

Omega-3 fatty acids and cardiovascular disease: a continuum of nutrition and medicine

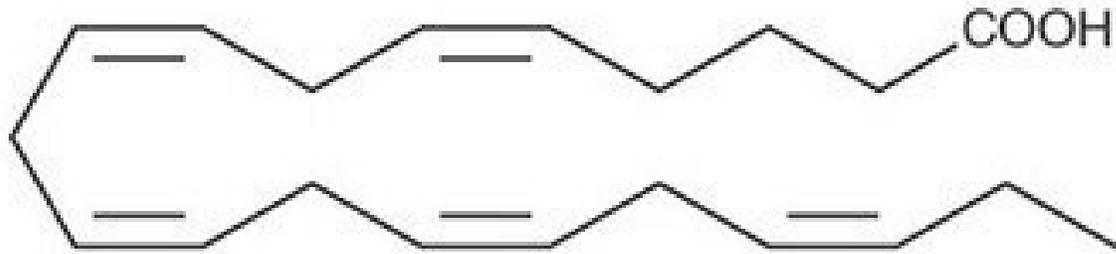
Ann C. Skulas-Ray, PhD
Food, Bioactives, & Health Lab

Department of Nutritional Sciences
Department of Immunobiology
Arizona Center on Aging
Physiological Sciences GIDP

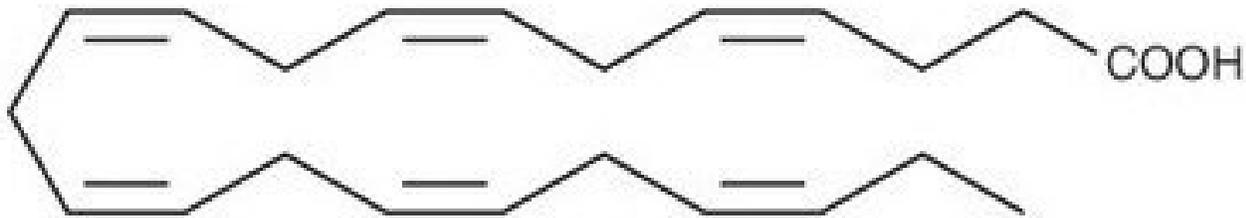
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Nutritional Sciences



EPA (20:5)



DHA (22:6)

Outline

- Dose-response considerations
- Nutrition vs. medical
- Disease prevention
- Triglyceride lowering
- What's next?

How much?

DGA: 2 servings of fish *per week*

- ~ 250 mg/d

2 servings of oily fish *per week*

- Up to 500 mg/d

1 fish oil capsule

- 300+ mg

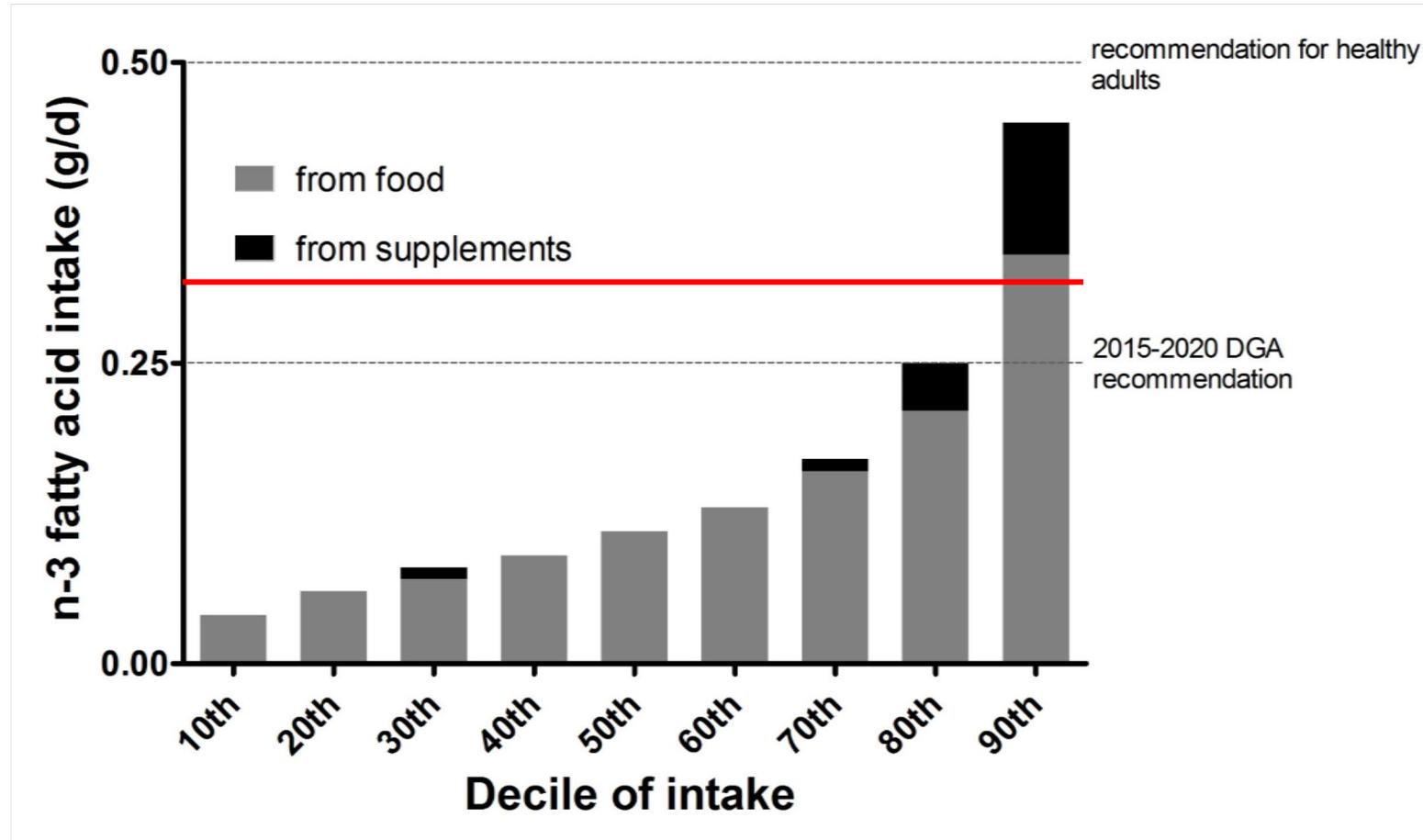
1 prescription capsule

- 840 mg EPA + DHA
- or 960 mg EPA

4 prescription capsules

- 3.4-3.8 g

Current omega-3 fatty acid intakes





What are the differences between supplements and prescription agents?

Nutrition/Dietary Supplements

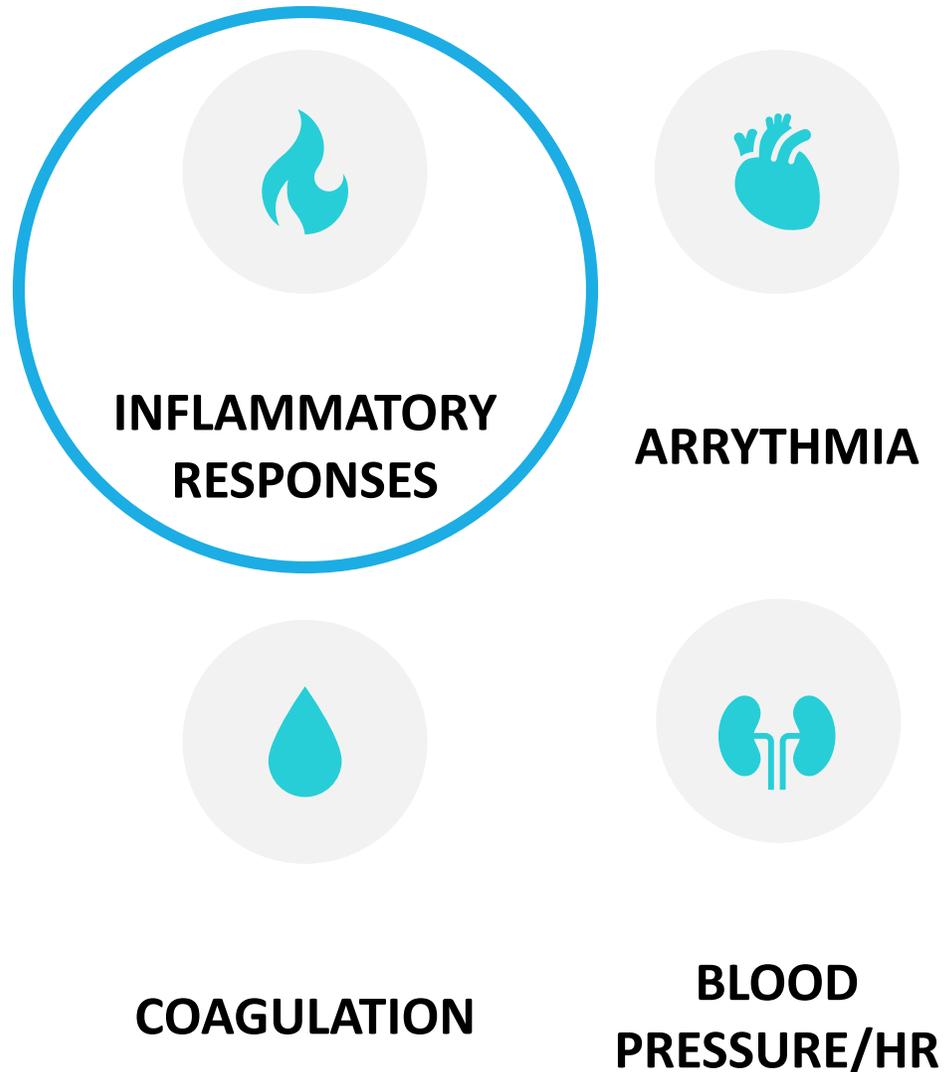
- Subtle effects
- Excellent safety profile
- Recommendations at a population level
- Meant to be consumed for a lifetime
- **Maintain health**
- FDA: safe until evidence otherwise
- Some degree of variability is to be expected

Medical/Pharmacological

- Consistent, measurable benefits
- Adequate safety profile relative to benefits for indicated use
- Indicated for subset of the population
- Varying duration of use
- **Indication to treat/prevent disease** (or established risk factors)
- FDA: safety demonstrated in clinical trials
- Strict regulatory specs for composition

Nutritional/Dietary Supplements vs.
Medical/Pharmacological Paradigms

Health maintenance, disease *prevention*



Nutrition/Dietary Supplements

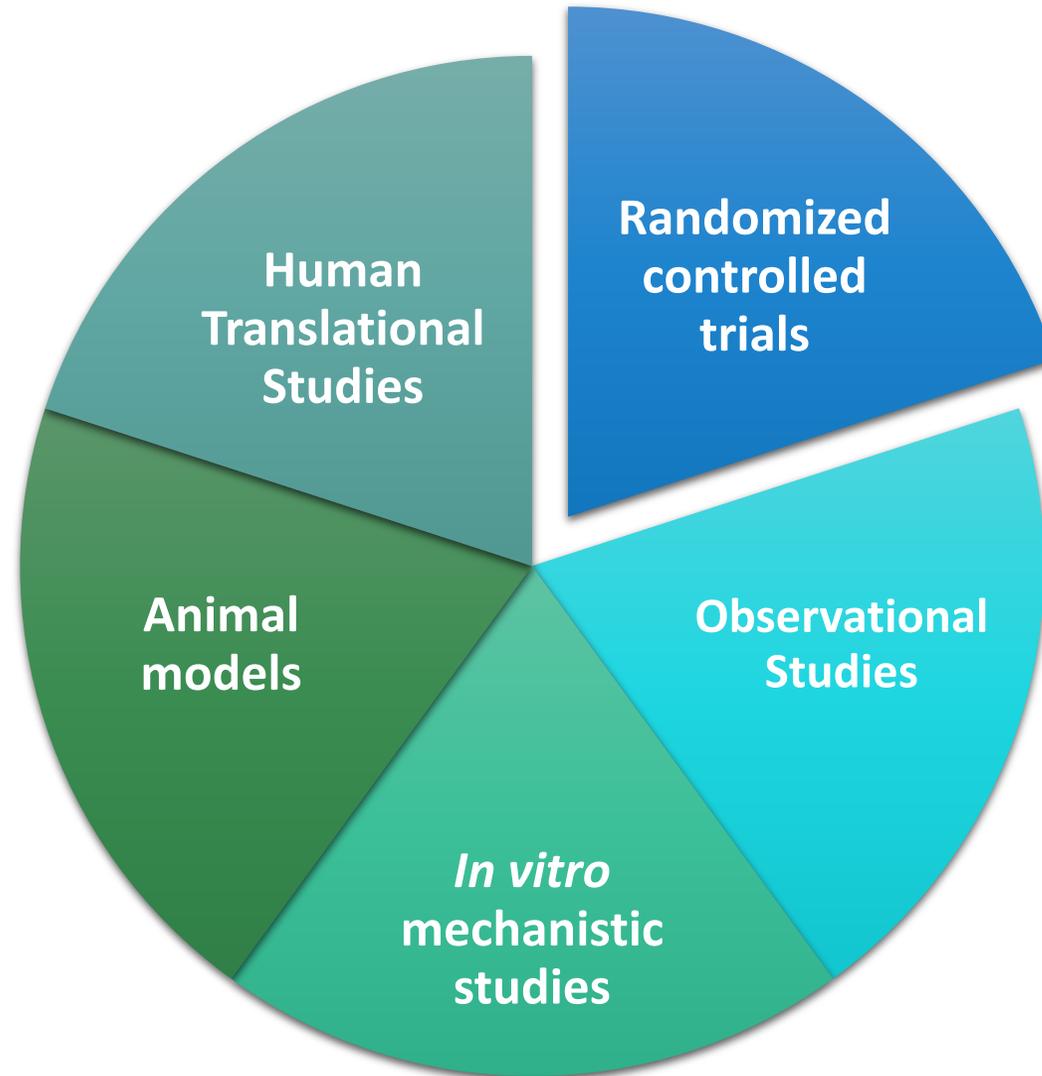
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An apple a day keeps the doctor away

...But we do not have a randomized controlled trial in which apples are proven effective at a specified dose for preventing or treating disease.



How might we evaluate the role of dietary omega-3 fatty acids in PREVENTING disease?



Omega-3 fatty acids and inflammation



hs-CRP Value	Cardiovascular Disease Risk Level*
< 1 mg/L	Low risk
1-3 mg/L	Average risk
> 3 mg/L	High risk

*Risk levels published in 2003. American Heart Association/Centers for Disease Control and Prevention Scientific Statement.

CRP = C-Reactive Protein

Prostaglandins & other Lipid Mediators 116-117 (2015) 104-111

Contents lists available at ScienceDirect

ELSEVIER Prostaglandins and Other Lipid Mediators

Review

Omega-3 fatty acids and inflammation: A perspective on the challenges of evaluating efficacy in clinical research

Ann C. Skulas-Ray*

Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, United States

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ABSTRACT

Chronic inflammation is a common feature of many diseases. There is a strong pre-clinical evidence base demonstrating the efficacy of omega-3 fatty acids for ameliorating inflammation and thereby reducing disease burden. Clinical studies have shown that omega-3 fatty acids are both a reliable marker for monitoring inflammation and a modifiable risk factor for many pharmaceuticals. However, clinical omega-3 fatty acid supplementation has not consistently yielded clinical findings in terms of consistent CRP reductions. Methods for evaluating clinical studies in translating pre-clinical evidence to clinical results are discussed, and clearly distinguish between the reversal of established inflammation and the prevention of inflammation. Future clinical studies evaluating the efficacy of omega-3 fatty acids in reducing inflammation, such as low-dose omega-3 fatty acid supplementation, may be advanced.

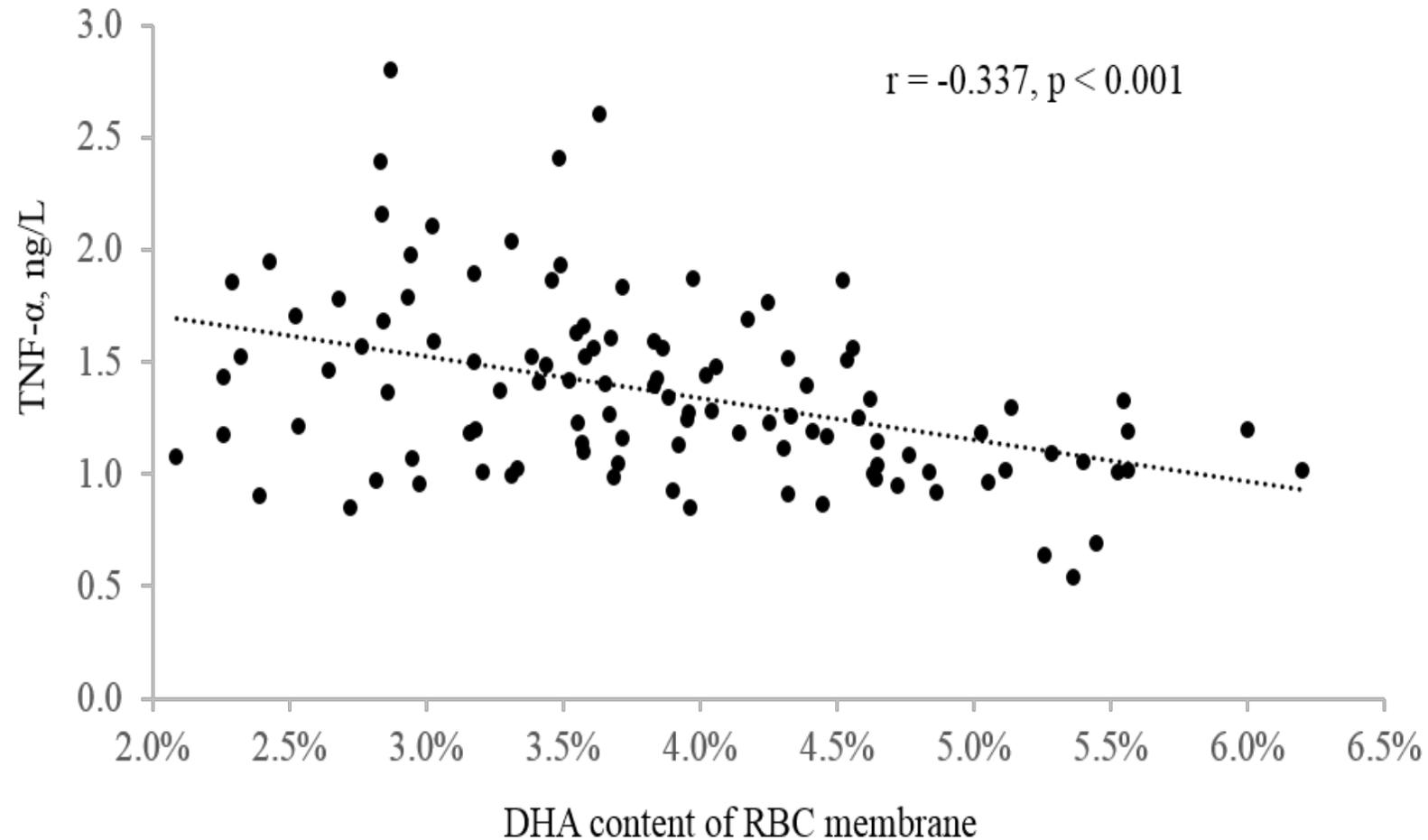
Randomized controlled trials

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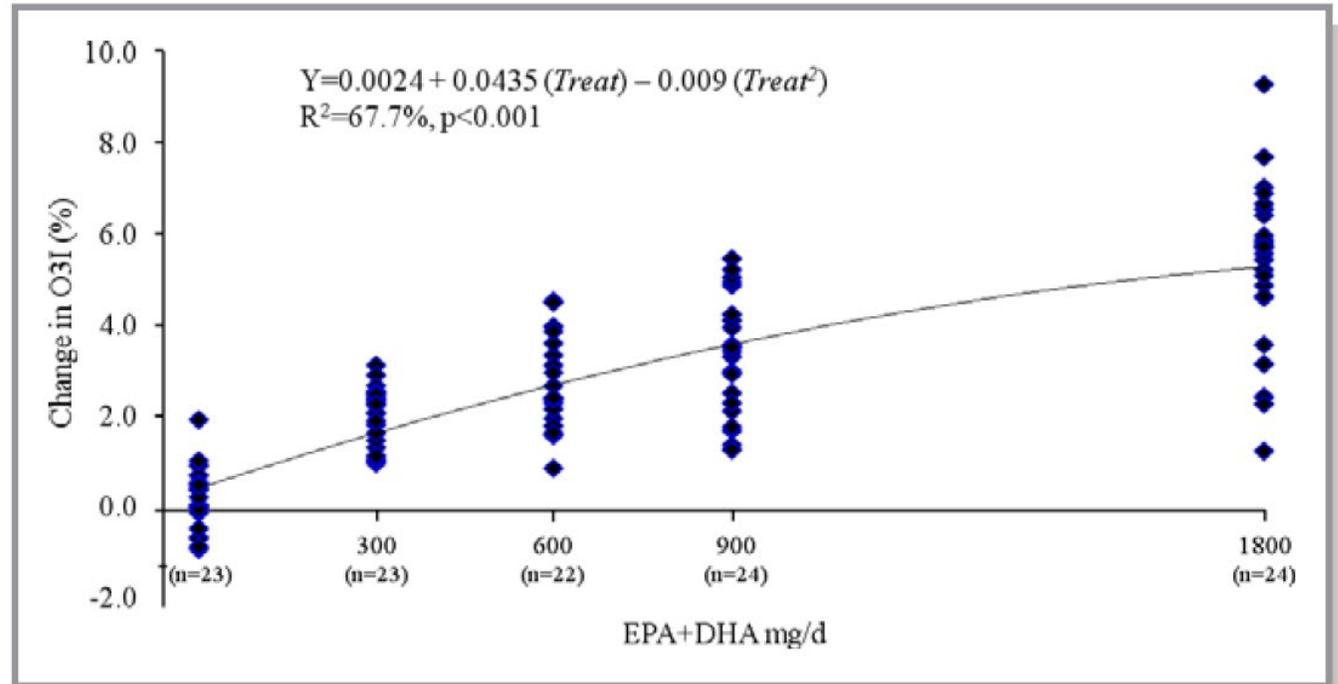
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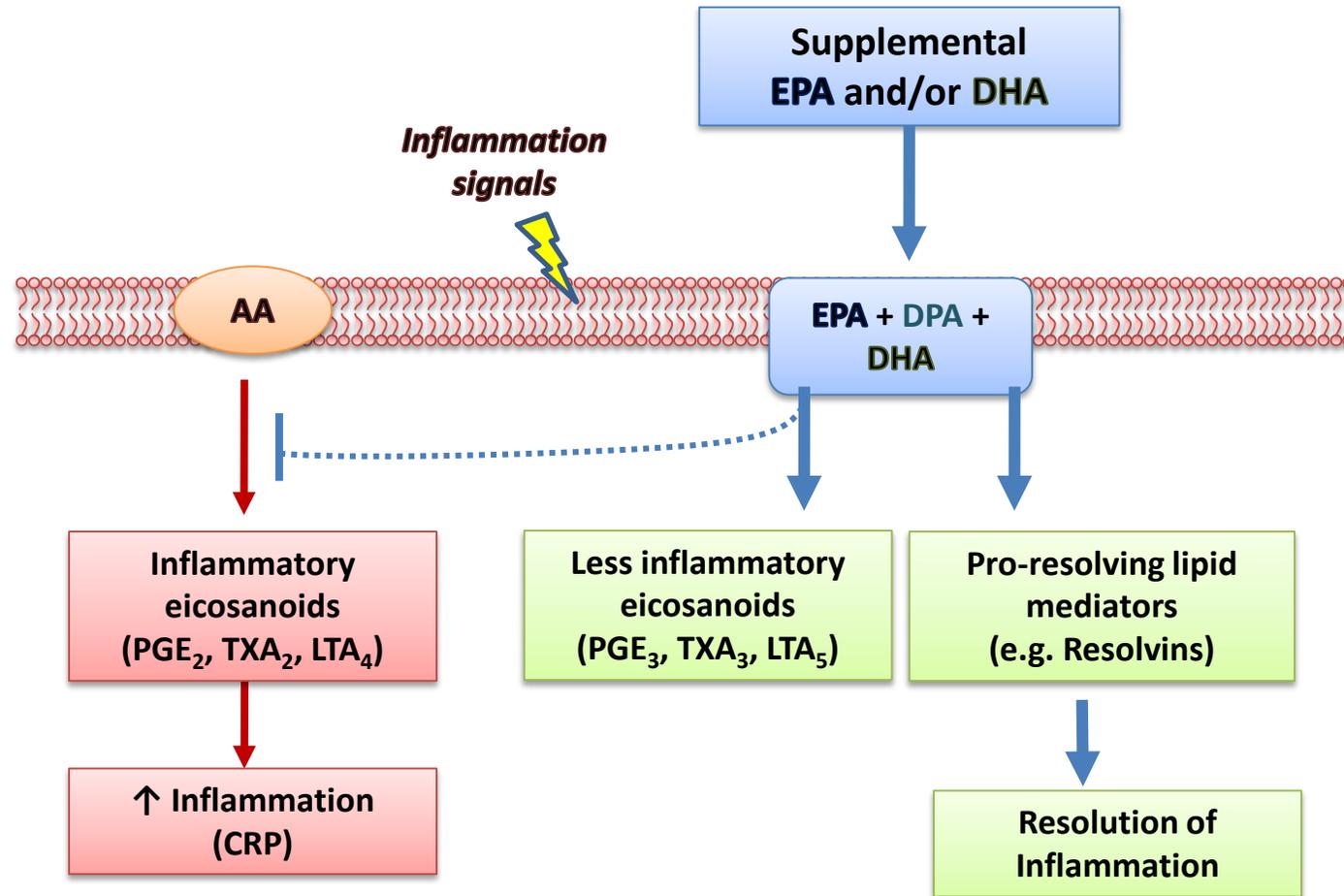
Observational evidence: a marker of habitual omega-3 fatty acid intake is inversely associated with inflammation



We have a biomarker for intake that responds dose dependently



We have mechanistic evidence of the importance of omega-3 fatty acids in regulating inflammatory responses



Pharmacological indication



**ELEVATED
TRIGLYCERIDES***

Medical/Pharmacological

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***ICOSAPENT ETHYL HAS AN ADDITIONAL INDICATION FOR REDUCING THE RISK OF HEART ATTACK, STROKE AND CERTAIN TYPES OF HEART ISSUES REQUIRING HOSPITALIZATION IN ADULTS WITH HEART (CARDIOVASCULAR) DISEASE, OR DIABETES AND 2 OR MORE ADDITIONAL RISK FACTORS FOR HEART DISEASE.**

FDA-approved n-3 FA agents

Omega-3 fatty acid ethyl esters
(O3AEE, EPA + DHA)

Icosapent ethyl
(IPE, EPA-only)

Omega-3 carboxylic acids
(O3CA, EPA + DHA)

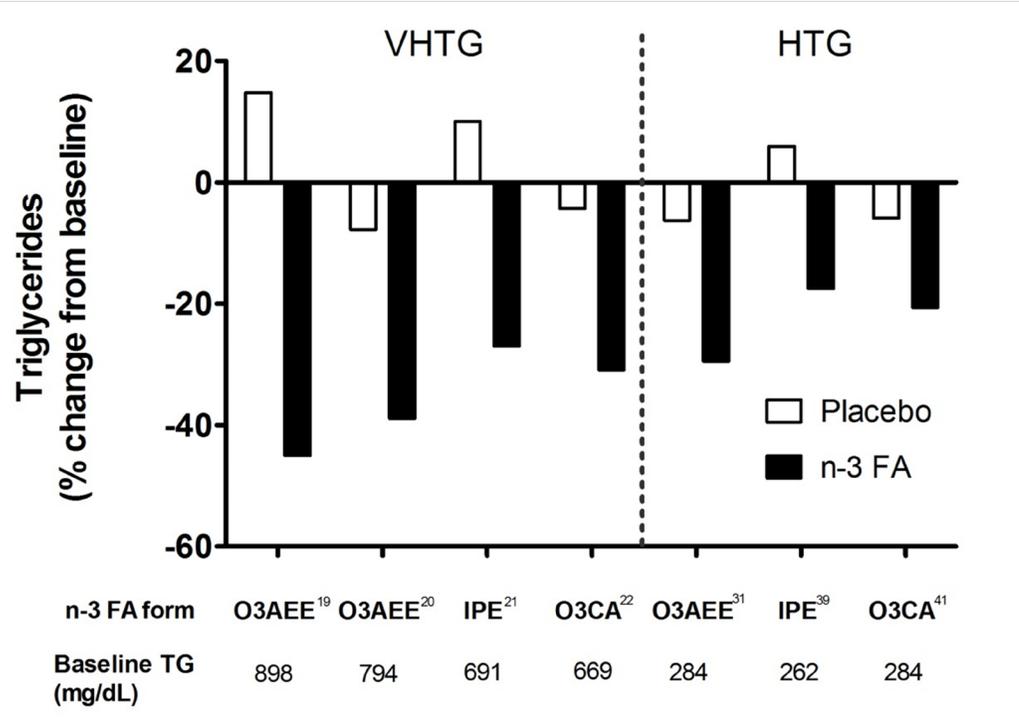
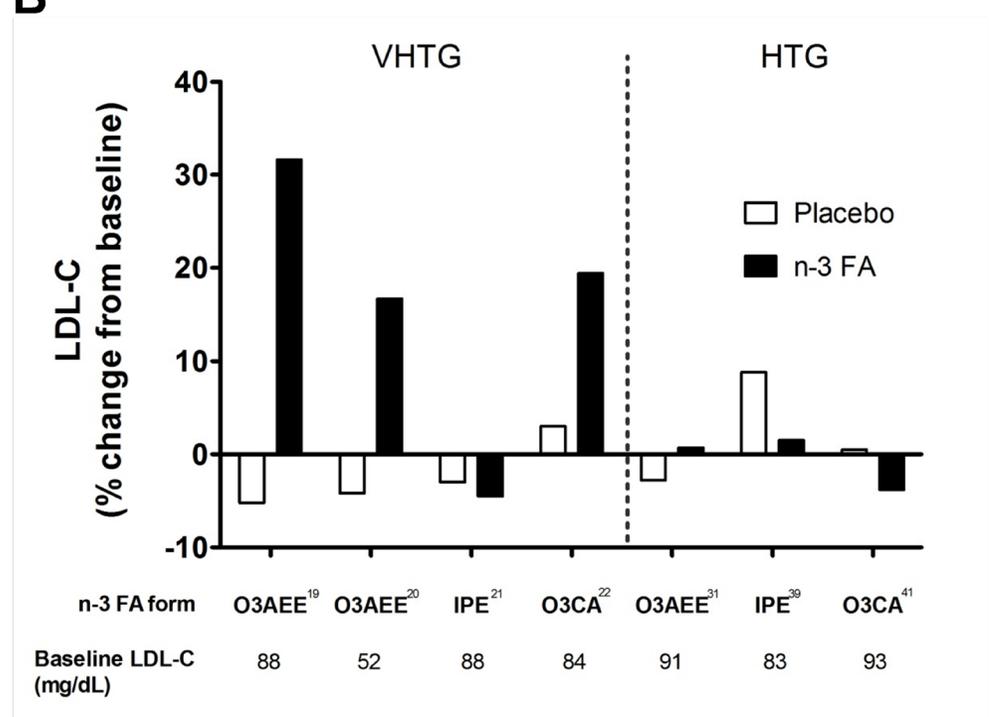
HTG and VHTG

Normal TG < 150 mg/dL

Borderline TG = 150 – 199

High TG (HTG) = 200 – 499

Very high TG (VHTG) = 500+

A**B**

Effect of FDA-approved agents in VHTG and HTG (FDA-reviewed studies)

Dietary supplements, fish oil concentrates: HTG

Author, year (country)	EPA + DHA per day	n per arm (Active/placebo)	Baseline TG (mg/dL)	Effect of omega-3 on TG	Effect of omega-3 on LDL-C & HDL-C	Effect of omega-3 on non-HDL-C & apo B
Bairati, 1992 ^{42, 43} (Canada)	4.5 g (2.7 g EPA, 1.8 g DHA)	66 (n-3 FA) 59 (placebo)	205	↓ 39%	↔ /↑ LDL-C 8% ↑ HDL-C 10%	non-HDL-C and apo B not reported
Minihane, 2000 ⁴⁴ (United Kingdom)	3 g (1.7 g EPA, 1.3 g DHA)	50 (n-3 FA) 50 (placebo)	220	↓ 35%	↑ LDL-C 7% ↔ HDL-C	non-HDL-C and apo B not reported
Shaikh, 2014 ⁴⁵ (Canada)	3.2 g (2.7 g EPA, 0.4 g DHA)	20 (n-3 FA) 22 (placebo)	305 ^c	↓ 48%	↔ LDL-C ↑ HDL-C 9%	↔ non-HDL-C and apo B

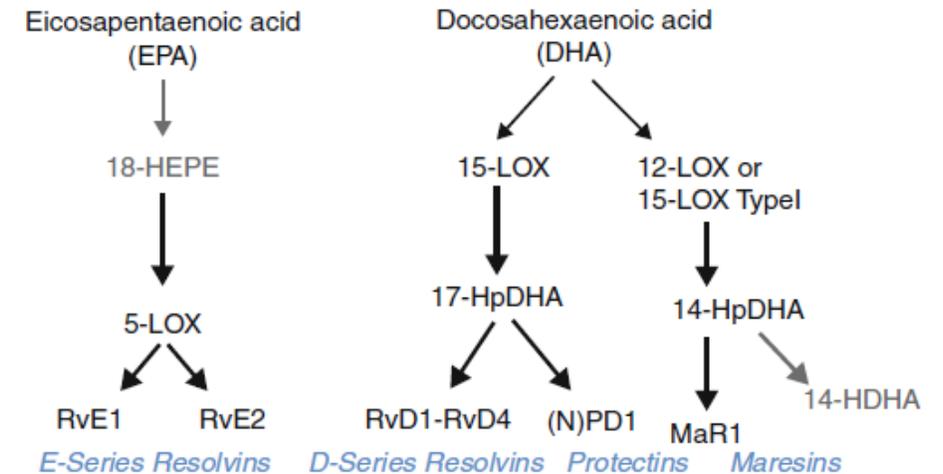
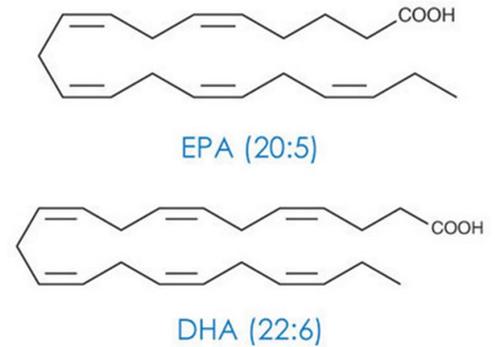


Why not use supplements for high TG?

- Supplement concentrations and serving size varies; patients get the dosing wrong even with training
- Potential for a sub-standard product to be sold (FDA regulates supplements post-marketing) or product with additional ingredients that could introduce negative health effects at high doses long-term
- Prescription agents standardized to exact specifications—clinicians can be assured patients receiving exactly what they intend
- Prescription more pragmatic and safest long term solution for patients, insurance should cover

EPA vs DHA effects?

- Lipids and lipoproteins
- Blood pressure / vascular effects
- Arrhythmia risk
- Inflammation



Takeaways: Effects of n-3 FA for Managing TG

TG 200 – 499 mg/dL	20-30% reduction in TG and no LDL-C increase with 4 g/d prescription n-3 FA
TG ≥ 500 mg/dL	≥ 30% reduction in TG with 4 g/d prescription n-3 FA, LDL-C increase with DHA-containing agents
Children/adolescents	Apparently safe, but more research needed to further evaluate efficacy
Use with other lipid therapy	Safe and apparently additive TG-reduction with statin therapy. Apparently safe with fibrates or niacin, but more research needed to evaluate efficacy
Prescription n-3 FA agent	Based on available data, all prescription agents appear comparably effective, but head-to-head comparisons are lacking

Beyond Lipids— Evidence from Recent Outcome Trials

**VITAL: 840 mg/d EPA + DHA for 5 years in
25,871 older adults (primary prevention)**

- Risk for heart attack decreased 28%
- Risk for total coronary heart disease decreased by 17%
- Risk for primary composite endpoint decreased significantly in low fish consumers in secondary analyses (overall risk for primary composite endpoint not significant)

**REDUCE-IT: 3600 mg/d EPA for 5 years
in 8,179 people with HTG taking statin**

- Risk of composite endpoint decreased by 25%

Food
(*as well as
supplements
and drugs*) for
thought

VITAL results indicated that people who eat < 1.5 serving/week of oily fish could benefit from lower doses of n-3 FA

REDUCE-IT results showed benefit of treating HTG with 4 g/d prescription agent (3.6 g/d EPA-only)

- People were recruited based on fasting TG
- First outcomes trial to administer 4 g/d concentrate (> 3 g/d EPA + DHA)
- Is presence of HTG the defining characteristic of people who most benefit from n-3?
- Would this dose benefit other populations if administered longer term?

Manson et al. NEJM 2009 380(1):23-32

Bhatt et al. NEJM 2019. 380(1):11-22



Happy to take questions during our panel discussion

