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Chapter 7

Role of Supplementation with Omega-3 Fatty Acids in Preventing Cardiac Arrhythmias and Sudden Cardiac Death

Bernhard Rauch*[1] and Jochen Senges[2]
[1]ZAR- Zentrum für Ambulante Rehabilitation am Klinikum der Stadt Ludwigshafen
[2]Institut für Herzinfarktforschung Ludwigshafen, Germany

Abstract

For several decades supplementation with omega-3 polyunsaturated fatty acids (Ω-3) has been believed to reduce cardiovascular risk in primary and secondary prevention, and potential risk reduction especially was attributed to prevention of tachyarrhythmias and sudden cardiac death (SCD). However, recent randomized controlled trials and meta-analyses challenge a general efficacy of Ω-3 supplementation in reducing cardiovascular risk. Especially, an anti-arrhythmic effect as proposed in earlier studies cannot be expected in general, and under certain conditions even pro-arrhythmic effects may occur. Based on molecular interactions of Ω-3 at the cellular level and results of earlier and recent experimental animal studies the following chapter will critically discuss recent clinical studies, emphasizing the individual background conditions that may determine the clinical outcome of Ω-3 supplementation. By this way the hypothesis will be delineated, that the efficacy of Ω-3 supplementation to prevent cardiac arrhythmias strongly depends on the underlying clinical and pharmacological conditions and – at the present stage of knowledge - may be difficult to be predicted in some cases.

Keywords: Omega-3 polyunsaturated fatty acids; cardiac arrhythmia; prevention; cardiovascular disease; myocardial infarction; death, sudden

* Corresponding author address: Email: rauch@zar-kardio-ludwigshafen.de.

Introduction

Omega-3 polyunsaturated fatty acids (Ω-3), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), if supplemented to daily nutrition, have been believed for decades to safely reduce cardiovascular risk. Indeed, this hypothesis was supported by observational and clinical studies as well as by experimental animal studies, and there was evidence that prevention of tachyarrhythmias could be a major mechanism of the Ω-3 related cardiovascular risk reduction.

In the meantime, a huge amount of data has been accumulated on this topic and an impressive number of position papers, reviews and meta-analyses have been published (Bucher HC et al. 2002; Whelton SP et al. 2004; Dhein S et al. 2005; Reiffel JA & McDonald A 2006; Wang C et al. 2006; Siddiqui RA et al. 2008; Marik PR & Varon J 2009; Mozaffarian D et al. 2011).

The primary enthusiasm, however, declined in recent years, as more and more clinical and experimental data were published, that challenged a general beneficial effect of Ω-3, and systematic reviews and meta-analyses conducted more recently were not able anymore to demonstrate a clear beneficial effect of Ω-3 supplementation (Yzebe D & Lievre M 2004;. Hooper L et al. 2006; Léon H et al. 2008; Jenkins DJA et al. 2008a; Cheng JWM & Santoni F 2008; Zhao YT et al. 2009; Filion KB et al. 2010; Kotwal S et al. 2012; Rizos EC et al. 2012). This partly may be due to the rapid development in prevention and treatment of cardiovascular disease including effective medical treatment (i.e. beta-blockers, statins, ACE-inhibitors, platelet aggregation inhibitors), early revascularization in acute myocardial infarction and finally increasing implementation of protective life style changes (i.e. exercise training, mediterranean diet including fish consumption, smoking cessation).

Even more important may be to reflect the interactions of Ω-3 at the molecular and cellular level. These interactions are complex and the biological effects strongly depend on the specific conditions at the cellular level, which makes it difficult to safely predict clinical effects (Lombardi F & Terranova P 2007; Den Ruijter HM et al. 2007; Rauch B & Senges J 2012, Billman GE et al. 2012).

Actual Knowledge from Experimental and Clinical Studies

Molecular and Cellular Interactions

The molecular and cellular interaction has been delineated extensively in several reviews (Leaf A et al. 2005b; Dhein S et al. 2005; McLennan PL & Abeywardena MY 2005; Lombardi F 2007; Den Ruijter HM et al. 2007; Siddiqui RA et al. 2008). In the following some important aspects potentially explaining heterogeneous clinical effects of Ω-3 on cardiac rhythm are summarized:

There are three major ways in which Ω-3 may interfere with cellular and membrane function, thereby potentially moderating cardiac rhythm (see also Figure 1):

a) *Direct interactions of Ω-3 with membrane bound proteins* like the fast sodium channel, the voltage-gated L-type Ca^{2+} channel, specific potassium channels, and the Na^{+}/Ca^{++}-exchanger (Hallaq H et al. 1990 & 1992; Honore E et al. 1994; Xiao YF et al. 1995 & 1997; Kang JX & Leaf A 1996, Leifert WR et al. 1999; Leaf A 2003; Den Ruijter HM et al. 2007; Wang RX et al. 2010). Such interactions may occur predominantly with circulating Ω-3, when it is delivered by acute administration and infusion.

b) *Incorporation into the phosholipid bilayer*, thereby potentially changing membrane fluidity, and/or forming Ω-3 rich micro-domains, and/or interacting with internal binding sites. This may result in a change of the function of membrane bound proteins like ion channels, receptors and signal transduction systems (McMurchie EJ et al. 1988; Croset M et al. 1989; Kinoshita I et al. 1994; Grynberg A et al. 1996; Leifert WR et al. 1999 &2000; McLennan PL 2001; Den Ruijter HM et al. 2007). Incorporation into the cellular membranes predominantly is achieved by dietary long-term administration of Ω-3.

c) *Interaction with intracellular pathways* including gene expression and metabolism of phospho-inositides (Judé S et al. 2006).

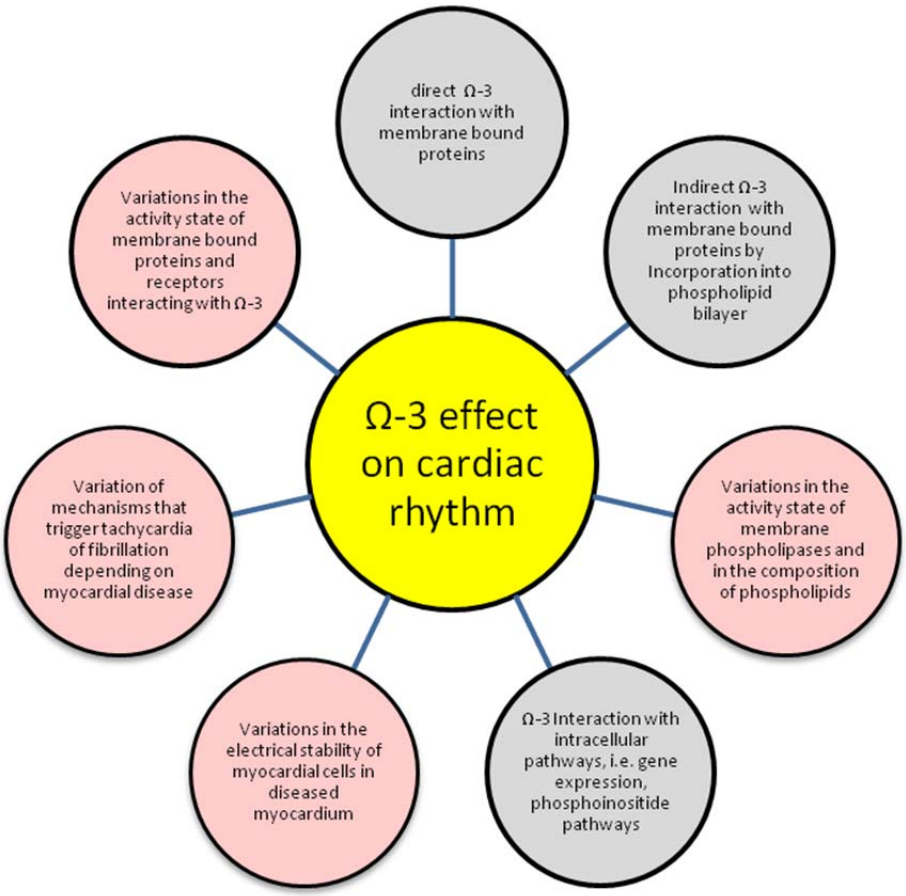

Figure 1. Summary of mechanisms that potentially mediate the clinical effect of Ω-3 supplementation of cardiac rhythm.

Circulating Ω-3 compounds are likely to have different electrophysiological effects, if compared to Ω-3 incorporated into the membranes (Den Ruijter HM et al. 2007 for review). For example, peak cardiac sodium current was reduced by 51% after acute administration of EPA and DHA in neonatal rat cardiomyocytes (Xiao YF et al. 1995), but remained unaffected by Ω-3 incorporated in pig and rat cardiomyocytes (Verkerk AO et al. 2006; Leifert WR et al. 2000). Differential effects of circulating versus incorporated Ω-3 have also been demonstrated with respect to various potassium channels and the regulation of calcium homeostasis (Den Ruijter HM et al. 2007 for review). Incorporated Ω-3, however, also may prevent further AP shortening induced by circulating Ω-3. Patients with high levels of incorporated Ω-3 therefore may not have a further benefit from short term Ω-3 supplementation (Den Ruijter HM et al. 2010). This mechanism may have contributed to negative results in some clinical studies including the JELIS trial (Yokoyama M et al.2007)

Apart from these considerations the molecular interactions of Ω-3 and their effects on cardiac rhythm may be influenced by a large variety of additional conditions (Figure 1):

a) *The various kinds of Ω-3 formulations* being used (re-esterified tri-acyl-glycerides, ethyl-esters or phospholipids; Neubronner J et al. 2011; Schuchardt JP et al. 2011)
b) The *activity state of membrane bound proteins and ligand occupation* of specific receptors involved in signal transduction (Den Ruijter HM et al. 2007; Xiao YF et al 1998; Rauch B et al. 1989), or the increased responsiveness of inhibitory G-proteins after ischemic preconditioning (Niroomand F et al. 1995).
c) The *activity of cellular phospholipases* and the presence of lysophosphatides that change phospholipid environment and function of membrane bound proteins (Chien KR et al. 1981; Corr PB et al. 1984; Rauch B et al. 1994). The activity of phospholipases may vary between different myocardial regions depending on the degree of ischemia and/or inflammation.
d) The *heterogeneity of electrical stability of myocardial cells in the diseased heart* muscle due to regional differences with regard to various degrees of ischemia and tissue damage, ischemic preconditioning, etc. (Dhein S et al. 2005). In this respect it should also be remembered, that in patients with coronary artery disease, myocardium is not presenting as a homogeneous and healthy tissue experiencing acute ischemia in a well-defined area, but rather as a mixture of healthy myocardium, hypertrophied tissue, scar tissue and ischemic myocardium and also includes areas of tissue with ischemic preconditioning, inflammation, various degrees of membrane phospholipid degradation and with more or less acute or chronic stretch etc. (Janse MJ et al. 2003).
e) The *species (human, various animals) being studied.* The characteristics of action potentials (APs) vary significantly between human and various animal myocardial cells and with gender (Karagueuzian HS et al. 1982; Shattock MJ & Bers DM 1989; Cheng J 2006; Tanaka H et al. 2008).
f) The *various mechanisms that trigger ventricular tachycardia and fibrillation*. Under clinical conditions ventricular tachycardia or fibrillation are predominantly caused by triggered activity or by reentry mechanisms. Fish oil shortens cardiac AP and accentuates the AP notch, which may lead to depression or even loss of the AP dome (Verkerk AO et al. 2006, 2007). Under clinical conditions, where AP is prolonged triggered activity may be the predominant pro-arrhythmic mechanism, which could

be inhibited by superfusion with Ω-3 of isolated cardiomyocytes from rabbits and from patients with end stage heart failure (Den Ruijter HM et al. 2008). Triggered activity also could be inhibited in pig cardiomyocytes (Den Ruijter HM et al. 2006). In keeping with these experimental results Ω-3 were effective in reducing the arrhythmic risk in patients with idiopathic dilated cardiomyopathy (Nodari S et al. 2009).

Conversely, AP shortening may be pro-arrhythmic by reducing the refractory period and thereby promoting re-entry. Supplementation with Ω-3 may increase a preexisting heterogeneity in AP duration and repolarization (Verkerk AO et al. 2009), as can be seen in acute ischemia (Yan GX et al. 2004). By this way the occurrence of unidirectional block and re-entry may be facilitated (Janse MJ& Wit AL 1989). In the clinical situation therefore supplementation with Ω-3 may prevent or facilitate ventricular tachyarrhythmias depending on the predominant underlying arrhythmic mechanism (Den Ruijter HM et al. 2007).

Based on these considerations it becomes apparent that Ω-3 do not have one single specific way to act, but rather possess multiple sites of potential actions, that may be influenced by a number of external conditions at the cellular and molecular level. Multiple sites of interaction between Ω-3 and myocardial tissue in combination with various possible ways of interference with these biochemical interactions, are unlikely to result in an unequivocally predictable and homogeneous beneficial effect on clinical outcomes. This is reflected by the results of animal studies and finally by the results of clinical trials.

Animal Studies

Animal studies (mostly using the rat or canine model) in general support an effect of Ω-3 supplementation on cardiac rhythm. An anti-arrhythmic effect of Ω-3 especially could be shown with respect to ischemia induced ventricular tachycardia (VT) or fibrillation (VF) (Matthan NR et al. 2005; Billman GE 2006). The clearest effect in the prevention of VF by Ω-3 was demonstrated in infusion studies using a special experimental canine model. In this model acute myocardial ischemia was induced at a site distant from a previous myocardial infarction during submaximal exercise thereby activating the autonomic nervous system (Billman GE 2006) and inducing VF.

However, these clear effects of Ω-3 under well-defined experimental conditions cannot simply be translated into the clinical situation, and several aspects have to be considered (Billman GE 2006):

a) In this canine model not only superfusion with Ω-3 but also the application of β-receptor antagonists, calcium channel blockers, and endurance exercise training – all interventions that are routinely used in actual clinical practice – were effective in VF prevention (Billman GE 2009).
b) Not all dogs were susceptible to ischemia induced VF in this model. Animals resistant to VF were characterized by reduced β-receptor responsiveness and an intact parasympathetic regulation, indicating that these are first line mechanisms to prevent ischemia induced tachyarrhythmias.

c) Finally, incorporation of Ω-3 into the phospholipid bilayer can be expected to be significantly less in infusion studies as compared to feeding studies.

Feeding studies more closely imitate the clinical situation, and under these conditions Ω-3 can be expected to exert their effect primarily after being incorporated into the cellular membrane (see chapter above). Numerous animal feeding studies have been published between 1987 -1999, and the results showed a considerable heterogeneity. Still, a meta-analysis of these studies suggests fish oil to prevent ischemia and ischemia-reperfusion induced VT/VF (Matthan NR et al. 2005). This conclusion however remains questionable as a recent feeding study using the above mentioned canine model failed to show a reduction of life-threatening ventricular arrhythmias in post myocardial infarction dogs at risk for ventricular fibrillation (Billman GE et al. 2012). Moreover Ω-3 treatment even increased the susceptibility to malignant arrhythmias in low risk dogs with or without acute myocardial infarction (Billman GE et al. 2012). In isolated hearts of pigs fed with fish oil for 8 weeks, spontaneous ischemia-induced sustained VT/VF also was facilitated in the Ω-3 group (Coronel R et al. 2007), whereas other studies report increased resistance to ischemia-reperfusion injury after dietary Ω-3 application, which also could be a basis to protect against reperfusion arrhythmias (Abdukeyum GG et al. 2008; Zeghichi-Hamri S et al. 2010).

In summary, the heterogenous results of animal studies strengthen the hypothesis that Ω-3 supplementation does not protect against serious cardiac arrhythmias under any condition. Moreover, Ω-3 even may facilitate malignant arrhythmias under certain conditions that include animals with primarily low arrhythmic risk (Billman GE et al 2012).

Earlier Clinical Studies

An inverse relationship between consumption of fish oil and cardiovascular risk was shown in early observational, case-control, and cohort studies, with respect to the occurrence of cardiovascular disease (Whelton SP et al. 2004), sudden and non-sudden cardiac death from coronary heart disease (Daviglus M et al. 1997), and with regard to SCD in apparently healthy persons (Siscovick D et al. 1995; Albert CM et al. 2002; Hu F et al. 2002; Mozaffarian D et al. 2003). Ω-3 levels in erythrocyte membranes were directly associated with a reduced rate of primary cardiac arrest (Siscovick D et al. 1995). Similarly, elevated Ω-3 blood levels were associated with a reduced risk of sudden death among men without evidence of prior cardiovascular disease (Albert CM et al. 2002).

These data were supported by prospective and randomized nutritional intervention studies of secondary prevention after acute myocardial infarction. In the Diet and Reinfarction Trial (DART) a diet rich in fish and cereals was associated with a significant 29% reduction of all-cause mortality within 2 years after acute myocardial infarction (Burr ML et al. 1989). In the Lyon Diet Heart Study the Mediterranean diet group (enriched in alpha-linolenic acid [Ω-3] and olive oil, more cereals, fresh fruit, vegetables and fish, limited intake of saturated fat and linoleic acid [Ω-6]) had a significantly lower rate of the combined endpoint cardiac death and nonfatal myocardial infarction, if compared to the control group taking a prudent western-type diet($p = 0.0001$; follow-up 27 months; de Lorgeril M et al. 1994; de Lorgeril M et al. 1998; de Lorgeril M et al. 1999).

It has to be noted that these trials primarily evaluated healthy nutrition including elevated fish consumption but not supplementation with purified Ω-3 compounds.

A predefined supplementation of Ω-3 was used in the large placebo-controlled, open labeled GISSI Prevenzione Trial (EPA+DHA 1g/day, or placebo; GISSI Prevenzione Investigators 1999), focusing on secondary prevention after acute myocardial infarction. In this study the intervention arms using Ω-3 showed a significant reduction of sudden cardiac death (SCD) - though this was not the primary endpoint of this trial but calculated by secondary analysis (Table 1). In combination with the older studies focusing on nutrition with increased fish consumption the GISSI Prevenzione Trial for several years served as a basis to treat patients after AMI with highly purified Ω-3 compounds and this even was recommended in earlier clinical guidelines (Kris-Etherton PM et al. 2003). In a consequence it was estimated that 5 -10% of the adult US population used fish oil supplements spending more than seven billion dollars by the end of 2011 (www.marketresearch.com, cited in Billman GE et al 2012). However research continued and the results of more recent clinical trials challenge a global beneficial effect of Ω-3 supplementation especially with respect to the prevention of cardiac arrhythmias.

Clinical Studies Using Patients with Implanted Cardioverter Defibrillator (ICD)

Three randomized prospective studies evaluating the effect of high doses of Ω-3 in patients with ICD-devices failed to give homogeneous results (Table 1).

In a study predominantly including patients with coronary artery disease, Ω-3 supplementation was associated with a non-significant reduction of the primary endpoint defined as time to the first ICD-event or death from any cause (reduction by28%; p=0.057). However, the death rates did not significantly differ between the study groups. Remarkably, in this study no significant effect of Ω-3 could be shown in the subgroups of patients without coronary artery disease or with a left ventricular ejection fraction above 30% (Leaf A et al. 2005a).

In another study recurrent VT events not due to myocardial ischemia were even more common in patients treated with fish oil (Raitt MH et al. 2005).

Finally the SOFA-study did not show a significant effect of Ω-3 supplementation on the primary endpoint defined as appropriate ICD-interventions for recurrent VT/VF or death from any cause. The majority of the patients included in the SOFA-study had coronary artery disease, more than 60% with previous myocardial infarction. Almost 40% of the study participants had various forms of cardiomyopathy or valvular heart disease (Brouwer IA et al. 2006). In a meta-analysis of these three studies all-cause mortality did not significantly differ between the fish oil and the control groups (relative risk 0.70; 75% CI 0.42 – 1.15; Jenkins AJA et al. 2008).

In a sub-study of the GISSI-HF trial (566 heart failure patients with implanted ICD-devices) a statistically non-significant trend towards a lower risk of ICD-discharges in patients treated with Ω-3 was shown. However, total mortality was similar in both groups (Ω-3 26.6%, placebo 24.3%), and there even was a trend for increased arrhythmia induced mortality (Ω-3 3.6%, placebo 2.1%; Table 1; Finzi AA et al 2011).

Table 1. Selected studies evaluating the effect of Ω-3 supplementation on clinical outcomes, especially cardiac arrhythmias, in primary and secondary prevention of cardiovascular disease (also see text)

Study	- Study population, - number of participants, - Intervention, - duration of follow-up	- Primary endpoints (EP1) - Secondary endpoints (EP2)	Results	Comments
Earlier clinical studies				
GISSI Prevenzione 1999	Secondary prevention after AMI n = 11,324 4 intervention arms: Ω-3, Ω-3 + vitamin E, vitamin E, placebo; Ω-3: 850-882 mg EPA+DHA (ratio 1:2) daily 3,5 years	EP1a: cumulative rates of all cause death, nonfatal AMI, nonfatal stroke, EP1b: cumulative rates of cardiovasc. death, nonfatal AMI, nonfatal stroke; secondary analysis for all cause death, SCD and others	EP1a: Ω-3 group: reduced rate RR 95% CI: 0.85 (0.74-0.98) EP1b: Ω-3 group: reduced rate RR 95% CI: 0.80 (0.68-0.95) Secondary analysis: Ω-3 group: reduced rate for SCD, RR 95% CI, 0.55 (0.40-0.76)	a) No "up to date" treatment of AMI: i.e. low rates of acute PCI, low rates of statin application b) SCD was no primary endpoint, but evaluated by secondary data analysis
Clinical studies using patients with implanted cardioverter defibrillator (ICD)				
Leaf A et al. 2005a	ICD-patients predominantly with CHD n =402 2.6 g Ω-3 ethyl esters daily 12 months	EP1: Time to first ICD-event for VT or VF or all cause death	EP1: Ω-3 group: Primary analysis: trend for a decreased event rate (p=0.057) If therapies for probable VT or VF were included: risk reduction by 31% (p=0.033) No Ω-3 effect in subgroups without CHD or LVEF < 30%	randomized, double blind study

Study	- Study population, - number of participants, - Intervention, - duration of follow-up	- Primary endpoints (EP1) - Secondary endpoints (EP2)	Results	Comments
Raitt MH et al.2005	ICD-patients with a recent episode of sustained VT of VF n =200 fish oil 1.8 g daily, containing 42% EPA, 30% DHA median 718 days; range 20 – 828 days	EP1: Time to first episode of ICD-event for VT or VF not due to ischemia	EP1: Ω-3 group: Increased rate of recurrent VT/VF (p = 0.007)	a) Randomized, placebo-controlled, double-blind study b) Ω-3 concentrations measured in red blood cells
Brouwer IA et al. 2006 (SOFA)	ICD-patients with recent episodes of VT or VF n=546 4 capsules of fish oil daily, each containing 464 mg EPA, 335 mg DHA, 162 mg other Ω-3 median 356 days; range 14-379 days	EP1: Appropriate ICD-interventions for recurrent VT/VF or all-cause death	EP1: Ω-3 group: No difference compared to control group HR, 95% CI: 0.86, 0.64-1.16	Randomized, placebo-controlled, double-blind study
Finzi AA et al. 2002	ICD-patients with heart failure, 57% with previous AMI n=566 Ω-3: 850-882 mg EPA+DHA (ratio 1:2) daily mean 928 days	EP1: Appropriate ICD-intervention EP2: All cause death Mortality for arrhythmias	EP1: Ω-3 group: No significant reduction HR, 95% CI: 0.80, 0.59-1,09 EP2: Ω-3 group: Total mortality: no effect HR, 95%CI: 1.25, 0.89-1.75	Substudy of the GISSI-HF study

Table 1. (Continued)

Study	- Study population, - number of participants, - Intervention, - duration of follow-up	- Primary endpoints (EP1) - Secondary endpoints (EP2)	Results	Comments
			Ω-3 group: Trend for increased mortality for arrhythmias: HR, 95% CI 1.84; 0.67-5.05	
Clinical trials for primary and secondary prevention including SCD in the era of primary PCI and intensified cardiovascular prevention				
Yokoyama M et al. 2007 (JELIS)	Hyperlipidemic patients without previous AMI, no serious cardiac disease but treated with statins n=18,645 1.8 g EPA daily mean 4.6 years	EP1: Any major coronary event, combining SCD, fatal and nonfatal AMI and others (see text) EP2: SCD, cardiac death, all cause death	EP1: Ω-3 group: Significant 19% relative risk reduction EP2: Ω-3 group: neither reduction of SCD, nor reduction of coronary death or all cause death	a) Prospective randomized trial b) Low rate of SCD of 0.2%; c) assumed high fish intake at baseline in both study groups
Kromhout Det al. 2010 (Alpha-Omega)	Patients 60 – 80 years of age in the chronic stable phase after AMI Four intervention arms: 1. EPA/DHA 400mg daily, 2. ALA 2 g daily, 3. EPA/DHA+ALA, 4. placebo n=4,837	EP1: combined endpoint including death, non-fatal CV events, cardiac intervention	EP1: Ω-3 group: no reduction	a) Randomized, placebo-controlled, double-blind trial b) In a secondary analyses less VT-events in patients after AMI plus diabetes
Rauch B et al.2010 (OMEGA)	Patients directly after AMI 1 g EPA/DHA ethyl esters daily n =3,851 one year	EP1: SCD EP2: All cause death, major cardiovascular and cerebrovascular events and others	EP1: no difference between the Ω-3 group and the placebo group	a) randomized, placebo-controlled, double-blind trial

Study	- Study population, - number of participants, - Intervention, - duration of follow-up	- Primary endpoints (EP1) - Secondary endpoints (EP2)	Results	Comments
			EP2: no difference between the Ω-3 and the placebo group.	b) Study underpowered for EP1 due to unexpected low rates of SCD; c) a secondary analysis showed increased rate of non sudden cardiac death in Ω-3 group (Rauch G et al 2012)
Clinical trials for prevention of atrial fibrillation				
Mozzafarian D et al 2004	Adults > 65 years; assessment of dietary intake 1989 and 1990 n=4,815 tuna, other broiled or baked fish 12 years	EP1: incidence of AF during 12 years follow-up	EP1: Fish-group: lower incidence of AF	a) Prospective polulation-based cohort study b) control of plasma Ω-3 levels
Nodari S et al.2001	Patients after electrical conversion for persistent AF treated with amiodaron and ACE-inhibitors n =199 850-882 mg EPA/DHA (ratio 0.9-1.5) daily one year	EP1: probability of maintenance of SR 1 years after cardioversion	EP1: Ω-3 group: improved probability for SR maintenance	Randomized, double-blind, placebo-controlled study
Macchia A et al. 2008	Post AMI patients free of AF during the acute event Ω-3 population: n=215	EP1: Death from any cause; hospitalization for AF	EP1: Group with elevated Ω-3 intake: Reduced EP1 with respect to both, rehospitalization and all cause death	Prospective population study, using propensity score

Table 1. (Continued)

Study	- Study population, - number of participants, - Intervention, - duration of follow-up	- Primary endpoints (EP1) - Secondary endpoints (EP2)	Results	Comments
	Control: 3.027 At least one prescription of Ω-3 preceding or following index hospitalization 360 days			
Saravanan D et al. 2010	Patients undergoing bypass surgery n=103 2g EPA/DHA ethyl esters (ratio 1.2/1), start 5 days before surgery Follow-up 5 days after bypass surgery	EP1: occurrence of episodes of AF post surgery	EP1: No difference between study groups	Randomized, double-blind, placebo controlled study
Kowey PR et al. 2010	Outpatient participants with paroxysmal (n=542) or persistent AF (n=121), no structural heart disease, SR at baseline Loading: 7 days 8 capsules of 1 g Ω-3 (EPA/DHA 465/375 mg) Continuous treatment: 24 weeks 4 capsules per day) 6 months	EP1: Patients with paroxysmal AF: First symptomatic recurrence of AF.	EP1: No difference between study groups	Randomized, double-blind, placebo controlled study
Bianconi L et al. 2011	Patients after electrical conversion for persistent AF n =204	EP1: recurrence rate of AF	EP1: No difference between study groups	Randomized, double-blind, placebo controlled study

Study	- Study population, - number of participants, - Intervention, - duration of follow-up	- Primary endpoints (EP1) - Secondary endpoints (EP2)	Results	Comments
	850 mg EPA/DHA (ratio 0.9-1.5) 3-times daily, 7 days before cardioversion and 6 months thereafter			
Farquharson AL et al. 2011	Patients after cardiac surgery n = 194 4.6 g dietary Ω-3 daily, start 3 weeks before surgery 6 days post surgery	EP1: incidence of AF	EP1: No difference between study groups	Randomized, double-blind placebo-controlled study
Mozaffarian D et al 2012	Patients after cardiac surgery n =1,516 1 g capsule containing EPA 465 mg + DHA 375 mg daily; 10g as loading dose over 3-5 days pre surgery 10 days post- surgery or hospital discharge	EP1: occurrence of post-surgery AF,duration > 30 seconds EP2: a variety of clinical events including 30-day mortality	EP1: Ω-3 group: no reduction of post- surgery AF EP2: no effect of Ω-3 supplementation on any of the secondary endpoints	Randomized, double-blind placebo-controlled trial

AF, atrial fibrillation; ALA, alpha-linolenic acid; AMI, acute myocardial infarction; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; ICD, implanted cardioverter defibrillator; SCD, sudden cardiac death; SR, sinus rhythm; VT, ventricular tachycardia; VF, ventricular fibrillation.

In conclusion, the apparent heterogeneity in the response of ICD-patients to Ω-3 supplementation may be regarded as a consequence of different study populations and different arrhythmic origins (ischemic versus non ischemic). However, heterogeneity also could be the result of different concomitant medications of the study populations including β-blockers, digoxin, and amiodaron.

Clinical Trials for Primary and Secondary Prevention Including Sudden Cardiac Death in the Era of Primary PCI and Intensified Cardiovascular Prevention (Table 1)

The multicenter Japan EPA Lipid Intervention Study (JELIS; Yokoyama M et al. 2007) investigated the consumption of 1.8 g EPA per day over a mean period of 4.6 years in hyperlipidemic patients without previous AMI and no apparent serious heart disease but treated with statins. The data showed a reduction of the combined endpoint of major cardiovascular events (including sudden cardiac death, fatal and nonfatal myocardial infarction, and other nonfatal events including unstable angina, angioplasty, stenting, or coronary bypass grafting) from 3.5% to 2.8% (p=0.011; hazard ratio [HR] 0.81, 95% CI 0.69-0.95). The limitation of using combined competing endpoints becomes apparent, as subgroup analyses neither showed a reduction of sudden cardiac death (0.2 % in both study arms; HR 1.06, 95% CI 0.55-20.07) nor of coronary death (0.3 % in both study arms; HR 0.94, 95% CI 0.57-1.56) or all-cause mortality (control 2.8%, EPA-group 3.1 %; HR 1.09, 95% CI 0.92-1.28).

Compared to the GISSI Prevenzione trial death rates and especially the rates of sudden cardiac death were very low in both groups and therefore may be difficult to be further reduced by any intervention (rates for sudden cardiac death: JELIS 0.2 % in both groups; GISSI 2.2%/2.9% Ω-3 versus control; Yokoyama M et al. 2007; GISSI-Prevenzione Investigators 1999). Furthermore, these low event rates may at least in part be the result of a high fish consumption of the Japanese population at baseline. As it has been reported that the major part of risk reduction already occurs at about 250 mg EPA/DHA per day (Mozaffarian D & Rimm EB 2006) a further increase of Ω-3 intake may not have a substantial additional effect on cardiac death reduction (Mozaffarian D 2007).

In the Alpha-Omega-Study 4,837 patients in the chronic stable phase after myocardial infarction were randomly assigned to one of four trial arms. Margarine was used in all trial arms, supplemented with either EPA/DHA, alpha-linolenic acid, EPA/DHA + ALA, or placebo, respectively (Kromhout D et al. 2010; Table 1). The rates of the primary combined endpoint (death, nonfatal cardiovascular events, or cardiac intervention) did not differ between the study groups. In addition, in all secondary endpoints, including ventricular-arrhythmia and total death, there was no significant difference between the study groups. Importantly, a high percentage of the patients received “state of the art medication”, including statins.

In a post hoc analysis after unblinding of the data in the subgroup of patients with diabetes ventricular arrhythmia related events tended to be reduced in the EPA-DHA group (HR 0.51; 95% CI 0.24-1.11) and significantly were reduced in the ALA-group (HR 0.39; 95% CI 0.17-0.88). In a secondary analysis of the Alpha-Omega Trial taking high risk

patients with previous myocardial infarction and diabetes the EPA-DHA plus ALA group experienced significantly less ventricular arrhythmia-related events (HR 0.16; 95% CI 0.04-0.69; Kromhout D et al. 2011). These differential results again underscore the necessity to exactly define the clinical conditions under which supplementation of Ω-3 may be beneficial.

The OMEGA trial tested the effect of supplementation with 1 g/day of esterified EPA/DHA on the rate of SCD and other clinical events within one year after acute myocardial infarction (AMI; 3,851 patients, 25.6% female, mean age 64.0 years; Rauch B et al.2006, 2010). A one year follow-up was chosen, as the risk of cardiac death after acute myocardial infarction including a presumed arrhythmic death is highest in the first three months after the event (Solomon SD et al. 2005; Pouleur AC et al. 2010). Furthermore, in the GISSI trial significance in lowering SCD by Ω-3 had already been reached within 120 days after AMI (Marchioli R et al. 2002). Following guidelines for the management of acute myocardial infarction and secondary prevention 77% of the patients in the OMEGA trial received acute percutaneous coronary intervention, and/or thrombolysis (8.3%). At hospital discharge the vast majority (> 90%) of the included patients received guideline adjusted medication including beta-blockers, ACE-inhibitors or ARBs, statins, acetylsalicylic acid, and clopidogrel. Under these conditions, the rates of SCD were unexpectedly low with 1.5 % in both study groups (OR 0.95, 95% CI 0.56-1.60), whereas total mortality was 4.6% in the Ω-3 group and 3.7% in the control group (OR 1.25. 95% CI 0.90-1.72). Furthermore, there was no significant difference between the study groups with regard to sudden cardiac death or total death in any of the predefined subgroups of patients with higher risk (diabetes, age > 70 years, no acute revascularization, ejection fraction < 35%).

Despite these apparently homogeneous results interpretation is limited as the case estimate in the OMEGA-study was based on an overestimation of the rate of SCD in the control group, thereby leading to an underpowering of the study.

Still, according to a secondary competing risk analysis of the OMEGA-study data, treatment with Ω-3 even tended to have a negative effect on all cause death and had a significant negative effect on non-sudden cardiac death (Rauch G et al. 2012).

Two other randomized controlled trials also failed to show a clear beneficial effect of Ω-3 supplementation. In 563 elderly Norwegian men at high cardiovascular risk a non significant tendency to a reduced all-cause mortality after three years could be observed (HR 0.53, 95% CI 0.27-1.04), but the rate of cardiovascular events remained unchanged (HR 0.89; 95% CI 0.55-1.45, Einvik G et al. 2010). In 2,501 patients with a history of myocardial infarction, unstable angina or ischemic stroke supplementation with EPA/DHA was not associated with a significant decrease of major vascular events during a follow-up of 4.7 years (HR 1.08; 95% CI 0.79-1.47; Galan P et al. 2010).

Clinical Trials for Prevention of Arial Fibrillation

Heterogeneity of the effect of Ω-3 supplementation also can be seen with respect to prevention of atrial fibrillation (Table 1). Positive results (Mozaffarian et al. 2004, primary prevention by fish intake in patients > 65 years of age; Calò L et al. 2005, patients undergoing coronary artery surgery; Macchia A et al. 2008, post myocardial infarction patients) were not confirmed in more recent studies and meta-analyses (Kowey PR et al. 2010; Saravanan P et al. 2010; Bianconi L et al. 2011; Farquharson AL et al. 2011; Liu T at al. 2011). In the

multinational OPERA trial including 1,516 patients undergoing cardiac surgery perioperative Ω-3 supplementation also did not reduce the risk of postoperative atrial fibrillation (Mozaffarian D et al. 2012). On the other hand supplementation with DHA 1.5 g and EPA 0.3g daily resulted in a prolongation and reduced dispersion of pulmonary venous and left atrial effective refractory periods in patients with paroxysmal atrial fibrillation (Kumar S et al. 2011). Furthermore, in patients with persistent atrial fibrillation on amiodarone and a renin-angiotensin-aldosterone system inhibitor, additional intake of Ω-3 (2g/day) improved the probability of maintaining sinus rhythm after direct current cardioversion (Nodari S et a. 2011). Therefore, prevention of atrial fibrillation also may depend on distinct clinical and pathophysiological conditions and concomitant medication.

Recent Meta-Analyses on the Effect of Ω-3 Supplementation on Major Clinical Events Including SCD

As mentioned at the beginning of this chapter, evaluation of the biological and clinical effects have attracted and still attract the scientific world for almost four decades and - apart from the numerous studies – many meta-analyses tried to summarize the clinical effect of Ω-3 supplementation. Of these two recently published meta-analyses have to be mentioned as they include all the recently published clinical trials that reflect actual medical and interventional treatments of cardiovascular disease.

In the first meta-analysis including 68,680 patients in 20 studies did not show a beneficial effect of Ω-3 supplementation with respect to total mortality (RR 0.96; 95% CI, 0.91-1.02) and sudden cardiac death (RR 0.87; 95% CI, 0.75-1.01) (Rizos EC et al, 2012).

In another meta-analysis published in parallel also 20 trials were included with a total of 62.851 patients. Supplementation with Ω-3 was associated with reduced vascular death (RR0.86; 95% CI, 0.75-0.99), but there neither was a reduction of total mortality (RR 0.95; 95% CI, 0.86-1.04) nor of the composite endpoint of myocardial infarction, stroke and cardiovascular death (RR0.96; 95% CI 0.90-1.03). There also was no effect on arrhythmias (RR 0.99; 95% CI, 0.85-1.16; p=0.92; Kotwal S et al. 2012).

Conclusion

a) Ω-3 clearly interfere with the physiology of myocardial cell membranes through a variety of specific and unspecific pathways, and thereby potentially influence cardiac rhythm. However, these membrane effects of Ω-3 are complex. This complexity makes it difficult to predict the effects of Ω-3 supplementation on cardiac rhythm within the wide variety of conditions that represent clinical practice.
b) The effect of Ω-3supplementation may depend on the background diet and the pre-existent intake of fish oil (Reiffel JA & McDonald A et al. 2006; Mozaffarian D & Rimm EB 2006; Mozaffarian D 2007).
c) With regard to earlier studies, treatment of patients with coronary artery disease, especially treatment of patients with myocardial infarction has improved markedly.

In the GISSI trial (inclusion period October 1993 – September 1995) only 4.4 % of the patients had acute coronary revascularization at baseline, and only 4.7% were on statins at hospital discharge, increasing to only 46% after 42 months of follow-up (GISSI-Prevenzione Investigators 1999). Furthermore, only 43.9% of the patients included in the GISSI trial were on beta-blocker treatment at the start of the study, and this percentage decreased during follow-up. It therefore may be speculated that up-to-date guideline adjusted treatment of AMI (including acute revascularization, medical treatment and support of life style changes) interferes with molecular and cellular Ω-3 interactions thereby weakening or competing with a potential beneficial Ω-3 effect. Although the available data not homogeneously support this hypothesis (Marchioli R et al. 2007), this aspect should strongly be considered in future research. Especially statin treatment may interfere with potential Ω-3 effects (Eussen SR et al 2012; de Lorgeril M et al 2013).

d) The potential clinical anti-arrhythmic effect of Ω-3 may depend on the pathophysiological conditions facilitating arrhythmias. In the case that Ω-3 supplementation especially protects against ischemia induced arrhythmias, prevention of ischemia by modern treatments (i.e. revascularization, beta-blockers, statins, ACE-inhibitors, inhibition of thrombocyte aggregation, physical exercise) could attenuate this beneficial effect of Ω-3. From this background it has to be remembered that beta-blockers are well known to prevent SCD, and even statins could have some anti-arrhythmic effects (Anh D 2004; Lorenz H et al. 2005).
e) In accordance to these considerations potential anti-arrhythmic effects of Ω-3 by augmentation of vagal activity (Mozaffarian D et al. 2005; O`Keefe JH et al. 2006) could be blunted by beta-blocker treatment and increased physical training during cardiac rehabilitation (Nolan JP et al. 2008; Billman GE 2009).

In summary, the anti-arrhythmic effect proven under some well-defined experimental conditions in animal models and suggested in the earlier clinical studies appears to depend on the clinical conditions being studied. These clinical conditions are determined by the type and stage of the underlying myocardial disease and represent a sum of various pathophysiological conditions (including ischemia, reperfusion, ischemic preconditioning, scar tissue, inflammation, congenital defects etc.), the effects of modern medication including beta-blockers, ACE-inhibitors, statins, but also nutrition determining preexisting Ω-3 levels and other interventions potentially interfering with the arrhythmic risk, such as exercise training. For the future it will be necessary to exactly define the clinical conditions in which supplementation with of Ω-3 may be beneficial, and without potentially harmful effects. As long as these conditions are not well defined supplementation with Ω-3 compounds remains questionable and Mediterranean diet including increased fish consumption remains the way to be preferred for cardiovascular disease prevention.

Conflict of Interest Statement

Rauch B.: no conflicts of interest;

Senges J: received honoraria for educational presentations from Trommsdorff GmbH & CoKG Arzneimittel, Alsdorf, Germany and Pronova Biopharma, Lysaker, Norway

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