Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial

*GISSI-HF investigators**

Summary

Background Several epidemiological and experimental studies suggest that n-3 polyunsaturated fatty acids (PUFA) can exert favourable effects on atherothrombotic cardiovascular disease, including arrhythmias. We investigated whether n-3 PUFA could improve morbidity and mortality in a large population of patients with symptomatic heart failure of any cause.

Methods We undertook a randomised, double-blind, placebo-controlled trial in 326 cardiology and 31 internal medicine centres in Italy. We enrolled patients with chronic heart failure of New York Heart Association class II–IV, irrespective of cause and left ventricular ejection fraction, and randomly assigned them to n-3 PUFA 1 g daily (n=3494) or placebo (n=3481) by a concealed, computerised telephone randomisation system. Patients were followed up for a median of 3·9 years (IQR 3·0–4·5). Primary endpoints were time to death, and time to death or admission to hospital for cardiovascular reasons. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00336336.

Findings We analysed all randomised patients. 955 (27%) patients died from any cause in the n-3 PUFA group and 1014 (29%) in the placebo group (adjusted hazard ratio [HR] 0·91 [95·5% CI 0·833–0·998], p=0·041). 1981 (57%) patients in the n-3 PUFA group and 2053 (59%) in the placebo group died or were admitted to hospital for cardiovascular reasons (adjusted HR 0·92 [99% CI 0·849–0·999], p=0·009). In absolute terms, 56 patients needed to be treated for a median duration of 3·9 years to avoid one death or 44 to avoid one event like death or admission to hospital for cardiovascular reasons. In both groups, gastrointestinal disorders were the most frequent adverse reaction (96 [3%] n-3 PUFA group *vs* 92 [3%] placebo group).

Interpretation A simple and safe treatment with n-3 PUFA can provide a small beneficial advantage in terms of mortality and admission to hospital for cardiovascular reasons in patients with heart failure in a context of usual care.

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See Comment page 1195

*Members listed at end of paper

Correspondence to: GISSI-HF Coordinating Centre, ANMCO Research Centre, Via La Marmora 34, 50121 Florence, Italy
gissihf@anmco.it

Introduction

Despite the impressive therapeutic advances made over the past 15 years, heart failure remains one of the main components of the overall burden of cardiovascular morbidity and mortality.[1] Finding innovative ways to prevent cardiovascular death, including sudden cardiac death which accounts for up to half of fatal events, is a major challenge.

The results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)-Prevenzione trial[2] showed a lower mortality rate in patients taking n-3 polyunsaturated fatty acids (PUFA) after myocardial infarction than in those allocated to the control group. This finding was mainly due to the prevention of sudden death,[2–6] and provided the first clinical controlled confirmation of the possible anti-arrhythmic activity of n-3 PUFA. The properties of n-3 PUFA, suggested by observational studies,[7–10] have been extensively documented in cellular and animal models.[11] The results of trials in primary and secondary prevention of coronary heart disease have been reviewed and overall suggest that n-3 PUFA is associated with a 20% relative risk reduction of death in high-risk populations, although their efficacy in primary prevention cannot yet be assessed since controlled trials of adequate size in primary prevention have not yet been terminated.[7,10] The potential antiarrhythmic efficacy of n-3 PUFA has been mainly assessed with controversial results in small trials with patients with implanted cardioverter defibrillators.[12–15]

No large-scale trial has so far assessed the efficacy of n-3 PUFA in heart failure. Two reasons lent support to the interest of testing n-3 PUFA in a large population of patients with heart failure: first was the large body of experimental evidence for the favourable effects that n-3 PUFA exert on inflammatory processes (including reduction of endothelial activation and cytokine production), platelet aggregation, blood pressure, heart rate, ventricular function, and autonomic tone;[16–22] and second was the safety and tolerability profile of the dose tested in the GISSI-Prevenzione trial,[2] which was not expected to cause problems in patients with heart failure

who were already pharmacologically treated for their index clinical disorder.

In line with previous GISSI studies,[23] a large-scale, randomised, placebo-controlled trial was proposed to a nationwide representative network of hospital and ambulatory-care facilities to test the hypothesis that n-3 PUFA could improve morbidity and mortality of patients with symptomatic heart failure of any cause and with any level of left ventricular ejection fraction (LVEF).

Methods

Patients

We did a randomised, double-blind, placebo-controlled, multicentre study, involving 326 cardiology and 31 internal medicine centres in Italy (figure 1). The design of the GISSI-HF trial has been described in detail elsewhere, including the randomisation, monitoring, and follow-up procedures.[24]

Eligible patients were men and women aged 18 years or older, with clinical evidence of heart failure of any cause that was classified according to the European Society of Cardiology (ESC) guidelines as New York Heart Association (NYHA) class II–IV, provided that they had had their LVEF measured within 3 months before enrolment. When LVEF was greater than 40%, the patient had to have been admitted at least once to hospital for heart failure in the preceding year to meet the inclusion criteria.

Major exclusion criteria included specific indication or contraindication to n-3 PUFA; known hypersensitivity to study treatments; presence of any non-cardiac comorbidity (eg, cancer) that was unlikely to be compatible with a sufficiently long follow-up; treatment with any investigational agent within 1 month before randomisation; acute coronary syndrome or revascularisation procedure within the preceding 1 month; planned cardiac surgery, expected to be done within 3 months after randomisation; significant liver disease; and pregnant or lactating women or women of childbearing potential who were not adequately protected against becoming pregnant.

All patients provided written informed consent before being enrolled. The trial was approved by the local ethics committees of all the participating sites. An independent data and safety monitoring board was established to oversee the safety of the patients enrolled in the trial and to monitor the trial's progress. This board had access to all data through an independent statistician. Efficacy in terms of all-cause mortality was monitored with pre-defined stopping rules.

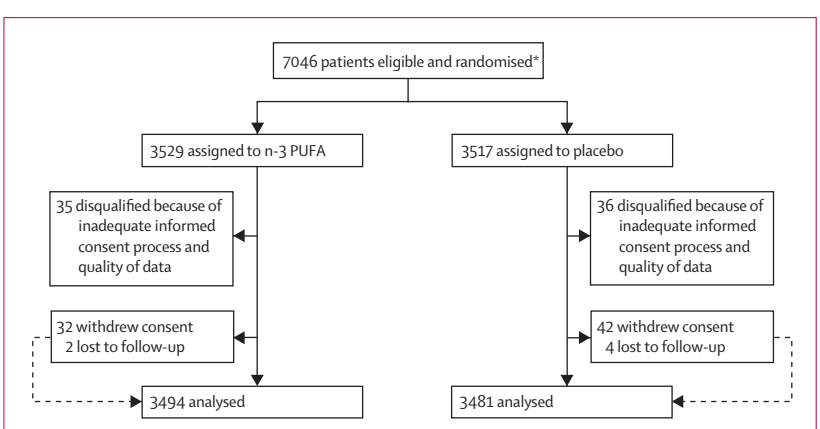

Figure 1: **Trial profile**
*The trial did not plan to have an eligibility period before randomisation. Eligible patients were immediately randomised to study treatments. PUFA=polyunsaturated fatty acids.

Procedures

Between Aug 6, 2002, and Feb 28, 2005, patients were randomly assigned to receive one capsule per day of 1 g n-3 PUFA (850–882 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the average ratio of 1:1·2) or to matching placebo. All patients and study personnel were blinded to treatment. Patients without specific indications or contraindications to statins were also randomly assigned, at the same time, to 10 mg per day of oral rosuvastatin or corresponding placebo.

Eligible patients were randomly assigned (with stratification by site) to treatment groups by a concealed, computerised telephone randomisation system. After randomisation, patients were required to return to their reference centre twice yearly to collect their drug supply and for the scheduled clinical visits at 1, 3, 6, and 12 months and then every 6 months until the end of the trial. Every study visit consisted of a cardiovascular examination, measurement of vital signs, 12-lead electrocardiogram, a check of compliance, assessment of serious adverse events, and blood chemistry tests. The study treatment was re-supplied every 6 months at these visits. Compliance was measured at every clinical examination during the study. We measured temporary and definite treatment withdrawals. We followed up patients having their treatment withdrawn for any reason for clinical events until the end of the study. A patient was regarded as compliant to the treatment if the study drug was administered for at least 80% of the days of observation.

All treatments of proven efficacy for chronic heart failure (eg, angiotensin-converting enzyme inhibitors, β blockers, diuretic drugs, digitalis, spironolactone) were positively recommended.

Study endpoints

The study was designed with two co-primary endpoints: time to death, and time to death or admission to hospital for cardiovascular reasons. Secondary outcomes included cardiovascular mortality, cardiovascular mortality or admission for any reason, sudden cardiac death, admission for any reason, admission for cardiovascular reasons, admission for heart failure, myocardial infarction, and stroke.

All the events recorded in the study were adjudicated blindly by an ad-hoc committee on the basis of pre-agreed

	n-3 PUFA (n=3494)	Placebo (n=3481)
Patients' characteristics		
Age (years)	67 (11)	67 (11)
Age >70 years	1465 (41·9%)	1482 (42·6%)
Women	777 (22·2%)	739 (21·2%)
Heart disease risk factors		
BMI (kg/m²)	27 (5)	27 (5)
SBP (mm Hg)	126 (18)	126 (18)
DBP (mm Hg)	77 (10)	77 (10)
Heart rate (beats per min)	72 (13)	73 (14)
Current smoking	502 (14·4%)	485 (13·9%)
History of hypertension	1886 (54·0%)	1923 (55·2%)
NYHA class		
II	2226 (63·7%)	2199 (63·2%)
III	1178 (33·7%)	1187 (34·1%)
IV	90 (2·6%)	95 (2·7%)
LVEF (%)	33·0% (8·5)	33·2% (8·5)
LVEF >40%	333 (9·5%)	320 (9·2%)
Medical history		
Admission for HF in previous year	1746 (50·0%)	1638 (47·1%)
Previous AMI	1461 (41·8%)	1448 (41·6%)
Previous stroke	168 (4·8%)	178 (5·1%)
Diabetes mellitus	992 (28·4%)	982 (28·2%)
CABG	614 (17·6%)	657 (18·9%)
PCI	425 (12·2%)	441 (12·7%)
ICD	248 (7·1%)	249 (7·2%)
Pacemaker	471 (13·5%)	421 (12·1%)
History of atrial fibrillation	682 (19·5%)	643 (18·5%)
Peripheral vascular disease	292 (8·4%)	318 (9·1%)
COPD	740 (21·2%)	793 (22·8%)
Neoplasia	125 (3·6%)	131 (3·8%)
Cause of heart failure		
Ischaemic	1717 (49·1%)	1750 (50·3%)
Dilatative	1053 (30·1%)	972 (27·9%)
Hypertensive	493 (14·1%)	543 (15·6%)
Other	107 (3·1%)	89 (2·6%)
Non-detectable/unknown	124 (3·6%)	127 (3·6%)
Physical examination		
Pulmonary rales	887 (25·4%)	882 (25·3%)
Third heart sound	897 (25·7%)	840 (24·1%)
Mitral insufficiency	2222 (63·6%)	2189 (62·9%)
Aortic stenosis	82 (2·4%)	61 (1·8%)
(Continues in next column)		

	n-3 PUFA (n=3494)	Placebo (n=3481)
(Continued from previous column)		
ECG findings		
QRS >120 ms*	1171 (33·9%)	1185 (34·4%)
Atrial fibrillation	573 (16·4%)	567 (16·3%)
Pathological Q waves	797 (22·8%)	807 (23·2%)
Left ventricular hypertrophy	660 (18·9%)	678 (19·5%)
Medical treatment		
ACE inhibitors	2696 (77·2%)	2678 (76·9%)
ARBs	673 (19·3%)	648 (18·6%)
ACE inhibitors/ARBs	3268 (93·5%)	3252 (93·4%)
β blockers	2275 (65·1%)	2247 (64·6%)
Spironolactone	1347 (38·6%)	1393 (40·0%)
Diuretic drugs	3127 (89·5%)	3133 (90·0%)
Digitalis	1296 (37·1%)	1292 (37·1%)
Oral anticoagulant drugs	1027 (29·4%)	982 (28·2%)
Aspirin	1673 (47·9%)	1685 (48·4%)
Other antiplatelet agents	345 (9·9%)	371 (10·7%)
Nitrates	1236 (35·4%)	1236 (35·5%)
Calcium-channel blockers	343 (9·8%)	366 (10·5%)
Amiodarone	668 (19·1%)	690 (19·8%)
Statin (open)	778 (22·3%)	801 (23·0%)

Data are mean (SD) or number (%). PUFA=polyunsaturated fatty acids. BMI=body-mass index. SBP=systolic blood pressure. DBP=diastolic blood pressure. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction. HF=heart failure. AMI=acute myocardial infarction. CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. ICD=implantable cardioverter defibrillator. COPD=chronic obstructive pulmonary disease. ACE=angiotensin-converting enzyme. ARBs=angiotensin receptor blockers. *Available for 6899 patients (3455 n-3 PUFA, 3444 placebo).

Table 1: **Baseline characteristics of patients**

definitions and procedures. All reports included a narrative summary with supporting documentation for every event (eg, clinical records, death certificates, and any other relevant documentation).

We defined sudden cardiac death as a death from cardiac cause occurring within 1 h from symptom onset. Presumed arrhythmic death was defined as cardiac death documented as arrhythmic in origin or presumed to be arrhythmic by the investigator and the adjudication committee.

The effect of study drugs on the combined outcome of all-cause mortality or hospital admission for cardiovascular reasons was assessed in subgroups of patients defined according to age (above *vs* below the median value); left ventricular function (LVEF >40% *vs* ≤40%); cause of heart failure (ischaemic *vs* non-ischaemic); functional capacity (NYHA class II *vs* III or IV); presence of diabetes (yes *vs* no); and baseline total cholesterol concentrations (above *vs* below the median value).

Statistical analysis

Statistical analyses were done at an overall significance level of 0·05, adjusted for the two primary endpoints, with the first (time to death) tested at a two-sided significance level of 0·045 and the second (time to death or admission for cardiovascular reasons) at a significance level of 0·01. In view of the correlation between the two co-primary endpoints, the net α spending was preserved.

Since we expected that about 70% of patients randomly assigned to test the n-3 PUFA hypothesis would have been enrolled in the rosuvastatin study,[25] we used the rosuvastatin randomised cohort as the reference for calculations of the sample size. The assumption was that n-3 PUFA treatment

would cause a 15% relative reduction of the expected absolute mortality rate of 25% in the placebo group (ie, a 3·75% absolute reduction) at 3 years of follow-up; the sample size was determined to detect this reduction with 90% power and a two-sided significance of 0·045.

To estimate treatment effect, the main analysis was undertaken by fitting Cox proportional hazards models adjusted for the variables that were unbalanced between randomised groups (p<0·1). Although only adjusting for covariates that are significantly out of baseline balance at p<0·1 is not recommended statistical practice, we did prespecify this approach in the protocol since importantly there is no agreed set of prognostic factors for patients presenting with this type of heart failure. Confidence intervals of 95·5% and 99% were calculated for the first and second co-primary endpoints, respectively. The assumption of proportional hazard for the randomised treatments was appropriately checked by means of the log (–log [survival]) plot and by the time-dependent covariate test. Plots of the Kaplan-Meier estimates of survival curves have been presented along with the results of the log-rank tests. To estimate the size of the effect on the secondary endpoints (adjusted analysis) and on the composite primary endpoint in the prespecified subgroups, hazard ratios (HR) with 95% CI were calculated with a Cox proportional hazards model. All the analyses were done in the intention-to-treat population, with the exception of a per-protocol analysis on the two co-primary endpoints that were undertaken in 4994 patients without major protocol violations (eg, five patients with myocardial infarction or revascularisation procedure within 30 days before randomisation) who had taken experimental treatments (n-3 PUFA or matching placebo) for at least 80% of the time of observation. Differences between randomised groups in lipids profile across the study (at baseline, and 1 and 3 years) were examined by repeated-measures analysis of variance. Whenever the laboratory parameters did not meet the normality assumptions, we applied a log transformation. We did all the analyses with SAS software (version 8.2).

This study is registered with ClinicalTrials.gov, number NCT00336336.

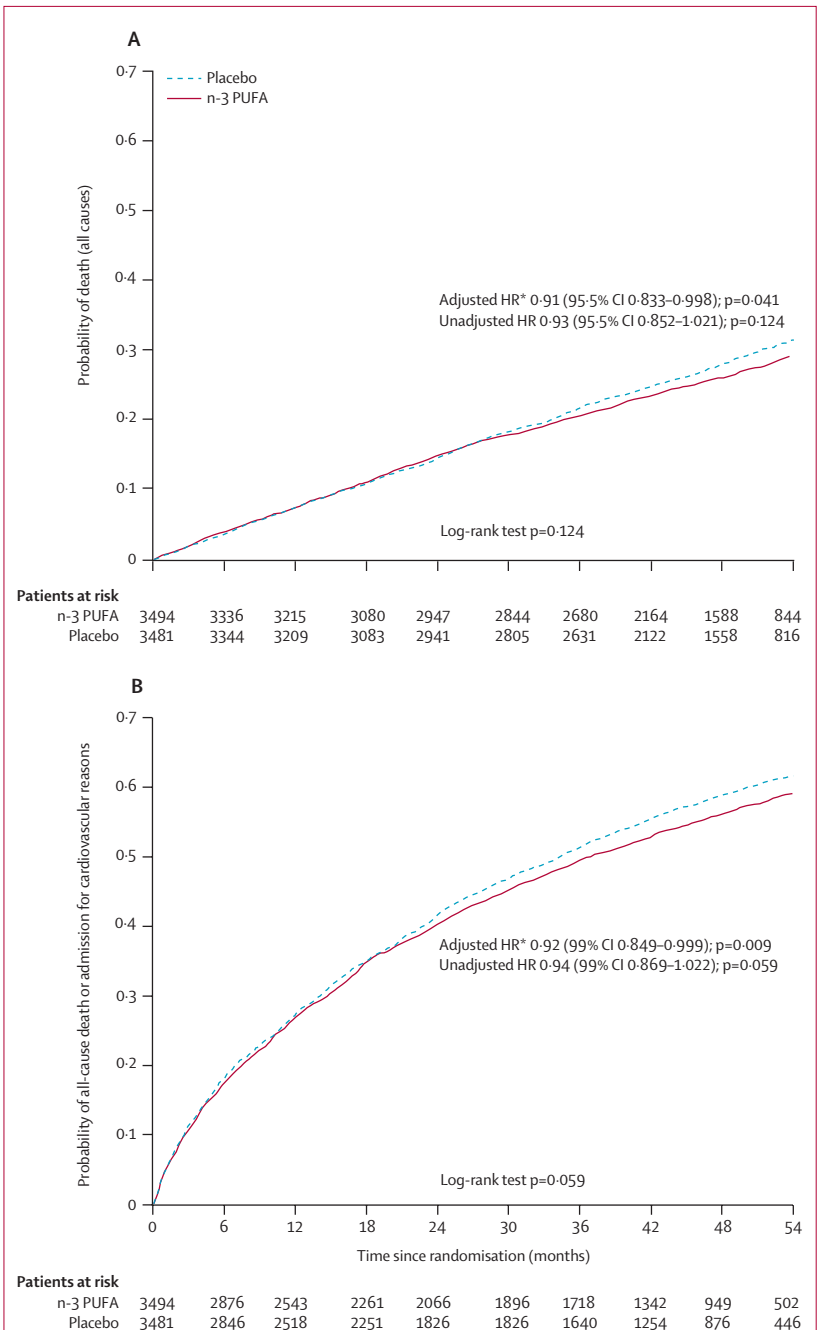

***Figure 2*: Kaplan-Meier curves for time to all-cause death (A) and for time to all-cause death or admission to hospital for cardiovascular reasons (B)**

PUFA=polyunsaturated fatty acids. *Estimates were calculated with a Cox proportional hazards model, with adjustment for admission to hospital for heart failure in the previous year, previous pacemaker, and aortic stenosis.

Role of the funding source

The GISSI-HF group coordinated the study, managed the data, and undertook analyses, under the supervision of the steering committee, who designed the GISSI-HF study. None of the funding sources had a role in the trial design, conduct, data collection, analyses, data interpretation, or writing of the report. The corresponding author had full access to all the data in the trial. Data were stored and analysed at the GISSI-HF Coordinating Centre (Florence and Milan). All members of the steering and writing committees had full access to the database and had final responsibility for the decision to submit for publication.

Results

7046 patients were randomly assigned (figure 1). We disqualified information from 71 patients at one site after randomisation, before unblinding, because the adequacy of the informed consent process and quality of data could not be ensured. Of the remaining 6975 patients, 3494 were

	n-3 PUFA (N=3494)	Placebo (N=3481)	Adjusted		Unadjusted	
			HR (95%CI)*	p value	HR 95%CI	p value
Patients who died of a cardiovascular cause	712 (20·4%)	765 (22·0%)	0·90 (0·81–0·99)	0·045	0·92 (0·83–1·02)	0·121
Patients who had an SCD	307 (8·8%)	325 (9·3%)	0·93 (0·79–1·08)	0·333	0·94 (0·80–1·10)	0·413
Patients admitted	1986 (56·8%)	2028 (58·3%)	0·94 (0·88–1·00)	0·049	0·96 (0·90–1·02)	0·178
Patients admitted for a cardiovascular reason	1635 (46·8%)	1687 (48·5%)	0·93 (0·87–0·99)	0·026	0·95 (0·89–1·02)	0·122
Patients admitted for heart failure	978 (28·0%)	995 (28·6%)	0·94 (0·86–1·02)	0·147	0·97 (0·89–1·06)	0·511
Patients who died of a cardiovascular cause or admitted for any reason	2157 (61·7%)	2202 (63·3%)	0·94 (0·89–0·99)	0·043	0·96 (0·90–1·02)	0·159
Patients with fatal and non-fatal MI	107 (3·1%)	129 (3·7%)	0·82 (0·63–1·06)	0·121	0·82 (0·64–1·06)	0·135
Patients with fatal and non-fatal stroke	122 (3·5%)	103 (3·0%)	1·16 (0·89–1·51)	0·271	1·18 (0·91–1·53)	0·225
Ischaemic	97 (2·8%)	79 (2·3%)				
Haemorrhagic	13 (0·4%)	10 (0·3%)				
Not known	12 (0·3%)	14 (0·4%)				

Data are number (%) unless otherwise stated. PUFA=polyunsaturated fatty acids. SCD=sudden cardiac death. MI=myocardial infarction. *95% CI was calculated with a Cox proportional hazards model with adjustment for admission to hospital for heart failure in the preceding year, previous pacemaker, and aortic stenosis.

Table 2: **Secondary outcomes**

assigned to receive n-3 PUFA and 3481 to placebo. The follow-up was concluded on March 31, 2008. The median duration of follow-up was 3·9 years (IQR 3·0–4·5).

Table 1 shows the baseline characteristics of all patients, including details of background medical treatment. The mean age of the patients was 67 years (SD 11), and 2947 (42%) were older than 70 years. 1516 (22%) were women. At study admission, 6520 (94%) patients were being treated with blockers of the renin-angiotensin system, 4522 (65%) with β blockers, and 2740 (39%) with spironolactone (table 1).

Figure 2 presents the findings for the two co-primary endpoints. In both cases, the Kaplan-Maier curves began to diverge after about 2 years after starting treatment: 955 (27%) patients in the n-3 PUFA group and 1014 (29%) in the placebo group died from any cause; the co-primary outcome of all-cause death or admission to hospital for cardiovascular reasons occurred in 1981 (57%) patients in the n-3 PUFA group and 2053 (59%) in the placebo group. In absolute terms, the risk reduction for all-cause mortality was 1·8% (95% CI 0·3–3·9) and for mortality or admission for cardiovascular reasons was 2·3% (0·0–4·6)—ie, 56 patients need to be treated to avoid one death or 44 patients to avoid one event like death or admission for cardiovascular reason for nearly 4 years.

Table 2 shows results for secondary outcomes. The rates of the outcome events in the n-3 PUFA group were lower than were those in the placebo group, apart from rates for stroke. The proportions of patients who died of a cardiovascular cause, who were admitted for any or a cardiovascular cause after randomisation, and who had the combined endpoint of cardiovascular death or admission for any cause were significantly lower in the n-3 PUFA group than in the placebo group. Sudden cardiac death arose in 307 (9%) patients allocated to n-3 PUFA and 325 (9%) in the placebo group (adjusted HR 0·93 [95% CI 0·79–1·08], p=0·333). The number of patients who had a first myocardial infarction after randomisation was 107 (3%) in the n-3 PUFA group and 129 (4%) in the placebo group (adjusted p=0·121); stroke occurred in 122 (4%) patients assigned to n-3 PUFA and in 103 (3%) in the placebo group (adjusted p=0·271). The rate of haemorrhagic events was similar in the two groups, and we noted no difference in the use of antithrombotic drugs in these patients. First admission for heart failure occurred in 978 (28%) patients in the n-3 PUFA group and 995 (29%) in the placebo group (adjusted HR 0·94 [95% CI 0·86–1·02], p=0·147). First hospital admission for ventricular arrhythmias occurred in 97 (3%) patients in the n-3 PUFA group versus 132 (4%) in the placebo group (adjusted HR 0·72 [95% CI 0·55–0·93], p=0·013).

	n-3 PUFA (N=3494)	Placebo (N=3481)
Total mortality	955 (27·3%)	1014 (29·1%)
Acute myocardial infarction	20 (0·6%)	25 (0·7%)
Worsening heart failure	319 (9·1%)	332 (9·5%)
Presumed arrhythmic	274 (7·8%)	304 (8·7%)
Stroke	50 (1·4%)	44 (1·3%)
Other cardiovascular reasons	49 (1·4%)	60 (1·7%)
Neoplasia	107 (3·1%)	112 (3·2%)
Other non-cardiovascular reasons	97 (2·8%)	102 (2·9%)
Not known	39 (1·1%)	35 (1·0%)

Data are number (%). PUFA=polyunsaturated fatty acids.

Table 3: **Causes of death**

Worsening heart failure accounted for most deaths, followed by presumed arrhythmic death (table 3). Presumed arrhythmic deaths occurred in 274 (8%) patients in the n-3 PUFA group and 304 (9%) in the placebo group (adjusted HR 0·88 [95% CI 0·75–1·04],

	n-3 PUFA Events/patients (%)	Placebo Events/patients (%)	HR (95% CI)*
Age <69 years (median)	856/1740 (49·2%)	906/1729 (52·4%)	0·92 (0·84–1·01)
Age ≥69 years (median)	1125/1754 (64·1%)	1147/1752 (65·5%)	0·96 (0·88–1·04)
LVEF ≤40%	1788/3161 (56·6%)	1871/3161 (59·2%)	0·94 (0·88–0·99)
LVEF >40%	193/333 (58·0%)	182/320 (56·9%)	1·02 (0·83–1·25)
Ischaemic cause	1079/1717 (62·8%)	1137/1750 (65·0%)	0·95 (0·87–1·03)
Non-ischaemic cause	902/1777 (50·8%)	916/1731 (52·9%)	0·94 (0·86–1·03)
NYHA II	1130/2226 (50·8%)	1170/2199 (53·2%)	0·93 (0·86–1·01)
NYHA III or IV	851/1268 (67·1%)	883/1282 (68·9%)	0·96 (0·87–1·05)
Diabetes	623/992 (62·8%)	660/982 (67·2%)	0·89 (0·80–0·99)
No diabetes	1358/2502 (54·3%)	1393/2499 (55·7%)	0·96 (0·89–1·04)
Total cholesterol ≤4·87 mmol/L†	1033/1748 (59·1%)	1080/1719 (62·8%)	0·91 (0·84–0·99)
Total cholesterol >4·87 mmol/L†	929/1719 (54·0%)	957/1732 (55·3%)	0·96 (0·88–1·05)

We recorded no significant interactions for any subgroup analysis. PUFA=polyunsaturated fatty acids. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction. *95% CI was calculated with a Cox proportional hazards model. †Median value. Data for total cholesterol were available for 6918 patients (3467 n-3 PUFA, 3451 placebo).

Table 4: **Predefined subgroup analysis—composite endpoint of all-cause death or admission to hospital for cardiovascular reasons**

	n-3 PUFA (N=3494)	Placebo (N=3481)	p value
Patients permanently discontinuing study treatment	1004 (28·7%)	1029 (29·6%)	0·45
ADR	102	104	
Patients' decision	478	500	
Practitioners' decision	33	41	
Investigators' decision	266	257	
Open label	11	10	
Other	114	117	
Patients permanently discontinuing study treatment due to ADR	102 (2·9%)	104 (3·0%)	0·87
Gastrointestinal disorder	96	92	
Allergic reaction	3	9	
Liver dysfunction	1	1	
Lipid abnormality	0	1	
Hepatocellular jaundice	0	1	
Subdural haematoma	1	0	
Muscle-related symptoms	1	0	
Patients permanently discontinuing study treatment due to serious ADR	1 (<0·1%)	0	
Subdural haematoma	1	0	

PUFA=polyunsaturated fatty acids. ADR=adverse drug reaction.

Table 5: **Permanent treatment discontinuations and adverse drug reactions**

p=0·141; table 3). Death from worsening heart failure occurred in 319 (9%) patients in the n-3 PUFA group and 332 (10%) in the placebo group (adjusted HR 0·92 [95% CI 0·79–1·07], p=0·275). The numbers of deaths from non-cardiovascular causes and from cancer were much the same in the two treatment groups (table 3).

The risk of all-cause death or admission to hospital for cardiovascular reasons was affected by n-3 PUFA in all predefined subgroups in much the same way, with no evidence of heterogeneity of treatment effect (table 4).

Neither blood pressure (systolic p=0·47, diastolic p=0·43) nor heart rate (p=0·73) was significantly modified by the study treatments. As expected, plasma concentrations of triglycerides decreased slightly from a median value of 1·42 mmol/L (IQR 1·05–1·98) at baseline to 1·36 mmol/L (0·99–1·93) after 1 year and 1·34 mmol/L (0·98–1·85) after 3 years, in patients allocated to n-3 PUFA treatment, but did not change in the placebo group (interaction time *vs* treatment p<0·0001). We recorded no differences in total, HDL, or LDL cholesterol between patients allocated to n-3 PUFA or placebo (data not shown).

By the end of the study, 1004 (29%) of patients in the n-3 PUFA group and 1029 (30%) in the placebo group were no longer taking study drug for various reasons (p=0·45; table 5). The rate of patients who had permanently discontinued taking the study drug because of adverse reactions was much the same in the n-3 PUFA and in the placebo groups (102 [3%] *vs* 104 [3%], p=0·87), with gastrointestinal disturbance being the most frequent cause in both groups (table 5).

In the per-protocol analysis undertaken on 4994 fully compliant patients, who were defined as those who had taken experimental treatments for at least 80% of the time of observation and without major protocol violations, the rate of all-cause death was 26% (658 of 2512) in the n-3 PUFA group and 29% (725 of 2482) in the placebo group (adjusted HR 0·86 [95·5% CI 0·77–0·95], p=0·004). We recorded no interaction between the effects of n-3 PUFA and statin (data not shown).

Discussion

Our study shows that the long-term administration of 1 g per day n-3 PUFA was effective in reducing both all-cause mortality and admissions to hospital for cardiovascular reasons. Although this moderate benefit was smaller than was expected, we should note that it was obtained in a population already treated with recommended therapies, was consistent across all the predefined subgroups, and was further supported by the findings of the per-protocol analysis. We noted no adverse effects in the population of symptomatic patients with heart failure in whom the n-3 PUFA had never been tested, confirming the safety of the drug.

The advantage of n-3 PUFA, documented for both co-primary endpoints (reduced fatal events and hospital admissions for cardiovascular cause), suggests that it has an effect on the mechanisms leading to progression of heart failure. This notion is consistent with the results of published epidemiological[19] and experimental research, as well as studies documenting reduction of vascular resistance and attenuation of vasoconstrictive responses to angiotensin II,[15,16] improvement in left ventricular diastolic function,[17] and reduction of hypertension-related ventricular hypertrophy.[15–18,21,26]

Attention should be focused on the effects of n-3 PUFA on fatal and non-fatal arrhythmic events, since the core

hypothesis we tested in this study was that such events could be reduced by the long-term administration of n-3 PUFA. Furthermore, this is the effect for which the most robust experimental, epidemiological, and clinical pretrial evidence exists.[11] The incorporation of n-3 PUFA into the membranes of target cells and tissues[27–29] is likely to produce a reduction in electrical excitability, decreasing the probability of fatal and non-fatal arrhythmic events (irrespective of the underlying mechanism documented in in-vitro and in-vivo experimental models).[11] An anti-arrhythmic activity could have major significance for a clinical disorder for which only implantable cardioverter defibrillators are available as a specific preventive measure for life-threatening arrhythmias. Of the absolute risk reduction on total mortality, the greatest proportion was attributed to presumed arrhythmic death (figure 2, table 3). Additionally, almost half the absolute risk reduction on first admission to hospital for cardiovascular reasons was due to a reduction of admissions for ventricular arrhythmias.

Although one could argue that both the size and the timing of the antiarrhythmic effect are different from those recorded in the GISSI-Prevenzione population,[3] we should note that the cohorts in the two studies are hardly comparable with respect to the expected timing and role of arrhythmic complications. By contrast with patients with recent myocardial infarction,[2–6] the divergence of survival curves after 2 years is not unexpected in chronic heart failure given that for this disorder there is no reason to expect an increased number of arrhythmic episodes at the beginning of the study, as was the case a few weeks after myocardial infarction in GISSI-Prevenzione trial. Accordingly, a therapeutic intervention is expected to take several months or years to express its beneficial effect for patients with heart failure. This timeframe was common to other trials that tested specific treatments (such as implantable defibrillators), for which benefit started to appear over periods of time comparable with what we recorded in this study.[30]

As reported by other trials,[29–32] we noted little benefit on atherothrombothic events—namely, myocardial infarction and stroke—in this study, according with the findings of GISSI-Prevenzione[3] in a population of patients in whom such events were fairly infrequent. Because of the increasing awareness on the epidemiological relevance of heart failure with preserved LVEF, no limit of the variable was considered in the entry criteria. However, we enrolled only less than 10% of such patients. Such a fairly small sample size precludes any meaningful assessment of the primary and secondary endpoints in the subgroup of patients with ejection fraction greater than 40%.

Although a higher dose of n-3 PUFA could be postulated to have greater efficacy, we tested in patients with heart failure the same dose that was used in the GISSI-Prevenzione trial, since this dose is associated with a significant reduction of mortality in patients after myocardial infarction. Further, we tried to avoid the risk of decreasing compliance by increasing the number of pills in patients with heart failure who already receive several drugs.

We have confirmed the safety of a treatment with n-3 PUFA, in addition to the multiagent therapy that characterises the management of heart failure. The adverse reactions leading to discontinuation of n-3 PUFA therapy were of minor clinical relevance (mostly gastrointestinal disorders). We recorded a slight excess of cerebrovascular events, which was a similar finding to that reported in the GISSI-Prevenzione trial. This excess was distributed fairly evenly between ischaemic and haemorrhagic cases.

In conclusion, we have shown that n-3 PUFA treatment is effective and safe in a large population of patients with heart failure of any cause, who are receiving standard clinical care provided in hospitals and ambulatory facilities in Italy. Since we invited all cardiology centres operating in Italy to participate in this trial, and most did so, the results indicate what is likely to happen in the real world during the course of several years of polipharmacy care.

Contributors

Luigi Tavazzi, Gianni Tognoni, Aldo P Maggioni, Roberto Marchioli, Roberto Latini, Maria Grazia Franzosi, Gian Luigi Nicolosi, and Maurizio Porcu contributed to the design of the study, and the collection and interpretation of the data. Simona Barlera and Donata Lucci were the responsible for all statistical analyses. Luigi Tavazzi and Aldo P Maggioni wrote the first draft of the report. All authors contributed to draft the report and read and approved its final version.

GISSI-HF Study Group

Steering committee—Luigi Tavazzi (Chairman), Gianni Tognoni (Co-Chairman), Maria Grazia Franzosi, Roberto Latini, Aldo P Maggioni, Roberto Marchioli, Gian Luigi Nicolosi, Maurizio Porcu. *Writing committee*—Luigi Tavazzi (GVM Hospitals of Care and Research, Cotignola, Italy), Aldo P Maggioni (ANMCO Research Centre, Florence, Italy), Roberto Marchioli (Consorzio Mario Negri Stud, S Maria Imbaro, Italy), Simona Barlera (Istituto Mario Negri, Milan, Italy), Maria Grazia Franzosi (Istituto Mario Negri, Milan, Italy), Roberto Latini (Istituto Mario Negri, Milan, Italy), Donata Lucci (ANMCO Research Centre, Florence, Italy), Gian Luigi Nicolosi (AO S Maria Angeli, Pordenone, Italy), Maurizio Porcu (AO Brotzu-S Michele, Cagliari, Italy), Gianni Tognoni (Consorzio Mario Negri Stud, S Maria Imbaro, Italy). *Data and safety monitoring board*—Salim Yusuf (Chairman), Fulvio Camerini, Jay N Cohn, Adriano Decarli, Bertram Pitt, Peter Sleight, Philip A Poole-Wilson. *Primary endpoint committee*—Enrico Geraci (Chairman), Marino Scherillo (Co-Chairman), Gianna Fabbri (Coordinator), Barbara Bartolomei (Secretary), Daniele Bertoli, Franco Cobelli, Claudio Fresco, Antonietta Ledda, Giacomo Levantesi, Cristina Opasich, Franco Rusconi, Gianfranco Sinagra, Fabio Turazza, Alberto Volpi. *Clinical monitoring*—Martina Ceseri, Gianluca Alongi, Antonio Atzori, Filippo Bambi, Desiree Bastarolo, Francesca Bianchini, Iacopo Cangioli, Vittoriana Canu, Concetta Caporusso, Gabriele Cenni, Laura Cintelli, Michele Cocchio, Alessia Confente, Eva Fenicia, Giorgio Friso, Marco Gianfriddo, Gianluca Grilli, Beatrice Lazzaro, Giuseppe Lonardo, Alessia Luise, Rachele Nota, Mariaelena Orlando, Rosaria Petrolo, Chiara Pierattini, Valeria Pierota, Alessandro Provenzani, Velia Quartuccio, Anna Ragno, Chiara Serio, Alvise Spolaor, Arianna Tafi, Elisa Tellaroli. *Subprojects*—Stefano Ghio, Elisa Ghizzardi *(Ventricular Remodeling–Echo)*, Roberto Latini, Serge Masson *(Biohumoral)*, Maria Grazia Franzosi, Lella Crociati *(Genetic)*, Maria Teresa La Rovere *(Arrhythmic and Autonomic Pattern–Holter monitoring)*, Ugo Corrà *(Exercise Capacity)*, Paola Di Giulio *(Quality of Life and Depression)*, Andrea Finzi

(Implantable Cardiac Defibrillator). Database management and statistics—Donata Lucci, Simona Barlera, Marco Gorini, Lucio Gonzini, Valentina Milani, Giampietro Orsini. *Regulatory, administrative, and secretariat*—Elisa Bianchini, Silvia Cabiddu, Ilaria Cangioli, Laura Cipressa, Maria Lucia Cipressa, Giuseppina Di Bitetto, Barbara Ferri, Luisa Galbiati, Andrea Lorimer, Carla Pera, Paola Priami, Antonella Vasamì. Participating centres and investigators are listed in the webappendix.

See Online for webappendix

Conflict of interest statement

LT, GT, APM, RM, MGF, and MP received research support and honoraria for lectures from SPA, Pfizer, and SigmaTau. RL, SB, and DL received research support from SPA, Pfizer, and SigmaTau. GLN declares that he has no conflict of interest.

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