Journal of the American Heart Association

EDITORIAL

Blood Pressure–Lowering Effects of Omega-3 Polyunsaturated Fatty Acids: Are These the Missing Link to Explain the Relationship Between Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Disease?

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In this issue of the *Journal of the American Heart Association* (*JAHA*), Zhang and colleagues[1] have reported that the intake of omega-3 (ω3) polyunsaturated fatty acids (PUFAs), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) are associated with a reduction in blood pressure (BP) and identified the optimal dose of 2 to 3 g/d. Although these findings are not entirely novel, they are robust and provide insights into the long-standing debate on the role of ω3 PUFAs in modifying cardiovascular risk.

See Article by Zhang et al.

The interest in ω3 PUFAs as potential therapeutics for the reduction of cardiovascular risk stemmed from early observational studies demonstrating an association between a marine diet and reduced incidence of cardiovascular disease in Eskimo populations.[2] Subsequently, a significant number of interventional studies examining the effects of purified ω3 PUFAs on cardiovascular risk[3–6] and its determinants, including hypertension,[7] have been conducted.

However, despite decades of research, the role of ω3 PUFAs in modifying cardiovascular risk remains controversial, and their usefulness in routine clinical practice is unclear.

ω3 PUFAS AND BP

The hypotensive effect of ω3 PUFAs has been well characterized across multiple trials and previous meta-analyses.[7] However, the findings on the dose–response relationship and linearity of dose and BP-lowering effect have been conflicting. Zhang and colleagues, in this new meta-analysis (including 71 studies involving 4973 individuals), have addressed previous shortcomings by applying a random-effects 1-stage cubic spline regression model to delineate the dose–response relationship between DHA/EPA and BP-lowering, and

Key Words: Editorials ■ docosahexaenoic acid ■ long-chain fatty acids ■ eicosapentaenoic acid ■ hypertension ■ one-stage regression

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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have identified an optimal dose of 2 to 3 g/d.[1] More importantly, they have demonstrated a significantly stronger and increased BP-lowering effect in higher cardiovascular risk groups, such as those with hypertension or hyperlipidemia. They report an impressive BP reduction in normotensive individuals of –2.61 systolic BP (SBP)/–1.8 mm Hg diastolic BP with a dose of 3 g/d.

The clinical significance of this 2.6-mm Hg reduction on a population level is likely to be significant. A 2-mm Hg reduction in SBP is estimated to reduce stroke mortality by 10% and deaths from ischemic heart disease by 7%.[8] Expressed another way, an analysis in the US population using 2010 data estimates that a population-wide reduction in SBP of 2 mm Hg in those aged 45 to 64 years would translate to 30 045 fewer cardiovascular events (coronary heart disease, stroke, and heart failure).[9]

Interestingly, in this new analysis,[1] the effect on BP lowering was more marked in participants with a baseline diagnosis of untreated hypertension (≥140/90 mm Hg). In this subpopulation, the reduction in SBP was also maximal at 3 g/d and greater than that seen in normotensive individuals at –4.54 mm Hg SBP. Although this effect is substantially lower than that achieved with standard pharmacological monotherapies for hypertension, these are clinically relevant reductions.

However, in this meta-analysis, Zhang et al excluded clinical trials in which patients were receiving concurrent BP-lowering medications.[1] This is important for understanding these apparently greater reductions, because previous reports suggest that the BP reduction may be attenuated if they also included participants who were on treatment.[7] For example, Campbell et al[7] included 8 studies of patients with hypertension receiving ω3 PUFA supplements (n=475), and found that BP was significantly lower in the treatment group, but the reported BP-lowering extent was only –2.56 mm Hg SBP/1.47 mm Hg diastolic BP, which is much lower than seen in the analysis by Zhang et al. Together, these findings suggest that some of the antihypertensive mechanisms of ω3 PUFAs may overlap with that derived from the existing pharmacological treatments, thereby diminishing beneficial return of ω3 PUFAs when used together with medications, although the additional BP reduction still will be clinically relevant.

Several mechanisms by which ω3 PUFAs reduce BP have been previously described.[10–15] One of the major such mechanisms is the reduction of oxidative stress that elevates BP by reducing circulating levels of vasodilatory mediators such as endothelial nitric oxide.[10] In animal models, PUFAs reduce oxidative stress by downregulating nicotinamide adenine dinucleotide phosphate oxidase,[10] suppression of the xanthine oxidase pathway,[11] and activation of the antioxidant enzyme superoxide dismutase.[12] ω3 PUFAs can also serve as the substrate for the synt46hesis of both classic oxylipins such as prostaglandins and thromboxanes as well as other oxylipins termed specialized preresolving mediators. Several of these oxylipins have also been described to have antioxidant effects.[13] Although these effects may explain some of the BP-reducing effects of ω3 PUFAs, similar antioxidative effects have also been described for drugs targeting the renin–angiotensin system.[16]

In addition to these antioxidant effects, ω3 PUFAs, when incorporated into the phospholipid bilayer of cell membranes, have multiple effects that modulate a wide range of cellular functions including that of ion channels and receptors. For example, in blood vessels, DHA modulates calcium signaling in vascular smooth muscle cells enhancing vasodilation,[14] and within the kidney, EPA regulates the epithelial sodium channel, leading to enhanced sodium excretion.[15] However, both of these effects are also achieved by calcium channel blockers and diuretics, respectively.

Thus, although ω3 PUFAs reduce BP by multiple mechanisms, their effect is both modest and overlaps with existing therapies.

PLEIOTROPIC EFFECTS OF ω3 PUFAS

Beyond their effect on blood pressure, ω3 PUFAs have other important effects on a wide range of other established cardiovascular risk factors including hyperlipidemia, inflammation, and thrombosis.

With regard to hyperlipidemia, ω3 PUFAs are effective at lowering triglyceride levels[3]; however, unlike LDL (low-density lipoprotein), the precise nature of the relationship between triglyceride concentrations and cardiovascular risk remains unclear. EPA and DHA also induce an increase in HDL (high-density lipoprotein), and higher levels of HDL are associated with cardioprotection.[17] The anti-inflammatory effect of ω3 PUFA are wide ranging, with evidence that they reduce concentrations of proinflammatory cytokines such as IL-6 (interleukin-6) and IL-8 (interleukin-8),[18] modulate the balance between pro- and anti-inflammatory oxylipins, and generate specialized preresolving mediators that can aid in the resolution of inflammation.[18] Reduced platelet aggregation was one of the earliest observed effects of ω3 PUFAs,[2] which is mediated via the generation of thromboxane A3 and prostacyclin. Thus, ω3 PUFAs have pleiotropic effects that target several well-described cardiovascular risk pathways.

ω3 PUFAS AND CARDIOVASCULAR RISK REDUCTION

Multiple phase 3 randomized clinical trials (RCTs) have investigated the therapeutic potential of ω3

PUFAs in the setting of both primary and secondary prevention.[3–6] However, recent trials have had mixed outcomes, resulting in a lack of clarity about their role in treating cardiovascular disease.[3,4]

Examples of recent RCTs using a combination of EPA+DHA showing no reduction in their composite cardiovascular end points include ASCEND (A Study of CV Events in Diabetes, 2018),[5] STRENGH (Long-Term Outcomes Study to Assess Statin Residual Risk With Epanova in High Cardiovascular Risk Patients With Hypertriglyceridemia, 2020),[4] and OMEMI (Omega-3 Fatty Acids in Elderly With Myocardial Infarction, 2020).[6] Of these studies, STRENGH, which randomized 13 078 patients with high cardiovascular risk, high triglyceride levels, and a low HDL, was stopped early because of futility.[4]

However, in contrast, REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial) used a purified EPA-only preparation and enrolled 8179 patients with a similar risk profile to the STRENGH trial (either established cardiovascular disease or diabetes and other risk factors, and high fasting triglyceride levels) and found a significant relative reduction in the primary composite cardiovascular end point of 25% (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina). These findings were in keeping with the earlier EPA-only open-label study JELIS (Japan EPA Lipid Intervention Study).[3] However, the effect on triglycerides in REDUCE-IT was disproportionally low (19.7%) relative to the large cardiovascular risk reduction that was apparent, suggesting other mechanisms were responsible for this benefit. There was a significant reduction in hsCRP (high-sensitivity C-reactive protein) between the EPA and placebo groups demonstrating an anti-inflammatory effect and a trend toward increased bleeding risk suggestive of reduced platelet aggregation. Although BP was not reported, there was a reduction in new-onset hypertension in those on active treatment, alluding to a BP-lowering effect.[3]

The stark difference between the findings of REDUCE-IT and other contemporary RCTs, particularly STRENGH, which was of a similar design and size, are unexplained and remain the subject of debate. Factors that have been considered are the type of ω3 PUFAs (EPA-only versus EPA+DHA [both 4 g/day]) and the placebo (mineral oil versus corn oil[19]).

ω3 PUFAs RCT results have been the subject of multiple meta-analyses over recent years. However, these have suffered from the significant heterogeneity within the field (eg, diet versus supplements, EPA+DHA versus EPA alone, primary versus secondary prevention, dose, eligibility criteria). One recent analysis, by the lead author of REDUCE-IT,[20] included 38 trials and 149 051 patients. Using a trial-level, random-effects model and pooling all doses used, they found ω3 PUFAs reduced cardiovascular mortality (number of RCTs=25; relative risk, 0.93 [95% CI, 0.88–0.98]) but not all-cause mortality or stroke. They were also associated with a reduction in nonfatal myocardial infarction and cardiovascular events. Effects were stronger with EPA monotherapy (4 trials), and the EPA effect remained after influence analysis removed REDUCE-IT. With regard to adverse effects, they identified an increased risk of atrial fibrillation and total bleeding on EPA monotherapy.[20] The authors commented that their analysis "provides reassurance about the role of omega-3 fatty acids, specifically EPA" in the treatment of cardiovascular risk.

Despite the uncertainty generated by discordant RCT results, pooled data suggest a net modest benefit effect of ω3 PUFAs, particularly on cardiovascular mortality in patients at high risk and with raised triglycerides. As described by Zhang et al,[1] the intake of ω3 PUFAs is associated with a BP-lowering effect, and a dose of 2 to 3 g appears to be optimal. Given the modest effect on triglycerides, this BP-lowering impact together with their other pleiotropic effects are likely the missing link to explain the cardiovascular risk reduction seen in REDUCE-IT[3] and subsequent meta-analyses.[20] However, further RCTs and postmarketing studies are required to resolve the remaining questions, particularly one that was raised by the disparity between REDUCE-IT[3] and STRENGH[4] of EPA monotherapy versus the combination of EPA and DHA. Therefore, ω3 PUFAs are still not fully ready for prime time, and physicians should keep an open mind on these compounds with acute awareness toward of the mixed evidence base and the potential risks of increased atrial fibrillation and bleeding when prescribing.

ARTICLE INFORMATION

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Disclosures

None.

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