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The effects of omega-3 polyunsaturated fatty acids on cardiac rhythm: A critical reassessment

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ABSTRACT

Although epidemiological studies provide strong evidence for an inverse relationship between omega-3 polyunsaturated fatty acids (n−3 PUFAs) and cardiac mortality, inconsistent and often conflicting results have been obtained from both animal studies and clinical prevention trials. Despite these heterogeneous results, some general conclusions can be drawn from these studies: 1) n-PUFAs have potent effects on ion channels and calcium regulatory proteins that vary depending on the route of administration. Circulating (acute administration) n−3 PUFAs affect ion channels directly while incorporation (long-term supplementation) of these lipids into cell membranes indirectly alter cardiac electrical activity via alteration of membrane properties. 2) n−3 PUFAs reduce baseline HR and increase HRV via alterations in intrinsic pacemaker rate rather than from changes in cardiac autonomic neural regulation. 3) n−3 PUFAs may be only effective if given before electrophysiological or structural remodeling has begun and have no efficacy against atrial fibrillation. 5) Despite initial encouraging results, more recent clinical prevention and animal studies have not only failed to reduce sudden cardiac death but actually increased mortality in angina patients and increased rather than decreased malignant arrhythmias in animal models of regional ischemia. 6) Given the inconsistent benefits reported in clinical and experimental studies and the potential adverse actions on cardiac rhythm noted during myocardial ischemia, n−3 PUFA must be prescribed with caution and generalized recommendations to increase fish intake or to take n−3 PUFA supplements need to be reconsidered.

Contents

Abbreviations: AF, atrial fibrillation; AFL, atrial flutter; ALA, alpha-linolenic acid; APD, action potential duration; BP, blood pressure; Ca-ATs, calcium aftertransients; CICR, calcium induced calcium release; DADs, delayed afterdepolarizations; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EADs, early afterdepolarizations; EPA, eicosapentaenoic acid; ERP, effective refractory period; HR, heart rate; HRV, heart rate variability; ICDs, implantable cardioverter defibrillators; MI, myocardial infarction; MSNA, muscle sympathetic nerve activity; n−3 PUFAs, omega-3 polyunsaturated fatty acids; n−6 PUFAs, omega-6 polyunsaturated fatty acids; RBC, red blood cell; RYRs, ryanodine receptors; SR, sarcoplasmic reticulum; VF, ventricular fibrillation; VT, ventricular tachycardia.

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1. Introduction

The effective management of cardiac arrhythmias, either of atrial or of ventricular origin, remains a major challenge for the cardiologist. Sudden cardiac death, most frequently due to ventricular tachyarrhythmias (Hinkle & Thaler, 1982; Bayes de Luna et al., 1989; Greene, 1990), remains the leading cause of death in industrially developed countries, accounting for 300,000 to 500,000 deaths each year in the United States (Abildstrom et al., 1999; Zheng et al., 2001). In a similar manner, atrial fibrillation is the most common rhythm disorder, accounting for about 2.6 million cases in the United States and contributes to approximately one quarter of the ischemic strokes in the elderly population (Anonymous, 1998; Kannel et al., 1998; Lakshminarayan et al., 2006; McManus et al., 2012). The emotional and economic consequences associated with the morbidity and mortality resulting from cardiac arrhythmias cannot be understated (the incremental cost per quality-adjusted life-year has been estimated to be as high as US $558,000 (Byrant et al., 2005)).

Despite the enormity of this problem, the development of safe and effective anti-arrhythmic agents remains elusive. Several anti-arrhythmic drugs have actually been shown to increase, rather than to decrease, the risk for arrhythmic death in patients recovering from myocardial infarction (Echt et al., 1991; Waldo et al., 1996), while even "optimal" pharmacological therapy fails to suppress these arrhythmias completely (Buxton et al., 1999). For example, the one-year mortality is 10% or higher, with sudden death accounting for approximately one-third of the deaths, in post-myocardial infarction patients treated with β-adrenergic receptor antagonists (Buxton et al., 1999). Implantable cardioverter defibrillators (ICDs) have been shown to reduce cardiac mortality, providing a better protection from sudden death than current pharmacological therapy in certain high-risk patient populations (Buxton et al., 1999; Connelly et al., 2000; Al-Khatib et al., 2013). However, these devices are expensive to use and maintain (Byrant et al., 2005; Groeneveld et al., 2006), negatively affect the patient's quality of life (Groeneveld et al., 2006), have a significant risk for inappropriate shock delivery (Poole et al., 2008), are ineffective in elderly and female patients (Henyan et al., 2006; Katritsis & Josephson, 2012), and, perhaps most importantly, only extend life by a mean of 4.4 months (Connelly et al., 2000). Given the adverse outcomes associated with ICDs and many anti-arrhythmic medications, as well as the partial protection afforded by even the best agents (e.g., β-adrenergic receptor antagonists and ICDs), it is obvious that more effective anti-arrhythmic therapies must be developed.

Dietary interventions have recently received considerable attention as viable alternatives to the less than effective current therapies. In particular, the cardiovascular benefits of dietary omega-3 polyunsaturated fatty acids (n−3 PUFA) have been actively investigated for nearly 40 years. Epidemiological data provide strong evidence for an inverse relationship between fatty fish consumption and cardiac mortality (Kromhout et al., 1985; Daviglus et al., 1997) while both experimental studies (McLennan et al., 1988; Billman et al., 1994) and clinical secondary preventions trials (Burr et al., 1989; Marchioli et al., 2002) have reported salutary actions of n−3 PUFAs against ventricular arrhythmias and sudden cardiac death. However, more recent studies in patients with heart disease (Burr et al., 2003; Raitt et al., 2005; Brouwer et al., 2006b; Yokoyama et al., 2007; GISSI-HF investigators, 2008; Kromhout et al., 2010; Rauch et al., 2010) or animals (Coronel et al., 2007; Billman et al., 2012) have yielded conflicting results, particularly with regards to the prevention of atrial fibrillation (Kowey et al., 2010; Mozaffarian et al., 2012; Sandesara et al., 2012). Thus, a scientific consensus on the effects of n−3 PUFA on cardiac rhythm has yet to be reached.

It is the purpose of this review to evaluate the putative benefits of n−3 PUFAs on cardiac rhythm. The review will first address the effects of n−3 PUFAs on heart rate variability (i.e., sinus rhythm) and then will provide a critical analysis of the effects of n−3 PUFAs on atrial fibrillation and ventricular arrhythmias/sudden cardiac death.

2. The effects of omega-3 fatty acids on heart rate and heart rate variability

There is a strong association between both heart rate (HR) and heart rate variability (HRV) and cardiovascular mortality. It is now well established that an elevated resting heart rate (>70–90 beats/min) is associated with a greater risk for sudden cardiac death in both individuals with and without pre-existing cardiovascular disease, even after adjusting for other established cardiovascular risk factors (Shaper et al., 1993; Palatini et al., 1999). Indeed, individuals with the lowest resting heart rates also exhibited the lowest long-term (>20 years) mortality rate (Jouven et al., 2009). Among the Framingham study cohort, resting HR was one of the strongest independent predictors of future sudden cardiac death with mortality rates progressively increasing as resting heart rate increased (Kannel et al., 1987). In a similar fashion, a reduced HRV (beat-to-beat variation in either HR or the duration of the R–R interval—the heart period) is associated with a poorer prognosis for a wide range of clinical conditions while, conversely, robust periodic changes in R–R interval are often a hallmark of health (Task Force of the European Society of Cardiology and the North American Society of Pacing & Electrophysiology, 1996; Berntson et al., 1997; Hohnloser et al., 1997; Billman, 2009; Thayler et al., 2010; Billman, 2011). It is now widely accepted that these beat-to-beat variations in HR reflect changes in cardiac autonomic regulation and several time and frequency domain techniques have been developed to quantify HRV, each with strengths and weaknesses (for reviews see: Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Hohnloser et al., 1997; Berntson et al., 1997; Thayler et al., 2010; Billman, 2011). In general, and at the risk of oversimplification, HRV can be considered to be directly related to cardiac parasympathetic regulation and to a lesser extent inversely related to sympathetic activity. However, it must be emphasized that the exact contributions of the parasympathetic and the sympathetic divisions of the autonomic nervous system to this variability are controversial and remain the subject of active investigation and debate (Parati et al., 2006; Billman, 2013; Reyes del Paso et al., 2013).

It is well established that interventions that decrease cardiac parasympathetic activity and/or enhance cardiac sympathetic decrease both HRV and cardiac electrical stability increasing the risk for life threatening arrhythmias (Billman, 2009). Furthermore a variety of cardiovascular risk factors and disease states have been shown to reduce HRV, including diabetes (Murray et al., 1975; Ewing et al., 1985; Vinik et al., 2003; Rosengard-Barlund et al., 2009), smoking (Mancia et al., 1997; Karakaya et al., 2007), obesity (Skrapari et al., 2007), and work stress (Thayler et al., 2010). Of particular interest, HRV is reduced in patients recovering from a myocardial infarction and, further, those patients with the greatest reduction in this variable also have the greatest risk for sudden death (Myers et al., 1986; Kleiger et al., 1987; La Rovere et al., 1988; Malik et al., 1989; Farrell et al., 1991; Bigger et al., 1992; Mazzuero et al., 1992; Huikuri et al., 1996; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Hohnloser et al., 1997; La Rovere et al., 1998; Lanza et al., 1998). Indeed, low HRV is one of the strongest independent predictors of mortality following myocardial infarction. (La Rovere et al., 1988; Malik et al., 1989; Mazzuero et al., 1992; La Rovere et al., 1998). Similar findings have been reported in animals models of human disease (Billman & Hoskins, 1989; Collins & Billman, 1989; Halliwill et al., 1998; Houle & Billman, 1999; Smith et al., 2005; Billman, 2006a,b; Billman & Kukielka, 2006; Billman, 2009).

Heart rate reduction lowers the metabolic demand placed on the heart and could thereby indirectly decrease the risk for adverse cardiac events while HRV increases may reflect increased cardiac parasympathetic regulation which has been shown to protect against ventricular arrhythmias (Billman, 2009, 2011). Thus, interventions that reduce resting HR and improve cardiac autonomic balance as measured by an

increased HRV could thereby protect against sudden death in high-risk patient populations. Indeed, the beneficial actions of β-adrenergic receptor antagonists on cardiac mortality following myocardial infarction have been attributed to the negative chronotropic actions of these drugs (Held & Yusuf, 1989, 1993) and are often prescribed specifically to lower HR (Arshald et al., 2008). A number of experimental and clinical studies also demonstrate that n−3 PUFAs both lower resting heart rate and increase resting HRV (Billman et al., 1994; Christensen et al., 1999; Christensen & Schmidt, 2007; Billman et al., 2010; Billman & Harris, 2011; Christensen, 2011). It has been proposed that the cardiovascular benefits ascribed to dietary n−3 PUFAs could result, at least in part, from these reductions in HR (Christensen et al., 1999; Christensen & Schmidt, 2007; Christensen, 2011). This section will first review the evidence that demonstrates that n−3 PUFAs lower HR and increase HRV and then consider possible mechanisms that may mediate these HR changes; specifically, changes in cardiac autonomic regulation as opposed to changes in pacemaker intrinsic rate.

2.1. Effect on baseline heart rate and heart rate variability

In 1990, the acute application of purified n−3 PUFAs was shown to the decrease the spontaneous beating rates of neonatal rat cardiomyocytes (Hallaq et al., 1990). This observation was subsequently confirmed in a conscious canine model in which the intravenous administration of an emulsion of either fish oil or purified n–3 PUFA reduced HR and increased HRV (Billman et al., 1994, 1997, 1999). There have been numerous studies that have confirmed these earlier observations. Both clinical (Christensen et al., 1999; Villa et al., 2002; Dallongesville et al., 2003; Holguin et al., 2005; Christensen & Schmidt, 2007; Carney et al., 2010; Dai et al., 2010; Sjoberg et al., 2010; Christensen, 2011) and experimental studies (Laustiola et al., 1986; Kang & Leaf, 1994; Ayalew-Pervanchon et al., 2007; Billman et al., 2010; Billman & Harris, 2011; Mayyas et al., 2011) report that n–3 PUFA ingestion or acute intravenous administration (Billman et al., 1994) lower HR and increase HRV, suggestive of an increase in cardiac parasympathetic regulation (Billman, 2009, 2011). Billman and Harris (2011) further report that these HR reductions and HRV increases were dose-independent (1–4 mg/kg per day for 3 months), suggesting a low threshold for this effect. In a similar fashion, infants fed formulas supplemented with varying concentrations of docosahexaenoic acid (DHA) also exhibited dose-independent reductions in HR (Columbo et al., 2011). Omega-3 PUFA supplements (1 g/day) also reduced HR and increased indices of HRV in heart failure patients independent of β-adrenergic receptor blocker therapy and fish consumption, reaching a maximum by 3 months of treatment (La Rovere et al., 2013). Red blood cell (RBC) membrane n−3 PUFA content was also negatively associated with resting heart rate (lower heart rate with higher RBC n−3 PUFA content) among Alaskan Eskimos participating in the Genetics of Coronary Disease in Alaska Natives study (Ebbesson et al., 2010) and dose-dependent reductions in resting heart rate have also been reported in interventional studies (Skulas-Ray et al., 2012). Both red blood cell membrane DHA and eicosapentaenoic acid (EPA) content negatively correlated with resting heart rate and positively correlated with HRV in Nunavik Inuit women; no significant associations were observed in men (Valera et al., 2011). These results contrast somewhat with a previous study in which fish oil treatment increased HRV and reduced HR in men but not women (Christensen et al., 1999).

It should be emphasized that not all studies have reported positive actions of n−3 PUFAs on either HR or HRV. In several studies, n−3 PUFAs failed to alter either HR, HRV or other measures of autonomic function (Russo et al., 1995; Geelen et al., 2003; Monahan et al., 2004; Hamaad et al., 2006; S.H. Kim et al., 2011), such as baroreceptor sensitivity (Geelen et al., 2003) or resting muscle sympathetic nerve activity (Monahan et al., 2004; Carter et al., 2012, 2013). DHA has also been reported to enhance rather than reduce the positive chronotropic response to β-adrenergic receptor stimulation in cultured rat cardiomyocytes (Grynberg et al., 1995). The HR and HRV effects of n−3 PUFAs often were not maintained for the long-term. For example, although n−3 PUFA supplements initially reduced HR and increased HRV in heart failure patients, these effects were absent by 12 months of treatment (La Rovere et al., 2013). Furthermore, even in the studies that reported a positive action of n−3 PUFAs on HR or HRV, the effect was often quite small (Mozaffarian et al., 2005b, 2006, 2008). For example, a meta-analysis of 30 trials found that fish oil supplements (~3.5 g/day of EPA + DHA) reduced baseline HR by 2.5 beats/min (Mozaffarian et al., 2005b), while Mozaffarian et al. (2008) reported that individuals with the highest fish consumption (≥5 meals/week) only exhibited 1.5 ms greater HRV compared to those with the lowest fish consumption. Although this difference was statistically significant, such a small change in resting HRV is not likely to be physiologically relevant. Indeed, these investigators calculated that only a 1.1% reduction in the relative risk for sudden cardiac death could be associated with this very modest increase in HRV (Mozaffarian et al., 2008). However, these small changes could have important consequences if they are maintained during a physiological stressor such as exercise or acute myocardial ischemia. Reductions in HR would reduce metabolic demand placed on the heart, particularly when oxygen supply is compromised by coronary artery lesions/obstructions. The resulting better match between oxygen supply and oxygen demand would, indirectly, decrease the risk for adverse cardiac events associated with myocardial ischemia. Therefore, it is critical to also evaluate the effects of n−3 PUFAs on the heart rate and HRV responses to physiological challenges.

2.2. Effect on the heart rate and heart rate variability response to physiological challenges

The effects of n−3 PUFAs on HR and HRV responses to several different physiological challenges have been evaluated. Monahan et al. (2004) reported that 1 month of daily treatment with either fish oil (500 mg/day DHA + EPA) or placebo (olive oil) did not alter baseline blood pressure (BP), HR, or muscle sympathetic nerve activity (MSNA) while the MSNA (but neither HR or BP) response to the cold pressor test and ischemic handgrip to fatigue was significantly greater in the individuals treated with fish oil capsules as compared to placebo group. In contrast, baseline HR and the peak HR rate response to either the cold pressor test or to a mental stress (speaking task) were reduced after treatment (8 weeks, a placebo-controlled double-blind, randomized, cross over trial) with either a low (0.85 g/day EPA + DHA) or a high (3.4 g/day EPA + DHA) dose compared to a placebo (corn oil) (Skulas-Ray et al., 2012). In a similar manner, both the HR and MSNA increase elicited by mental arithmetic (serial subtraction) was attenuated in normotensive subjects treated with fish oil capsules (9 g/day for 8 weeks) as compared to placebo (olive oil) treatment (Carter et al., 2013). Circulating catecholamine levels also increased to a smaller extent during a mental challenge in fish-oil treated subjects as compared to the placebo group (Delarue et al., 2003). Dose and treatment duration may account for the divergent responses noted in these studies, as a greater attenuation of the response was noted with higher doses or longer treatment durations.

Omega-3 fatty acids have been consistently shown to attenuate the HR and HRV response to exercise in both animals (Lortet & Verger, 1995; Billman & Harris, 2011; Billman, 2013) and humans (O'Keefe et al., 2006; Ninio et al., 2008; Peoples et al., 2008; Buckley et al., 2009; Moyers et al., 2011). In perhaps the most comprehensive study, Billman and Harris (2011) found that n−3 PUFA treatment induced reductions in resting HR that were accompanied by increases in HRV and further, that these changes were maintained during exercise (the peak values obtained during the stimulus were lower after n−3 PUFA treatment as compared to values reached before the treatment began). However, the absolute magnitude of the change in HR

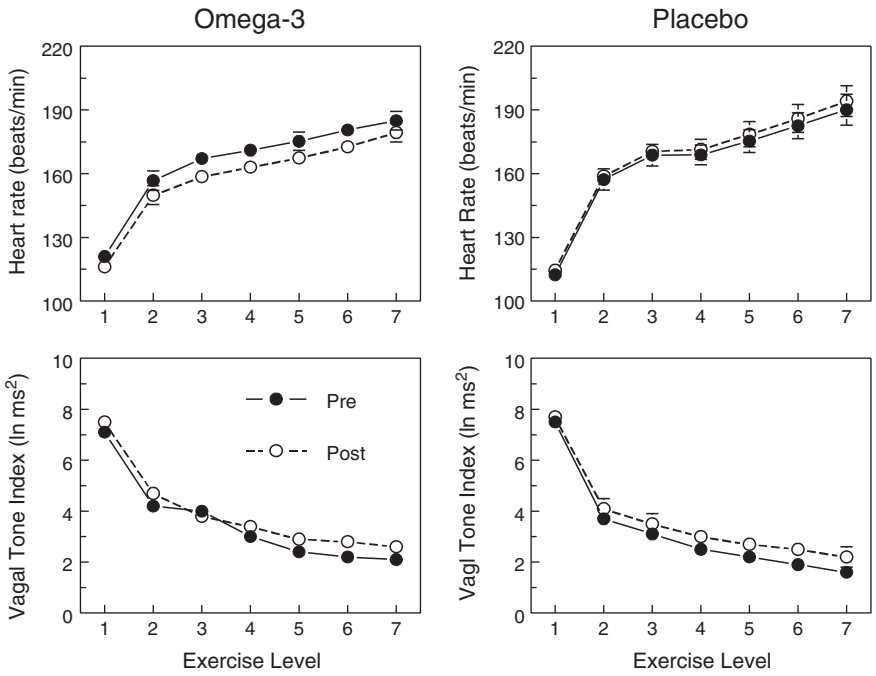

Fig. 1. Effect of omega-3 polyunsaturated fatty acids (n−3 PUFAs) on the heart rate and heart rate variability response to submaximal exercise. Dietary n−3 PUFA, but not the placebo, produced a significant downward shift of the heart rate response curve that was accompanied by an upward shift in the high frequency component of the R–R interval variability (vagal tone index 0.24 to 1.04 Hz) (i.e., significant pre-post effect). Despite the shifts in the curves, the absolute change in these variables induced by the exercise was not altered before or after the treatment (i.e., there was no significant pre-post treatment × exercise interaction). The data were averaged over the last 30 s of given exercise level. Exercise levels are as follows: 1 = 0 kph and 0% grade; 2 = 4.8 kph and 0% grade; 3 = 6.4 kph and 0% grade; 4 = 6.4 kph and 4% grade; 5 = 6.4 kph and 8% grade; 6 = 6.4 kph and 12% grade; 7 = 6.4 kph and 16% grade. pre = before placebo (n = 16) or n−3 PUFA (1–4 g/day, n = 35) treatment began, post = after 3 months of treatment. Reproduced with permission from Billman & Harris, 2011.

and HRV provoked by exercise was not altered by n−3 PUFA treatment and was similar to that recorded for the placebo (Fig. 1). In other words, the n−3 PUFA treatment produced parallel shifts in the response to exercise due to changes in resting (pre-challenge) HR and HRV (Fig. 1). A more rapid HR recovery following the termination of exercise was also noted after n−3 PUFA treatment compared to placebo treated animals (Billman & Harris, 2011). Interestingly, the faster HR recovery was not accompanied by corresponding increases in the high frequency component of R–R interval variability, suggesting that cardiac vagal regulation was not affected by the n−3 PUFA treatment. Similar responses were also noted in animals both at a high and at a low risk for ventricular fibrillation (Billman, 2012).

Relatively few studies have evaluated the effects of n−3 PUFA on the response to exercise in humans (O'Keefe et al., 2006; Ninio et al., 2008; Peoples et al., 2008; Buckley et al., 2009; Moyers et al., 2011). Dietary fish oil supplements (8-wks, 8 g/day) produced HR reductions both at rest and at peak work load in well trained men (bicyclists) during submaximal exercise (Peoples et al., 2008). In a similar manner, fish oil (5-wks, 6 g/day) reduced HR during exercise in a group of Australian rules football players (Buckley et al., 2009). Finally, fish oil supplements (12 wks, 6 g/day DHA-rich tuna oil) produced small reductions in baseline HR and larger reductions in HR with increasing work-load in sedentary overweight adults (Ninio et al., 2008). Unlike the previous clinical studies (O'Keefe et al., 2006; Peoples et al., 2008; Buckley et al., 2009), these investigators also evaluated the effects of the interventions on the HRV (Ninio et al., 2008). The fish oil supplement also increased the high frequency component of HRV both at rest and during exercise. The changes in HR and HRV induced by the fish oil supplements were similar to those recorded in a group of exercise-trained subjects (Ninio et al., 2008). The authors concluded that fish oil supplements "reduced HR and modulated HRV in keeping with an improved parasympathetic-sympathetic balance in overweight adults" (Ninio et al., 2008). These latter results contrast somewhat with the canine studies (Billman & Harris, 2011; Billman, 2012), in that the tuna oil supplements induced modest changes in baseline HRV and HR but also attenuated both the HR and the HRV responses to exercise. Species (dog vs. human) may account for the seemingly disparate results. Finally, n−3 PUFA did not alter the HR or the HRV response to exercise onset but provoked a more rapid decline in HR (i.e., a faster recovery) following the termination of exercise in both humans (O'Keefe et al., 2006; Moyers et al., 2011) and animals (Billman & Harris, 2011; Billman, 2012).

The effects of n−3 PUFA treatment on the HR and HRV response to acute myocardial ischemia have been less extensively investigated. It is well established that acute myocardial ischemia in both humans and animals will elicit large increases in HR that are accompanied by reductions in HRV (Collins & Billman, 1989; Halliwill et al., 1998; Houle & Billman, 1999; Billman, 2006a, 2009); changes that are indicative of potentially pro-arrhythmic changes in cardiac autonomic balance (Billman, 2009). Despite alterations in pre-occlusion HR and HRV, the cardiac response to coronary artery occlusion was not altered by n−3 PUFA treatment (Billman & Harris, 2011; Billman, 2012). As was noted in response to exercise, n−3 PUFA treatment produced parallel shifts in the coronary occlusion response curves (due to changes in the pre-occlusion HR and HRV) but the magnitude of the change in these variables was not altered by n−3 PUFA treatment (Fig. 2). Similar changes were induced by n−3 PUFA treatment in animals both at a low and at a high risk for ischemically-induced lethal arrhythmias (Billman, 2012). As the robust autonomic response to the coronary occlusion was not altered, the changes in pre-ischemic HR and HRV induced by the n−3 PUFA may be insufficient to prevent malignant changes in the cardiac rhythm.

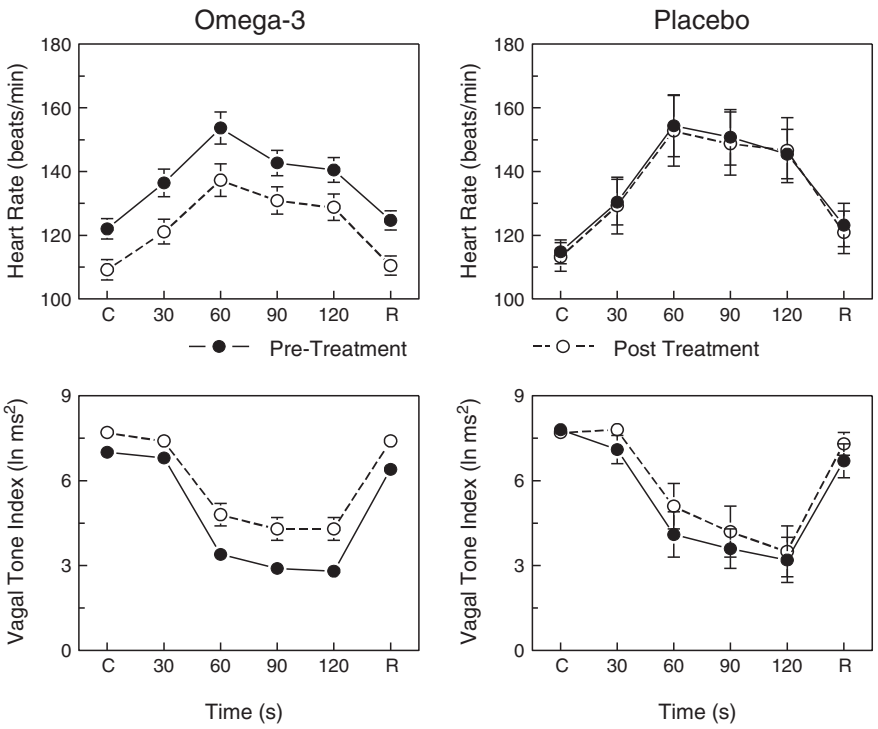

Fig. 2. Effect of omega-3 polyunsaturated fatty acids (n−3 PUFAs) on the heart rate and heart rate variability response to acute myocardial ischemia (2 min left circumflex coronary artery occlusion). Dietary n−3 PUFA, but not the placebo, produced a significant downward shift of the heart rate response that was accompanied by an upward shift in the high frequency component of the R–R interval variability (vagal tone index 0.24 to 1.04 Hz) (i.e., significant pre-post treatment effect). Despite the shifts in the curves, the absolute change in these variables induced by the exercise was not altered before or after the treatment (i.e., there was no significant pre-post treatment × ischemia interaction). Placebo (n = 15) or n−3 PUFA (1–4 g/day, n = 39), pre = before treatment began, post = after 3 months of treatment. Reproduced with permission from Billman & Harris, 2011.

2.3. Possible heart rate and heart rate variability mechanisms

The mechanisms responsible for the small changes in HR and HRV that are associated with n−3 PUFA treatment remain largely to be determined. However, there are at least two possible explanations for these observations: HR reductions could result from changes in cardiac autonomic regulation (enhanced parasympathetic and/or reduced sympathetic activity) and/or from alterations in intrinsic pacemaker rate (Billman & Harris, 2011). Although there are limitations with various indices of HRV (Task Force of the European Society of Cardiology and the North American Society of Pacing & Electrophysiology, 1996; Berntson et al., 1997; Parati et al., 2006; Billman, 2011, 2013), it is now generally accepted that these indices provide an indirect and qualitative assessment of cardiac parasympathetic regulation (Berntson et al., 1997; Parati et al., 2006; Billman, 2011). As such, the reduction in HR that accompanies n−3 PUFA treatment could reflect an enhanced parasympathetic efferent (either of central or peripheral origin) regulation of the heart. However, many physiological challenges elicited similar changes in HR and HRV before and after n−3 PUFA treatment (Billman & Harris, 2011; Billman, 2012; Skulas-Ray et al., 2012). The parallel shifts in the HR and HRV response curves after n−3 PUFA treatment are more consistent with reductions in the intrinsic pacemaker rate than with alterations in autonomic neural regulation. If parasympathetic activity had been enhanced or sympathetic activity reduced following n−3 PUFA treatment, then one would expect smaller changes in HR and HRV during physiological interventions (as has been observed following endurance exercise training (Billman & Kukielka, 2006, 2007)) rather than the similar responses that were noted in n−3 PUFA and placebo treated animals (Billman & Harris, 2011; Billman, 2012; Skulas-Ray et al., 2012). Furthermore, Billman and Harris (2011) observed an accelerated HR recovery following the termination of exercise after n−3 PUFA as compared to placebo treated animals without corresponding changes in the high frequency component of R–R interval variability, an index believed to reflect changes in cardiac parasympathetic regulation (Billman, 2011). Importantly, acute administration of purified n−3 PUFAs decreased the spontaneous contraction rate of neonatal rat cardiomyocytes (Hallaq et al., 1990) and n−3 PUFA elicited reductions in HR in cardiac transplant patients (Harris et al., 2006) and isolated perfused rabbit hearts (Dhein et al., 2005), hearts that presumably would lack intact cardiac autonomic nerves. Despite similar changes in HRV, the peak HR response to exercise was also attenuated in the n−3 PUFA treated but not in the placebo treated dogs (Billman & Harris, 2011; Billman, 2012). Finally, the pacemaker current (I_f) was reduced in sino-atrial node cells obtained from rabbits fed diets enriched with fish oil but not in cells isolated from the hearts of animals fed sunflower oil (Verkerk et al., 2009a). These data strongly suggest that intrinsic changes in pacemaker rate may play a more important role in n−3 PUFA induced HR reductions than do changes in cardiac autonomic regulation.

If n−3 PUFA induced changes in intrinsic pacemaker rate are responsible for (or at least contribute to) the HR reductions associated with this treatment, then one can make several predictions that remain to be tested (Billman & Harris, 2011). In vivo: 1) One would predict that selective antagonists of the pacemaker current (I_f) should elicit parallel shifts in the HR response to physiological challenges similar to those that have been reported following n−3 PUFA treatment. In fact, the I_f antagonist zatebradine produced parallel shifts in HR before and during an exercise stress test (Frishman et al., 1995). 2). One would predict that after complete cardiac autonomic neural blockade, HR would be lower in n−3 PUFA treated than in placebo treated subjects. If, however, intrinsic rate is not altered by this intervention, then alterations in autonomic regulation could play an important role in mediating the HR reduction following n−3 PUFA treatment. In vitro: 3) One would predict a reduced I_f current density in sinus nodal myocytes obtained after n−3

PUFA treatment. 4) This reduced pacemaker current could result from either reduced expression of the pacemaker channel (i.e., reduced HCN protein content) or from the post-translational modification of this protein (trafficking, phosphorylation, oxidation, etc.). 5) In contrast, if the HR reduction resulted from increased parasympathetic activity, then one would expect an increase in the acetylcholine activated potassium current ($I_{K\text{-}Ach}$) accompanied by an increased expression of this channel protein and/or the muscarinic (M_2) receptors (and associated signaling pathway proteins). The determination of the relative contribution of putative changes in intrinsic pacemaker rate and cardiac autonomic regulation to n−3 PUFA mediated reductions in HR will require further investigation.

When considered together, these data suggest that n−3 PUFA treatment consistently produces small but statistically significant reductions in baseline HR that are accompanied by increases in HRV. The effects of n−3 PUFA on the response to physiological challenges are more variable; enhancement, attenuation, and no change in the response have all been reported. The following sections evaluate whether or not the small changes in HR and HRV have physiologically significant actions on cardiac rhythm.

3. The effects of omega-3 fatty acids on atrial fibrillation

As previously noted, atrial fibrillation (AF) is the most commonly treated arrhythmia, with an estimated incidence of 28 per 1000 person years in the United States and a national incremental cost of approximately $26 billion (M.H. Kim et al., 2011; Piccini et al., 2012). The lifetime risk for AF after age 40 is 1 in 4 (Lloyd-Jones et al., 2004) and the incidence of AF has been projected to increase by 2.5 fold over the next half century affecting up to 12 million Americans by 2050 (Anonymous, 1998; Lloyd-Jones et al., 2004). Indeed, the prevalence of this arrhythmia increases with each decade of life (0.5% the patients aged 50 to 59 years climbing to almost 9% in patients between 80 and 89 years old) (Kannel et al., 1998; Lakshminarayan et al., 2006). Currently available therapies often prove to be ineffective and many have the potential to cause harm. As both oxidant stress and inflammation are believed to play a central role the genesis and maintenance of AF (Van Wagoner, 2008) and n−3 PUFAs have both anti-oxidant and anti-inflammatory activity (Zampelas et al., 2005; Rennison & Van Wagoner, 2009), n−3 PUFA supplementation has been proposed as a possible novel treatment for AF (Korantzopoulos et al., 2005). As a consequence, the effects of n−3 PUFA supplements on AF have been extensively investigated during the last few years.

3.1. Epidemiological studies

There have been several epidemiological studies that have evaluated the effects of fish or marine-derived n−3 PUFA consumption on the risk for AF as summarized in Table 1. Mozaffarian and co-workers (Mozaffarian et al., 2004) were the first to evaluate the association between fish consumption and the incidence of AF. They reported that the consumption of tuna and other boiled or baked fish correlated with plasma n−3 PUFA levels and was inversely related to incidence of AF during a 12-year follow-up period. There was a 28% and 31% lower risk for AF with the ingestion of 1–4 and ≥5 fish meal per week, respectively (Mozaffarian et al., 2004). In contrast, the consumption of fried fish or fish sandwiches did not correlate with plasma n−3 PUFAs and was not associated with any change in the AF incidence rates (Mozaffarian et al., 2004). Subsequent studies have yielded mixed results. In agreement with this earlier study, treatment with n−3 PUFAs was associated with a reduced incidence of AF and all-cause mortality during the first year following myocardial infarction (Macchia et al., 2008) while coronary artery bypass graft patients that received perioperative n−3 PUFA treatment had a 46% lower risk for “early” AF (AF that occurred while the patient was in the surgery department) but not “late” AF (AF that occurred during cardiac rehabilitation) as compared to patients that received other anti-arrhythmic therapies (Mariscalco et al., 2010). In a similar manner there was an inverse relationship between serum DHA levels and AF in Finnish men (Virtanen et al., 2009) and hemodialysis patients (Kirkegaard et al., 2012); neither study found an association between AF and serum docosapentaenoic acid (DPA) or EPA. Both total plasma n−3 PUFA and DHA content were also inversely related to the incidence of AF during a 14 year follow-up period (3326 individuals, with 789 cases of AF); once again there was no relationship to both plasma EPA or DPA content and AF (Wu et al., 2012). In marked contrast, several studies have either failed to find a relationship between fish/fish-derived n−3 PUFA consumption (Frost & Vestergaard, 2005; Brouwer et al., 2006a; Berry et al., 2010; Gronroos et al., 2012) or actually reported an increased risk for AF in those individuals with the highest n−3 PUFA content (Viviani-Anselmi et al., 2010; Skuladottir et al., 2011; Tomita et al., 2012). For example, neither total fish intake, dietary DHA and EPA, nor plasma DHA + EPA were associated with AF risk during a 17.6 year follow-up period (14,222 individuals, 1604 AF events) (Gronroos et al., 2012). The serum (Tomita et al., 2012) and red blood cell membrane EPA (Viviani-Anselmi et al., 2010) content was also found to be higher in patients with AF than in healthy subjects without atrial arrhythmias. Overall fish consumption was not associated with AF in the Framingham study but an exploratory analysis found a significantly higher AF risk in a small subset of individuals that ate >4 dark fish meals/week as compared to those that consumed <1 fatty fish meal/week (Shen et al., 2011). Furthermore, a subgroup analysis of patients that were treated with n−3 PUFAs before surgery described a U-shaped relationship between the incidence of post-operative AF (coronary artery bypass graft surgery) and pre-treatment plasma DHA levels; the patients in both the highest and the lowest plasma DHA quartile exhibited an increased incidence of AF (Skuladottir et al., 2011). When considered together, these data suggest that specific n−3 PUFAs may have differing effects on AF; high concentrations of EPA could be pro-arrhythmic while DHA supplements might decrease AF in patients with low DHA levels (but could be harmful in patients with pre-existing high DHA levels).

3.2. Clincal studies—interventional trials

Clinical trials that have investigated the efficacy of n−3 PUFA in the prevention or treatment of AF have produced similar conflicting results (Tables 2a and 2b). These trials can be separated into two categories; those that examined the effects of n−3 PUFAs on AF following cardiac surgery (Table 2a) and those that used n−3 PUFA to treat patients with either persistent or recurrent AF (Table 2b).

Pretreatment with 2 g/day n−3 PUFA for at least 5 day prior to coronary artery bypass surgery was initially reported to reduce the incidence of postoperative VF as compared to patients assigned to placebo group (incidence of AF: placebo 33%, 27 of 79 vs. n−3 PUFA 15% 12 of 81, $P = 0.013$) (Calò et al., 2005). The perioperative intravenous infusion (hospital admission to discharge from intensive care unit) (100 mg/kg/day) of n−3 PUFAs (100 mg/kg/day) elicited similar reductions in postoperative AF (incidence of AF: control 30.6% 15 of 50 vs. n−3 PUFA 17.3%, 9 of 52, $P < 0.05$) (Heidt et al., 2009). In another small study, n−3 PUFA treatment (2 g/day for 5 days prior to surgery, $n = 96$) also reduced AF but only in patients undergoing “on pump” coronary bypass graft surgery (Sorice et al., 2011). However, more recent and larger single- (Heidarsdottir et al., 2010; Saravanan et al., 2010; Farquharson et al., 2011) and multi-center double-blind (Mozaffarian et al., 2012; Sandesara et al., 2012) placebo-controlled trials failed to confirm these earlier studies; n−3 PUFA treatment did not significantly alter post-operative AF in any of these studies. In the largest study to date, patients from 28 centers in the United States, Italy, and Argentina were randomly assigned to either placebo (olive oil, $n = 758$)

Table 1
Effect of fish or omega-3 polyunsaturated fatty acids on atrial fibrillation: Results of major epidemiological and case controlled studies.

Study	Population	Atrial Fibrillation	Comment
Mozaffarian et al., 2004	USA M, F, n = 4815 12 y follow-up	↓	Reduced AF risk tuna, baked or boiled fish Fried fish—no association
Frost & Vestergaard, 2005	Denmark M, F n = 47,949, 5.7 y follow-up	No association	Fish intake
Brouwer et al., 2006a	The Netherlands M,F n = 5184 6.4 y follow-up	No association	Fish intake or EPA + DHA supplements
Macchia et al., 2008	Italy M, F, Acute MI, AF free at hospital release n = 3242 215 treated with n−3 PUFAs	↓	n−3 PUFA group lower 1 y AF rate Also reduced all-cause mortality
Virtanen et al., 2009	Finland M n = 2174 17.7 y follow-up	↓	Total n−3 PUFA and DHA associated with reduced AF risk ALA and DPA no association
Berry et al., 2010	USA F n = 44,720 6 y follow-up	No association	Non-fried fish
Viviani-Anselmi et al., 2010	Italy M, F n = 93 40 with AF or atrial flutter 53 healthy control	NA	↑ total n−3 PUFA RBC AF/AFL patients compared to control
Mariscalco et al., 2010	Italy M, F, cardiac surgery patients n = 530 84 with n−3 PUFAs treatment	↓ early AF or no association late AF	Preoperative recued early but not late occurrence of post-operative AF
Skuladottir et al., 2011	Iceland M,F coronary artery bypass surgery n = 125 Pre-surgery blood n−3 PUFA levels	↓ or ↑ or no association	U shaped relationship between plasma DHA and post-operative AF (higher rate both high and low DHA values EPA no association
Shen et al., 2011	USA M, F n = 4526 4 y follow-up	No association or ↑	Fish intake not associated with AF However, small subgroup analysis, >4 dark fish meals/wk ↑AF risk compared to <1/wk
Tomita et al., 2012	Japan M, F, n = 192 110 with AF 46 CHD 36 healthy subjects	↑ or no association	EPA ↑ AF risk DHA no association
Gronroos et al., 2012	USA M, F, n = 14222 (Plasma n−3 PUFA n = 3757) 17.6 y follow-up	No association	Also no race or gender effect
Wu et al., 2012	USA M, F ≥ 65 y n = 3326	↓ or no association	Total plasma n−3 PUFA or DHA ↓ AF risk no association EPA or DPA

AF = atrial fibrillation, AFL = atrial flutter, MI = myocardial infarction, n−3 PUFA = omega-3 polyunsaturated fatty acids, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid, ALA = alpha linolenic acid, DPA = docosapentaenoic acid.
NA = not applicable

or n−3 PUFA (preoperative loading 10 g over 2–5 or 8 g over 2 days followed postoperatively by 2 g/day until hospital discharge or postoperative day 10, whichever came first, n = 758) groups. Neither the primary endpoint (AF lasting longer 30 s; placebo 30.7% [233 of 758] vs. n−3 PUFA 30.0% [227 of 758], P = 0.74) nor the secondary endpoints (AF that lasted more than 1 h, resulted in symptoms or was treated with cardioversion: placebo 30.0% vs. n−3 PUFA, 29.6%, P = 0.70; number of AF episodes per patient: 1 episode placebo 20.6% vs. 20.7; 2 episodes, placebo 7.8% vs. n−3 PUFA, 6.5%; ≥3 episodes placebo 2.4% vs. n−3 PUFA 2.8%, P = 0.73) were significantly altered by n−3 PUFA treatment. Thus, with the possible exception of individuals with very low pre-treatment plasma DHA levels (Skuladottir et al., 2011); the preponderance of evidence strongly suggests that the initiation of n−3 PUFA treatment during the perioperative period (up to 3 weeks prior to the surgery, Farquharson et al., 2011) is ineffective for the prevention of post-operative AF. Indeed, a recent meta-analysis of the 538 patient enrolled in the previously discussed random trials (three double blind, one open label) failed to find an association between n−3 PUFA

Table 2a
Effect of omega-3 polyunsaturated fatty acids on post-operative AF: clinical studies.

Study	Patients	Treatment	AF
Calò et al., 2005	CABG n = 160 n−3 PUFA, n = 79 placebo, n = 81	2 g/day (~1800 mg EPA + DHA) 5 day before surgery to discharge	↓
Heidt et al., 2009	CABG n = 102 n−3 PUFA, n = 52 control, n = 50	100 mg/kg/day IV infusion hospital admission until discharge from ICU	↓
Saravanan et al., 2010	CABG n = 103 n−3 PUFA, n = 52 placebo, n = 51	2 g/day (~1800 mg EPA + DHA/day) 5 day before surgery to discharge	No effect
Heidarsdottir et al., 2010	CABG n = 168 n−3 PUFA, n = 83 placebo, n = 85	2 g/day (2240 mg EPA + DHA/day) 5–7 days before surgery to discharge	No effect
Sorice et al., 2011	CABG On and off pump subgroups n = 201 n−3 PUFA, n = 96 placebo, n = 105	2 g/day (~1800 mg EPA + DHA/day) 5 days before surgery to discharge	↓ On-pump group only
Farquharson et al., 2011	Cardiac surgery CABG or valve replacement n = 194 n−3 PUFA, n = 97 placebo, n = 97	4.6 g/day EPA + DHA 3 wks prior to surgery until 6 day post-surgery	No effect
OPERA study (Mozaffarian et al., 2012)	Cardiac surgery CABG or valve replacement n = 1516 n−3 PUFA, n = 758 placebo, n = 758	1 g n−3 PUFA (≥840 mg EPA + DHA) loading dose 10 g over 3–5 day (or 8 g over 2 days) prior to surgery 2 g/day until discharge or post-op day 10 whichever came first	No effect
FISH Trial (Sandesara et al., 2012)	CABG n = 243 n−3 PUFA, n = 120 placebo, n = 123	2 g (~1800 mg EPA + DHA/day) BID prior to surgery (minimum 6 g) 3–2 g/day post-op until AF or maximum of 2 weeks 5 days before surgery to discharge	No effect

AF = atrial fibrillation, n−3 PUFA = omega-3 polyunsaturated fatty acids, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid, CABG = coronary artery bypass graph.

treatment and the prevention of post-operative AF (Armaganijan et al., 2011). Therefore, these authors concluded that n−3 PUFA should not be recommended for patients undergoing cardiac surgery (Armaganijan et al., 2011).

Equally ambiguous results have been obtained in from trials that have evaluated the effects of n−3 PUFAs on recurrent and persistent AF; n−3 PUFA treatment has been shown both to reduce (Patel et al., 2009; Nodari et al., 2011; Kumar et al., 2012) and to not alter (Kowey et al., 2010; Kumar et al., 2011a; Ozaydin et al., 2011; Watanabe et al., 2011; Macchia et al., 2013) the recurrence of AF in patients with either paroxysmal or persistent AF. Kowey et al. (2010) found that n−3 PUFA treatment (8 g/day for 7 days followed by 4 g/day for 24 weeks) did not alter the recurrence of symptomatic AF in patients with either confirmed paroxysmal AF (n−3 PUFA 52%, 135 of 258 vs. placebo 48%, 129 of 269 participants) or persistent AF (50%, 32 of 64 vs. placebo 33%, 18 of 54 subjects). All patients were in sinus rhythm at the onset of the study and had no structural heart disease. Recently, n−3 PUFA treatment (1 g/day for 1 year) also failed to prevent the recurrence of AF (placebo 56 of 297 [18.9%] vs. n−3 PUFA 69 of 289 [24.0%], P = 0.17) in patients with confirmed symptomatic AF (Macchia et al., 2013). Two smaller studies yielded similar results. Omega-3 PUFA supplements (2 g/day for 12 months of 1st AF recurrence plus amiodarone did not reduce the recurrence of AF (39.1% 9 of 23) following cardioversion as compared to amiodarone alone (37.5%, 9 of 24) (Ozaydin et al., 2011) while EPA (1.8 g/day for 6 months) did not reduce the AF burden (defined as days of AF per month) or alter C-reactive protein levels in paroxysmal AF patients (Watanabe et al., 2011). In contrast, patients that had used n−3 PUFAs exhibited a lower procedure failure rate (n−3 PUFA, 23.2%, 29 of 129 vs. control, 31.7%, 41 of 129, P < 0.003) and recurrence of AF following pulmonary vein catheter ablation to treat persistent AF (Patel et al., 2009) as compared to matched subjects that had not been using n−3 PUFA supplements (n−3 PUFA: 27.1%, 35 of 129 vs. control, 44.1%, 57 of 129, P < 0.0001). However, as the authors did not control (or report) the amount of n−3 PUFAs ingested nor provide any measure of plasma or erythrocyte n−3 PUFA content, the exact relationship between n−3 PUFAs and AF could not be ascertained. This major deficiency has been addressed in two more recent studies (Nodari et al., 2011; Kumar et al., 2012). A randomized open label study of 178 patients with persistent AF evaluated the effects of n−3 PUFAs on the recurrence of AF following cardioversion assigned to either an untreated group (control, n = 87) or n−3 PUFA group (6 g/day, n = 91). The n−3 PUFA treatment began one month prior to cardioversion and continued until the recurrence of AF or until the end of the study (1 year). The n−3 PUFA treatment significantly increased serum EPA and DHA content and lowered incidence of AF 90 days following cardioversion as compared to the untreated group (n−3 PUFA, 38.5% vs. control 77.5%, P < 0.001) (Kumar et al., 2012). Similar results were obtained in a double blind placebo controlled study (Nodari et al., 2011). The addition of n−3 PUFAs (2 g/day beginning one month before cardioversion) to the control therapy (amiodarone plus a renin–angiotensin–aldosterone inhibitor) significantly increased the probability of the maintenance of sinus rhythm at 1 year following cardioversion as compared to the standard therapy alone (Nodari et al., 2011). Omega-3 PUFA supplements (6 g/day for 1 month) also increased left atrial and pulmonary vein effective refractory period, as well as decreased the induction of AF during electrophysiological testing studies in both patients that had paroxysmal AF (Kumar et al., 2011a) and patients without AF or structural heart disease (Kumar et al., 2011b). The divergent results obtained with patients

Table 2b
Effect of omega-3 polyunsaturated fatty acids on persistent and recurrent AF: clinical trials.

Study	Patients	Treatment	AF
Patel et al., 2009	Pulmonary vein ablation n = 258 n−3 PUFA, n = 129 untreated n = 128 8 wk follow-up	≥655 mg fish oil capsules Treatment period not specified	↓ Lower recurrence and procedure failure
Kowey et al., 2010	Confirmed AF patients no structural heart disease n = 663 Symptomatic paroxysmal AF, n = 542 Persistent AF, n = 121	n−3 PUFA 8 g/day 1st week, then 4 g/day for 24 weeks 1 g n−3 PUFA = 465 mg EPA + 375 mg DHA	No effect
Ozaydin et al., 2011	AF patients after electrical cardioversion n = 47 amiodarone, n = 24 amiodarone + n−3 PUFAs, n = 23 12 month follow-up	500 mg DHA + EPA/day for 12 month or until AF recurrence	No Effect Also no effect on inflammation
Nodari et al., 2011	Persistent AF with at least 1 relapse after cardioversion, treated with amiodarone and renin-angiotensin-aldosterone system inhibitors n = 199 n−3 PUFAs, n = 100 Placebo, n = 99 12 month follow-up	2 g/day (~1800 mg EPA + DHA) 4 weeks prior to cardioversion	↓ Lower recurrence after cardioversion
Kumar et al., 2011b	Paroxysmal AF, pulmonary vein ablation n = 36 n−3 PUFAs, n = 18 placebo, n = 18	6 g/day (1800 mg EPA + DHA) for at least 30 days prior to ablation	No effect
Watanabe et al., 2011	Paroxysmal AF n = 50 6 month standard pharmacology treatment followed by 6 month with addition of EPA	EPA 1.8 g/day for 6 months	No effect Also no effect on inflammation (c-reactive protein levels)
Kumar et al., 2012	Persistent AF n = 178 n−3 PUFAs, n = 91 placebo, n = 87	6 g/day (1.72 g EPA + DHA) > 1 month prior to cardioversion then continued until return of persistent AF or 1 year	↓ Lower recurrence after cardioversion
Kirkegaard et al., 2012	Hemodialysis patients n = 137 n−3 PUFAs, n = 67 Placebo, n = 70	2 g/day (~1.7 g EPA + DHA for 3 months	Inverse relationship between plasma DHA and AF
Macchia et al., 2013	Paroxysmal AF n = 586 (required cardioversion n = 428; 2 episodes of AF before randomization n = 55; or both, n = 103) n−3 PUFA, n = 289 Placebo, n = 297	1 g/day (465 mg EPA + 375 mg DHA) for 1 year	No effect

AF = atrial fibrillation, n−3 PUFA = omega-3 polyunsaturated fatty acids, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid.

with recurrent or paroxysmal AF, may reflect differences in treatment concentration/duration or patient populations (i.e., with and without structural heart disease). Indeed, n−3 PUFA treatment only reduced AF if administered before atrial remodeling had occurred in a canine tachypacing model of heart failure (Ramadeen et al., 2012b). Animal studies also suggest that n−3 PUFAs could be effective in the prevention of atrial remodeling (Sakabe et al., 2007; Sarrazin et al., 2007; Laurent et al., 2008; Kitamura et al., 2011; Lau et al., 2011; Ramadeen et al., 2012a) but are not beneficial once these structural and electrophysiological changes had occurred (Ramadeen et al., 2012b).

When the various clinical and epidemiological studies are considered as a whole, there does not appear to be any association, either positive or negative, between dietary fish consumption or acute treatment with n−3 PUFAs and AF. Indeed, two recent meta-analyses that either evaluated only randomized clinical trials (1955 patients with either recurrent AF or post-operative AF) (Liu et al., 2011) or both randomized clinical trials (n = 11) and cohort (n = 7) studies (Khawaja et al., 2012) support this conclusion as neither analysis revealed any relationship between n−3 PUFA and AF risk or prevention. This finding was true even with subgroup analysis (Liu et al., 2011; Khawaja et al., 2012). Therefore, patients with AF are unlikely to receive any benefit from n−3 PUFA supplement therapy. Further investigation of the protective effects of n−3 PUFA against AF does not seem to be warranted.

3.3. Experimental studies—animal models

In contrast to the clinical studies, the majority of animal studies have reported a positive association between n−3 PUFA treatment and the prevention of AF as summarized in Table 3. Stretch induced AF was significantly attenuated in isolated rabbit hearts obtained from animals that had been fed n−3 PUFAs (tuna oil, 5% of body weight for 6 weeks) as compared to placebo (sunflower oil, 5% body weight for 6 weeks) treated animals (Ninio et al., 2005) while the acute application of EPA to pulmonary myocytes reduced the amplitude of delayed afterdepolarizations (Suenari et al., 2011). The electrophysiological effects of EPA could be prevented by treatment with the non-selective nitric oxide (NO) synthase antagonist L-NAME, suggesting that the protective actions of n−3 PUFAs on cellular arrhythmias could be via NO production (Suenari et al., 2011). In human atrial myocytes, both EPA and DHA concentration-dependently inhibited sodium current (I_{Na}) and potassium currents (transient outward current, I_{to}, and the ultra-rapid potassium currents, I_{Kur}) (Li et al., 2009) that contribute to AF (Ravens, 2010).

Similar results have been obtained in intact rabbits (Kitamura et al., 2011), dogs (da Cunha et al., 2007; Sakabe et al., 2007; Sarrazin et al., 2007; Laurent et al., 2008; Ramadeen et al., 2010; Mayyas et al., 2011; Ramadeen et al., 2012a), and sheep (Lau et al., 2011). The acute intravenous infusion of an emulsion of n−3 PUFAs (EPA + DHA 2.65–5.91 g

Table 3
Effects of omega-3 polyunsaturated fatty acids on atrial fibrillation: animals studies.

Study	Model/species	Treatment	Results
Ninio et al., 2005	Rabbit Stretch induced AF	Oral tuna fish oil or sunflower oil, 12 weeks	↓ susceptibility to AF
da Cunha et al., 2007	Dog Acute atrial tachypacing induced atrial EP changes	IV infusion 2.65–5.91 g EPA + DHA over 1 h or saline or soybean oil	Attenuated tachypacing induced shortening of atrial effective refractory period (ERP)
Sakabe et al., 2007	Dog Two AF models: 1 wk atrial tachypacing, 2 wk ventricular tachypacing induced heart failure	Oral 5.28 g/day EPA + DHA or placebo 3 wks (1 wk prior to pacing)	Suppressed atrial structural (fibrosis) and AF induction (burst pacing) ventricular tachypacing model No effect on in atrial tachypacing atrial EP changes of AF induction
Sarrazin et al., 2007	Dog Vagally-induced AF	Oral 480 mg EPA + DHA/day, 2 wks	↓ susceptibility to AF Reduced connexin40 expression No change atrial ERP
Laurent et al., 2008	Dog, 2 wk simultaneous atrioventricular pacing	Oral n−3 PUFAs 1 g/day began or placebo 3 wk (1 wk prior to pacing)	↓ susceptibility to AF (burst pacing) Attenuated collagen turnover
Ramadeen et al., 2010	Dog 2 wk simultaneous atrioventricular pacing	Oral n−3 PUFA 850 mg/day or placebo 3 wks (1 wk prior to pacing)	Decreased expression of fibrotic, hypertrophic and inflammatory related genes
Lau et al., 2011	Sheep Heart failure induced by doxorubicin	Oral 3.0 g EPA + DHA/day or olive oil for 7 wks (began 1 wk before doxorubicin)	Prevented atrial fibrosis and atrial conduction abnormalities No effect on AF induction but ↓ AF duration
Kitamura et al., 2011	Rabbit Ventricular tachypacing induced heart failure	Oral EPA 750–1050 mg/day for 5 wks (1 wk prior to pacing)	Attenuated fibrosis ↑ anti-inflammatory and ↓ pro-inflammatory proteins ↓ AF duration (burst pacing)
Mayyas et al., 2011	Dog Post-operative AF	Oral n−3 PUFAs 9–15/day 3 wks prior to surgery	Attenuated inflammation Completely suppressed post-op AF
Zhang et al., 2011	Dog Sterile pericarditis	Oral n−3 PUFA 2 g/day 4 wks prior to surgery	↓ susceptibility to AF (burst pacing) ↓ AF duration ↓ pro-inflammatory proteins
Ramadeen et al., 2012a	Dog 2 wks simultaneous atrioventricular pacing	Oral EPA ~1 g/day or DHA ~1 g/day or olive oil for 3 wks (1 wk prior to pacing)	DHA ↓ susceptibility to AF (burst pacing) EPA no effect on AF susceptibility
Ramadeen et al., 2012b	Dog 2 wks simultaneous atrioventricular pacing	Oral n−3 PUFA 850 mg/day Either 1 wk prior to pacing or 1 wk after pacing began	n−3 PUFA before pacing ↓ susceptibility to AF (burst pacing) and atrial fibrosis n−3 PUFA post pacing (i.e. after injury onset) no effect on susceptibility to AF or atrial fibrosis

AF = atrial fibrillation, ERP = effective refractory period, n−3 PUFA = omega-3 polyunsaturated fatty acids, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid.

infused over 1 h) attenuated the electrophysiological remodeling (i.e., reduction in effective refractory period, ERP) induced by rapid atrial pacing (400 beats/min) as compared to either the infusion of saline or n−6 PUFAs (soy bean oil) in anaesthetized close chest dogs (da Cunha et al., 2007). In a similar manner, n−3 PUFA supplementation reduced the production of inflammatory proteins, the inducibility of AF, and AF duration in a canine model of sterile pericarditis (Zhang et al., 2011), while very high doses (fish oil, 9–15 g/day for 3 weeks prior to surgery) reduced atrial inflammation and completely suppressed post-operative AF (control, 4 of 6 vs. fish oil supplementation, 0 of 9 had AF) (Mayyas et al., 2011). Omega-3 PUFA treatment (1.2 g/day for 14 days) significantly reduced (by 79%) both AF induced by vagal nerve stimulation during programmed electrical stimulation or burst pacing and connexin 40 and connexin 43 expression (Sarrazin et al., 2007). The acute intravenous infusion of a n−3 PUFA emulsion further reduced AF inducibility in those dogs that had not be protected by the oral supplementation (Sarrazin et al., 2007). Furthermore, n−3 PUFA pre-treatment prevented the expression of pro-fibrotic proteins, atrial fibrosis and AF inducibility and/or duration in several different animal models of heart failure (dogs: ventricular tachypacing - Sakabe et al., 2007; simultaneous atrioventricular tachypacing—Laurent et al., 2008; Ramadeen et al., 2010; rabbits: ventricular tachypacing—Kitamura et al., 2011; and sheep: doxorubicin infusion—Lau et al., 2011). In contrast, n−3 PUFAs failed to prevent atrial remodeling and AF if the treatment was initiated 1 week after the onset of a simultaneous atrioventricular tachypacing protocol (Ramadeen et al., 2012b) and had no beneficial effects in a canine model in which heart failure was induced by atrial tachypacing (Sakabe et al., 2007). Thus, while n−3 PUFA supplements can attenuate structural and electrophysiological remodeling and could, thereby, prevent AF in animal models, this treatment may be ineffective if administered after cardiac injury has occurred. This latter observation has important clinical implications and may partially explain the inconsistent results that have been obtained from clinical studies.

4. The effect of omega-3 fatty acids on ventricular fibrillation

4.1. Epidemiological studies

The potential benefits of dietary n−3 PUFAs on ventricular rhythm and sudden cardiac death have been the extensively investigated for several decades. In the 1970s, Bang and Dyerberg were the first to document that age-adjusted mortality from myocardial infarction among Greenland Inuits was approximately 10% to 40% of that noted for Danes, despite similar consumption of dietary fat and cholesterol (Bang et al., 1971; Dyerberg et al., 1978). Dietary analysis revealed that most of the fat and calories in the Inuit diet were from fish and marine mammals rich in n−3 PUFAs, whereas typical Western diets contain twice as much saturated fatty acids and more n−6 PUFAs (Bang et al., 1980). These investigators insightfully suggested that the low mortality rate noted for the Inuit people most likely resulted from their high intake of n−3 PUFAs perhaps by protecting against atherosclerosis and thrombosis (Dyerberg et al., 1978). In agreement with these findings, the majority of subsequent epidemiological studies have reported an inverse relationship between fish consumption and cardiac mortality (Table 4) (Kromhout et al., 1985; Shekelle et al., 1985; Norell et al., 1986; Dolecek, 1992; Feskens et al., 1993; Kromhout et al., 1995; Salonen et al., 1995; Siscovick et al., 1995; Daviglus et al., 1997; Albert et al., 1998;

Table 4
Effect of fish or omega-3 polyunsaturated fatty acids on mortality and sudden cardiac death: Results of major epidemiological and case controlled studies.

Study	Population	Cardio vascular mortality	Sudden cardiac death	Comments
Kromhout et al., 1985	The Netherlands, M without CHD n = 852, 20 y follow-up	↓	Not reported	Inverse dose–response relationship between fish consumption and death from CHD
Shekelle et al., 1985	USA M without CV risk factors n = 1931	↓		Inverse relationship between fish consumption and death from CHD
Norell et al., 1986	Sweden, M, F n = 10966, 14 y follow-up	↓	Not reported	Inverse relationship between fish consumption and death from MI and CHD
Dolecek, 1992	USA, M at high risk of CHD n = 6258, 10.5 y follow-up	↓	Not reported	Inverse relationship between estimated n−3 PUFA consumption and death from CHD
Feskens et al., 1993	The Netherlands, M, F n = 272, 83 glucose intolerant, 189 normoglycemic, 17 y follow-up	↓	Not reported	Smaller protective effect of fish in glucose intolerant population
Kromhout et al., 1995	The Netherlands M, F n =272 17 y follow-up	↓	Not reported	Inverse relationship between fish consumption and death from CHD
Siscovick et al., 1995, 2000	USA M, F, n = 827, Case controlled, 334 cardiac arrest cases, 493 control	NA	↓	inverse relationship between RBC n−3 PUFA (EPA + DHA), 70% risk reduction if RBC n−3 PUFA > 5.0% total fatty acids. No evidence that greater fish intake was associated with further risk reductions (after adjustment for RBC n−3 PUFA)
Ascherio et al., 1995	USA M n = 44,895, 6 y follow-up	No association		No association between fish consumption and CDH or death from CHD
Salonen et al., 1995	Finland M n = 1833, 7 year follow-up	↑		Increased risk for MI and death from CHD associated with increased Hg exposure
Kromhout et al., 1996	5 European + countries, USA, & Japan M n = 12,763 25 y follow-up	↓ or no association	Not reported	Inverse relationship between fish consumption and death from CHD. However, no association after controlling for confounding factors (saturated fatty acids, flavonoids and smoking)
Daviglus et al., 1997	USA M without CHD n = 1822 30 y follow-up	↓	↓	Inverse relationship between fish consumption and death from CDH, stronger association with non-sudden death
Pietinen et al., 1997	Finland M, smokers without CV disease n = 21930, 6.1 y follow-up	↑	Not reported	Trend toward an increased risk for death from CHD as n−3 PUFA from fish increased (P = 0.06)
Albert et al., 1998	USA M, without CHD n = 20,551	No association	↓	Reduced risk for sudden death but no association with increasing fish intake
Guallar et al., 1999	8 European + Israel M, F, n = 1339 Case n = 639 1st MI Control n = 700	Not reported	Not Reported	No association with adipose tissue DHA and risk for MI
Gillum et al., 2000	USA M, F n = 8,825 22 y follow-up	no association	Not reported	No association with death from cardiovascular disease, no gender or race effects
Oomen et al., 2000	Finland, Italy & the Netherlands M n = 2738, 20 y follow-up	↓ or no association	Not reported	Total fish and lean fish consumption not associated with lower CHD mortality. However, lower risk for death from CHD fatty fish vs. non-fatty fish consumption
Rissanen et al., 2000	Finland M, without CHD n = 1871 10 y follow-up	Not reported	Not reported	Serum DHA + DPA inversely related to risk for adverse CV events in men with low hair Hg content, no association in men with high Hg content. No association to with EPA CV events irrespective of Hg content
Yuan et al., 2001	China M n = 18,244 9–12 y follow-up	↓	Not reported	Fish/shellfish consumption inversely fatal MI but not rated to ischemic heart disease or stroke

(continued on next page)

Table 4 (*continued*)

Study	Population	Cardio vascular mortality	Sudden cardiac death	Comments
Albert et al., 2002	USA M n = 278 94 sudden death during 17 y follow-up period 184 matched control	NA	↓	Strong inverse relationship between baseline whole blood n−3 PUFA levels and risk for sudden cardiac death
Hu et al., 2002	USA F n = 84,688 16 y follow-up	↓	Not reported	Stronger inverse relationship between fish/n−3 PUFA intake and CHD or CHD deaths than for nonfatal MI
Mozaffarian et al., 2003	USA, M, F n = 3910 9.3 y follow-up	↓ or no association	↓ or no association	Tuna, baked, and boiled fish associated with lower risk for CHD death and arrhythmic death but not nonfatal MI. There was no association between fried fish intake and adverse CV events
Hu et al., 2003	USA, F with diabetes n = 5103 16 y follow-up	Not reported	Not reported	Inverse relationship between fish consumption and total mortality and incidence of CHD
Erkkilä et al., 2003	Finland M, F n = 415 5 y follow-up	no association		Fish consumption inversely related to total mortality, no relationship with stroke or CHD death
Lemaitre et al., 2003	USA M, F n = 358 54 ischemic death, 125 nonfatal MI 179 controls	↓	NA	EPA + EPA but not ALA associated with lower risk for fatal ischemic heart disease, no association with nonfatal MI.
Mozaffarian et al., 2005a	USA M without CV disease n = 45,722 14 y follow-up	Not reported	↓	EPA + DHA associated with lower risk for sudden death but not non-fatal MI, ALA not associated with sudden death or CHD. Effects independent of n−6 PUFA background levels.
Iso et al., 2006	Japan M, F n = 41,578 10 y follow-up	no association	no association	No effect on sudden death or total mortality reduced risk for nonfatal
Yamagishi et al., 2008	Japan M, F n = 57,972 12.7 y follow-up	↓	no association	No association with MI or CHD reduced heart failure mortality but no association with cardiac arrest or stroke mortality
Wilhelm et al., 2008	Germany M, F n = 127 102 heart failure ICD implantation 25 control	NA	↑ Ventricular arrhythmias	n−3 PUFA higher in ICD patients than control, patients with highest n−3 PUFA had the most ventricular arrhythmias
Smith et al., 2009	USA M, F with acute MI n = 260	NA	↓ Ventricular arrhythmias	Inverse relation between n total n−3 PUFA (self-reported) and ventricular arrhythmias (P = 0.011). Significantly lower arrhythmias for ALA (P = 0.024) but not EPA + DHA (P = 0.06)
Pottala et al., 2010	USA M, F., with CHD n = 956, 5.9 y follow-up	Not reported	Not reported	Inverse relationship between all-cause mortality and whole blood n DHA + EPA content

CHD = coronary heart disease, MI = myocardial infarction, ICD = implantable cardioverter defibrillator, CV = cardiovascular, n−3 PUFA = omega-3 polyunsaturated fatty acids, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid, ALA = alpha linolenic acid, DPA = docosapentaenoic acid.
NA = not applicable

Zhang et al., 1999; Siscovick et al., 2000; Yuan et al., 2001; Albert et al., 2002; Hu et al., 2002; Erkkilä et al., 2003; Hu et al., 2003; Lemaitre et al., 2003; Mozaffarian et al., 2003, 2005a). To cite one example, in a 20-year follow-up study of the Dutch city of Zutphen, men who consumed 30 g of fish per day exhibited a 50% decrease in mortality due to coronary artery disease compared with those with those that did not eat fish (Fig. 3) (Kromhout et al., 1985). The reduced cardiac mortality rates in many of these studies appeared to result from a reduction in sudden cardiac death as the myocardial infarction rate was often similar in both the high and low fish consumption subgroups. Indeed, the Physician's Health Study reported a 52% reduction in the risk of sudden death in subjects who ingested fish at least once per week but no reduction in the risk for myocardial infarction (Albert et al., 1998, 2002). The incidence of ventricular arrhythmias was inversely related to dietary n−3 PUFAs; an effect that remained even after other cardiovascular comorbidities were controlled (Smith et al., 2009). An even more striking association between n−3 PUFA consumption and reduced risk for sudden death has been reported in studies in which blood n−3 PUFA levels were determined (Siscovick et al., 1995; Albert et al., 2002; Pottala et al., 2010; Aarsetoey et al., 2011); the subjects with the highest n−3 PUFA blood levels exhibited a 70% to 90% reduction in the risk for sudden cardiac death (Albert et al., 2002). Individuals in the highest quintile of plasma n−3 PUFA phospholipid level also had lower cardiovascular mortality and lived on average of 2.22 years more after age 65 than did those in the lowest quintile (Mozaffarian et al., 2013). A multivariate logistic regression of patients with sudden cardiac arrest (n = 25) compared to healthy individuals (n = 5) or patients with myocardial infarction without cardiac arrest (n = 15) found that every 1% increase in RBC membrane omega-3 index (EPA + DHA) was associated with a 58% reduction in the risk of ventricular fibrillation (Aarsetoey et al., 2011). An

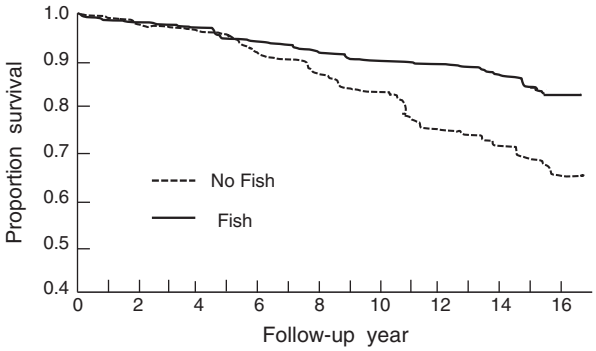

Fig. 3. Effect of fish consumption on survival on elderly men and women—the Zuphen study. Kromhout et al., 1995; Reproduced with permission from Oxford University Press.

equal protection was also afforded whether the n−3 PUFAs were obtained from seafood or plant sources (Mozaffarian et al., 2005a). However, it must be acknowledged that an association between fish ingestion and a lower risk for sudden cardiac death has not been reported in every epidemiological study (Ascherio et al., 1995; Salonen et al., 1995; Kromhout et al., 1996; Pietinen et al., 1997; Guallar et al., 1999; Gillum et al., 2000; Oomen et al., 2000; Rissanen et al., 2000; Iso et al., 2006; Yamagishi et al., 2008). Although fish consumption and n−3 PUFAs were correlated with reduced risk for coronary heart disease and nonfatal cardiac events, there was no such association with fatal cardiac events (Iso et al., 2006). In a similar manner, neither fish nor dietary n−3 PUFA consumption was associated with cardiac arrest or stroke mortality (Yamagishi et al., 2008). Furthermore, heart failure patients with implantable cardioverter defibrillators (ICDs) exhibited a greater risk for ventricular arrhythmias as RBC n−3 PUFA content increased (ventricular arrhythmia incidence: lowest n−3 PUFA quartile 12% vs. 54% in the highest quartile, P = 0.022) (Wilhelm et al., 2008). The omega-3 index was the only independent predictor for ventricular arrhythmias for up to 9 months; at 12 months a reduced ejection fraction became an additional risk predictor (Wilhelm et al., 2008). Estimated n−3 PUFA intake (from fish consumption) was also directly related to an increased risk for coronary death after adjustment for trans-, saturated, and cis-monounsaturated fatty acids (Pietinen et al., 1997). Thus, n−3 PUFAs could be pro-arrhythmic in some high risk patient populations. The type of fish (fresh water vs. marine, fried vs. baked) consumed or mercury contamination may abrogate the benefits of dietary fish (Salonen et al., 1995; Oomen et al., 2000; Rissanen et al., 2000; Mozaffarian et al., 2003). Modest consumption of boiled fish, but not fried fish, was

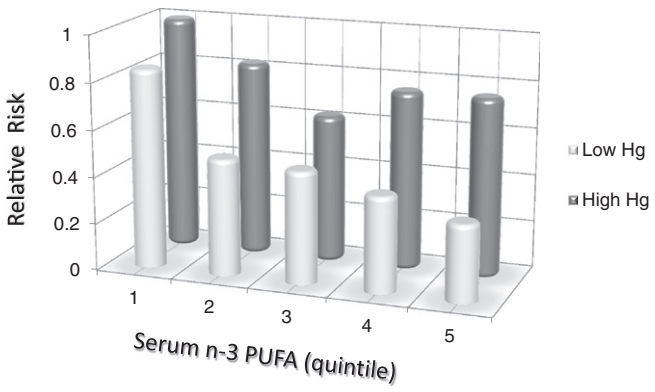

Fig. 4. Effect of hair mercury content relative risk of adverse coronary events with increasing serum n−3 PUFA (DHA + DPA) content. Serum DHA + DPA quintiles: 1 = <2.3%, 2 = 2.38–2.73%, 3 = 2.74–3.07%, 4 = 3.08–3.58%, 5= > 3.58% Hair mercury (Hg) content: low = 0–2.0 μg/g; High= > 2.0 μg/g. DHA = docosahexaenoic acid DPA = docosapentaenoic acid. The figure is based upon data reported in Rissanen et al., 2000.

associated with lower risk for arrhythmic death (Mozaffarian et al., 2003). In a similar manner, coronary heart disease mortality was lower in individuals that consumed fatty fish as compared to either lean fish or no fish among men from each of seven European countries (Oomen et al., 2000). Although serum DHA (but not EPA) was associated with a lower risk of acute coronary events, this effect was significantly attenuated as hair mercury content increased (Fig. 4) (Rissanen et al., 2000). In fact, mercury intake was associated with an increased risk for myocardial infarction and death from coronary disease despite a high fish intake in men located in Eastern Finland (Salonen et al., 1995). Thus, mercury contamination could counteract the cardiovascular benefits of n−3 PUFAs. Finally, it must be acknowledged that fish consumption may be a marker of a healthy "lifestyle". As such, it is difficult to determine the relative cardiovascular benefits of each of the individual factors that constitute a healthy lifestyle by means of epidemiological studies alone. Interventional trials are necessary to provide a more direct assessment of the role that n−3 PUFAs may play in the prevention of adverse changes in cardiac rhythm.

4.2. Clinical studies—interventional trials

Interventional clinical trials for the secondary prevention of adverse cardiovascular events following myocardial infarction or in heart failure patients that have particularly focused on ventricular arrhythmias/sudden cardiac death have yielded conflicting results (Table 5). In 1989, Burr and co-workers reported that men advised to increase their fish consumption during a two year period following myocardial infarction (MI) had a 29% decrease in all-cause mortality compared to those given standard dietary advice (Burr et al., 1989). The lower mortality rate in the fish advice group presumably resulted from reductions in deaths due to arrhythmias as the re-infarction rates were similar in both groups. Subsequent studies confirmed this earlier observation (Nilsen et al., 2001; Marchioli et al., 2002). Perhaps the most striking results were reported in the GISSI-Prevenzione trial (Marchioli et al., 2002). This study treated 11,324 patients with a recent myocardial infarction with fish oil capsules (850 mg DHA + EPA) and reported a 45% reduction in sudden cardiac death (Marchioli et al., 2002). The induction of ventricular tachycardia (VT) in patients undergoing electrophysiological testing for ICD implantation was also significantly lower in patients treated with oral n−3 PUFA supplements (n = 12, 3 g/day for 6 weeks compared to a control group (n = 14) (Metcalf et al., 2008). In the fish oil group, 42% were not inducible, 42% required more aggressive stimulation to induce VT, 8% required less stimulation and 7% there was no change compared with 7%, 36%, 36% and 21% in the control group (P = 0.003), respectively (Metcalf et al., 2008). The acute intravenous infusion of n−3 PUFAs (~4.0 g, 100 ml) also reduced the induction of sustained monomorphic VT as compared to the prior placebo treatment in two small studies of patients undergoing electrophysiology testing; reducing the inducibility of VT in 4 of 5 (Madsen et al., 2010) and in 5 of 7 (Schrepf et al., 2004) of the patients that experienced VT under baseline condition. However, perhaps due to the small sample size the stimulation required to induce arrhythmias did not differ after placebo and n−3 PUFA infusion (P = 0.063, Madsen et al., 2010; P = 0.10, Schrepf et al., 2004).

More recent studies have failed to confirm these earlier observations, reporting that n−3 PUFAs either had no effect on ventricular arrhythmias/sudden death (Brouwer et al., 2006b; Yokoyama et al., 2007; GISSI-HF investigators, 2008; Kromhout et al., 2010; Rauch et al., 2010) or actually increased adverse cardiac events (Burr et al., 2003; Raitt et al., 2005). For example, Burr et al. (2003) reported that n−3 PUFAs increased, rather than decreased, all-cause mortality in angina patients (15% increase over 9 year follow-up period, with a 54% increase in sudden death), while the JELIS trial found that EPA supplements did not alter either sudden death or fatal MI despite decreasing non-fatal coronary events (Yokoyama et al., 2007). More recently, both the OMEGA (n = 4837) (Rauch et al., 2010) and the

Table 5
Effect of fish or omega-3 polyunsaturated fatty acids on mortality and sudden cardiac death: Results of secondary prevention trials.

Study	Patient population	Treatment	Mortality	Sudden cardiac death
DART (Burr et al., 1989)	Post MI Fish advice n = 1018 No advice n = 1015	Advised to eat 100 g portion fatty fish at least twice per week	↓	Not reported
Nilsen et al., 2001	Post MI n−3 PUFA n = 150 placebo n = 150	n−3 PUFA 4 g/day (~1.2 g EPA + ~2.4 g DHA per day)	↓	No change
GISSI-Prevenzione, (Marchioli et al., 2002)	Post MI n−3 PUFA n = 5666 Placebo n = 5658	n−3 PUFA 1 g/day (300 mg EPA + 600 mg DHA per day)	↓	↓
Burr et al., 2003	Stable angina Fish advice/n−3 PUFA n = 1571 Placebo n = 1543	Advice to eat 2 oily fish portions/week or to take fish oil capsules (540 mg EPA + 360 mg DHA per day)	↑	↑
JELIS (Yokoyama et al., 2007)	Hypercholesterolemic on statins (30% had prior MI) n−3 PUFA n = 9326 Placebo n = 9319	EPA 1.8 g/day	No change	No change
GISSI-HF (GISSI-HF investigators, 2008)	Chronic heart failure ~ 42 had prior MI n−3 PUFA n = 3494 Placebo n = 3481	n−3 PUFA 1 g/day (~300 mg EPA + ~600 mg DHA per day)	↓	No change
OMEGA-trial (Rauch et al., 2010)	Post MI n−3 PUFA n = 1919 Placebo n = 1885	n−3 PUFA 1 g/day (~300 mg EPA + ~600 mg DHA per day)	No change	No change
Alpha-Omega trial (Kromhout et al., 2010)	Post MI n−3 PUFA + ALA n = 1212 n−3 PUFA n = 1192 ALA n = 1197 Placebo n = 1236	226 mg EPA + 150 mg DHA per day or 1.9 g/day ALA or Both	No change	No change
ORIGIN Trial (the ORIGIN Investigators, 2012)	Patients with dysglycemia, (impaired fasting glucose, impaired glucose intolernace or diabetes) n−3 PUFA n = 6281 Placebo n = 6255	n−3 PUFA 1 g/day (~300 mg EPA + ~600 mg DHA per day)	No change	No change
Alpha-Omega trial Sub-group analysis (Kromhout et al., 2011)	Post MI + diabetes n−3 PUFA + ALA n = 245 n−3 PUFA n = 262 ALA n = 258 Placebo n = 249	226 mg EPA + 150 mg DHA per day or 1.9 g/day ALA or Both	↓ n−3 PUFA + ALA group	↓ n−3 PUFA + ALA group

MI = myocardial infarction, n−3 PUFA = omega-3 polyunsaturated fatty acids, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid, ALA = alpha linolenic acid, NA = not applicable.

Alpha Omega (n = 3851) (Kromhout et al., 2010) trials reported that n−3 PUFA supplements failed to alter either total mortality or sudden death rates in post-MI patients. Similar results were obtained in diabetic patients (n = 12,536) at high risk for cardiovascular events; n −3 PUFA (1 g/day) while reducing triglyceride levels had no significant effect on major vascular events, all-cause mortality (n−3 PUFA: 15.1%, 951 vs. placebo, 15.4% 964, 15.4% P = 0.63) and death from arrhythmia (n−3 PUFA: 4.6%, 288 vs. placebo, 4.1%, 259 P = 0.26) (Origin Trial Investigators, 2012). In contrast, a sub-group analysis of the Alpha Omega Trial post-MI patients with diabetes found that the n−3 PUFA group had a lower incidence of ventricular arrhythmia-related events and fatal MI as compared to the placebo group (Kromhout et al., 2011). However, it should be emphasized that the number of patients experiencing these adverse events was low (ventricular arrhythmias, n = 29; fatal MI, n = 27 of 1014 post-MI patients with diabetes) (Kromhout et al., 2011). Not surprisingly, meta-analysis of these studies have yielded similar conflicting results (Hooper et al., 2004; Jenkins et al., 2008; Brouwer et al., 2009; Leon et al., 2009; Zhao et al., 2009; Filion et al., 2010) with the most recent study finding that omega-3 fatty acids were neutral, neither increasing nor decreasing the risk for arrhythmias (Rizos et al., 2012).

An improvement in the standard of care with the greater application of newer cardiovascular drugs could provide one explanation for the divergent results noted between the earlier and more recent randomized placebo controlled interventional trials. In particular, the introduction of statins in the 1990s could confound the interpretation of the results. For example, only 5% of the patients in the GISSI-Prevenzione study (Marchioli et al., 2002) were receiving statin therapy at the onset of the study while 82–85% of the patients in the Alpha-Omega Trial (Kromhout et al., 2010) and OMEGA (Rauch et al., 2010) studies and 98% of the patients in the JELIS trial were treated with statins. Thus, additional benefits of n−3 PUFAs could be difficult to detect against the background of improved cardiac mortality and/or statins could interfere with the actions of n−3 PUFAs. In fact, de Lorgeril et al. (2013) recently proposed that statins could inhibit n−3 PUFAs actions and thereby counteract any benefit of these lipids. However, statin therapy did not attenuate the positive actions of n−3 PUFAs on either HR/HRV (S.H. Kim et al., 2011) or plasma triglyceride levels (Durrington et al., 2001; M.H. Kim et al., 2011; S.H. Kim et al., 2011; Origin Trial Investigators, 2012). Furthermore, although the majority of patients had received statin therapy, n−3 PUFA supplements reduced arrhythmia related events in post-MI patients with diabetes (Kromhout et al., 2011) or attenuated the induction of VT by programmed electrical stimulation (Schrepf et al., 2004). Conversely, n−3 PUFA supplements were ineffective in animal models that had not been treated with statins (Coronel et al., 2007; Billman et al., 2012). Therefore, statin mediated inhibition of the cardiac actions of n−3 PUFAs cannot adequately explain the limited efficacy of these lipids noted in more recent clinical trials and animal studies; other yet to be identified factors must also contribute to this observation.

The beneficial actions of n−3 PUFAs on sudden death are dominated by a single very large trial. The GISSI-prevenzione trail (n = 11,324) reported an astonishing 45% reduction in sudden death rates in post-MI patients treated with n−3 PUFAs supplements as compared to the placebo treated group (Marchioli et al., 2002). A reduction of this magnitude has not been reported for even the most effective existing anti-arrhythmic therapies (e.g., β-adrenergic receptor antagonists

reduce sudden death by ~20%, (Held & Yusuf, 1989, 1993)) and has not been confirmed in any subsequent or contemporary n−3 PUFA trial. Thus, there may be something unique about the GISSI patient population that contributed to the remarkable success of this study. There are at least two possible factors that contributed to this success: a common genetic background and a uniform "healthy" diet. The GISSI study population was culturally and racially homogeneous and consumed a Mediterranean-type diet that contains less saturated fat and n−6 PUFAs than the typical Northern European/American diet. Saturated fats can be pro-arrhythmic (McLennan, 1993; Pan et al., 2012) and it has been proposed that n−6 PUFAs attenuate the effects of n−3 PUFAs (i.e., more n−3 PUFAs are required to achieve the same effects if diets contain excess n−6 PUFAs (Hibbeln et al., 2006)). A recent re-analysis of the Sydney Diet Heart Study in which saturated fats were replaced with linoleic acid (a n−6 PUFA) found a significant positive association between n−6 PUFA consumption and both all-cause mortality and death from cardiovascular disease (Ramsden et al., 2013); the effect of n−6 PUFAs on sudden death or arrhythmias was not evaluated in this study. However, n−6 PUFAs (sunflower oil) did not adversely affect the induction of arrhythmias in animal models (McLennan et al., 1987). Furthermore, n−6 PUFA intake did not alter the association between n−3 PUFA consumption and risk for sudden cardiac death (there was a similar risk reduction with either high or low n−6 PUFA intake) (Mozaffarian et al., 2005a). The preponderance of evidence does not support the n−6/n−3 balance hypothesis. After reviewing the literature, the AHA science advisory nutrition subcommittee made the following conclusion: "*Advice to reduce omega-6 PUFA intakes is typically framed as a call to lower the ratio of dietary omega-6 to omega-3 PUFAs. Although increasing omega-3 PUFA tissues does reduce the risk for CHD, it does not follow that decreasing omega-6 levels will do the same. Indeed, the evidence considered here suggests that it would have the opposite effect.*" (Harris et al., 2009). The role of n−6 PUFAs and cardiovascular disease is controversial and remains to be fully elucidated. Based upon the foregoing discussion, one may conclude that a satisfactory explanation for the disparate findings of the GISSI-prevenzione study and more recent clinical trials has not yet been achieved

Omega-3 PUFA supplements have also been given to patients with a demonstrated risk for ventricular arrhythmias (patients with implanted ICDs) yielding similar mixed results (Table 6). Leaf et al. (2005) reported that fish oil supplements (EPA + DHA, 2.6 g/day) did not reduce death rates but they found a trend (P = 0.057) toward benefit in the combined endpoint of time to ICD discharge and all-cause mortality. The ventricular tachycardia and ventricular fibrillation rates did not differ in placebo and n−3 PUFA treated heart failure patients with ICDs (n = 566, placebo 34% vs. n−3 PUFA 27% P = 0.15); the number of patients receiving 1, 2 or >3 ICD discharges were also similar in both groups (overall P = 0.30) (Finzi et al., 2011). In contrast, Raitt et al. (2005) reported that fish oil supplements not only did not reduce ICD events or mortality but also increased arrhythmic events in the subgroup of patients (67%) who received an ICD with ventricular tachycardia as an indication. Heart failure patients (NYHA classes II and III) with the highest RBC n−3 PUFA levels also exhibited an increased risk for ventricular arrhythmias that required anti-tachycardic therapy (Wilhelm et al., 2008). However, the largest ICD study to date found that n−3 PUFA treatment had no significant anti-arrhythmic or pro-arrhythmic effect in these high-risk patients and did not affect the occurrence of adverse cardiac events (Brouwer et al., 2006b). Accordingly, meta-analysis of these ICD trials found that n−3 PUFA treatment was neither anti-arrhythmic nor pro-arrhythmic in this patient population (Jenkins et al., 2008; Brouwer et al., 2009). The ICD studies suggest that not all patient populations benefit equally from n−3 PUFAs supplement therapy. For example, n−3 PUFA supplements may be ineffective in patients with anatomical substrates for re-entrant arrhythmias (ICD patients) yet exert positive actions on arrhythmias triggered by the ion channel and/or intracellular calcium abnormalities that arise as a consequence of myocardial ischemia. Thus, the clinical studies cited above demonstrate that the efficacy and safety of fish oil supplements for secondary prevention of lethal or potentially lethal ventricular tachyarrhythmias remains unclear.

4.3. Experimental studies—animal models

Finally, variable results have also been reported in animal studies as summarized in Table 7 (Culp et al., 1980; Murnaghan, 1981; Hartog et al., 1987; McLennan et al., 1987, 1988, 1989; Hock et al., 1990; McLennan et al., 1990, 1992; McLennan, 1993; McLennan et al., 1993; Yang et al., 1993; Billman et al., 1994; Isensee & Jacob, 1994; Kinoshita et al., 1994; al Makdessi et al., 1995; Anderson et al., 1996; McLennan et al., 1996; Pepe & McLennan, 1996; Billman et al., 1997, 1999;

Table 6
Effect of omega-3 polyunsaturated fatty acids on cardiac events in major ICD patient trials.

Study	Patients	Treatment	Time to first event or death	Comment
Leaf et al., 2005	50% EF ≤ 30% ~78% CHD ~47% VT on entry MI not reported n−3 PUFA n = 200 Placebo n = 202	EPA 18.2 mg + DHA 2.4 g/day	↑	
Raitt et al., 2005	~46% EF ≤ 30% ~73% CHD ~64% VT on entry ~55% MI n−3 PUFA n = 100 Placebo n = 100	756 mg EPA + 540 DHA mg per day	No change	Increased VT in subgroup analysis
Brouwer et al., 2006b	~33% EF ≤ 30% ~76% CHD ~75% VT on entry ~68% MI n−3 PUFA n = 273 Placebo n = 273	464 mg EPA + 335 mg DHA per day	No change	
Finzi et al., 2011	GISSI-HF patients 95% EF <40% ~45% had AF ~57% MI n−3 PUFA n = 278 Placebo n = 288	~300 mg EPA+ ~600 mg DHA per day	No change	

EF = ejection fraction, MI = myocardial infarction, ICD = implantable cardioverter defibrillator, VT = ventricular tachycardia, n−3 PUFA = omega-3 polyunsaturated fatty acids, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid.

Table 7
Effect of omega-3 fatty acids on ventricular arrhythmias and ventricular fibrillation: animal studies.

Study	Species	Treatment	Ventricular arrhythmias	Ventricular fibrillation
Culp et al., 1980	Dog, Acute MI	Oral menhaden oil 25% total calories 36–45 days	↓	No effect
Murnaghan, 1981	Rabbit, isolated heart acute hypoxia	Acute Na^+ salts of various fatty acids perfusion	long-chain polyunsaturated fatty acids antagonized effects of hypoxia long-chain saturated and mono-unsaturated fatty acids potentiated effects of hypoxia	
Hartog et al., 1987	Pig Ischemia/reperfusion	Mackerel oil 4.5%	↓ Reperfusion only	No effect
McLennan et al., 1987	Rat Isolated papillary muscle β-adrenergic receptor stimulation	Oral tuna fish oil 12% of calories for 12 months	↓	
McLennan et al., 1988, 1989, 1990	Rat Ischemia/reperfusion	Oral tuna fish oil 12% of calories for 12 months	↓	↓
Hock et al., 1990	Rat Ischemia/reperfusion	Oral menhaden oil 12% total calories for 4 wks	↓	↓
McLennan et al., 1992	Marmoset monkeys Ischemia β-adrenergic receptor stimulation	Oral tuna fish oil 25% % total calories 30 months		↑ VF threshold
McLennan, 1993	Rat Ischemia	Oral fish oil 12% total calories for 12 wks	↓	↓
McLennan et al., 1993	Marmoset monkeys Ischemia	Oral fish oil 3% total calories for 16 wks		↑ VF threshold
Yang et al., 1993	Rat Isolated heart global ischemia	Oral fish oil 3% total calories for 5 days	↓ Not quantified	
Kinoshita et al., 1994	Dog Acute MI With digitalis toxicity	Oral EPA 800–1200 mg/day for 8 wks	↓ During ischemia	↓ Time to VF induced by digitalis
Billman et al., 1994, 1997	Dog Post MI, exercise + ischemia	Acute IV fish oil 1–10 g infused over 1 h		↓
Isensee & Jacob, 1994	Rat isolated heart regional ischemia	Oral 10% total calories 10 wks	↓ Time to 1st arrhythmia	↓
al Makdessi et al., 1995	Rat Ischemia/reperfusion	Oral fish oil 10% total calories for 10 wks	↓	
Pepe & McLennan, 1996	Rat Isolated heart global ischemia	Fish oil 16 wks	↓	↓ and ↑ VF threshold
Anderson et al., 1996	Rat Isolated heart global or regional ischemia	Max EPA 41% total fat for 8 weeks	↓	↓
McLennan et al., 1996	Rat Ischemia/reperfusion	Oral EPA DHA or DHA + EPA ~0.4–1.1% total calories for 5 wks	DHA or DHA + EPA ↓ EPA no effect	DHA or DHA + EPA ↓ EPA no effect
Billman et al., 1999	Dog Post MI, exercise + ischemia	Acute IV EPA, DHA or ALA ~0.9 g infused over 1 h		All 3 purified n−3 PUFAs ↓
Anders et al., 2004	Rabbit Isolated, heart global ischemia/reperfusion	Oral, flax seed oil 10% total calories for 16 wks		Ischemia ↓ Reperfusion no effect
Dhein et al., 2005	Rabbit Isolated heart Electrically induced	Acute infusion DHA, EPA or ALA Dose-response	EPA or DHA concentration-dependently ↓ ALA no effect	
Coronel et al., 2007	Pig Isolated heart, regional ischemia	Oral fish oil ~3.0% total calories for 8 wks	↑	↑
Pepe & McLennan, 2007	Rat Isolated heart, regional ischemia/reperfusion	Oral, 3, 6 or 12% of total calories for 6 wks	All three fish oil doses ↓	
Tsuburaya et al., 2011	Pig acute MI	Oral EPA 12-18 g/day for 3 wks		↓
Abdukeym et al., 2008	Rat Isolated heart, regional ischemia/reperfusion Ischemia preconditioning	Oral, high DHA tuna fish oil 7% of total calories for 6 wks	fish oil alone ↓ no additional benefit of preconditioning	
Bacova et al., 2010	Rat hypertriglyceremic and normal isolated heart electrically-induced VF	Oral, n−3 PUFA 30 mg/100 g/day for 2 months or atrovastatin		Both n−3 PUFA or atorvastatin ↑ Both normal and hypertriglyceremic hearts
Billman et al., 2012	Dog Post MI, exercise + ischemia	Oral n−3 PUFA 0, 1, 2, 4 g/day 12–14 wks		no effect dogs previous shown to have VF ↑ dogs previously shown to be resistant to VF

Anders et al., 2004; Coronel et al., 2007; Den Ruijter et al., 2007; Pepe & McLennan, 2007; Abdukeym et al., 2008; Den Ruijter et al., 2008; Bacova et al., 2010; Tsuburaya et al., 2011; Billman et al., 2012). McLennan and associates demonstrated that dietary n−3 PUFAs could profoundly influence the incidence of VF during myocardial ischemia and reperfusion in anesthetized rats (McLennan et al., 1987, 1988, 1989, 1990, 1992; McLennan, 1993; McLennan et al., 1993; Pepe & McLennan, 1996, 2007). They demonstrated that hearts from animals fed diets enriched with fish oil (tuna fish oil for 9 months) did not develop ventricular tachyarrhythmias during myocardial ischemia and reperfusion (McLennan et al., 1988). In contrast, hearts from animals fed either diets rich in saturated fat or olive oil (rich in oleic acid, a monounsaturated fatty acid) exhibited an increased number and severity of arrhythmias, or no change in arrhythmia, during ischemia and reperfusion, respectively, when compared to the fish oil group. In a similar manner, McLennan et al. (1992, 1993), found that long-term (16 week) dietary lipid modulation (tuna fish oil) increased the VF threshold (the amount of current necessary to induce VF) in non-human primates (marmosets) both before and during myocardial ischemia. Murnaghan previously reported that long-chain polyunsaturated fatty acids antagonized the effects of hypoxia on the ventricular arrhythmia threshold in isolated rabbit hearts but did not alter arrhythmia type or duration while monounsaturated fatty acids potentiated the effects of hypoxia on the arrhythmia threshold (Murnaghan, 1981). More recently using porcine model, EPA (12–18 g/day for 3 weeks) attenuated the shortening of monophasic action potential duration and the occurrence of VF induced by acute myocardial ischemia (90 min) and markedly reduced mortality (control 50% vs. EPA 0%, $P < 0.05$) (Tsuburaya et al., 2011). The protective effects of n−3 PUFA, were abolished the ATP-sensitive potassium channel (K_{ATP}) agonist, cromakalim, and the expression of Kir6.2, a major component of the sarcolemmal K_{ATP} channels (Billman, 2008) was depressed in the n−3 PUFA fed pigs (Tsuburaya et al., 2011). These data suggest that n−3 PUFAs may attenuate the activation of sarcolemmal K_{ATP} channels during ischemia; a current that has been implicated in the induction of malignant arrhythmias (Billman, 2008). The current necessary to induce extrasystoles was also increased by the perfusion of isolated rabbit hearts with n−3 PUFAs (concentration-dependent, EPA or DHA but not alpha-linolenic acid, ALA) (Dhein et al., 2005).

Similar results were obtained in myocyte preparations (Kang & Leaf, 1994, 1995; Kang et al., 1995; Kang & Leaf, 1996; Macleod et al., 1998; Den Ruijter et al., 2006; Verkerk et al., 2006; Berecki et al., 2007; Den Ruijter et al., 2008; Verkerk et al., 2009b; Den Ruijter et al., 2010; Milberg et al., 2011). For example, Leaf and co-workers extensively evaluated the acute application of n−3 PUFAs to cultures of neonatal rat ventricular myocytes (Kang & Leaf, 1994, 1995; Kang et al., 1995; Kang & Leaf, 1996). These cells contract spontaneously in a rhythmic and synchronous fashion. However, a disruption of this rhythmic beating can be induced by the addition of substances that induce a cellular calcium overload, including: elevated extracellular calcium, the cardiac glycoside ouabain, the β-adrenergic receptor agonist isoproterenol, lyophosphatidyl choline, acyl carnitine, and the calcium ionophore A23187 (Kang & Leaf, 1994, 1995; Kang et al., 1995; Kang & Leaf, 1996). The addition of EPA or DHA to the medium bathing the isolated myocytes terminated the rhythm disorder induced by the arrhythmogenic toxins (Kang & Leaf, 1994, 1995; Kang et al., 1995; Kang & Leaf, 1996). These investigators also used whole cell voltage clamp techniques to evaluate the effects of n−3 PUFAs on specific ion channels in either cardiac myocytes or on ion channels expressed in different cell lines (Xiao et al., 1995, 1997, 1998, 2001, 2002, 2004b, 2006). These studies demonstrated that the acute administration of n−3 PUFAs has potent effects on many ion channels (Table 8) (Honoré et al., 1994; Xiao et al., 1995; Bogdanov et al., 1998; Hazama et al., 1998; Xiao et al., 1998; Leifert et al., 1999; Rodrigo et al., 1999; Singleton et al., 1999; Leifert et al., 2000, 2001; Doolan et al., 2002; Ferrier et al., 2002; Xiao et al., 2002; Judé et al., 2003; Dhein et al., 2005; Guizy et al., 2005; Den Ruijter et al., 2006; Verkerk et al., 2006; Xiao et al., 2006; Berecki et al., 2007; Den Ruijter et al., 2007; Szentandrássy et al., 2007; Den Ruijter et al., 2008; Dujardin et al., 2008; Verkerk et al., 2009b; Den Ruijter et al., 2010; Milberg et al., 2011; Moreno et al., 2012; van Borren et al., 2012; Zhao et al., 2012). These substances shift the inactivation threshold for sodium channels to a more negative potential (thereby decreasing cell excitability) (Xiao et al., 1995, 1998; Leifert et al., 1999, 2000; Xiao et al., 2001, 2004b, 2006; Dujardin et al., 2008; Li et al., 2009; Zhao et al., 2012), attenuate the late sodium current (Zhao et al., 2012), inhibit calcium entry through the L-type calcium channels ($I_{Ca\text{-}L}$) (Xiao et al., 1997; Hazama et al., 1998; Rodrigo et al., 1999; Ferrier et al., 2002; Verkerk et al., 2006) and via the Na^+/Ca^{2+} exchanger (Xiao et al., 2004a), and inhibit several potassium channels (transient outward current, I_{to}, the rapid component of the delay rectifier current, I_{Kr}, and the ultra-rapid current, I_{Kur})(Honoré et al., 1994; Bogdanov et al., 1998; Singleton et al., 1999; Leifert et al., 2000; Doolan et al., 2002; Xiao et al., 2002; Judé et al., 2003; Guizy et al., 2005, 2008; Zhao et al., 2012). The n−3 PUFAs also inhibit the Na^+/H^+ exchanger that promotes sodium loading (thereby indirectly increasing calcium overload) during myocardial ischemia (Goel et al., 2002; van Borren et al., 2012). Acute applications of n−3 PUFAs also have a number of effects on calcium handling mechanisms in cardiac myocytes (Xiao et al., 1997; Hazama et al., 1998; Negretti et al., 2000; Leifert et al., 2001; Ferrier et al., 2002; O'Neill et al., 2002; O'Neill, 2002; Honen et al., 2003; Swan et al., 2003; Xiao et al., 2004a; Sankaranarayanan & Ventucci, 2012). While generally depressing surface membrane electrical excitability, they also inhibit $I_{Ca\text{-}L}$ (Xiao et al., 1997; Hazama et al., 1998; Rodrigo et al., 1999; Ferrier et al., 2002; Verkerk et al., 2006; Szentandrássy et al., 2007; Sankaranarayanan & Ventucci, 2012; Zhao et al., 2012). Accordingly, n−3 PUFAs reduce the amplitude of depolarization-induced calcium transients (Berecki et al., 2007; Szentandrássy et al., 2007; Den Ruijter et al., 2008; Sankaranarayanan & Ventucci, 2012). In addition to suppressing sarcoplasmic reticulum (SR) calcium release simply by reducing the calcium trigger, n−3 PUFAs have been shown to have more direct effects on mechanisms that operate at the level of the SR. For example, n−3 PUFAs are reported to inhibit spontaneous calcium waves and local calcium release events (calcium sparks) in cardiac myocytes (Negretti et al., 2000; O'Neill et al., 2002; Honen et al., 2003; Swan et al., 2003; Sankaranarayanan & Ventucci, 2012). Moreover, n−3 PUFAs have been shown to inhibit the open probability (P_o) of single ryanodine (RyR) channels incorporated into planar lipid bilayers (Swan et al., 2003). Interestingly, depression of RyR functional activity was not accompanied by a decrease in gain of calcium induced calcium release (CICR, the calcium release normalized to the calcium trigger), a variable used to characterize the functional state of the calcium release mechanism in cardiac myocytes. This lack of depression of CICR might be an indication that n−3 PUFAs act through a mechanism more complex than simply blocking the RyRs. One interesting possibility is that n−3 PUFAs act by reducing the sensitivity of the RyRs to luminal calcium. This could explain how n−3 PUFAs depress spontaneous diastolic release without affecting CICR. Recently, the acute administration of EPA or DHA to myocytes obtained from the rabbits (with and without heart failure) and to myocytes from human heart failure patients, decreased action potential duration, lowered intracellular calcium, reduced both the number of calcium after transients (Ca-AT) and delayed afterdepolarization (DADs) and abolished trigger activity induced by norepinephrine. In contrast, superfusion with oleic acid did not alter calcium levels or prevent the DADs or Ca-ATs induced by norepinephrine (Den Ruijter et al.,

Notes to Table 7:
MI = myocardial infarction, VF = ventricular fibrillation, n−3 PUFA = omega-3 polyunsaturated fatty acids, EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid, ALA = alpha linolenic acid.

Table 8
Effects of circulating (acute administration) and incorporated (chronic, dietary supplementation) omega-3 polyunsaturated fatty acids on ion channels and intracellular calcium regulation.

Membrane current	Circulating (i.e., acute administration)	Reference	Incorporated (i.e., long-term supplementation)	Reference
I_{Na}	↓	Xiao et al., 1995, 1998, 2001, 2004b, 2006; Leifert et al., 1999; Dujardin et al., 2008; Li et al., 2009	No effect	Leifert et al., 2000; Verkerk et al., 2006
$I_{Na\text{-}late}$	↓	Zhao et al., 2012		
I_{to}	↓ or no effect	Macleod et al., 1998; Bogdanov et al., 1998; Singleton et al., 1999; Judé et al., 2003; Li et al., 2009; Zhao et al., 2012	No effect	Verkerk et al., 2006
I_K	↓	Xiao et al., 2002		
I_{Kur}	↓	Honoré et al., 1994; Guizy et al., 2008; Li et al., 2009	↓ or ↑	Guizy et al., 2008; Koshida et al., 2009
I_{Kr}	↓	Guizy et al., 2005	no effect	Verkerk et al., 2006
I_{Ks}	↑	Doolan et al., 2002	↑	Verkerk et al., 2006
I_{K1}	no effect	Xiao et al., 2002	↑	Leifert et al., 2000; Verkerk et al., 2006
$I_{Ca\text{-}L}$	↓	Hazama et al., 1998; Rodrigo et al., 1999; Ferrier et al., 2002; Xiao et al., 1997; Zhao et al., 2012	↓ or no effect	Verkerk et al., 2006; Billman, 2009
Calcium regulation				
EADs	↓	Milberg et al., 2011	↓	Den Ruijter et al., 2006
DADs	↓	Den Ruijter et al., 2008	↓ or ↑	Berecki et al., 2007; Billman et al., 2011
NCX	↓	Xiao et al., 2004a	↓	Verkerk et al., 2006
NHE	↓	Goel et al., 2002	no effect (normal rabbit) or ↓ (rabbit heart failure models)	van Borren et al., 2012
Diastolic Ca^{2+}	↓	Den Ruijter et al., 2008	no effect	Leifert et al., 2001; Verkerk et al., 2006
Ca^{2+} transients	↓	Berecki et al., 2007; Szentandrássy et al., 2007; Den Ruijter et al., 2008	no effect or ↑	Verkerk et al., 2006; Billman et al., 2011
SR Ca^{2+} content	↑	Negretti et al., 2000; O'Neill et al., 2002; Swan et al., 2003	no effect or ↓	Leifert et al., 2001; Billman et al., 2011
Ca^{2+} Sparks/spontaneous Ca^{2+} release	↓	Negretti et al., 2000; O'Neill et al., 2002; Honen et al., 2003; Swan et al., 2003; Den Ruijter et al., 2008	no effect or ↑	Verkerk et al., 2006; Billman et al., 2011
Ryanodine receptor P_o	↓	Swan et al., 2003; Honen et al., 2003		

NCX = sodium/calcium exchanger, NHE = sodium/hydrogen exchanger, EADs = early afterdepolarizations, DADs = delayed afterdepolarizations, P_o = open probability. Modified and updated from Den Ruijter et al., 2007 with permission from Oxford University Press.

2006; Berecki et al., 2007; Szentandrássy et al., 2007; Den Ruijter et al., 2008). The acute application of DHA to rabbit myocytes also prevented increases in action potential duration, and early afterdepolarization induced by oxidant stress (H_2O_2) via inhibition of the late sodium current and $I_{Ca\text{-}L}$ (Zhao et al., 2012). As previously noted, digitalis failed to induce ventricular tachyarrhythmias in dogs fed EPA (100 mg/kg for 8 weeks) (Kinoshita et al., 1994), further suggesting that dietary supplements protected the heart from arrhythmias induced by cytosolic calcium overload.

The effects of acute intravenous injection of a fish oil emulsion on VF induced by acute ischemia in a conscious canine model of sudden cardiac death have also been evaluated (Billman et al., 1994, 1997, 1999). An emulsion prepared from concentrated fish oil (1 to 10 g slowly infused over 1 h) prevented VF in 10 of 13 susceptible dogs (Billman et al., 1994). In contrast, the infusion of an emulsion made from soybean oil (Intralipid®, n = 7) failed to protect any of these animals [Fig. 6]. As fish oil is composed of a number of fatty acids with EPA and DHA being the active ingredients, the studies were repeated after treatment with purified n−3 PUFAs (Billman et al., 1999). Both DHA and EPA significantly reduced the incidence of VF protecting 6 of 8 and 5 of 7 susceptible dogs, respectively. Similar results have been obtained with dietary supplements in a canine model of acute myocardial infarction (Kinoshita et al., 1994). EPA (100 mg/kg for 8 weeks) significantly reduced the incidence and severity of arrhythmias induced by coronary occlusion compared to the control group on a standard diet. This diet also prevented calcium overload-induced ventricular tachyarrhythmias due to digitalis toxicity (Kinoshita et al., 1994). Acute application of DHA or EPA completely suppressed early afterdepolarization formation

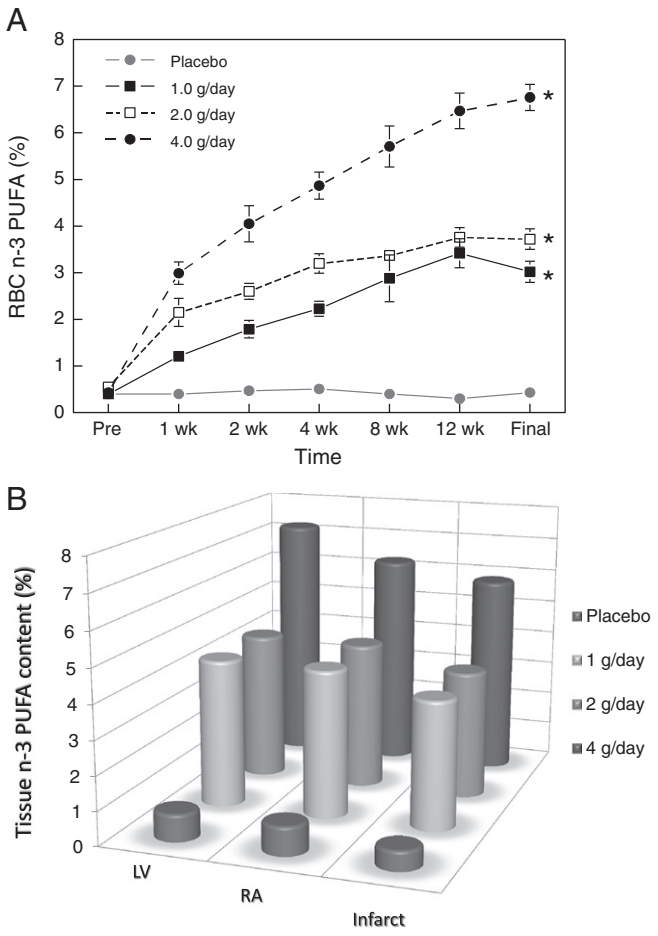

Fig. 5. Effect of increasing doses of omega-3 polyunsaturated fatty acid (n−3 PUFA) supplements on red blood cell (RBC) and cardiac tissue fatty acid content. **A**. Effect on the RBC Omega-3 Index (i.e., EPA + DHA). Note that the RBC n−3 PUFA content increased significantly after 1 wk of supplementation and peak values were reached between the 8th and 12th week treatments. Every time point for each n−3 PUFA dose was significantly (* $P < 0.01$) different from the corresponding placebo time point, except at baseline (i.e., before treatment began). **B**. Cardiac tissue EPA + DHA at the end of the study period (~14 wks after supplementation began). LV = left ventricle; RA = right atrium; Infarct = left ventricular infarction region. For all tissue regions n−3 PUFA content (all three doses) was significantly greater than placebo. All values are reported as the % n−3 PUFA in the total phospholipid content. Placebo n = 6, 1 g/day n = 7; 2 g/day n = 8; and 4 g/day n = 12. Modified and reproduced with permission from Billman et al., 2010.

and abolished Torsades de Pointes in an isolated rabbit heart model of long QT syndrome (Milberg et al., 2011; Zhao et al., 2012). A meta-analysis of 27 (23 feeding, 4 acute intravenous infusion) animal studies found that n−3 PUFA (fish oil, EPA or DHA, but not ALA) treatment attenuated ischemia-induced ventricular arrhythmias but was ineffective in ischemia–reperfusion models (Matthan et al., 2005).

More recent studies (that were not part of this meta-analysis) documented pro-arrhythmic consequences of long-term n−3 PUFA supplementation (Coronel et al., 2007; Billman et al., 2012). For example, hearts isolated from the pigs given fish oil supplements were more prone to ventricular arrhythmias during regional ischemia than hearts from pigs given the standard diet (Coronel et al., 2007). In the most comprehensive study to date, Billman et al. (2012) evaluated the effects of long-term n−3 PUFA (1–4 g/day for 12-14 weeks) in a canine model of sudden cardiac death, the same model in which the acute intravenous infusion of an emulsion of n−3 PUFAs had previously been shown to protect against VF (Billman et al., 1994, 1997, 1999). Despite large dose-dependent increases in RBC and cardiac tissue n−3 PUFA concentration (Fig. 5), n−3 PUFA treatment not only did not reduce life-threatening ventricular arrhythmias in post-MI dogs at high risk for ventricular fibrillation (n−3 PUFA decreased VT/VF in 6 of 21 dogs, 28.6% compared to placebo, 4 of 15, 26.7%, P = 0.5209, Fig. 7) but actually significantly increased the susceptibility to malignant arrhythmias in low risk dogs (both dogs with and without MI) (Fig. 8). Long-term dietary n−3 PUFA treatment induced ventricular tachyarrhythmias in one third of the post MI dogs previously shown to be resistant to malignant arrhythmias (n−3 PUFA, 7 of 21 vs. placebo 0 of 10, P = 0.0442), while two non-infarcted dogs died spontaneously during the 3-month n−3 PUFA treatment. This latter observation is particularly noteworthy, as these non-infarcted dogs would normally exhibit a negligible risk for sudden death; no non-infarcted dogs had died suddenly following thoracic surgery during the last 35 years (n = 195) (Billman et al., 2012). Furthermore, it should also be emphasized that it is difficult to induce ventricular tachyarrhythmias in VF resistant dogs (Billman, 2006a); repeated testing (exercise plus acute ischemia) never induced malignant arrhythmias in post-MI dogs (n > 220) initially classified as resistant to VF. When considered together, these data strongly suggest that dietary n−3 PUFAs not only lack significant antiarrhythmic benefits in this canine model but also actually enhance the risk for severe ventricular tachyarrhythmias in some settings.

The electrophysiological basis for the apparent pro-arrhythmic action of the n−3 PUFA treatment remains to be determined. However, there are at least two mechanisms by which n−3 PUFA might enhance the risk for arrhythmias in the canine model: alterations in repolarizing currents and/or myocyte calcium dysregulation. In a canine model of sudden death, myocardial infarction provoked an increased heterogeneity in regional repolarization in animals that were both resistant and susceptible to VF, with the largest disparity in repolarization noted in the susceptible dogs (Swann et al., 2003; Sridhar et al., 2008). As dietary n−3 PUFA treatment has been shown to inhibit outward potassium currents (Honoré et al., 1994; Bogdanov et al., 1998; Singleton et al., 1999; Leifert et al., 2000; Doolan et al., 2002; Xiao et al., 2002; Judé et al., 2003; Guizy et al., 2005; Den Ruijter et al., 2007; Zhao et al., 2012), these fatty acids could exacerbate these regional differences in repolarization during myocardial ischemia. Indeed, dietary n−3 PUFAs enhanced arrhythmia formation in isolated porcine hearts during ischemia but not during normoxic conditions (Coronel et al., 2007). Thus, changes in repolarizing currents could explain both the lack of beneficial actions and the induction of tachyarrhythmias in some individuals (by forming a substrate for re-entry). The effects of n−3 PUFAs on repolarization heterogeneity remain to be determined. These regional differences in repolarization would be difficult to detect with a body surface ECG but should be more obvious with multi-electrode mapping and refractory period studies.

Cardiomyocyte calcium dysregulation also appears to contribute to arrhythmia formation in VF susceptible dogs. Myocytes from these animals exhibit greater spontaneous calcium release and calcium alternans, phenomena that could be eliminated by reducing agents and replicated in control myocytes by oxidant stress (Belevych et al., 2009, 2012). It is possible that n−3 PUFA treatment could further disrupt the regulation of sarcoplasmic reticular calcium release particularly during the oxidant stress associated with ischemia and/or in response to sympathetic nerve activation (β-adrenoceptor stimulation) in dogs previously shown to be resistant to VF. Indeed, long-term n−3 PUFA supplementation (2–4 g/day for12–14 weeks) increases spontaneous calcium release and calcium transient alternans in dogs treated with n−3 PUFA supplements (Billman et al., 2011).

Recent studies also suggest that the acute and chronic administration of n−3 PUFAs exert profoundly different electrophysiological actions as summarized in Table 8 (Den Ruijter et al., 2007), that may contribute to the inconsistent actions of n−3 PUFAs on cardiac rhythm. Circulating n−3 PUFAs may have direct interactions with ion channels while incorporation of n−3 PUFA in the cell membrane (resulting from the consequence of long-term dietary supplementation) could alter local membrane properties (e.g., change fluidity),

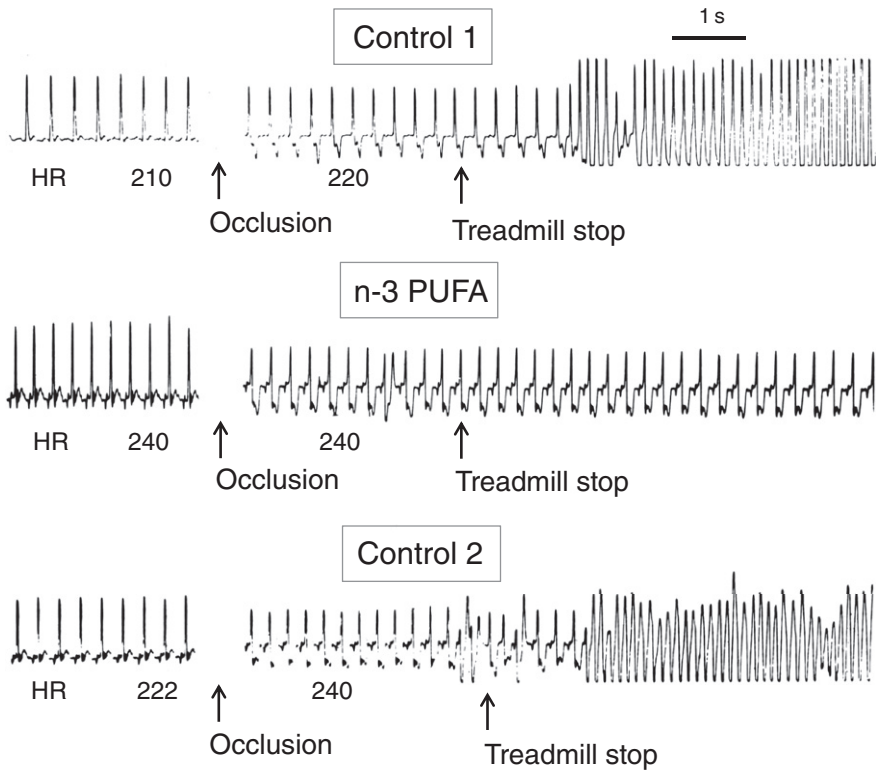

Fig. 6. Representative ventricular electrogram recordings from the same animal without and without treatment with an intravenous infusion of an emulsion (1 g over 1 h) omega-3 polyunsaturated fatty acids (n−3 PUFAs). Control 1: Response to the exercise plus ischemia test 1 wk before treatment with n−3 PUFAs. Control 2: Response to a second exercise plus ischemia test after infusion of a soy bean oil emulsion (Intralipid®). This 2nd control test was performed 1 wk after the n−3 PUFA treatment. Dark bar = 1.0 s, paper speed 25 mm/s. HR = heart rate. Reproduced with permission from Billman et al., 1994.

indirectly altering ionic currents (Turk & Chapkin, 2013). The chemical form of the n−3 PUFA could also elicit varying ion channel responses. Naturally occurring n−3 PUFAs have a superior bioavailability as compared to pharmaceutical preparations of n−3 PUFA ethyl esters (Neubronner et al., 2011; Schuchardt et al., 2011) and DHA ethyl esters antagonize the stimulatory effect of DHA on vascular smooth muscle large-conductance Ca^{2+} and voltage-activated K^+ channels (Hoshi et al., 2013). As a consequence, it is likely that acute circulating and incorporated n−3 PUFAs produce different effects on ion channel currents. For example, unlike the acute application of n−3 PUFAs (Xiao et al., 1995, 1998; Leifert et al., 1999; Xiao et al., 2001, 2004b, 2006; Dujardin et al., 2008; Li et al., 2009; Zhao et al., 2012), sodium current (I_{Na}) was not altered in myocytes obtained from either rats (Leifert et al., 2000) or pigs (Verkerk et al., 2006) fed diets enriched with fish oil. Similar differences have been reported for repolarizing currents. Acute administration of n−3 PUFAs reduced the transient outward current (I_{to}) (Bogdanov et al., 1998; Macleod et al., 1998; Judé et al., 2003; Zhao et al., 2012), and the rapid component of delayed rectifier current (I_{Kr}) (Guizy et al., 2005) but enhanced the slow component of the delayed rectifier current (I_{Ks}, by ~32% DHA but not EPA) (Doolan et al., 2002). In contrast, neither I_{to} nor I_{Kr} were altered, while the inward rectifying current, I_{K1}, (Leifert et al., 2000; Verkerk et al., 2006) was activated and I_{Ks} was even further enhanced (~70%), following long-term dietary fish oil supplements (Verkerk et al., 2006). Chronic treatment with EPA has also been shown to enhance I_{Kur} via stabilization of Kv1.5 protein trafficking (Koshida et al., 2009). Activation of this current would tend to reduce APD with larger effects in the atria, and as a result, would tend to promote rather than terminate AF. The L-type calcium current ($I_{Ca\text{-}L}$) was inhibited by the acute application (Xiao et al., 1997; Hazama et al., 1998; Ferrier et al., 2002; Zhao et al., 2012) while long-term supplementation either did not alter this current (Billman et al., 2010) or reduced it and also inhibited the re-activation of this channel during the plateau phase of the ventricular action potential (Verkerk et al., 2006). This latter action would attenuate early afterdepolarizations and prevent Torsades de Pointes (Den Ruijter et al., 2006; Dujardin et al., 2008; Milberg et al., 2011). However, long-term n−3 PUFA supplementation increased rather, than decreased, the ventricular myocyte response to isoproterenol; β-adrenergic stimulation elicited larger increases ryanodine receptor activity (increased calcium sparks) that provoked diastolic calcium waves and Ca-T alternans in myocytes isolated from n−3 PUFA as compared placebo treated animals (Billman et al., 2011). These data suggest that the incorporation of n−3 PUFAs could destabilize intercellular calcium handling increasing the propensity for arrhythmias, that could become particular obvious when calcium handling is further compromised as during myocardial ischemia (Billman, 1991). Finally, the incorporation of n−3 PUFAs into myocyte membrane has also been shown to prevent further reductions in action potential duration by acutely administered circulating n−3 PUFAs (Den Ruijter et al., 2010), suggesting that patients with pre-existing high levels of n−3 PUFAs would not benefit from additional supplementation. As a consequence of the complex and differing electrophysiological actions of acute and chronic n−3 PUFA therapy, these lipids could have both anti-arrhythmic and pro-arrhythmic actions in different clinical settings (Den Ruijter et al., 2006; Den Ruijter & Coronel, 2009). Coronel and co-workers have proposed that the electrophysiological actions of n−3 PUFAs would favor activation of re-entrant circuits during ischemia but could prevent triggered activity and arrhythmias that result from prolonged action potential duration as is seen in heart failure patients (Coronel et al., 2007; Den Ruijter et al., 2007, 2012). Indeed, n−3 PUFA supplementation reduced triggered activity, decreased Ca-ATs, and attenuated reductions in action potential duration (by increasing I_{to} and I_{K1}) in a rabbit model of heart failure (Den Ruijter et

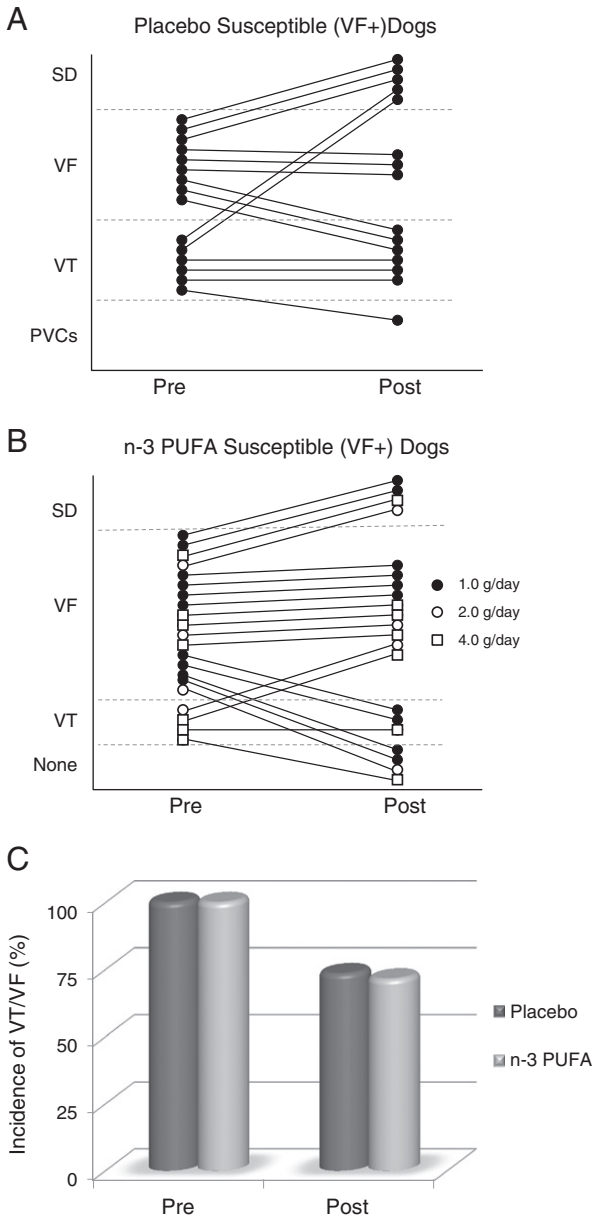

Fig. 7. The effect of dietary omega-3 polyunsaturated fatty acids (n−3 PUFAs) on susceptibility to ventricular tachyarrhythmias in dogs previously shown to be susceptible malignant arrhythmias (VF+). The response of each susceptible (VF+) dog before and at the end of a 3 month treatment period with either placebo (**a**, 1 g/day corn oil, n = 15) or n−3 PUFA (**b**, 1–4 g/day, n = 21). Composite data are shown in **c**. Note that 9 dogs died spontaneously (SD; 5 placebo, 4 n−3 PUFA) and could not receive a post-treatment exercise + ischemia test. The n−3 PUFA treatment did not prevent ventricular tachyarrhythmias for any n−3 PUFA dose (1 g/day P = 0.7278; 2 g/day, P = 0.4769; 4 g/day P = 0.5159). VF = ventricular fibrillation; PVCs = premature ventricular complexes; Pre = before the onset of treatment; Post = after 3 months of treatment. Open circle = 1 g/day; open square = 2 g/day, and closed circle = 4 g/day. Reproduced with permission from Billman et al., 2012.

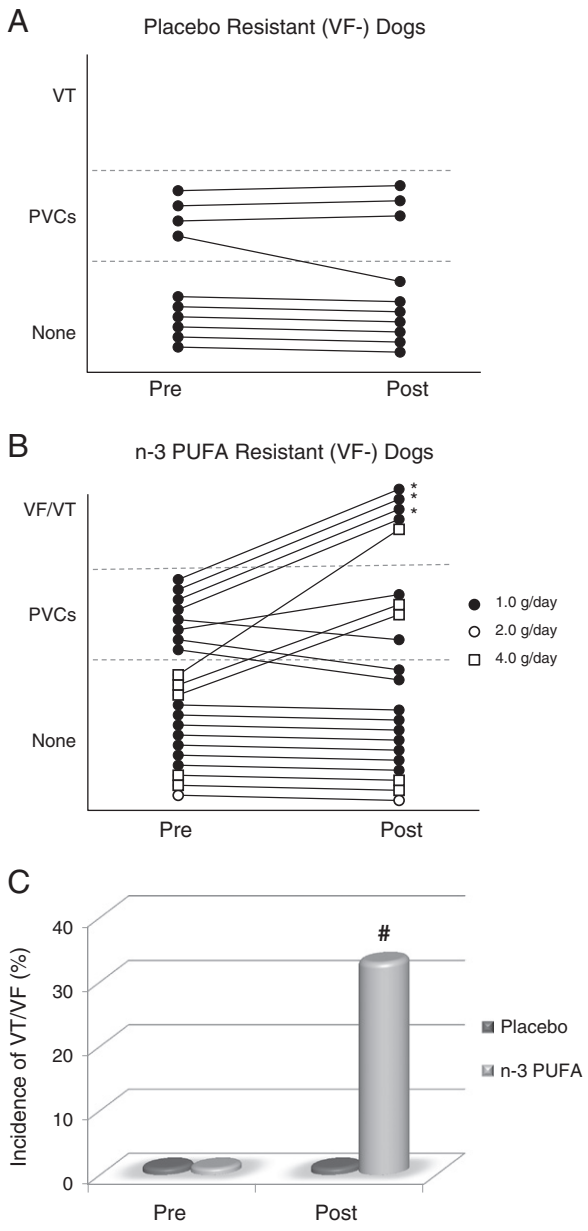

Fig. 8. The effect of dietary omega-3 polyunsaturated fatty acids (n−3 PUFAs) on susceptibility to ventricular tachyarrhythmias in dogs previously shown to be resistant to malignant arrhythmias(VF-). The response of each resistant (VF-) dog before and at the end of a 3 month treatment period with either placebo (**a**, 1 g/day corn oil, n = 10) or n−3 PUFA (**b**, 1–4 g/day, n = 21). Composite data are shown in **c**. Note that the n−3 PUFA treatment increased (# P = 0.0442) the severity of arrhythmias in one third (7 of 21; 3 of 5 with 2 g/day & 4 of 15 with 4 g/day) of these dogs while the placebo treatment did not induce arrhythmias in any animal. * indicates an episode of ventricular fibrillation (VF). VT = ventricular tachycardia; PVCs = premature ventricular complexes; none = no arrhythmias; Pre = before the onset of treatment; Post = after 3 months of treatment. Open circle = 1 g/day; open square = 2 g/day, and closed circle = 4 g/day. Reproduced with permission from Billman et al., 2012.

al., 2012). However, as n−3 PUFAs alter myocyte calcium regulation, these lipids could further compromise contractile function, reducing the risk for ventricular arrhythmias but at the expense of a possibly deleterious impairment of mechanical function. Thus, heterogeneous responses to n−3 PUFA treatment are not surprising as heart disease patients can have arrhythmias that result from both re-entry and triggered automaticity (Janse & Wit, 1989; Di Diego & Antzelevitch, 2011; Cherry et al., 2012). As emphasized in a recent review (De Caterina, 2011), the effects of n−3 PUFAs on sudden death—whether harmful or beneficial—have yet to be convincingly demonstrated.

5. Summary and conclusions

As now should be obvious, despite decades of intensive investigation, a consensus as to the effects of n−3 PUFAs on cardiac rhythm has not yet been reached. Nonetheless, some general conclusions can be made from these often contradictory data:

- n−3 PUFAs reduce baseline HR and increase HRV via alterations in intrinsic pacemaker rate rather than from changes in cardiac autonomic neural regulation. Further, these small changes, while reducing

cardiac metabolic demand, appear to be of insufficient magnitude to account for the putative cardiac benefits of n−3 PUFAs.

- Although the efficacy of individual n−3 PUFAs has not been extensively studied and these limited studies have produced inconsistent findings, the relative potency of n−3 PUFAs may be as follows: DHA ≥ EPA ≫ ALA. However, it should also be noted that several studies suggest that n−3 PUFAs derived from either plant or marine animal sources are equally effective (or ineffective as the case may be).
- With the possible exception of patients with very low pre-treatment plasma DHA levels, n−3 PUFAs have no efficacy against perioperative AF and a very limited, if any, effect on recurrent or persistent AF. These lipids may be only effective if given before electrophysiological or structural remodeling has begun.
- n−3 PUFAs have potent electrophysiological actions, inhibiting many ion channels and calcium regulatory proteins. However, circulating (i.e., acute administration—direct action on ion channels) and incorporated (long-term use that results in the insertion into cell membranes—indirect action via altered membrane properties) have quite different electrophysiological actions. Further, incorporated n−3 PUFAs prevent the actions of circulating n−3 PUFAs.
- Despite strong epidemiological evidence for an inverse relationship between fish/n−3 PUFA consumption and cardiac mortality and very encouraging initial clinical prevention trials, more recent studies have failed to confirm these earlier studies; finding no association between n−3 PUFAs and sudden cardiac death. In fact, some studies actually found that n−3 PUFAs increased mortality in angina patients and increased rather than decreased malignant arrhythmias during regional myocardial ischemia isolated porcine hearts and a canine model of sudden cardiac death. Conversely, n−3 PUFAs suppressed delayed afterdepolarizations and prevented triggered activity in myocytes from heart failure patients and animal models. Thus, n−3 PUFAs could be both pro-arrhythmic and anti-arrhythmic depending on the underlying arrhythmic mechanisms (promoting re-entry but preventing triggered automaticity).

Given the inconsistent benefits reported in clinical and experimental studies and the potential adverse actions on cardiac rhythm noted during myocardial ischemia, n−3 PUFA must be prescribed with caution. The generalized recommendations made by the American Heart Association and American College of Cardiology for healthy individuals and patients with cardiovascular disease to take n−3 PUFA supplements (~500 mg/day and 1 g/day, respectively) (Kris-Etherton et al., 2003; Gebauer et al., 2006; Smith et al., 2006) need to be reconsidered.

Conflict of interest

There are no conflicts of interest to declare.

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