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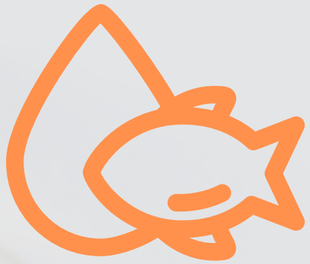


OMEGA 3 & HEART HEALTH

CLARIFICATION & CONTROVERSIES

DR. ALEXANDRA VERGE ND

Review > Curr Atheroscler Rep. 2023 Jan;25(1):1-17. doi: 10.1007/s11883-022-01075-x. Epub 2022 Dec 29.

Role of Omega-3 Fatty Acids in Cardiovascular Disease: the Debate Continues

Samuel C R Sherratt [1 2] ... R Preston Mason [6 7]

Affiliations + expand

PMID: 36580204 PMCI

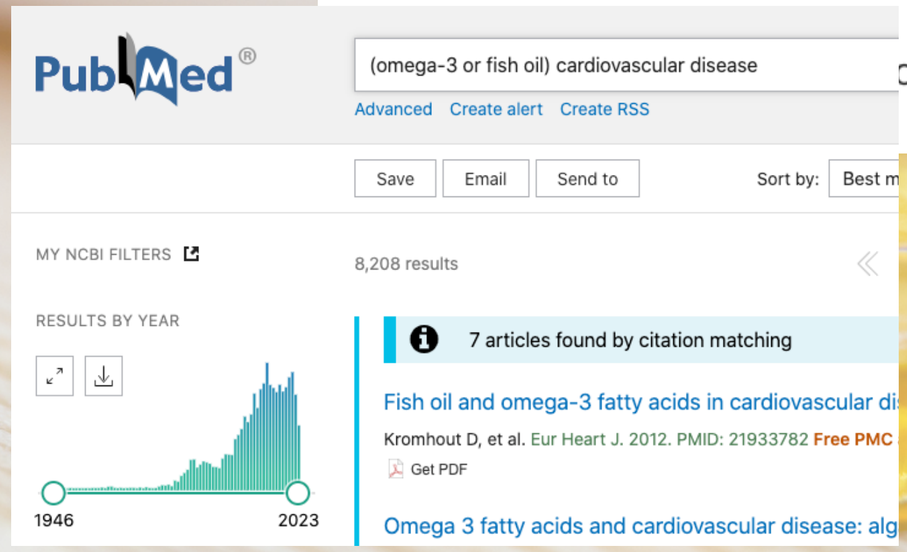
Free PMC article

Review > Heart Int. 2021 Jul 15;15(1):7-13. doi: 10.17925/HI.2021.15.1.7. eColle

The Evolving Role of Omega 3 Fatty Acids in Cardiovascular Disease: Is Icosapent Ethyl the Answer?

Suvasini Lakshmanan [1], Matthew J Budoff [1]

OI: 10.17925/HI.2021.15.1.7



Review > Pharmacol Res. 2022 Aug:182:106342. doi: 10.1016/j.phrs.2022.106342. Epub 2022 Jul 4.

Omega-3 and cardiovascular prevention - Is this still a choice?

Massimiliano Ruscica [1], Cesare R Sirtori [2], Stefano Carugo [3], Philip C Calder [4], Alberto Corsini [2]

Affiliations + expand

PMID: 35798287 DOI: 10.1016/j.phrs.2022.106342

Free article

Review > Curr Probl Cardiol. 2021 Mar;46(3):100718. doi: 10.1016/j.cpcardiol.2020.100718. Epub 2020 Sep 25.

Fish Oil Dilemma: Does It Increase the Risk of Ventricular Arrhythmias and Death? Can Fish Oil Kill You?

Addis Asfaw, Sheharyar Minhas, Amir R Khouzam, Nadim R Khouzam, Rami N Khouzam

PMID: 33097299 DOI: 10.1016/j.cpcardiol.2020.100718

Cochrane Review 2020

'This is the most extensive systematic assessment of effects of omega-3 fats on cardiovascular health to date. Moderate- and low-certainty evidence suggests that increasing LCn3 slightly reduces risk of coronary heart disease mortality and events, and reduces serum triglycerides (evidence mainly from supplement trials).'

Abdelhamid, A. S. et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst. Rev. 2020, CD003177 (2020).

AS GOOD AS IT GETS?

“Blood levels of EPA + DHA are variable across the globe, with most of the countries and regions of the world having levels that are considered low to very low.”

Stark, K. D., Elswyk, M. E. V., Higgins, M. R., Weatherford, C. A. & Salem, N. Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. Prog. Lipid Res. 63, 132–152 (2016)

In 2017-2018, omega-3s were the 3rd most common supplement used by Americans adults

Mishra S, Stierman B, Gahche JJ, Potischman N. Dietary supplement use among adults: United States, 2017–2018. NCHS Data Brief, no 399. Hyattsville, MD: National Center for Health Statistics. 2021. DOI: https://doi.org/10.15620/cdc:101131

In 2015, 11.8% of Canadians used omega-3 supplements

https://www150.statcan.gc.ca/n1/pub/82-625-x/2017001/article/14831-eng.htm#shr-pg0

20+ million people in the US and Canada alone

2020 Canadian Health Measures Survey

Almost 40% of Canadians had an undesirable omega-3 index (<4%)

Most strongly related to supplement use, fish intake, and race.

Who was most likely to have better score?

eating fish >2X/week
non-smokers
Asians
older adults

Demonty, I., Langlois, K., Greene-Finestone, L. S., Zoka, R. & Nguyen, L. Proportions of long-chain ω-3 fatty acids in erythrocyte membranes of Canadian adults: Results from the Canadian Health Measures Survey 2012-2015. Am. J. Clin. Nutr. 113, nqaa401- (2020).

Dr. Alex Verge, ND
@alexvergend

Who am I?

Naturopathic doctor and clinic owner
in practice for over 20 years.

Memberships include Hypertension Canada, National Lipid Association (NLA), European Society of Cardiology, American College of Cardiology, and the American Society for Preventive Cardiology.

Completed the National Lipid Association's Foundations of Lipidology training and have been certified by the Accreditation Council for Clinical Lipidology to have passed the Lipid Competency Certificate Examination.

Conflict of Interest

THE confident clinician

I am an ‘Expert Clinician’ with The Confident Clinician and am paid as an educational contractor.

I also have pay-per-use courses that I receive royalties on through The Confident Clinician.

What is today about?

What isn’t this about?

What should you leave with?

Learning Objectives

1. Update your knowledge about the currently supported cardiovascular benefits of omega-3 fatty acids while better understanding the potential risk (s) associated with supplementation.

2. Learn why and how omega-3-based drugs are used conventionally in cardiovascular disease.

3. Leave understanding which cardiovascular patient populations might best benefit from omega-3 support.

Omega-3 Speed Recap

Definition

Saturated fatty acid

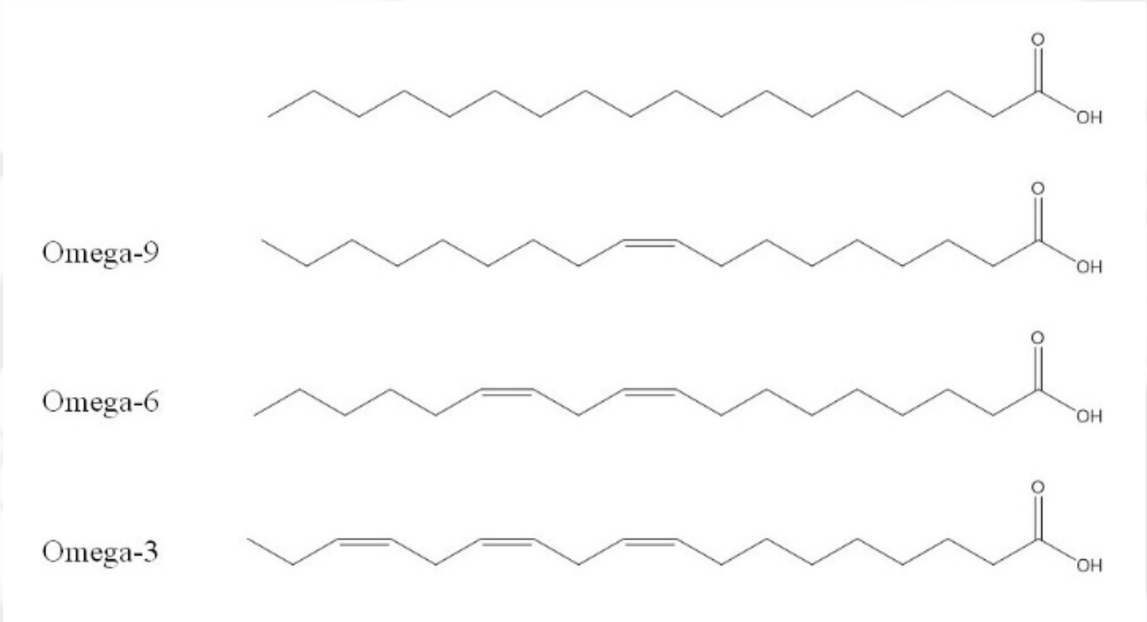
- just single bonds (no double bond in structure)

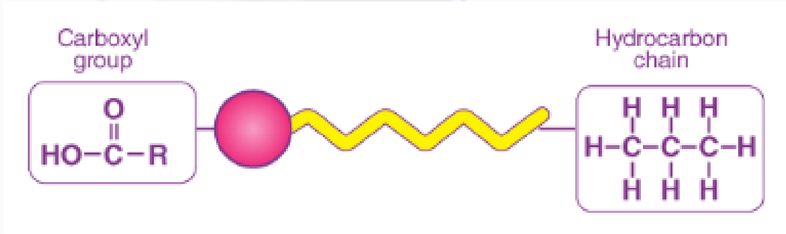
Unsaturated fatty acid

- at least 1 double bond in structure

MONOunsaturated fatty acid (MUFA) = only 1 bond

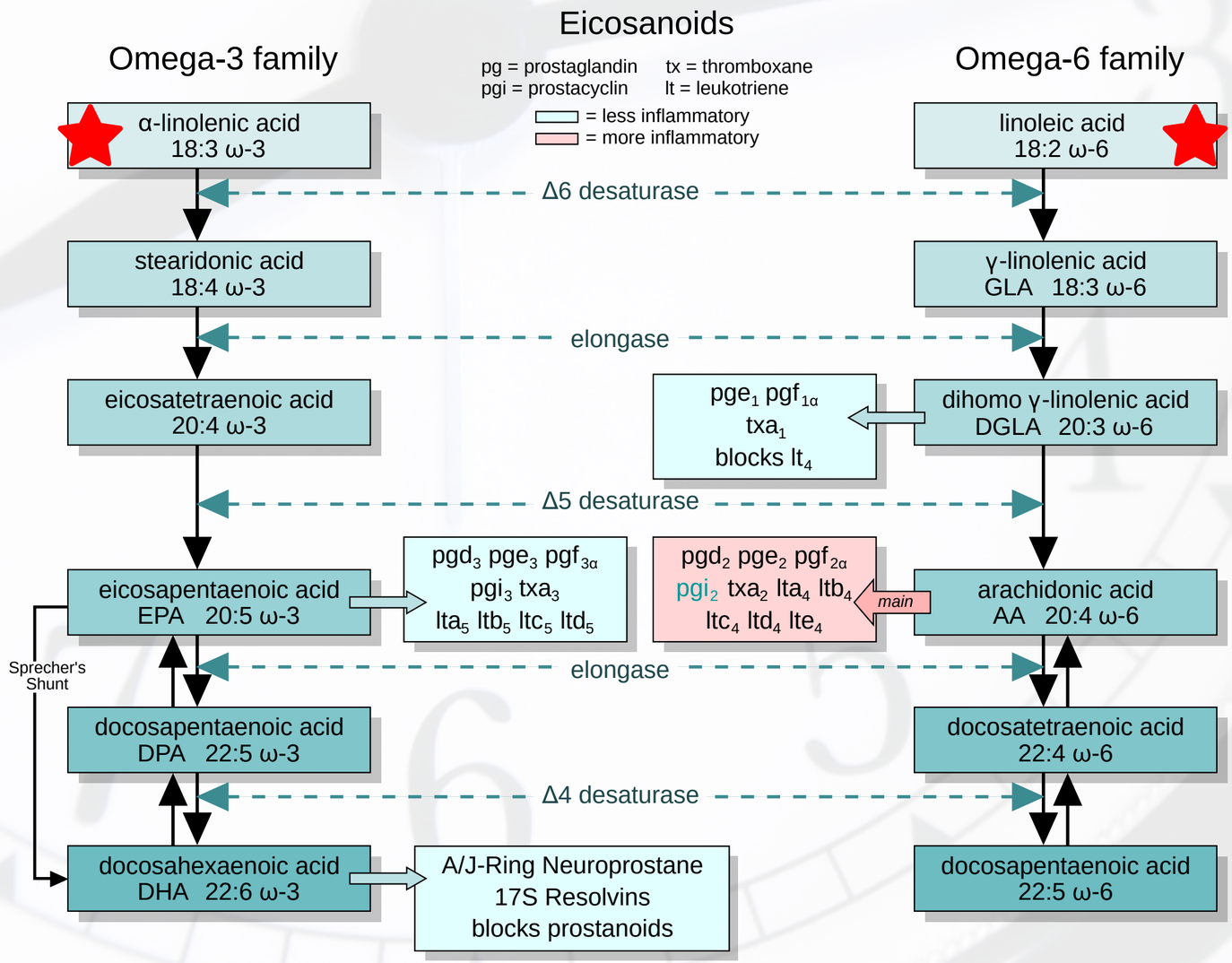
POLYunsaturated fatty acid (PUFA) = two or more bonds





omega-n where n = carbon
where first double bond located
(from the methyl (CH3) end of chain)

omega-3 oil = type of PUFA
with 1st double bond starting
on 3rd carbon from methyl end



Created by David R. Throop, vectorized by Fvasconcellos, Public domain, via Wikimedia Commons

Essential FA – cannot endogenously make

Conversion of ALA to EPA/DHA

approximately 8-12% to EPA

approximately ~1% to DHA

Baker, E. J., Miles, E. A., Burdge, G. C., Yaqoob, P. & Calder, P. C. Metabolism and functional effects of plant-derived omega-3 fatty acids in humans. Prog. Lipid Res. 64, 30–56 (2016).

Sources: Food

ALA - plant sources

- such as vegetable oils, certain nuts, flaxseeds and certain beans (e.g soy)

EPA and DHA - marine sources

- such as seafood, fish oils, and some microalgae

Sources: Supplements/Drugs

Supplements

- triglyceride form
- ethyl ester form

Drugs

- Icosapent ethyl
- carboxylic acid
- EPA+DHA (+/- DPA)

Omega-3 Content (g/100g)

Food	ALA	EPA	DHA
Herring	0.10	0.71	0.86
Salmon (Atlantic, farmed)	0.15	0.86	1.10
Salmon (Atlantic, wild)	0.30	0.32	1.11
Sardines (canned)	0.50	0.47	0.51
Trout	0.16	0.20	0.53
Mackerel	0.16	0.90	1.40
Tuna (canned, water)	-	0.03	0.20

Omega-3 Content (g/100g)

Food	ALA	EPA	DHA
Chia	22.81	-	-
Walnuts	9.08	-	-
Flax	22.81	-	-
Flaxseed Oil	53.37	-	-
Canola Oil	7.45	-	-
Salmon Oil	1.06	13.02	18.23
Sardine Oil	1.33	10.14	10.66
Herring Oil	0.76	6.27	4.21

Agricultural Research Service, U.S. Department of Agriculture. "FoodData Central". Available at: https://fdc.nal.usda.gov/index.html/. Accessed September 10, 2023.

History of omega-3 and heart health

This whole idea began more than 50 years ago with the observation
that Greenland Inuit had a lower risk of cardiovascular disease.

Danish researcher Dr. Jorn Dyerberg had and his mentor Dr. Bang
went to Greenland with a mobile lab able to analyze lipoproteins.

Took blood samples from 130 Inuit:
published in 1971 how lipid levels were lower but low enough to explain lower CVD levels.

Eventually looked at fatty acids, and noticed a different pattern compared to Dane controls.
Heard about researchers linking omega-6 arachadonic acid to prostaglandins
and blood clotting which prompted curiosity.

Went back to Greenland in 1979 to examine bleeding times and discovered major differences.

This opened the floodgates of interest.

Want to hear Dr. Dyerberg discuss his experience?
Omega-3 in heart disease; the original story from the source
Behind Omega-3 Wiley Podcast

Historical use over time for lipid-lowering and general heart health; observational + cell cultures/animal studies suggesting cardio-protective nature of omega-3s.

Things started to come together with the GISSI-PREV trial (1999) - group of MI survivors followed for 3-5 years

Med Diet + Standard Care; split into 4 groups

1. Omega-3 (1 gram: 850 mg EPA+DHA ethyl esters)
2. Vitamin E (300 mg synthetic alpha-tocopherol)
3. Both
4. Neither

Result: Fish oil but not vitamin E reduced CVD morbidity and mortality

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet (Lond., Engl.) 354, 447–55 (1999)

Omega-3 Index (OI)

EPA+DHA content of erythrocytes expressed as
a percent of total identified fatty acids

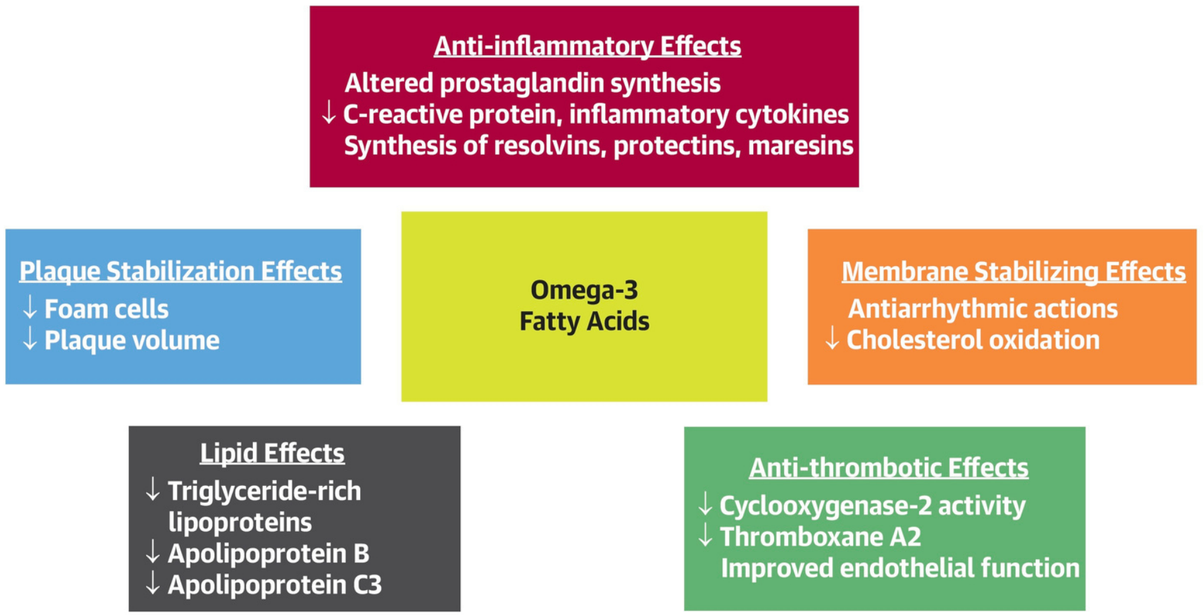
<u>Things to know about the Omega-3 Index</u>

Developed by Drs. Bill Harris and Clemens von Schacky in 2004
Used to quantify omega-3 status in many studies
Range: <4% = high risk, 4-8% = intermediate, >8% = low risk
Originally used to classify CVD risk, it is now being used in other areas

Harris, W. S. & Schacky, C. von. The Omega-3 Index: a new risk factor for death from coronary heart disease? Prev. Med. 39, 212–220 (2004)

Benefits – Recent Support

CENTRAL ILLUSTRATION: Hypothesized Mechanisms of Omega-3 PUFAs That Decrease Cardiovascular Disease Risk

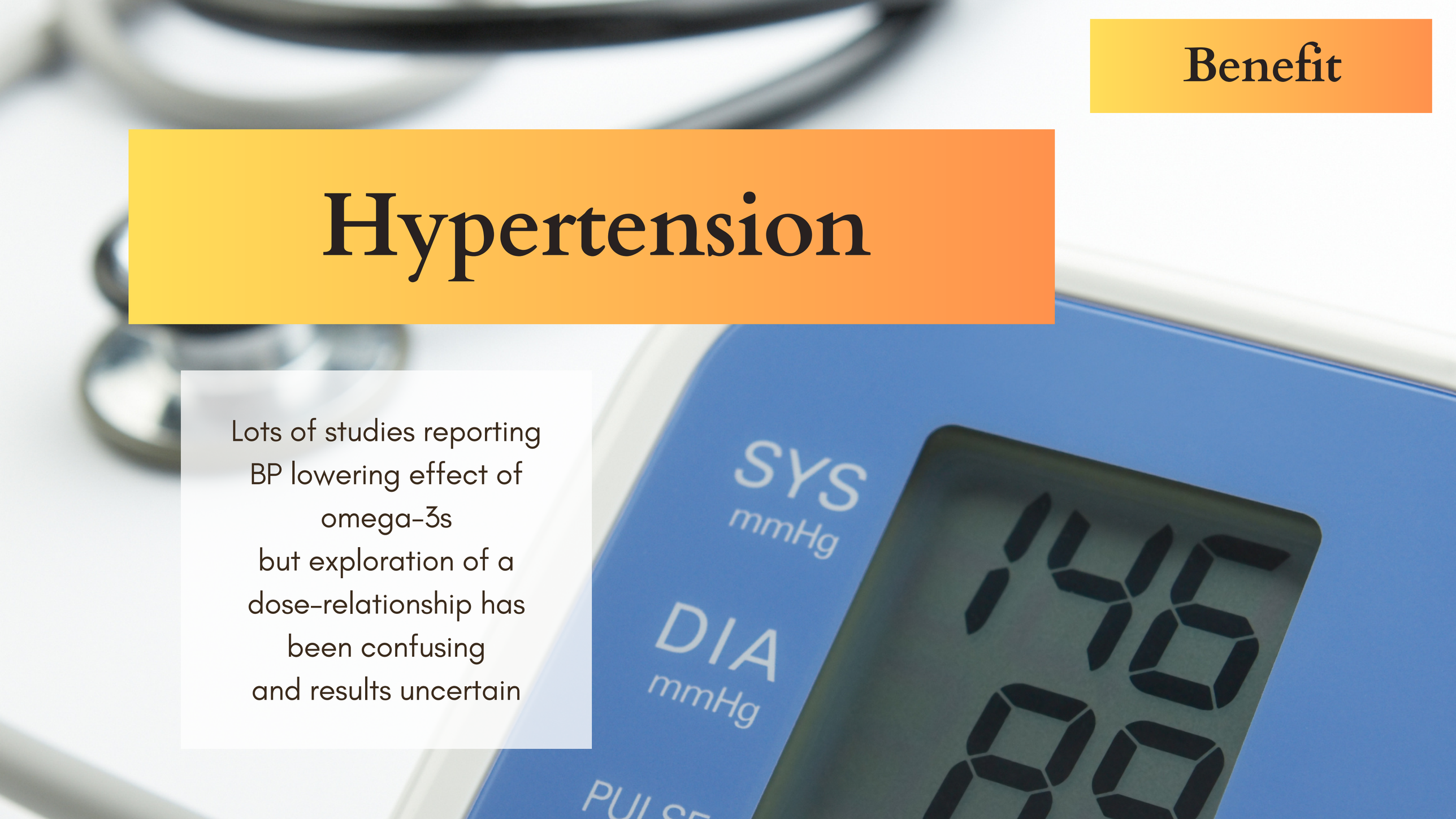


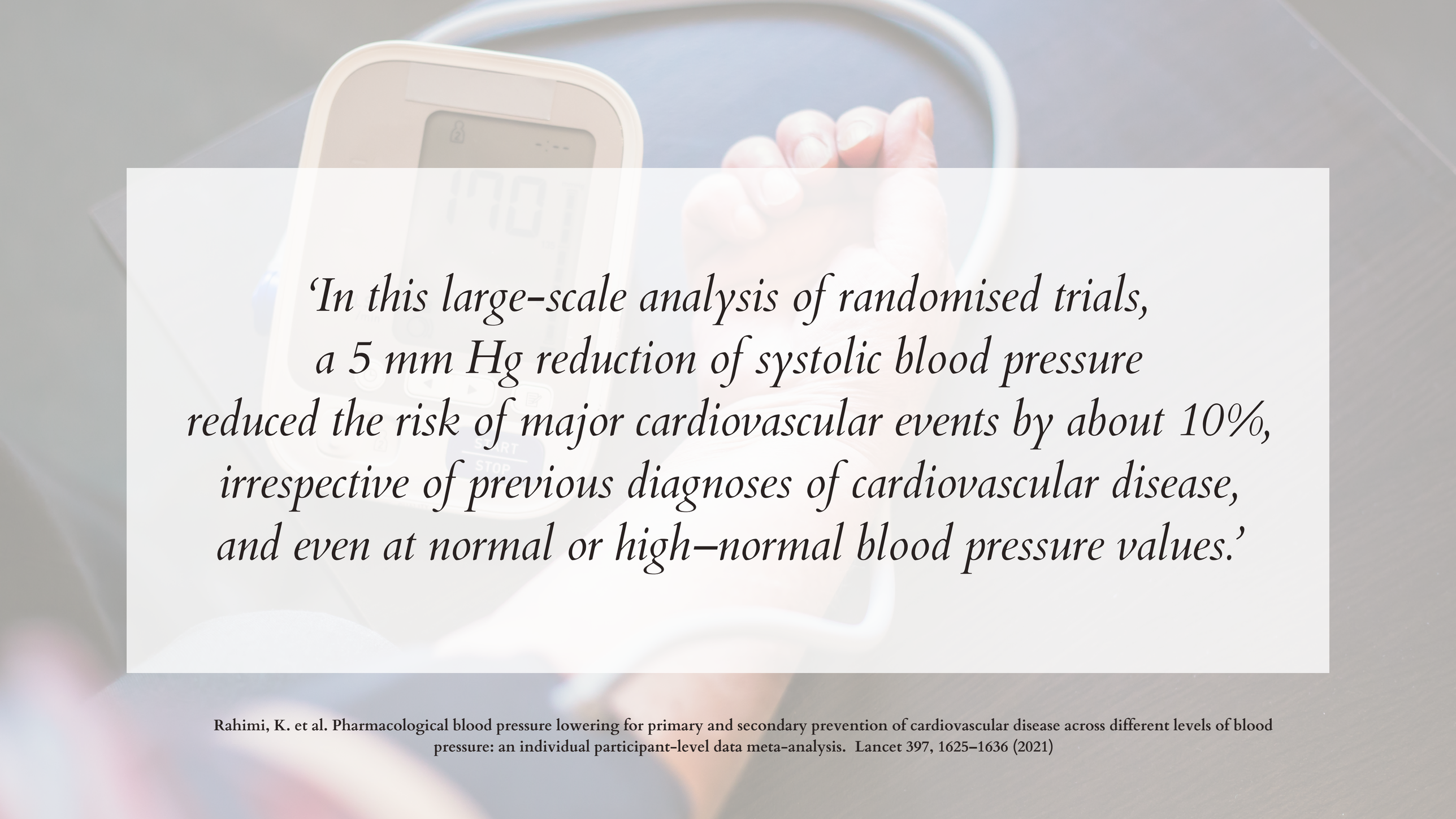
Weinberg, R.L. et al. J Am Coll Cardiol. 2021;77(5):593-608.

Benefit

Hypertension

Lots of studies reporting
BP lowering effect of
omega-3s
but exploration of a
dose-relationship has
been confusing
and results uncertain





'In this large-scale analysis of randomised trials, a 5 mm Hg reduction of systolic blood pressure reduced the risk of major cardiovascular events by about 10%, irrespective of previous diagnoses of cardiovascular disease, and even at normal or high–normal blood pressure values.'

Rahimi, K. et al. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. Lancet 397, 1625–1636 (2021)

Past data suggests modest anti-hypertensive impact of omega-3 supplementation

2022 Umbrella Meta-Analysis – confirms oemga-3 supplementation reduces both systolic and diastolic blood pressure

Overall Results:

- **Systolic** BP decrease = **-1.19 mmHg**; 95% CI: -1.76, -0.62; p < 0.001
- Diastolic BP decrease = -0.91 mmHg, 95% CI: -1.35, -0.47; p < 0.001

Generally high heterogeneity – good to examine subgroup analysis

- most important impact on systolic BP
  - greater dose
    - EPA > 2000 mg (vs under) = **-2.98 mmHg**; 95% CI (-4.25, -1.70); p <0.001
  - baseline BP
    - normotensive = -0.78 mmHg; 95% CI (-1.51, -0.06); p<0.035
    - hypertensive = **-2.71 mmHg**; 95% CI (-5.26, -0.17); p<0.03

Conclusion: consider as adjunctive support

Musazadeh, V., Kavyani, Z., Naghshbandi, B., Dehghan, P. & Vajdi, M. The beneficial effects of omega-3 polyunsaturated fatty acids on controlling blood pressure: An umbrella meta-analysis. Front. Nutr. 9, 985451 (2022)

Hypertension

2022 Meta-Analysis identifying non-linear dose-response curve (previous studies assumed linear relationships)

Big - 71 RCTs, 4973 people, age 22-86 yoa

- 90% used supplementation, 10% fish meals or fish-oil-fortified foods
- important exclusion: **treated with anti-hypertensives**

Results - mostly j-curves with some linear subgroups

General: non-linear dose-response relationship; j-shaped curve

- improvement from 0-5 g/d with **strongest change at 2-3 g/d combined EPA+DHA** (then weaker and null)
- average mean change SBP at 2 g/d = -2.61 mm/Hg and DBP at 3 g/d = -1.80 mmHg

Subgroups

- hypertensives (baseline SBP ≧ 130 mmHg) -- linear reduction up to 5 g/d (-3.88 mmHg), then plateaud
- hyperlipidemics (TC >5.2 mmol/L and TG >1.7 mmol/L) -- linear SBP reduction up to 5 g/d (-4.24 mmHg) then non-significant
- age > 45 yrs -- linear decrease up to 5g/d (-2.91 mmHg) then non-significant (note: no impact on SBP for <45 yrs)

Conclusion:

- most useful for older populations, hypertensives, and hyperlipidemics (metabolic syndrome?)
- generally aim for 2-3 grams combine EPA+DHA although higher may be better (up to 5 grams) for those "higher-risk" groups

Note: insufficient data to detect difference between EPA and DHA

Zhang, X., Ritonja, J. A., Zhou, N., Chen, B. E. & Li, X. Omega-3 Polyunsaturated Fatty Acids Intake and Blood Pressure: A Dose-Response Meta-Analysis of Randomized Controlled Trials. J Am Hear Assoc Cardiovasc Cerebrovasc Dis 11, e025071 (2022)

Inflammation

Benefit

Multiple theorized mechanism of action

- altered prostaglandin synthesis, decreased inflammatory cytokines, impact on resolvins, protectins, and maresins (Weinberg et al., 2021)
- 'Inflammation as a Cardiovascular Risk Factor' - 2004 AHA article (Willerson and Ridker) reviewing the multiple ways inflammation increases CVD risk and the predictive value of inflammatory markers

Anti-inflammatory drugs reduce risk

- canakinumab (CANTOS trial, Ridker et al., 2017) in secondary prevention population
  - decreased pro-inflammatory CRP and IL-1β
  - reduced CVD risk (multiple endpoints), despite unchanged lipids and blood pressure
- colchicine (LoDoCo2, Nidorf et al., 2020) in secondary prevention population
  - reduced CVD risk (multiple endpoints)

Inflammatory conditions, especially Immune-Mediated Inflammatory Diseases (IMIDs) increase cardiovascular risk (Agca et al., 2022)

Omega-3s reduce multiple eicosanoids in various populations (Jiang et al., 2016)

- 18 RCTs, 826 subjects
- Results - omega-3 reduced inflammatory eicosanoids:
  - prostaglandin E2 in “healthy” subjects
  - thromboxane B2 in high CVD-risk patients
  - leukotriene B4 in patients with rheumatoid arthritis

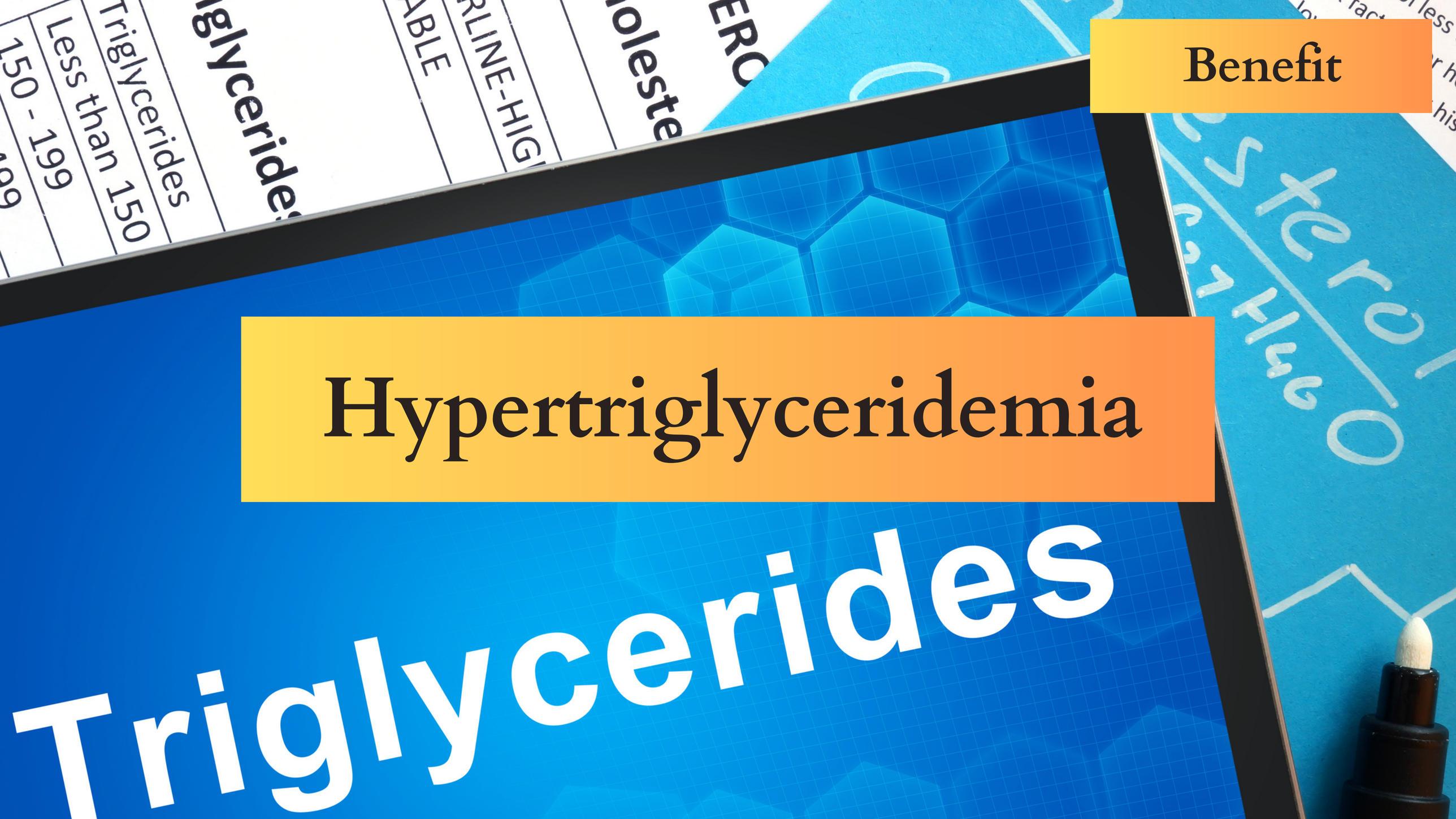
Omega-3s reduced CRP, TNFα, and IL-6 in adults with various health conditions (Kavyani et al., 2022)

No effect on endothelial inflammatory markers von Willebrand factor and soluble vascular cell adhesion molecule 1 (Gao et al., 2022)

- however a *non-dose related reduction of plaque volume* + a reduction in the loss of diameter of the narrowest segments of coronary arteries in CHD (but 1 study provided all that significance)

Benefit

Hypertriglyceridemia



Hypertriglyceridemia

Definition:

- optimal = <0.6 mmol/L?
  - likely lower than we once thought (Aberra et al., 2020)
- normal <1.7 mmol/L
- moderate hypertriglyceridemia - 1.7 to 5.6 mmol/L
- moderate to severe hypertriglyceridemia - 5.65 to 11.3 mmol/L
- severe hypertriglyceridemia - ⩾11.3 mmol/L

Causes:

- secondary causes most common (see next slides)
- genetic (from rare to common)
  - most like to see familial combined hyperlipidemia
    - ⬆LDL and VLDL particles so ⬆ total cholesterol and **triglycerides**

High Triglycerides are a Problem?

1. Increased risk of pancreatitis (if high enough) - YES
2. Increased cardiovascular disease risk (residual risk) - Yes. No?
3. Flag for other risk-enhancing issues - YES

<u>Important note</u>: elevated triglycerides will lead to underestimated calculated LDL-cholesterol levels on lipid panel

Secondary Causes

High TG

Major Secondary Causes	
Diseases	• poorly controlled diabetes mellitus • chronic kidney disease, nephrotic syndrome • familial partial lipodystrophy • uncontrolled hypothyroidism • Cushing syndrome • immune-mediated inflammatory disorders: RA, SLE, psoriasis • glycogen storage disease • acute hepatitis • multiple myeloma • sepsis
Dietary	• history of alcohol abuse/excess • diets high in saturated fat, sugar, or high-glycemic-index foods • sedentary lifestyle • total parenteral nutrition with lipid emulsions

Virani SS, Morris PB, Agarwala A, Ballantyne CM, Birtcher KK, Kris-Etherton PM, Ladden-Stirling AB, Miller M, Orringer CE, Stone NJ. 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;78(9):960-993

Secondary Causes

High TG

Major Secondary Causes	
Drugs	• anesthesia: propofol • cardiology: beta-blockers, thiazide and loop diuretics, bile-acid sequestrants • endocrine: glucocorticosteroids, anabolic steroids, oral estrogens (raloxifene, clomiphene citrate, estradiol, ethinyl estradiol, conjugated estrogens, tamoxifen) • dermatology: isotretinoin • infectious disease: HIV protease inhibitors • oncology: tamoxifen, l-asparaginase, bexarotene, cyclophosphamide • psychiatry: atypical antipsychotic agents (e.g. olanzapine, mirtazapine, clozapine) • immunosuppressive agents: tacrolimus, sirolimus, cyclosporine, interferons
Metabolic Disorders	• higher BMI • insulin resistance/metabolic syndrome • weight gain after weight loss • pregnancy (especially 3rd trimester)

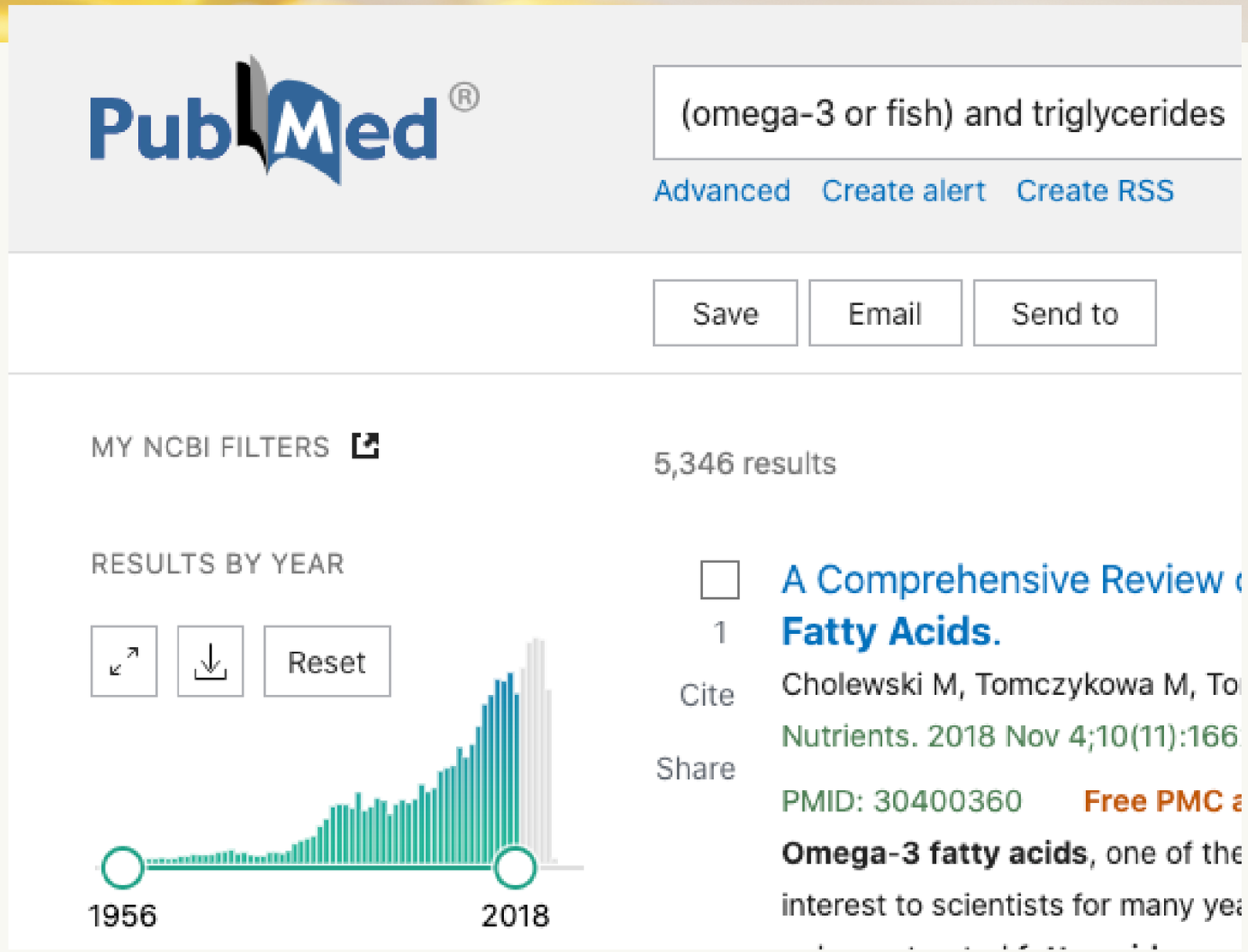
Virani SS, Morris PB, Agarwala A, Ballantyne CM, Birtcher KK, Kris-Etherton PM, Ladden-Stirling AB, Miller M, Orringer CE, Stone NJ. 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with persistent hypertriglyceridemia: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;78(9):960-993

ADDRESS SECONDARY CAUSES FIRST

Hypertriglyceridemia

Why Omega-3?

Observation of this relationship is not new



Hypertriglyceridemia

2018-2020 were big years for omega-3 research

ASCEND – *A Study of Cardiovascular Events in Diabetes* (ASCEND Study Collaborative Group, 2018) ***no overall benefit**

- dose: 1 g/d fish oil (460 mg EPA/380 mg DHA) vs olive oil (+/- aspirin X 100 mg)

VITAL – Vitamin D and Omega-3 primary prevention trial (Manson et al., 2019) ***no overall benefit**

- dose: 1 g/d fish oil (460 mg EPA/380 mg DHA)
- **BUT always check the details:** total MI risk reduced: HR 0.72; 95% CI, 0.59-0.90
  - reduced overall risk in those eating <1.5 median servings fish/week (only subgroup that saw a difference)
  - no increased bleeding (remember for later!)

Triglyceride-specific

REDUCE-IT (2019) – **shockingly good results** (Bhatt et al., 2019)

- high-risk or secondary prevention populations – statin background + high triglycerides (1.5-5.6 mmol/L)
- dose: 4 g/d icosapent ethyl (IPE) vs placebo *(mineral oil)*
- hazard ratio for MACE = 0.75; 95% CI, 0.68-0.83; P<0.001
- this overwhelmingly positive result led to inclusion of IPE in several guidelines, scientific and consensus statements including ACC, AHA, AACE, ADA, NLA, CCS, ESC/EAS

Hypertriglyceridemia

Story continues with **STRENGTH** trial ***stopped slightly early due to futility**

- Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk (Nicholls et al., 2020)
- high-risk or secondary prevention populations – statin background + high triglycerides (2.0–5.6 mmol/L)
- dose: 4 g/d EPA+DHA carboxylic acid vs placebo (corn oil)

Why were the results so different?

Drug type?

Icopent ethyl (EPA only) vs carboxylic acid (EPA+DHA)

Comparator/Placebo?

Mineral oil vs corn oil

Hypertriglyceridemia

Part of the answer come out last year (June 2022)

A REDUCE-IT secondary study investigating biomarkers

- measured a wide variety of inflammatory biomarkers at baseline, at 12 months, at 24 months, and at the end-of-study visit
- results: mineral oil placebo led to a worsening of all inflammatory biomarkers (vs. no change with IPE) 😬

However, the current best estimates are that this does not explain the bulk of the improvement, so IPE is still recommended.

Ridker, P. M. et al. Effects of Randomized Treatment With Icosapent Ethyl and a Mineral Oil Comparator on Interleukin-1β, Interleukin-6, C-Reactive Protein, Oxidized Low-Density Lipoprotein Cholesterol, Homocysteine, Lipoprotein(a), and Lipoprotein-Associated Phospholipase A2: A REDUCE-IT Biomarker Substudy. Circulation 146, 372–379 (2022)

Drug Therapy for High Triglycerides

<u>Currently only reasonable option</u>

Icosapent ethyl (IPE)
95+% purified EPA ethyl ester (synthetic derivative)

Others mentioned in trials included:
EPA +DHA ethyl esters
EPA+DHA carboxylic acid
EPA+DHA+DPA – better at absorption than IPE,
no outcome trials (Maki et al., 2021)

How does it work? Who really knows.

1. Icosapent ethyl is de-esterified and converted into active EPA which is absorbed in the small intestine.
2. Peak plasma concentration is reached 5 hours post-oral administration.
3. Virtually all the EPA incorporates into phospholipids, TGs, and cholesteryl esters.

Studies suggest that EPA may particularly impact VLDLs.

1. May reduces hepatic VLDL-triglyceride synthesis and/or secretion
2. Enhance triglyceride clearance from circulating VLDL particles
3. Potential mechanisms of action for the above include increased β-oxidation, inhibition of DGAT enzyme need for synthesis, decreased lipogenesis in the liver, and/or increased plasma lipoprotein lipase activity (which breaks down lipoprotein and mediates TG storage in adipose)

Drug Bank Online - https://go.drugbank.com/drugs/DB08887
Bornfeldt, K. E. Triglyceride lowering by omega-3 fatty acids: a mechanism mediated by N-acyl taurines. J. Clin. Investig. 131, e147558 (2021)

So when is IPE technically indicated?

1. Secondary prevention, adjunct to maximally tolerated statin in those with elevated triglycerides (≧ 1.7 mmol/L)
    a. secondary prevention = established CVD or diabetes mellitus and 2 or more additional risk factors
2. Severe hypertriglyceridemia (≧ 5.6 mmol/L), adjunct to diet

How is it currently covered in Ontario?

In-label coverage by the Ontario Drug Benefit (since July 2022) and most (95%) of private insurance

- in-label = secondary prevention of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization or hospitalization for unstable angina) in statin-treated patients with established cardiovascular disease and elevated triglycerides

Dose:

- 4 grams daily (2g bid **with food**)

Common adverse reactions:

- musculoskeletal pain (4% vs 3%)
- peripheral edema (7% vs 5%)
- constipation (5% vs 4%)
- gout (4% vs 3%)
- atrial fibrillation (5% vs 4%)

Drug Interactions:

- caution with anti-thrombotic agents (see bleeding section)

Inactive ingredients:

- tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water

Inter-professional - referral letter example

Dear Dr. [DOCTOR NAME]

Re: [PATIENT NAME – DOB]

I have been working with a mutual patient, [PATIENT NAME] since [DATE].

We have been focusing on assessing and supporting [NAME]'s cardiovascular health. In reviewing recent blood work, I noticed that [NAME]'s triglyceride levels continue to be elevated, despite a fasting sample.

There may be a few reasons for this, but [NAME] is not diabetic and has no obvious secondary causes for this elevation. We are working on diet and lifestyle strategies, but this elevated level does increase overall CVD risk.

We discussed exploring the use of icosapent ethyl *Although I could recommend an over-the-counter alternative (purified EPA ethyl ester), the data supports the icosapent form most strongly and is likely to be more financially viable long term.*

Current data also suggests high dose of omega-3 fatty acids, including icosapent ethyl, may increase the risk of atrial fibrillation and has been discussed with [NAME].

In summary, my hope is that you'll consider the following:

- Consider/explore use of for elevated triglycerides

If you have any questions regarding these suggestions, please don't hesitate to contact me office.

Yours sincerely,

Benefit

Coronary Plaques

IPE (4 g/d) reduces plaque volume in people with known coronary artery disease (Budoff et al., 2020)

- known as the EVAPORATE trial, could this partly explain the magnitude of effect in REDUCE-IT?

Imaging meta-analysis found that adding EPA to statin background lead to plaque regression while EPA+DHA does not (Sheppard et al., 2022)

- no dosage ranges provided

High-dose EPA+DHA leads to plaque regression, but only in normotensives (HEARTS trial - Welty et al., 2023)

- dose: 3.36 g/d omega-3 (1.86 g EPA/1.5 g DHA)

Bleeding - Good/Neutral/Bad?

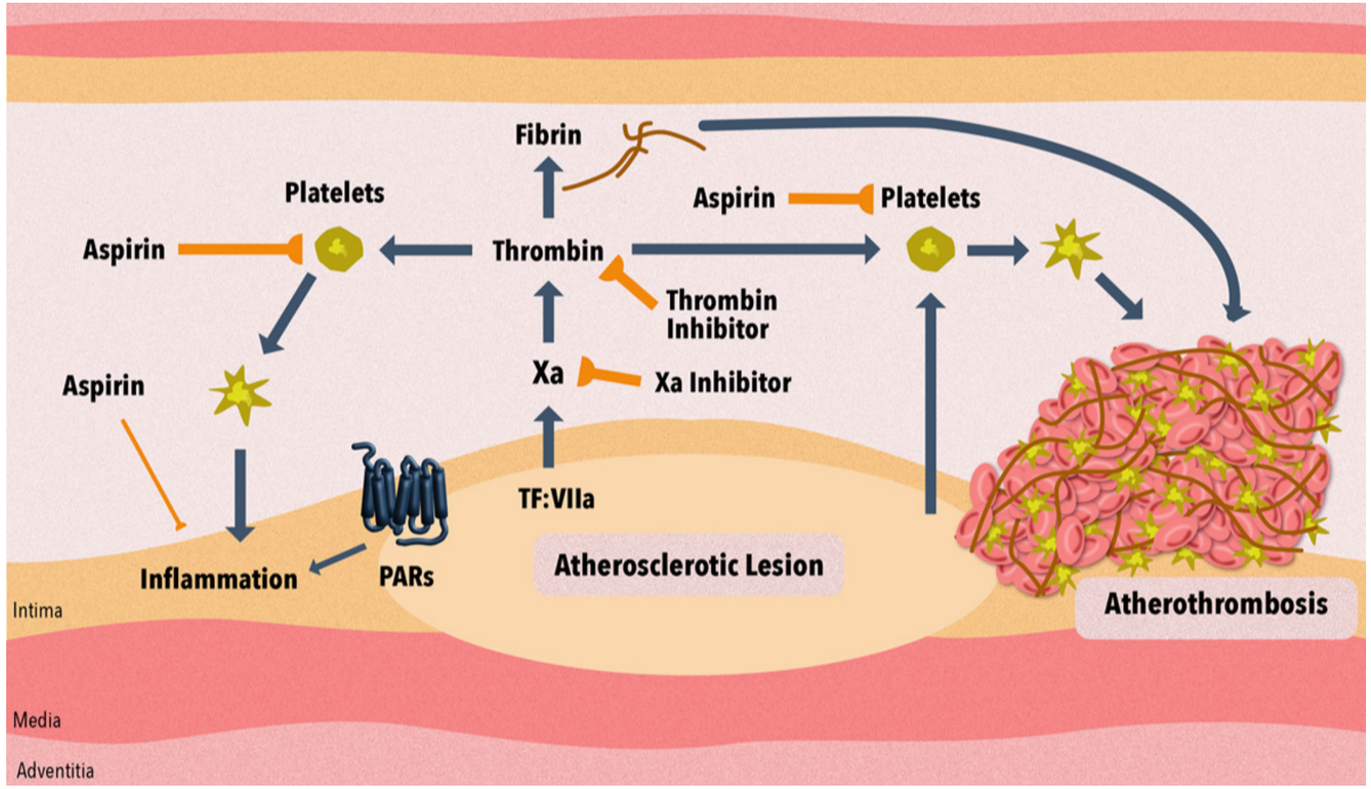
First observed in Greenland Inuit in earliest omega-3 studies (Dyerberg and Bang, 1979)

-24 people (from a population of only 50) vs Danish controls

-had significantly longer bleeding time (approx. 8 vs 5 minutes) and lower platelet aggregation

-believed due to omega-3 PUFA impact on prostaglandins

Thrombosis



Mackman, N., Spronk, H. M. H., Stouffer, G. A. & Cate, H. ten. Dual Anticoagulant and Antiplatelet Therapy for Coronary Artery Disease and Peripheral Artery Disease Patients. Arter., Thromb., Vasc. Biol. 38, 726–732 (2018).

Thrombosis = blend of platelet aggregation and coagulation working together

Both play a central role in an acute arterial thrombotic events such as myocardial infarction and ischemic stroke.

Vascular injury leads to platelet adherence and activation, then aggregation - while coagulation also occurs. Separate but together!

Platelet adhesion + aggregation lead to development of thrombi which can occlude at site of ruptured plaque.

Where do the (omega-3) fatty acids come in?

PUFAs hydrolyzed from local cell membranes and release free fatty acids which are metabolized by oxygenases into active substances which regulatory roles in hemostastis/thrombosis.

Early on, part of the risk-reducing potential of omega-3s was thought to be due to anti-thrombosis

In a small older study, omega-3 use was deemed to have a "**hypocoagulant**" effect (Vanschoonbeek et al., 2004)

- details hard to find (including most of the methods)
- dose = 3 g/d fish oil X 4 weeks
- population = 25 men considered to be at slightly increased thrombotic risk ("borderline overweight")
- before and after comparison: fish oil decreased thrombin generation as well as fibrinogen and factor V (vitamin K independent)
    - this hypocoagulant effect was clustered in a subgroup with relatively high baseline levels of fibrinogen (genetically-induced)

Omega-3 intake reduced **platelet aggregation** specifically in those with "poor health" (Gao et al, 2013)

- studies of those in "poor health" = various chronic disease such as end stage kidney disease, diabetes, coronary artery disease
    - there was NO reduced aggregation in those who were healthy!
- conclusion:
    - omega-3s may help normalize increased thrombotic potential
    - may be more helpful in secondary prevention

Bleeding

Over the years, mechanistic studies showed diminished platelet aggregation
so **precautionary pre-surgical discontinuation became standard of practice**

But other investigations suggested this wasn't a problem.

2013 systematic review of fish oil use in older adults
concluded no additional risk of bleeding (Villani et al., 2013)

2014 review of RCTs, epidemiological studies, indirect evidence from multiple fields,
PLUS biochemical/mechanistic evidence of fish oil intake and bleeding concluded
although there may be (modest) changes to platelet biochemistry,
bleeding risk is not of concern (Wachira et al., 2014)

Bleeding

KEY POINTS

Clinicians have expressed concern about a potentially increased bleeding risk during surgery in patients who take fish oil supplements.

Fish oil supplements reduced primary haemostasis measured biochemically in healthy subjects.

Fish oil supplementation before or immediately after surgery did not increase intra- or postoperative bleeding in randomised controlled trials.

Based on this systematic review, discontinuation of fish oil supplements prior to surgery is not recommended.

2017

Begtrup, K. M., Krag, A. E. & Hvas, A.-M. No impact of fish oil supplements on bleeding risk: a systematic review. Dan. Méd. J. 64, (2017)

But *still* wanted more robust overview of bleeding specifically so ...
OPERA (secondary analysis)

Bleeding

OPERA secondary analysis - 2018 (original study 2012)

- multinational population of patients undergoing cardiac surgery, 1516 patients total, 72% were men
- randomized to 1g capsules containing prescription fish oil (465 mg EPA + 375 mg DHA) or matched olive oil placebo
- pre-surgical dosing 8-10 g/day for 2-5 days (including 2 grams morning of surgery)
- post-surgical dosing: 2g/day until discharge or day 10, whichever came first
- main end point = major bleed (with other bleeds as secondary outcomes)
- result: no difference bleeding episodes
    - but **fewer** episodes of transfusions (fewer units transfused) - this is actually the 2nd study to report this (Farquharson et al, 2011)

Working theory is that omega-3 fish oil is "platelet-sparing"

Acute inflammation and biochemical changes associated with components of cardiac surgery have been shown to lead to platelet activation and paradoxically increase loss of platelet function and increase bleeding risk (meds are often given to buffer this)

Akintoye, E. et al. Fish Oil and Perioperative Bleeding. Circ.: Cardiovasc. Qual. Outcomes 11, e004584 (2018)

Bleeding

OPERA is commonly considered to be the last word on this topic (as much as anything can be).

Strengths

largest study on this topic
standardized bleeding end points
RCT
broad inclusion criteria
multinational population
similar results across multiple subgroups
similar conclusions to prior small trials

Weaknesses

secondary analysis
placebo = olive oil*
long term exposure may differ from short term exposure
disclosures include avocado board and Omegaquant/Boston Heart**

What do we see in the major trials/cohorts though?

JELIS (Yokoyama et al., 2007) - primary and secondary prevention

- exclusively Japanese population (consider background intake)
- hypercholesterolemia outcome study: EPA ethyl ester (1800 mg/d) vs placebo (background statin)
- results:
  - **all bleeding higher** in EPA group (1.1% vs 0.6%, p<0.0006)

REDUCE-IT (Bhatt et al., 2019) - high-risk/secondary prevention

- hypertriglyceridemia outcome study
- high dose icosapent ethyl (IPE) (4 g/d) vs placebo (background statin)
- results:
  - **non-significant increase in severe bleeding** in those taking IPE - (2.7% vs 2.1% p=0.06)

Major trials/cohorts (continued)

STRENGTH (Nicholls et al., 2020) - high-risk/secondary prevention

- dyslipidemia outcome study
- high dose EPA+DHA carboxylic acid (4g/d) vs placebo (background statin)
- trial halted early due to low probability of benefit (mean 38 months)
- results: **no difference any bleeding event** (4.9% both groups)

Multi-Ethnic Study of Atherosclerosis (MESA) cohort (Kapoor et al., 2021) - primary prevention only

- looked plasma omega-3 status vs. omega-3 supplement/drug use RCT
- results: significantly **reduced hazard of major bleeding** was observed with higher plasma EPA and EPA+DHA, but not DHA
    - no association with addition of aspirin or self-reported omega-3 supplementation (4.1% of total pop)
- theorize that threshold may exist - above threshold with higher dose omega-3 drugs may risk bleeding; unclear motivation for statement

Bleeding

There is *sort-of* an exception (isn't there always?)

Icosapent Ethyl - purified EPA drug used for hypertriglyceridemia

Remember REDUCE-IT? (Bhatt et al., 2019)
Concluded there was a non-significant increase in severe bleeding in those taking IPE - *"Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group (P=0.06)"*

The package insert refers to overall bleeding rates and suggests that they are higher in those taking other blood thinners - *"... associated with an increased risk (12% vs 10%) of bleeding in a double-blind, placebo-controlled trial. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel or warfarin"*.

It also add a drug interaction warning claiming increased bleeding risk with antiplatelet and anticoagulant agents due to omega-3 studies showing prolonged bleeding time despite it not being an issue: *"Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Monitor patients receiving* IPE *and concomitant anticoagulants and/or antiplatelet agents for bleeding."*

Early observational enthusiasm.
Many potential mechanisms of action.
Decades-long investigation with variable conclusions.

Overall Benefit (AKA What Really Matters)

Individual cardiovascular outcomes
Collective MACE (Major Adverse Cardiac Events)

NOT CONSISTENT in the literature
– it's rarely apples to apples.

Main outcomes of interest = fatal CHD, non-fatal MI, stroke, major vascular event, and all-cause mortality (ACM)

Secondary outcomes = major vascular events in prespecified subgroups

9 trials EPA+DHA ethyl esters
1 trial EPA-only (1800 mg)

Mean study length = 4.4 years

Population = mostly high-risk

Did NOT include REDUCE-IT

Meta-Analysis > JAMA Cardiol. 2018 Mar 1;3(3):225-234. doi: 10.1001/jamacardio.2017.5205.

Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77 917 Individuals

Theingi Aung [1 2 3], Jim Halsey [1 2], Daan Kromhout [4], Hertzel C Gerstein [5 6], Roberto Marchioli [7 8], Luigi Tavazzi [9], Johanna M Geleijnse [10], Bernhard Rauch [11], Andrew Ness [12], Pilar Galan [13], Emily Y Chew [14], Jackie Bosch [6 15], Rory Collins [1 2], Sarah Lewington [1 2], Jane Armitage [1 2], Robert Clarke [1 2]; Omega-3 Treatment Trialists' Collaboration

Affiliations + expand

PMID: 29387889 PMCID: PMC5885893 DOI: 10.1001/jamacardio.2017.5205

Free PMC article

Conclusion:

No risk reduction with omega-3 supplementation in any category

Aung, T. et al. Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks: Meta-analysis of 10 Trials Involving 77 917 Individuals. JAMA Cardiol. 3, 14–22 (2018)

Meta-Analysis > Ann Intern Med. 2019 Aug 6;171(3):190-198. doi: 10.7326/M19-0341. Epub 2019 Jul 9.

Effects of Nutritional Supplements and Dietary Interventions on Cardiovascular Outcomes: An Umbrella Review and Evidence Map

Safi U Khan [1], Muhammad U Khan [1], Haris Riaz [2], Shahul Valavoor [1], Di Zhao [3], Lauren Vaughan [4], Victor Okunrintemi [4], Irbaz Bin Riaz [5], Muhammad Shahzeb Khan [6], Edo Kaluski [7], M Hassan Murad [5], Michael J Blaha [8], Eliseo Guallar [9], Erin D Michos [10]

Affiliations + expand

PMID: 31284304 PMCID: PMC7261374 DOI: 10.7326/M19-0341

Free PMC article

Erratum in

Correction: Effects of Nutritional Supplements and Dietary Interventions on Cardiovascular Outcomes.

[No authors listed]

Ann Intern Med. 2020 Jan 7;172(1):75-76. doi: 10.7326/L19-0721. Epub 2019 Dec 17.

PMID: 31842231 No abstract available.

Main outcome of interest = all-cause mortality

The secondary outcomes = cardiovascular mortality, myocardial infarction (MI), stroke, and coronary heart disease (CHD

Conclusion:

Long chain omega-3 very modestly reduced risk for

MI - RR 0.92 [CI, 0.85 to 0.99]

CHD - RR 0.93 [CI, 0.89 to 0.98]

Did NOT include REDUCE-IT

Khan, S. U. et al. Effects of Nutritional Supplements and Dietary Interventions on Cardiovascular Outcomes: An Umbrella Review and Evidence Map. Ann. Intern. Med. 171, 190 (2019)

Main outcomes of interest basically everything cardiovascular.

No all-cause mortality.

This M/A added recent big RCTs and significantly increased sample size.

11 trials EPA+DHA
2 trials EPA-only

Mean study length = 5 years

Population = many high-risk + 73% on cholesterol-lowering drugs, 40% diabetic

Meta-Analysis > J Am Heart Assoc. 2019 Oct;8(19):e013543. doi: 10.1161/JAHA.119.013543. Epub 2019 Sep 30.

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

Yang Hu [1], Frank B Hu [1 2 3], JoAnn E Manson [2 3 4]

Affiliations + expand

PMID: 31567003 PMCID: PMC6806028 DOI: 10.1161/JAHA.119.013543

Free PMC article

With and without REDUCE-IT!!

Hu, Y., Hu, F. B. & Manson, J. E. Marine Omega-3 Supplementation and Cardiovascular Disease: An Updated Meta-Analysis of 13 Randomized Controlled Trials Involving 127 477 Participants. J. Am. Hear. Assoc.: Cardiovasc. Cerebrovasc. Dis. 8, e013543 (2019)

Conclusion

1. Marine omega-3 supplementation was associated with significantly lower risk [RR] [95% CI] for most outcomes
2. Dose-dependent relationship exists for total CVD and major vascular events.

Meta-Analysis > J Am Heart Assoc. 2019 Oct;8(19):e013543. doi: 10.1161/JAHA.119.013543. Epub 2019 Sep 30.

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

Yang Hu [1], Frank B Hu [1 2 3], JoAnn E Manson [2 3 4]

Affiliations + expand

PMID: 31567003 PMCID: PMC6806028 DOI: 10.1161/JAHA.119.013543

Free PMC article

Myocardial infarction
- without REDUCE-IT = 0.92 (0.86, 0.99); p=0.020
- with REDUCE-IT = 0.70 (0.60, 0.82); p<0.001
- overall = 0.88 (0.83, 0.94); p<0.001

CHD Death
- without REDUCE-IT = 0.92 (0.86-0.98); p=0.014

Total CHD
- without REDUCE-IT = 0.95 (0.91, 0.99); p=0.008
- with REDUCE-IT = 0.77 (0.68, 0.88); p<0.001
- overall = 0.93 (0.89-0.96); p<0.001

CVD Death
- without REDUCE-IT = 0.93 (0.88, 0.99); p=0.013
- with REDUCE-IT = 0.82 (0.67, 0.99); p<0.043
- overall = 0.92 (0.88, 0.97); p=0.003

Total CVD
- without REDUCE-IT = 0.97 (0.94, 0.99); p=0.015
- with REDUCE-IT = 0.76 (0.68, 0.85); p<0.001
- overall = 0.95 (0.92, 0.98); p<0.001

Total stroke: without REDUCE-IT not significant (NS), REDUCE-IT significant (SS), overall NS

Major Vascular events: without REDUCE-IT NS, REDUCE-IT SS, overall SS = 0.95 (0.93, 0.98); p<0.001

Effect of omega-3 fatty acids on cardiovascular outcomes: A systematic review and meta-analysis

Safi U Khan [1], Ahmad N Lone [1], Muhammad Shahzeb Khan [2], Salim S Virani [3], Roger S Blumenthal [4 5], Khurram Nasir [6 7], Michael Miller [8], Erin D Michos [4 5], Christie M Ballantyne [3], William E Boden [9], Deepak L Bhatt [10]

Affiliations + expand

PMID: 34505026 PMCID: PMC8413259 DOI: 10.1016/j.eclinm.2021.100997

Free PMC article

Included
REDUCE-IT
(in fact, carried most of the EPA-only weight)

Conclusion:

Both primary and secondary prevention

EPA > EPA+DHA

EPA increased risk of AFib and bleeding > EPA+DHA

Khan, S. U. et al. Effect of omega-3 fatty acids on cardiovascular outcomes: A systematic review and meta-analysis. EClinicalMedicine 38, 100997 (2021).

Comparative efficacy of omega-3 polyunsaturated fatty acids on major cardiovascular events: A network meta-analysis of randomized controlled trials

Bo Yang [1], Ping-Tao Tseng [2], Xiang Hu [3], Bing-Yan Zeng [4], Jane Pei-Chen Chang [5], Yang Liu [6], Wei-Jie Chu [6], Shuang-Shuang Zhang [6], Zhi-Liang Zhou [7], Chih-Sheng Chu [8], Cheng-Ho Chang [9], Yu-Kang Tu [10], Yi-Cheng Wu [11], Brendon Stubbs [12], Andre F Carvalho [13], Pao-Yen Lin [14], Yutaka J Matsuoka [15], Mein-Woei Suen [16], Kuan-Pin Su [17]

Affiliations + expand

PMID: 36341839 DOI: 10.1016/j.plipres.2022.101196

With REDUCE-IT

Conclusion:

Primary Prevention – no evidence

Secondary prevention – EPA only

Yang, B. et al. Comparative efficacy of omega-3 polyunsaturated fatty acids on major cardiovascular events: A network meta-analysis of randomized controlled trials. Prog. Lipid Res. 88, 101196 (2022)

Omega-3 Fatty Acid Supplementation and Coronary Heart Disease Risks: A Meta-Analysis of Randomized Controlled Clinical Trials

ShiChun Shen [1], Chen Gong [2], KaiQin Jin [3], Lei Zhou [4], Yin Xiao [5], Likun Ma [1]

Affiliations + expand

PMID: 35187035 PMCID: PMC8850984 DOI: 10.3389/fnut.2022.809311

Free PMC article

With REDUCE-IT

Conclusion:

Secondary prevention – Reduced MACE, cardiovascular death, and MI

Most effective dose = 0.8 – 1.2 g/d (vs more or less)

Shen, S. et al. Omega-3 Fatty Acid Supplementation and Coronary Heart Disease Risks: A Meta-Analysis of Randomized Controlled Clinical Trials. Front. Nutr. 9, 809311 (2022)

Effects of omega-3 fatty acid on major cardiovascular outcomes: A systematic review and meta-analysis

Fangyu Yu [1], Shun Qi, Yanan Ji, Xizhi Wang, Shaohong Fang, Ruokui Cao

Affiliations + expand

PMID: 35905212 PMCID: PMC9333496 DOI: 10.1097/MD.0000000000029556

Free PMC article

With REDUCE-IT

Conclusion:

Reduced risk of cardiac death (and maybe MACE)

Yu, F. et al. Effects of omega-3 fatty acid on major cardiovascular outcomes: A systematic review and meta-analysis. Medicine 101, e29556 (2022)

Marine omega-3 fatty acid supplementation and prevention of cardiovascular disease: update on the randomized trial evidence

Shari S. Bassuk [1] and JoAnn E. Manson [1,2]*, for the VITAL Research Group†

[1]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 900 Commonwealth Avenue, 3rd Floor, Boston, Massachusetts 02215, USA; and [2]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts 02115, USA

Received 12 July 2022; revised 13 October 2022; accepted 17 October 2022; online publish-ahead-of-print 15 November 2022

To date, the *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL) is the only large-scale randomized trial of marine omega-3 fatty acid (*n*−3 FA) supplementation for cardiovascular disease (CVD) prevention in a general population unselected for elevated cardiovascular risk. We review the findings of VITAL, as well as results from recent secondary prevention trials and updated meta-analyses of *n*−3 FA trials in the primary and secondary prevention of CVD. In VITAL, a

Conclusion:

Benefit is there, but probably related to certain populations (e.g in individuals with low dietary fish intake or with cardiovascular risk factors, and in African Americans.

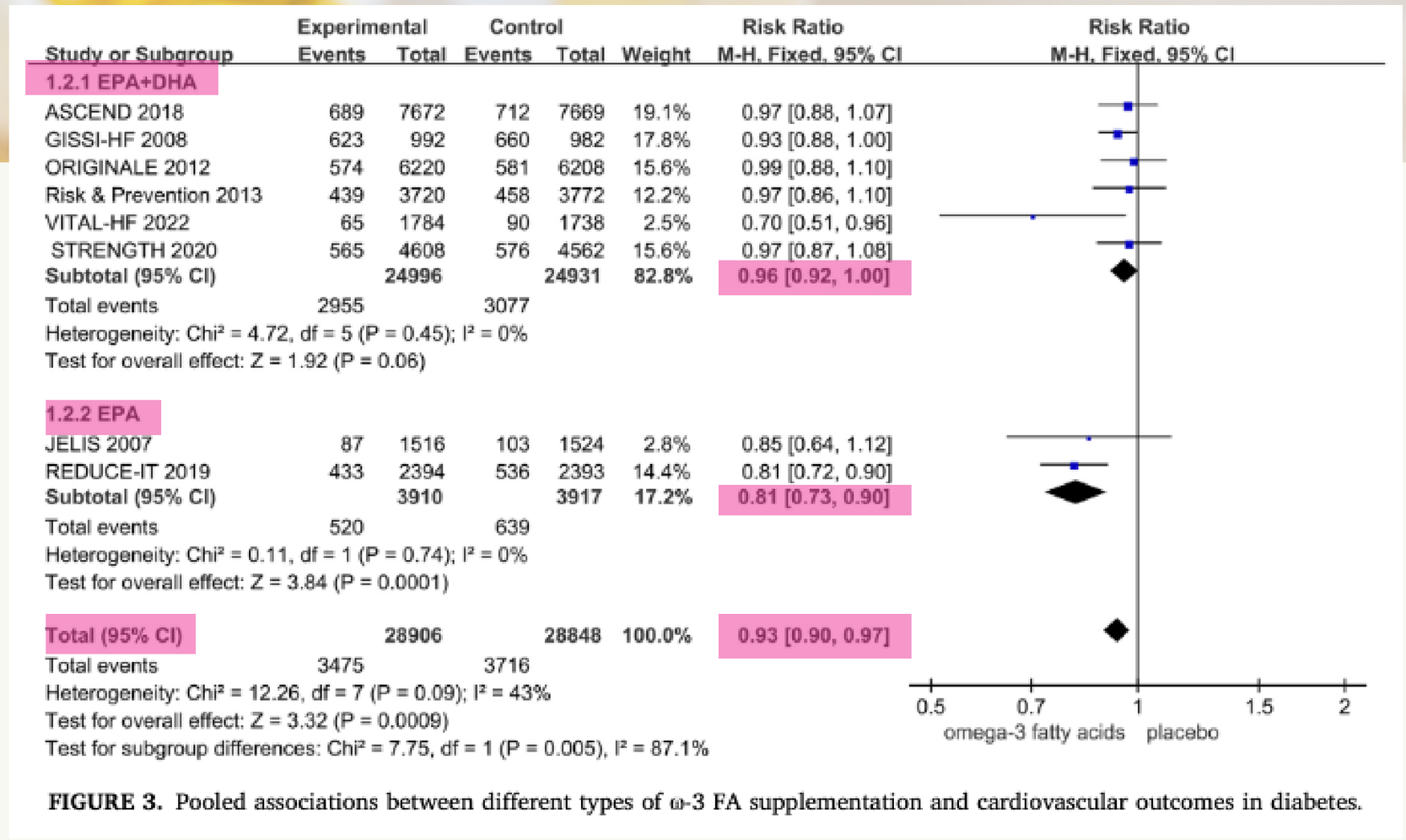
"Additional research is needed to determine which individuals may be most likely to derive a net benefit from such supplementation."

Bassuk, S. S., Manson, J. E. & Group, V. R. Marine omega-3 fatty acid supplementation and prevention of cardiovascular disease: update on the randomized trial evidence. Cardiovasc. Res. 119, 1297–1309 (2022).

Diabetes

Omega-3 supplementation reduces CVD risk in patients with diabetes

RR 0.93
95% CI (0.90,0.97)
p=0.0009



Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 EPA+DHA						
ASCEND 2018	689	7672	712	7669	19.1%	0.97 [0.88, 1.07]
GISSI-HF 2008	623	992	660	982	17.8%	0.93 [0.88, 1.00]
ORIGINALE 2012	574	6220	581	6208	15.6%	0.99 [0.88, 1.10]
Risk & Prevention 2013	439	3720	458	3772	12.2%	0.97 [0.86, 1.10]
VITAL-HF 2022	65	1784	90	1738	2.5%	0.70 [0.51, 0.96]
STRENGTH 2020	565	4608	576	4562	15.6%	0.97 [0.87, 1.08]
Subtotal (95% CI)		**24996**		**24931**	**82.8%**	**0.96 [0.92, 1.00]**
Total events	2955		3077			
Heterogeneity: Chi² = 4.72, df = 5 (P = 0.45); I² = 0%						
Test for overall effect: Z = 1.92 (P = 0.06)						
1.2.2 EPA						
JELIS 2007	87	1516	103	1524	2.8%	0.85 [0.64, 1.12]
REDUCE-IT 2019	433	2394	536	2393	14.4%	0.81 [0.72, 0.90]
Subtotal (95% CI)		**3910**		**3917**	**17.2%**	**0.81 [0.73, 0.90]**
Total events	520		639			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 3.84 (P = 0.0001)						
Total (95% CI)		**28906**		**28848**	**100.0%**	**0.93 [0.90, 0.97]**
Total events	3475		3716			
Heterogeneity: Chi² = 12.26, df = 7 (P = 0.09); I² = 43%						
Test for overall effect: Z = 3.32 (P = 0.0009)						
Test for subgroup differences: Chi² = 7.75, df = 1 (P = 0.005), I² = 87.1%						

FIGURE 3. Pooled associations between different types of ω-3 FA supplementation and cardiovascular outcomes in diabetes.

Sounds great BUT ...

Huang, L. et al. Effect of Omega-3 Polyunsaturated Fatty Acids on Cardiovascular Outcomes in Patients with Diabetes: A Meta-analysis of Randomized Controlled Trials. Adv. Nutr. 14, 629–636 (2023)

Oily Fish vs Non-Oily Fish

Reduced ACM and CVD mortality with 1 svg/week vs never

Oily fish especially mackeral, tuna, sardines, and salmon

Outcome	Never	Fish intake, hazard ratios (95% confidence interval)		
		< 1 serving/week	1 serving/week	≥ 2 serving/week
Oily fish intake				
All cause mortality				
Event, n (%)	3027 (6.33)	8086 (5.57)	9643 (5.93)	5143 (6.81)
Basic model*	1 (Reference)	0.82 (0.78–0.86)	0.79 (0.76–0.83)	0.85 (0.80–0.89)
Multivariable model#	1 (Reference)	0.92 (0.86–0.98)	0.93 (0.87–0.98)	0.98 (0.92–1.04)
Cancer mortality				
Event, n (%)	1383 (2.89)	4061 (2.80)	4986 (3.07)	2440 (3.23)
Basic model*	1 (Reference)	0.88 (0.82–0.94)	0.87 (0.81–0.93)	0.86 (0.80–0.93)
Multivariable model#	1 (Reference)	0.96 (0.89–1.05)	1.01 (0.92–1.10)	0.98 (0.89–1.08)
CVD mortality				
Event, n (%)	599 (1.25)	1588 (1.09)	1771 (1.09)	1076 (1.42)
Basic model*	1 (Reference)	0.81 (0.73–0.90)	0.74 (0.66–0.82)	0.90 (0.80–1.01)
Multivariable model#	1 (Reference)	0.93 (0.81–1.06)	0.85 (0.74–0.98)	1.02 (0.88–1.18)
Nonoily fish intake				
All cause mortality				
Event, n (%)	1279 (6.22)	7071 (5.59)	13,100 (6.12)	4449 (6.35)
Basic model*	1 (Reference)	0.91 (0.85–0.97)	0.93 (0.87–0.99)	0.98 (0.92–1.06)
Multivariable model#	1 (Reference)	0.93 (0.85–1.01)	0.96 (0.88–1.05)	1.02 (0.93–1.12)
Cancer mortality				
Event, n (%)	545 (2.65)	3576 (2.83)	6635 (3.10)	2114 (3.02)
Basic model*	1 (Reference)	1.05 (0.95–1.16)	1.07 (0.97–1.19)	1.07 (0.97–1.19)
Multivariable model#	1 (Reference)	0.99 (0.87–1.12)	1.01 (0.89–1.14)	1.03 (0.90–1.17)
CVD mortality				
Event, n (%)	242 (1.18)	1384 (1.09)	2551 (1.19)	857 (1.22)
Basic model*	1 (Reference)	0.95 (0.81–1.10)	0.97 (0.84–1.13)	1.00 (0.85–1.18)
Multivariable model#	1 (Reference)	0.95 (0.78–1.16)	1.02 (0.84–1.24)	1.05 (0.86–1.30)

Zhou, J. et al. Association of oily fish and nonoily fish intakes with all-cause mortality and cause-specific mortality: a large population-based prospective study. J. Transl. Med. 21, 280 (2023).

Subgroup analysis - many details

- reduced ACM in > 60 yoa, **male**, non-smoker, higher alcohol, **higher BMI (30+)**, hypertensives, non-diabetics, **lower physical activity**, **non-user of fish oil**, **higher processed meat intake** (≧2 svgs), lower tea intake (<4/d *UK Biobank)
  - strongest associations in older and non-smokers

- reduce CVD mortality in > 60 yoa, **female**, non-smoker, higher alcohol, **BMI <30**, hypertensives, non-diabetics, **higher physical activity**, **fish oil users**, **lower processed meat intake**, lower tea intake

Zhou, J. et al. Association of oily fish and nonoily fish intakes with all-cause mortality and cause-specific mortality: a large population-based prospective study. J. Transl. Med. 21, 280 (2023).

Extra Insight

What's the deal with DHA?

Higher docosahexaenoic acid levels lower the protective impact of eicosapentaenoic acid on long-term major cardiovascular events

Viet T Le [1 2], Stacey Knight [1 3], Jeramie D Watrous [4], Mahan Najhawan [4], Khoi Dao [4], Raymond O McCubrey [1], Tami L Bair [1], Benjamin D Horne [1 5], Heidi T May [1], Joseph B Muhlestein [1 3], John R Nelson [6], John F Carlquist [1 3], Kirk U Knowlton [1 3 4], Mohit Jain [4], Jeffrey L Anderson [1 3]

Affiliations + expand

PMID: 37680562 PMCID: PMC10482040 DOI: 10.3389/fcvm.2023.1229130

Free PMC article

Conclusion:

DHA may blunt (but not eliminate) EPA effects

Dose: Aim for EPA:DHA ≧ 1

May explain the discrepancy in study results

Le, V. T. et al. Higher docosahexaenoic acid levels lower the protective impact of eicosapentaenoic acid on long-term major cardiovascular events. Front. Cardiovasc. Med. 10, 1229130 (2023).

Could there be a final word?

Omega-3 for the prevention of cardiovascular diseases: meta-analysis and trial-sequential analysis

Maria Francesca Cabiddu [# 1], Alberto Russi [# 2], Lucia Appolloni [3], Daniele Mengato [4], Marco Chiumente [5]

Affiliations + expand

PMID: 32546568 PMCID: PMC9047929 DOI: 10.1136/ejhpharm-2020-002207

Free PMC article

"...no further trials are needed to better evaluate the efficacy of PUFAs in preventing death related to CVD."

Cabiddu, M. F., Russi, A., Appolloni, L., Mengato, D. & Chiumente, M. Omega-3 for the prevention of cardiovascular diseases: meta-analysis and trial-sequential analysis. Eur. J. Hosp. Pharm. 29, 134–138 (2022)

Risk

Atrial Fibrillation

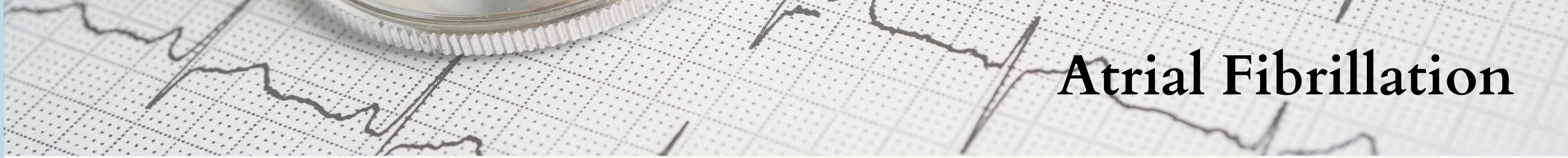
most common chronic arrhythmia
>33 million affected worldwide
37% lifetime risk in ≧ 55 yoa
associated with stroke, heart failure, and death

Risk

Risk factors include:

Older than 60 years of age
Diabetes
High blood pressure
Coronary artery disease
Cardiomyopathy
Pericardial inflammation
Prior heart attacks
Congestive heart failure
Structural heart disease
Prior open-heart surgery
Untreated atrial flutter
Thyroid disease
Chronic lung disease
Sleep apnea
Excessive alcohol or stimulant use
Serious illness or infection

Chung, M. K. et al. Lifestyle and Risk Factor Modification for Reduction of Atrial Fibrillation: A Scientific Statement From the American Heart Association. Circulation 141, e750–e772



Atrial Fibrillation

In September 2023,
the Pharmacovigilance Risk Assessment Committee
of the European Medicines Agency (EMA)
recommended that atrial fibrillation be added
as a common side effect in products containing
omega-3-acid ethyl esters.

Stated that anyone developing AFib
should stop the medication permanently.

www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-25-28-september-2023

Atrial Fibrillation - Trials

Timeline

Hints of issues first surfaced with the REDUCE-IT trial, surprising everyone (Bhatt et al., 2019)

- intervention = IPE X 4 g/d
- rate of AFib = 5.3% vs 3.9%; p =0.003 - **SIGNIFICANT**

started to investigate in other outcome trials ...

STRENGTH trial (Nicholls et al., 2020)

- intervention = EPA+DHA carboxylic acid X 4 g/d
- rate of AFib = 2.2% vs 1.3% (HR 1.69 (1.29-2.21); 95% CI) - **SIGNIFICANT**

OMEMI - Effects of n-3 Fatty Acid Supplements in Elderly Patients After Myocardial Infarction (Kalstad et al., 2020)

- intervention = EPA+DHA X 1.8 g/d (930 mg EPA/660 mg DHA)
- rate of AFib = 7.2% vs 4.0% (HR 1.84 (0.98-3.45); p=0.06 - **NOT SIGNIFICANT**
- then a secondary analysis was done, specifically looking to link serum levels to outcomes (Myrhe et al., 2022)
  - discovered linear association between EPA levels and risk of AFib (but no association with DHA levels)
  - HR 1.36 (1.07-1.72); p=0.011 - **SIGNIFICANT**

VITAL Rhythm (ancillary AFib specific trial embedded in VITAL) (Albert et al., 2021)

- intervention = EPA+DHA X 1 g/d (460 mg EPA/380 mg) DHA
- rate of AFib = 3.7% vs 3.4% (HR 1.09 (0.96-1.24); p=0.19) - **NOT SIGNIFICANT**

Atrial Fibrillation - Meta-Analysis

A clarification study!

Goal = summarize conflicting results

- looked at 7 studies with a total of 81,210 patients
- divided into low dose (73%) and high dose (27%)
  - low dose was ≤ 1g/d (but actually was just 1 g/d)
  - high dose = > 1g/d (which ranged from 1.8 g/d (930 EPA and 660 DH) to 4 g/d (EPA+DHA or IPE)
- LOTS of heterogeneity - dosage, placebo, follow-up duration, study population, age, CVD, varying prevalence of pre-existing AF
  - most reported new-onset AF even if AF at baseline included in analysis, but 2 studies didn't exclude pre-esixting in outcomes (e.g. self-reported AF or hospitalization for AF
  - BUT ASCEND (the patient reported one) did a post-hoc analysis looking at new-onset AF which made the low dose HR become insignicant
- no increased risk in low dose individual studies, only in pooled HR

Gencer, B. et al. Effect of Long-Term Marine Omega-3 Fatty Acids Supplementation on the Risk of Atrial Fibrillation in Randomized Controlled Trials of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. Circulation (2021) doi:10.1161/circulationaha.121.055654.

Atrial Fibrillation – Meta-Analysis

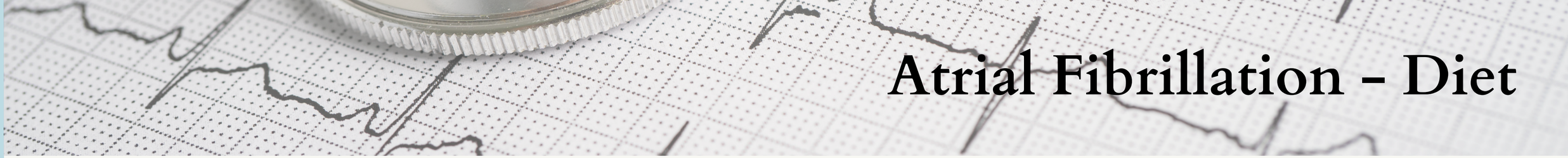
Results:

- general: use of marine omega-3s increased AFib - HR = 1.25 (1.07-1.46); p = 0.013
- dose-relationship:
  - > 1g/d HR 1.49 (1.04-2.15), p=0.042
  - ≤ 1 g/d HR 1.12 (1.03-1.22) p=0.024
  - per 1 g higher dosage HR = 1.11 (1.06-1.15) p = 0.001
- sensitivity analysis using post-hoc ASCEND data (where they dealt with pre-existing AFib)
  - general: HR = 1.20 (1.01-1.43)
  - dose-relationship:
    - >1g/d HR 1.49 (1.04-2.15)
    - ≤ 1g/d HR 1.08 (0.99-1.17)
      - NOT SIGNIFICANT until statistically fixed a heterogeneity problem in low dose groups
      - then BARELY SIGNIFICANT HR = 1.075 (1.003-1.153)

Conclusion:

- MA is big enough to suggest small-to-moderate dose-dependent AF risk increase
- lots of limitations, unfortunately

Gencer, B. et al. Effect of Long-Term Marine Omega-3 Fatty Acids Supplementation on the Risk of Atrial Fibrillation in Randomized Controlled Trials of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis. Circulation (2021) doi:10.1161/circulationaha.121.055654.



Atrial Fibrillation – Diet

A diet study!

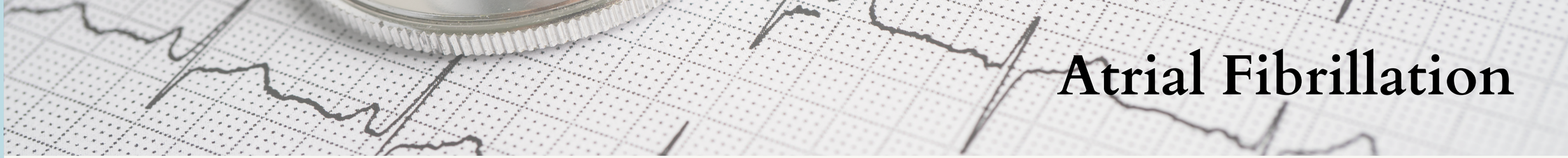
Goal = impact of long-term intake vs short term and habitual non-supplement intake

- observational but prospective, using 17 cohorts with 54,799 participants from 21 countries
- looked at lots of biomarker in various compartments: RBC/plasma or serum phopholipids, tota plasma/serum, cholesterol esters, adipose tissue
    - adipose chosen preferentially as best reflecting long-term dietary intake (then RBC phospholipid)
- AFib diagnosis was NOT self-reported, nor was fish intake – that's why biomarkers were used

Results:

- **EPA levels not associated with AFib**
    - hazard ratio (HR) per interquintile range (b/w 10th and 90th percentile) = 1.00 (0.95–1.05); 95% CI
- HR for all others (DPA, DHA, and EPA+DHA) show **reduced risk**
- relationship did NOT vary across age, sex, global region or across lipid compartments
- more importantly, relationship did NOT differ in those with elevated CV risk

Qian, F. et al. Omega-3 Fatty Acid Biomarkers and Incident Atrial Fibrillation. J. Am. Coll. Cardiol. 82, 336–349 (2023)

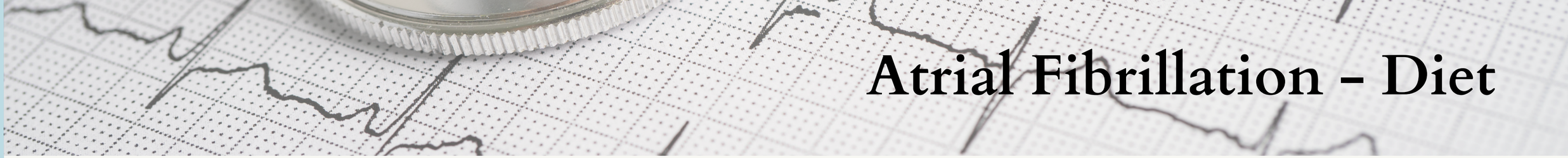


Atrial Fibrillation

	EPA	DPA	DHA	EPA+DHA
Overall	1.00 (0.95-1.05)	0.89 (0.83-0.95)	0.90 (0.85-0.96)	0.93 (0.87-0.99)
Elevated CV Risk	0.94 (0.88-1.02)	0.88 (0.80-0.96)	0.89 (0.82-0.97)	0.91 (0.85-0.98)

HR (95% CI) - interquintile range, multivariable-adjusted

Qian, F. et al. Omega-3 Fatty Acid Biomarkers and Incident Atrial Fibrillation. J. Am. Coll. Cardiol. 82, 336–349 (2023)



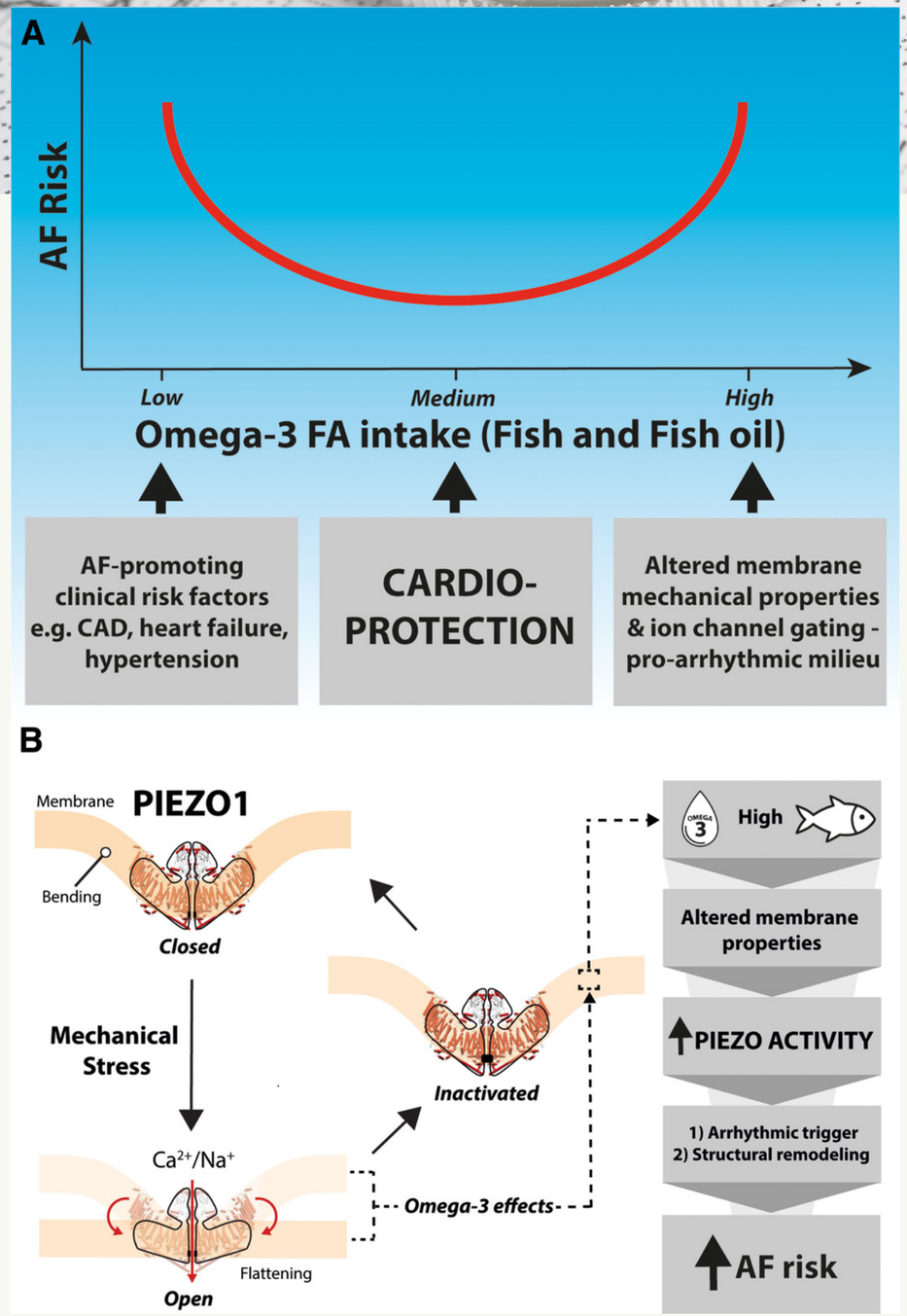
Atrial Fibrillation – Diet

Diet vs supplement - complete opposite ... WHY?

1. Few people with elevated CVD risk (or secondary prevention) vs most interventional studies (although small subgroup was examined)
2. Supplement use in these cohorts was very low and biomarkers represented habitual dietary intake
    a. how can we tell? details per cohort!
        i. either assessed and deemed low (e.g. 2%)
        ii. not assessed but sampling occurred before supplementation was common (e.g. pre-1990)
        iii. just not assessed (6/19)
3. Based on global survey of seafood omega-3 intake by country
    - mean intake in studied countries = 0.43 +/- 0.35 g/d (much less than the supplement added in short-term RCTs) (Micha et al., 2014)
4. Longer follow-up

Qian, F. et al. Omega-3 Fatty Acid Biomarkers and Incident Atrial Fibrillation. J. Am. Coll. Cardiol. 82, 336–349 (2023)

Atrial Fibrillation



But why?
No one knows.

Theory

A pro-arrhythmic environment may be created by the high level of omega-3s incorporated into cells. The high omega-3 content may affect membrane properties such as PIEZO channels, voltage-gated ion channels, ionic pumps, cell surface receptors, and extracellular matrix-cytoskeletal interactions.

Fatkin, D., Cox, C. D. & Martinac, B. Fishing for Links Between Omega-3 Fatty Acids and Atrial Fibrillation. Circulation 145, 1037–1039 (2022)

Risk

Hyperlipidemia

Various studies in the last 20+ years have suggested that EPA/DHA intake may increase LDL-cholesterol.

This was seen most often in those with very high triglycerides (>5.6 mmol/L) and suspected to be caused by DHA component.

Skulas-Ray, A. C. et al. Omega-3 Fatty Acids for the Management of Hypertriglyceridemia: A Science Advisory From the American Heart Association. Circulation 140, e673–e691 (2019)

Hyperlipidemia

In an often-cited 2013 review article, the authors cautioned that using other methods of treating high triglycerides should be found in case the LDL-C increase led to negatives outcomes. (Bradberry et al., 2013).

Small studies since then have not conclusively answered the question - for example:

- prospective study of population at typical CHD risk (mostly men) (Harris et al., 2021)
  - results: a rise in DHA markers (via diet or supplement) was associated with a small, but statistically significant **decrease** in LDL-C levels
  - impossible to imagine clinical relevance (0.05 mmol/L)
- meta-analysis and systematic review of impact of omega-3s on lipids in post-menopausal women (Wang et al., 2023)
  - omega-3 supplementation led to decreases in triglycerides (0.2 mmol/L), **increased HDL-C** (0.05 mmol/L), and increased LDL-C (0.1 mmol/L) but no change total cholesterol
  - again, these increases were considered clinically irrelevant (<5%)

I feel that the (very) modest magnitude of effect regardless of direction suggests 2 things about omega-3 and dyslipidemia:

1. Efficacy: Don't use omega-3s for dyslipidemia other than high triglycerides.
2. Safety: Supplementation with omega-3s is unlikely to affect lipids in a clinically relevant way, but not impossible - maybe more caution in patients with high triglycerides and/or using higher dose of DHA

Risk

Drug Interactions

Drug(s) of concern = blood thinners

Visual summary

Combining antiplatelets and anticoagulants

Antiplatelets

APL

Monotherapy

ASP Aspirin

Aspirin should be prescribed as the first-line antiplatelet agent unless the patient is intolerant or has a compelling contraindication

+

Dual therapy

For dual antiplatelet therapy, a $P2Y_{12}$ inhibitor can be added:

CLO Clopidogrel

PRA Prasugrel

TIC Ticagrelor

Combining novel $P2Y_{12}$ inhibitors with oral anticolaguants increases risk of bleeding, and cannot currently be recommended

Oral anticoagulants

OAC

WAR Warfarin

Warfarin is the most commonly used anticoagulant

DOAC

Direct oral anticoagulants

These are thought to be a safe alternative to warfarin, although there remains uncertainty about risks versus benefits

Patients should be prescribed the lower licenced dose of a DOAC when combined with an antiplatelet

API Apixaban

DAB Dabigatran

RIV Rivaroxaban

Floyd, C. N. & Ferro, A. Indications for anticoagulant and antiplatelet combined therapy. BMJ 359, j3782 (2017)

Antiplatelets

Small retrospective review (Watson et al., 2009)

- compared group taking ASA (mean dose 161 mg) and clopidogrel (mean dose 75 mg) vs group taking ASA, clopidogrel, AND high dose omega-3 (mean dose 3 g)
- results: no difference in bleeding over mean follow-up of 33 months

Not much recent research, often as secondary outcome

- e.g. study looking at population with high risk colorectal adenomas (Hull et al., 2018)
  - randomized to 2 g/d EPA, 300 mg/d aspirin, both treatments in combination, or placebo for 12 months
  - bleeding episodes not significantly different between groups
- 2022 review looking at studies (in vitro, animal, and human) blending ASA and omega-3 PUFAs didn't note any bleeding concerns (Wang et al., 2022)

OAC – Warfarin

1998

Older, very small RCT with warfarin (Bender et al., 1998)

- 5 control vs 3 people X 3g fish oil vs 3 people X 6 gr fish oil X 1 month
- fish oil = 180mg EPA/120 mg DHA per g omega-3
- <u>results</u>: no INR change within or between groups

2004

"Famous" case study – 67 yo woman on warfarin X 1.5 yrs for recurrent TIA (Buckley et al., 2004)

- 1000 mg fish oil = no change
- 2000 mg increased INR
- INR normalized on reduction
- no known info on fish oil details

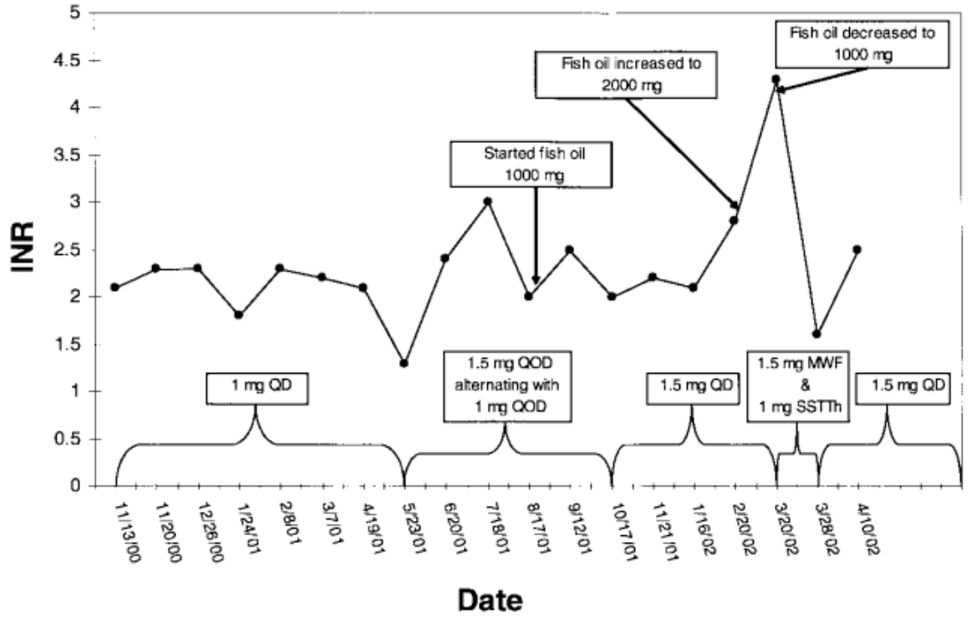


Figure 1. INR values over time with coinciding warfarin dose during anticoagulation management. MWF = Monday, Wednesday, and Friday; SSTTh = Saturday, Sunday, Tuesday, and Thursday.

OAC – Warfarin

Another case study – 65 yo man on warfarin X 6 mths for post-operative PTE (Jalili et al., 2007)

- started trazadone (50 mg) and omega-3 (2 gr) for "not-very-well-defined complaints" (abdominal symptoms and insomnia??)
- 2 weeks later, INR was 8.06 vs. 2.56
- INR normalized within 2 days of discontinuing everything
- could this have been due to trazadone? YES, but no way to know

2007

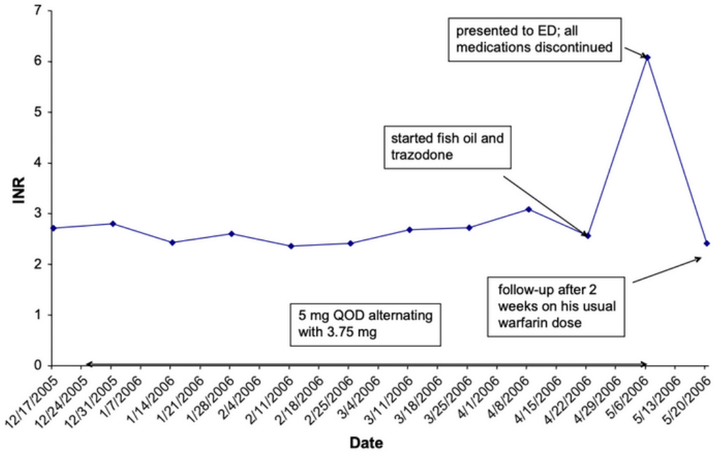


Figure 1. International normalized ratio (INR) values over time with coinciding warfarin dose during anticoagulation management. ED, Emergency Department; QOD, every other day.

Retrospective study

- looked at people with AF or DVT who were on warfarin AND fish or krill oil vs those who didn't take fish/krill
- <u>results</u>:
  - time in therapeutic range was the same
  - no difference minor-bleeding episodes (and no major ones in either group)

2016

Pryce, R., Bernaitis, N., Davey, A. K., Badrick, T. & Anoopkumar-Dukie, S. The Use of Fish Oil with Warfarin Does Not Significantly Affect either the International Normalised Ratio or Incidence of Adverse Events in Patients with Atrial Fibrillation and Deep Vein Thrombosis: A Retrospective Study. Nutrients 8, 578 (2016).

OAC – DOACs

That's warfarin (vitamin K antagonist or VKA) ... but what about the newer class of anticoagulants the direct oral anti-coagulants (DOACs)?

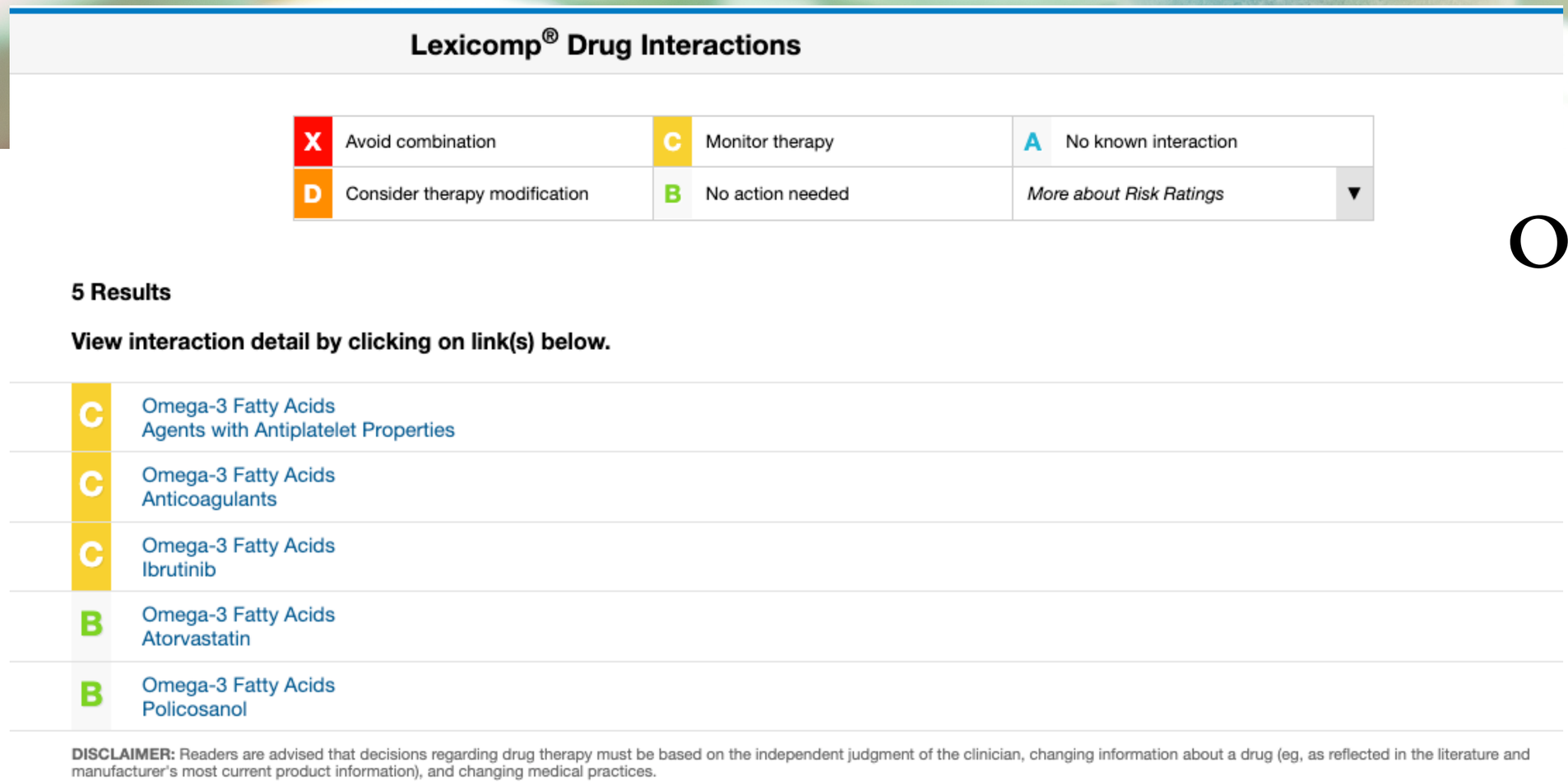
The Clinical Significance of Drug-Food Interactions of Direct Oral Anticoagulants (Grześk et al., 2021) outlines a theoretical concern based on the following:

1. Omega-3s have an anti-platelet effect.
2. Anti-platelet drugs may increase risk of bleeding with DOACs.
3. So maybe omega-3s increase risk of bleeding?

There are many concerns with DOAC drug interactions, usually due to liver metabolism, but omega-3 are rarely mentioned (and if they are, it's usually the case studies).

1. *Old and new oral anticoagulants: Food, herbal medicines and drug interactions (Minno et al., 2017)* - NO MENTION
2. *Drug Interactions Affecting Oral Anticoagulant Use (Mar et al., 2022)* - ONLY mention is 2004 case study

Other Drugs



Lexicomp® Drug Interactions

X	Avoid combination	C	Monitor therapy	A	No known interaction
D	Consider therapy modification	B	No action needed	*More about Risk Ratings*	▼

5 Results

View interaction detail by clicking on link(s) below.

C	Omega-3 Fatty Acids Agents with Antiplatelet Properties
C	Omega-3 Fatty Acids Anticoagulants
C	Omega-3 Fatty Acids Ibrutinib
B	Omega-3 Fatty Acids Atorvastatin
B	Omega-3 Fatty Acids Policosanol

DISCLAIMER: Readers are advised that decisions regarding drug therapy must be based on the independent judgment of the clinician, changing information about a drug (eg, as reflected in the literature and manufacturer's most current product information), and changing medical practices.

Drug interactions on resources like Lexicomp or Drugs.com refer almost exclusively to omega-3s **theoretical** blood-thinning impact and encourage "**monitoring**".

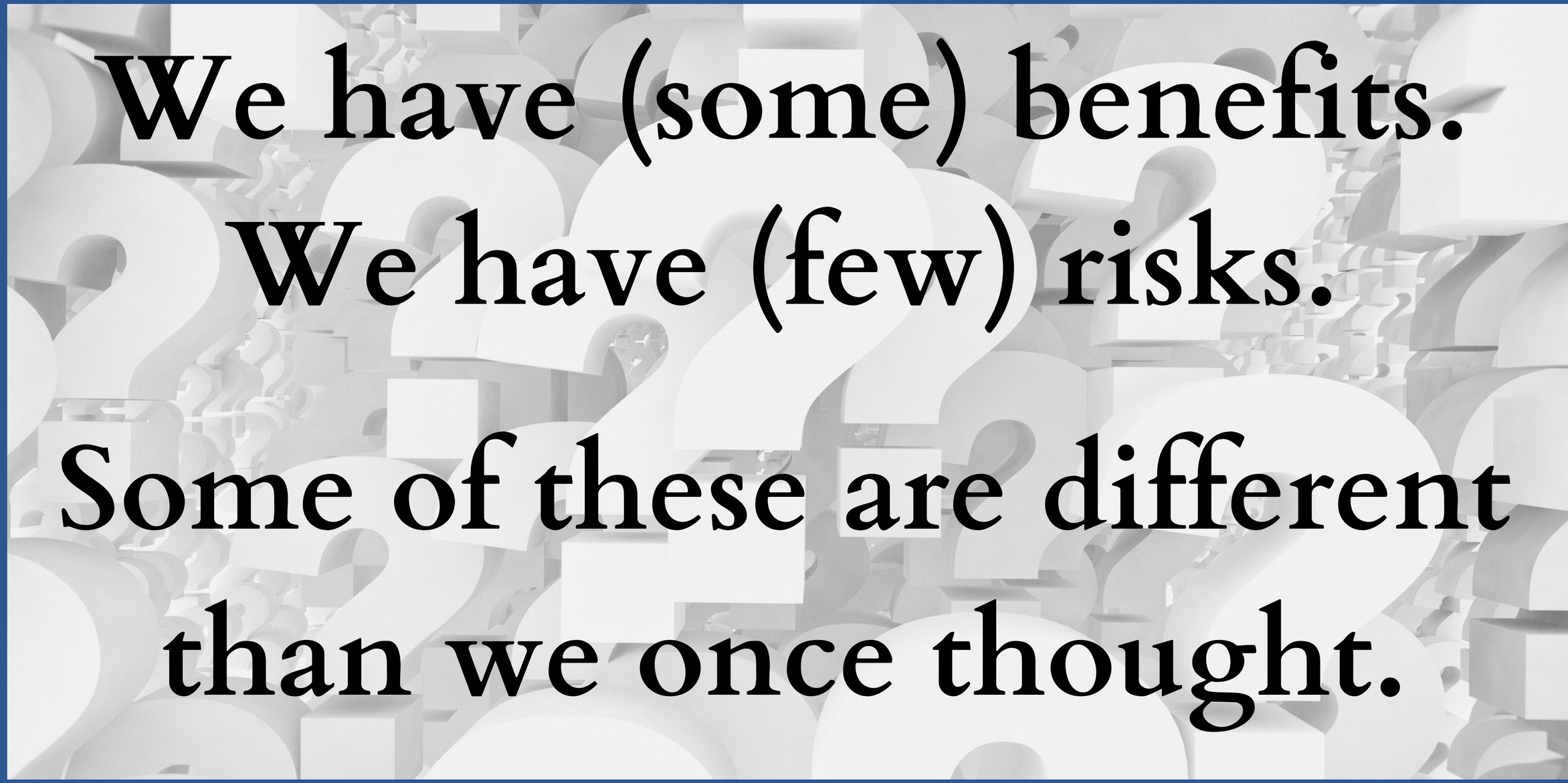
One exception include atorvastatin due to one study showing change to metabolism of atorvastatin metabolite with unknown impact **note many studies show concurrent use of atorvastatin and omega-3 (usually as IPE) for high TG.

Drug Summary

Remember than the anti-thrombolytic effect
can be a benefit as well as a harm.

Omega-3 supplementation does not seem to be an issue, but we can't seem to get rid of the "what if" cautionary default.
(IPE is an good example.)

Are there scenarios (conditions, pharmacotherapy, surgical) where this might not be appropriate?


We have (some) benefits.
We have (few) risks.
Some of these are different
than we once thought.


SO WHERE DOES
THAT LEAVE US?

SUMMARY:

SLOWLY CIRCLING AROUND BETTER ANSWERS, COMPLICATED BY MULTIPLE EFFECTS

Risk factor benefits include:

- lowering inflammatory markers
- anti-hypertensive effect
- normalization of thrombolytic potential
- reducing high triglycerides

Cautions:

- AFib, especially at higher doses
  - note: higher doses would likely being used in those who could benefit most from omega-3s

Population specifics:

- secondary prevention > primary prevention
- possible threshold of effect
  - additional omega-3 intake in populations with high background fish intake (and already lower CVD risk) are unlikely to see added benefit
- better results in those with low fish intake

Outcomes benefits:

- secondary prevention > primary prevention
- modest overall reduction (but this corresponds to big global impact given preponderance of both heart disease and omega-3 supplement use)
- not likely to be uniformly beneficial across all types of CVD

Dose:

- considering potential threshold of effect, relationship with AFib, and general outcome data
  - ≤ 1 gram combined EPA+DHA/EPA likely sufficient for primary prevention
  - higher amounts appropriate in specifically circumstance

Type:

- EPA > DHA generally
- supplement vs food
  - either but slight edge to fish intake
- supplement vs drug
  - drug use specific to TG-lowering only at this time

SUMMARY

Consuming 0-1 servings (fatty) fish per week?
Increase omega-3 intake.

Fish oil only for primary prevention?
Keep ≤ 1 g/day EPA+DHA.

Fish oil for secondary prevention?
Variable dosing depending on details.
Consider IPE X 4 g/d in hypertriglyceridemia.

Fish oil for other reasons such as rheumatoid arthritis or cognition?
Screen for and discuss AFib risk.
Consider inflammatory control.

(Additional info re: fish - Rimm et al., 2018)

OMEGA 3 & HEART HEALTH

CLARIFICATION & CONTROVERSIES

DR. ALEXANDRA VERGE ND

OANDCon

Thank You!

Bonus
(Fish Bites)

Mercury contamination

- Investigators, P. S. et al. Mercury exposure and risk of cardiovascular disease: a nested case-control study in the PREDIMED (PREvention with MEDiterranean Diet) study. BMC Cardiovasc. Disord. 17, 9 (2017).
- Sun, Y. et al. Association of Seafood Consumption and Mercury Exposure With Cardiovascular and All-Cause Mortality Among US Adults. JAMA Netw. Open 4, e2136367 (2021).

Type of seafood	Omega-3	Mercury
Atlantic salmon	High	Low
Wild salmon	High	Low
Mackerel - Pacific	High	Low
Herring	High	Low
Rainbow trout	High	Low
Sardines	High	Low
Swordfish	High	High

Omega-3 (mg per 3 oz): High >1000 mg; Medium 200 – 1000 mg; Low <200 mg

Mercury (PPM): Low <0.1; Medium 0.1-0.4; High 0.5-1

https://www.heartandstroke.ca/articles/your-healthy-fish-guide

Farmed fish

- farmed fish is generally found to be lower in omega-3 (%) while higher in fat content than wild ... BUT due to higher fat content, total omega-3 content (g) is higher
  - Jensen, I.-J., Eilertsen, K.-E., Otnæs, C. H. A., Mæhre, H. K. & Elvevoll, E. O. An Update on the Content of Fatty Acids, Dioxins, PCBs and Heavy Metals in Farmed, Escaped and Wild Atlantic Salmon (Salmo salar L.) in Norway. Foods 9, 1901 (2020)

Cooking fish

- does not reduce omega-3 content (in fact, may increase it)
- Bastías, J. M., Balladares, P., Acuña, S., Quevedo, R. & Muñoz, O. Determining the effect of different cooking methods on the nutritional composition of salmon (Salmo salar) and chilean jack mackerel (Trachurus murphyi) fillets. PLoS ONE 12, e0180993 (2017)
- also keep in mind that most people aren't eating it raw and yet we see improvements in omega-3 status with higher fish intake

Sustainability

- considerations: continued seafood intake (including farmed), algal oil supplementation, industrial extraction using algal sources
- Bianchi, M. et al. Assessing seafood nutritional diversity together with climate impacts informs more comprehensive dietary advice. Commun. Earth Environ. 3, 188 (2022)
- Sivakumar, R., Sachin, S., Priyadarshini, R. & Ghosh, S. Sustainable production of eicosapentaenoic acid-rich oil from microalgae: Towards an algal biorefinery. J. Appl. Microbiol. 132, 4170–4185 (2022)

Omega 6:3 Ratio - things to consider

- discussion/conclusions usually based on observational research, typically of small populations
  - results varied and inconclusive
  - underpowered, hard to find/adjust for potential confounders
- various concerns re: methodology, confounders, points of comparison
    - simple serum samples representing general status
    - self-reported intake groups based on 24-hour recall
    - manipulating chosen populations to get balanced numbers because high omega-3 intake under-represented (Sheppard et al., 2017)
    - high 6:3 ratio can be due to high omega-6, low omega-3, or a blend of both; high omega-3 can be independently positive so high 6:3 ratio being detrimental may simply be insufficient omega-3
    - different effects of different in-group omega fatty acids (e.g. GLA vs AA, EPA vs DHA)
    - proxy for other things often not accounted for (e.g. high omega-6 = high meat/fried food/processed foods?)
    - other concurrent shifts may be responsible
        - e.g. omega-6 higher in group with type 2 DM but oleic acid was also lower vs non-diabetics (Shetty et al., 2020)
- different populations may reflect different levels of effect possibly due to background intake or a variety of other factors (Zhuang et al., 2019)
- **almost most importantly, there is no data/consensus on what the "right" ratio is even if the suggestion is that lower is better**

Omega 6:3 Ratio - summary

"The use of the n-6 to n-3 fatty acid ratio ignores the contribution of each class of fatty acid and even individual fatty acids. This approach assumes that all n-6 fatty acids and all n-3 fatty acids are biologically equivalent to one another which is not correct, and supports that the actions of n-6 and n-3 fatty acids always oppose one another. The bulk of current evidence suggests that it is the absolute intakes of specific n-6 and n-3 PUFA that are associated with many different endpoints. Thus, considerations about adequate intakes for both n-3 and n-6 fatty acids are relevant. ***The use of a ratio can disguise extremely low or very high intakes of n-6 and/or n-3 fatty acids.***"

Aranceta, J. & Pérez-Rodrigo, C. Recommended dietary reference intakes, nutritional goals and dietary guidelines for fat and fatty acids: a systematic review. Br. J. Nutr. 107, S8-S22 (2012)