ACC Middle East Conference 2018

In partnership with:

جمعية القلب السعودية
Saudi Heart Association

Omega-3 Fatty Acids

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Disclosures

- None

Objectives

- Describe omega-3 fatty acids

- Review the historic data supporting omega-3 fatty acid supplementation and health benefit

What are omega-3 fatty acids?

- Alphalinoleic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) are omega-3 polyunsaturated fatty acids and are essential fatty acids
- ALA is found in plants and nuts (chia, flax, walnuts) and can be converted into EPA/DHA although inefficient
- EPA and DHA are found in seafood and algae

Omega-3 PUFA: Prescription or OTC

Prescription Omega-3 PUFA

- Omega-3 acid ethyl ethers
  - Lovaza®
  - Omytrg®
- Icosopent ethyl ethers
  - Vascepa®
- Omega-3 carboxylic acids
  - Epanova®

- A recent US Department of Agriculture survey of omega-3 PUFA supplements concluded that the most common amounts per dose were 180 mg for EPA and 120 mg for DHA.

https://medlineplus.gov/druginfo/meds/a607065.html

Early data on Essential Fatty Acids—1956

- HM Sinclair Letter to the Editor of the Lancet suggests that Western diseases are due to deficiency of EFA—which means a low ratio of EFA to long-chain saturated and *trans* fatty acids based on his work with Eskimos (high fat, high EFA diet and low levels of CHD)

Sinclair HM. *Lancet* 1956

Omega-3 Fatty acids and CHD

- High levels of omega-3FAs linked to low levels of CHD in Greenland Inuit Eskimos

C20:5 AS PERCENTAGE OF TOTAL FATTY ACIDS IN LIPID FRACTIONS OF BLOOD IN ESKIMOS AND DANES[4]

	A.A. (C20:4)			E.P.A. (C20:5)		
	P.L.	C.E.	T.G.	P.L.	C.E.	T.G.
Eskimos	0·8	0·0	0·0	7·1	15·4	4·0
Danes	8·0	4·4	0·0	0·2	0·0	0·0

P.L.=phospholipid, C.E.=cholesterol esters, T.G.=triglycerides.

Dyerberg J. *Lancet* 1978

DART: Dietary and Reinfarction Trial

- Factorial design to test three interventions simultaneously and independently in non-diabetic men <70 years with recent MI:
  - A reduction in fat intake with an increase in the ratio of PU to saturated fat;
  - An increase in cereal fiber intake;
  - An increase in the intake of fatty fish

Burr ML. *Lancet* 1989

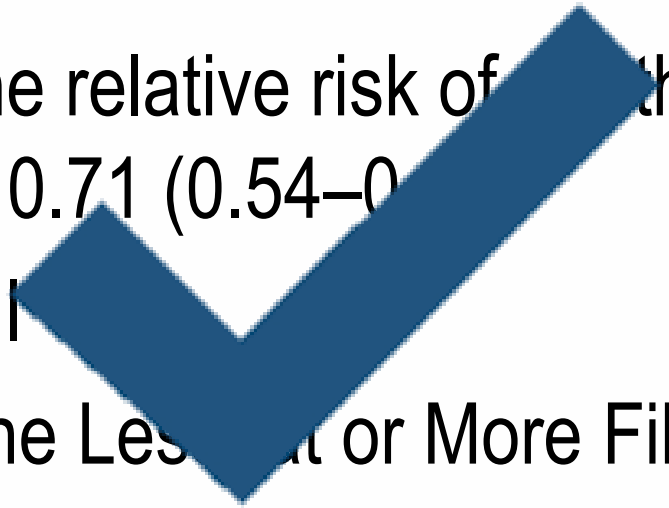
DART: Dietary and Reinfarction Trial

- Subjects in the fish group were advised to eat at least 2 portions each week (200–400 g) of fatty fish
- Those who could not eat this amount of fish were given fish oil capsules as a substitute for fish

Burr ML. *Lancet* 1989

DART: Dietary and Reinfarction Trial

- After 2 years, the relative risk of [illegible]th in those given fish advice was 0.71 (0.54–0[illegible]
- No change in MI
- No benefits in the Les[illegible]t or More Fiber groups



Burr ML. *Lancet* 1989

GISSI-Prevenzione

- 11,324 patients with recent AMI randomized to n-3 PUFA 1 g daily (EPA/DHA 1:2), vitamin E 300 mg daily, both, or none for 3.5 years
- The primary combined efficacy endpoint was death, non-fatal MI, and CVA

GISSI-Prevenzione Investigators. *Lancet* 1999

GISSI-Prevenzione

- **Death non-fatal MI, non-fatal CVA: ↓15%; p=0·023**
- CV death, non-fatal MI, non-fatal CVA: ↓20%; p=0·008
  - Death: ↓20%
  - CV Death: ↓ 30%
  - Sudden Death: ↓45%

GISSI-Prevenzione Investigators. *Lancet* 1999

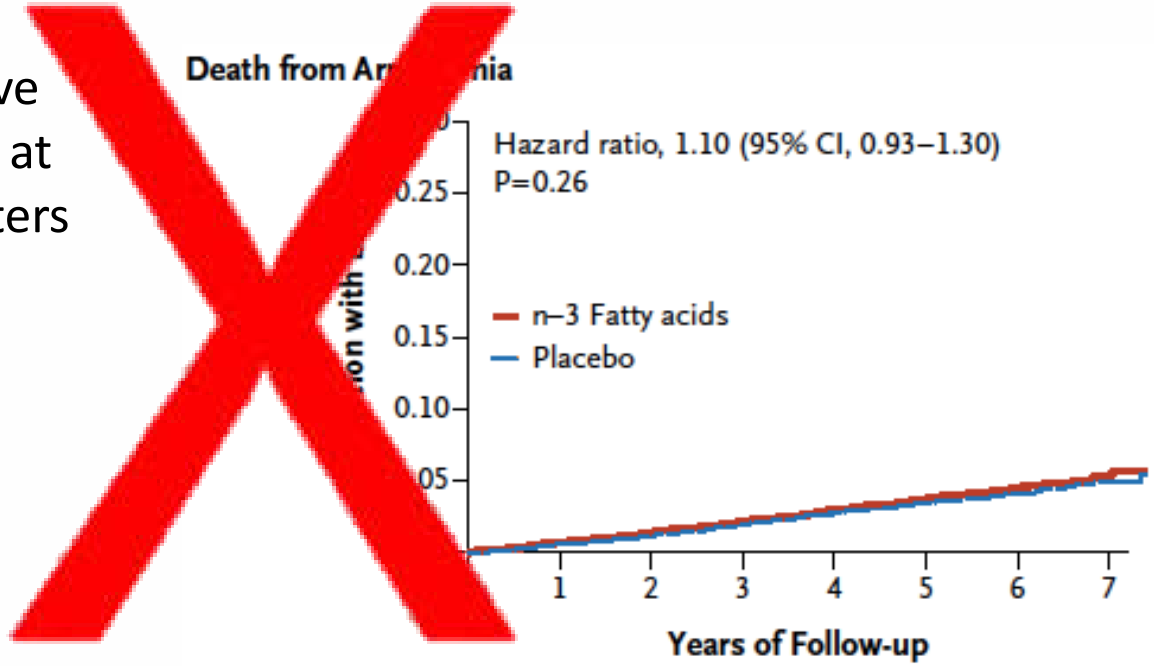
AHA Guideline 2002

- The AHA recommended that patients with documented CHD consume ≈ 1 g/d EPA+DHA, preferably from oily fish, but EPA+DHA supplements could be considered

Kris-Etherton PM. *Circulation* 2002

ORIGIN: IFG/IGT/DM2 at High CV Risk

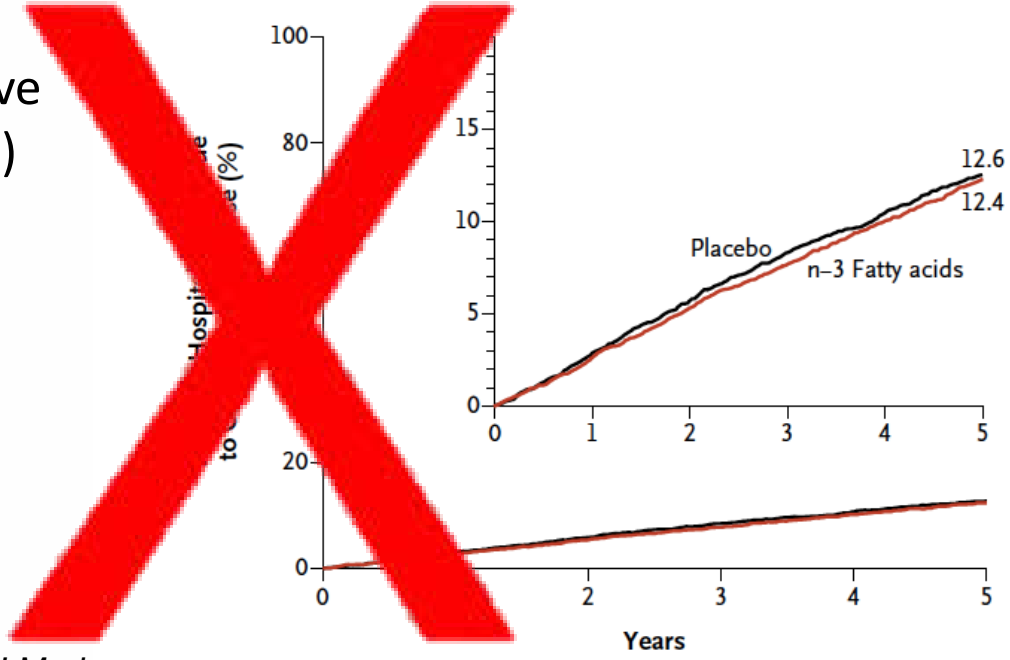
- 12,536 patients to receive a 1-g capsule containing at least 900 mg of ethyl esters of n–3 fatty acids or placebo daily



Bosch J. *N Engl J Med* 2012

PUFA with CV Risk Factors or ASCVD (no MI)

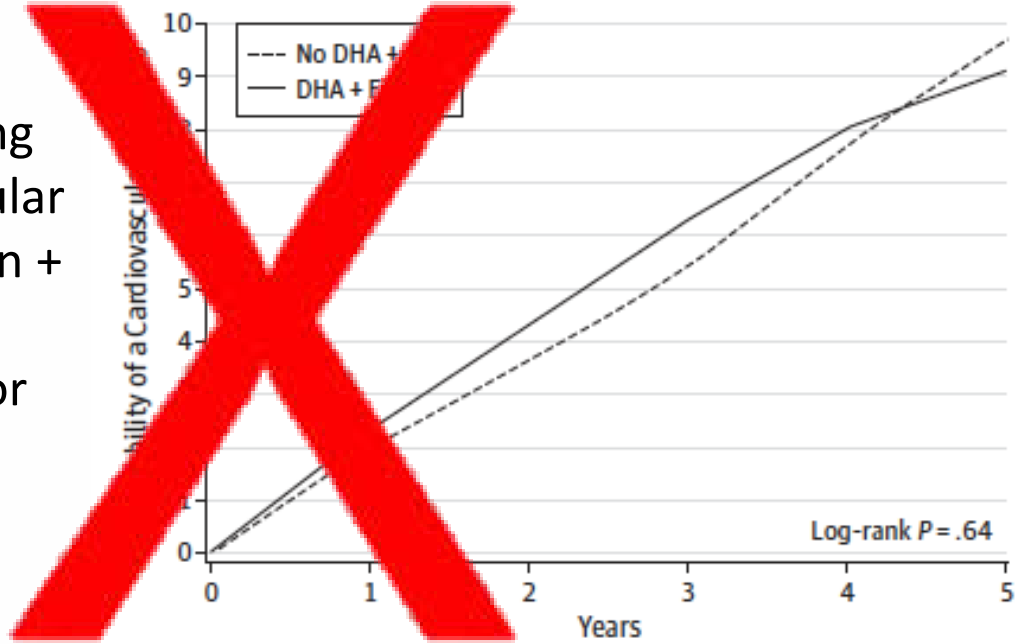
- 12,513 patients to receive n−3 fatty acids (1 g daily) or placebo (olive oil)



Risk and Prevention Study Group. *N Engl J Med* 2013

AREDS2: 50-85 yo, macular degeneration

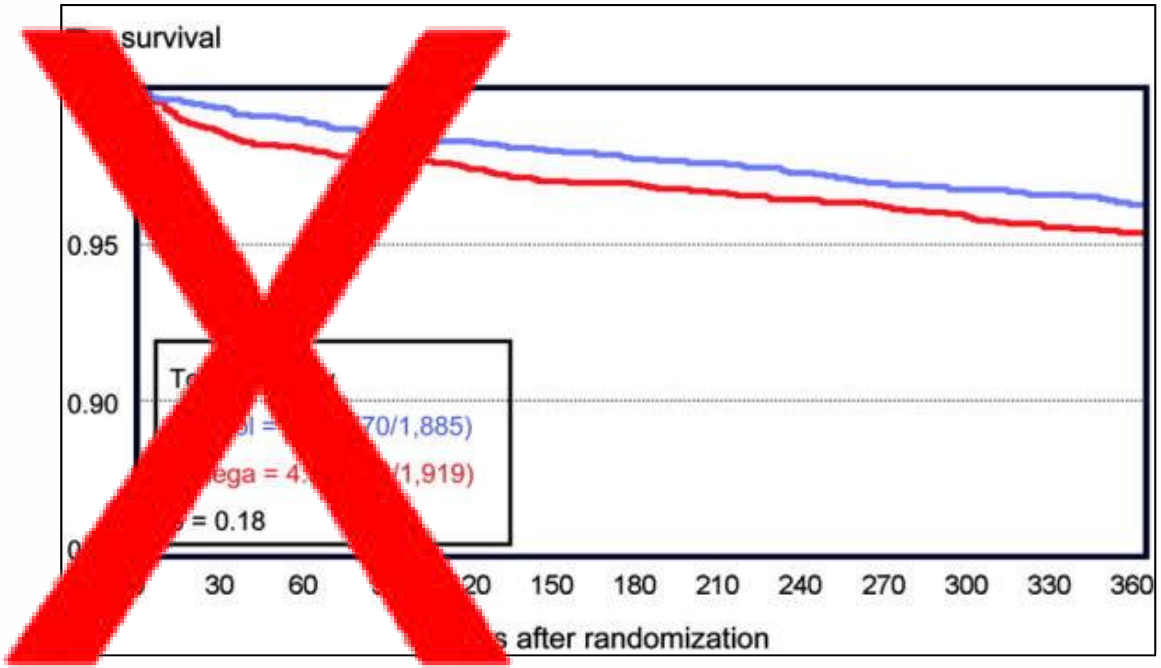
- 4203 patients to receive ω−3 PU fatty acids (350 mg DHA + 650 mg EPA), macular xanthophylls (10-mg lutein + 2-mg zeaxanthin), combination of the two, or matching placebos
- Stable ASCVD OK



Bonds DE. *JAMA Intern Med* 2014

OMEGA: Purifed omega-3 after Recent MI

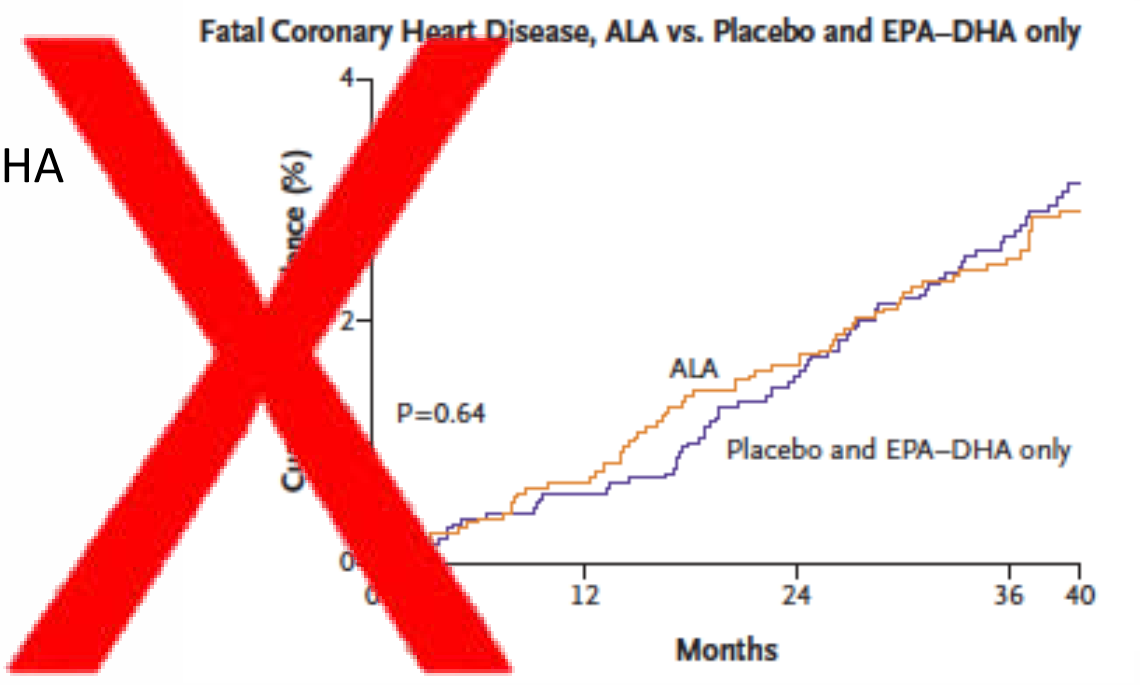
- 3851 patients 3-14 days after MI receive highly purified omega-3 fatty acids



Rauch B. *Circulation* 2010

Alpha Omega: Prior MI and low dose EPA/DHA

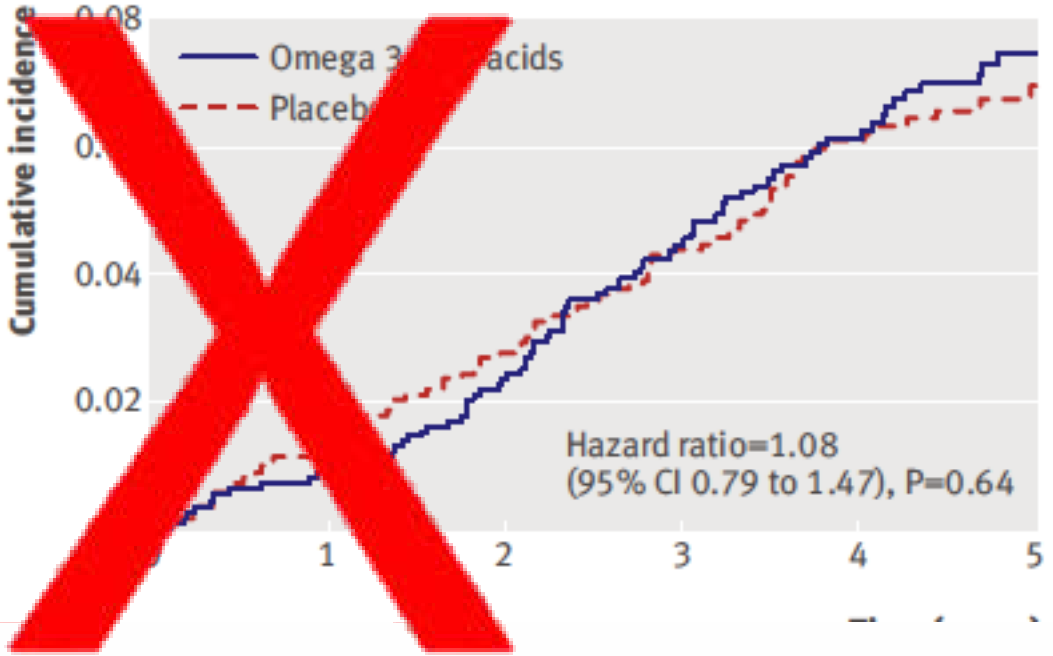
- 4837 patients receive marine n−3 fatty acids DHA + EPA (400 mg); ALA (2 gms); DHA—EPA + ALA, placebo.



Kromhout D. *N Engl Med* 2010

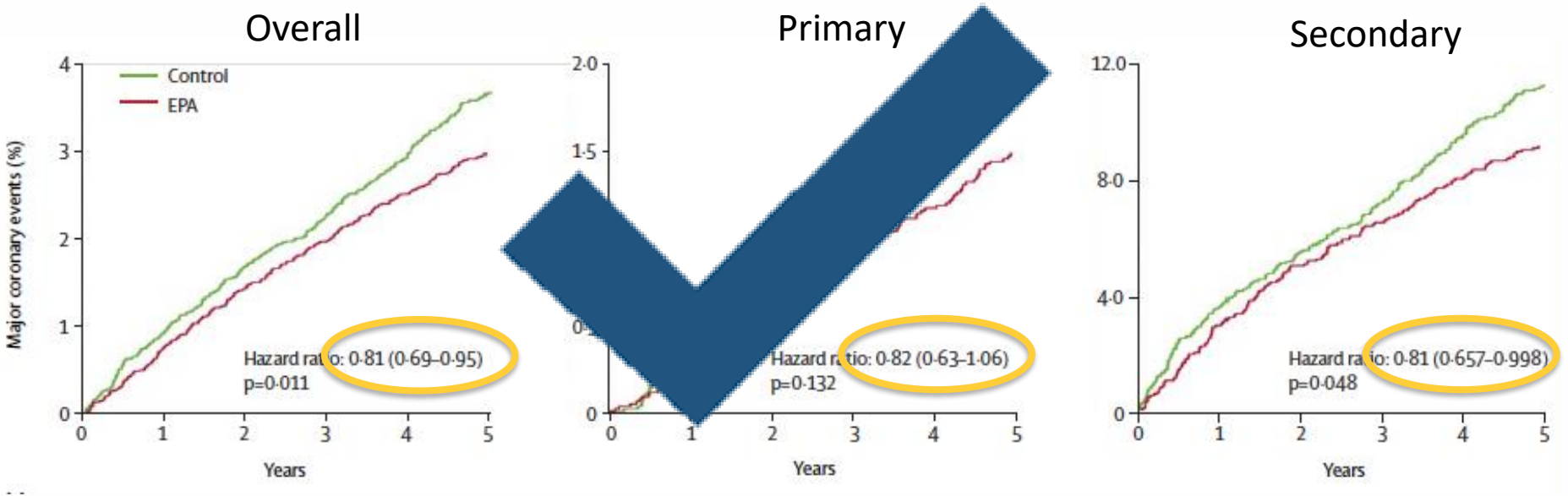
SU.FOL.oM3: Prior CV event and EPA/DHA

- 2501 patients with h/o UA UA or ischemic CVA
- 600 mg EPA and DHA 2



Galan P. *BMJ* 2010

JELIS: Total Cholesterol >6.5 mmol/L



Yokoyama M. *Lancet* 2007

Primary Prevention of CVD with Omega-3s

- No trials looking at primary prevention of CVD with Omega-3 PUFAs

Siscovick DS. *Circulation* 2017

AHA Science Advisory 2017

Siscovick DS. *Circulation* 2017

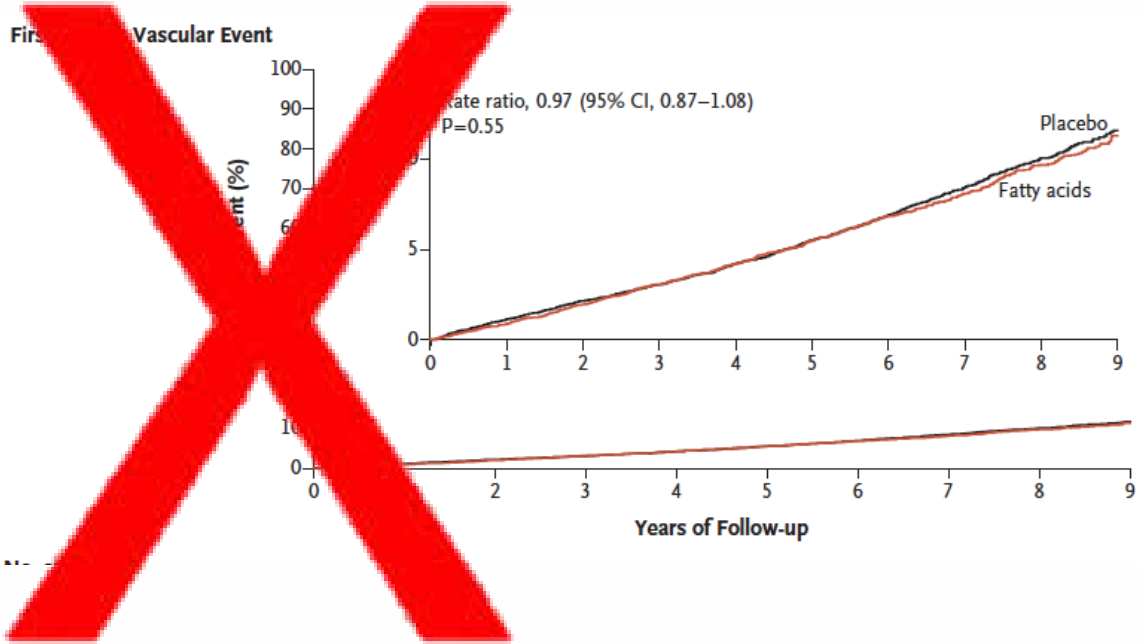
AHA Science Advisory 2017

- Primary Prevention: **No recommendation**
- DM/IGT at high risk: **Not recommended**
- High CV Risk: **Not recommended**
- Secondary prevention: **Reasonable**

Siscovick DS. *Circulation* 2017

ASCEND: DM with no CVD

- 15480 DM patients with no history of CVD
- 1-g capsules containing either n−3 fatty acids (fatty acid group) or matching placebo (olive oil)



ASCEND Collaborative Group. *N Engl J Med* 2018

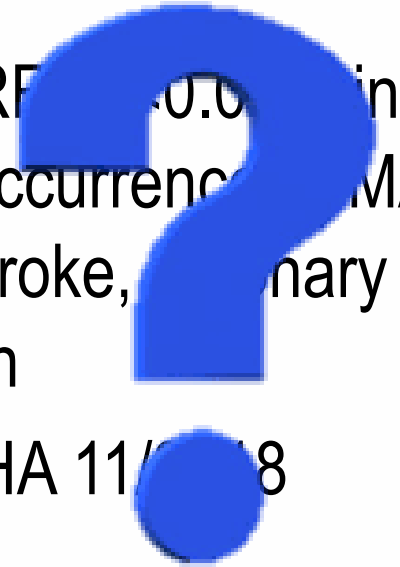
REDUCE IT: CVD or DM + CV RF and ↑TG

- 8179 patients on statin LDL:
  - 41-100 mg/dL (median LDL-C 75 mg/dL)
- Various CV risk factors including persistently elevated TGs between 150-499 mg/dL (median 216 mg/dL) AND
- Either established CVD (secondary prevention cohort) or DM2 and at least one other CV risk factor (primary prevention cohort)

https://investor.amarincorp.com/node/15741/pdf

REDUCE IT: CVD or DM + CV RF and ↑TG

- Approximately 25% RRR (p<0.0[illegible]) in the primary endpoint composite of the first occurrence of MACE, including CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or UA requiring hospitalization
- Will be presented at AHA 11/[illegible]8

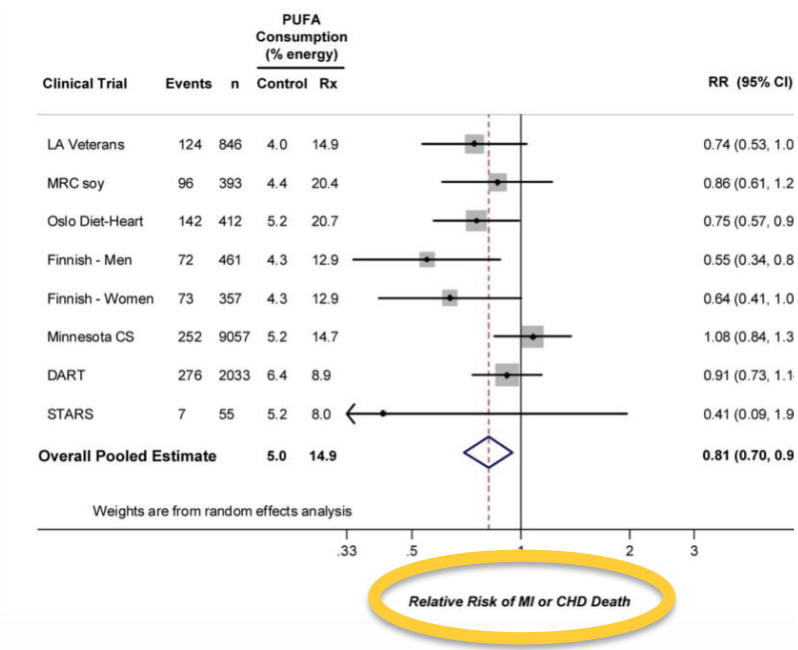


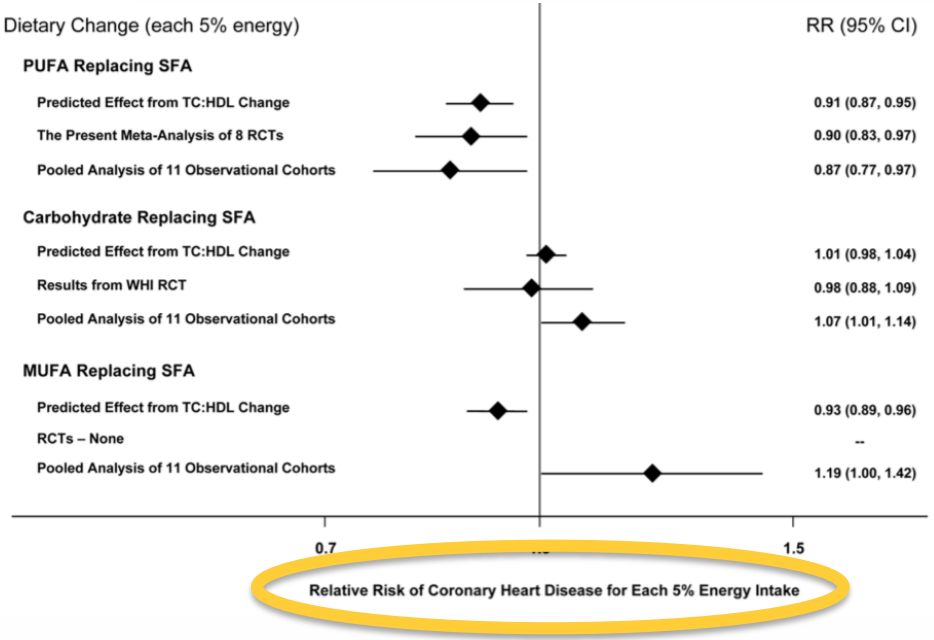
https://investor.amarincorp.com/node/15741/pdf

On-going trials

- REDUCE-IT: Reduction of Cardiovascular Events With EPA–Intervention Trial
- VITAL
- STRENGTH: Statin Residual Risk Reduction With Epanova in High CV Risk Patients With Hypertriglyceridemia

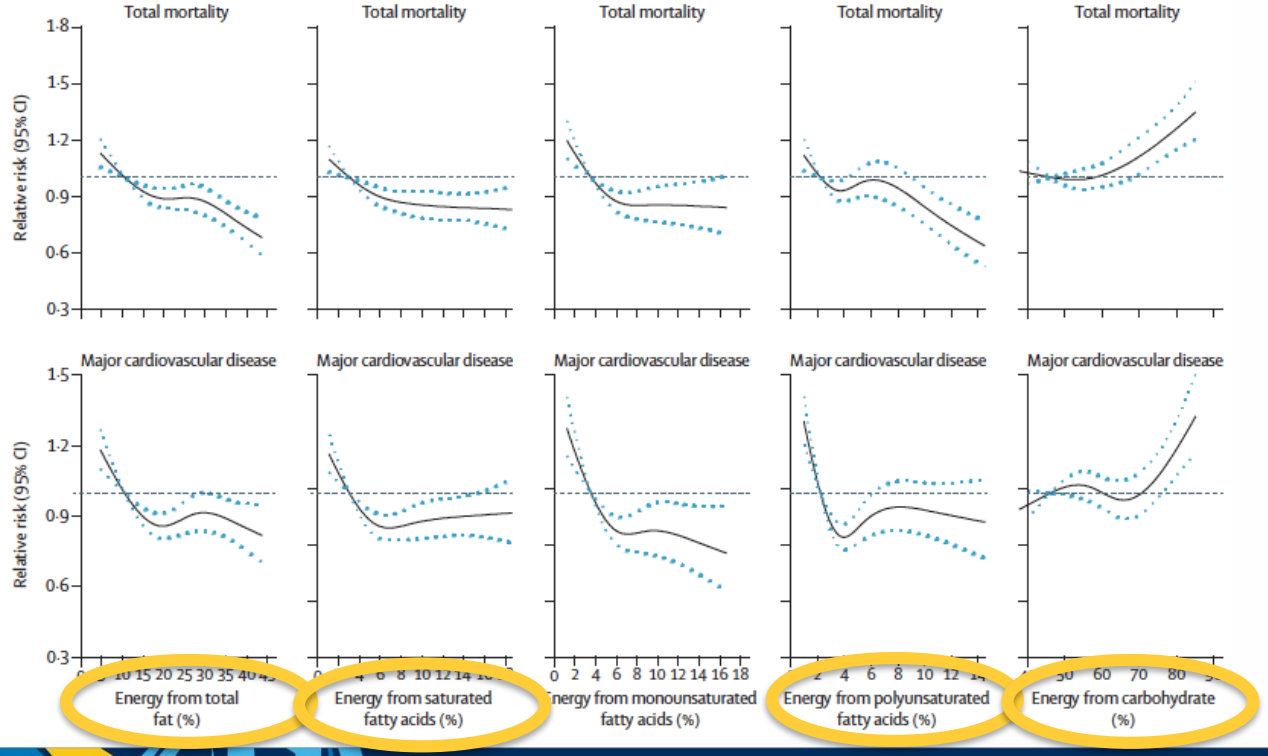
Dietary PUFA and disease





Mozaffarian D. *PLoS Med* 2010

PURE: Dietary PUFA and disease



Dehghan M. Lancet 2017

Dietary PUFA and disease

- Higher fat intake was associated with lower risk of total mortality, non-CVD mortality, and stroke
- Higher intakes of individual types of fat were associated with lower total mortality, non-CVD mortality, and stroke risk and were not associated with risk of major CVD events, MI, or CVD mortality

HF, Depression and ↓Omega-3 levels

- >20% of the 6 million HF patients in the US experience depression
- SADHART showed that improvement of depression = a decrease in CV events in patients with HF
- 80% of depressed → low plasma omega-3 levels
- HF and low omega-3 levels, especially EPA had increased mortality

Jiang W. *J Am Coll Cardiol* 2018

OCEAN: EPA/DHA vs EPA vs placebo

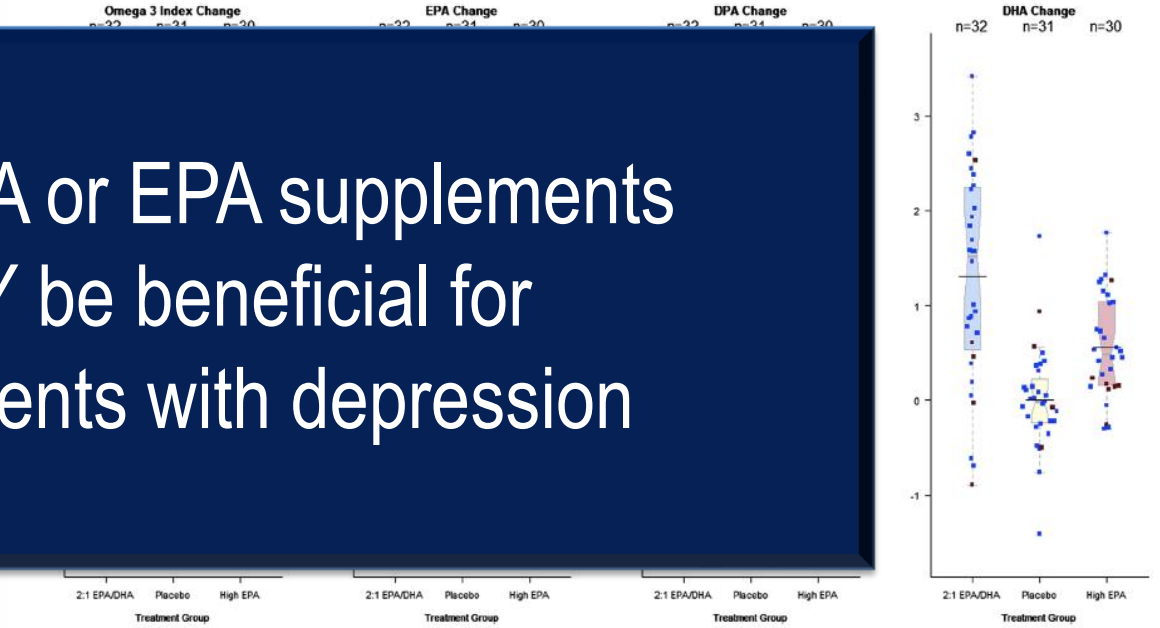
- A multicenter, double-blind, placebo-controlled, parallel group, randomized clinical pilot trial
- 1:1:1 fashion to receive 4 capsules daily for 12 weeks:
  - 400/200 EPA/DHA 500 mg per capsule (“2:1 EPA/DHA”)
  - Almost pure EPA 500 mg per capsule (“high EPA”)
  - Corn oil (“placebo”)

Jiang W. *J Am Coll Cardiol* 2018

OCEAN: EPA/DHA vs EPA vs placebo

- RBC indice
- No change
- 2:1 EPA/DI improvem measure o patients in 0.04)
- Trend towa in omega-3

EPA/DHA or EPA supplements MAY be beneficial for HF patients with depression



Jiang W. *J Am Coll Cardiol* 2018

Conclusions

- Epidemiological data suggests a benefit of PUFA
- There is no convincing data of a benefit for supplementation in primary prevention, even in a high-risk cohort with DM
- Supplementation with Omega-3 fatty acids is reasonable for secondary prevention
- More to come….