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 (prescription; Vascepa® and Epadel®)

Evidence Summary

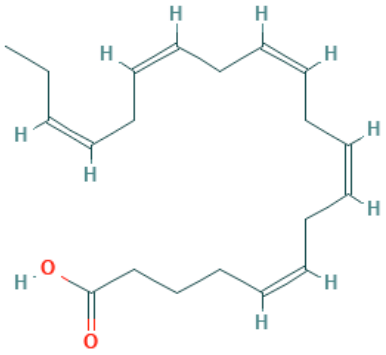
This summary is focused on purified eicosapentaenoic acid (EPA) prescription drugs, such as Vascepa® and Epadel®, as well as EPA epidemiology. Prescription EPA is different from fish oil that can be bought over the counter, as fish oil contains a mix of EPA and docosahexaenoic acid (DHA) while prescription EPA is purified EPA in the form of an ethyl ester.

Vascepa and Epadel effectively reduces triglycerides without increasing LDL-c. Cardiovascular outcome trials suggest that Vascepa and Epadel may reduce the risk of cardiovascular disease in patients with high triglycerides.

Neuroprotective Benefit: Not likely beneficial unless you have low levels of EPA or high triglycerides.

Aging and related health concerns: Clinical studies show that EPA effectively lowers triglyceride levels and cardiovascular disease – whether it is beneficial in individuals with high plasma EPA levels or low triglycerides is unknown.

Safety: Some minor side effects have been observed in clinical trials. EPA may be associated with a slight increased risk of serious bleeding or atrial fibrillation, and one epidemiology study suggests high levels of EPA may be associated with prostate cancer.

Availability: As a prescription	**Dose**: 2-4g/day (Vascepa)	**Chemical formula:** $C_{20}H_{30}O_2$ **MW**: 302.458g/mol  Source: Pubchem
Half-life: 37 hours	**BBB**: penetrant	
Clinical trials: One ongoing in Alzheimer's disease	**Observational studies**: > 24 for EPA levels and different outcomes	

What is it?

Eicosapentaenoic acid (EPA) is an omega-3 fatty acid derived from alpha-linolenic acid (ALA). 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. fresh water 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).

Neuroprotective Benefit: *Not likely beneficial unless you have low levels of EPA or high triglycerides.*

Types of evidence:

- *6 epidemiology studies for risk of dementia, cognitive decline, or brain imaging*
- *1 meta-analysis for levels in dementia patients*
- *1 pilot open-label study in dementia patients*
- *1 preclinical study in PBMCs from Alzheimer's 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 coronary artery disease (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.
- 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 standard deviation (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**). Reduced 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 confidence intervals (CI), EPA **HR = 0.52; 95%CI 0.08-3.24**).

Human research to suggest benefits to patients with dementia:

- Lin et al (2012) - Meta-analysis of 10 studies (cannot access): 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 two times per day) had no effect on cognition.

- Freund Levi et al (2014) - EPA was shown to cross the blood brain barrier.

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).

Aging and related health concerns: *Clinical studies show that EPA effectively lowers triglyceride levels and reduces cardiovascular disease risk – whether it is beneficial in individuals with high EPA levels or low triglycerides is unknown.*

Types of evidence:

- *1 meta-analysis and 1 epidemiology study of EPA for mortality and aging*
- *13 epidemiology studies for levels of EPA for CVD*
- *1 meta-analysis of omega-3 trials on potential for CVD outcomes*
- *3 RCTs for Epadel (Mochida Pharmaceuticals)*
- *2 RCTs and multiple sub-analyses for Vascepa (Amarin Pharmaceuticals)*
- *1 review of imaging studies after EPA supplementation (mostly Epadel studies)*

Mortality

- 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**). 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**).

Epidemiology to support increasing EPA for cardiovascular disease (CVD)

- 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 myocardial infarction 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 myocardial infarction (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.

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 of increased hsCRP.
- 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 vessels diseased) 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 events 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**).

Meta-analysis of increasing omega-3s (through diet or supplements – most not prescription)

- 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).

Prescription EPA Trials

Epadel – Mochida Pharmaceuticals

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) 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).

Vascepa – Amarin

On September 24th, 2018, Amarin announced that its EPA drug, Vascepa, reduced the rate of cardiac events by 25% in a phase 3 clinical study (REDUCE-IT) (Bhatt et al, 2019). 8719 patients with fasting triglyceride levels of 135-499 mg/dl and LDL-c levels of 41-100 mg/dl who were on statin therapy (70.7% for secondary prevention) were enrolled and followed for a median of 4.9 years. The primary endpoint (composite of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization, or

unstable angina) occurred in 17.2% of EPA group compared to 22% of placebo group (ARR = ~5%; HR = 0.75; 95%CI 0.68-0.83). The secondary endpoint (composite of cardiovascular death, non-fatal MI, or non-fatal stroke) occurred in 11.2% of EPA group and 14.8% of placebo (HR = 0.74; 95%CI 0.65-0.83). More patients in EPA group hospitalized for atrial fibrillation (3.1% vs. 2.1%) and serious bleeding occurred more in EPA group (2.7% vs. 2.1%).

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 2 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 other 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)

Measure	MARINE (2g/d)	MARINE (4g/d)	ANCHOR (2g/d)	ANCHOR (4g/d)
Lipids				
Triglycerides	-19.7	-33.1	-10.1	-21.5
Non-HDL-c	-8.1	-17.7	-5.5	-13.6
VLDL-c	-15.3	-28.6	-10.5	-24.4
apoB	-2.6 (n.s.)	-8.5	-3.8	-9.3
TC	-6.8	-16.3	-4.8	-12.0
LDL-c	5.2 (n.s.)	-2.3 (n.s.)	-3.6 (n.s.)	-6.2
HDL-c	1.5 (n.s.)	-3.6 (n.s.)	-2.2 (n.s.)	-4.5
VLDL-TG	-17.3 (n.s.)	-25.8	-11.3	-26.5
apoC-III	-14.3	-25.1	-8.5	-19.2
Remnant-like particle cholesterol	-14.9 (n.s.)	-29.8	-16.7	-25.8
Inflammatory markers				
hs-CRP	-10.1 (n.s.)	-36.0	-6.8 (n.s.)	-22.0

Ox-LDL	-1.4 (n.s.)	-6.6 (n.s.)	-5.8 (n.s.)	-13.3
Lp-PLA_2	-5.1 (n.s.)	-13.6	-8.0	-19.0
IL-6	4.7 (n.s)	11.0 (n.s.)	-1.0 (n.s.)	7.0 (n.s.)
ICAM-1	-2.3 (n.s.)	-2.5 (n.s.)	-2.2 (n.s.)	-2.4 (n.s.)

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 the 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.)

Imaging studies

Most imaging studies show benefits on plaque size and composition with prescription EPAs in patients with dyslipidemia or undergoing percutaneous coronary intervention (PCI) (Nelson et al, 2017)

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 TNFα (Nelson et al, 2017).

Cancer Risk

Prostate cancer

- Crowe et al (2014) – Meta-analysis of 7 studies: comparing the top quintile to the bottom quintile of circulating EPA, high levels of EPA were associated with an increased risk of prostate cancer (**OR = 1.14; 95%CI 1.01-1.29**). 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.

Orthostatic hypotension

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

Safety: *Some minor side effects have been observed in clinical trials. EPA may be associated with a slight increased risk of serious bleeding or atrial fibrillation, and one epidemiology study suggests high levels of EPA may be associated with prostate cancer.*

Types of evidence:

- *4 RCTs with EPA*

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%).

In the Vascepa phase 3 REDUCE-IT, more patients in EPA group hospitalized for atrial fibrillation (3.1% vs. 2.1%) and serious bleeding occurred more in EPA group (2.7% vs. 2.1%). However, there were lower rates of anemia, diarrhea, and gastrointestinal side effects (Bhatt et al, 2019).

An epidemiology study (Crowe et al (2014), above) suggested higher levels of EPA were associated with an increased risk of prostate cancer, though there are some caveats.

Drug interactions:
Drugs.com mentions 86 moderate drug interactions – most are drugs that could increase bleeding (e.g. aspirin, acetaminophen, clopidogrel, dabigatran, cilostazol, etc.)

Sources and dosing:
Vascepa is available with a prescription and is used at 2-4g/day. Epadel (1.8g/day) is only available in Japan.

Research underway:
There are 5 ongoing trials using prescription EPA – one for atherosclerosis in people with high triglycerides, one looking at brain amyloid and vascular effects in Alzheimer's disease, one for fatigue in cancer patients, and two for cancer.

Search terms:
Pubmed

- eicosapentaenoic acid + Alzheimer
- Eicosapentaenoic acid ethyl ester
- AMR101
- epadel
- eicosapentaenoic acid carotid ultrasound
- eicosapentaenoic acid ivus
- eicosapentaenoic acid optical coherence tomography
- EPA/AA ratio cardiovascular

- plasma omega-3 cardiovascular [meta-analysis]
- circulating epa (or omega 3 or fatty acids) cancer
- circulating omega 3 mortality
- omega 3 osteoarthritis
- omega 3 orthostatic