*Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.*

# EPA

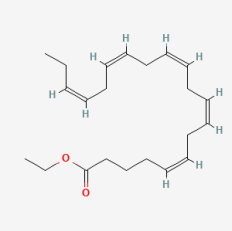
**Evidence Summary**

Recent studies of prescription EPA have indicated a potentially large cardiovascular benefit. However, the direct neuroprotective effect is unclear. Serious side effects include atrial fibrillation.

**Neuroprotective Benefit:** No benefit of omega-3 fatty acids has been shown in large analyses. However, no large trials that tested high doses of EPA or differentiated between omega-3s were found, so the effect of EPA itself on neuroprotection is unclear.

**Aging and related health concerns:** Clinical studies show that EPA effectively lowers triglyceride levels and lowers risk of cardiovascular events, including stroke.

**Safety:** Recent studies have repeatedly found an increased risk of atrial fibrillation. Studies have also reported increased risk of bleeding events, gastrointestinal effects, prostate cancer, and edema.

| | | |
|---|---|---|
| **Availability**: Rx | **Dose**: 4 grams daily, either as two 1-gram pills twice daily, or four 0.5-gram pills twice daily | **Chemical formula**: $C_{22}H_{34}O_2$<br>**MW**: 330.5<br>  <br>Source: PubChem |
| **Half-life**: 89 hours | **BBB**: Penetrant | |
| **Clinical trials**:<br>Largest meta-analysis of RCTs included 162,796 patients | **Observational studies**:<br>Numerous observational studies have included more than 100,000 people | |

**What is it?**

Eicosapentaenoic acid (EPA) is an omega-3 fatty acid derived from alpha-linolenic acid (ALA). Highly purified prescription forms of eicosapentaenoic acid are known as icosapent ethyl; Vascepa is one brand-name icosapent ethyl. Two other omega-3 fatty acids derived from ALA include docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA). These serve as precursors to bioactive lipid mediators such as eicosanoids, prostaglandins, leukotrienes, protectins, and resolvins. Omega-3 and omega-6 polyunsaturated fatty acids (PUFA) have opposing effects on metabolic function in the body. Omega-6 PUFAs are generally considered pro-inflammatory through the action of the omega-6 PUFA arachidonic acid (AA). Omega-3 PUFAs are generally considered anti-inflammatory with beneficial effects on cardiovascular disease and brain health.

The body cannot produce omega-3 and omega-6 PUFAs; thus, they must be obtained through diet. Foods such as flax seed, green leafy vegetables, and salmon (esp. freshwater salmon) are good sources of omega-3 PUFAs while foods such as soybean and corn are sources of omega-6 PUFAs. The recommended dietary ratio of omega-6/omega-3 PUFAs is 1:1-2:1, though typical Western diets contain ratios of 15:1-17:1 (Saini and Keum, 2018).

While the nomenclature is not always consistent in the literature, omega-3 fatty acids is often used as an umbrella term, particularly when the formulation in question is of a mix of ALA, EPA, DHA, and/or DPA. EPA is a general term for eicosapentaenoic acid (dietary, supplement, clinical trial, prescription, or

otherwise), whereas icosapent ethyl (IPE) is specifically used for the highly purified formulations of EPA available by prescription; Vascepa is the brand name of one IPE (See 'Sources and Dosing' for more information). Where possible, this report will specify what formulation each study tested.

**Neuroprotective Benefit:** No benefit of omega-3 fatty acids has been shown in large analyses. However, no large trials that tested high doses of EPA or differentiated between omega-3s were found, so the effect of EPA itself on neuroprotection is unclear.

*Types of evidence:*

- 2 Cochrane meta-analyses
- 3 meta-analyses and systematic reviews
- 6 randomized-controlled trials
- 8 epidemiological studies for risk of dementia, cognitive decline, or brain imaging
- 1 pilot open-label study in dementia patients
- 3 reviews
- 2 experimental studies using samples from patients

***Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function***:

- Samieri et al., 2008 – Four-year prospective cohort in 1214 cognitively normal individuals: high levels of EPA reduced the risk of dementia, even after controlling for factors such as age, education, ApoE status, etc. High levels of DHA did not reduce the risk of dementia in fully adjusted models (although DHA/AA ratio did). Low EPA levels were associated with dementia risk even after controlling for depressive status.
- Yagi et al., 2014 – In CAD patients (avg age 71): serum EPA and EPA/AA ratio, but not DHA, were positively associated with MMSE scores (suggesting that lower EPA was associated with lower cognition). However, the data suggests that it may be driven by some outliers with the lowest levels of EPA (see figure right).
- Nagai et al., 2015 – In 150 individuals (avg age 80 with avg MMSE to suggest mild-dementia): low serum EPA/AA ratio, but not serum DHA, was associated with increased periventricular white matter hyperintensities (even after controlling for age, sex, and vascular risk factors) but was not significantly associated with deep white matter hyperintensities.

- Suwa et al., 2015 – In 286 cognitively normal individuals with at least 1 atherosclerotic risk factor: age, the presence of internal carotid plaques, and an EPA/AA ratio < 0.38 (but not DHA/AA ratio) was associated with a greater burden of deep white matter hyperintensities.
- Ammann et al., 2017 – The Women's Health Initiative Study (a trial on estrogen replacement in post-menopausal women) (n=6706; 9.8-year average follow up): red blood cell (RBC) DHA+EPA one SD above the mean compared to one SD below the mean was associated with a decreased risk of probable dementia (**HR = 0.91; 95%CI 0.83-0.99**). Risk of MCI was slightly attenuated and non-significant. The cumulative incidence of probable dementia over 15 years was 12.1% in the highest DHA+EPA group and 14.2% in the lowest DHA+EPA group. RBC DHA and EPA individually were associated with a similar decreased risk of incident dementia but were not significant.
- Otsuka et al., 2014 – High levels of serum DHA (but not EPA) was associated with a reduced risk of cognitive decline (though EPA had large CI's, EPA **HR = 0.52; 95%CI 0.08-3.24**).
- Brainard et al., 2020 is a Cochrane systematic review and meta-analysis of RCTs that compared lower or higher intake of fatty acids, including omega-3s, and their effect on cognition. The intake could be through dietary advice, food, or dietary supplements, and did not differentiate between different omega-3 fatty acids. The authors included 38 RCTs comprising of 49,757 patients. They found no or very little association between intake and new neurocognitive illness, cognitive impairment, or global cognition.
- Patan et al., 2021 described results from 310 healthy young adults who were given either 'EPA-rich oil' (900 mg EPA + 360 mg DHA), 'DHA-rich oil' (900 mg DHA + 270 mg EPA) or placebo (olive oil) for 26 weeks. The study examined cognition, memory consolidation, and prefrontal cortex hemoglobin oxygenation. The authors found that the group taking the EPA-rich formulation performed better than placebo or DHA-rich group on global accuracy and speed on cognition assessments, and that the EPA-rich formulation group had improved accuracy of memory in comparison to the DHA-rich group.
- DM van Lent et al., 2021 performed a prospective analysis of 1,264 non-demented seniors in Germany who were 84 (+/- 3) years old. The study authors followed patients for 7 years and investigated the association of several fatty acids (EPA, DHA, ALA, LA, DGLA, and AA) in serum with all-cause dementia and Alzheimer's disease. They found that higher concentrations of EPA were associated with decreased risk of AD (HR=0.76; 95% CI 0.63 – 0.93).
- Kang et al., 2022 published a substudy named VITAL-COG that included 4,218 participants and tested the effects of vitamin D and/or 1g daily total of EPA+DHA or placebos on cognitive function. The authors did not find any effects of vitamin D and/or the EPA+DHA formulation. This study is currently listed as Active, Not Recruiting on clinicaltrials.gov.

***Human research to suggest benefits to patients with dementia***:

- Lin et al., 2012 – Meta-analysis of 10 studies (cannot be accessed): low levels of EPA and DHA were associated with dementia, but only low EPA was associated with pre-dementia.
- Boston et al., 2004 – Pilot, open-label study in 20 patients over 24 weeks reported that ethyl-EPA (500mg bid) had no effect on cognition.
- Freund Levi et al., 2014 – EPA was shown to cross the blood brain barrier.
- Burckhardt et al., 2016 is a Cochrane meta-analysis and systematic review of RCTs that ran for at least 26 weeks that assess the efficacy and safety of omega-3 supplementation on patients with dementia. The authors found and analyzed three studies that included 632 patients, all of which had a placebo group and a group that took capsular omega-3s. The authors found no effect of omega-3s on cognitive function when measured at 6 months. They also did not find any difference in adverse effects between the placebo and treatment groups. The three studies all used different doses and mixtures of omega-3s, and no study administered more than 1g/daily of EPA.

***Mechanisms of action for neuroprotection identified from laboratory and clinical research***:

In an *in vitro* study of PBMCs stimulated by phytohaemagglutinin (PHA), PBMCs from Alzheimer's patients release more inflammatory cytokines than those from healthy controls. Although DHA reduced the release of individual cytokines more than EPA, EPA's reduced inflammatory profile was more similar to PBMCs from healthy controls (Serini et al, 2012).

The exact mechanism of action for how EPA may exert a neuroprotective role is unclear. EPA may reduce cardiovascular risks such as stroke, which then may in turn reduce neurological risk factors. EPA is incorporated into neuronal cell membranes (albeit at a significantly lower extent than DHA), and lipid metabolites of EPA have anti-inflammatory roles. EPA and its metabolites are also agonists of PPARγ, a transcription factor with numerous gene targets involved in activities like glucose and lipid metabolism and modulation of inflammation (reviewed in Dyall 2015).

***APOE4 interactions***:

Uncertain. There is a theoretical basis for differential effects in APOE4 carriers, as APOE4 is involved in lipid transport. It is possible that E4 carriers would have different levels of blood or brain EPA, and/or respond differently to supplementation. This hypothesis has not been rigorously explored in large trials,

and results thus far have been mixed, with some studies finding responses to supplementation only in carriers or only in non-carriers (partly reviewed in Dyall 2015, reviewed more thoroughly Barberger-Gateau et al., 2011).

**Aging and related health concerns:** Clinical studies show that EPA effectively lowers triglyceride levels and lowers risk of cardiovascular events, including stroke.

*Types of evidence:*

- 3 Cochrane meta-analyses
- 4 meta-analyses
- 9 randomized controlled trials
- 13 epidemiological studies for levels of EPA for CVD
- 1 epidemiological study of EPA for mortality and aging
- 3 reviews
- 1 population database modeling paper
- 6 commentary, letters, or editorials
- 4 conference presentations

***Mortality*:** POTENTIAL BENEFIT THROUGH DECREASED CARDIOVASCULAR **EVENTS (See cardiovascular section for further information)**

- Lai et al., 2018 – Longitudinal study of 2622 individuals (avg age 74 at baseline) over 22 years: higher levels of EPA (but not DHA) were associated with a decreased risk of unhealthy aging (**HR = 0.76; 95%CI 0.65-0.85**) (Figure below). Healthy aging was defined as survival without CVD, cancer, lung disease, severe chronic kidney disease, absence of cognitive dysfunction, and physical dysfunction. Over time 89% of all individuals experienced unhealthy aging while 11% experienced healthy aging.
- Chen et al., 2016 – Meta-analysis of 3 studies: Increased serum EPA levels were associated with a decreased risk of all-cause mortality (**RR = 0.83; 95%CI 0.75-0.92**). Each 1% increment in the proportion of circulating EPA was associated with a decreased risk of mortality (**RR = 0.80; 95%CI 0.65-0.98**).

***Cardiovascular Health*:** POTENTIAL BENEFIT

- Urabe et al., 2013 – Enrolled 172 patients and split them into groups above and below median EPA level (61.3ug/ml): individuals in the low-EPA group had a higher incidence of 3-vessel plaques (**62% vs. 43%**), noncalcified plaques (NCPs) (**74% vs. 52%**), more extensive NCPs (>2 segments) (**56% vs. 34%**), and high-risk plaques (**42% vs. 22%**). However, there were no differences in significant stenosis, any type of coronary plaque, or calcified plaques. Low EPA was an independent predictor for coronary plaque findings.
- Harris et al., 2013 – Enrolled 1144 patients with a myocardial infarction and measured RBC levels of 20 fatty acids: only three predicted 2-year mortality (EPA, DPA, DGLA). After adjusting for GRACE scores (a score that predicts mortality in MI patients), those in the lowest tertile of EPA levels had a greater risk of death over two years (**HR = 3.71; 95%CI 1.81-7.61**).
- Bargallo et al., 2017 – From the PREDIMED study: RBC EPA levels were not associated with the presence or size of atherosclerotic plaques. However, RBC EPA levels were inversely associated with plaque lipid burden, a marker of plaque instability. Plaque lipid burden did not correlate with DHA, ALA, or AA levels. They suggest this supports the notion that EPA may not prevent plaque formation in the presence of other risk factors but may reduce plaque vulnerability.
- Chien et al., 2013 – Community-based cohort study of 1833 participants: comparing the top quartile of plasma EPA to the bottom quartile was associated with a decreased risk of CVD or all-cause mortality (**RR = 0.77; 95%CI 0.59-1.00**).
- Del Gobbo et al., 2016 – Meta-analysis of 19 studies (none of the studies mentioned previously); each SD increase in EPA was associated with a decreased risk of fatal CHD (**RR = 0.91; 95%CI 0.82-1.00**) but not non-fatal MI. Comparing the top quintile of EPA to the bottom quintile was associated with a reduced risk of nonfatal MI (**RR = 0.71; 95%CI 0.56-0.90**). These studies used phospholipid, total plasma, adipose tissue, and cholesterol ester measures, with the greatest association seen in phospholipid measure.
- Abdelhamid et al., 2018 – A Cochrane meta-analysis reviewed 79 RCTs > 12 months in length for potential effects of omega-3 fatty acids supplements (both DHA and EPA) on mortality and cardiovascular outcomes. They report no effect of omega-3 supplementation on any outcome including all-cause mortality, cardiovascular mortality, and cardiovascular events. Omega-3 supplements did reduce triglyceride levels and increased HDL-c. This meta-analysis included all omega-3 studies (DHA and EPA) and other methods to increase omega-3s (such as diet)
- Abdelhamid et al., 2020 – The authors published an update to this meta-analysis in 2020. The update included a total of 86 trials encompassing 162,796 patients. As before, the authors included any omega-3 supplementation and dosage in their meta-analysis, whether from EPA-only

formulations like Vascepa, formulations with a mix of EPA, DHA, and/or ALA, or from diet. The mixed formulations also varied by precise composition, and the percent EPA, DHA, and/or ALA was different in many studies. Given the studies available for analysis, the authors were not able to run an adequate analysis to parse apart the effects of the different proportions of EPA vs. DHA or another omega-3 fatty acid.

In this updated meta-analysis, they found that taking omega-3 vs placebo may slightly reduce coronary heart disease mortality (RR=0.90; 95% CI 0.81 – 1.00; 127,378 participants; 3598 coronary heart disease deaths in 24 RCTs, low-certainty evidence) and coronary heart disease events (RR=0.91; 95% CI 0.85 – 0.97; 134,116 participants; 8791 people experienced coronary heart disease events in 32 RCTs, low-certainty evidence). Increased consumption of omega-3 fatty acids through diet or supplementation did reduce plasma triglycerides by about 15% (high certainty evidence).

*EPA/AA ratio*

- Ninomiya et al., 2013 – In 3103 community dwelling adults over the age of 40: individuals in the lowest quartile of EPA/AA ratio (< 0.29) with hsCRP > 1mg/L were at increased risk of cardiovascular disease (**HR = 3.84; 95%CI 1.56-9.44**) but not in individuals with hsCRP < 1mg/L. For every decrement of 0.2 EPA/AA ratio there was increasing risk with increased hsCRP (figure right).
- Wakabayashi et al., 2015 – In 59 patients with acute coronary syndrome (ACS): a thin fibrous cap (measured with optical coherence topography) was associated with a lower EPA/AA serum ratio (**0.35 vs. 0.54**), and EPA/AA ratio was an independent predictor of a thin fibrous cap. Additionally, a lower EPA/AA ratio was associated with lipid-rich and ruptured plaques. Similar results were found in patients with stable angina (Hasegawa et al., 2014) and in patients that underwent percutaneous coronary intervention (Nozue et al., 2013).
- Yagi et al., 2015 – Patients admitted to the hospital for acute coronary syndrome under the age of 50 had a lower EPA/AA ratio (**0.17**) than those over the age of 50 (**0.26**).
- Nagahara et al., 2016 – Retrospective study of 193 patients with no known CAD: low EPA/AA ratio (along with smoking and number of vessel disease) was an independent predictor for high-risk plaques on a coronary computed tomography angiography scan (CCTA). Based on the ROC curve, the cut-off value to predict a high-risk plaque was an EPA/AA ratio of **0.3**. Although the EPA/AA ratio was not an independent predictor of future cardiovascular event over a mean 504 days; however, after excluding events that occurred 90 days after the CCTA, the EPA/AA ratio (along with male sex and the presence of high-risk plaques) was a significant predictor of future cardiovascular events (**HR = 0.47; 95%CI 0.31-0.98**).

- Muroya et al., 2018 – In 108 patients with suspected coronary ischemia: EPA/AA ratio was inversely associated with the hyperemic microvascular resistance index (hMVRI – a lower index suggests a positive outcome) and was the only independent predictor of hMVRI when considering traditional cardiovascular risk factors.
- Nishizaki et al., 2014 – In 1119 patients reporting to cardiology department: EPA/AA ratio < 0.33 had a greater probability for having acute coronary syndrome than those with an EPA/AA ratio > 0.55 **(OR = 3.14; 95%CI 1.16-8.49**).

***Prescription EPA Trials***

The first outcomes study for prescription purified EPA was conducted in Japan and published in 2007 (the JELIS trial). Patients with total cholesterol > 251mg/dl were given purified EPA (1800mg daily; Epadel, developed by Mochida Pharmaceuticals), over a background of statin therapy over 4.6 years. There was a reduced risk for the primary endpoint (any coronary event **HR = 0.81; 95%CI 0.69-0.95**; **absolute risk reduction = 0.7%**) with significant benefits for unstable angina, coronary artery bypass graft and non-fatal coronary events with no significant benefit for sudden cardiac death, myocardial infarction, or coronary death. In subgroup analyses of patients for primary or secondary prevention, there were trends for reduced risk of CAD (primary prevention **HR = 0.82; 95%CI 0.63-1.06**; secondary prevention **HR = 0.81; 95%CI 0.66-1.00**). Triglyceride levels decreased **9%** in the EPA group vs. **4%** in the control group (Yokoyama et al., 2007).

Abe et al (2018) reported that in CAD patients, there was a trend toward reduced cardiovascular death in patients taking EPA with an EPA/AA ratio **< 0.4**. Toyama et al (2014) reported that in 80 CAD patients, 5-month treatment with EPA (1800mg/day) improved endothelial dysfunction (flow-mediated dilation – 2.6% at baseline to 3.2% - p<0.05 compared to placebo).

REDUCE-IT was a multi-center double-blind, trial of 8179 patients receiving statins with established cardiovascular disease or diabetes. These patients were at high cardiovascular risk, including stroke. Patients were randomly assigned to receive either placebo (mineral oil) or 4 g/day of icosapent ethyl (Vascepa, Amarin) and followed for a median time of 4.9 years. The primary and secondary endpoints were cardiovascular events, including stroke. Of the patients treated with icosapent ethyl, 17.2% experienced a primary endpoint event compared to 22% of the placebo group patients (HR=0.75; 95% CI, 0.68 – 0.83; P<0.001). The treatment group had lower rates of cardiovascular death (4.3% vs. 5.2%; HR=0.80; 95% CI, 0.66 – 0.98; P=0.03) and trended towards lower rates of total death overall (6.7% vs

7.6%; (HR=0.87; 95% CI, 0.74 – 1.02) (Bhatt et al., 2019). As a result of this study, the American Diabetes Association wrote that icosapent ethyl can be considered for use in patients to reduce cardiovascular risk for those on statins with controlled LDL-C but elevated triglycerides (American Diabetes Association – Standards of Care in Diabetes 2023).

The STRENGTH trial evaluated the efficacy of a carboxylic acid formulation of 75% EPA and 25% DHA (4g / day total; Epanova, AstraZeneca) on cardiovascular events compared to corn oil placebo in patients with moderate to high risk of cardiovascular disease. This multi-center, double-blind, randomized trial enrolled 13,078 patients, and was prematurely ended when an interim analysis indicated a low probability of clinical benefit. Of the omega-3 treated patients, 12% experienced a primary endpoint event compared to 12.2% of the placebo group (HR=0.99; 95% CI, 0.90 – 1.09; P=0.84).

Given that two large studies on similar drugs published seemingly contradictory results in rapid succession, there were several commentary and follow-up articles on how to interpret the findings. There was some controversy in the cardiovascular community regarding the choice of placebo in the two trials. Some posited that the mineral oil used in the REDUCE-IT study was actually a harmful comparator, and that the benefits seen were due to the detrimental effects of the placebo rather than the positive effects of Vascepa.

This was in part based on a biomarker substudy of the REDUCE-IT trial published in 2022 that found increases in biomarkers such as LDL-C, C-reactive protein, lipoprotein(a), IL-6, and IL-1β in the placebo group at 12 months that were sustained at 24 months as compared to baseline, but no significant changes in the treatment group (Ridker et al., 2022). However, an independent group compared STRENGTH and REDUCE-IT to the Copenhagen General Population study, and found that the possible harm of mineral oil did not account for the extent of benefit seen in the Vascepa treated group. Moreover, they found that the corn oil used in the STRENGTH trial could potentially have had a weak benefit (Doi et al., 2021).

While this remains an unsettled debate, it appears that in terms of cardiovascular risk, some element of discrepancy may be attributed to the formulation. Studies of icosapent-ethyl-only medications (JELIS, REDUCE-IT, and a recent RESPECT-EPA study) all show at least trends towards lower risk of cardiovascular events, whereas studies with mixed EPA and DHA like STRENGTH do not show the same effects. At the 2020 American College of Cardiology Together With World Congress Cardiology Virtual Congress, authors announced that plasma EPA levels were also correlated with significant decreases in

the risk of cardiovascular events, cardiovascular death, and total mortality (p<0.001) in REDUCE-IT. But the plasma levels of EPA were lower in the STRENGTH trial compared to the REDUCE-IT trial (STRENGTH baseline= 21.0 µg/mL, 1 year=89.6 µg/mL; REDUCE-IT baseline= 26.1 µg/mL, 1 year=144.0 µg /mL) (Pirillo and Catapano, 2021; Mason and Eckel, 2021).

RESPECT-EPA is an ongoing study in Japan testing 1.8 g daily of EPA (Epadel, Mochida Pharmaceuticals) in patients with low EPA/AA ratio (<0.4). They enrolled 2,506 patients and randomized them 1:1 to either EPA and standard statin or control of standard statin only. They presented initial results at the American Heart Association meeting in November 2022. They found a trend towards reduction in cardiovascular events in the treatment group (10.9% of the icosapent ethyl group vs. 14.9% of the control group; p = 0.055). A post-hoc analysis that excluded patients with a plasma EPA increase in the control group and those without a plasma EPA increase in the treatment group found a reduction in risk of cardiovascular events (HR=0.725; 95% CI 0.553-0.951, P=0.0202). While the full published study will be necessary to make more final conclusions, the preliminary results presented suggest that this study is in rough agreement with the JELIS and REDUCE-IT trial (ACC Summary; PACE-CME Summary).

Vascepa was previously tested in two studies, ANCHOR (n=702) (Ballantyne et al, 2012) and MARINE (n=229) (Bays et al, 2011). Both studies treated patients with q2 or 4 g/day of Vascepa over 12 weeks. The studies were similar except that ANCHOR enrolled patients with high triglycerides (between 200 and 500mg/dl) at high risk for coronary heart disease (CHD) who were on statin treatment optimized to achieve LDL-c levels between 40-100mg/dL (73% of whom were diabetics) while MARINE enrolled patients with very high triglyceride levels (between 500 and 2000mg/dl) with no lipid requirements.

**Results from Vascepa treatment in MARINE (very high triglycerides, at risk for CHD) and ANCHOR (high triglycerides) study (results presented as placebo-corrected percent change from baseline – significant results highlighted in yellow). Results from the REDUCE-IT trial have also been added. These are between-group differences in median percent changes from baseline at 1 year unless otherwise specified; further data is available in the supplemental appendix in Bhatt et al., 2018 and in one biomarker follow up, Ridker et al, 2022.**

| Measure | MARINE (2g/d) | MARINE (4g/d) | ANCHOR (2g/d) | ANCHOR (4g/d) | REDUCE-IT (4g/day) |
|---|---|---|---|---|---|
| ***Lipids*** | | | | | |
| Triglycerides | -19.7 | -33.1 | -10.1 | -21.5 | -18.3 |
| Non-HDL-c | -8.1 | -17.7 | -5.5 | -13.6 | -13.1 |
| VLDL-c | -15.3 | -28.6 | -10.5 | -24.4 | NA |
| apoB | -2.6 (n.s.) | -8.5 | -3.8 | -9.3 | -9.7 (2 Years) |
| TC | -6.8 | -16.3 | -4.8 | -12.0 | NA |
| LDL-c (mg/dl) | 5.2 (n.s.) | -2.3 (n.s.) | -3.6 (n.s.) | -6.2 | -6.6 |
| HDL-c | 1.5 (n.s.) | -3.6 (n.s.) | -2.2 (n.s.) | -4.5 | -6.3 |
| VLDL-TG | -17.3 (n.s.) | -25.8 | -11.3 | -26.5 | NA |
| apoC-III | -14.3 | -25.1 | -8.5 | -19.2 | NA |
| Remnant-like particle cholesterol | -14.9 (n.s.) | -29.8 | -16.7 | -25.8 | NA |
| ***Inflammatory markers*** | | | | | |
| hs-CRP | -10.1 (n.s.) | -36.0 | -6.8 (n.s.) | -22.0 | -39.9 |
| Ox-LDL | -1.4 (n.s.) | -6.6 (n.s.) | -5.8 (n.s.) | -13.3 | NA |
| Lp-$PLA_2$ | -5.1 (n.s.) | -13.6 | -8.0 | -19.0 | -21.13 |
| IL-6 | 4.7 (n.s) | 11.0 (n.s.) | -1.0 (n.s.) | 7.0 (n.s.) | -16.29 |
| ICAM-1 | -2.3 (n.s.) | -2.5 (n.s.) | -2.2 (n.s.) | -2.4 (n.s.) | NA |

In ANCHOR, those treated with a more effective statin regimen had a greater reduction in LDL-c and apoC-III with 4g/d.

Investigators in MARINE also compared lipoprotein particle concentration using NMR. LDL and HDL size did not change significantly. Compared to placebo, Vascepa reduced concentrations of large VLDL **(-27.9%; p = 0.02**), total LDL **(-16.3%; p = 0.0006**), total HDL **(-7.4%; p = 0.0017**), and reduced VLDL particle size (**-8.6%; p = 0.0017**) (Bays et al, 2012).

(Data from : Bays et al, 2011; Ballantyne et al, 2012; Bays et al, 2013; Ballantyne et al, 2016; Ballantyne et al, 2016).

**Results from Vascepa in ANCHOR (high triglycerides) study who had metabolic syndrome (results presented as placebo-corrected percent change from baseline) (Bays et al, 2015).**

| Measure | 4g/d | 2g/d |
|---|---|---|
| hsCRP | -23 | -7.6 (n.s.) |
| TG | -21.7 | -10.3 |
| LDL-c | -5.2 (n.s.) | -2.4 (n.s.) |
| Non-HDL-c | -13.5 | -4.4 |
| apoB | -8.8 | -2.6 |
| HDL-c | -4.0 | -1.4 (n.s.) |

**Atherosclerotic Plaques: POTENTIAL BENEFIT**

EVAPORATE, a 2020 study from Budoff and colleagues, examined the effects of icosapent ethyl as an adjunct to statin and diet on the progression of coronary plaques in patients with elevated triglycerides. Eighty patients were randomized to take either 4g a day of icosapent ethyl or mineral oil, and received scans to assess plaque characteristics at baseline, 9 months, and 18 months. Plaque characteristics are strongly predictive of cardiovascular events. The authors found that compared to placebo, the treatment group had significantly less plaque volume than placebo (decrease of 9% in treatment, increase of 11% in placebo, p=0.0019). They also had less volume of low-attenuation plaques (LAP) with a decrease of 17% in the treatment group, while in the placebo group the plaque volume more than doubled (+109%) (P = 0.0061). LAP volume is a strong prognostic indicator, with higher LAP volume being a strong indicator of potential future heart attack (Budoff et al., 2020; Tokgozoglu & Catapano, 2020).

*Preclinical Studies*

Preclinical studies have suggested numerous mechanisms for how EPA may benefit atherosclerosis. Treatment in mice increased the stability of atherosclerotic plaques by decreasing lipid deposition, decreasing macrophage accumulation, increasing smooth muscle cells, and increasing collagen content. It also reduced the levels of proinflammatory cytokines and chemokines, such as interferon-γ, MCP-1, and TNF-α (Nelson et al., 2017).

*Orthostatic hypotension*

- Nyantika et al., 2016 – 1666 middle-aged or older men and women free of CVD, diabetes, or hypertension: no associations between serum EPA or DHA levels and orthostatic hypotension.

**Safety:** Recent studies have repeatedly found an increased risk of atrial fibrillation. Studies have also reported increased risk of bleeding events, gastrointestinal effects, prostate cancer, and edema.

*Types of evidence:*

- 2 Cochrane meta-analyses
- 1 meta-analysis
- 5 randomized controlled trials
- 1 conference summary

The REDUCE-IT trial found that compared to mineral oil placebo, icosapent ethyl use was associated with significantly higher incidences of atrial fibrillation (5.3% vs. 3.9%), hospitalization for atrial fibrillation (3.1% vs. 2.1%, P=0.004), and peripheral edema (6.5% vs. 5.0%). There was a strong trend towards increased serious bleeding events in the icosapent ethyl group (2.7% vs 2.1%, p=0.06). Overall, there were approximately equal adverse events in the icosapent ethyl and placebo groups that lead to discontinuation in the study (7.9% in the icosapent ethyl group, 8.2% in the placebo group) (Bhatt et al., 2019).

The STRENGTH trial comparing a mix of EPA and DHA to corn oil found that more patients discontinued or had a dose reduction in the treatment group compared to the placebo group (10.8% vs 8% for discontinuation; 12% vs 6.1% for dose reduction). They also found increased new-onset atrial fibrillation in the treatment vs placebo group (2.2% vs 1.3%; HR, 1.69; 95% CI, 1.29 - 2.21). There were also significantly more gastrointestinal side effects in treatment vs placebo group (24.7% vs 14.7%) (Nicholls et al., 2020).

The preliminary results from the RESPECT-EPA trial also indicate an increase in atrial fibrillation events and gastrointestinal complaints (ACC Conference Summary).

The most common adverse events in the three large-scale EPA trials were gastrointestinal disturbances. In the JELIS trial these were more common in the EPA group than in the placebo group (3.8% vs. 1.7%).

They were balanced in the MARINE and ANCHOR trials (12%-37%). Conceivably, both the high dose of EPA and the high dose of liquid paraffin (in the placebo pill) could both cause gastrointestinal problems.

In the ANCHOR study there was an increase in arthralgia (joint pain) (~2-3% of patients), but this was not seen in the MARINE study. In the JELIS study, there was also an increase in skin abnormalities (e.g. itching, eczema: 1.7% vs. 0.7%) and in haemorrhage (1.1% vs. 0.6%).

The JELIS (1.8g/day) study was five years while ANCHOR and MARINE (2-4g/day) were 12 weeks, so it is not clear what additional side effects might occur with longer term treatment with 2-4g/day EPA.

Notably, higher levels of EPA are associated with reduced all-cause mortality. However, EPA levels should be periodically measured to ensure they do not get too high.

Two Cochrane systematic reviews and meta-analyses examined the effects of different fatty acids, including omega-3s as a whole, on cardiovascular risk and cancer risks. Both of these studies included RCTs that involved increasing fatty acid consumption through diet or dietary supplements, and neither specifically examined EPA. However, the safety findings have been included as the analyses are large.

The 2020 Cochrane meta-analysis of the effect of omega-3 fatty acids on cardiovascular outcomes in studies enrolling a total of 162,796 patients reported on side effects of omega-3s (See Aging & Related Health Concerns section for further information on this meta-analysis). In their analysis of adverse events, they found that those who took or increased consumption of omega-3 fatty acids had an increase in serious GI events (RR=1.34, 95% CI 0.64 - 2.80; I2 22%; 3 trials, 774 participants, 49 events). They also found increased risk of nausea (RR=1.20, 95% CI 0.96 - 1.49; I2 = 54%; 8 trials, > 35,000 participants, 7639 events) in those taking omega-3 vs placebo. They found potential but not confirmatory evidence for other side effects such as bleeding, pulmonary embolism, and gastrointestinal side effects such as discomfort or diarrhea (Abdelhamid et al., 2020).

A meta-analysis of 7 studies comparing the top quintile to the bottom quintile of circulating EPA reported that high levels of EPA were associated with an increased risk of prostate cancer (**OR = 1.14; 95%CI 1.01-1.29**) (Crowe et al, 2014). The authors suggest that individuals with high levels of EPA are likely to be more health conscious and therefore more likely to take a PSA test which may be why prostate cancer is recognized. Additionally, if high levels of EPA decrease the risk of cardiovascular disease, perhaps these patients live longer and are therefore at an increased risk of prostate cancer.

A companion Cochrane systematic review and meta-analysis was also published in 2020 and examined the association between treatment with different fatty acids, including omega-3, and cancer diagnosis and mortality. The authors included any randomized trial that examined higher vs lower intake of several fatty acids, including omega-3s. The authors did not differentiate or discuss different omega-3 fatty acids included in trials (e.g EPA vs DHA). The authors found that higher intake of omega-3 was not associated with cancer diagnosis or death, though it might be associated with a slightly increased risk of prostate cancer (RR=1.10; 95% CI 0.97–1.24) (Hanson et al., 2020).

***Drug interactions***: Drugs.com mentions 86 moderate drug interactions – most are drugs that could increase bleeding (e.g. aspirin, acetaminophen, clopidogrel, dabigatran, cilostazol, etc.) Patients with a history of atrial fibrillation or who have liver disease should be particularly cautious about use of this medication.

**Research underway:**

There are currently 27 ongoing trials involving EPA in the US or in the EU, and approximately 80 active studies in the US involving omega-3 fatty acids. The trials cover a diverse range of conditions, including cancers, cardiovascular disease, COVID-19, neuropsychiatric conditions, and peripheral neuropathy. There are 4 or 5 ongoing trials investigating the effects of EPA on cognitive decline, aging, and dementia (NCT02719327; NCT03691519; NCT05573269; NCT05628155; NCT01669915). One additional study is an early-phase pharmacokinetic study comparing two different omega-3 formulations in APOE4 carriers versus non-carriers (NCT04279743).

Of particular interest is a study titled "Brain Amyloid and Vascular Effects of Eicosapentaenoic Acid (BRAVE-EPA)" (NCT02719327). This is an active trial that is examining the effects of Vascepa (4g/daily) vs placebo in 150 cognitively healthy veterans 50-75 years of age over the course of 1.5 years. The primary outcome is cerebral blood flow; secondary outcomes include CSF biomarkers of AD (tau and amyloid-beta) and cognitive performance. The study is due to be completed in 2023.

The other four studies are potentially edifying, but they do not test Vascepa, and use mixed formulations of EPA + DHA with lower overall EPA doses than Vascepa.

A study titled "Prevention of Cognitive Decline in Older Adults With Low Dha/Epa Index in Red Blood Cells (LO-MAPT)" is a 400-person trial examining the effects of 972 mg DHA +555 mg EPA / day- vs placebo on cognitive status over the course of 18 months (NCT03691519). This trial is notable because it specifically looks at patients with low DHA/EPA status and who also have subjective memory complaints and/or family history of dementia.

A 60-person study is investigating the combined effects of 350 mg EPA + 250 mg DHA plus pine extract or placebo on cognitive function over the course of 6 months (NCT05573269).

A study titled "MAÏA - MAintain the Level of Independence Through Alimentation (MAÏA)" is a 465-person study examining the level of omega-3 fatty acids on dietary menus in nursing homes, and their effect on independence level of residents (NCT05628155).

A Large Randomized Trial of Vitamin D, Omega-3 Fatty Acids and Cognitive Decline (VITAL-Cog) (NCT01669915) is listed as ongoing, but results appear to be published as of April 2022 (Kang et al., 2022).

**Search terms:**

Pubmed, Google: EPA, Vascepa, omega-3

- + cognition, +dementia, +Alzheimer's, +cancer,+ APOE4, +APOE

Websites visited for EPA and/or Vascepa:

- Clinicaltrials.gov (Icosapent Ethyl); Clinicaltrials.gov (EPA)
- Examine.com
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca
- Cafepharma

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