The Impact of the Omega-6 : Omega-3 Balance on Cardiovascular Health

Scientific Evidence for Prevention and Optimization of Cardiological Outcomes

Presentation for a Panel of Cardiologists

Based on Randomized Clinical Trials, Meta-Analyses and Cohort Studies

Agenda

The Omega-6 : Omega-3 Ratio

OMEGA-6 (Arachidonic Acid)

Precursor of PRO-inflammatory eicosanoids:

PGE_2 → vasoconstriction, platelet aggregation
LTB_4 → neutrophil recruitment, inflammation
TXA_2 → thrombosis, vascular spasm

Activates NF-κB → endothelial dysfunction
Increases COX-2 → atherosclerotic progression

OMEGA-3 (EPA + DHA)

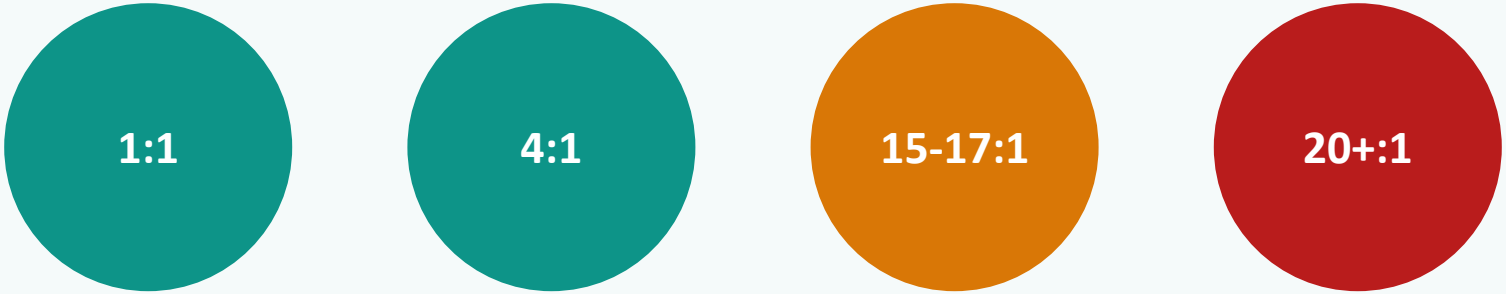
Precursor of ANTI-inflammatory mediators:

Resolvins (RvE1, RvD1) → active resolution
Protectins (PD1) → cardiac neuroprotection
Maresins (MaR1) → tissue repair

Inhibits NF-κB → endothelial protection
Reduces COX-2 → plaque stabilization

The RATIO determines the balance between thrombosis and protection, inflammation and resolution — a critical factor in cardiovascular prevention

The Evolution of the Ratio in the Modern Diet



The Cardiovascular Context

Simopoulos (2002/2008): A ratio of 4:1 was associated with a 70% reduction in total mortality in secondary cardiovascular prevention (Lyon Diet Heart Study).

The current Western diet (15-17:1) promotes CVD pathogenesis through activation of inflammatory pathways, platelet aggregation, vasoconstriction and endothelial dysfunction.

Cardiac patients frequently present ratios >20:1 due to excessive consumption of processed vegetable oils (sunflower, soy, corn) and scarcity of EPA+DHA in the diet.

The Omega-3 Index: A New CV Risk Factor

Harris & von Schacky (2004): EPA+DHA in erythrocytes as a validated cardiac risk biomarker

≤4%

HIGH RISK

High-risk zone for coronary death and sudden cardiac death

4-8%

INTERMEDIATE RISK

Transition zone — progressive benefit with increasing index

≥8%

LOW RISK

Maximum cardioprotection
Recommended therapeutic target for cardiac patients

Meta-analysis of 10 cohorts (Harris et al. 2017): Moving from O3I 4% to 8% → ~30% reduction in coronary death risk. The O3I compares favorably with other risk factors for sudden cardiac death. Only statins and omega-3 demonstrated significant reduction in total mortality across 97 studies analyzed (Studer et al. 2005).

RATIO ≥ 15:1

The Pro-Atherogenic and Pro-Thrombotic Environment

Evidence across 5 critical cardiovascular domains

High Ratio: Atherosclerosis and Endothelial Dysfunction

Pro-Atherogenic Mechanisms

Excess AA → ↑ PGE_2 and LTB_4 → monocyte recruitment to the arterial intima

↑ NF-κB → expression of VCAM-1, ICAM-1 and MCP-1 → leukocyte adhesion to endothelium

↑ OXLAMs (oxidized metabolites of LA) → inflammatory activation 50× more abundant than AA metabolites

↓ NO bioavailability → vasoconstriction, ↑ blood pressure, endothelial dysfunction

↑ LDL oxidation → foam cell formation → plaque necrotic core

Evidence

Animal model (apoE-/-/LDLR-/-): Variation of n-6/n-3 ratio in diet altered thrombosis tendency and atherosclerosis progression (Yamashita et al. 2005).

DiNicolantonio & O'Keefe (2018): A high ratio promotes low-grade vascular inflammation, the biochemical substrate of atherosclerosis. OXLAMs activate NF-κB and endothelial adhesion molecules.

UK Biobank (n=85,425): Highest quintile of ω-6/ω-3 ratio → +31% cardiovascular mortality (HR 1.31, 95% CI: 1.10-1.55). Mediated via CRP and inflammatory markers.

Ratio 15-20:1 → lipid and inflammatory profile that promotes all phases of atherosclerosis: initiation, progression and plaque rupture

High Ratio: Thrombosis, Arrhythmia and Hypertension

Thrombosis

- ↑ TXA_2 (derived from AA) → vasoconstriction and platelet aggregation
- ↓ PGI_3 (derived from EPA) → loss of antithrombotic effect
- TXA_2/PGI_3 imbalance → pro-thrombotic state
- Increased risk of AMI and ischemic stroke

Arrhythmia

- ↓ EPA/DHA incorporation in cardiomyocyte membranes
- ↓ Electrical membrane stability
- ↓ Threshold for ventricular arrhythmias
- GISSI: 1g/day EPA+DHA → -45% sudden cardiac death

Hypertension

- ↑ PGE_2 and TXA_2 → systemic vasoconstriction
- ↓ Endothelial NO production
- ↑ Arterial stiffness and peripheral resistance
- Meta-analysis: EPA+DHA reduce systolic BP by 2-5 mmHg

UK Biobank: High Ratio and Mortality

n = 85,425 participants | 6,461 deaths | 1,668 CV deaths | eLife 2024 (PMC9882493)

+26%

Total Mortality

+31%

Cardiovascular Mortality

+14%

Cancer Mortality

Highest vs. lowest quintile of plasma ω-6/ω-3 ratio. All Ptrend < 0.05

Cardiological Relevance

Cardiovascular mortality was the most strongly associated with elevated ratio (+31%). Mediated via CRP (systemic inflammation), SHBG, testosterone and IGF-1. Dose-dependent effects — each increment in the ratio progressively increased CV risk.

WHAT IF WE REDUCE THE RATIO?

Ratio ≤ 3:1 — Evidence-Based Cardioprotection

Cardioprotection Mechanisms with Ratio ≤3:1

Anti-Arrhythmic

EPA/DHA incorporate into cardiomyocyte membranes → stabilize Na^+ and Ca^{2+} channels → ↑ ventricular fibrillation threshold → ↓ sudden cardiac death

Anti-Thrombotic

↑ PGI_3 (vasodilation) and ↓ TXA_2 (aggregation) → favorable hemostatic balance → ↓ platelet aggregation → ↓ coronary thrombosis risk

Anti-Inflammatory

Resolvins and protectins actively resolve inflammation → ↓ TNF-α, IL-6, CRP → ↓ vascular inflammation → atherosclerotic plaque stabilization

Endothelial Function

↑ Endothelial NO (+44%) → vasodilation → ↓ BP → ↑ FMD (flow-mediated dilation) → improved myocardial perfusion

Lipid Profile

↓ Triglycerides (25-30%) → ↑ HDL → ↑ large buoyant LDL particles → ↓ VLDL → ↓ residual risk beyond statins

Cardiac Remodeling

↓ Adverse post-AMI remodeling → ventricular function preservation → ↓ myocardial fibrosis → OMEGA-REMODEL: ↓50% MACE at 6 years

Harris WS. PMC1899522 | von Schacky C. PMC3942733 | Zebrowska et al. EJSS 2015 | OMEGA-REMODEL 2024

Lyon Diet Heart Study — The Study that Changed Everything

RCT | n=605 | Post-AMI | Mediterranean Diet (ratio ~4:1) vs. Prudent Western Diet | 46 months

-70%

Recurrent Non-Fatal AMI

14 vs 44 events

-65%

Cardiovascular Death

HR 0.35 (0.15-0.82)

-56%

Total Mortality

HR 0.44 (0.21-0.92)

Clinical Implications

The study was stopped early by the ethics committee — it was considered unethical to keep the control group without access to the protective diet. The reduction was achieved WITHOUT significant changes in cholesterol levels — demonstrating that the mechanism goes well beyond the lipid profile. The AHA classified the study as evidence that ω-3 are cardioprotective through multiple mechanisms: anti-arrhythmic, anti-inflammatory, anti-thrombotic, vasodilator (NO) and anti-atherosclerotic.

de Lorgeril M et al. Circulation 1999;99:779-785 | Kris-Etherton P et al. Circulation 2001;103:1823

GISSI-Prevenzione: Omega-3 and Sudden Death

RCT | n=11,324 | Post-AMI (<3 months) | 1g/day EPA+DHA vs. Control | 3.5 years | Lancet 1999

-20%

Total Mortality

Reduction of all causes of death

-30%

Cardiac Death

Reduction of death from cardiac causes

-45%

Sudden Cardiac Death

The most striking effect of the study

The 45% reduction in sudden cardiac death with just 1g/day of EPA+DHA was the largest observed effect.

The benefit appeared within the first 3 months and was maintained throughout follow-up.

Based on this study, the AHA began recommending ~1g/day EPA+DHA for secondary prevention.

GISSI-Prevenzione Investigators. Lancet 1999;354:447-455

REDUCE-IT: Pure EPA and Cardiovascular Events

Double-blind RCT | n=8,179 | Icosapent ethyl 4g/day vs. Placebo | Median 4.9 years | NEJM 2019

Placebo

22.0%

Primary CV Events

P < 0.00001

Icosapent Ethyl

17.2%

Primary CV Events

-25% CV events | -20% CV death | -26% CV death + AMI + stroke | NNT = 21 in 4.9 years

"This may be the greatest advance in secondary cardiovascular prevention since statins."

— Dr. Deepak Bhatt, Brigham and Women's Hospital

First study to show benefit on CV death with non-statin lipid therapy in the statin era.

Bhatt DL et al. N Engl J Med 2019;380:11-22

OMEGA-REMODEL and Cardiovascular Parameters

OMEGA-REMODEL (2024)

Double-blind RCT post-acute AMI.
3.36g/day EPA+DHA × 6 months.
Median follow-up of 6.6 years.

Patients who achieved ↑O3I ≥5%:

MACE rate: 2.9% vs. 7.1% in controls.

Reduction of >50% in major adverse cardiac event risk long-term — when the Omega-3 Index responded to treatment.

Parameters Improved by O3I

Increasing the Omega-3 Index in RCTs improved:

- ↓ Resting heart rate
- ↑ Heart rate variability (vagal marker)
- ↓ Systolic and diastolic blood pressure
- ↓ Platelet reactivity
- ↓ Triglycerides
- ↑ Large LDL particles (less atherogenic)
- ↓ VLDL
- ↓ Pro-inflammatory cytokines (TNF-α, IL-6, IL-1β)
- ↑ Anti-inflammatory oxylipins

Key message: The benefit depends on ACHIEVING an Omega-3 Index ≥8% — not just taking a supplement. Measuring is essential.

von Schacky C. PMC3942733 | OMEGA-REMODEL 2024 (PubMed Int J Cardiol)

Direct Comparison: Ratio ≥15:1 vs. ≤3:1

Domain	Ratio ≥15:1	Ratio ≤3:1
Endothelium	Endothelial dysfunction, ↓NO, ↑VCAM-1	↑NO (+44%), ↑FMD, endothelial protection
Atherosclerosis	Plaque progression, ↑ox-LDL, instability	Plaque stabilization, ↓vascular inflammation
Thrombosis	↑TXA_2, ↑platelet aggregation	↑PGI_3, ↓aggregation, hemostatic balance
Arrhythmia	Membrane instability, ↑SCD risk	Ion channel stabilization, ↓45% SCD
Blood Pressure	↑BP (vasoconstriction, ↓NO)	↓Systolic BP 2-5 mmHg
Triglycerides	↑TG, ↑VLDL, atherogenic profile	↓TG 25-30%, ↑HDL, ↑large LDL
Inflammation	↑CRP, IL-6, TNF-α chronic	↓CRP/IL-6, ↑resolvins/protectins
CV Mortality	+31% (UK Biobank)	-65% CV death (Lyon), -20% (REDUCE-IT)

Clinical Scenario: Same Patient, Two Ratios

Male, 58 years, post-AMI, on statin, controlled hypertension, TG 210 mg/dL

RATIO 20:1 | O3I = 3.8%

- Chronic vascular inflammation (elevated CRP)
- Endothelial dysfunction, ↓NO, ↑BP
- Atherogenic lipid profile (TG↑, dense LDL)
- Pro-thrombotic state (TXA_2 dominant)
- Electrical instability → arrhythmia risk
- Adverse post-AMI remodeling
- Significant residual risk despite statin
- Risk of new CV event: HIGH

Prognosis: Uncontrolled residual risk

RATIO ≤3:1 | O3I = 8-10%

- Inflammation resolved (active resolvins)
- Optimized endothelial function, ↑NO, ↓BP
- TG reduced 25-30%, improved HDL
- Hemostatic balance (PGI_3 dominant)
- Stabilized membranes → arrhythmic protection
- Attenuated remodeling, preserved LV function
- Significantly reduced residual risk
- Risk of new CV event: REDUCED

Prognosis: Complementary cardioprotection

Protocol: Measure, Correct, Monitor

1. MEASURE

Request the dried blood fatty acid test (BalanceTest) to determine the patient's Omega-3 Index and ω-6:ω-3 ratio. Essential baseline before any intervention.

2. CORRECT

Supplementation with high-bioavailability EPA+DHA with polyphenols (BalanceOil+). Dose adjusted to body weight (~0.15ml/kg). Simultaneous reduction of processed vegetable oils (sunflower, soy, corn). Mediterranean-type anti-inflammatory diet.

3. MONITOR

Retest at 120 days to assess membrane incorporation. Target: Omega-3 Index ≥8% and ω-6:ω-3 ratio ≤3:1. Adjust dose if necessary. The test is the differentiator — it transforms supplementation into a measurable intervention.

Dose: 1-2g EPA+DHA/day (primary prevention) | ≥2g/day (secondary prevention, HiTG) | EFSA: safe up to 5g/day

Safety and International Recommendations

Safety Profile

GISSI, Lyon, REDUCE-IT: no increase in serious adverse effects in ω-3 groups

EFSA: EPA+DHA safe up to 5g/day

No clinically significant interaction with anticoagulants at tested doses

No increase in hemorrhage in multiple RCTs

Note: doses >3g/day of pure EPA associated with slight increase in AF in some studies — monitor in susceptible patients

Official Recommendations

AHA: ~1g/day EPA+DHA for secondary CHD prevention

ESC/EAS 2019: ω-3 (EPA 2×2g/day) recommended for HiTG (Class IIa)

ACC 2019: icosapent ethyl for residual CV risk reduction in HiTG

Omega-3 Index ≥8%: proposed as therapeutic target (Harris & von Schacky 2004)

Bioavailability matters: triglycerides > ethyl esters; taking with a fatty meal increases absorption up to 13×

Studer et al. (97 studies): Only statins and omega-3 demonstrated significant reduction in total mortality

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Conclusion

Regulating the omega-6:omega-3 balance to ≤3:1 is an evidence-based complementary intervention with the potential to:

- Reduce cardiovascular mortality by up to 65% (Lyon) and CV events by 25% (REDUCE-IT)
- Decrease sudden cardiac death by 45% (GISSI-Prevenzione)
- Improve endothelial function, lipid profile and blood pressure
- Stabilize atherosclerotic plaque and reduce vascular inflammation
- Attenuate adverse cardiac remodeling post-AMI
- Reduce residual cardiovascular risk beyond statins

THE FIRST STEP: MEASURE THE PATIENT'S RATIO AND OMEGA-3 INDEX

Once you know the number, the intervention becomes personalized, measurable and verifiable every 120 days.