

Fish oils in cardiovascular prevention: new evidence, more questions

Colloque du jeudi 20 janvier 2022
Service de cardiologie

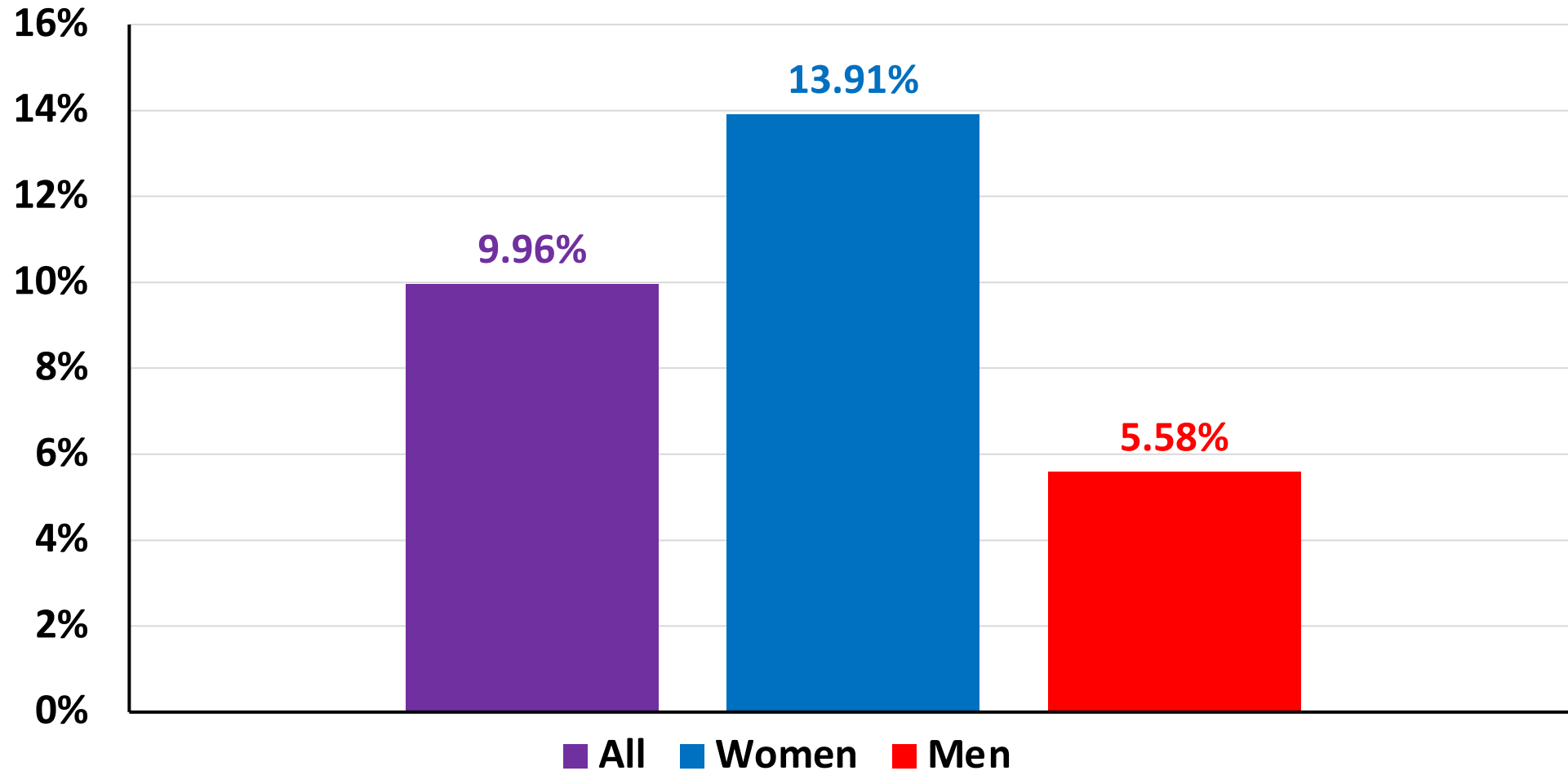
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Chef de Clinique, Cardiology Division, HUG, Geneva University

Deputy Director, Institute of Primary Health Care (BIHAM), Bern University

Use of Dietary Supplements in CH

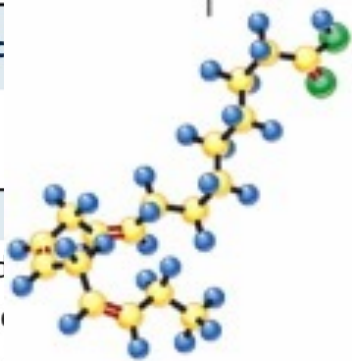
Use of Dietary Supplements in Colaus (N=6186)



Omega-3 PUFAs Composition

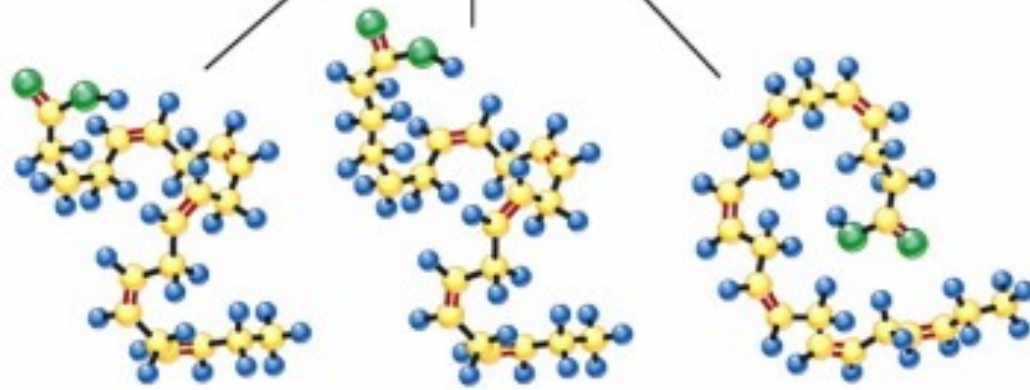
TABLE 1 Biochemic	
Name	
Omega-3 PUFAs	
Alpha-linolenic acid	
Eicosapentaenoic acid	
Docosahexaenoic acid	
Omega-6 PUFAs	
Linoleic acid	
Arachidonic acid	
PUFA = polyunsaturated	

Plant n-3 PUFA



Alpha-linolenic acid
ALA (18:3n-3)

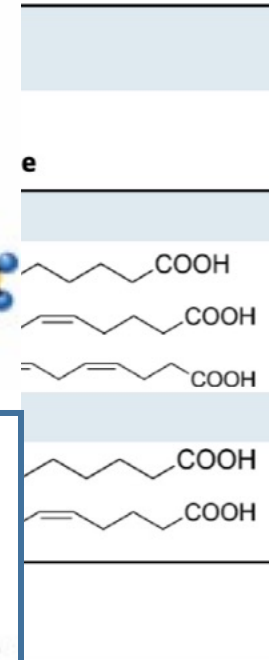
Seafood n-3 PUFA



Eicosapentaenoic acid
EPA (20:5n-3)

Docosapentaenoic acid
DPA (22:5n-3)

Docosahexaenoic acid
DHA (22:6n-3)



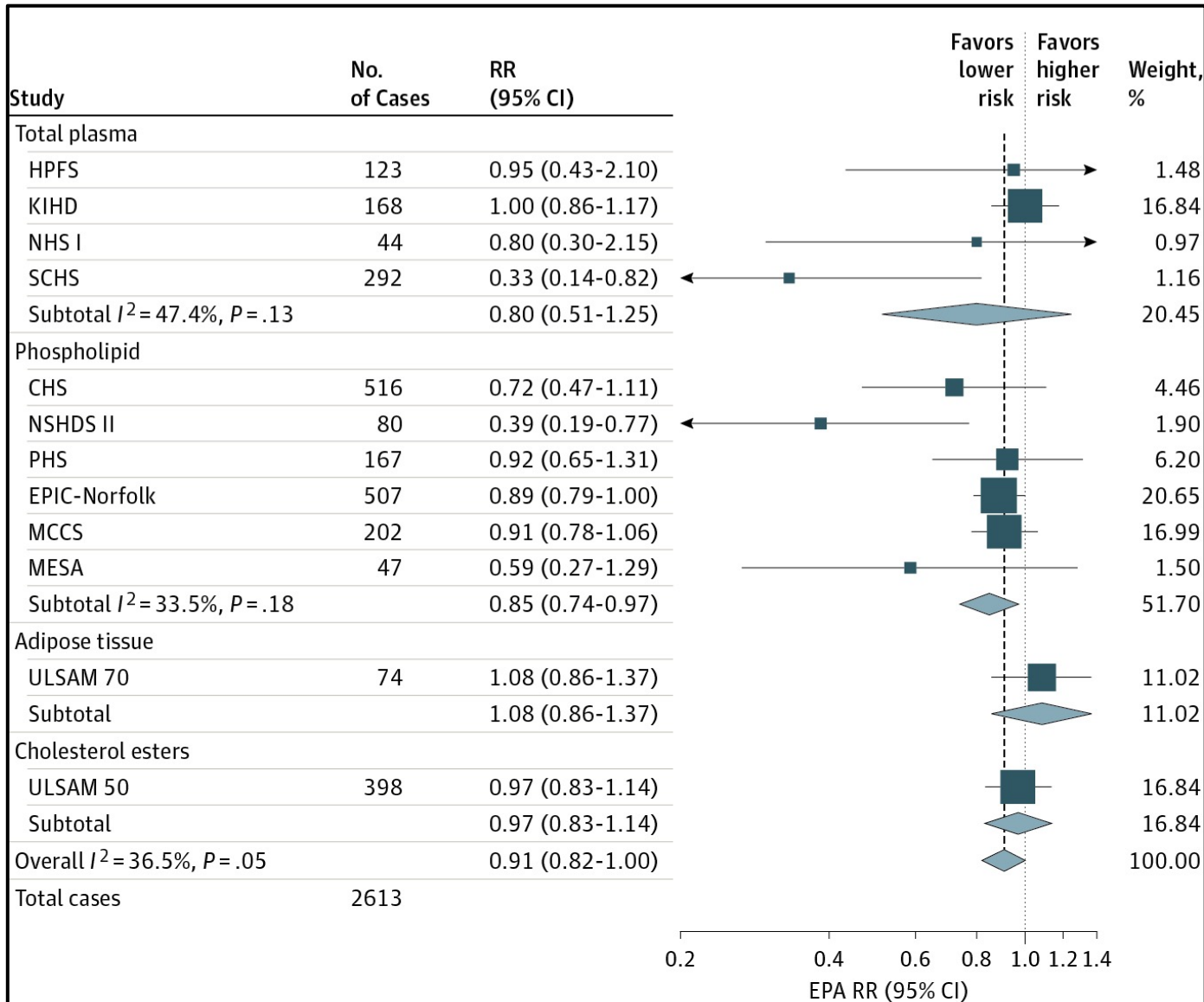
Contents of EPA and DHA in Fishes

Food	EPA (g/100g)	DHA (g/100g)
Fish		
Salmon, Atlantic farmed	0.86	1.10
Salmon, Atlantic wild	0.32	1.11
Herring, Atlantic	0.71	0.86
Anchovy, canned	0.76	1.29
Sardines, canned	0.47	0.51
Mackerel	0.90	1.40
Cod, Pacific	0.042	0.005
Fish Oil		
Salmon	13.02	18.23
Sardine	10.14	10.66
Menhaden	13.17	8.56



Plasma ω -3 Polyunsaturated FA (EPA) and CHD

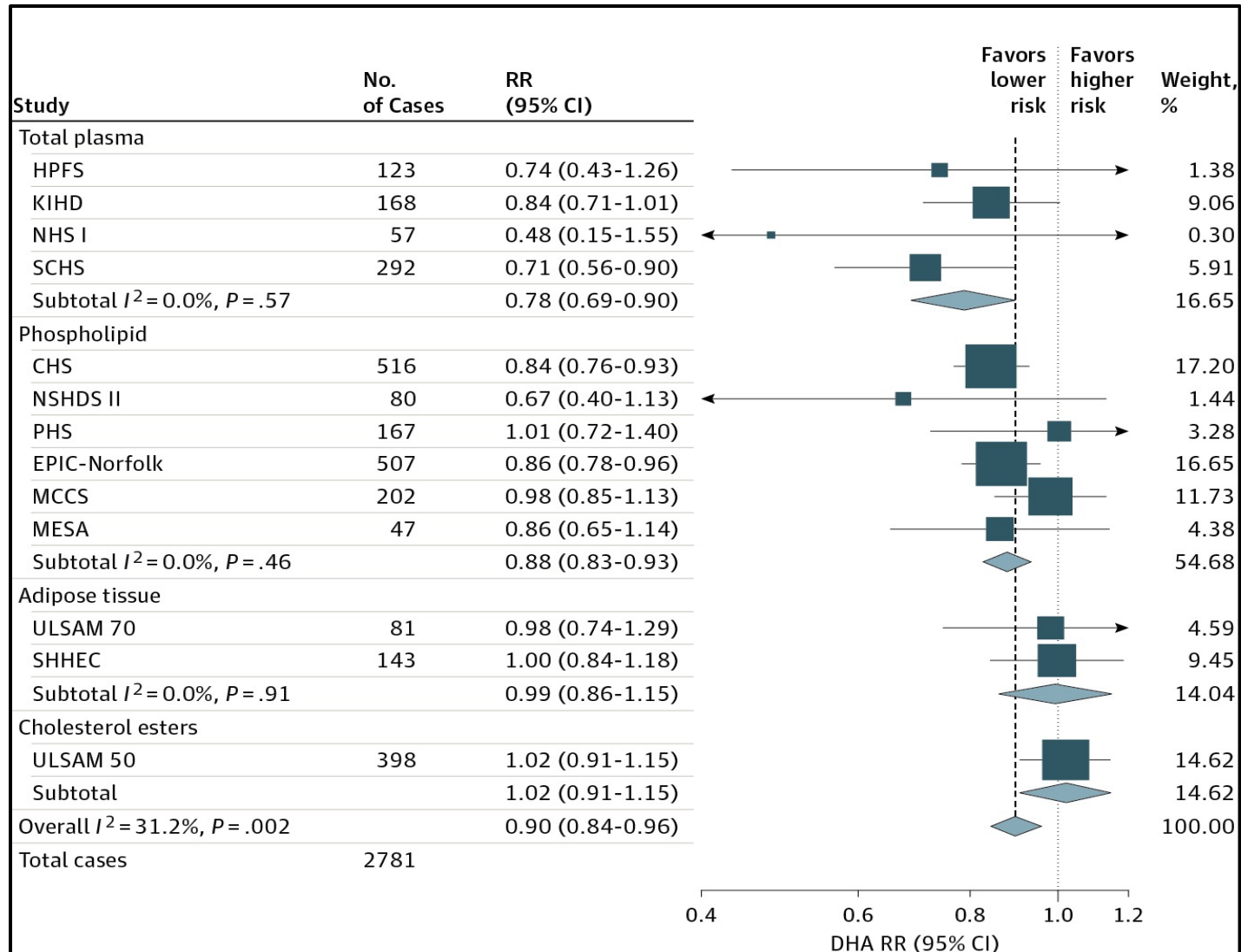
19 studies, 45'637 patients and 7973 CHD events



Per each 1-SD increase in EPA, there is a **reduction of 9%** of the risk of CHD

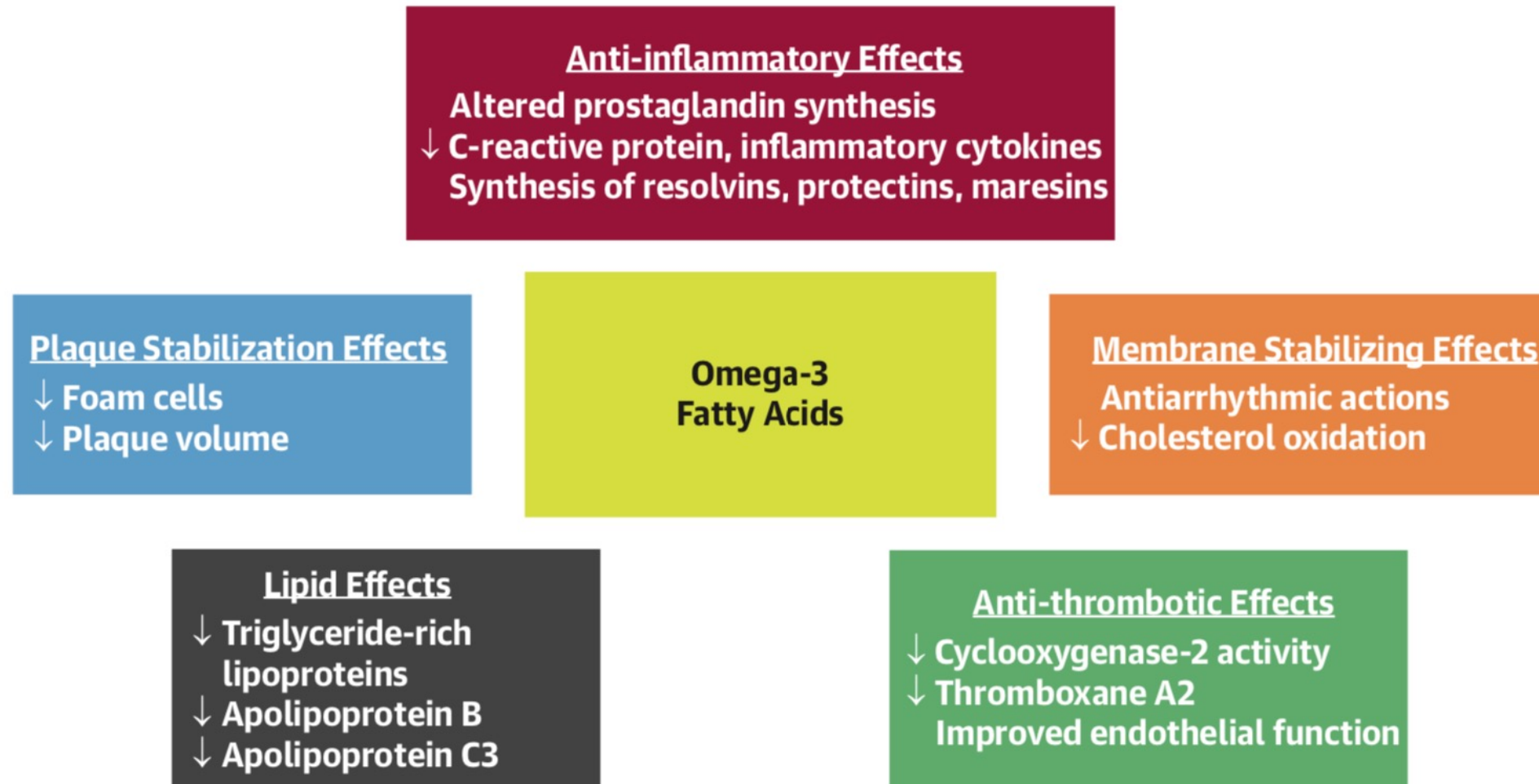
Plasma ω -3 Polyunsaturated FA (EPA) and CHD

19 studies, 45'637 patients and 7973 CHD events



Per each 1-SD increase in DHA, there is a **reduction of 10%** of the risk of CHD

Potential Mechanisms of ω -3 PUFAs Protection



Recommendations for drug treatments of patients with hypertriglyceridaemia (1)

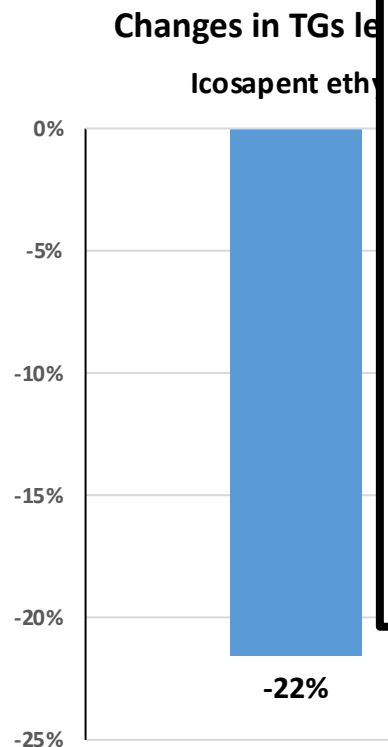
Recommendations	Class	Level
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia (TG >2.3 mmol/L (>200 mg/dL)).	I	B
In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2 g/day) should be considered in combination with statin.	Ia	B

©ESC

REDUCE-IT Trial (N=8179)

4 g of EPA (Icosapent ethyl) vs Placebo

- Patients with ASCVD (71%)
- Mean age 64y, m
- Background of s
- Fasting TGs 135
- LDL-C 41-100 m

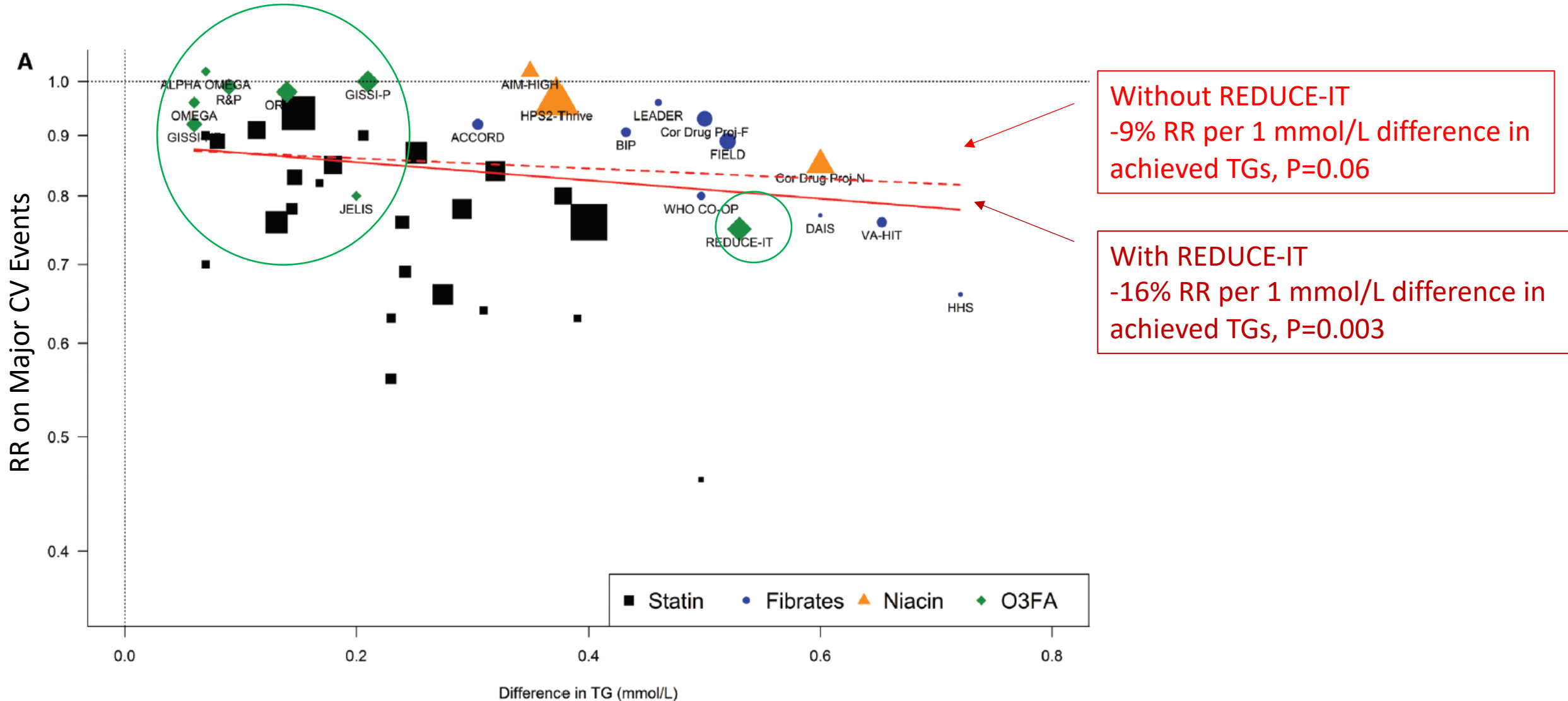


- Persisting residual CV risks with elevated triglycerides (TGs) despite maximal statin therapy.
- Icosapent ethyl is a purified omega-3 poly-unsaturated fatty acid (EPA 4g) that reduced TGs levels without decreasing low-density lipoprotein cholesterol (LDL-C).
- In the REDUCE-IT trial, EPA 4g reduced major CV events by 25% and total CV events by 32%.

A Primary End Point

MI, nonfatal stroke, coronary revascularization, or unstable angina

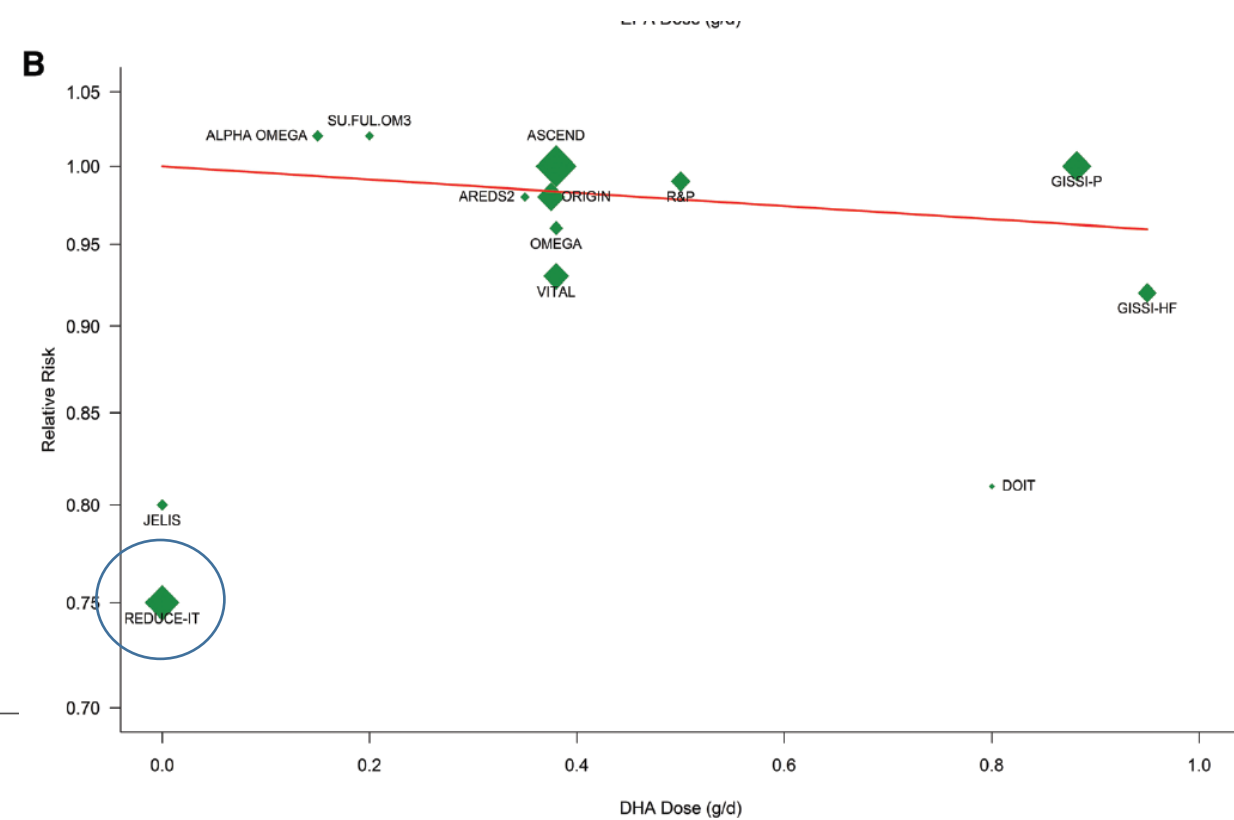
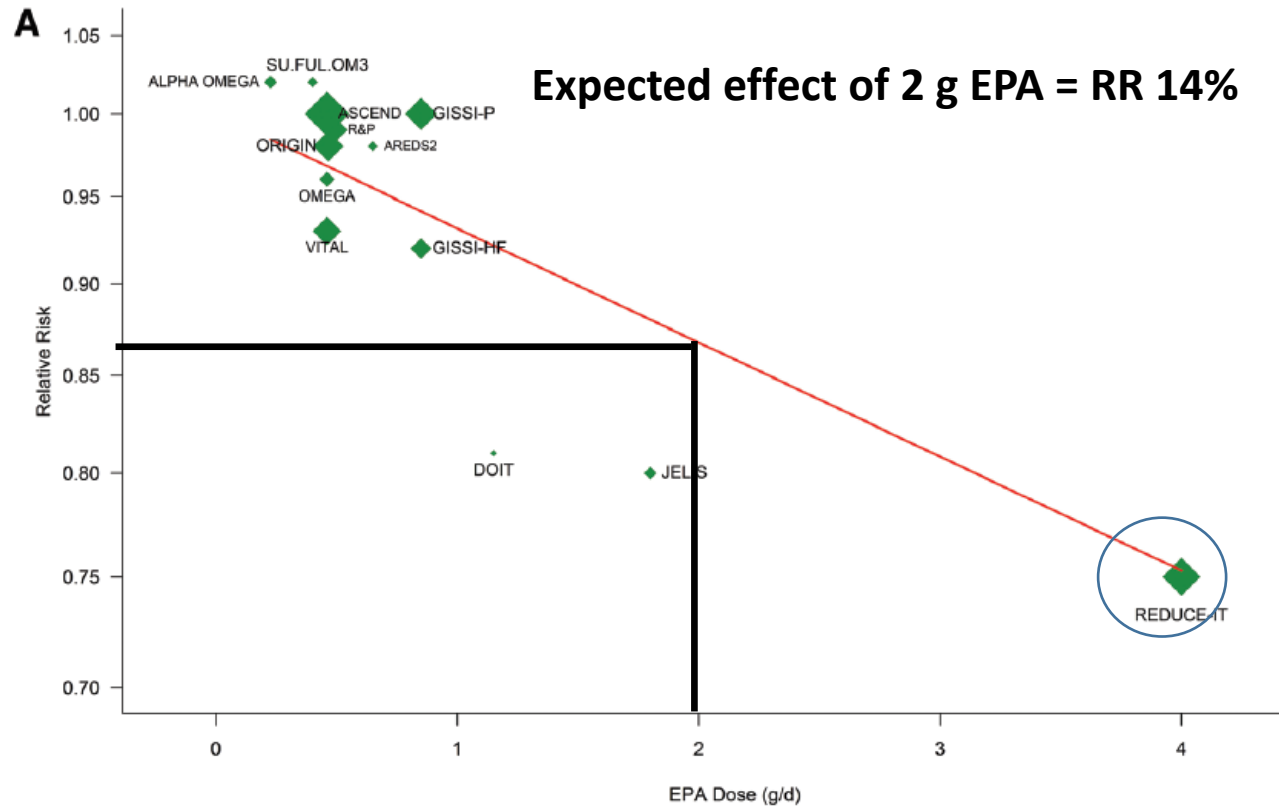
Reduction of TGs and CV Risk Protection



Dosage of EPA vs. DHA and CV Risk Protection

Eicosapentaenoic acid (EPA)

Docosahexaenoic acid (DHA)

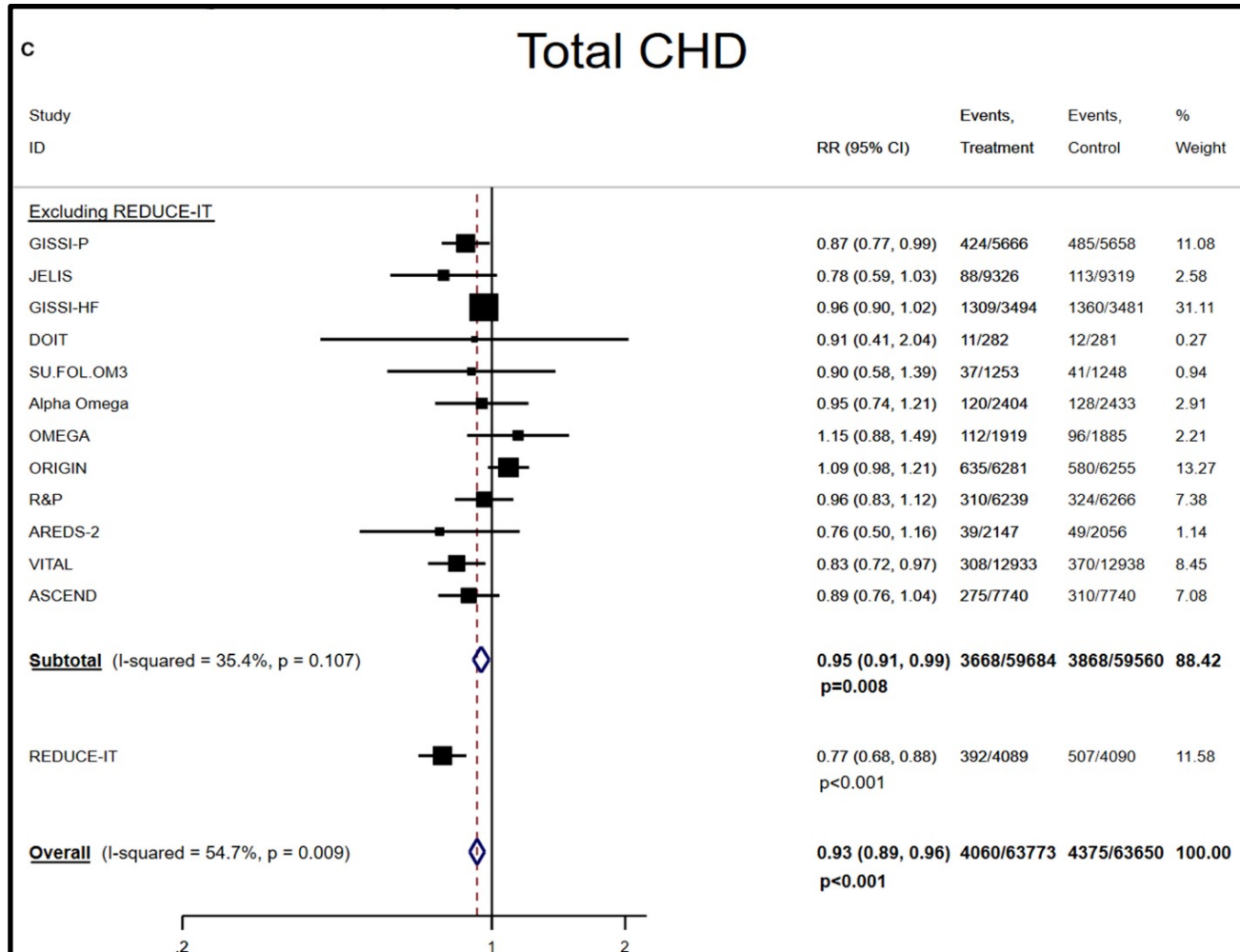


RR per 1 g/d EPA **0.93** (95%CI 0.91-0.95, **P<0.0001**)

RR per 1 g/d DHA **0.96** (95%CI 0.89-1.03, **P=0.27**)

Marine Omega-3 Supplementation and CHD

Meta-analysis of 13 Randomized Controlled Trials and 127'477 subjects



A mean treatment duration of 5.0 years, 8435 total CHD events

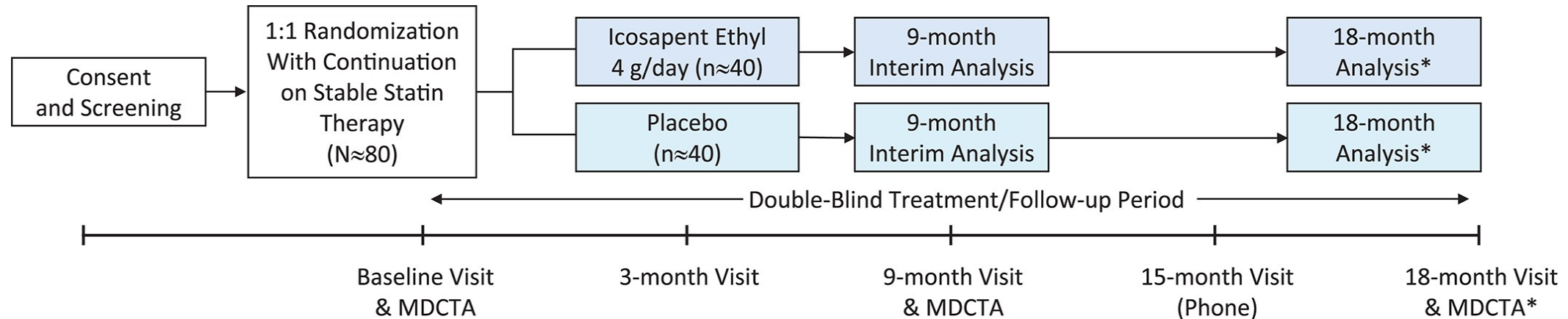
Without REDUCE-IT:

RR 0.95, 95%CI 0.91-0.99, P=0.008

With REDUCE-IT:

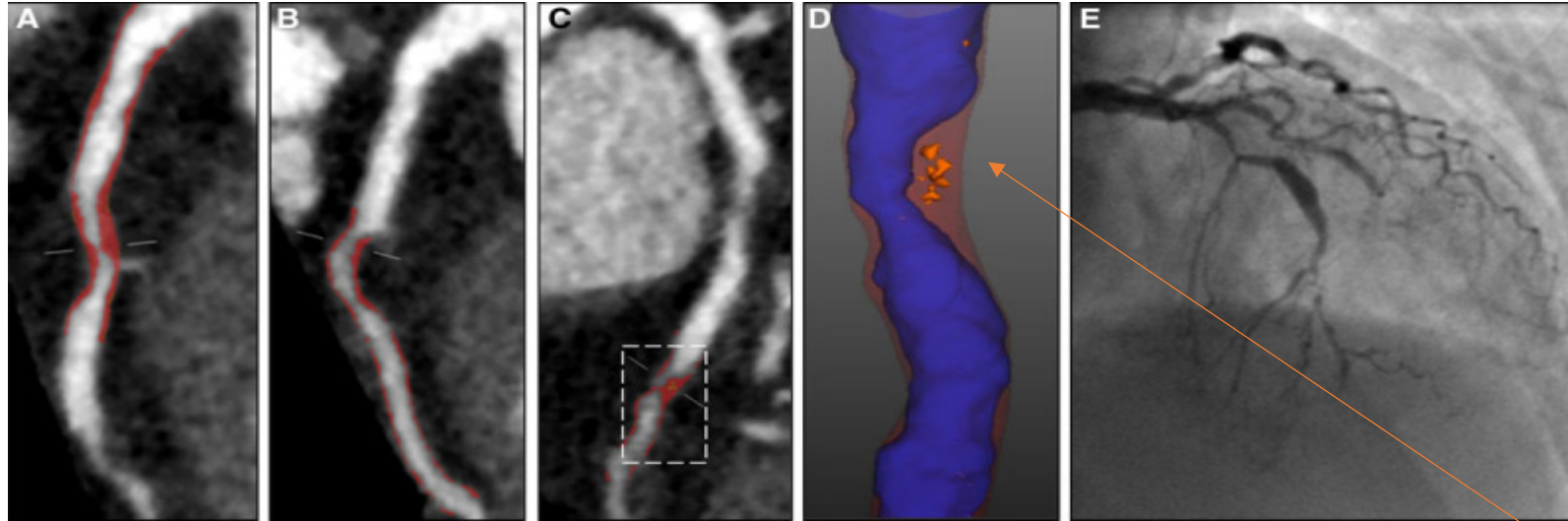
RR 0.93, 95%CI 0.89-0.96, P<0.001.

Effect of 4 g of EPA on Coronary Plaque



- Randomized, double-blind, multi-centric, placebo-controlled trial.
- Allocation 1:1 **Icosapent Ethyl** 4 grams/day vs. mineral oil placebo.
- Multidetector computed tomography (MDCT) at baseline, at 9-months (interim) and 18-months (final).
- Outcome: Plaque volume progression (low-attenuation plaque)
- Funded by Amarin Pharma.

Coronary CT angiography (CCTA) plaque analysis



Circulation 2020 May 5; 141(18): 1452-1462.

Plaque composition was based on predefined fixed intensity cut-off Hounsfield units (HU) values of CT attenuation:

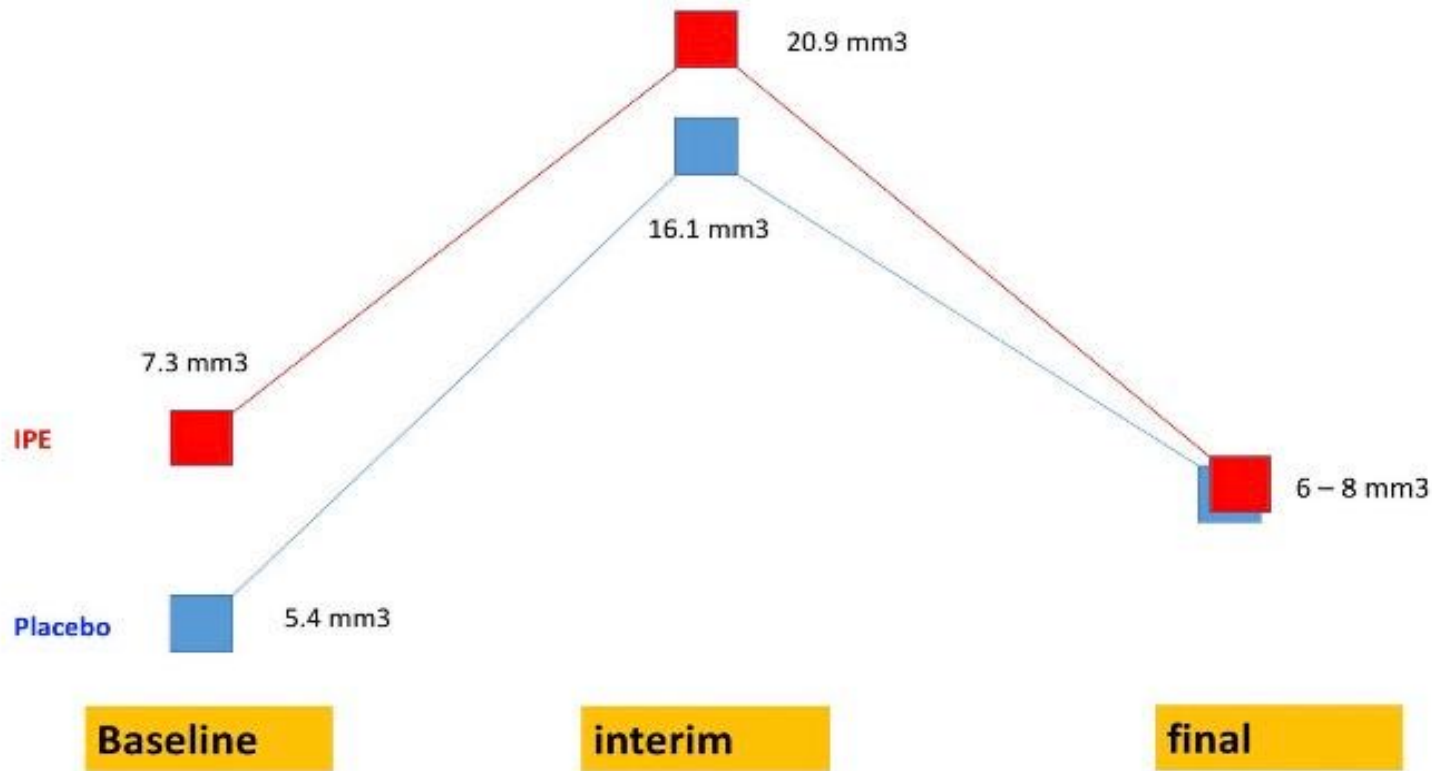
- **-50 to 50 HU** for low-attenuation plaque => necrotic + vulnerable plaque
- **51-130 HU** for fibrofatty plaque.
- **131-350 HU** for fibrotic plaque.
- **>350 HU** for dense calcium.

Low-attenuation Plaque

Changes in Plaque with Icosapent Ethyl in EVAPORATE

Primary endpoint of low-attenuation plaque

4g of icosapent ethyl per day demonstrated significantly regression of low-attenuation plaque volume compared with placebo (mineral oil) over 18 months in the EVAPORATE trial (N=68)



+109% of plaque increase in the mineral oil arm

2021 ESC Prevention Guidelines

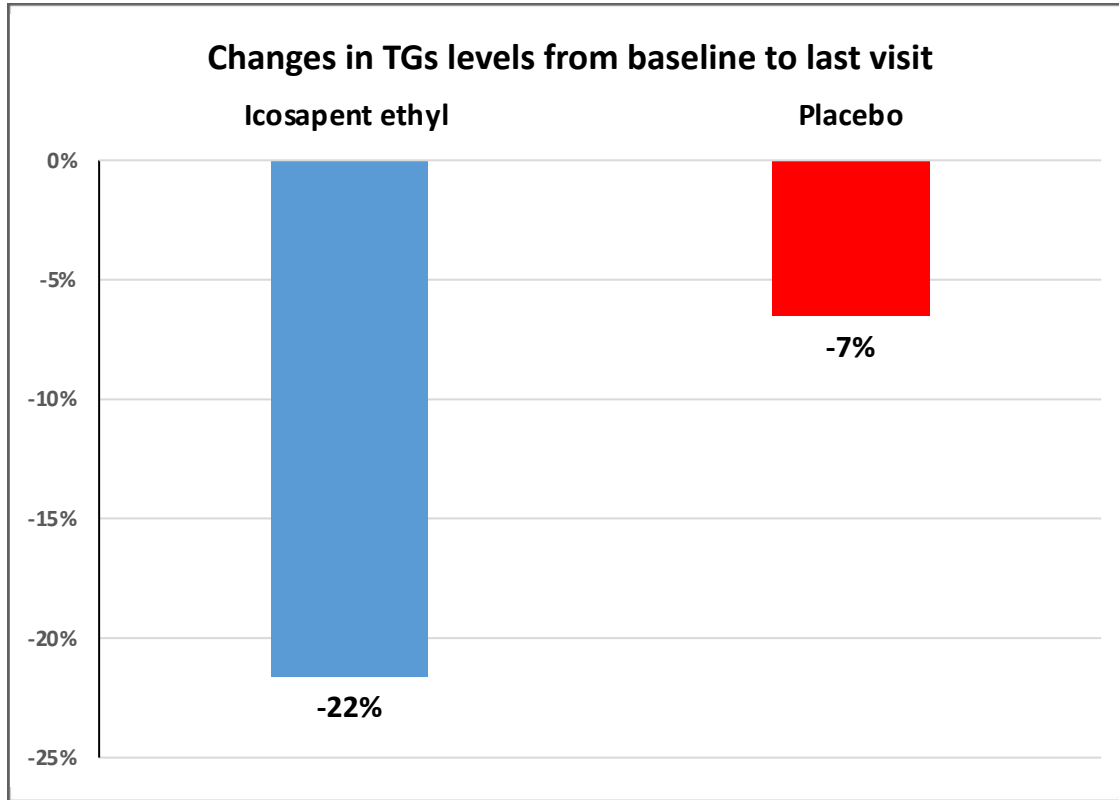
Recommendations for drug treatments of patients with hypertriglyceridaemia

Recommendations	Class ^a	Level ^b
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [triglycerides >2.3 mmol/L (200 mg/dL)]. ⁵³³	I	A
In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered. ^{534–536}	IIb	B
In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2 × 2 g/day) may be considered in combination with a statin. ⁸⁴	IIb	B

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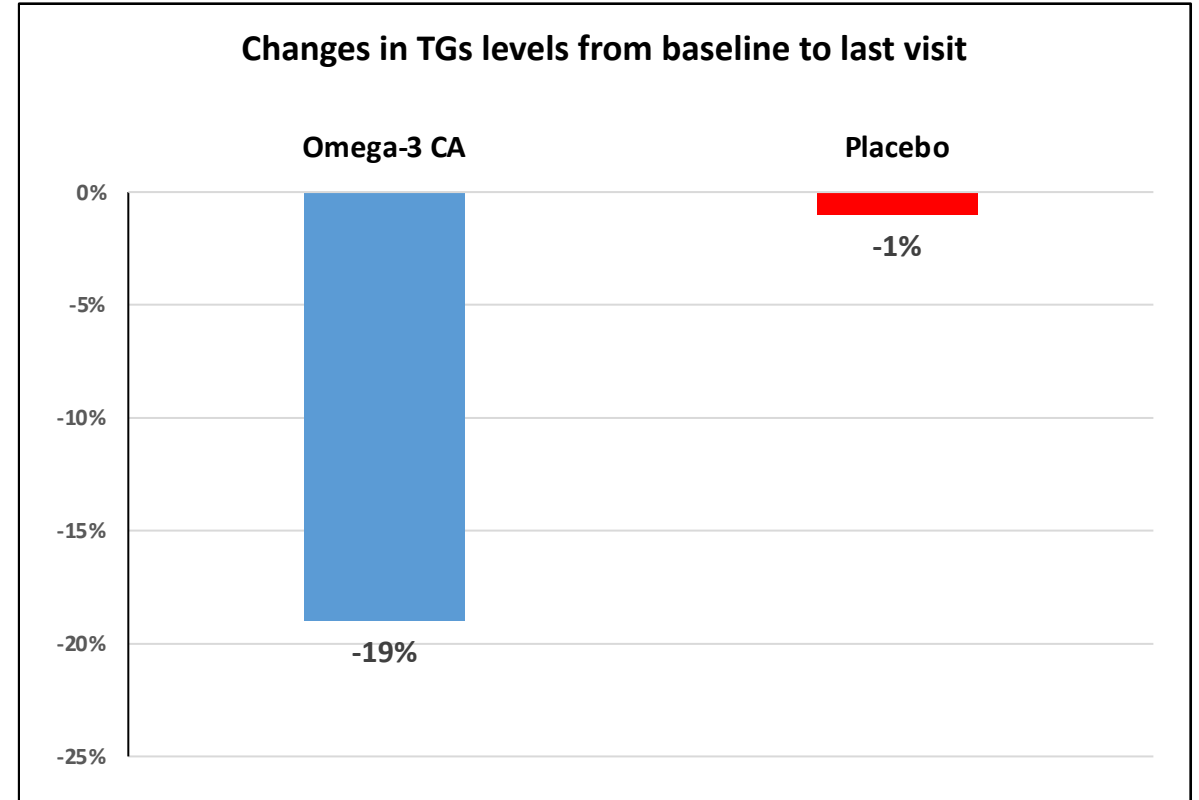
REDUCE-IT vs STRENGTH Trials

4 g of EPA (Icosapent ethyl) vs Mineral Oil



N Engl J Med. 2019 Jan 3;380(1):11-22

4 g of Omega-3 CA (EPA+DHA) vs Corn Oil



JAMA. 2020;324(22):2268-2280.

STRENGTH vs REDUCE-IT Trials

We believe that STRENGTH demonstrates that REDUCE-IT is a false-positive result.

There is no effect of fish oil on CV outcomes, just as all of the other trials have shown. REDUCE-IT we think is positive because it used a negative control rather than a neutral control.

Prof Steven Nissen, PI of STRENGTH

I think at a certain point it's just ridiculous to not believe something. All omega-3 fatty acids aren't created equal. They have different physiochemical properties, different biochemical properties, and therefore could have different effects on human health in different situations.

Prof Deepak Bhatt, PI of REDUCE-IT

STRENGTH vs REDUCE-IT Trials

Why different results?

Secondary Prevention

HR 0.94 (95%CI 0.84-1.05)

HR 0.73 (95CI 0.65-0.81)

Omega 3

Placebo

Omega-3

Placebo

Risk of Major CV events (%)

30
25
20
15
10
5
0

15.6

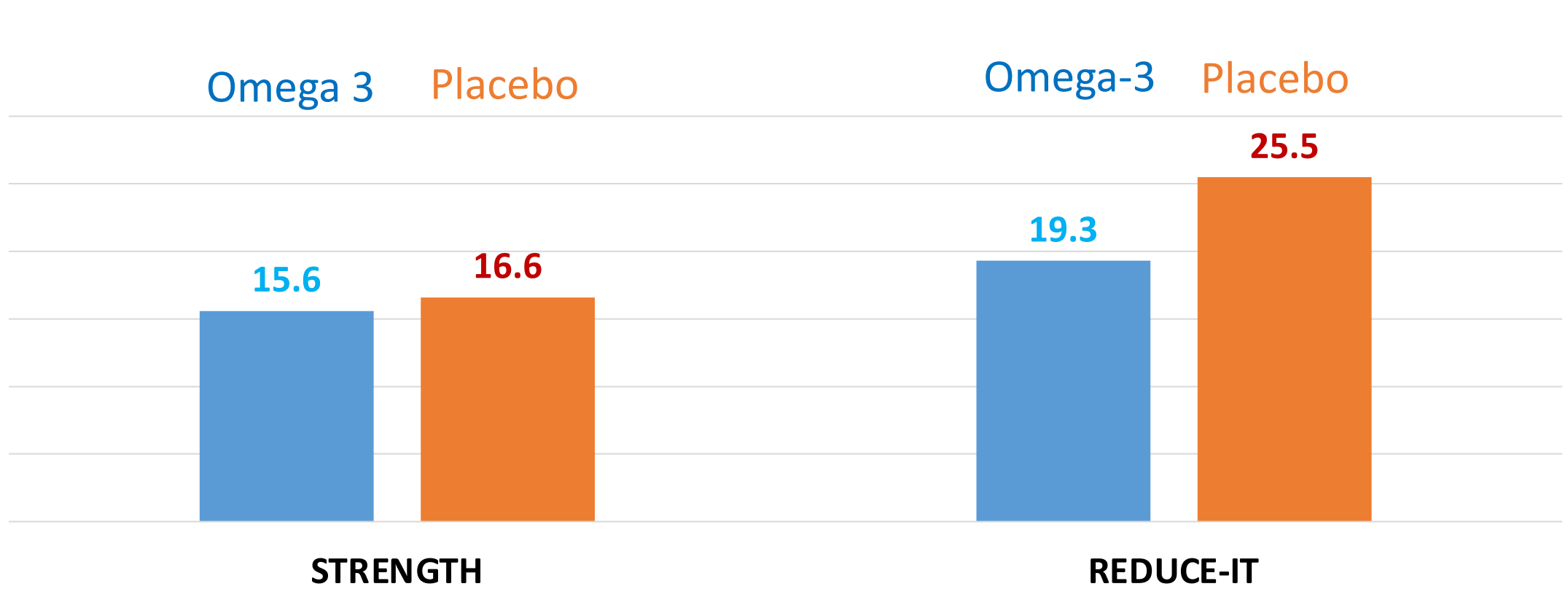
16.6

19.3

25.5

STRENGTH

REDUCE-IT



STRENGTH vs REDUCE-IT Trials

Why different results?

- Icosapent ethyl (pure EPA) produces higher EPA Levels?

Median value	Omega-3 CA (STRENGTH)				Icosapent ethyl (REDUCE-IT)			
	Baseline	Follow-up (12 months)	Absolute Change	% Change	Baseline	Follow-up (12 months)	Absolute Change	% Change
Plasma EPA (µg/mL)	21.0	89.6	+68.6	268.8%	26.1	144.0	+117.9	393.5%
TG (mg/dL)	239	191	-48	-19.0%	217	175.0	-42	-18.3%
LDL (mg/dL)	75	76	+1	+1.2%	74	77	+3	+3.1%
hsCRP (mg/L)	2.1	1.7	-0.4	-20.0%	2.2	1.8	-0.4	-12.6%

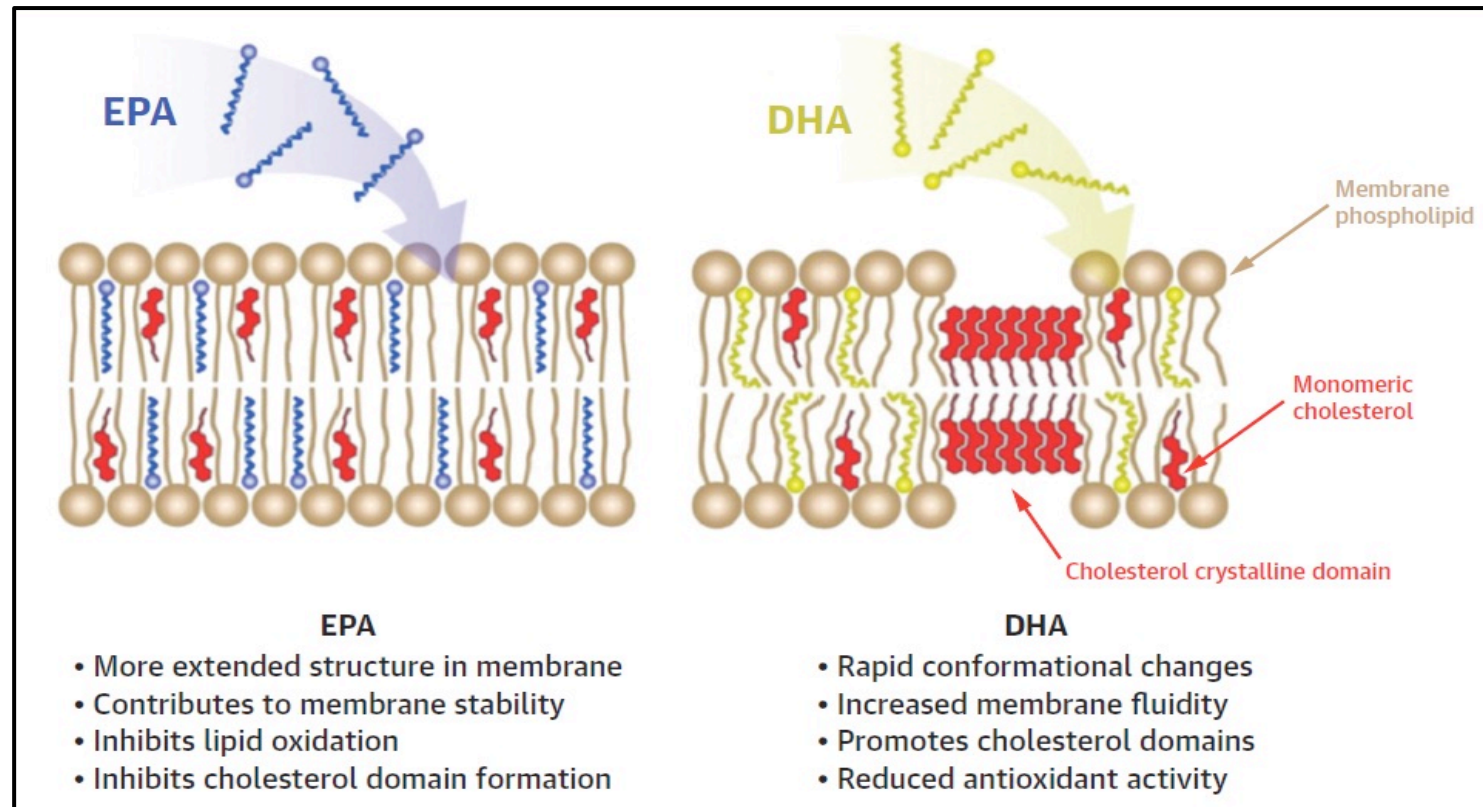
STRENGTH vs REDUCE-IT Trials

DHA toxic? Neutralized favorable effects of EPA?

Review

Do Eicosapentaenoic Acid and Docosahexaenoic Acid
Have the Potential to Compete against Each Other?

Nutrients. 2020 Dec 2;12(12):3718



Placebo in STRENGTH vs. REDUCE-IT

Corn-Oil

Fatty acid composition of corn oil comprises a relatively high level of omega-6 FA ([linoleic acid](#), 58–62%), monounsaturated FA (27-28%) and saturated FA.



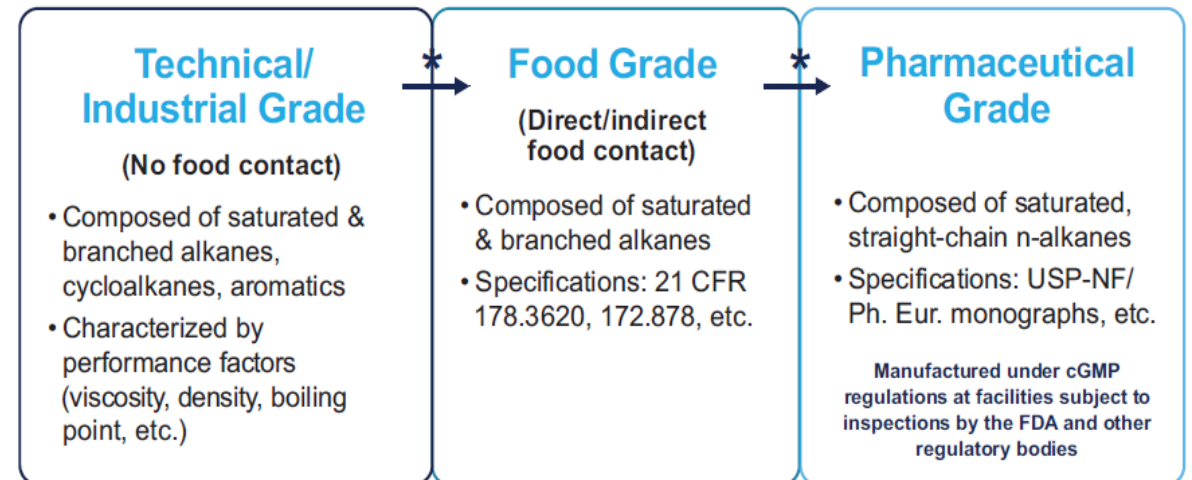
<https://www.hsph.harvard.edu/nutritionsource/2014/11/05/dietary-linoleic-acid-and-risk-of-coronary-heart-disease/>

Mineral oil: safety and use as placebo in REDUCE-IT and other clinical studies



Increasing Purity (Refinement)

Increasing Regulatory Requirements for Manufacturing and Release



STRENGTH vs REDUCE-IT Trials

Why different results?

- Unfavorable effects of mineral oil placebo control led to exaggerated efficacy of icosapent ethyl in REDUCE-IT?

	Corn Oil (STRENGTH)	Mineral Oil (REDUCE-IT)
TG	-0.9%	+2.2%
LDL-C	-1.1%	+10.1% (+ 9.0 mg/dL)
ApoB	-1.0%	+7.8%
hsCRP	-6.3%	+32.3% (+ 0.5 mg/L)

- LDL-C reduction of **38.67** mg/dL is associated with a reduction of MACE by **21%**.
=> **+ 9** mg/dL equals to a relative increased risk of **~5%**
- CRP reduction of **1.6** mg/L is associated with a reduction of MACE by **17%**
=> **+ 0.5** mg/L equals to a relative increased risk of **~5-6%**

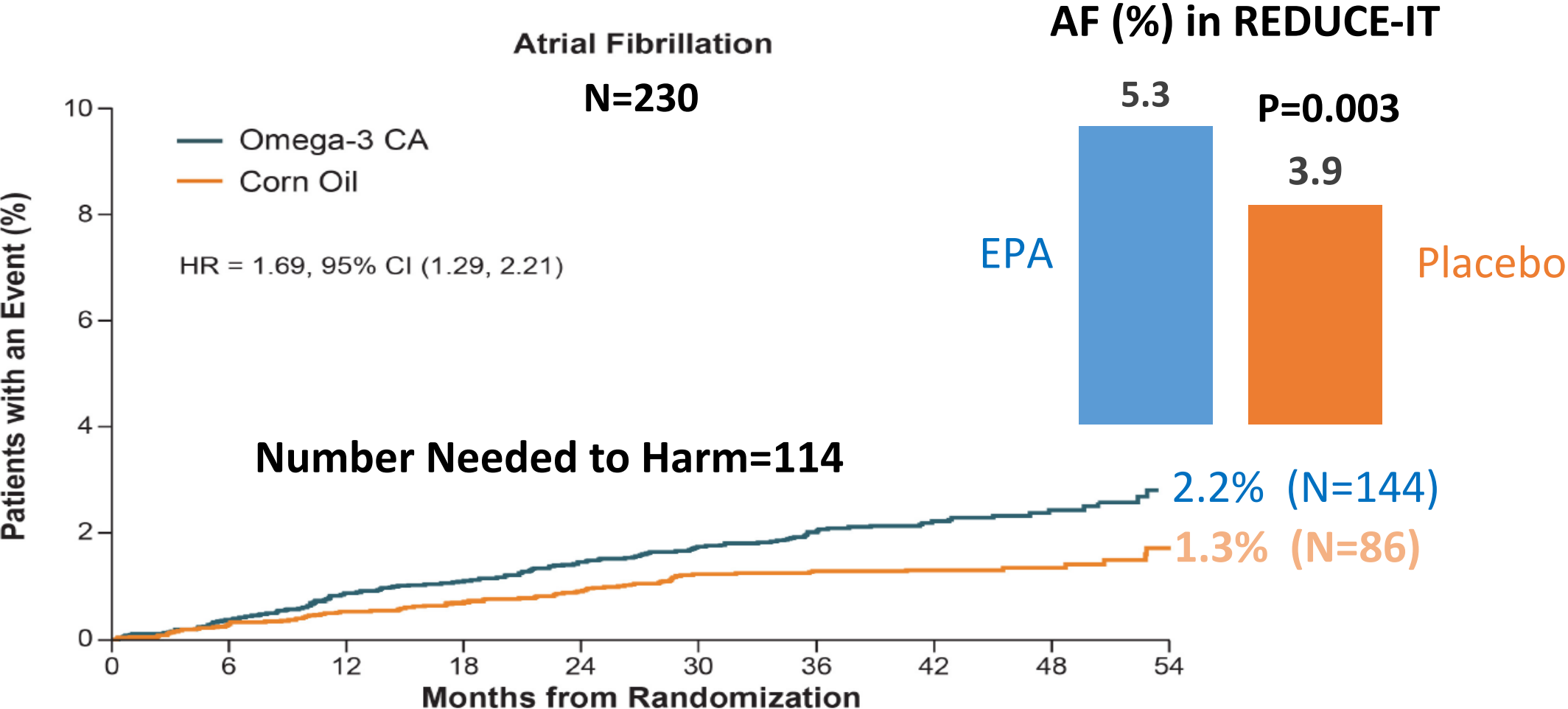
=> At least half of the effect size in REDUCE-IT is explained by the mineral oil

Next trial Icosapent ethyl vs. corn oil?

Editor's Note by Dr Gregory Curfman (JAMA):

«Only a new clinical trial of icosapent ethyl vs corn oil would settle the question definitively, but this is unlikely to be undertaken. Given the current uncertain state of knowledge, neither patients nor physicians can be confident that omega-3 fatty acids have any health benefits, yet in 2019 the global market for omega-3 fatty acids reached \$4.1 billion and is expected to double by 2025. To resolve the discrepancy between STRENGTH and REDUCE-IT, the FDA should require a postmarketing clinical trial of high-dose icosapent ethyl vs corn oil in patients at risk for cardiovascular events. This is a critical next step to shed further light on this perplexing clinical issue and research question.»

Risk of Atrial Fibrillation (AF) in STRENGTH



Number at Risk

Omega-3 CA	6539	6452	6348	6264	6168	6053	5178	3174	1641	613
Corn Oil	6539	6461	6385	6311	6209	6112	5231	3237	1657	612

Omega-3 Supplements and risk of AF

ORIGINAL RESEARCH ARTICLE

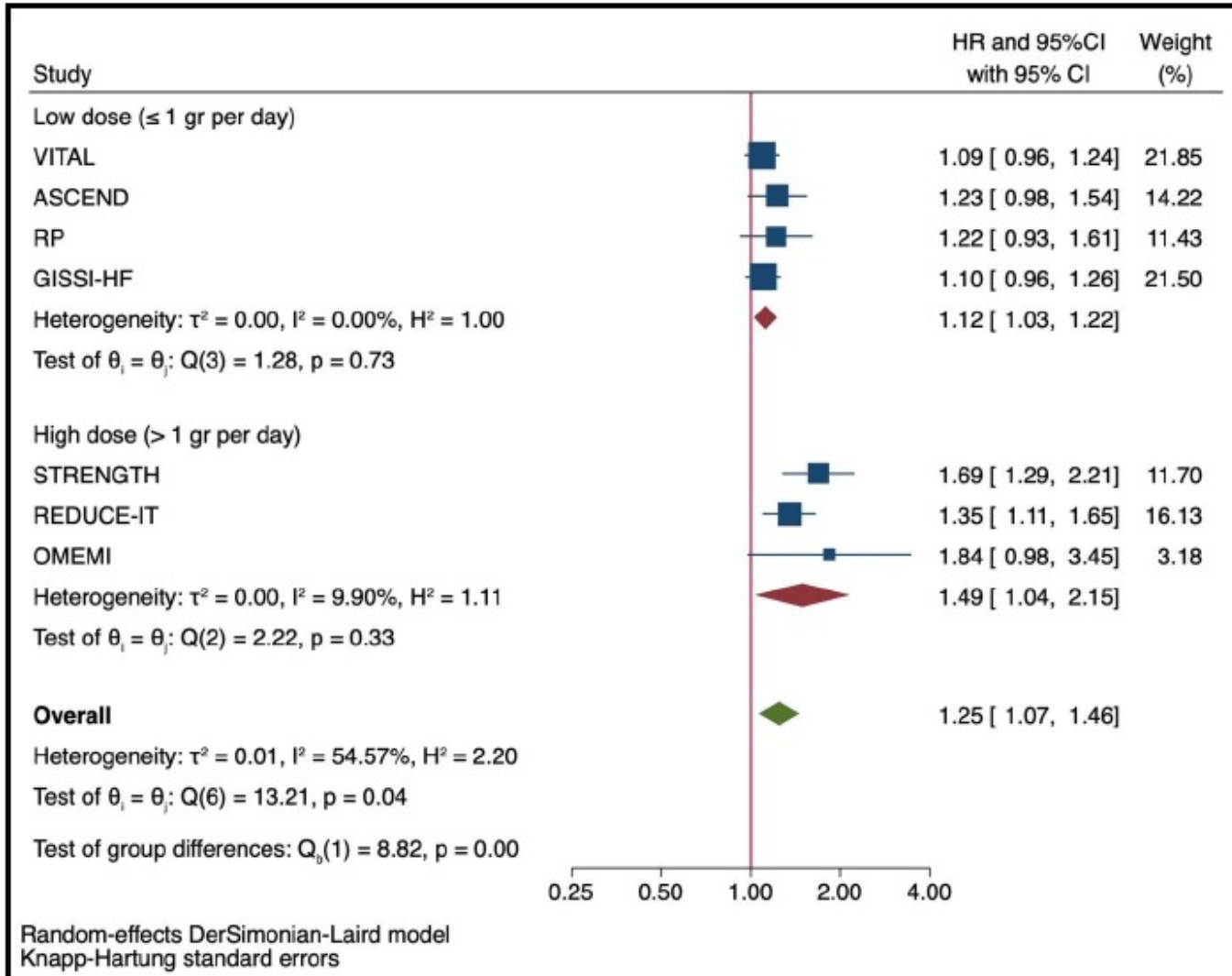


Effect of Long-Term Marine ω -3 Fatty Acids Supplementation on the Risk of Atrial Fibrillation in Randomized Controlled Trials of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis

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

Omega-3 Supplements and risk of Atrial Fibrillation

81 210 patients from 7 trials, 2905 incident AF events



Low dose (≤ 1 g/d) of omega-3 trials:

+ 12% risk of AF events (95%CI + 3%-22%)

High dose (> 1 g/d) of omega-3 trials:

+ 49% risk of AF events (95%CI + 4%-46%)

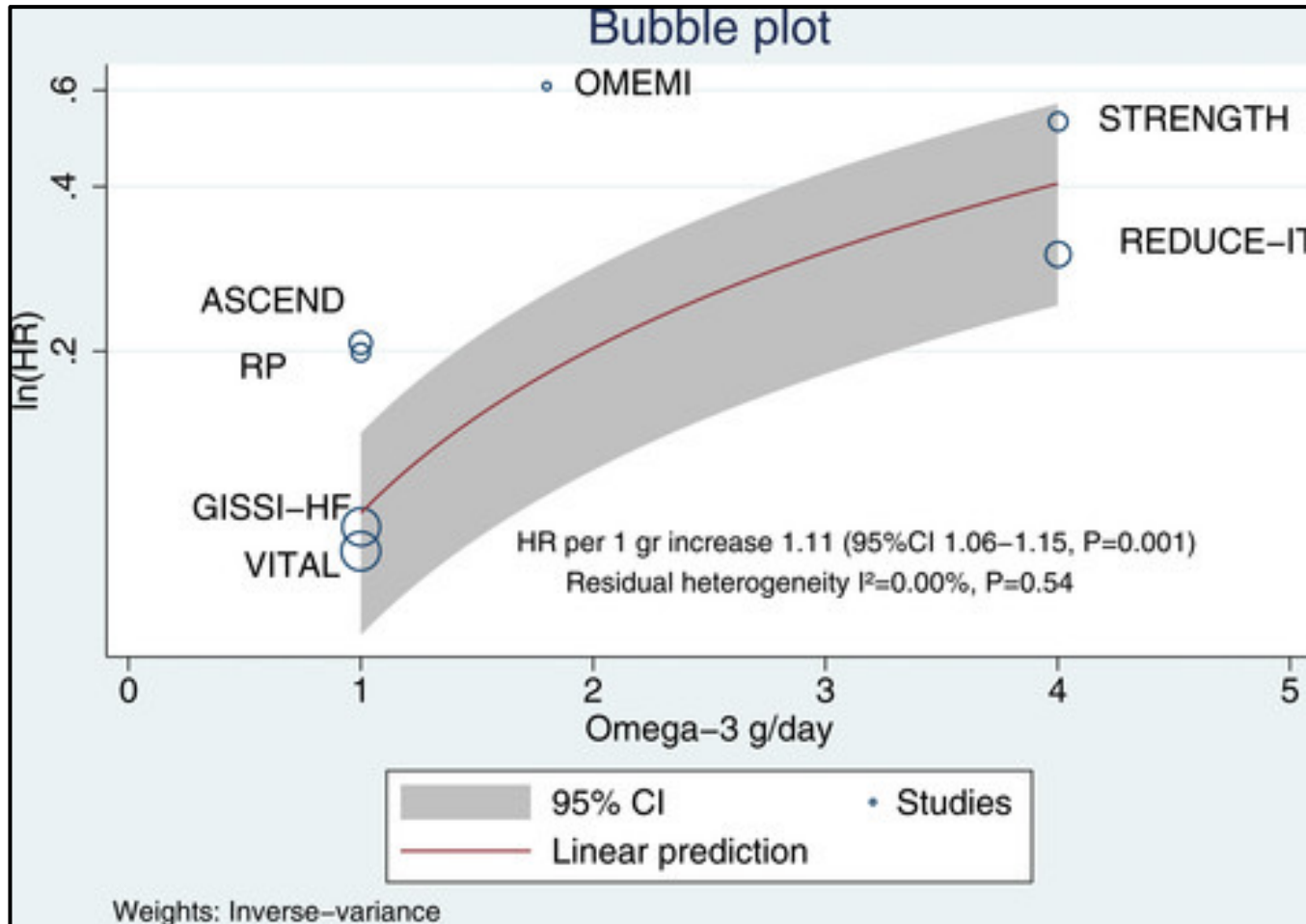
All trials:

+ 25% risk of AF events (95%CI + 7%-46%)

Omega-3 Supplements and risk of Atrial Fibrillation

81 210 patients from 7 trials, 2905 incident AF events

Meta-regression



+ 11% risk of Afib per 1 gr increase in omega-3 supplements (P=0.001)

Conclusion

- Guidelines recommend ≥ 2 servings per week of fish
- Marine omega-3 supplementation may reduce the risk of CV disease in some patients, especially with a higher dosage
- Marine omega-3 supplementation in doses of 2 to 4 g/day lower blood triglycerides levels
- The potential risk of developing atrial fibrillation should be discussed with the patients when prescribing marine omega-3 supplementation, especially when prescribing a higher dosage.

Merci pour votre attention

