Icosapent ethyl

Potential mechanisms of benefit

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Disclosures

Grants/ honoraria from Amarin, Amgen, Daiichi-Sankyo, Dalcor, Novartis, Pfizer.

Possible pathways to benefit

Insights from REDUCE-IT and STRENGTH

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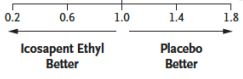
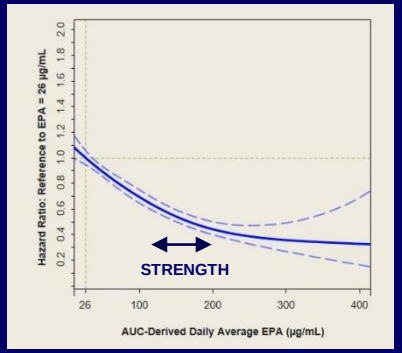
Subgroup	Icosapent Ethyl	Placebo	Hazard Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
Diabetes at baseline				0.56
Yes	433/2394 (18.1)	536/2393 (22.4)	0.77 (0.68–0.87)	
No	272/1695 (16.0)	365/1694 (21.5)	0.73 (0.62–0.85)	
Baseline estimated GFR				0.41
<60 ml/min/1.73 m²	197/905 (21.8)	263/911 (28.9)	0.71 (0.59–0.85)	
≥60 to <90 ml/min/1.73 m²	380/2217 (17.1)	468/2238 (20.9)	0.80 (0.70–0.92)	
≥90 ml/min/1.73 m²	128/963 (13.3)	170/939 (18.1)	0.70 (0.56–0.89)	
Baseline triglycerides				0.45
≥200 mg/dl	430/2481 (17.3)	559/2469 (22.6)	0.73 (0.64–0.83)	
<200 mg/dl	275/1605 (17.1)	342/1620 (21.1)	0.79 (0.67–0.93)	
Baseline triglycerides				0.83
≥150 mg/dl	640/3674 (17.4)	811/3660 (22.2)	0.75 (0.68–0.83)	
<150 mg/dl	65/412 (15.8)	90/429 (21.0)	0.79 (0.57–1.09)	
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl				0.04
Yes	149/823 (18.1)	214/794 (27.0)	0.62 (0.51–0.77)	
No	554/3258 (17.0)	687/3293 (20.9)	0.79 (0.71–0.88)	
Baseline statin intensity				0.12
High	232/1290 (18.0)	310/1226 (25.3)	0.69 (0.58–0.82)	
Moderate	424/2533 (16.7)	543/2575 (21.1)	0.76 (0.67–0.86)	
Low	48/254 (18.9)	45/267 (16.9)	1.12 (0.74–1.69)	
Baseline LDL cholesterol (derived) in thirds				0.62
≤67 mg/dl	244/1481 (16.5)	302/1386 (21.8)	0.72 (0.61–0.85)	
>67 to ≤84 mg/dl	248/1347 (18.4)	307/1364 (22.5)	0.81 (0.68–0.96)	
>84 mg/dl	213/1258 (16.9)	292/1339 (21.8)	0.74 (0.62–0.89)	
Baseline high-sensitivity CRP				0.07
≤2 mg/liter	288/1919 (15.0)	407/1942 (21.0)	0.68 (0.58–0.79)	
>2 mg/liter	417/2167 (19.2)	494/2147 (23.0)	0.81 (0.71–0.93)	



1. Risk reduction not related to baseline TG or reduction in TG

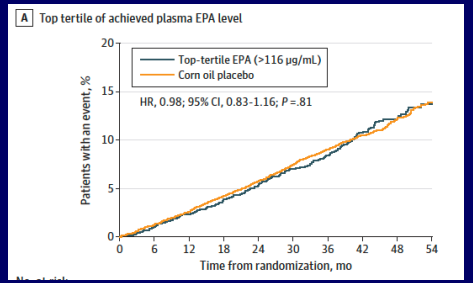


Bhatt DL Presented at ACC/WCC 2020

2. Association of risk reduction with achieved EPA level in REDUCE-IT

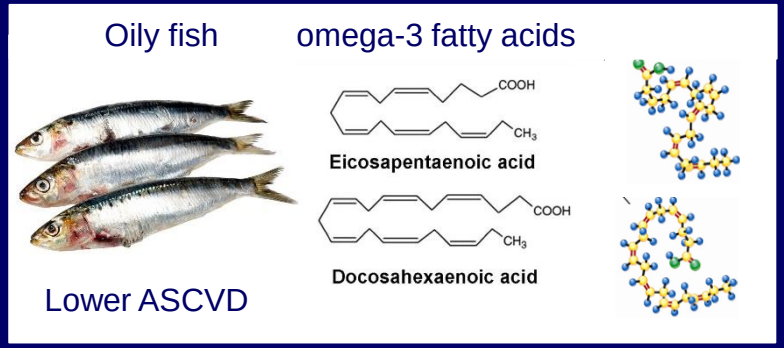
Bhatt et al NEJM (2019) 380:11-22.

3. No association of high achieved EPA levels with risk reduction in STRENGTH (concomitant increased DHA).



Nissen et al JAMA Cardiol (2021) 6:1-8.
Nicholls et al JAMA (2020) 324:2268-80

Potential mechanisms of icosapent ethyl action



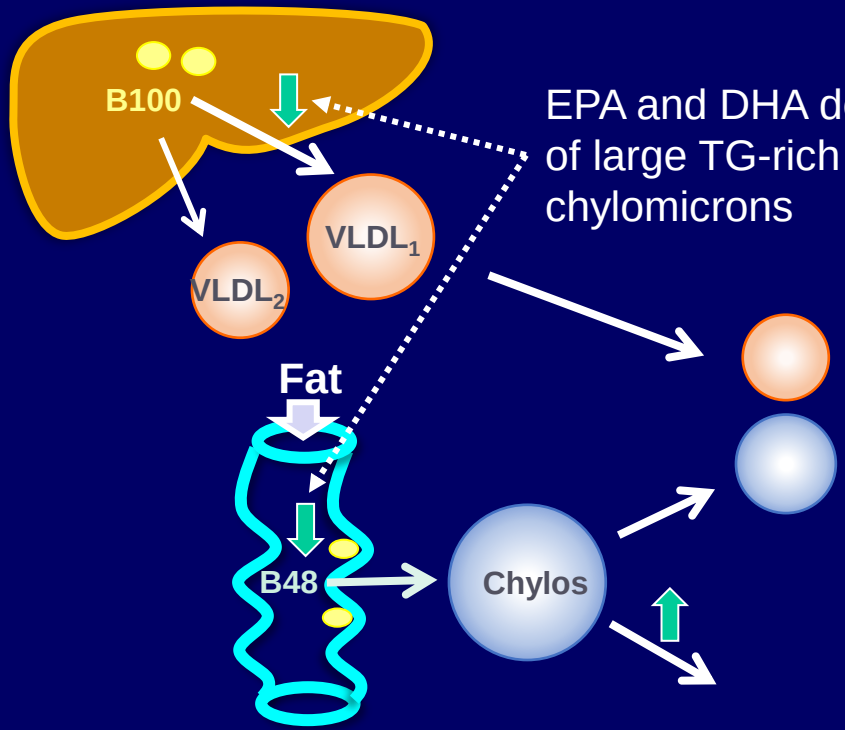
active agents

- lipid metabolism
- inflammation
- clotting
- prostaglandins
- oxidation etc.

- Action in the intestine and liver on the assembly and secretion of chylomicrons and VLDL.
- Alterations in plasma lipid profile - LDL, HDL, remnant lipoproteins.
- Anti-inflammatory/anti-thrombotic effects of EPA in the artery wall.
- Perturbations in cell membrane cholesterol metabolism.

Potential mechanisms of icosapent ethyl action

Focus on lipoprotein synthesis



EPA and DHA decrease production of large TG-rich VLDL and chylomicrons

REDUCE-IT
TG Baseline 217mg/dl
TG change *-18.3%*

STRENGTH
TG Baseline 240mg/dl
TG change *-19.0%*

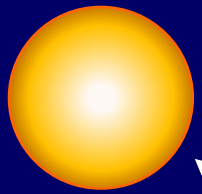
Dose dependent decreased numbers of
- apoB48-chylomicron and remnants
- apoB100-VLDL and remnants

In the circulation

Chan et al (2016) JCEM 101:3732-39

Potential mechanisms of icosapent ethyl action
Focus on plasma lipoproteins

Chylo/VLDL remnants



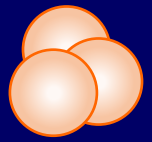
Largest VLDL particles 42% ↓
Remnant (RLP) –Cholesterol 25-30%[1] ↓

Atherogenic properties
Partial lipolysis products
High chol/apoB ratio
Decreased particle lipid fluidity

REDUCE-IT Non-HDL-C -3.6%, LDL-C *+3%, HDL-C -1.2%*

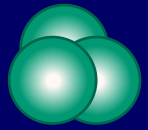
STRENGTH Non-HDL-C -6.1%, LDL-C *+1.2%, HDL-C +5%*

LDL



LDL-C/ LDL particles → or ↗ ← *DHA>EPA*[2]

HDL



HDL-C/ HDL particles → or ↗

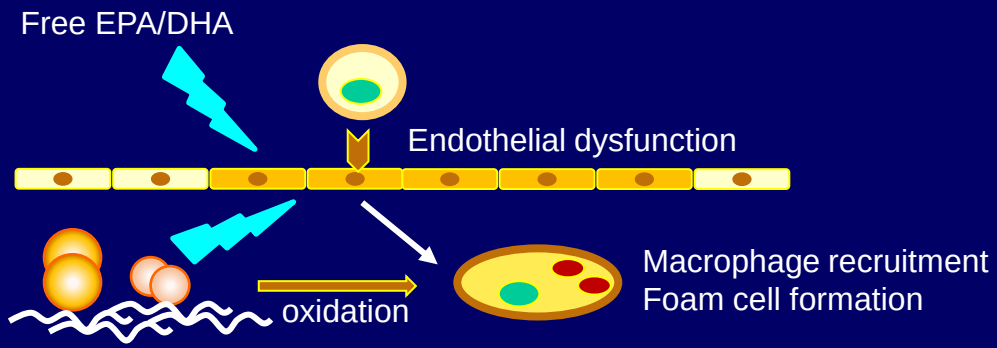
[1]MARINE /ANCHOR trials with EPA 4g/d
Ballantyne et al (2016) Atherosclerosis 253:81-87
Ballantyne et al (2015) J Clin Lipidol 9:377-383
[2]Olano-artin et al (2010) Atherosclerosis 209:104-110

Potential mechanisms of icosapent ethyl action

Focus on chronic inflammation

EPA/DHA

- Pro-/anti- inflammatory mediators
  (Increased EPA/AA ratio generates anti-inflammatory mediators/resolvins)
- Remnant/ LDL particle oxidation
  (anti-oxidant EPA>DHA)



REDUCE-IT
20% decrease in CRP on EPA,
32% increase in CRP on placebo
No interaction CRP x RRR

STRENGTH
No change in CRP

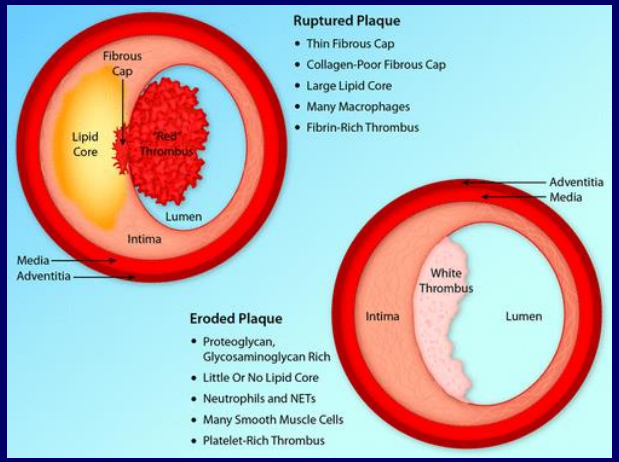
Bhatt et al NEJM (2019) 380:11-22.
Nicholls et al JAMA (2020) 324:2268-80
Nelson JR et al, Postgrad Med 2021
Mason et al ATVB 2020.40:1135-47

Potential mechanisms of icosapent ethyl action
Focus on atherothrombosis

EPA (DHA)

Metabolised by cyclooxygenase to prostaglandins (PGI_3) that have antiaggregatory and vasodilation effects.

Anti-coagulation action
Reduced thrombus size

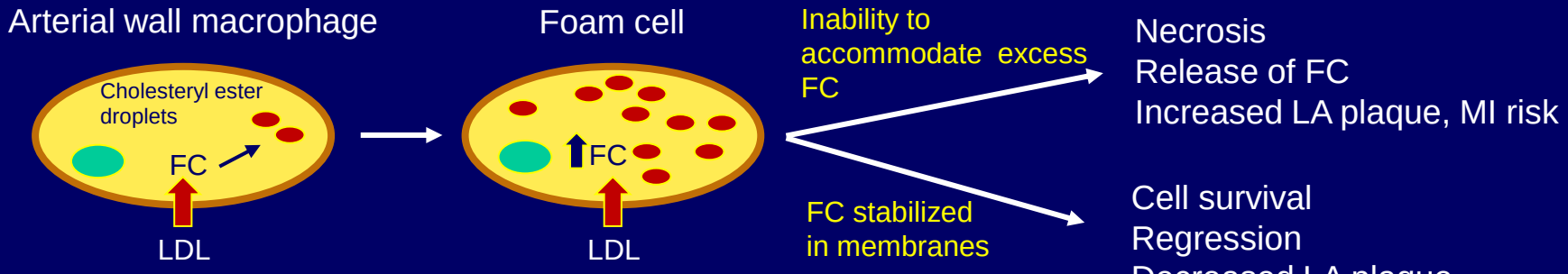


Libby et al Circ Res (2019) 124:150-160

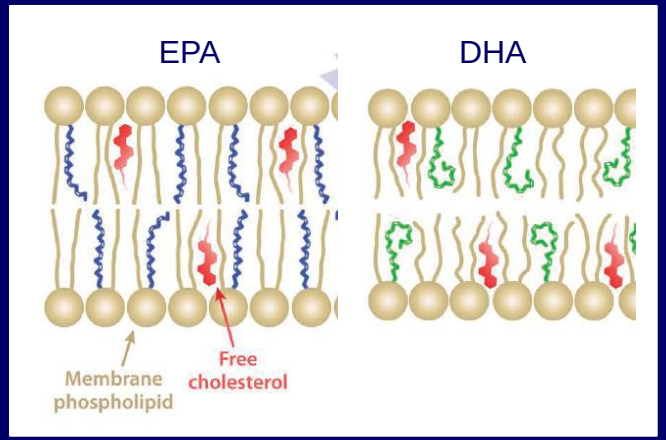
REDUCE-IT
Serious adverse events linked to bleeding higher on EPA (2.7% vs 2.1%, P=0.06).
No difference in haemorrhagic stroke.
STRENGTH
No difference in adverse bleeding event.
No difference in stent thrombosis
MESA[2]
Lower rates of major incident bleeding on EPA or EPA/DHA

[1]Mason et al ATVB (2020);40:1135-47.
Harris WS Am J Cardiol 2007;**99**:S44–S46
[2]Kapoor et al JAHA (2021) 10:e021431

Potential mechanisms of icosapent ethyl action
Focus on cell membrane cholesterol



In model systems:
EPA stabilizes lipid/cholesterol membrane rafts
EPA inhibits cholesterol domain formation
DHA does not[1].



- Critical macrophage transition from foam cell to necrotic/ inflammatory cell is membrane cholesterol-load dependent [2].
- Low attenuation plaque (LAP) has a large lipid rich, necrotic core.

[1]Mason et al ATVB 2020.40:1135-47.
[2]Tabas, I J Clin Invest, 2002. 110: 905-11.
[3] EVAPORATE trial – Budoff et al EHJ (2020) 311:30-36

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