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Background—Our purpose was to assess the time course of the benefit of n-3 polyunsaturated fatty acids (PUFAs) on mortality documented by the GISSI-Prevenzione trial in patients surviving a recent (<3 months) myocardial infarction.

Methods and Results—In this study, 11 323 patients were randomly assigned to supplements of n-3 PUFAs, vitamin E (300 mg/d), both, or no treatment (control) on top of optimal pharmacological treatment and lifestyle advice. Intention-to-treat analysis adjusted for interaction between treatments was carried out. Early efficacy of n-3 PUFA treatment for total, cardiovascular, cardiac, coronary, and sudden death; nonfatal myocardial infarction; total coronary heart disease; and cerebrovascular events was assessed by right-censoring follow-up data 12 times from the first month after randomization up to 12 months. Survival curves for n-3 PUFA treatment diverged early after randomization, and total mortality was significantly lowered after 3 months of treatment (relative risk [RR] 0.59; 95% CI 0.36 to 0.97; $P=0.037$). The reduction in risk of sudden death was specifically relevant and statistically significant already at 4 months (RR 0.47; 95% CI 0.219 to 0.995; $P=0.048$). A similarly significant, although delayed, pattern after 6 to 8 months of treatment was observed for cardiovascular, cardiac, and coronary deaths.

Conclusions—The early effect of low-dose (1 g/d) n-3 PUFAs on total mortality and sudden death supports the hypothesis of an antiarrhythmic effect of this drug. Such a result is consistent with the wealth of evidence coming from laboratory experiments on isolated myocytes, animal models, and epidemiological and clinical studies. (***Circulation***. 2002;105: 1897-1903.)

Key Words: fatty acids ■ death, sudden ■ trials ■ coronary disease ■ antiarrhythmia agents

A growing consensus for a direct relationship between increased intake of n-3 polyunsaturated fatty acids (PUFAs) either from dietary sources or as a pharmacological supplementation and decreasing risk of coronary heart disease has become apparent over the years.[1–15]

See p 1874

As a large-scale, clinical trial of patients surviving recent myocardial infarction, GISSI-Prevenzione[16–18] has provided solid evidence of the efficacy of low-dose (1 g/d) n-3 PUFAs in reducing overall and cardiovascular mortality without affecting the risk of nonfatal coronary events. Such results support the hypothesis, already suggested by laboratory, epidemiological, and clinical data, that the benefit of n-3 PUFAs may not be mediated via antiatherosclerotic and antithrombotic effects.[19] On the other hand, the large size of the trial and the number of end-point events allow the ad hoc detailed analysis of the time course of the benefit of n-3 PUFAs, focusing on the different causes of death in the early phase of treatment, to explore the hypothesis of an antiarrhythmic effect of the drug on sudden death.

Methods

For the purpose of this analysis, the essential information of the study protocol[16–18] can be summarized as follows. In the study, 11 323 patients with recent (≤3 months, median 16 days) myocardial infarction were enrolled in a multicenter, open-label, parallel, clinical trial with a follow-up duration of 3.5 years on the efficacy of n-3 PUFAs 1 g/d, vitamin E 300 mg/d, a combination of the 2, and control. Regardless of their allocation, all patients received the same strategies of care, including lifestyle recommendations and up-to-date preventive interventions. The main demographic, clinical, and cardiological characteristics of the study population were balanced across randomized groups and depict a relatively low-risk population of acute myocardial infarction survivors (Table 1).

The combined efficacy end points of the trial were the cumulative rate of all-cause death, nonfatal myocardial infarction, and nonfatal stroke; and the cumulative rate of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The validation of the clinical events included in the primary end points was ensured by an ad hoc committee of expert cardiologists and neurologists unaware of the patients' treatment assignments on the basis of available documents (case report forms, original clinical records, death certificates).

With respect to published data,[16] the completion of the ascertainment of the vital status of 5 of the 13 patients who had been censored alive with incomplete follow-up, together with the modification of the vital status of 18 patients (the dates reported in the death certificates obtained from census offices only after publication imposed a different qualification with respect to the index day of the right-censoring at 3.5 years of follow-up), determined an increase of the number of deaths from 1017 to 1031. A careful check of the database, in addition, allowed us to identify and eliminate from the analysis 1 patient erroneously randomized twice.

Definition and Validation of Causes of Death

The causes of death were classified according to codes in the *International Classification of Diseases, Ninth Revision* (ICD-9) (Table 2). Information on the causes of the 1031 deaths was retrieved through the study case report forms (760, 73.7%), clinical records (217, 21.0%), and death certificates from census offices (495, 48.0%). More than one source of information was available for 47.6% of deceased patients.

Sudden death was defined as natural death, instantaneous or within 1 hour of the onset of acute symptoms, and unexpected as to the time and mode of death. Because of the characteristics of the studied population (patients with recent myocardial infarction and relatively preserved heart function), it was stipulated that unwitnessed deaths with no known preceding illness other than coronary heart disease were classified as sudden cardiac deaths.

Because of the interest raised by the results of the sudden death component of the mortality end point, an ad hoc reanalysis of all causes of death was performed blinded to randomized treatments and relying also on the documentation received after the closure of the main analysis.

Overall, the validation processes led to the retention of 251 cases of sudden death out of the 314 reported in the case report forms by the investigators; on the other hand, 14 cases not classified as sudden deaths by the investigators were validated as sudden death cases by the ad hoc committee, thus leading to the total of 265 patients considered in the present analysis: 146 instantaneous, 103 within 1 hour of symptoms onset, 10 definitely arrhythmic, and 6 unwitnessed sudden deaths.

It should be noted that the analyses conducted on the figures of the database used in the original publication (with 286 attributed sudden deaths)[16] yielded strictly overlapping results.

Statistical Methods

Data analysis was carried out according to intention to treat and adjusted for interaction between treatments to ensure the full assessment of the independent effects of n-3 PUFAs.[20–22] Such an approach allows the optimal exploitation of the database by using in

TABLE 1.   Baseline Characteristics of Randomized Patients

	All (n=11 323)
Female	1665 (14.7%)
Age, y, mean (SD)	59.3 (10.6)
Days since diagnosis of AMI, median	16
Total blood cholesterol, mg/dL	211±42
Arterial hypertension	4026 (35.6%)
Diabetes mellitus	1683 (14.9%)
Ex-smokers	3935 (35.0%)
Smokers before the index event	4808 (42.8%)
Body mass index 30 kg/m^2	1644 (14.7%)
Previous myocardial infarction	1357 (12.1%)
Claudication	501 (4.4%)
Angina grade (CCVS)	
No angina	6729 (60.9%)
No limitation (I)	3596 (32.6%)
Slight limitation (II)	509 (4.6%)
Severe limitation (III)/at rest (IV)	209 (1.9%)
Dyspnea grade (NYHA)	
No dyspnea	3829 (34.1%)
No limitation (I)	6252 (55.7%)
Dyspnea on normal/mild exertion (II–III)	1136 (10.1%)
Ejection fraction >0.40	8319 (86.3%)
Premature ventricular beats >10/h	1068 (13.5%)
Previous sustained ventricular tachycardia	73 (0.9%)
Ventricular arrhythmias	1876 (23.5%)
Positive exercise-stress test	2137 (28.9%)
Dietary habits	
Fish (1 per week)	
Baseline	8212 (73.2%)
42 months	6558 (87.7%)
Fruit (1 per day)	
Baseline	9009 (80.3%)
42 months	6546 (88.0%)
Fresh vegetables (1 per day)	
Baseline	4460 (39.7%)
42 months	4085 (54.5%)
Olive oil (regularly)	
Baseline	8259 (73.6%)
42 months	6161 (82.5%)
Pharmacological therapy	
Antiplatelet drugs	
Baseline	10 309 (91.0%)
42 months	6699 (82.9%)
ACE inhibitors	
Baseline	5280 (46.9%)
42 months	3162 (39.1%)
β-Blockers	
Baseline	4986 (44.3%)
42 months	3108 (38.4%)
Cholesterol-lowering drugs	
Baseline	534 (4.7%)
42 months	3934 (45.5%)
Revascularization procedures*	
CABG or PTCA	
Baseline	560 (5.0%)
42 months	2723 (24.0%)

AMI indicates acute myocardial infarction; CCVS, Canadian Cardiovascular Society; and NYHA, New York Heart Association. In some sections, numbers do not add up because of missing values. Patients alive at baseline, 11 323; 6 months, 11 089; and 42 months, 10 081.

*Number and percentage of patients revascularized during study are cumulative.

TABLE 2. Distribution of Causes of Death (n=1031) in the GISSI-Prevenzione Trial

Cardiovascular	680
Cardiac	553
CHD	467
AMI	98
Sudden coronary death	265
Instantaneous	146
<1 hour	103
Arrhythmic	10
ND	6
Other CHD	104
Heart failure	85
ND	1
Noncardiac	127
Stroke	57
Ischemic	13
Hemorrhagic	13
ND	31
Other noncardiac	70
Pulmonary embolism	8
Haemorrhage	9
Surgical procedure	33
Other	10
ND	10
Noncardiovascular	207
Cancer	157
Infection	15
Surgical procedure	2
Other	33
Unknown	144

AMI indicates acute myocardial infarction; CHD, coronary heart disease; and ND, not defined.

the analysis all the fatal events observed in patients allocated to n-3 PUFA treatment versus control and consequently increases its statistical robustness.

The various causes of death have been managed in the analysis according to a Chinese box–like approach. Coronary heart disease death included death from coronary heart disease (eg, myocardial infarction and sudden death); cardiac death included death from coronary heart disease plus any death of cardiac origin (eg, from heart failure); and cardiovascular death included cardiac death plus any death of cardiovascular origin (eg, stroke). Early efficacy of n-3 PUFA treatment for the various outcome measures was assessed by repeatedly right-censoring follow-up data during the first 12 months of follow-up after randomization. We analyzed data by Kaplan-Meier survival curves and the log-rank test. Treatment efficacy was assessed by baseline values of the risk-stratification variables fitting various Cox regression models adjusted for the confounding effect of relevant prognostic indicators.[23] The following confounding variables known to be relevant prognostic indicators were included in the multivariable analysis based on the Cox proportional hazards model: (1) nonmodifiable risk factors: age and sex; (2) complications after myocardial infarction: left ventricular dysfunction (defined as signs or symptoms of acute left ventricular failure during hospitalization, or afterward, left ventricular ejection fraction ≤40%, extent of left ventricular asynergy ≥36% at echocardiography), electrical instability (defined as ≥10 premature beats per hour, sustained

or repetitive arrhythmias during 24-hour Holter monitoring), residual ischemia (spontaneous angina pectoris, class I to IV, according to the Canadian Angina Classification and positive exercise testing), heart rate; and (3) cardiovascular risk factors: smoking habits, history of diabetes mellitus and arterial hypertension, total blood cholesterol, HDL cholesterol, fibrinogen, leukocyte count, and claudicatio intermittens.

All probability values are 2-sided. All computations used the SAS statistical package (SAS Institute Inc).

Results

Over the 38 417.9 person-years of follow-up, 1031 deaths (9.1%) from any cause were recorded. Mortality rate was higher in the first year (3.4%) after randomization than in the second (2.0%) and in the third (2.3%) years of follow-up. Deaths from noncardiovascular disease and from unknown causes were balanced across the treatment groups.

Time Course of Benefit

Table 3 provides the full details of the time course of n-3 PUFA benefit. Patients allocated to n-3 PUFA treatment had a significantly lower mortality even after only 3 months of treatment (1.1% versus 1.6%; RR 0.59; 95% CI 0.36 to 0.97; *P*=0.037), which was confirmed at the end of the trial (8.4% versus 9.8%; RR 0.79; 95% CI 0.66 to 0.93; *P*=0.006). The reduction in risk of sudden cardiac death by n-3 PUFA treatment was nearly significant at only 3 months, accounting for up to 57% of the overall mortality benefit (0.5% versus 0.7%; RR 0.44; 95% CI 0.19 to 1.02; *P*=0.058); it became significant at 4 months (0.5% versus 0.7%; RR 0.467; 95% CI 0.219 to 0.995; *P*=0.048) and was highly statistically significant at 42 months (2.0% versus 2.7%; RR 0.55; 95% CI 0.39 to 0.77; *P*=0.0006), when it accounts for 59% of the n-3 PUFA advantage on mortality. As shown in Figure 1, A and B, the early divergence of survival curves of n-3 PUFA and control groups (Figure 1A) is paralleled by a similar profile for sudden death (Figure 1B).

The reduction of the other causes of death became significant somewhat later than that of sudden death: cardiac death at 6 months (1.2% versus 1.7%; RR 0.61; 95% CI 0.38 to 0.97; *P*=0.036), coronary death at 8 months (1.3% versus 1.8%; RR 0.62; 95% CI 0.40 to 0.98; *P*=0.040), and cardiovascular death at 8 months (1.8% versus 2.4%; RR 0.64; 95% CI 0.44 to 0.94; *P*=0.024). The curves related to death for coronary heart disease and cardiovascular disease (Figure 1, C and D) are characterized by an early overlapping and a first evidence of separation after 2 to 3 months.

The 2 main combined end points of the study were significantly lowered after 9 months of treatment, whereas total coronary heart disease events were significantly lower after 5 months (2.2% versus 2.8%; RR 0.707; 95% CI 0.500 to 0.999; *P*=0.0495). The reduction in risk of nonfatal myocardial infarction never reached the nominal level of statistical significance during the 12-month follow-up: 2.1% versus 2.3%; RR 0.78; 95% CI 0.54 to 1.12; *P*=0.1727; at 42 months, 3.9% versus 4.1%; RR 0.91; 95% CI 0.70 to 1.18; *P*=0.473.

Such results were obtained in a population of patients also exposed to standard preventive interventions (Table 1) and with slight modification of blood lipid levels during the study

TABLE 3. Overall Efficacy Profile of n-3 PUFAs During GISSI-Prevenzione Follow-Up

	T (%) vs C (%) RR (95% CI)				
	3 mo	6 mo	9 mo	12 mo	42 mo
Main end points					
Death, nonfatal MI, and nonfatal stroke	130 (2.3%) vs 148 (2.6%)	197 (3.5%) vs 229 (4.1%)	254 (4.5%) vs 296 (5.2%)	304 (5.4%) vs 354 (6.3%)	718 (12.7%) vs 795 (14.1%)
	0.86 (0.61–1.22)	0.78 (0.60–1.03)*	0.76 (0.60–0.97)†	0.79 (0.63–0.98)†	0.85 (0.74–0.98)†
CVD death, nonfatal MI, and nonfatal stroke	122 (2.2%) vs 136 (2.4%)	179 (3.2%) vs 207 (3.7%)	224 (4.0%) vs 265 (4.7%)	265 (4.7%) vs 310 (5.5%)	556 (9.8%) vs 621 (11.0%)
	0.93 (0.65–1.35)	0.80 (0.60–1.07)	0.75 (0.58–0.97)†	0.78 (0.62–0.99)†	0.80 (0.68–0.94)‡
Secondary analyses					
All fatal events	63 (1.1%) vs 88 (1.6%)	102 (1.8%) vs 130 (2.3%)	140 (2.5%) vs 180 (3.2%)	178 (3.1%) vs 212 (3.8%)	477 (8.4%) vs 554 (9.8%)
	0.59 (0.36–0.97)†	0.66 (0.45–0.96)†	0.62 (0.45–0.86)‡	0.72 (0.54–0.96)†	0.79 (0.66–0.93)‡
CVD death	55 (1.0%) vs 76 (1.3%)	84 (1.5%) vs 107 (1.9%)	110 (1.9%) vs 148 (2.6%)	139 (2.5%) from 166 (2.9%)	310 (5.5%) vs 370 (6.5%)
	0.64 (0.37–1.12)	0.66 (0.43–1.01)*	0.57 (0.39–0.83)‡	0.70 (0.51–0.98)†	0.70 (0.56–0.86)§
Cardiac death	45 (0.8%) vs 65 (1.2%)	66 (1.2%) vs 95 (1.7%)	86 (1.5%) vs 134 (2.4%)	112 (2.0%) vs 149 (2.6%)	247 (4.4%) vs 306 (5.4%)
	0.62 (0.34–1.15)	0.61 (0.38–0.97)†	0.50 (0.33–0.75)§	0.65 (0.45–0.93)†	0.65 (0.51–0.82)§
Coronary death	42 (0.7%) vs 56 (1.0%)	60 (1.1%) vs 80 (1.4%)	76 (1.3%) vs 115 (2.0%)	99 (1.8%) vs 127 (2.2%)	209 (3.7%) vs 258 (4.6%)
	0.72 (0.38–1.38)	0.69 (0.42–1.14)	0.54 (0.35–0.83)‡	0.72 (0.49–1.05)*	0.68 (0.53–0.88)‡
Sudden death	26 (0.5%) vs 37 (0.7%)	33 (0.6%) vs 52 (0.9%)	45 (0.8%) vs 72 (1.3%)	59 (1.0%) vs 78 (1.4%)	111 (2.0%) vs 154 (2.7%)
	0.44 (0.19–1.02)*	0.43 (0.22–0.86)†	0.37 (0.20–0.67)‡	0.53 (0.32–0.88)†	0.55 (0.39–0.77)§
Nonfatal CVD events					
Nonfatal MI	55 (1.0%) vs 58 (1.0%)	81 (1.4%) vs 93 (1.6%)	100 (1.8%) vs 108 (1.9%)	116 (2.1%) vs 131 (2.3%)	223 (3.9%) vs 233 (4.1%)
	0.89 (0.51–1.54)	0.70 (0.45–1.09)	0.81 (0.55–1.20)	0.78 (0.54–1.12)	0.91 (0.70–1.18)
Nonfatal stroke	14 (0.3%) vs 5 (0.1%)	18 (0.3%) vs 10 (0.2%)	20 (0.4%) vs 14 (0.3%)	21 (0.4%) vs 19 (0.3%)	62 (1.1%) vs 57 (1.0%)
	10.51 (1.34–82.42)†	6.66 (1.50–29.6)†	3.08 (1.12–8.51)†	1.88 (0.80–4.45)	1.22 (0.75–1.97)
Subsidiary analyses					
CHD death and nonfatal MI	95 (1.7%) vs 114 (2.0%)	138 (2.4%) vs 173 (3.1%)	173 (3.1%) vs 222 (3.9%)	211 (3.7%) vs 256 (4.5%)	418 (7.4%) vs 475 (8.4%)
	0.83 (0.55–1.26)	0.70 (0.50–0.97)†	0.67 (0.50–0.90)‡	0.75 (0.58–0.98)†	0.78 (0.65–0.94)‡
Fatal and nonfatal stroke	17 (0.3%) vs 10 (0.2%)	23 (0.4%) vs 15 (0.3%)	26 (0.5%) vs 19 (0.3%)	28 (0.5%) vs 25 (0.4%)	92 (1.6%) vs 77 (1.4%)
	3.23 (0.89–11.77)*	3.20* (1.04–9.85)†	2.16 (0.88–5.32)*	1.48 (0.66–3.30)	1.22 (0.81–1.85)

Relative risk, calculated by Cox regression analysis adjusted for main confounders. CVD indicates cardiovascular disease; MI, myocardial infarction; and CHD, coronary heart disease. Patients with ≥2 events of different types appear more than once in columns but only once in rows.

*$P<0.10$, †$P<0.05$, ‡$P<0.01$, §$P<0.001$.

(Figure 2). Compared with baseline values, total and LDL cholesterol levels increased slightly at 6 months and then declined, reaching approximately the same levels as measured at baseline. HDL cholesterol levels were increased in a similar way in active and control groups. Mean triglyceride values during follow-up were 155.1±73.6 mg/dL and 162.6±85.5 mg/dL for the n-3 PUFA and control groups, respectively, documenting a small but significant change in triglyceride concentrations in patients receiving n-3 PUFAs (−4.6%) and not in controls (+0.4%). Finally, compared with controls, n-3 PUFA treatment did not change glycemia and blood fibrinogen levels.

Discussion

The analysis of the time course of the appearance of the effects of n-3 PUFAs showed an early and highly significant reduction of sudden cardiac death, the major component of total mortality reduction, with no indication of a decrease of nonfatal myocardial infarction. The strength of the results pointing to an antiarrhythmic/antifibrillatory effect of n-3 PUFAs can be seen in a triple consistency, as follows.

Internal
The strength of the relative risk reduction observed at the end of the study with n-3 PUFA treatment clearly increased, passing from total to cardiovascular to coronary mortality, and reached its maximum for sudden death. The early effects on total mortality were closely parallel and well explained by the reduction of sudden death.

External
Several prospective cohort studies found an inverse relationship between n-3 PUFAs from fish intake and coronary heart disease death: the Zutphen study,[6] the 30-year follow-up in the Western Electric Study,[7] the Multiple Risk Factor Interventional Trial,[8] and the Honolulu Heart Program.[9] In addition, the Lyon Diet Heart Study[10] and the Indian Trial[11,12] strongly suggest a protective effect of n-3 PUFAs. In the
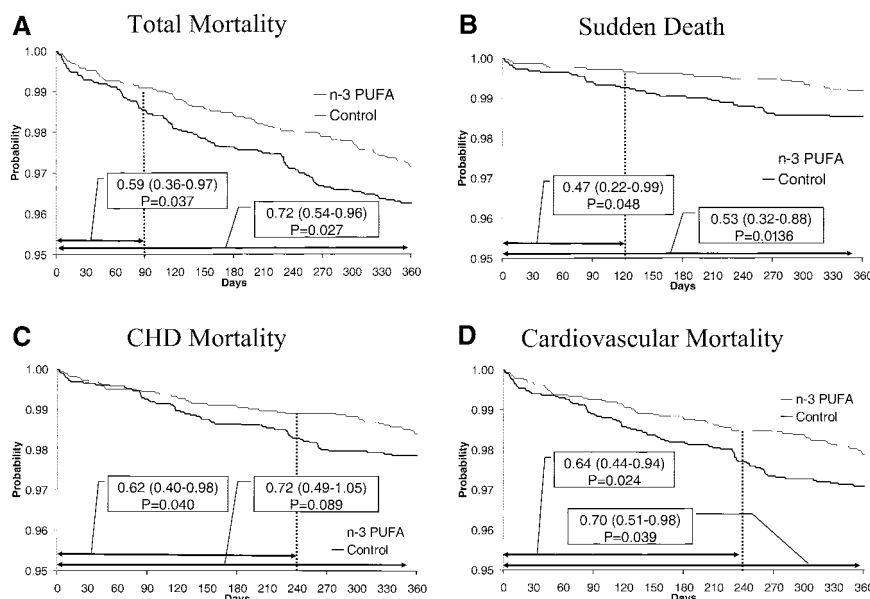
Figure 1. Early benefit of n-3 PUFA therapy. A, Total mortality; B, sudden death; C, coronary heart disease mortality; and D, cardiovascular mortality.

20 551 male subjects of the US Physicians' Health Study, regular fish consumption ($\geq$1 meals of fish per week) conferred a 52% risk-adjusted reduction in sudden deaths compared with fish intake less than once monthly.[5] Siscovick et al[24] reported that little or no fish intake (or low n-3 PUFA blood levels) was associated with an increased risk of primary out-of-hospital cardiac arrest compared with regular fish consumption. Furthermore, various researchers have found a positive correlation between n-3 PUFA intake and decreased heart rate variability, which in turn is strongly associated with increased risk of sudden death.[25–28] The pattern of results obtained in GISSI-Prevenzione are also consistent with the findings of the DART trial,[14] in which the 29% decrease of total mortality over 2 years corresponds to an unchanged rate of nonfatal myocardial infarction. A similar absence of influence of unsaturated fatty acids on progression of coronary heart disease was noted in the US Health Professionals Study[5] and in the Alpha-Tocopherol, Beta-Carotene cancer study.[29]

Figure 2. Effects of n-3 PUFA treatment on blood lipids.

Growing Evidence in the Experimental Field

The antiarrhythmic and antifibrillatory effects of n-3 PUFAs have been reported in animal studies on marmosets, rats, and dogs, as well as in laboratory experiments on isolated myocytes,[30–32] and were recently comprehensively reviewed.[19] Infusion of an emulsion of n-3 PUFAs just before coronary artery obstruction in an exercising, unanesthetized dog model prevented ischemia-induced sudden cardiac death by preventing ventricular fibrillation. n-3 PUFAs prevented induced fibrillation of cultured neonatal rat cardiomyocytes when various cardiotoxins were tested, and after fibrillation was induced, the arrhythmias were terminated by the PUFAs. According to the results of electrophysiological studies, n-3 PUFAs seem to modulate ion currents (primarily of Na^+ and Ca^{2+}) in the myocyte sarcolemma, shifting the steady-state inactivation potential to more negative values, increasing the depolarizing current necessary to elicit an action potential by $\approx$50% and prolong the refractory period by $\approx$3-fold.[19,31,32]

The strength of the early effects of n-3 PUFAs on sudden death was maintained and confirmed at the end of the study, whereas the 41% relative risk reduction of total mortality observed after 3 months of treatment was disproved (relative risk reduction 21% at 3 years). Such a decrease of n-3 PUFA benefit, however, was paralleled by (1) a lower rate (1.4%) of death in the last period of the follow-up, this finding being consistent with the well-known higher risk of patients recruited early (median 16 days in GISSI-Prevenzione) after the index event; (2) a decreasing proportion of the ratio of sudden death to the total rate of death during follow-up, with sudden deaths being 42% and 26% of total deaths in the first 3 months and during the whole study, respectively; and (3) an increasing noncompliance with allocated treatment during follow-up. In particular, 8%, 18%, 24%, 29%, and 32% of patients stopped to take the allocated intervention after 6, 12, 18, 30, and 42 months, respectively. Side effects explained the discontinuation of study treatments only in a few cases (4%).

Taken together, the aforementioned findings suggest a redefinition of n-3 PUFAs in terms of an antifibrillatory drug.
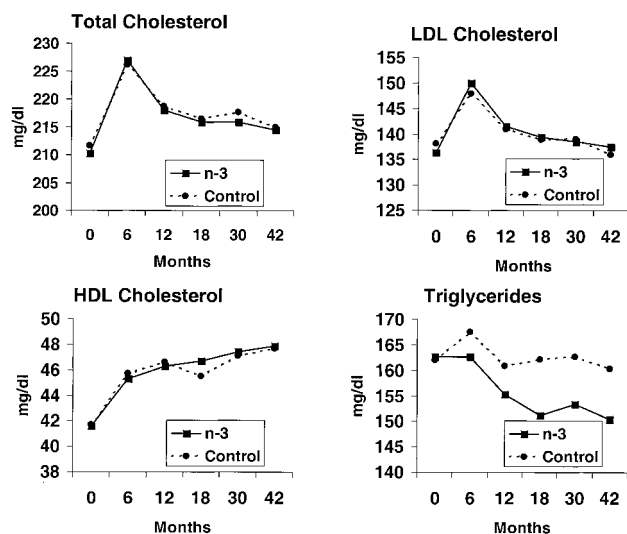
Such a statement clearly needs a careful qualification. When the GISSI-Prevenzione trial was planned and started, attention was on much higher doses of n-3 PUFAs to aim at antiatherosclerotic and antithrombotic effects[16] via antiplatelet and anti-inflammatory mechanisms, decrease of triglycerides and fibrinogen levels, inhibition of cytokines and gene expression of adhesion molecules, and improvement in arterial compliance and endothelial function.[3,16–18,33,34] As a consequence, GISSI-Prevenzione was designed to assess the combined effects of n-3 PUFAs on death, nonfatal myocardial infarction, and stroke. Sudden death was not a primary outcome measure, although its documentation was explicitly foreseen in the collection of end-point events.

Further limitations are well known to exist in the definition of sudden deaths: on one hand, the difficulties and differences in the attribution of the cause of death in ambulatory long-term follow-up; on the other, the fact that not all sudden deaths are due to primary ventricular fibrillation initiated by altered membrane ion channel function. Plaque rupture, ischemia, and coronary thrombosis can cause sudden death as a result of pump failure, potassium loss from ischemic cells that initiates injury currents, and inhomogeneities in refractoriness and action potential duration that set up reentrant circuits.

Such an interpretation of the results can find some confirmation in the absence of effects on events more directly attributable to atherothrombosis, which in turn may be partly explained by the full adoption of intensive preventive interventions that were documented for the whole duration of the study (Table 1).

There is no doubt, however, that the antiarrhythmic profile of n-3 PUFAs requires confirmation in settings in which the control of arrhythmia-related events is the direct end point. The spectrum of the clinical conditions that could be considered (eg, patients with implanted cardiac defibrillators, heart failure, prevention of first cardiac event) and an outline of the related ongoing and planned trials were recently reviewed.[35]

Conclusions

The significant reduction of mortality documented in the GISSI-Prevenzione trial, with a low dose (1 g/d) of n-3 PUFAs appears very early in the course of the treatment and is explained mainly by the decrease of sudden death.

To save 1 patient, in a population at relatively low risk (annual mortality 2.6%), 164 patients would need to be treated for 1 year with n-3 PUFAs.

The findings provide an important support to the hypothesis of an antiarrhythmic and/or antifibrillatory role of n-3 PUFAs, which should be formally tested with adequately sized trials on well-defined candidate clinical conditions.

Acknowledgments

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