

# Omega-3 polyunsaturated fatty acids: Their potential role in blood pressure prevention and management

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*ABSTRACT: Omega-3 polyunsaturated fatty acids (PUFAs) from fish and fish oils appear to protect against coronary heart disease: their dietary intake is in fact inversely associated to cardiovascular disease morbidity/mortality in population studies. Recent evidence suggests that at least part of their heart protective effect is mediated by a relatively small but significant decrease in blood pressure level. In fact, omega-3 PUFAs exhibit wide-ranging biological actions that include regulating both vasomotor tone and renal sodium excretion, partly competing with omega-6 PUFAs for common metabolic enzymes and thereby decreasing the production of vasoconstricting rather than vasodilating and anti-inflammatory eicosanoids. PUFAs also reduce angiotensin-converting enzyme (ACE) activity, angiotensin II formation, TGF-beta expression, enhance eNO generation and activate the parasympathetic nervous system. The final result is improved vasodilation and arterial compliance of both small and large arteries. Preliminary clinical trials involving dyslipidemic patients, diabetics and elderly subjects, as well as normotensive and hypertensive subjects confirm this working hypothesis. Future research will clarify if PUFA supplementation could improve the antihypertensive action of specific blood pressure lowering drug classes and of statins. (Heart International 2006; 2: 98-105)*

*KEY WORDS: Fish, Fish oil, Omega 3 fatty acids, Polyunsaturated fatty acids, PUFA, Eicosapentaenoic acid, EPA, Docosahexaenoic acid, DHA, Blood pressure, Hypertension*

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## INTRODUCTION

Despite the development of ever more efficacious and safe pharmacological treatments, cardiovascular diseases are still the leading cause of death and invalidity in the developed countries, and in most of the so called "second world" (1). Arterial hypertension is one of the most relevant independent cardiovascular disease risk factor and recent studies show that the maintenance of normal blood pressure level also in not frankly hypertensive subjects is associated to a significant reduced incidence of cardiovascular events (2). Of course, it is not plausible to pharmacologically treat all

subjects with normal-high blood pressure and all international guidelines stress the relevance of an adequate dietary and life-style intervention in order to reach and maintain optimal blood pressure levels. Moreover, in our era of multiple pharmacological treatments for cardiovascular diseases, some researchers believe that simple dietary interventions or nutritional supplements may be a more natural and acceptable method of providing benefits, and patients appear very keen to spontaneously use different dietary supplements (whose efficacy is not always evident) to reduce their blood pressure, without asking their physicians for information (3).

Both health professionals and the public are increas-

ingly interested in the supposed role of omega-3 polyunsaturated fatty acids (PUFAs) from fish and fish oils in the prevention and management of coronary heart disease (4).

Moreover, the worldwide use of PUFA supplementation has recently received a large implementation even in fields unrelated to cardiovascular diseases, such as neurology (epilepsies), psychiatry (psychosis, severe depressions), rheumatology (osteoarthritis, psoriasis), clinical immunology (allergy), gastroenterology (inflammatory bowel diseases), nephrology (autoimmune nephropathies) (i.e.: chronic renal failure, congestive heart failure) (5).

If PUFAs also have a small but significant blood pressure lowering effect, this potential wide use could have a relevant epidemiological effect on blood pressure at the population level, because of the high *a priori* probability of comorbidity between those conditions and arterial hypertension.

The aim of this review is to critically evaluate the available information about PUFA effect on blood pressure control and prevention.

### Data sources

We searched PubMed and Embase for relevant articles by using the key words “fish”, “fish oils”, “omega 3 fatty acids”, “polyunsaturated fatty acids”, “PUFA”, “Eicosapentaenoic acid”, “EPA”, “Docosahexaenoic acid”, “DHA” and “blood pressure” or “arterial hypertension”, using a combined text word and MESH heading search strategy. Then we cross-matched references with those found in each paper.

### Biochemical classification and food sources

Alpha-linolenic acid (ALA; 18:3 omega-3) together with linoleic acid (LA; 18:2 omega-6) are essential fatty acids for humans. LA is the most predominant omega-3 PUFA in our diet, which is commonly found in vegetable seed oils. ALA is less abundant than LA; ALA is also present in some vegetable oils such as perilla, flaxseed, canola, soybean and walnut oils. Dietary LA is converted to gamma linolenic acid (GLA, 18:3 omega-6) and di-homo-GLA (DGLA, 20:3 omega-6) by specific enzymes

(6-desaturase, elongase) that are controlled by genetic hormonal and nutritional factors. Then, DGLA compete with alpha-linolenic acid (ALA, 18:3 omega-3) derived products on the enzyme 5-desaturase for the synthesis of arachidonic acid or eicosapentaenoic (EPA, 20:5 omega-3). EPA is yet elongated and desaturated to docosahexaenoic acid (DHA, 22:6 omega-3) (Fig. 1). Fish and fish oils are the main dietary sources of EPA and DHA. The content of EPA and DHA in different kinds of fish is reported in Table I. Even if less concentrated, EPA and DHA are also available in some vegetables, such as corn (and corn oil), lean meat and meat products, offal, egg yolk, milk and dairy products (5).

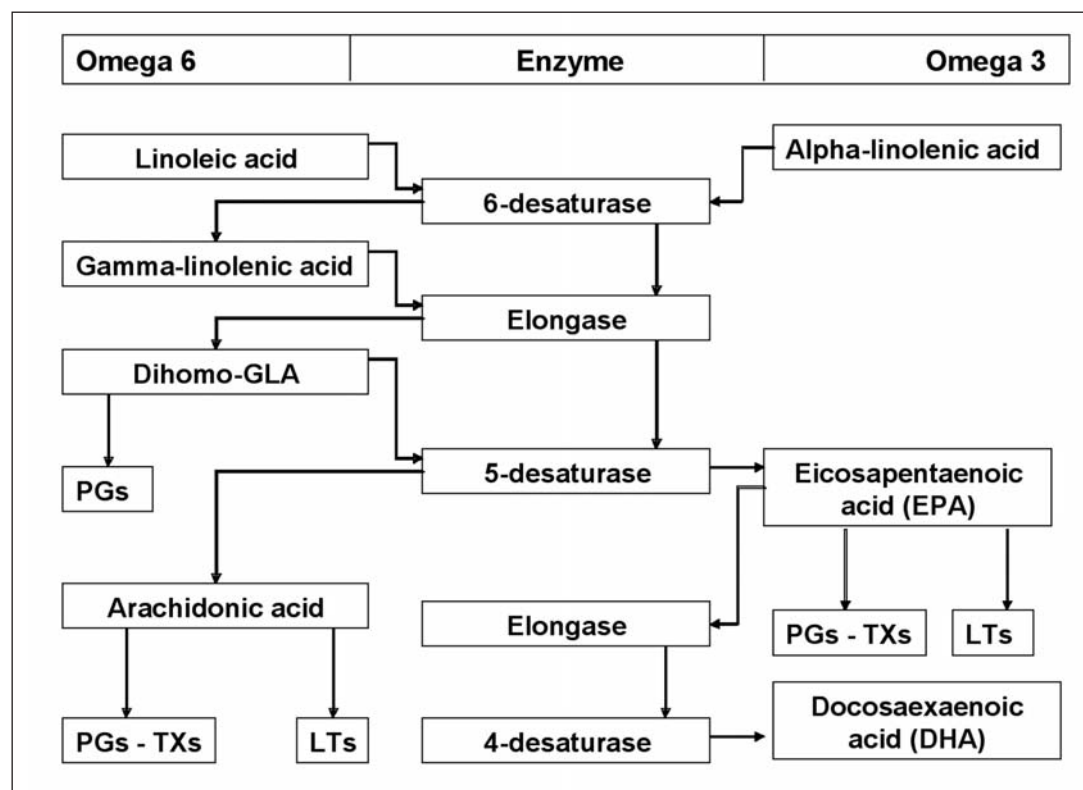
### Pharmacological aspects

As cyclooxygenase (COX) inhibition is often associated with sodium retention leading to edema and hypertension (6), prostanoids appear to have a role in preventing the development of high blood pressure. On the other

**TABLE I** - MEAN CONTENT OF OMEGA 3 FATTY ACIDS OF SELECTED FISH AND SEAFOOD

FISH	EPA+/DHA content (g) per 100 g serving of fish (edible portion)	Amount of fish (in g) required to provide 1 g EPA+/DHA
Tuna (fresh)	0.28-1.51	66-357
Atlantic salmon	1.28-2.15	42.5-70.9
Mackerel	0.4-1.85	54-250
Atlantic herring	2.01	50
Rainbow trout	1.15	87
Sardines	1.15-2	50-87
Halibut	0.47-1.18	85-213
Tuna (canned)	0.31	323
Cod	0.28	357
Haddock	0.24	417
Catfish	0.18	556
Flounder or sole	0.49	204
Oyster	0.44	227
Shrimp	0.32	313
Scallop	0.2	500
Cod liver oil capsule	0.19	5

EPA=eicosapentaenoic acid, DHA=docosahexaenoic acid. Omega 3 content varies markedly depending on species, season, diet, and packaging and cooking methods, and the figures above are therefore rough estimates.



**Fig. 1** - Endogenous metabolism omega-6 and omega-3 polyunsaturated fatty acids (PG= prostaglandin, TX= Thromboxane, LT= Leukotriene).

hand, prostaglandin  $E_2$  ( $PgE_2$ ) and  $Pgl_2$  have also been implicated as determinants of renin secretion. A recent study suggests that  $Pgl_2$  plays a critical role in stimulating renin release and promoting hypertension following renal artery stenosis (7).

Patients with uncontrolled essential hypertension have elevated concentrations of superoxide anion ( $O_2^{\cdot-}$ ), hydrogen peroxide ( $H_2O_2$ ), lipid peroxides, endothelin, and transforming growth factor-beta (TGF-beta) with a simultaneous decrease in endothelial nitric oxide (eNO), superoxide dismutase (SOD), vitamin E, and long-chain PUFAs (8). Physiological concentrations of angiotensin II activate NAD(P)H oxidase and trigger free radical generation (especially that of  $O_2^{\cdot-}$ ). Usually, angiotensin II-induced oxidative stress is abrogated by adequate production and release of eNO, which quenches  $O_2^{\cdot-}$  to restore normotension. Angiotensin II also stimulates the production of endothelin and TGF-beta. TGF-beta enhances NO generation, which in turn suppresses TGF-beta production (8). Thus, NO has a regulatory role on TGF-beta production and is also a physiological antagonist of endothelin. Antihypertensive drugs suppress

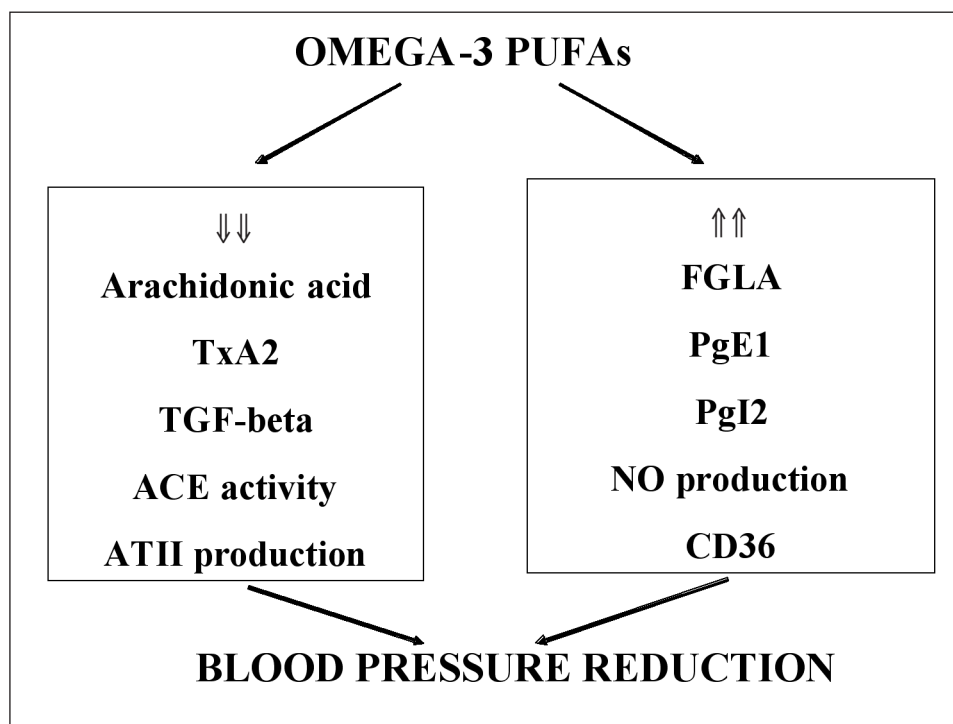
the production of  $O_2^{\cdot-}$  and TGF-beta and enhance eNO synthesis to bring about their beneficial actions (9).

Omega-3 PUFAs exhibit wide-ranging biological actions that include regulating both vasomotor tone and renal sodium excretion, partly competing with omega-6 PUFAs for common metabolic enzymes and thereby decreasing the production of prothrombotic and vasoconstricting rather than vasodilating, antithrombotic, antiaggregatory, and antiinflammatory eicosanoids (10).

Opposite to saturated and trans-fatty acids, omega-3 PUFAs contrast the formation of thromboxane  $A_2$  ( $TxA_2$ ), a potent vasoconstrictor, and enhance that of  $Pgl_2$ , a well-known vasodilator. In addition, EPA lowers tissue levels of arachidonic acid and enhance that of FGLA, the precursor of  $PgE_1$ , another vasodilator agent (10).

PUFAs not only enhance the formation of beneficial PGs, but also suppress angiotensin-converting enzyme (ACE) activity, reduce angiotensin II formation, enhance eNO generation, and suppress TGF-beta expression (11) (Fig. 2). In experimental animal models it has been observed that the L-arginine-NO system upregulates

**Fig. 2** - Main pharmacological activities involved in omega-3 PUFA anti-hypertensive action.



the PUFA metabolism, so that a strict correlation between PUFA concentration and NO endothelial production has been supposed (12). Following control of hypertension with calcium antagonists, beta-blockers, and ACE inhibitors, the concentration of NO and  $O_2^-$  reverted to normalcy, whereas those of PUFAs remain low (13): it opens the possibility of further blood pressure improvement by PUFA supplementation. The discovery that PUFA could have a direct blood pressure lowering effect finally justifies why DHA appears to be as effective or even slightly more effective than EPA (10), even if DHA is not a substrate for the cyclooxygenase and lipoxygenase enzymes involved in eicosanoid metabolism.

Moreover, consumption of breast milk (which is rich in PUFAs) in perinatal life is associated to a higher PUFA tissue content in infants and to a lower insulin-resistance and hypertension rate in adult life, whereas PUFA deficiency in the perinatal period results in raised blood pressure later in life (14). The exact mechanism of this phenomenon has yet to be elucidated, however some authors have postulated the hypothesis that perinatal dietary PUFA deficiency could lead to developmental alteration of membrane bound receptors related to the

sodium metabolism, such as osmoceptors or angiotensin II receptor (14). Patients with essential hypertension and population genetically prone to develop arterial hypertension (15) have low concentrations of various PUFAs in their plasma phospholipid fraction. Based on this, it is proposed that PUFAs serve as endogenous regulators of ACE activity,  $O_2^-$ , eNO generation, and TGF-beta expression. Further, PUFAs have actions similar to statins, inhibit (especially omega-3 PUFAs) cyclooxygenase activity and suppress the synthesis of proinflammatory cytokines, and activate the parasympathetic nervous system, all actions that reduce the risk of major vascular events. Hence, it is proposed that availability of adequate amounts of PUFAs during the critical periods of growth prevents the development of hypertension in adulthood (15).

In addition, PUFAs have antiinflammatory and endothelial action similar to the so called pleiotropic effect of the 3-hydroxy-3-Methyl-Glutaryl-Coenzyme A reductase inhibitors (statins), and also statin use has been observed to slightly but significantly reduce blood pressure level both in clinical trial setting and at population level (16).

A recent report suggests that PUFAs could also exert

their effect on metabolism and hypertension through induction of Cd36 expression whose deficiency underlies insulin resistance, defective fatty acid metabolism and hypertriglyceridemia in spontaneously hypertensive rats (SHRs), and whose expression is modulated through peroxisome proliferator-activated receptor (PPAR) transcription factors, by conditions that alter lipid metabolism such as diabetes mellitus and high-fat feeding (17).

Always in experimental models, fish oil supplementation shows to have protective effects on long-term hypertension-related organ damages such as glomerular enlargement, and glomeruli loss (18).

### *Clinical data*

From an epidemiological point of view, the inverse association between omega-3 PUFA intake and cardiovascular disease morbidity/mortality was established following the observation that the Greenland Inuit had low mortality from coronary heart disease despite a diet that is rich in fat. In the 1970s the Danish investigators Bang and Dyerberg proposed that this could be because of the omega-3 PUFA high content in the Inuit diet, which consisted largely of fish, seal, and whale (19). In fact, in these subjects, plasma omega-3 PUFA concentrations are highly correlated with dietary PUFAs and inversely correlated with diastolic blood pressure (20).

Compared with traditional diets, patterns of PUFA intake in industrialized nations have shifted markedly during the past 150 years toward higher amounts of omega-6 PUFAs and lower amounts of omega-3 PUFAs, with parallel increases in coronary heart disease incidence in ecological studies (21).

The inverse correlation between PUFAs intake and blood pressure could be not true in each ethnicity: for instance in the Tanzania population it has not been observed (22).

Minimally invasive methods allowed repeat measurements in individuals in whom fish oil supplementation was tested in the setting of clinical trials. Measurements have included systemic arterial compliance index, flow-mediated dilation of the muscular conduit brachial artery and blood flow in the microcirculation of the forearm and of coronary arteries. Endothelial dysfunction

that partly explains reduced vascular dilatation appears to predict future adverse coronary heart disease outcomes. Fish oil supplementation has significantly improved endothelial function measured in terms of nitric oxide- and flow-mediated dilation and vasodilation of resistance vessels of the forearm (23). Systemic arterial compliance index, which reflects distensibility in elastic proximal large arteries, was equally improved with 3g DHA (+27%) and 3g EPA (+36%), whereas consumption of the placebo did not, in a double-blind, parallel design, placebo-controlled randomized trial (24). Tomiyama et al showed that EPA supplementation (1.8 g/day) is able to attenuate age-related increase in arterial stiffness in dyslipidemic patients (25). Distensibility of the common carotid artery has also been shown to improve with EPA alone. Left ventricular function also improved in patients taking either EPA or DHA (26). These effects appear not to be related to alterations in vascular responses to norepinephrine, angiotensin II or potassium (27).

In a dietary intervention study, 69 overweight (BMI >25 kg/m<sup>2</sup>) medication-treated hypertensive subjects were randomized to either a daily fish meal (3.65 gr/dL of omega-3 PUFA approximately), a weight reduction regimen, the two regimens combined, or a control regimen for 16 weeks. Sixty-three subjects completed the study. Both systolic (SBP) and diastolic (DBP) blood pressure, body weight and heart rate significantly decreased in the fish diet group compared with the controlled diet group, even after adjustment for changes in urinary sodium, potassium, or the sodium/potassium ratio, as well as dietary macronutrients. From this data it could be argued that weight loss in overweight people can augment the effects of eating fish on ambulatory 24h blood pressure (28).

Then, an observational study was carried out in which the effects of fish-derived omega-3 PUFA on blood pressure, platelet fatty acid levels and heart rate variability (an independent protective factor against cardiovascular mortality), were investigated in 43 subjects (male 24, female 19, aged 18 to 62 years) with type 1 diabetes mellitus, and 38 subjects (male 24, female 14, aged 37 to 77 years) with type 2 diabetes mellitus (29). The study found that fish intake was significantly associated with platelet membrane DHA levels. According to the platelet DHA levels, patients were divided into three tertiles: the first tertile (n = 14) had the lowest



DHA level, the third tertile ( $n = 15$ ) the highest DHA level and the second tertile was in between. Compared with the first tertile, the third tertile had a significantly lower DBP. In a further double blind, randomized, placebo-controlled human study, it was found that EPA and DHA differed in their effects on blood pressure and heart rate (30). In this study, 55 overweight (Body Mass Index = 25-30 kg/m<sup>2</sup>) subjects, aged 20-65 years, were randomized to 4 g/d of purified EPA, DHA, or placebo (olive oil) capsules for 6 weeks. Compared to the placebo group, DHA significantly reduced both SBP and DBP (measured over 24 hours) by 5.8 and 3.3 mmHg, and the waking SBP and DBP by 3.5 and 2.0 mmHg, respectively ( $p < 0.05$ ). Compared to the placebo group, heart rate over a 24-hour period, when awake and when asleep, was significantly reduced by  $3.5 \pm 0.8$ ,  $3.7 \pm 1.2$ , and  $2.8 \pm 1.2$  bpm, respectively. On the other hand, EPA showed no significant effect on blood pressure and heart rate. This study has however the limit to not have tested if the EPA-DHA association has additive or synergic effects on blood pressure, or not. Authors explain the antihypertensive effect of DHA suggesting that there may be a significant cardiac component, as demonstrated by the concomitant reduction in heart rate, possibly mediated by effects on autonomic nerve function or  $\beta$ -adrenoceptor activity.

A meta-analysis of 36 randomised trials, including the last cited ones, found a mean reduction in SBP of 2.1 mmHg and in DBP of 1.6 mmHg (31), significantly inferior to that reported in some single trials. The main reason of this low observed effect is that in the meta-analysis were included also trials where low dosed or unpurified formulation were used, and where blood pressure reduction was not a main outcome of the study.

Recently, Sanders et al showed that PUFAs extracted from marine algae (not from fish) had no effects on the blood pressure levels of seventy-nine patients randomized to 4 g/day (providing 1.5 g DHA and 0.6 g DPA) or placebo in a 4-week double-blind randomized trial (32).

In normotensive adults, PUFA supplementation appears not to have significant effect on blood pressure values if compared to saturated and monounsaturated fatty acids (33). However, 5 mL fish oil supplementation is significantly associated to lower SBP levels ( $-6.3$  mmHg 95% CI 0.9, 11.7;  $p = 0.02$ ) in children taking them mixed in milk-formulation for one year, as com-

pared with control children (34).

Further clinical research is needed to evaluate the real antihypertensive effect of EPA and DHA, their differential effects, and to identify *a priori* the best responders or candidates for that treatment.

Of course, any recommendations regarding fish and fish oils should be balanced against safety issues. Side effects such as fishy aftertaste are uncommon, and gastrointestinal upset is infrequent at moderate intakes (4). Some reports show that fish oil may worsen glycemic control in diabetes, but a recent meta-analysis excludes this adverse effect (35). Concerns have been raised regarding adverse effects on low density lipoprotein (LDL) cholesterol and oxidative stress, but increases in LDL cholesterol are modest and studies about oxidative stress have been contradictory. Overall these effects are unlikely to be dominant given the apparent cardiac benefits of omega-3 PUFAs (36). More specific concerns regarding dietary fish relate to environmental contaminants, and a recent study showed that mercury in fish may attenuate their cardioprotective effects (37). Contaminants accumulate in larger, predatory fish, and consumption of a variety of fish should minimise any possible adverse effects (4).

No significant negative interaction has been observed until now between antihypertensive therapy and fish oil supplementation.

## CONCLUSION

Preliminary data suggest that an adequate PUFA dietary intake or supplementation (2-4 g/day) could slightly but significantly reduce systolic and diastolic blood pressure level and prevent blood pressure increase in either dyslipidemic, diabetics, elderly, normotensive and hypertensive subjects, contributing to their cardiovascular protective role. Present and future research will identify which categories of subjects will more significantly benefit from PUFA supplementation in order to maintain adequate levels of blood pressure.

Some research lines are trying to clarify which specific sub-categories of subjects at cardiovascular risk could obtain the maximal benefit from an EPA/DHA supplementation and which is the most cost-effective dosage and EPA/DHA ratio to be employed. In the specific context of blood pressure management it is proba-

ble that the on-going Gissi-Heart Failure Study, designed to evaluate the effect of EPA/DHA supplementation or statin treatment on the prognosis of patients affected by chronic heart failure, could furnish relevant data as it regards the blood pressure control in both groups of treatment. Because of the specific mechanism of action of PUFA it could be also interesting to study if PUFA could improve the antihypertensive action of specific blood pressure lowering drug classes and of statins. Future guidelines for hypertension management may suggest to increase the nutritional intake of EPA/DHA or to supplement it in order to prevent blood pressure increases or improve the blood pressure con-

trol, especially in subjects that could have special benefit for other concomitant pathologies (e.g. dyslipidemias, rheumatological disorders, and perhaps chronic heart failure and chronic renal failure).

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