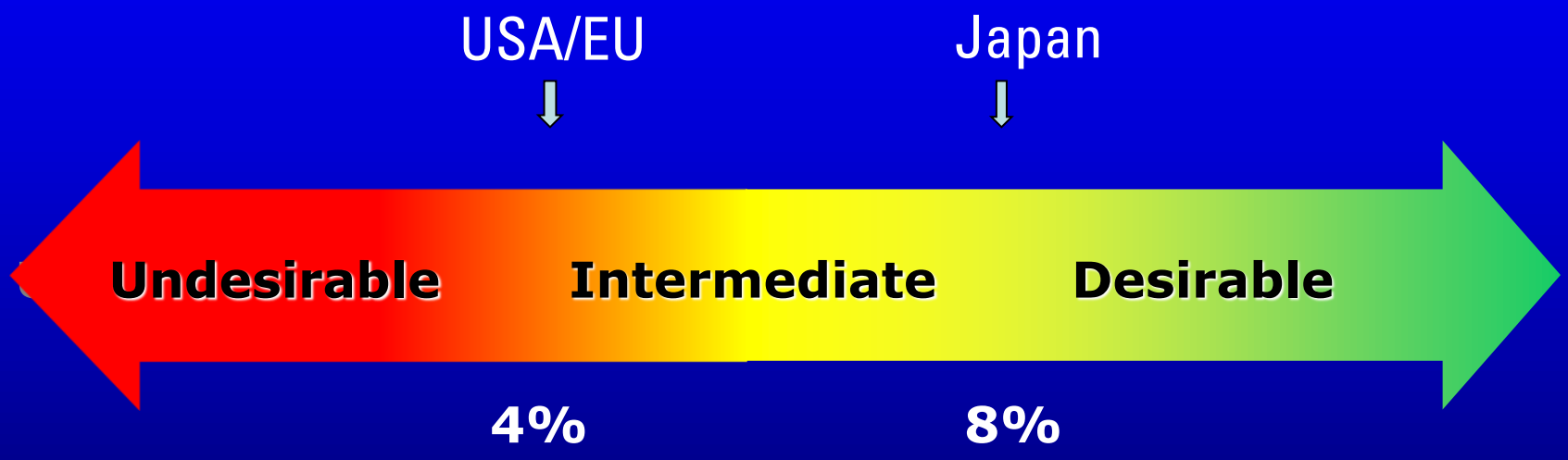
3/64 = 4.6%

HS-Omega-3 Index = 4.6%

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

Proposed HS-Omega-3 Index Risk Zones

Relative Risk for Death from CHD

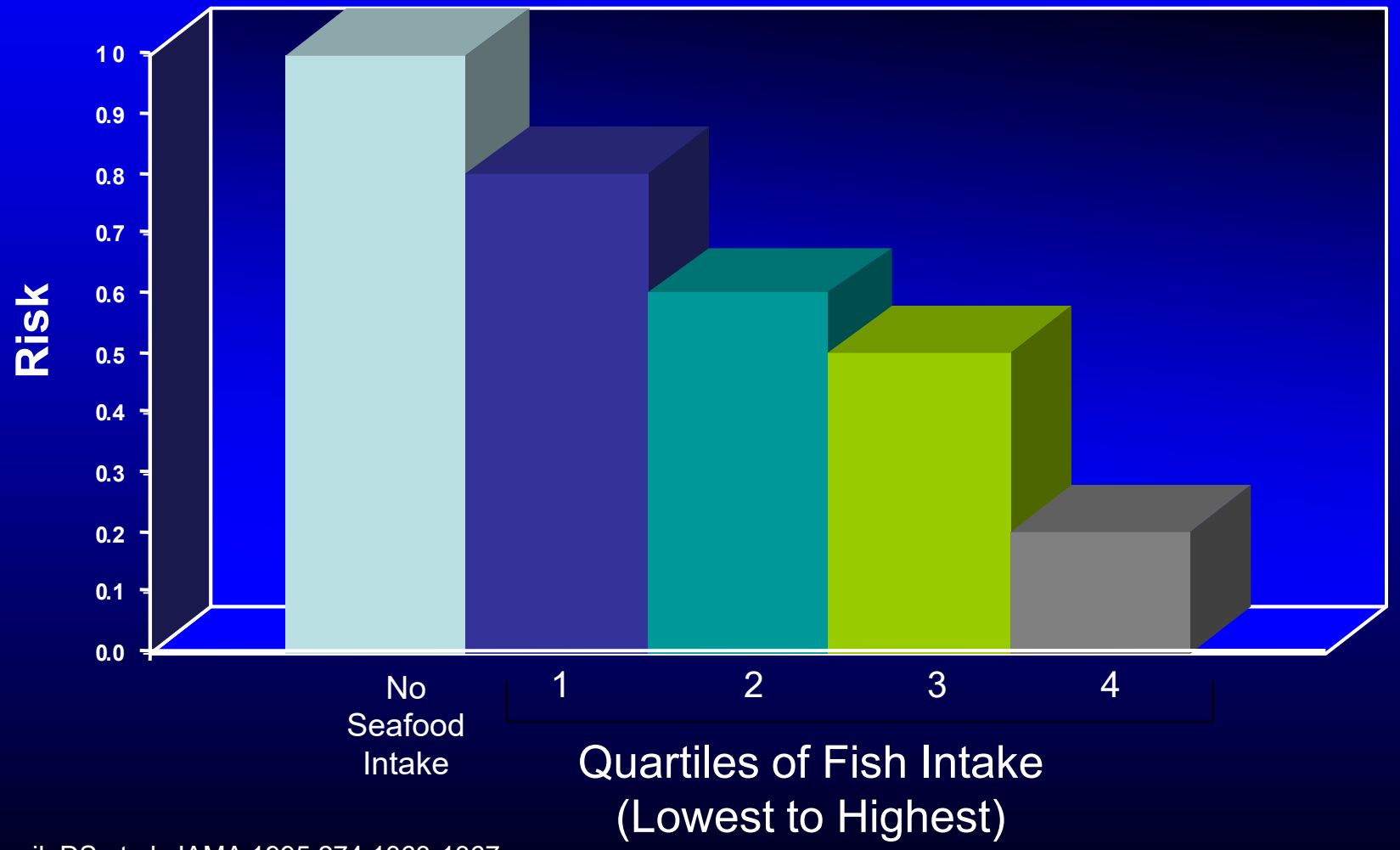


Percent of EPA+DHA in RBC

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

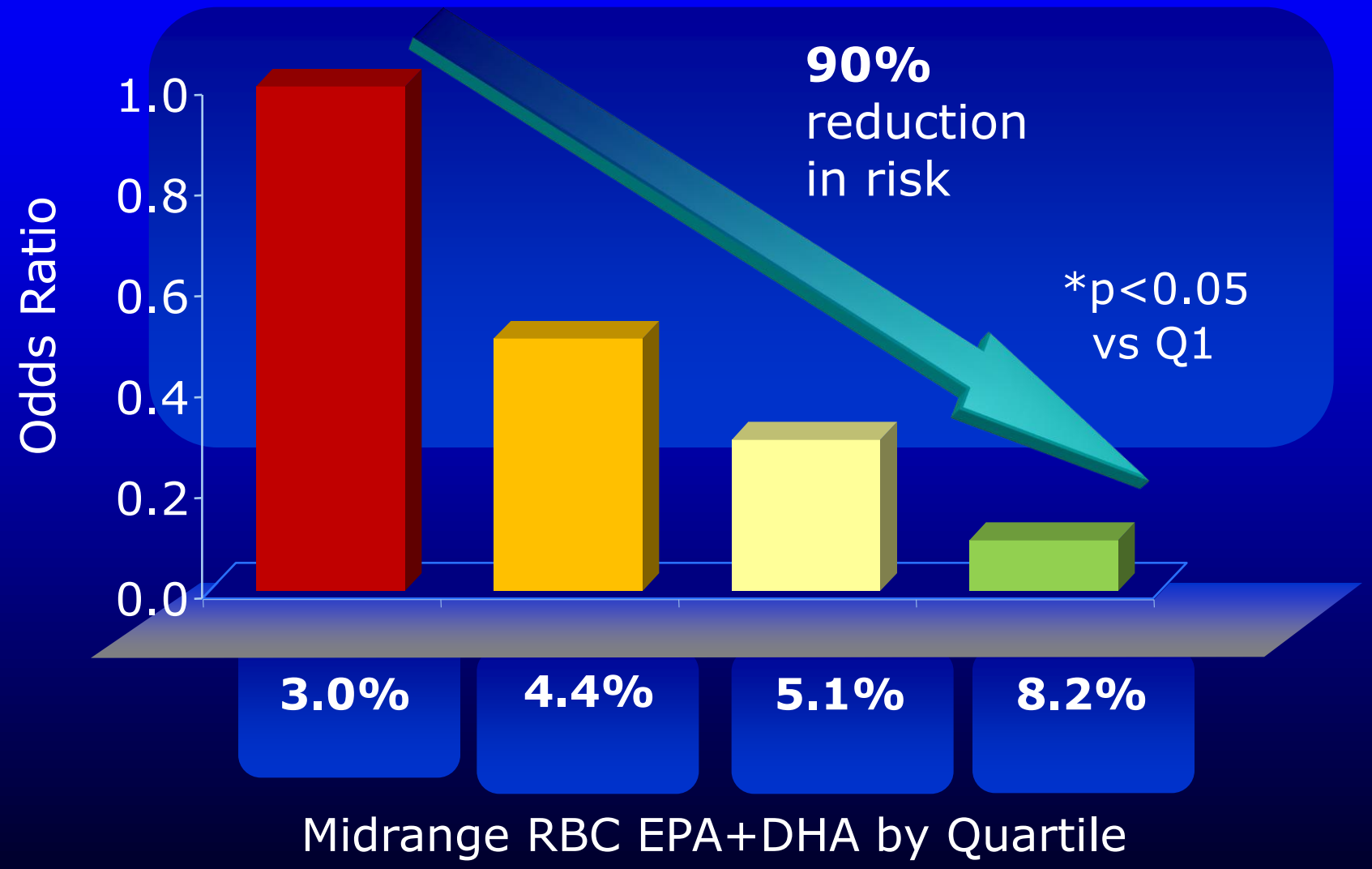
Itomura, *in vivo* 2008;22:131-136.

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



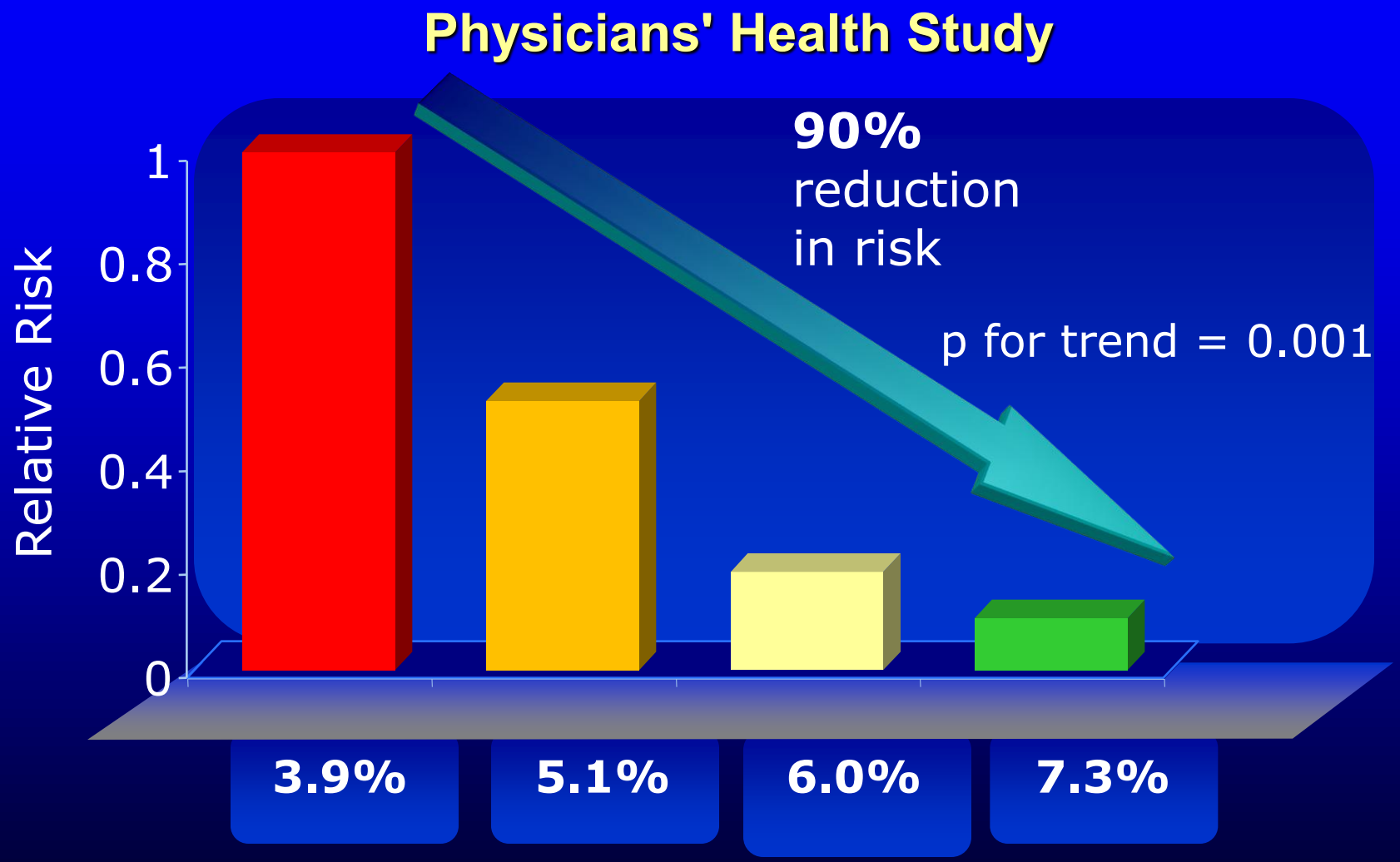
Siscovik DS et al. JAMA 1995;274:1363-1367.

Risk for Primary Cardiac Arrest and Red Blood Cell EPA+DHA Level



Adapted from Siscovick DS et al. *JAMA* 1995;274:1363-1367.

Relative Risk of Sudden Cardiac Death and Blood Omega-3 Levels



Albert CM et al. *N Engl J Med* 2002:346:1113-1118.

Circulation

ORIGINAL RESEARCH ARTICLE

Effect of Long-Term Marine ω-3 Fatty Acids Supplementation on the Risk of Atrial Fibrillation in Randomized Controlled Trials of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis

Baris Gencer, MD, MPH; Luc Djousse, MD, ScD, MPH; Omar T. Al-Ramady, MD; Nancy R. Cook, ScD; JoAnn E. Manson, MD, DrPH; Christine M. Albert, MD, MPH

BACKGROUND: Some, but not all, large-scale randomized controlled trials (RCTs) investigating the effects of marine ω-3 fatty acids supplementation on cardiovascular outcomes have reported increased risks of atrial fibrillation (AF). The potential reasons for disparate findings may be dose-related.

METHODS: The MEDLINE and Embase databases were searched for articles and abstracts published between January 1, 2012, and December 31, 2020, in addition to a meta-analysis of large cardiovascular RCTs published in 2019. RCTs of cardiovascular outcomes of marine ω-3 fatty acids that reported results for AF, either as a prespecified outcome, an adverse event, or a cause for hospitalization, with a minimum sample size of 500 patients and a median follow-up of at least 1 year were included. RCTs specifically examining shorter-term effects of ω-3 fatty acids on recurrent AF in patients with established AF or postoperative AF were not included. The hazard ratio (HR) for the reported AF outcomes within each trial was meta-analyzed using random effects model with Knapp-Hartung adjustment and evaluated a dose-response relationship with a meta-regression model.

RESULTS: Of 4049 screened records, 7 studies were included in the meta-analysis. Of those, 5 were already detected in a previous meta-analysis of cardiovascular RCTs. Among the 81 210 patients from 7 trials, 58 939 (72.6%) were enrolled in trials testing ≤1 g/d and 22 271 (27.4%) in trials testing >1 g/d of ω-3 fatty acids. The mean age was 65 years, and 31 842 (39%) were female. The weighted average follow-up was 4.9 years. In meta-analysis, the use of marine ω-3 fatty acid supplements was associated with an increased risk of AF (n=2905; HR, 1.25 [95% CI, 1.07–1.46]; P=0.013). In analyses stratified by dose, the HR was greater in the trials testing >1 g/d (HR, 1.49 [95% CI, 1.04–2.15]; P=0.042) compared with those testing ≤1 g/d (HR, 1.12 [95% CI, 1.03–1.22]; P=0.024; P for interaction <0.001). In meta-regression, the HR for AF increased per 1 g higher dosage of ω-3 fatty acids dosage (HR, 1.11 [95% CI, 1.06–1.15]; P=0.001).

CONCLUSIONS: In RCTs examining cardiovascular outcomes, marine ω-3 supplementation was associated with an increased risk of AF. The risk appeared to be greater in trials testing >1 g/d.

Gencer B et al. Circulation 2021;144: 1981-1990

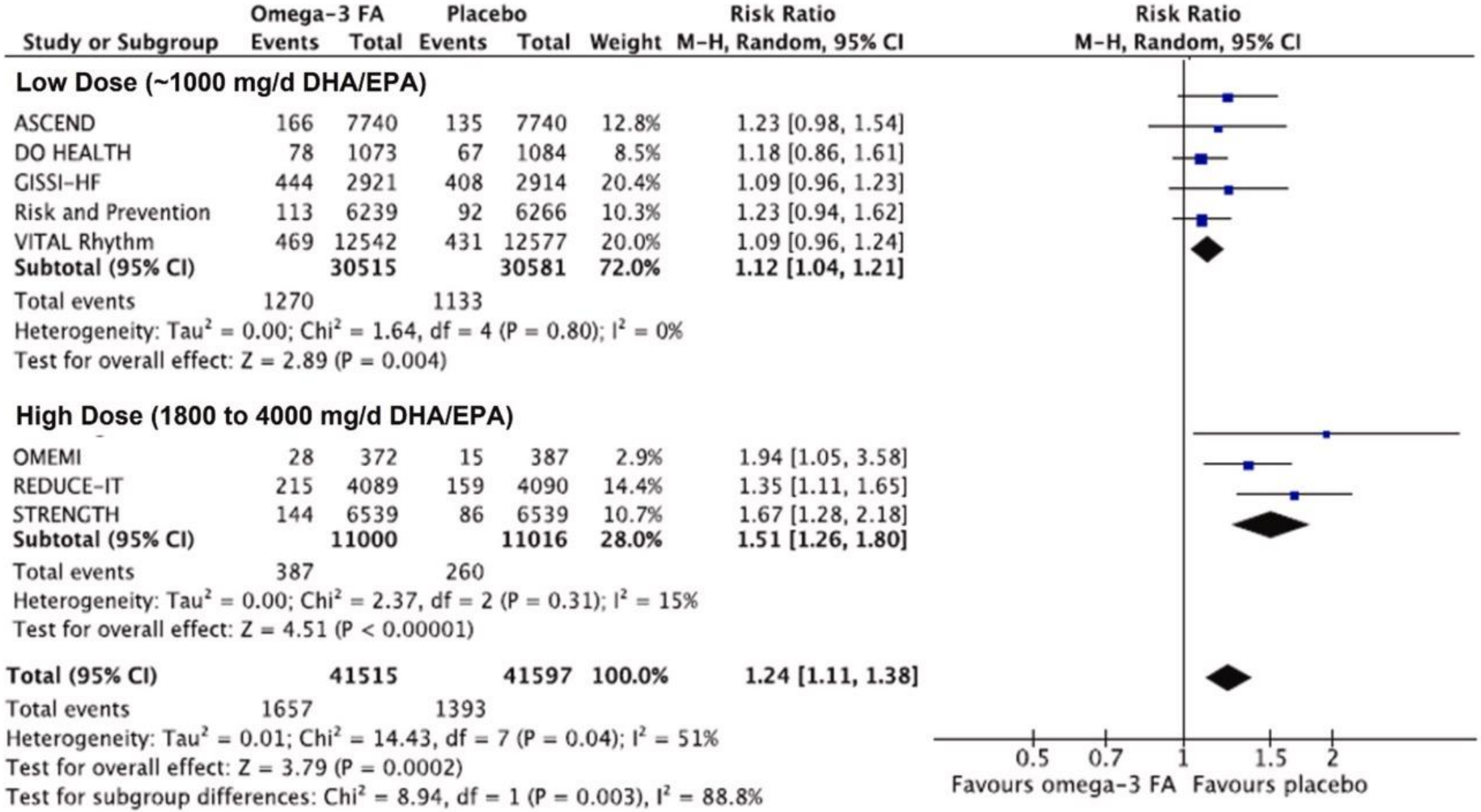


Fig. 1. Meta-analysis of association between omega-3 fatty acid treatment with atrial fibrillation. Forest plot shows overall pooled data as well as by subgroups of lower dose (≤ 1 g/d) and higher dose (> 1 g/d). Trials included in the analysis were ASCEND; DO-Health; GISSI-HF; Risk and Prevention; VITAL Rhythm; OMEMI; REDUCE-IT; STRENGTH.[3]

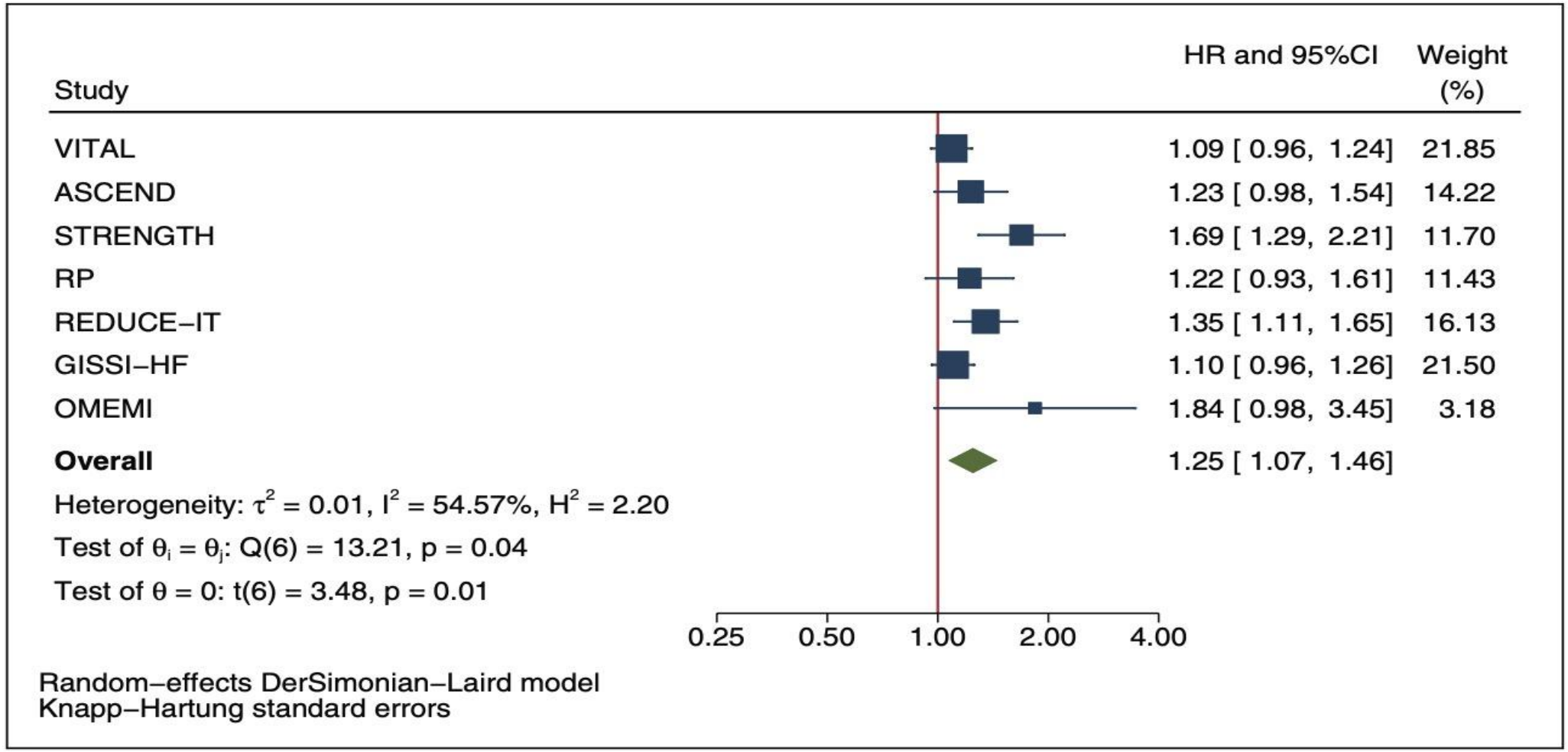


Figure 1. Effect of marine ω-3 fatty acids supplements on the risk of atrial fibrillation events using Knapp-Hartung adjustment for random effect model.

ASCEND indicates A Study of Cardiovascular Events in Diabetes; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca; HR, hazard ratio; OMEMI, Omega-3 Fatty Acids in Elderly With Myocardial Infarction; REDUCE-IT, Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial; RP, Risk and Prevention Study; STRENGTH, Long-Term Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High Cardiovascular Risk Patients With Hypertriglyceridemia; and VITAL, Vitamin D and Omega-3 Trial.

Gencer B et al. Circulation 2021;144: 1981-1990

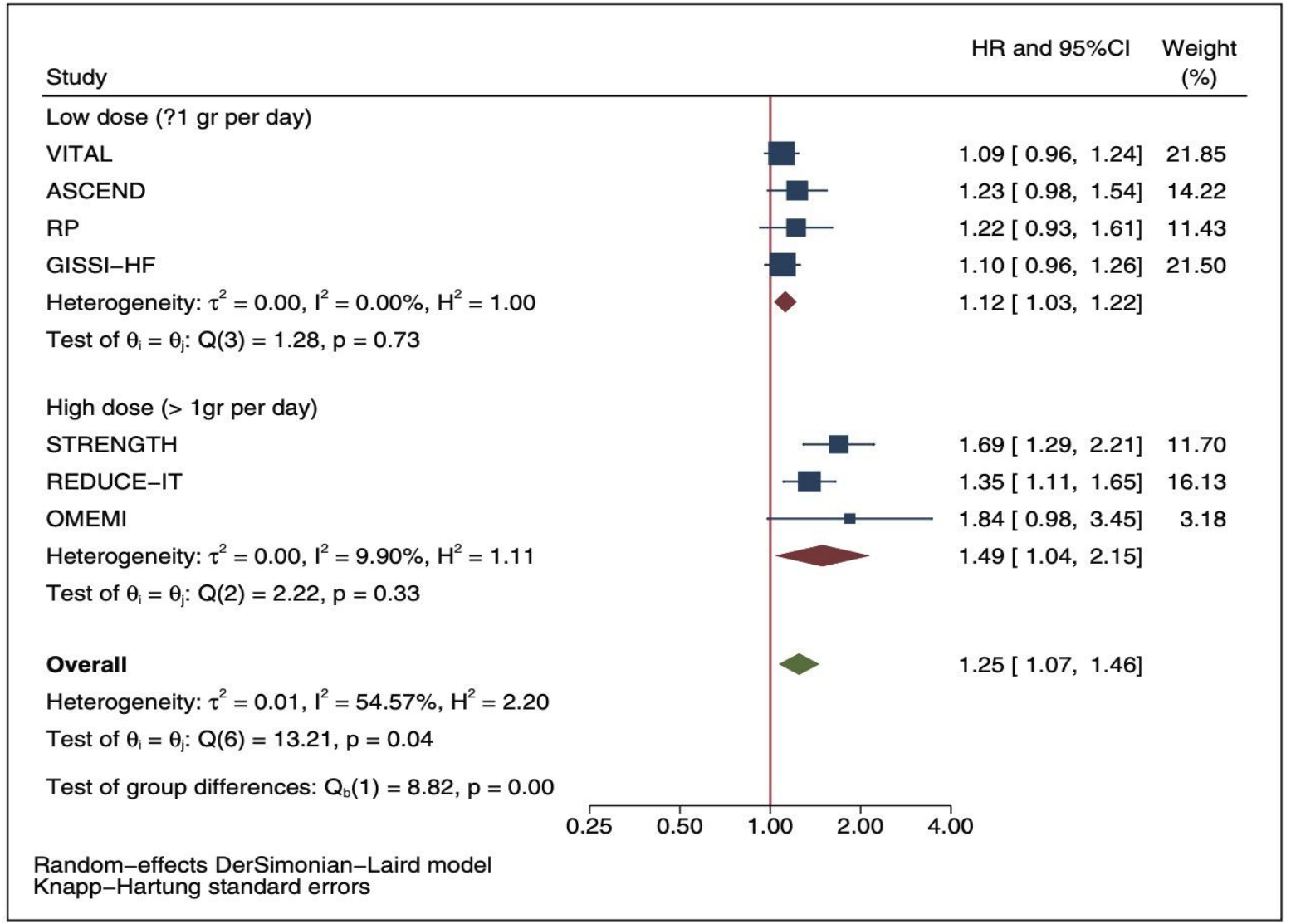


Figure 2. Effect of marine ω-3 fatty acids supplements on the risk of atrial fibrillation events stratified by low dose (≤1 g/d) versus high dose (>1 g/d) using Knapp-Hartung adjustment for random effect model.

ASCEND indicates A Study of Cardiovascular Events in Diabetes; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca; HR, hazard ratio; OMEMI, Omega-3 Fatty Acids in Elderly With Myocardial Infarction; REDUCE-IT, Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial; RP, Risk and Prevention Study; STRENGTH, Long-Term Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High Cardiovascular Risk Patients With Hypertriglyceridemia; and VITAL, Vitamin D and Omega-3 Trial.

Gencer B et al. Circulation 2021;144: 1981-1990

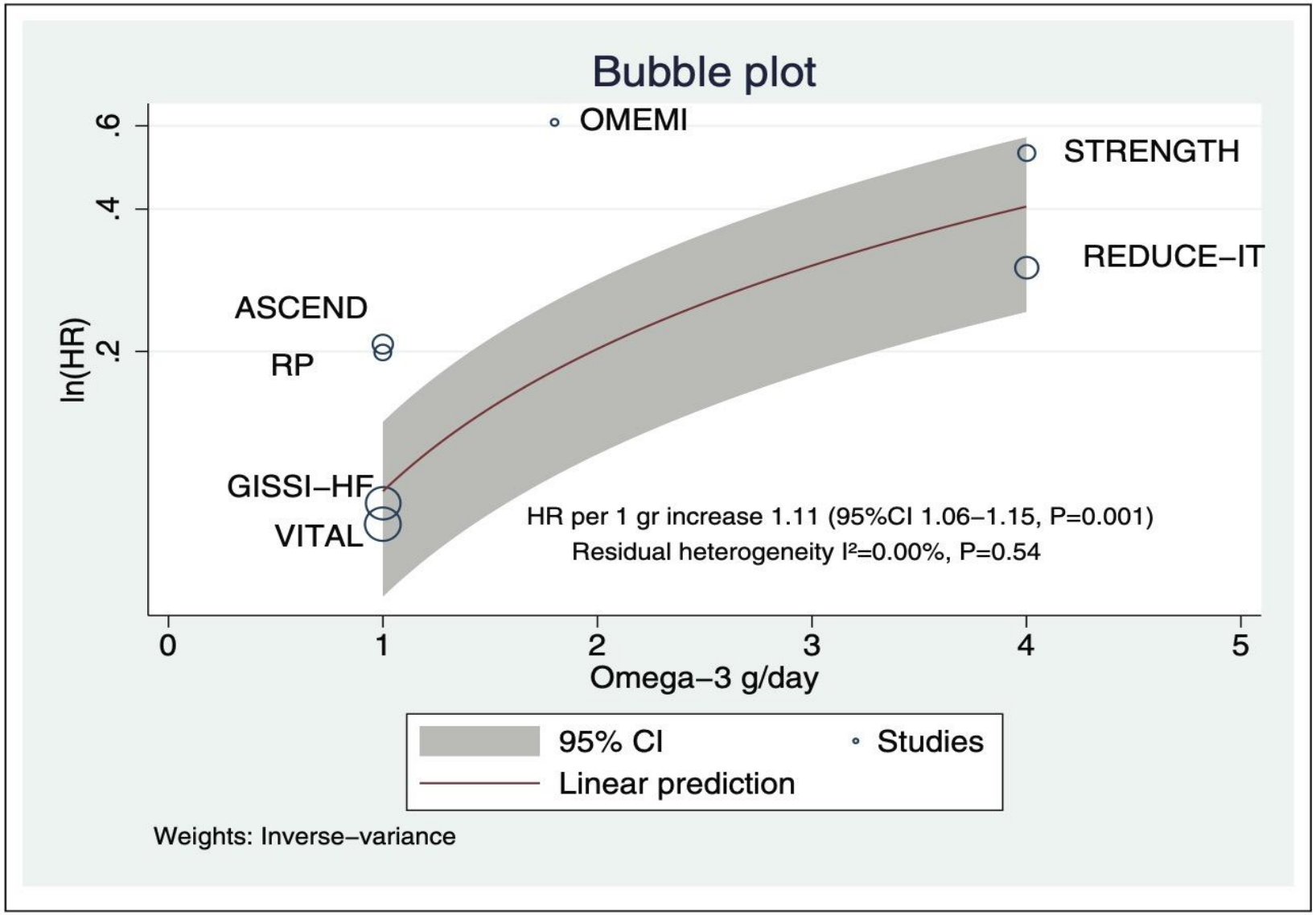


Figure 3. Regression of ω-3 fatty acids dosage and risk for atrial fibrillation events in 7 randomized controlled trials using Knapp-Hartung adjustment for random effect model.

ASCEND indicates A Study of Cardiovascular Events in Diabetes; GISSI-HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca; HR, hazard ratio; OMEMI, Omega-3 Fatty Acids in Elderly With Myocardial Infarction; REDUCE-IT, Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial; RP, Risk and Prevention Study; STRENGTH, Long-Term Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High Cardiovascular Risk Patients With Hypertriglyceridemia; and VITAL, Vitamin D and Omega-3 Trial.

Gencer B et al. Circulation 2021;144: 1981-1990

Omega 3 Meta-Analysis and AF

- 8 Trials , N=83,112
- 5 trials dose< 1g (N=61,096)
- 3 trials dose> 1 g(N=22,016)
- 24% increase in AF with O3
- 12% increase with low dose
- 51% increase with high dose

Jia X et al. Cardiovascular Drug Therapy 2021; 35: 793-800

Stroke

CLINICAL AND POPULATION SCIENCES

Omega-3 Blood Levels and Stroke Risk: A Pooled and Harmonized Analysis of 183 291 Participants From 29 Prospective Studies

James H. O'Keefe, MD; Nathan L. Tintle, PhD; William S. Harris, PhD; Evan L. O'Keefe, MD; Aleix Sala-Vila, PhD; John Attia, MD, PhD; G. Manohar Garg, PhD; Alexis Hure, PhD; Christian Sørensen Bork, MD, PhD; Erik Berg Schmidt, MD, DMSc; Stine Krogh Venø, MD; Kuo-Liong Chien, MD, PhD; Yun-Yu (Amelia) Chen, MPH; Sarah Egert, PhD; Tobias Rudholm Feldreich, PhD; Johan Ärnlöv, MD, PhD; Lars Lind, MD, PhD; Nita G. Forouhi, MD, PhD; Johanna M. Geleijnse, MD, PhD; Kamalita Pertiwi, PhD; Fumiaki Imamura, PhD; Vanessa de Mello Laaksonen, PhD; W. Matti Uusitupa, MD, PhD; Jaakko Tuomilehto, MD, PhD; Markku Laakso, MD; Maria Anneli Lankinen, PhD; Danielle Laurin, PhD; Pierre-Hugues Carmichael, MSc, PhD; Joan Lindsay, PhD; Karin Leander, PhD; Federica Laguzzi, PhD; Brenton R. Swenson, PhD; William T. Longstreth, MD; JoAnn E. Manson, MD; Samia Mora, MD, Nancy R. Cook, ScD; Matti Marklund, PhD; Debora Melo van Lent, PhD; Rachel Murphy, PhD; Vilmundur Gudnason, MD; Toshihara Ninomiya, MD, PhD; Yoichiro Hirakawa, MD, PhD; Frank Qian, MD; Qi Sun, MD, ScD; Frank Hu, MD, PhD; Andres V. Ardisson Korat, PhD; Ulf Risérus, MD, PhD; Iolanda Lázaro, PhD; Cecilia Samieri, PhD; Mélanie Le Goff, MPH; Catherine Helmer, MD, PhD; Marinka Steur, PhD; Trudy Voortman, PhD; M. Kamran Ikram, MD, PhD; Toshiko Tanaka, PhD; Jayanta K. Das, PhD; Luigi Ferrucci, PhD; Stefania Bandinelli, MD; Michael Tsai, PhD; Weihua Guan, PhD; Parveen Garg, MD; W.M. Monique Verschuren, PhD; Jolanda M.A. Boer, PhD; Anneke Biokstra, MSc; Jyrki Virtanen, PhD; Michael Wagner, PhD; Jason Westra, MS; Luc Albuisson; Kazumasa Yamagishi, MD, PhD; David S. Siscovick, MD; Rozenn N. Lemaitre, PhD; Dariush Mozaffarian, MD

BACKGROUND: The effect of marine omega-3 PUFAs on risk of stroke remains unclear.

METHODS: We investigated the associations between circulating and tissue omega-3 PUFA levels and incident stroke (total, ischemic, and hemorrhagic) in 29 international prospective cohorts. Each site conducted a de novo individual-level analysis using a prespecified analytical protocol with defined exposures, covariates, analytical methods, and outcomes; the harmonized data from the studies were then centrally pooled. Multivariable-adjusted HRs and 95% CIs across omega-3 PUFA quintiles were computed for each stroke outcome.

RESULTS: Among 183 291 study participants, there were 10 561 total strokes, 8220 ischemic strokes, and 1142 hemorrhagic strokes recorded over a median of 14.3 years follow-up. For eicosapentaenoic acid, comparing quintile 5 (Q5, highest) with quintile 1 (Q1, lowest), total stroke incidence was 17% lower (HR, 0.83 [CI, 0.76–0.91]; $P<0.0001$), and ischemic stroke was 18% lower (HR, 0.82 [CI, 0.74–0.91]; $P<0.0001$). For docosahexaenoic acid, comparing Q5 with Q1, there was a 12% lower incidence of total stroke (HR, 0.88 [CI, 0.81–0.96]; $P=0.0001$) and a 14% lower incidence of ischemic stroke (HR, 0.86 [CI, 0.78–0.95]; $P=0.0001$). Neither eicosapentaenoic acid nor docosahexaenoic acid was associated with a risk for hemorrhagic stroke. These associations were not modified by either baseline history of AF or prevalent CVD.

CONCLUSIONS: Higher omega-3 PUFA levels are associated with lower risks of total and ischemic stroke but have no association with hemorrhagic stroke.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cerebrovascular disease ■ atrial fibrillation ■ fish ■ fish oil ■ stroke

Omega-3 Blood Levels and Stroke Risk

Table. Hazard Ratios (95% CI) for Stroke by FA Quintile (Versus Quintile 1) Excluding the UK Biobank

Fatty acid		Total stroke	Ischemic stroke	Hemorrhagic stroke
DHA	Quintile 1 (reference)	1.0	1.0	1.0
	Quintile 2	0.92 (0.85–1)*	0.9 (0.82–0.99)*	1.08 (0.82–1.42)
	Quintile 3	0.93 (0.86–1.02)	0.9 (0.82–0.99)*	1.03 (0.78–1.36)
	Quintile 4	0.90 (0.83–0.98)*	0.88 (0.8–0.96)†	1.02 (0.77–1.36)
	Quintile 5	0.88 (0.81–0.96)†	0.86 (0.78–0.95)†	1.09 (0.82–1.46)
	P value for trend	0.04	0.03	0.79
EPA	Quintile 1 (reference)	1.0	1.0	1.0
	Quintile 2	1.00 (0.92–1.08)	0.99 (0.9–1.08)	0.96 (0.73–1.26)
	Quintile 3	0.82 (0.75–0.89)‡	0.81 (0.74–0.9)‡	0.82 (0.62–1.09)
	Quintile 4	0.91 (0.83–0.99)*	0.91 (0.82–1.00)	0.86 (0.65–1.14)
	Quintile 5	0.83 (0.76–0.91)‡	0.82 (0.74–0.91)‡	0.9 (0.67–1.21)
	P value for trend	0.001	0.002	0.45
DPA	Quintile 1 (Reference)	1.0	1.0	1.0
	Quintile 2	1.00 (0.91–1.11)	1.04 (0.94–1.16)	0.83 (0.61–1.13)
	Quintile 3	1.03 (0.93–1.13)	1.04 (0.93–1.16)	0.64 (0.47–0.89)†
	Quintile 4	1.01 (0.91–1.12)	1.04 (0.94–1.16)	0.89 (0.66–1.22)
	Quintile 5	0.89 (0.8–0.99)*	0.93 (0.83–1.05)	0.79 (0.57–1.09)
	P value for trend	0.21	0.47	0.45
EPA+DHA	Quintile 1 (Reference)	1.0	1.0	1.0
	Quintile 2	0.94 (0.86–1.02)	0.93 (0.85–1.02)	1.14 (0.86–1.51)
	Quintile 3	0.92 (0.84–0.99)*	0.88 (0.8–0.97)*	1.00 (0.75–1.35)
	Quintile 4	0.92 (0.84–0.99)*	0.89 (0.81–0.98)*	1.17 (0.87–1.57)
	Quintile 5	0.83 (0.76–0.91)‡	0.82 (0.74–0.91)‡	1.04 (0.76–1.42)
	P value for trend	0.007	0.006	0.82

O'Keefe JH et al . Stroke 2024;55: 50-58

Bottom Line –Who Really Needs Omega-3 Supplements?

- Patients with known ASCVD or high ASCVD risk
- Hypercholesterolemia
- Hypertriglyceridemia
- Post –MI
- Systolic HF

Bottom Line –Who May Not Benefit from Omega-3 Supplements

- Patients w/o dyslipidemia
- Patients with very high exercise w/o other strong reasons for O3
- Patients with bradycardia without other strong reasons for O3
- Patients with high baseline vagal tone

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 and doses that may increase AF Risk

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

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

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

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- RNs must complete the evaluation to receive CE certificate.
- RD/RDNs: Although completing an evaluation is not required, we truly appreciate your feedback.

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Q&A

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If you are an RD or RDN and have any questions or concerns about this continuing education activity, you may contact CDR directly at QualityCPE@eatright.org.

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