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

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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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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.

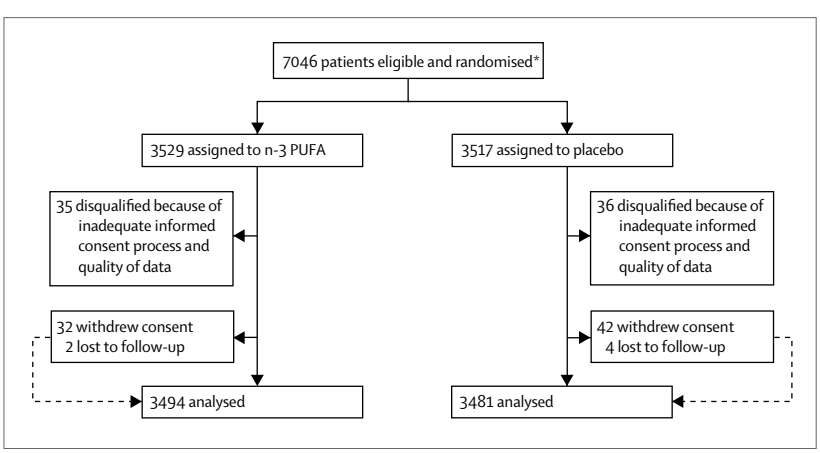

Figure 1: **Trial profile**
*The trial did not plan to have an eligibility period before randomisation. Eligible patients were immediately randomised to study treatments. PUFA=polyunsaturated fatty acids.

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%)
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.

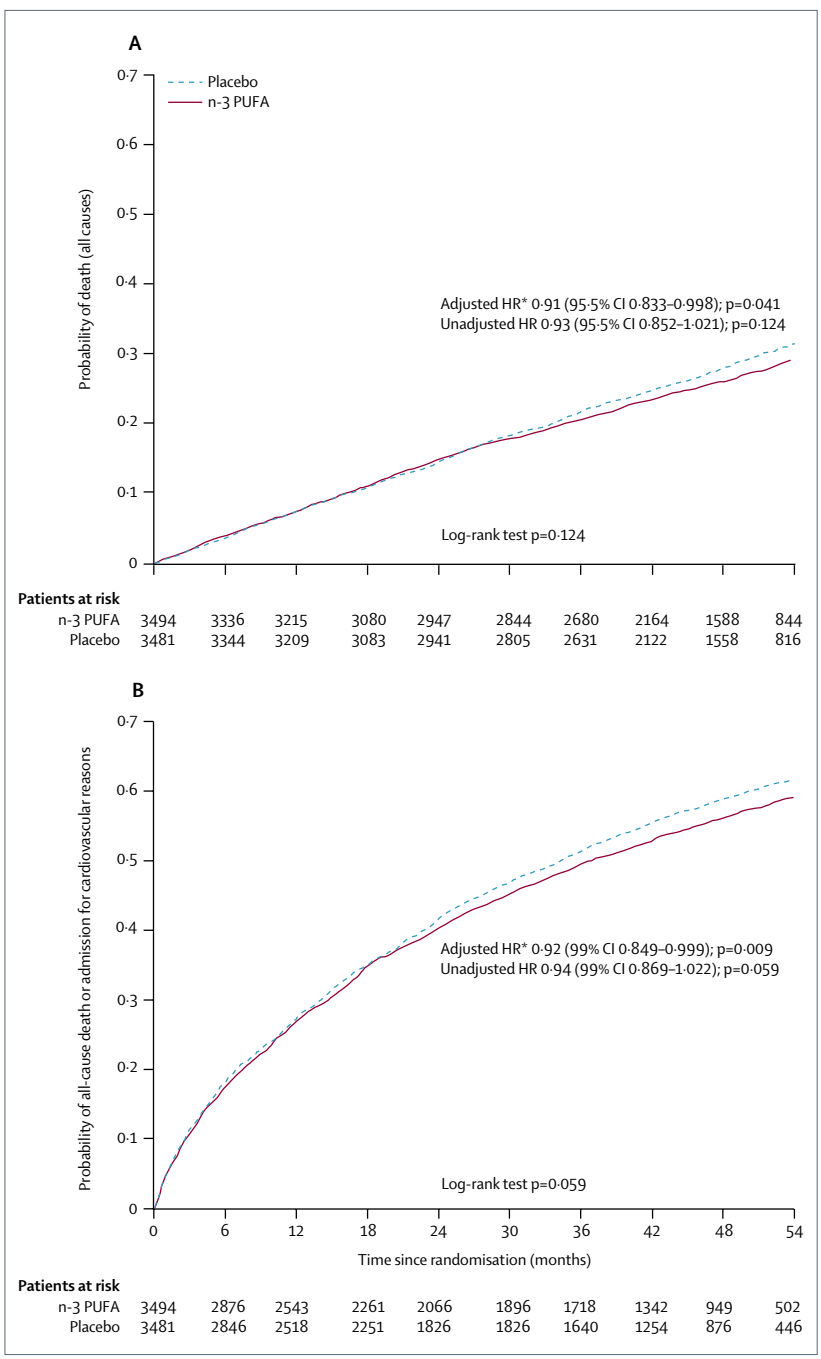

***Figure 2*: Kaplan-Meier curves for time to all-cause death (A) and for time to all-cause death or admission to hospital for cardiovascular reasons (B)**

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.

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

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.

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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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Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial

*GISSI-HF investigators**

Summary

Background **Large observational studies, small prospective studies and post-hoc analyses of randomised clinical trials have suggested that statins could be beneficial in patients with chronic heart failure. However, previous studies have been methodologically weak. We investigated the efficacy and safety of the statin rosuvastatin in patients with heart failure.**

Methods **We undertook a randomised, double-blind, placebo-controlled trial in 326 cardiology and 31 internal medicine centres in Italy. We enrolled patients aged 18 years or older 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 rosuvastatin 10 mg daily (n=2285) or placebo (n=2289) by a concealed, computerised telephone randomisation system. Patients were followed up for a median of 3·9 years (IQR 3·0–4·4). 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. 657 (29%) patients died from any cause in the rosuvastatin group and 644 (28%) in the placebo group (adjusted hazard ratio [HR] 1·00 [95·5% CI 0·898–1·122], p=0·943). 1305 (57%) patients in the rosuvastatin group and 1283 (56%) in the placebo group died or were admitted to hospital for cardiovascular reasons (adjusted HR 1·01 [99% CI 0·908–1·112], p=0·903). In both groups, gastrointestinal disorders were the most frequent adverse reaction (34 [1%] rosuvastatin group *vs* 44 [2%] placebo group).**

Interpretation **Rosuvastatin 10 mg daily did not affect clinical outcomes in patients with chronic heart failure of any cause, in whom the drug was safe.**

Funding **Società Prodotti Antibiotici (SPA; Italy), Pfizer, Sigma Tau, and AstraZeneca.**

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Introduction

Hydroxymethylglutaryl-coenzyme A reductase inhibitors (known as statins) are among the most successful drugs discovered and incorporated into clinical practice over the past decades for both primary and secondary prevention of atherothrombosis. In addition to their lipid-lowering action, statins have been postulated to have so-called pleiotropic actions,[1] including anti-inflammatory, antihypertrophic, antifibrotic, and anti-oxidant effects; improvement of endothelial dysfunction; inhibition of neurohormonal activation; and prevention of cardiac arrhythmias.[1–5] Most of these effects can target important components of the complex physiopathology of heart failure.[6]

Large observational studies,[2,7] several post-hoc analyses of randomised clinical trials testing drugs that differ from statins,[8–15] and small prospective trials[16–19] have suggested that statins could be beneficial to patients with heart failure. Furthermore, two meta-analyses of statin use in observational and randomised clinical trials[2,8] confirmed a reduction in cardiovascular mortality in patients with heart failure of both ischaemic and non-ischaemic cause. However, randomised controlled trials specifically investigating the efficacy and safety of statins in heart failure were needed because of the methodological weaknesses that were inherent in previous studies.

The Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca (GISSI) decided to undertake a study in patients with symptomatic heart failure of any cause and with any level of left ventricular systolic function, to test the hypothesis that the administration of the statin rosuvastatin would be effective and safe.

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.[20]

Eligible patients were men and women aged 18 years or older, with symptomatic heart failure that was classified as New York Heart Association (NYHA) functional class II–IV, who were being treated according to European Society of Cardiology (ESC) guidelines. The left ventricular ejection fraction (LVEF) was measured within 3 months before enrolment. Patients with an

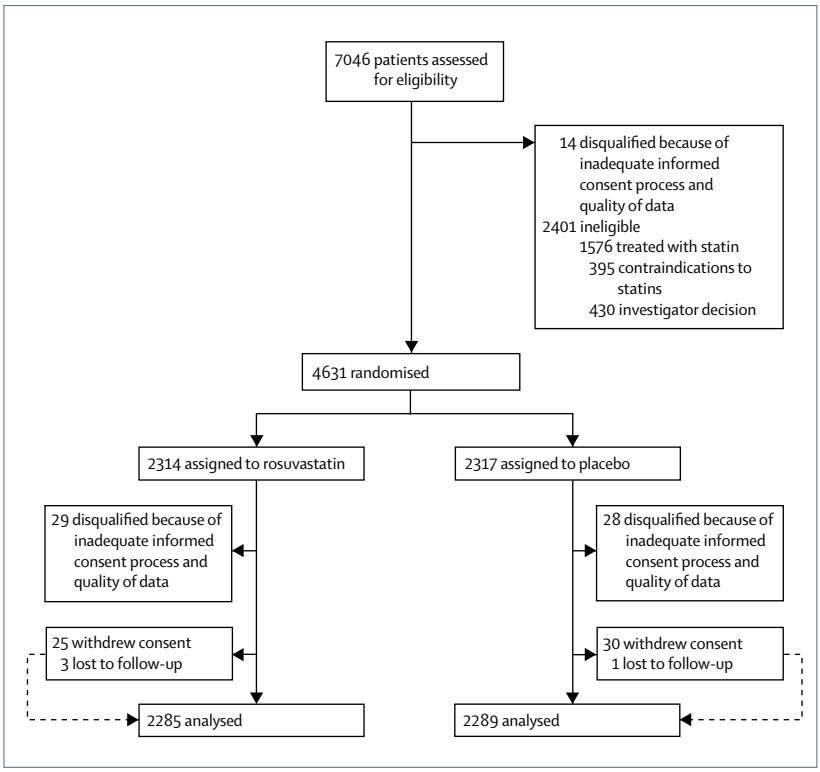

Figure 1: **Trial profile**

LVEF greater than 40% had to have had at least one hospital admission for congestive heart failure in the preceding year to meet the inclusion criteria.

Major exclusion criteria included known hypersensitivity to study treatment; 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 a revascularisation procedure within 1 month before randomisation; planned cardiac surgery, expected to be done within 3 months after randomisation; significant liver disease; serum creatinine concentration greater than 221 μmol/L; alanine and aspartate transaminase concentrations more than 1·5 times the upper normal limit; creatine phosphokinase concentrations above the upper normal limit; and pregnant or lactating women or women of childbearing potential who were not adequately protected against becoming pregnant.

All patients provided written informed consent to participation in the study before being enrolled. The trial was approved by the local ethics committees of all the participating sites. An independent data safety monitoring board was established to oversee the safety of the patients enrolled in the trial and to monitor the trial's progress.

Procedures

Between Aug 6, 2002, and Feb 28, 2005, patients were randomly assigned to receive one tablet per day of rosuvastatin 10 mg or matching placebo. All patients and study personnel were blinded to treatment. Eligible patients were randomly assigned (with stratification by site) to treatment groups by a concealed, computerised telephone randomisation system.

After randomisation, study visits were scheduled 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. 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 events recorded in the study were adjudicated blindly by an ad-hoc committee on the basis of pre-agreed definitions and procedures. The effect of rosuvastatin on the combined outcome measure of all-cause mortality or hospital admission for cardiovascular reasons was assessed in subgroups of patients that were predefined 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 correlations between the two co-primary endpoints, the net α spending was preserved. We based the calculation of sample size on the first co-primary endpoint: time to death. The number of events needed to detect a 15% reduction in the rosuvastatin group, with 90% power and assuming an expected mortality rate at 3 years of 25% in the placebo group, was calculated to be 1252. All analyses were done in the intention-to-treat population, with the exception of a per-protocol analysis on the two co-primary endpoints that was undertaken in patients without major protocol violations and who had taken

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study treatments for at least 80% of the time of observation.

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. Since all the patients randomly assigned to rosuvastatin or placebo had also been assigned, at the same time, to n-3 polyunsaturated fatty acids (PUFA) or matching placebo,[21] the existence of an effect modification in patients receiving both treatments was explored by fitting a Cox proportional hazards model with terms for n-3 PUFA, rosuvastatin, and their interaction. To estimate the size of the effect on the secondary endpoints (adjusted analysis) and in the prespecified subgroups, we calculated hazard ratios (HR) with 95% CI with a Cox proportional hazards model. Differences between randomised groups in laboratory examinations across the study (at 1 and 3 years) were examined by repeated-measures analysis of variance, with adjustment for their respective baseline value. Whenever the laboratory parameters did not meet the normality assumptions, we applied a log transformation.

	Rosuvastatin (N=2285)	Placebo (N=2289)
Patients' characteristics		
Age (years)	68 (11)	68 (11)
Age >70 years	1002 (43·9%)	1012 (44·2%)
Women	543 (23·8%)	489 (21·4%)
Heart disease risk factors		
BMI (kg/m²)	27·1 (4·6)	27·1 (4·4)
SBP (mm Hg)	127 (18)	127 (18)
DBP (mm Hg)	77 (10)	77 (10)
Heart rate (beats per min)	73 (14)	73 (13)
Current smoking	323 (14·1%)	321 (14·0%)
History of hypertension	1260 (55·1%)	1224 (53·5%)
NYHA class		
II	1398 (61·2%)	1462 (63·9%)
III	828 (36·2%)	771 (33·7%)
IV	59 (2·6%)	56 (2·4%)
LVEF (%)	33·4% (8·8)	33·1% (8·7)
LVEF >40%	236 (10·3%)	225 (9·8%)
Medical history		
Admission for HF in previous year	1189 (52·0%)	1131 (49·4%)
Previous AMI	727 (31·8%)	774 (33·8%)
Previous stroke	99 (4·3%)	109 (4·8%)
Diabetes	625 (27·4%)	571 (25·0%)
CABG	296 (13·0%)	319 (13·9%)
PCI	185 (8·1%)	192 (8·4%)
ICD	146 (6·4%)	155 (6·8%)
Pacemaker	300 (13·1%)	263 (11·5%)
History of atrial fibrillation	440 (19·3%)	477 (20·8%)
Peripheral vascular disease	184 (8·1%)	160 (7·0%)
COPD	538 (23·5%)	522 (22·8%)
Neoplasia	76 (3·3%)	91 (4·0%)
Heart failure cause		
Ischaemic	909 (39·8%)	919 (40·2%)
Dilatative	793 (34·7%)	783 (34·2%)
Hypertensive	409 (17·9%)	414 (18·1%)
Other cause	70 (3·1%)	65 (2·8%)
Non-detectable/unknown	104 (4·5%)	108 (4·7%)
(Continues in next column)		
(Continued from previous column)		
Physical examinations		
Pulmonary rales	646 (28·3%)	614 (26·8%)
Third heart sound	576 (25·2%)	552 (24·1%)
Mitral insufficiency	1467 (64·2%)	1462 (63·9%)
Aortic stenosis	44 (1·9%)	49 (2·1%)
ECG findings		
QRS >120 ms*	794 (35·2%)	761 (33·6%)
Atrial fibrillation	430 (18·8%)	454 (19·8%)
Pathological Q waves	384 (16·8%)	439 (19·2%)
Left ventricular hypertrophy	492 (21·5%)	449 (19·6%)
Medical treatment		
ACE inhibitors	1766 (77·3%)	1784 (77·9%)
ARBs	442 (19·3%)	392 (17·1%)
ACE inhibitors/ARBs	2150 (94·1%)	2126 (92·9%)
β blockers	1433 (62·7%)	1420 (62·0%)
Spironolactone	890 (39·0%)	945 (41·3%)
Diuretic drugs	2057 (90·0%)	2061 (90·0%)
Digitalis	915 (40·0%)	915 (40·0%)
Oral anticoagulant drugs	681 (29·8%)	698 (30·5%)
Aspirin	1020 (44·6%)	1044 (45·6%)
Other antiplatelet agents	179 (7·8%)	188 (8·2%)
Nitrates	729 (31·9%)	761 (33·3%)
Calcium-channel blockers	230 (10·1%)	231 (10·1%)
Amiodarone	464 (20·3%)	421 (18·4%)

Data are mean (SD) or number (%). BMI=body-mass index. SBP=systolic blood pressure. DBP=diastolic blood pressure. 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 4523 patients (2257 rosuvastatin, 2266 placebo).

Table 1: **Baseline characteristics of patients**

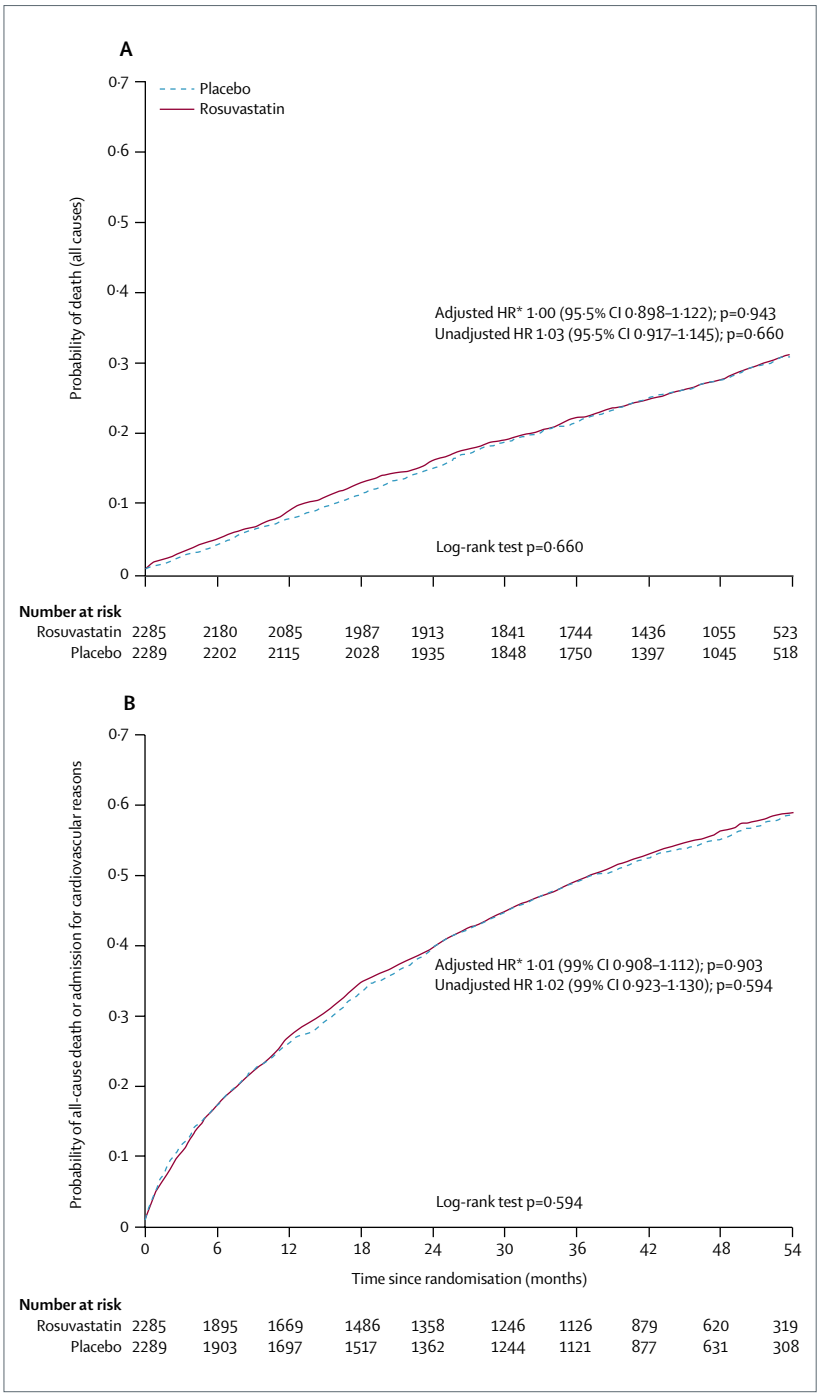

***Figure 2*: Kaplan-Meier curves for time to all-cause death (A) and for time to all-cause death or admission for cardiovascular reasons (B)**

*Estimates were calculated with a Cox proportional hazards model, with adjustment for admission to hospital for heart failure in the previous year, previous pacemaker, sex, diabetes, pathological Q waves, and angiotensin receptor blockers.

High sensitivity C-reactive protein (hsCRP) concentrations were log transformed because they were highly skewed. We analysed changes from baseline to 3 months by analysis of variance, with adjustment for their baseline value. We did all analyses with SAS software (version 8.2).

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

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

4631 patients were randomly assigned (figure 1). We disqualified information from 57 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 4574 patients, 2285 were assigned to receive rosuvastatin and 2289 to receive placebo. Follow-up ended on March 31, 2008. The median duration of follow-up was 3·9 years (IQR 3·0–4·4).

Table 1 shows the baseline characteristics of all patients, including details of previous medical treatment. Mean age was 68 years (SD 11), and 2014 (44%) patients were older than 70 years. 1032 (23%) were women. The cause of heart failure was ischaemic in 1828 (40%) patients, primary dilated cardiomyopathy in 1576 (35%), and hypertensive in 823 (18%). Background treatment included a blocker of the renin-angiotensin system in 4276 (94%) patients, a β blocker in 2853 (62%), and spironolactone in 1835 (40%) (table 1).

We recorded 657 deaths of any cause in the rosuvastatin group (29%) and 644 in the placebo group (28%) (figure 2). The co-primary outcome of all-cause death or admission to hospital for cardiovascular reasons occurred in 1305 (57%) patients in the rosuvastatin group and 1283 (56%) in the placebo group (figure 2). Effect modification for patients taking both rosuvastatin and n3-PUFA was excluded for both outcomes (interaction term p=0·76 for all-cause death and p=0·95 for the combined endpoint).

The rates of secondary outcomes in the rosuvastatin group were similar to those noted in the placebo group, with respect to death for a cardiovascular cause; first hospital admission for any, cardiovascular, or heart failure cause; and the combined outcome measure of cardiovascular death or admission to hospital for any cause (table 2). Furthermore, we recorded no significant differences in the rates of sudden cardiac death, myocardial infarction, and stroke (table 2).

We noted no significant difference in the various causes of death, irrespective of whether the cause was

	Rosuvastatin (N=2285)	Placebo (N=2289)	Adjusted		Unadjusted	
			HR (95% CI)*	p value	HR (95% CI)	p value
Patients who died of cardiovascular reasons	478 (20·9%)	488 (21·3%)	0·96 (0·85–1·09)	0·550	0·98 (0·87–1·12)	0·804
Patients who had an SCD	220 (9·6%)	196 (8·6%)	1·12 (0·92–1·36)	0·257	1·13 (0·93–1·37)	0·221
Patients admitted	1278 (55·9%)	1286 (56·2%)	0·99 (0·92–1·07)	0·776	1·00 (0·93–1·08)	0·962
Patients admitted for a cardiovascular reason	1033 (45·2%)	1060 (46·3%)	0·96 (0·88–1·05)	0·371	0·98 (0·90–1·07)	0·613
Patients admitted for heart failure	629 (27·5%)	634 (27·7%)	0·97 (0·87–1·09)	0·610	1·00 (0·90–1·12)	0·987
Patients who died of a cardiovascular cause or were admitted for any reason	1417 (62·0%)	1385 (60·5%)	1·02 (0·95–1·10)	0·626	1·03 (0·96–1·11)	0·409
Patients with fatal and non-fatal MI	61 (2·7%)	70 (3·1%)	0·89 (0·63–1·26)	0·516	0·88 (0·63–1·24)	0·459
Patients with fatal and non-fatal stroke	82 (3·6%)	66 (2·9%)	1·23 (0·89–1·70)	0·211	1·25 (0·91–1·73)	0·174

Data are number (%) unless otherwise stated. SCD=sudden cardiac death. MI=myocardial infarction. ARBs=angiotensin receptor blockers. *95% CI was calculated with a Cox proportional hazards model with adjustment for admission for heart failure in the preceding year, previous pace-maker, sex, diabetes, pathological Q waves, and angiotensin receptor blockers.

Table 2: **Secondary outcomes**

cardiovascular or non-cardiovascular (table 3). The risk of all-cause death or admission to hospital for cardiovascular reasons was not affected by rosuvastatin in any of the predefined subgroups (including that of ischaemic *vs* non-ischaemic cause), with no evidence of heterogeneity of a treatment effect (table 4). In an extensive post-hoc analysis limited to 1828 patients with heart failure of ischaemic cause, the rosuvastatin and placebo groups did not differ significantly with respect to either the primary or secondary endpoints (data not shown).

In the rosuvastatin group, concentrations of LDL cholesterol decreased from 3·16 mmol/L at baseline to 2·15 mmol/L after 1 year (–32%) and 2·31 mmol/L after 3 years (–27%). However, we noted no significant change in the placebo group, in which concentrations were 3·13 mmol/L at baseline and 3·37 mmol/L after 1 year and 3·06 mmol/L after 3 years (interaction time *vs* treatment p<0·0001). Concentrations of HDL cholesterol were not significantly modified in patients receiving rosuvastatin compared with those given placebo (time *vs* treatment p=0·67). To test the hypothesis that patients in whom LDL cholesterol is greatly decreased by study treatment might have an increased risk of events, we did an exploratory subgroup analysis splitting the population in thirds of LDL reduction. We recorded no difference in treatment effects in these subgroups of patients (data not shown).

In a subgroup of 626 patients in whom we assayed hsCRP, rosuvastatin lowered hsCRP over 3 months by a median of 0·45 mg/L (IQR –2·29 to 0·53) from a baseline of 2·71 mg/L (1·22–5·99), which was significantly different from the decrease of 0·10 mg/L (–1·37 to 0·85) from a baseline of 2·17 mg/L (1·07–4·92) that we noted in the placebo group (analysis of variance p=0·0195).

By the end of the study, 790 (35%) patients allocated to rosuvastatin and 831 (36%) allocated to placebo were no longer taking the study drug for various reasons (p=0·22) (table 5). We noted no difference in the permanent discontinuations of study treatment because of an

	Rosuvastatin (N=2285)	Placebo (N=2289)
Total mortality	657 (28·8%)	644 (28·1%)
Acute myocardial infarction	10 (0·4%)	15 (0·7%)
Worsening of heart failure	203 (8·9%)	231 (10·1%)
Presumed arrhythmic	198 (8·7%)	182 (8·0%)
Stroke	38 (1·7%)	29 (1·3%)
Other cardiovascular reasons	29 (1·3%)	31 (1·4%)
Neoplasia	81 (3·5%)	75 (3·3%)
Other non-cardiovascular reasons	75 (3·3%)	55 (2·4%)
Not known	23 (1·0%)	26 (1·1%)

Data are number (%).

Table 3: **Causes of death**

	Rosuvastatin Events/patients (%)	Placebo Events/patients (%)	HR (95% CI)*
Age <70 years (median)	606/1178 (51·4%)	575/1176 (48·9%)	1·08 (0·96–1·21)
Age ≥70 years (median)	699/1107 (63·1%)	708/1113 (63·6%)	0·97 (0·88–1·08)
LVEF ≤40%	1166/2049 (56·9%)	1151/2064 (55·8%)	1·02 (0·94–1·11)
LVEF >40%	139/236 (58·9%)	132/225 (58·7%)	1·05 (0·83–1·33)
Ischaemic cause	588/909 (64·7%)	579/919 (63·0%)	1·03 (0·92–1·16)
Non-ischaemic cause	717/1376 (52·1%)	704/1370 (51·4%)	1·02 (0·92–1·13)
NYHA II	714/1398 (51·1%)	747/1462 (51·1%)	1·00 (0·90–1·10)
NYHA III or IV	591/887 (66·6%)	536/827 (64·8%)	1·02 (0·91–1·15)
Diabetes	397/625 (63·5%)	364/571 (63·8%)	1·00 (0·87–1·16)
No diabetes	908/1660 (54·7%)	919/1718 (53·5%)	1·02 (0·93–1·12)
Total cholesterol ≤4·97 mmol/L†	685/1135 (60·4%)	676/1153 (58·6%)	1·06 (0·95–1·17)
Total cholesterol >4·97 mmol/L†	609/1131 (53·9%)	595/1118 (53·2%)	1·00 (0·89–1·11)

We recorded no significant interactions for any subgroup analysis. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction. *95% CI was calculated by Cox proportional hazards model. †Median value. Data for total cholesterol were available for 4537 patients (2266 rosuvastatin, 2271 placebo).

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

	Rosuvastatin (N=2285)	Placebo (N=2289)	p value
Patients who permanently discontinued study treatment	790 (34·6%)	831 (36·3%)	0·22
ADR	104	91	
Patients' decision	357	377	
Doctors' decision	30	39	
Investigators' decision	205	227	
Open label	10	22	
Other	84	75	
Patients who permanently discontinued study treatment due to ADR	104 (4·6%)	91 (4·0%)	0·36
Gastrointestinal disorders	34	44	
Asthenia	1	0	
Allergic reaction	7	7	
Liver dysfunction	26	12	
Lipid abnormality	0	1	
Creatine phosphokinase increase	4	1	
Renal dysfunction	6	4	
Acute renal failure	2	0	
Hepatocellular jaundice	0	1	
Acute dermatitis*	1	0	
Muscle-related symptoms	23	21	
Patients who permanently discontinued study treatment due to serious ADR	2 (<0·1%)	0	
Acute renal failure	1	0	
Acute dermatitis*	1	0	

ADR=adverse drug reaction. *Diagnosed as Stevens Johnson syndrome by the investigator, not confirmed by an expert adjudicator.

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

adverse reaction between the rosuvastatin and the placebo groups (table 5). Muscle-related symptoms occurred in 23 patients allocated to rosuvastatin and in 21 allocated to placebo, whereas we recorded rises in liver enzyme concentrations in 26 patients in the rosuvastatin group and in 12 in the placebo group. Total creatine kinase concentrations rose to above five times the upper normal limit in nine patients and to ten times the upper normal limit in one patient in the rosuvastatin group, and in two and one patient, respectively, in the placebo group. No patients had rhabdomyolysis attributable to the use of rosuvastatin. Serum creatinine concentrations increased from a median of 94·59 μmol/L (IQR 79·56–109·62) at baseline to 96·36 μmol/L (79·56–114·92) after 1 year and to 97·24 μmol/L (79·56–116·69) after 3 years in the rosuvastatin group, and from 95·47 μmol/L (IQR 79·56–114·92) at baseline to 97·24 μmol/L at 1 year (IQR 80·44–114·92) and 3 years (83·98–123·76) in the placebo group (interaction time *vs* treatment p=0·04). During follow-up, the rate of patients with doubling of serum creatinine concentrations was much the same in the rosuvastatin and placebo groups (65 [3·0%] *vs* 57 [2·6%], p=0·43).

In the per-protocol analysis of the 2874 fully compliant patients, who had taken experimental treatments for at least 80% of the time of observation and had no major protocol violations, the rate of all-cause death was 29% (429 of 1461) in the rosuvastatin group and 27% (377 of 1413) in the placebo group (adjusted HR 1·12 [95·5% CI 0·97–1·29], p=0·16).

Discussion

This trial aimed to investigate the efficacy and safety of rosuvastatin at the usual start dose (10 mg daily) in a broad population of symptomatic patients with heart failure, irrespective of age, ischaemic and non-ischaemic cause, and LVEF. We consistently noted no effect on primary and secondary endpoints, and on all planned subgroup analyses.

Almost uniformly, several observational studies undertaken in different experimental and clinical conditions, and post-hoc analyses of randomised controlled trials in patients with heart failure, have indicated beneficial effects of statins on several endpoints, including mortality.[2,7,8] However, two randomised controlled studies specifically addressing the issue of the effects of statins in heart failure—GISSI-HF and CORONA[22]—reported opposite results, with both showing no benefit. This finding suggests that making conclusions about drug efficacy from any type of observational studies or post-hoc analyses is not reliable, irrespective of what statistical adjustments are made.

Direct comparisons of different statins or different doses of the same statins in patients with coronary artery disease consistently showed a reduced incidence of heart failure in patients treated with the more powerful regimens.[9–14] An overview of these studies showed a 27% benefit in the prevention of admissions to hospital with heart failure.[15] This finding is not in contrast with the results of this GISSI-HF study. A drug might not be effective in prevention of cardiovascular events in patients with chronic heart failure and yet be able to prevent the occurrence of this disorder by directly affecting a potentially failing cardiovascular system or by preventing the development or destabilisation of coronary artery disease.

Many,[16–19] but not all,[23,24] small randomised studies of patients with heart failure have shown several biological and clinical effects of statins. They reported anti-remodelling effects associated with improvement of left ventricular function, reduction in circulating inflammatory markers, improvement in endothelial function, and a possible antiarrhythmic activity. Investigators also reported some reductions in hard endpoints, but the small number of patients in these studies prevented any reliable conclusion. Overall these findings strongly lent support to the notion that statins were effective in patients with heart failure.

The CORONA trial[22] and the GISSI-HF study, testing rosuvastatin at the same dose, were undertaken almost simultaneously and have been widely cited in the

published work as providing a solid experimental confirmation to the multitude of positive signals on the beneficial effect of statins in patients with heart failure on several endpoints, including mortality. In the CORONA trial,[22] the primary composite endpoint of death from cardiovascular causes, non-fatal myocardial infarction, or stroke was reduced by a non-significant 8%, although there were fewer admissions for cardiovascular causes and for heart failure in the rosuvastatin group than in the placebo group. The main differences between the CORONA and the GISSI-HF trials are in the populations enrolled—the CORONA study enrolled all patients with ischaemic heart failure compared with only 40% in the GISSI-HF trial. The studies also had different endpoints—the CORONA study focused on ischaemic events whereas GISSI-HF focused on events related to heart failure. Moreover, patients were older (mean age 73 *vs* 68 years) and more symptomatic (NYHA class III or IV 63% *vs* 37%) in the CORONA trial than in the GISSI-HF trial.

Our findings clearly suggest that rosuvastatin has no beneficial effect in patients with chronic heart failure who were not already receiving statins, irrespective of the cause of the disorder. Results from the CORONA trial, which included a larger population of ischaemic patients, accord with signals suggesting that some effects in prevention of acute ischaemic episodes are still possible in patients with heart failure, as shown by a post-hoc analysis of a combined endpoint of non-fatal myocardial infarction and non-fatal stroke.[22] This result might also account for the reduction in the rate of admission for cardiovascular reasons that was recorded in CORONA and not in the GISSI-HF trial.

We did not include a discriminatory value of LVEF as an entry criterion. However, only 10% of the total population of patients had an LVEF greater than 40%, forming a subgroup that was too small to make conclusions about the effects of statins in the so-called heart failure group with preserved LVEF. By contrast with previous findings,[25] we noted no differences in outcomes between this subgroup and the overall population.

Notably, despite the absence of clinical effects, rosuvastatin was associated with substantial and sustained biological effects in both CORONA and GISSI-HF trials, consisting of relevant decreases of blood LDL cholesterol and C-reactive protein concentrations. These effects might no longer affect the progression of coronary artery disease in patients with ischaemic heart failure, perhaps because their effect is attenuated by a biological milieu not favouring the progression of coronary artery disease. The small number of acute ischaemic events in patients with heart failure precludes testing the effect of any drug on this target. The neutral effect of rosuvastatin, despite its anti-inflammatory activity, might indicate that the inflammatory component is pathophysiologically marginal in the progression of heart failure. This hypothesis might be supported by the negative findings of clinical trials testing agents blocking the effects of inflammatory cytokines, such as drugs blocking tumour necrosis factor α.[26] However, further analyses of both CORONA and GISSI-HF databases might improve clarification of these mechanistic aspects.

In view of the clear data confirming the adequateness of the tested dose on its classic pharmacological target, the clinical findings do not lend support to the significance, at least in the whole range of heart failure disorders, of all the so-called pleiotropic effects of statins which had received for years substantial, but probably overstated, support from the published work.

About a third of the patients were not fully compliant with treatment assignment, which is a limitation of the trial. However, common to many long-term trials, and an indicator of the pragmatic strategy of the GISSI-HF trials, all cardiology centres operating in Italy were invited to participate and most did so. Thus our results indicate what is likely to happen in real-world settings. The adherence to the intention-to-treat principle ensures that the effects correspond closely to what is achievable in clinical practice, and the results of the per-protocol analysis, which were similar to those recorded in the intention-to-treat population, prove that the dilution effect due to non-compliance does not substantially affect the overall clinical results.

Statins are usually regarded as a class of drugs, even if some members of the class have specific characteristics—harmful characteristics in the case of cerivastatin. The only evident difference between statins currently used is the efficacy power, which is mainly assessed according to the LDL-lowering effect. Thus, having used a low dose of a powerful drug, the results of GISSI-HF trial might be regarded as extendable to the statin class.

Concern has been raised about possible negative effects of statins: the block of the synthesis of mevalonate and consequently of the production of ubiquinone,[27] and a decrease in the ability to bind and detoxify bacterial lipopolysaccharides, which are strong stimulators of the release of proinflammatory cytokines, because of the reduction of serum lipoproteins.[28] Little difference in the effects of rosuvastatin or placebo on both efficacy and safety profiles—namely, in the subgroup of patients with low total cholesterol at baseline—does not lend support to the clinical relevance of such negative effects. Similar reassuring findings were also shown in the more severe patients who were enrolled in the CORONA trial.[22]

Opinion is divided about the potentially optimum dose of statins.[28–31] The main issue we considered in the design of this trial, which was undertaken in fragile patients not taking statins at enrolment or during the month before enrolment, was safety. Thus, our study confirms the safety of rosuvastatin 10 mg daily in view of a relevant reduction of circulating concentrations of LDL cholesterol.

The reported results do not challenge the use of statins in all disorders for which they are recommended. However, the prescription of rosuvastatin, and pre-

sumably of any statin, to patients with heart failure should be discouraged. In practice, a problematic issue, which will probably be widely debated, is whether a statin should be maintained or stopped in an ischaemic patient who is already taking this treatment when they decompensate. For example, some data suggest that statins might be useful early after acute ischaemic events associated with left ventricular dysfunction or failure.[32] This possibility has not been ruled out by the findings of the present trial.

See Online for webappendix

In conclusion, results from the GISSI-HF trial might help physicians in taking the following decisions. First, not prescribing statins to patients with heart failure of non-ischaemic cause. Second, stopping statins in patients with heart failure of ischaemic cause if the physician is convinced of the drug's futility, or to avoid multiple drug use or to not worsen compliance to other drugs that are proven to be effective in heart failure. Last, maintaining treatment in specific cases if the physician deems it useful, being reassured in doing so by the proven safety of the statins in this population of patients.

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 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.

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Conflict of interest statement

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Statins and n-3 fatty acid supplementation in heart failure

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Heart failure is common, and leads to substantial morbidity and mortality in most regions of the world.[1] Medical and device therapies have been successfully developed to improve outcomes in patients with systolic heart failure. Beneficial treatments include inhibitors of the renin–angiotensin–aldosterone system and sympathetic nervous system, use of implantable cardioverter defibrillators, and cardiac resynchronisation therapy in selected patients (table).[1] However, not all patients with systolic heart failure qualify for or tolerate these therapies and, even with the best treatment, heart failure remains a major cause of morbidity, mortality, and health-care expenditure. No drug or device has been definitively shown to improve outcomes in patients with heart failure and preserved systolic function.[1] New therapies and management strategies need to be identified.

There has been much interest in the potential therapeutic role of statins in heart failure.[2] Experimental studies, observational analyses, and limited prospective clinical investigations have suggested that statins improve ventricular function, heart-failure status, and clinical outcomes.[2–6] The potential of statins in heart failure comes from their antiatherogenic properties and their ability to improve endothelial function and stabilise plaque, which together could reduce the risk of acute coronary events and the ischaemic burden on the failing ventricle.[3,4] Additionally, statins might have beneficial effects independent of lipid lowering, including inhibition of pro-inflammatory cytokine activity, neoangiogenesis, downregulation of angiotensin-1 receptors, and favourable modulation of the autonomic nervous system.[3,4]

The first large-scale randomised trial with a clinical outcome for statin use in patients with symptomatic heart failure was reported last year. CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) randomised 5011 patients with a history of ischaemia to receive rosuvastatin 10 mg daily or placebo.[7] All patients were in New York Heart Association (NYHA) class II–IV, with a left-ventricular ejection fraction no higher than 40%, or 35% for those in NYHA class II. Over a median follow-up of 33 months, there were no significant differences in the composite primary endpoint of all-cause mortality, cardiovascular mortality, or non-fatal coronary events. There were statistically significant, but modest, reductions in the number of admissions to hospital for cardiovascular events, and, in a post-hoc analysis, in non-fatal ischaemic events.

In today's *Lancet*, the GISSI-HF investigators report the results of their multicentre trial of statin therapy in patients with chronic heart failure.[8] 4574 patients in NYHA class II–IV were enrolled, irrespective of the cause of heart failure or left-ventricular ejection fraction, and randomised to rosuvastatin 10 mg or placebo, both added to standard background therapy for heart failure. During a median follow-up of 3·9 years, rosuvastatin had no effect on the primary endpoints of time to death and time to death or admission to hospital for cardiovascular events. By contrast with the findings in the CORONA trial, the secondary outcomes of hospital admission for any cause, cardiovascular cause, or heart-failure cause were not favourably affected. There were also no significant differences in myocardial infarction, stroke, or sudden cardiac death. There were no discernible improvements in clinical outcomes in any clinically relevant subgroup, including patients with either an ischaemic or non-ischaemic cause of heart failure and those with reduced and preserved systolic function, although the last subgroup was small. Together, these two well-conducted clinical trials establish that, although statin therapy lowers concentrations of LDL cholesterol, is well tolerated, and seems reasonably safe, it does not produce meaningful improvements in survival in patients with chronic heart failure.

Therapy	Relative-risk reduction in all-cause mortality
Angiotensin-converting-enzyme inhibitors or angiotensin-receptor antagonists	17–25%
β blockers	34–35%
Aldosterone antagonists*	15–30%
Hydralazine-isosorbide dinitrate*	43%
Implantable cardioverter defibrillator*	23%
Cardiac resynchronisation therapy*	36%
n-3 polyunsaturated fatty acid supplementation	9%

*For patients with specific indications.

Table: **Evidence-based therapies for systolic heart failure**

How can the results of these clinical trials be reconciled with all the experimental, clinical investigation, and observational data? Pleiotropic effects of statins have yet to be found clinically. The proven clinical benefit of statins in patients with and at risk for coronary heart disease has been through reduction in acute coronary events. In GISSI-HF, CORONA, and other heart-failure trials, the rates of myocardial infarction and other atherothrombotic events were low compared with those in trials in patients with coronary artery disease without chronic heart failure.[7–10] Once heart failure is established, statins may not allow patients to escape the mortality associated with the underlying heart-failure disease process.[7,9] Also, in patients with heart failure, lower rather than higher levels of total cholesterol are associated with worse outcomes.[11] Lipoproteins may remove endotoxins that enter the circulation through the intestinal wall, which can be oedematous and more permeable in patients with heart failure.[12] Any potential benefits of statins in heart failure may be offset by detrimental effects of lowering cholesterol levels in this population.

Supplementation with n-3 polyunsaturated fatty acids has also been of potential interest as a therapy for heart failure. Trials in primary and secondary prevention of coronary heart disease showed that n-3 fatty acid supplementation results in a reduction in relative risk of 10–20% in fatal and non-fatal cardiovascular events.[13] The GISSI-HF investigators also randomised 6975 patients in class II–IV chronic heart failure to 1 g daily of n-3 polyunsaturated fatty acids (850–882 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the ratio of 1:1·2) or matching placebo.[14] Death from any cause was reduced from 29% with placebo to 27% in those treated with n-3 fatty acids (adjusted hazard ratio 0·91, 95·5% CI 0·833–0·998, p=0·041). The co-primary outcome of death or admission to hospital for a cardiovascular event was also reduced. Although the improvements in clinical outcomes were modest, they were additive to those of other therapies that are standard of care in heart failure. The therapy was safe and very well tolerated. Whilst questions remain about mechanisms of action, optimum dosing, and formulation, supplementation with n-3 polyunsaturated fatty acids should join the short list of evidence-based life-prolonging therapies for heart failure.

The new results from GISSI-HF reinforce the idea that findings in populations without heart failure may or may not extrapolate to patients with heart failure. Randomised trials to better define safety and efficacy in heart failure are required. For n-3 fatty acid supplementation, benefits observed in other populations apply to patients with heart failure. For statins, the benefits, unfortunately, seem not to. Although other promising treatments for heart failure are under investigation, every effort should be made to apply those therapies which are evidenced-based to all eligible patients with heart failure.

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