Results of the low-dose (20 mg) pravastatin GISSI Prevenzione trial in 4271 patients with recent myocardial infarction: do stopped trials contribute to overall knowledge?

GISSI Prevenzione Investigators
(Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico)

Italian National Association of Hospital Cardiologists (ANMCO), Mario Negri Pharmacologic Research Institute, Mario Negri South Consortium, S. Maria Imbaro (CH), Italy

Key words:
Cholesterol; Clinical trials; Coronary heart disease.

Background. **The aim of this study was to test the efficacy of a low-dose pravastatin regimen (20 mg daily) in patients with myocardial infarction.**

Methods. **GISSI Prevenzione (GISSI-P) is an open trial on secondary coronary heart disease prevention: 4271 recent acute myocardial infarction patients (≤ 6 months) with total blood cholesterol ≥ 200 mg/dl were randomized to low-dose cholesterol-lowering treatment (pravastatin 20 mg daily) or no treatment. GISSI-P was started in 1993 and its story was crossed by the publication of the results of similarly designed clinical trials. The publication of 4S results in 1994 prompted the Data Safety and Monitoring Board (DSMB) and the Steering Committee (SC) to change the protocol so that only patients whose total blood cholesterol was < 250 mg/dl could be randomized whilst patients with total blood cholesterol > 250 mg/dl who had already been enrolled in the study had to be re-evaluated and, if appropriate, pharmacologically treated. The DSMB and the SC agreed to stop randomization prematurely in late 1996 after the publication of CARE results.**

Results. **Mean follow-up time was 23.0 ± 6.7 months (median 24.3 months). The two treatment groups were well matched at baseline. Pharmacological interventions recommended by the protocol were widely prescribed (antiplatelet agents > 90%, beta-blockers 42.7%, and ACE-inhibitors 40.2%). Mainly because of the on-course modification of the study protocol, 402/2133 (18.8%) patients in the control group started a cholesterol-lowering treatment during follow-up. Conversely, 296/2138 (13.8%) patients permanently stopped taking their tablets. Side effects, however, were the reason for discontinuing therapy in 57 (2.7%) patients in the pravastatin group, and patient reluctance to continue accounted for most of the remainder. After excluding control patients who had started a cholesterol-lowering treatment during follow-up, the following changes of median lipid concentrations in the control group over the whole course were observed: total cholesterol -1.9%; LDL cholesterol -2.9%; triglycerides -2.0%; HDL cholesterol +1.4%. The analysis carried out excluding patients randomized to pravastatin treatment and actually not assuming the drug clearly indicated the cholesterol-lowering efficacy of low-dose pravastatin (total cholesterol -12.5%; LDL cholesterol -18.8%; triglycerides -7.9%; HDL cholesterol +3.4%). During the study 256 (6.0%) patients either died or had a non-fatal stroke or a myocardial infarction, 136 (6.4%) in the control group and 120 (5.6%) in the pravastatin group (relative risk 0.90, 95% confidence interval 0.71-1.15, p = 0.41); 160 patients died, 88 (4.1%) in the control group and 72 (3.4%) in the pravastatin group (relative risk 0.84, 94% confidence interval 0.61-1.14, p = 0.26). The few (n = 28) non-cardiovascular deaths were balanced: 16 (0.8%) in the control group and 15 (0.6%) in the pravastatin group. The reduction of cardiovascular events was more evident in the by-treatment analysis, with coronary heart disease deaths being significantly decreased (relative risk 0.60, 95% confidence interval 0.38-0.96, p = 0.04). The overall frequency of adverse events was similar in the two groups. No significant difference between treatment groups was found for total cases of cancer or at any particular site.**

Conclusions. **Despite the decreased statistical power due to its premature stopping, the results of the GISSI-P suggest that a low-dose treatment with pravastatin (20 mg daily) is effective in reducing blood lipids, and underline the importance of long-term compliance with treatments in the search for a maximal effective dosage. Furthermore, the effects of a statin on total and coronary mortality quantified for the first time in a population exposed to Mediterranean dietary and lifestyle habits are markedly consistent with those obtained in different settings.**

(Ital Heart J 2000; 1 (12): 810-820)

The names of GISSI Prevenzione Investigators are reported in Lancet 1999; 354: 447-55 (ref. no. 13).

Received May 17, 2000; revision received September 4, 2000; accepted October 12, 2000.

Address:

Dr. Roberto Marchioli

GISSI Prevenzione Coordinating Center Consorzio Mario Negri Sud Via Nazionale 66030 S. Maria Imbaro (CH) E-mail: marchioli@cmns.mnegri.it

Introduction

Thanks to the rapid accumulation of positive results from major trials, cholesterol-lowering pharmacological treatment has become one of the more reliably established strategies of secondary prevention for patients surviving an acute myocardial infarction[1-8]. Here we report the results of the GISSI Prevenzione (GISSI-P) trial launched in 1993 with two original goals: a) to test the efficacy of a low-dose pravastatin regimen (20 mg daily); b) to quantify the yield of a statin-based strategy in a population with a different background of cardiovascular risk profile[9-12]. The story of the trial was crossed by the publication of the results of other ongoing, similarly sized, major studies such as 4S[6], CARE[7], and LIPID[8], whose positive results caused two major interventions of the Data Safety and Monitoring Board (DSMB) and the Steering Committee (SC) of GISSI-P: firstly, the inclusion criteria were modified to avoid the risk of under-treatment for patients with clear-cut indication, and secondly, for the same reason, the trial was stopped when recruitment was nearly completed but follow-up was only half way through. Though underpowered to provide the planned efficacy evaluation, the results of GISSI-P have been considered worthy of presentation as they provide otherwise unavailable information on the effects of a statin regimen lower than the currently recommended ones in a population with Mediterranean dietary habits already exposed to maximal secondary prevention.

Methods

Study population. The framework of the trial is presented in figure 1. The population on which the cholesterol-lowering treatment was tested (R2) was derived from a broader cohort randomized to supplements of n-3 polyunsaturated fatty acids (PUFA, 1 g daily), vitamin E (300 mg daily), their combination or standard treatment (R1)[13]. The second randomization (R2) concerned those patients who, following a period of 3-6 months aimed at evaluating the effectiveness of dietary recommendations and the achieving of stable post-infarction clinical conditions, showed plasma cholesterol levels:

• between 200 and 250 mg/dl (i.e., patients who were

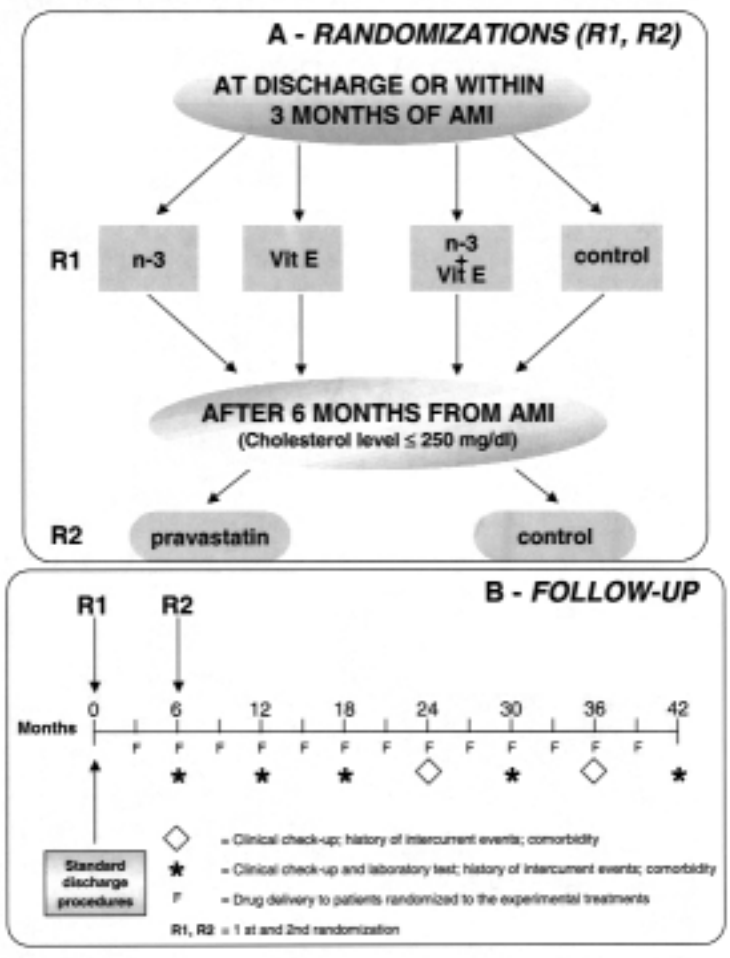

Figure 1. *The first randomization (R1) took place at hospital discharge for acute myocardial infarction (AMI) or in any case within 3 months of the index event. Three-six months after AMI, a second randomization (R2) assigned patients with plasma cholesterol levels ≤ 250 mg/dl, and no specific indication or contraindication to cholesterol-lowering treatment with low-dose pravastatin (20 mg daily) or no treatment.*

considered as having a mild elevation of cholesterol levels);
• > 250 mg/dl: patients who could be randomized into the study if, according to the clinician in charge, this cholesterol level was not in itself a sufficient reason for treating the patient (e.g., absence of any other risk factor).

The inclusion of the latter group of patients was strictly a function of the "uncertainty principle", formally outlined and applied in recent population trials[14], which is an option for intervention in the absence of data on efficacy produced by properly sized trials and reflects the "common sense" generally adopted in routine clinical practice in choosing between expected and interventional management strategies when compelling scientific evidence is currently not available.

The same exclusion criteria were applied for both randomizations (R1 and R2): a) contraindications to the study treatments; b) comorbid conditions indicating an unfavorable survival prognosis over a short period of time (e.g., overt heart failure, malignancy, etc.), which would not have allowed the assessment of the expected benefit; c) mental or physical disorders substantially affecting the patient's compliance, d) known congenital coagulation defects. The clinicians' decision of including elderly subjects in the main study (R1) depended merely on the expectation of potential benefits in the light of the patient's clinical conditions.

The following additional exclusion criteria were also adopted for R2: a) known hepatic diseases; b) renal diseases with serum creatinine ≥ 3.5 mg/dl; c) presence of other conditions requiring cholesterol-lowering treatment (e.g., hypertriglyceridemia ≥ 500 mg/dl); d) diseases requiring cyclosporin treatment.

Randomization and follow-up. For a period of 23 months, 11 323 patients were recruited at 172 cardiological centers in Italy in the main cohort. Central randomization was made in separate blocks for each center. All patients were informed and asked to give consent to participation in a long-term study.

The follow-up planned for a minimum duration of 3 years after R2 included: a) an administrative follow-up every 3 months to provide the drug(s); b) full clinical examination every 6 months (Fig. 1B).

Laboratory measurements. Lipid determinations were scheduled at baseline, and at 6, 12, 18, 30, and 42 months, with blood samples obtained when the patient had fasted at least for 12 hours. Each participating center defined the specific arrangements for carrying out laboratory tests, according to an *ad hoc* protocol. A quality control protocol of laboratory tests (which also included a central assessment of blood lipid levels at recruitment, annual and final tests and the long-term storage of all samples taken) was implemented. In particular, an external quality assessment for serum total cholesterol measurement involving about 100 laboratories out of the 172 hospitals participating in the study was carried out[15,16].

Management of experimental and routine treatments. Patients assigned to pravastatin assumed a 20 mg tablet daily (at bedtime). An increase in dosage to 40 mg per day, however, could be considered in those patients who did not show a decrease in LDL cholesterol levels of at least 15%. The treatment assigned had to be continued until the end of follow-up. As an "open" study, participating cardiologists were recommended to adopt the same care and treatment attitude for all patients, regardless of their allocation: a) all patients had to be provided adequate dietary recommendations; b) treatment with acetylsalicylic acid and beta-blockers was recommended for all patients without specific contraindications; c) treatment with ACE-inhibitors was recommended for patients with symptomatic and asymptomatic left ventricular dysfunction (clinical symptoms of congestive heart failure and/or left ventricular ejection fraction ≤ 40%).

Endpoint definition and validation. Two primary endpoints were established: a) the cumulative rate of total mortality, non-fatal myocardial infarction, and stroke; b) the cumulative rate of cardiovascular mortality, myocardial infarction, and non-fatal stroke. Subgroup analyses for females and patients aged > 70 years were pre-specified in the protocol. The validation of the events included in the primary endpoint addressing the evaluation of efficacy was assured through an *ad hoc* Committee of expert cardiologists and neurologists blind to study treatments.

Modifications of the study protocol. Based on the results of the 4S study[6] and on an *ad hoc* meta-analysis of available evidence[17], on February 1995 the DSMB suggested modifying the study protocol as follows (Fig. 2): a) patients with total blood cholesterol > 250 mg/dl could no longer be randomized in R2; b) cardiologists were asked to re-evaluate patients previously entered in the study to start, if not contraindicated, a cholesterol-lowering treatment in those with total blood cholesterol > 250 mg/dl; c) the lower cut-off of blood cholesterol (200 mg/dl) for randomization was abolished.

Following the results of the CARE trial[7] on a population of patients remarkably similar to that foreseen for GISSI-P, in December 1996 the SC and the external DSMB decided to stop the trial for two complementary reasons: a) an ethical one: patients had to be informed of a well-established, no longer controversial evidence of benefit; b) a "futility" one: the combined pressure of the recommendations and of the market were likely to create unacceptably high rates of drops-in/out from the randomized arms.

Statistical analysis. The study was planned to have 90% power to detect a 20% reduction in the primary end-

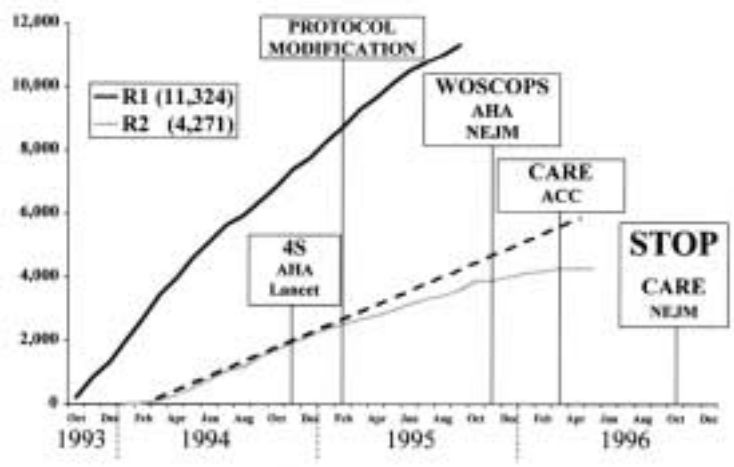

Figure 2. *Course of the GISSI Prevenzione study.* Black line: *randomization rate for R1;* grey line: *randomization rate for R2;* dotted line: *expected randomization rate for R2.*

point of death plus non-fatal myocardial infarction and stroke at $\alpha = 0.01$ (two-sided). To achieve this power the protocol specified that 6000 patients be followed up until the occurrence of 600 events in the control group, unless the trial was stopped early on the basis of either the results of an *interim* analysis or the publication of relevant clinical trials. Due to the premature stopping of the study, 4271 patients were randomized in R2. The overall rate of events observed at the time of study termination (6.0 vs 15% expected) could barely allow to detect a 30% reduction in the primary endpoint of death plus non-fatal myocardial infarction and stroke at $\alpha = 0.05$ (two-sided) and power 80%.

Statistical analyses on event-free survival have been carried out following the intention-to-treat principle. Data analysis included Kaplan-Meier survival curves and the log rank test. Treatment efficacy was evaluated in accordance with Cox proportional hazards models adjusted for unbalances of baseline patient characteristics as well as for n-3 PUFA and vitamin E treatment.

A by-treatment analysis of pravastatin cholesterol-lowering efficacy was also carried out to assess the pharmacological efficacy of statins, excluding patients either not compliant with the allocated treatment or controls having started a hypocholesterolemic treatment (mainly because of the on-course modification of the study design).

In order to ascertain to what extent variations in plasma lipid levels influenced outcome, mean total and LDL cholesterol concentrations during follow-up were used to compute categories of patients with progressively decreasing levels of blood lipids. Patients with clinical events in the first 6 months of follow-up (i.e., between randomization and the first follow-up visit) were excluded from the latter analyses in order to have at least one estimate of blood lipid concentrations during the course of the study. Finally, Cox proportional hazards models were also fitted after allowing for relevant baseline covariates to carry out a by-treatment analysis aimed at evaluating the clinical efficacy of pravastatin treatment.

Results

Study population. Mean follow-up time was 23.0 ± 6.7 months (median 24.3 months). The two treatment groups were well matched at baseline (Table I). Only revascularization procedures were somewhat higher in patients in the experimental group as compared to controls (17.1 vs 13.8%, $p < 0.05$). The main baseline characteristics of the randomized population were the following: 17.3% of patients were 70 years old or more, 16.9% of patients had suffered a myocardial infarction prior to the index event, 17.2% of patients had angina pectoris, 11.1% of patients had a left ventricular ejection fraction < 40%, 19.6% of patients had a positive exercise test (i.e., symptoms and/or electrocardiographic signs). Pharmacological interventions recommended by the protocol were widely prescribed (antiplatelet agents > 90%, beta-blockers 42.7%, and ACE-inhibitors 40.2%).

Among patients taking pravastatin, 4.1% had their dose raised to 40 mg during the first months after randomization, 2.2% of the patients were prescribed an adjunctive cholesterol-lowering drug, 3.1% of patients had a reduced dosage of 10 mg daily, according to the protocol.

Mainly because of the on-course modification of the study protocol, 402/2133 (18.8%) patients in the control group started a cholesterol-lowering treatment during follow-up. Conversely, 296/2138 (13.8%) patients permanently stopped taking their tablets. Side effects were the reason for discontinuing therapy in 57 (2.7%) patients in the pravastatin group, and patient reluctance to continue accounted for most of the remainder.

Table I. Baseline characteristics of randomized patients.

	Control	Pravastatin
No. patients	2133	2138
Male	1830 (85.8)	1854 (86.7)
Female	303 (14.2)	284 (13.3)
Age (years)		
≤ 50	393 (18.4)	411 (19.2)
51-60	637 (29.9)	641 (30.0)
61-70	739 (34.7)	717 (33.5)
71-80	317 (14.9)	323 (15.1)
> 80	47 (2.2)	46 (2.2)
Secondary diagnoses		
Arterial hypertension	786 (36.9)	774 (36.2)
Claudication	96 (4.5)	83 (3.9)
Diabetes mellitus	307 (14.4)	275 (12.9)
Non-smokers	487 (22.8)	462 (21.6)
Ex-smokers	1405 (65.9)	1411 (66.0)
Smokers	241 (11.3)	265 (12.4)
Body mass index ≥ 30 kg/m^2	328 (15.5)	275 (12.9)
Previous CABG or angioplasty	295 (13.8)	365 (17.1)
Previous myocardial infarction	335 (15.7)	361 (16.9)
Angina grade (CCS)		
No angina	1820 (85.3)	1770 (82.8)
No limitation (I)	155 (7.3)	184 (8.6)
Slight limitation (II)	111 (5.2)	127 (5.9)
Marked limitation (III)/at rest (IV)	47 (2.2)	57 (2.7)
Dyspnea grade (NYHA)		
No dyspnea/no limitation (I)	1915 (89.8)	1916 (89.6)
Dyspnea on normal exertion (II)	212 (9.9)	213 (10.0)
Dyspnea on mild exertion (III)	6 (0.3)	9 (0.4)
Ejection fraction		
≤ 0.30	42 (2.0)	43 (2.0)
0.31-0.40	199 (9.3)	194 (9.1)
> 0.40	1577 (73.9)	1602 (74.9)
Premature ventricular beats > 10/hour	198 (9.3)	195 (9.1)
Previous sustained ventricular tachycardia	14 (0.9)	15 (1.0)
Ventricular arrhythmias	317 (14.9)	317 (14.8)
Positive exercise test	425 (19.9)	420 (19.6)
Other therapy		
n-3 PUFA	1072 (50.3)	1071 (50.1)
Vitamin E	1048 (49.1)	1064 (49.8)
Aspirin	1658 (77.8)	1702 (79.8)
Other antiplatelet therapy	283 (13.3)	288 (13.5)
Beta-blockers	920 (43.2)	911 (42.7)
Calcium antagonists	685 (32.1)	668 (31.2)
ACE-inhibitors	914 (42.8)	858 (40.2)
Nitrates	1258 (59.0)	1261 (59.0)
Diuretics	230 (10.8)	217 (10.1)
Mean ± SD		
Age (years)	60.0 ± 10.4	59.7 ± 10.4
Months since diagnosis of AMI	6.4 ± 0.5	6.4 ± 0.6
Body mass index (kg/m^2)	26.6 ± 3.4	26.4 ± 3.3
Ejection fraction (%)	52.7 ± 10.4	52.6 ± 10.4
Lipids (mg/dl)		
Total blood cholesterol	229.0 (25.8)	229.6 (25.8)
LDL cholesterol	151.5 (26.0)	151.8 (25.8)
HDL cholesterol	45.7 (12.2)	45.7 (12.1)
Triglycerides	165.3 (85.1)	167.0 (92.0)

Values between brackets are percentages. In some cases sums do not add to totals because of missing values. AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; NYHA = New York Heart Association; PUFA = polyunsaturated fatty acids.

Changes in blood lipid concentration. Lipid concentrations showed little change in the control group. After 6 months of therapy with pravastatin, median lipid reductions were 9.9% for total cholesterol, 14.6% for LDL cholesterol (thus tightly approaching the 15% reduction of LDL cholesterol requested by the study protocol), and 8.0% for triglycerides, whereas HDL cholesterol rose by 1.6%. In subsequent years lipid concentrations were stable, and, over the whole course of the study, in the pravastatin group the median changes from baseline in total, LDL, and HDL cholesterol, and serum triglycerides were -9.8%, -14.8%, +2.7%, and -6.3%, respectively. The corresponding values in the control group were -1.9%, -3.0%, +2.1%, and -1.6%.

After excluding control patients starting a cholesterol-lowering treatment during follow-up, the changes of median lipid concentrations in the control group over the whole course did not vary significantly (total cholesterol -1.9%; LDL cholesterol -2.9%; triglycerides -2.0%; HDL cholesterol +1.4%). On the contrary, the exclusion of patients randomized to pravastatin treatment and not assuming the drug significantly improved the estimates of the effect of pravastatin on blood lipids (Fig. 3).

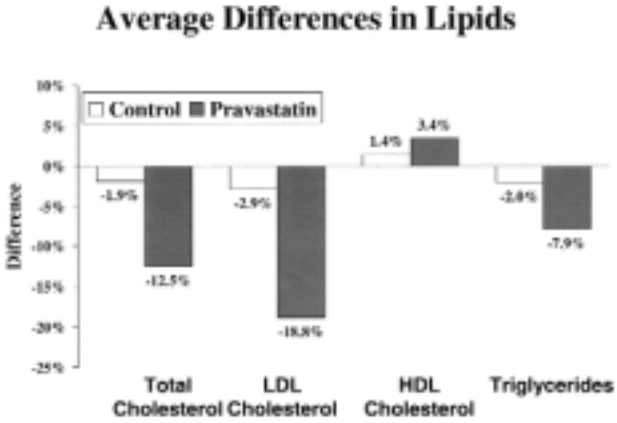

Figure 3. *Cholesterol-lowering efficacy of low-dose (20 mg daily) pravastatin treatment in the by-treatment analysis.*

Primary endpoints and mortality. During the study 256 (6.0%) patients either died or had a non-fatal stroke or a myocardial infarction, 136 (6.4%) in the control group and 120 (5.6%) in the pravastatin group (relative risk-RR 0.90, 95% confidence interval-CI 0.71-1.15, p = 0.41) (Table II). The Kaplan-Meier 2-year probability of event-free survival (Fig. 4) was 93.3% in the control group and 94.1% in the pravastatin group. Adjustment for revascularization procedures, other baseline covariates, and treatments tested in R1 did not change the results. A similar figure was obtained for the second primary endpoint: 214 (5.0%) patients either died of a cardiovascular cause or had a non-fatal stroke or a myocardial infarction, 113 (5.3%) in the control group and 101 (4.7%) in the pravastatin group (RR 0.91, 95% CI 0.70-1.19, p = 0.49).

During the follow-up period 160 patients died, 88 (4.1%) in the control group and 72 (3.4%) in the pravastatin group (RR 0.84, 95% CI 0.61-1.14, p = 0.26). There were 80 coronary deaths, 49 (2.3%) in the control group and 31 (1.5%) in the pravastatin group (RR 0.64, 95% CI 0.41-1.00, p = 0.051).

Cerebrovascular deaths were very rare (4 in the control group and 4 in the pravastatin group). The few non-cardiovascular deaths (n = 28) were balanced: 16 (0.8%) in the control group and 12 (0.6%) in the pravastatin group.

When the efficacy of pravastatin was evaluated according to the by-treatment analysis, somewhat better results were obtained for all cardiovascular fatal events, whereas the risk of coronary deaths was significantly lowered (RR 0.60, 95% CI 0.38-0.96, p = 0.03).

Non-fatal events. Both non-fatal myocardial infarction and stroke were found to be equally distributed in the two trial arms. During the study 80 (1.9%) patients had a non-fatal myocardial infarction, 41 (1.9%) in the control group and 39 (1.8%) in the pravastatin group; 31 (0.7%) patients had a non-fatal stroke, 15 (0.7%) in the control group and 16 (0.7%) in the pravastatin group.

Subsidiary analyses. The RR of being revascularized or having a major cardiovascular event in the pravastatin group was 0.92 (95% CI 0.78-1.10, p = 0.36). Pravastatin reduced (even though not significantly) the patient risk of undergoing coronary artery bypass surgery or angioplasty (Table II): the RR was 0.90 (95% CI 0.72-1.12, p = 0.33).

To allow an easier comparison with similar analyses carried out in other relevant trials, a subgroup analysis was performed (Table III). A non-significant trend towards a lower effect of cholesterol-lowering treatment was apparent for patients aged over 65, with diabetes mellitus, left ventricular dysfunction, LDL cholesterol ≤ 130 mg/dl, and HDL cholesterol ≤ 40 mg/dl.

The evaluation of the efficacy of pravastatin treatment in patients treated with either n-3 PUFA or vitamin E showed a non-significant trend towards a greater effect in patients not given n-3 PUFA treatment and in patients given vitamin E treatment (Table III).

Figure 5 shows the reduction of risk of death and non-fatal major cardiovascular events according to the concentration of blood lipids during follow-up: no clear trend towards a lower risk of death and major cardiovascular events was apparent for patients with lower total or LDL cholesterol values.

Adverse events. The overall frequency of adverse events was similar in the two groups. There were 25 cases of cancer (1.2%) in the control group and 16 (0.8%) in the pravastatin group, with a non-significant difference between treatment groups for neoplastic events as a whole

Table II. Endpoints of the study.

	Control (n=2133)	Pravastatin (n=2138)	Intention-to-treat analysis RR (95% CI)	By-treatment analysis RR (95% CI)
Fatal events	88 (4.1%)	72 (3.4%)	0.84 (0.61-1.14)	0.74 (0.53-1.04)
MI	10 (0.5%)	6 (0.3%)		
Sudden death	30 (1.4%)	23 (1.1%)		
Instantaneous death	18 (0.8%)	14 (0.7%)		
Death within 1 hour	10 (0.5%)	9 (0.4%)		
Other coronary deaths	9 (0.4%)	2 (0.1%)		
All coronary deaths	49 (2.3%)	31 (1.5%)	0.64 (0.41-1.00)	0.60 (0.38-0.96)
CHF	7 (0.3%)	10 (0.5%)		
All cardiac deaths	56 (2.6%)	40 (1.9%)	0.74 (0.50-1.11)	0.70 (0.46-1.06)
Stroke	4 (0.2%)	4 (0.2%)		
Ischemic	2 (0.1%)	1 (0.1%)		
Unknown	2 (0.1%)	3 (0.1%)		
Pulmonary embolism	1 (0.1%)	1 (0.1%)		
Hemorrhage	1 (0.1%)	3 (0.1%)		
Surgical procedures*	3 (0.1%)	2 (0.1%)		
Other CV deaths	0	2 (0.1%)		
All CV deaths	65 (3.1%)	52 (2.4%)	0.81 (0.56-1.17)	0.73 (0.50-1.08)
Cancer	14 (0.7%)	7 (0.3%)		
Infections	1 (0.1%)	3 (0.1%)		
Other	1 (0.1%)	2 (0.1%)		
All non-CV deaths	16 (0.8%)	12 (0.6%)	0.78 (0.37-1.64)	0.55 (0.23-1.32)
Unknown cause of death	7 (0.3%)	8 (0.4%)	1.20 (0.44-3.31)	1.32 (0.46-3.81)
Non-fatal CV events	55 (2.6%)	55 (2.6%)	1.02 (0.71-1.49)	1.00 (0.66-1.53)
Definite MI	28 (1.3%)	31 (1.4%)		
Probable MI	13 (0.6%)	8 (0.4%)		
Not confirmed MI	0	1 (0.1%)		
Non-fatal MI	41 (1.9%)	39 (1.8%)	0.97 (0.63-1.51)	0.93 (0.57-1.51)
Definite stroke	8 (0.4%)	11 (0.5%)		
Probable stroke	7 (0.3%)	5 (0.2%)		
Not confirmed stroke	2 (0.1%)	0		
Non-fatal stroke	15 (0.7%)	16 (0.7%)	1.10 (0.54-2.22)	1.15 (0.50-2.66)
Combined endpoints				
Death + non-fatal MI + non-fatal stroke	136 (6.4%)	120 (5.6%)	0.90 (0.71-1.15)	0.83 (0.64-1.09)
CV death + non-fatal MI + non-fatal stroke	113 (5.3%)	101 (4.7%)	0.91 (0.70-1.19)	0.85 (0.63-1.13)
CHD death + non-fatal MI	83 (3.9%)	67 (3.1%)	0.82 (0.59-1.13)	0.76 (0.54-1.07)
Fatal + non-fatal stroke	19 (0.9%)	20 (0.9%)	1.09 (0.58-2.04)	1.20 (0.56-2.56)
Other CV events				
Revascularization procedures	174 (8.2%)	156 (7.3%)	0.90 (0.72-1.12)	0.95 (0.75-1.21)
PTCA	61 (2.9%)	55 (2.6%)		
CABG	116 (5.4%)	102 (4.8%)		
Hospitalization for CHF	31 (1.5%)	35 (1.6%)	1.13 (0.70-1.83)	0.86 (0.51-1.46)
Hospitalization for arrhythmia	19 (0.9%)	21 (1.0%)	1.11 (0.59-2.06)	1.04 (0.53-2.04)

A patient with two or more events of different types will appear more than once in a column but only once in a row. CABG = coronary artery bypass graft; CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; PTCA = coronary angioplasty; RR = relative risk, calculated by Cox regression analysis.* cardiovascular death as a cause of surgical procedures.

or at any particular site. In addition to the cancer deaths reported in table II, there were 11 non-fatal cases of cancer in the control group and 10 in the pravastatin group, of which 0 and 3 respectively arose in the gastrointestinal system.

Overall, non-melanoma skin cancers were 1 and 1 in the control and pravastatin groups, respectively. For the control and pravastatin groups, respectively, there were 2 and 5 gastrointestinal cancers, 6 and 5 pulmonary cancers, and 16 and 5 other cancers. Of the fatal cancers, 2 out of 14 in the control group and 2 out of 7 in the pravastatin group arose in the gastrointestinal system. Six subjects in the pravastatin group reported muscular pain or weakness. No case of rhabdomyolysis occurred in the study. Elevations in aspartate aminotransferase and alanine aminotransferase values (> 3 times the upper reference limit) were recorded in 15 subjects in the pravastatin group and 9 led to permanent discontinuation of therapy. No suicide death was recorded in the study.

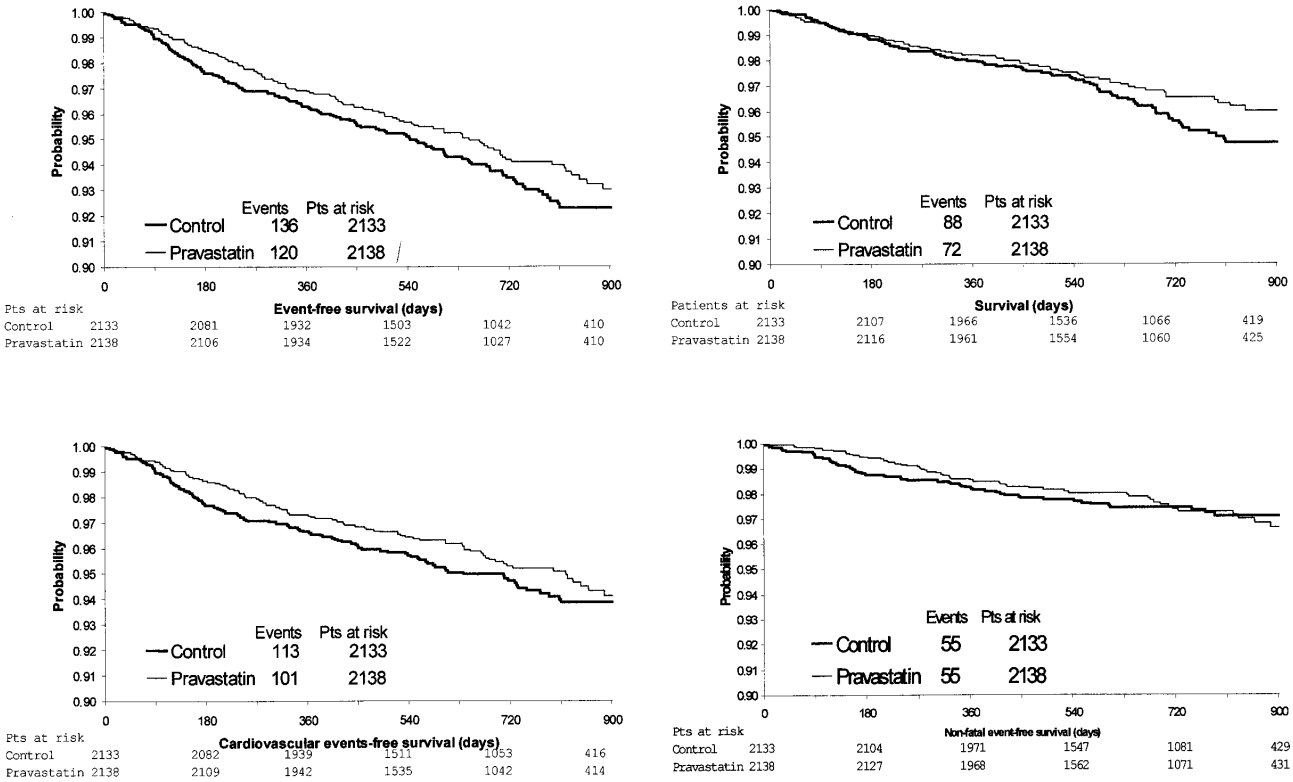

Figure 4. *Kaplan-Meier event-free survival curves (intention-to-treat analysis).*

Discussion

The data produced by the GISSI-P trial can be discussed under three main headings: 1) new information on the efficacy of a pravastatin regimen (20 mg daily) at least half that tested in other major trials[6-8,18]; 2) the implication of the non-statistically significant but strictly consistent results produced by a trial conducted in a Mediterranean country and stopped for ethical and public health reasons; 3) the motivation leading the DSMB and the SC to prematurely stop the trial.

The 18.8% reduction of LDL cholesterol observed in patients who complied with the given treatment compares favorably with those obtained with the almost double statin dosages of CARE, 4S, and WOSCOPS, i.e., 28, 25 and 26%, respectively. This result is in agreement with those of a recent meta-analysis suggesting a non-linear relation between dosage of statins and their cholesterol-lowering efficacy, with approximately two thirds of the expected maximum response being obtained with only one quarter of the highest dose[19]. This finding underlines the importance of checking compliance with drug treatment more than looking for a maximal effective dosage, according to what was suggested by the different results obtained with the analyses by efficacy and by intention-to-treat (i.e., 18.8 vs 14.6% absolute reduction of LDL cholesterol level, corresponding to a 22.3% relative difference). The lower efficiency of the randomized scheme observed in the whole population, however, can also be seen in the relatively important fraction of control patients (371/2133, 17.4%) who were switched to the active treatment following the first protocol modification. The setting of clinical trials represents a situation where particular care is dedicated to assure the best compliance with experimental treatments. The same is not necessarily true for "ordinary" clinical practice. In a sense, the very pragmatic strategy of the GISSI-P mimics what could happen in practice, i.e., the long-term fading of compliance with chronic treatments. This phenomenon has been observed, for instance, in several clinical trials in hypertension and diabetes, whereas various recent epidemiological studies indicate the need for optimizing prevention strategies[20].

In the intention-to-treat analysis, pravastatin treatment reduced fatal events by 16% (95% CI 0.61-1.14) and coronary deaths by 36% (95% CI 0.41-1.00). Non-compliance with allocated treatment, however, would also lead to the benefit of actually taking pravastatin being underestimated. In fact, somewhat better effects were obtained in the by-treatment analysis after excluding subjects who did not comply with pravastatin treatment as well as control patients who started cholesterol-lowering treatment because of the modification of the study protocol (total deaths: RR 0.74, 95% CI 0.53-1.04; coronary heart disease deaths: RR 0.60, 95% CI 0.38-0.96). The low incidence of adverse events leading to treatment discontinuation is reassuring as to the safety of treatment with low-dose pravastatin.

The data related to the effect of low-dose pravastatin even over a short period of time on the risk of death

Table III. GISSI Prevenzione results on the primary endpoint (death + non-fatal myocardial infarction + non-fatal stroke) according to subgroup analysis (intention-to-treat).

Variable	No. events/subject	Control	Pravastatin	p	Intention-to-treat analysis RR (95% CI)
Age (years)					
< 65	114/2859	67/1423	47/1436	0.07	0.71 (0.49-1.03)
≥ 65	142/1412	69/710	73/702	0.52	1.11 (0.80-1.55)
Sex					
Male	210/3684	113/1830	97/1854	0.31	0.87 (0.66-1.14)
Female	46/587	23/303	23/284	0.79	1.08 (0.61-1.93)
Arterial hypertension					
Absent	131/2711	72/1347	59/1364	0.24	0.81 (0.58-1.15)
Present	125/1560	64/786	61/774	0.94	1.01 (0.71-1.44)
Diabetes mellitus					
Absent	194/3689	104/1826	90/1863	0.30	0.86 (0.65-1.14)
Present	62/582	32/307	30/275	0.70	1.10 (0.67-1.83)
Ventricular dysfunction					
Absent	173/3374	96/1683	77/1691	0.19	0.82 (0.61-1.11)
Present	83/897	40/450	43/447	0.68	1.09 (0.71-1.68)
Myocardial ischemia					
Absent	95/1817	46/906	49/911	0.73	1.07 (0.72-1.61)
Present	161/2454	90/1227	71/1227	0.19	0.81 (0.60-1.11)
Electrical instability					
Absent	134/2488	72/1241	62/1247	0.44	0.87 (0.62-1.23)
Present	58/634	30/317	28/317	1.00	1.00 (0.60-1.68)
NA	64/1149	34/575	30/574	0.63	0.89 (0.54-1.45)
Total cholesterol level at baseline (mg/dl)					
≤ 200	10/358	8/189	2/169	0.09	0.26 (0.05-1.26)
200-240	152/2619	80/1296	72/1323	0.55	0.91 (0.66-1.25)
> 240	94/1294	48/648	46/646	0.90	0.97 (0.65-1.46)
LDL cholesterol level at baseline (mg/dl)					
≤ 130	37/749	18/393	19/356	0.53	1.23 (0.64-2.36)
> 130	204/3264	112/1628	92/1636	0.22	0.84 (0.64-1.11)
HDL cholesterol level at baseline (mg/dl)					
≤ 40	91/1490	45/760	46/730	0.60	1.09 (0.72-1.65)
> 40	156/2613	88/1300	68/1313	0.12	0.78 (0.57-1.07)
Triglyceride level at baseline (mg/dl)					
≤150	135/2207	71/1109	64/1098	0.67	0.93 (0.66-1.30)
> 150	121/2041	65/1016	56/1025	0.46	0.87 (0.61-1.25)
n-3 PUFA					
No	139/2128	78/1061	61/1067	0.17	0.79 (0.57-1.11)
Yes	117/2143	58/1072	59/1071	0.78	1.05 (0.73-1.51)
Vitamin E					
No	134/2159	67/1085	67/1074	0.79	1.05 (0.75-1.47)
Yes	122/2112	69/1048	53/1064	0.14	0.77 (0.54-1.10)

NA = not assessable. Other abbreviations as in tables I and II.

(-16%) are approximately in the middle between those observed in CARE (-9% in a population of approximately the same size) and those of LIPID (-23%). The similar mortality rates of GISSI-P and CARE placebo groups (21.9 per 1000 patient/years vs 18.9 per 1000 patient/years) further reinforce the consistency of this finding. At variance with these results, a significant 30% reduction of mortality was observed in the 4S study. Such discrepancy, however, is likely to be due to the inclusion of patients at higher risk, with "old" myocardial infarctions, as well as to the lower degree of "protection" ensured by the preventive interventions available at the time of this study (i.e., use of aspirin, ACE-inhibitors, and revascularization procedures).

New analyses of statin trials have recently addressed the issue of the goal of cholesterol-lowering therapy[21-24]. The large overlapping of CI in GISSI-P, however, did not allow either to infer or to deny that LDL cholesterol concentrations < 100 mg/dl would further improve the benefit already achieved by lowering LDL cholesterol concentrations < 130 mg/dl. From this point of view, it may be imagined that (considering also the very high cost of statins) even a low regimen could be clinically effective, provided it be included in a program where a high compliance is assured. There is no obvious reason to expect that the direction of the benefit/risk profile of cholesterol-lowering strategies could be different in those subgroups of patients who are less represented in

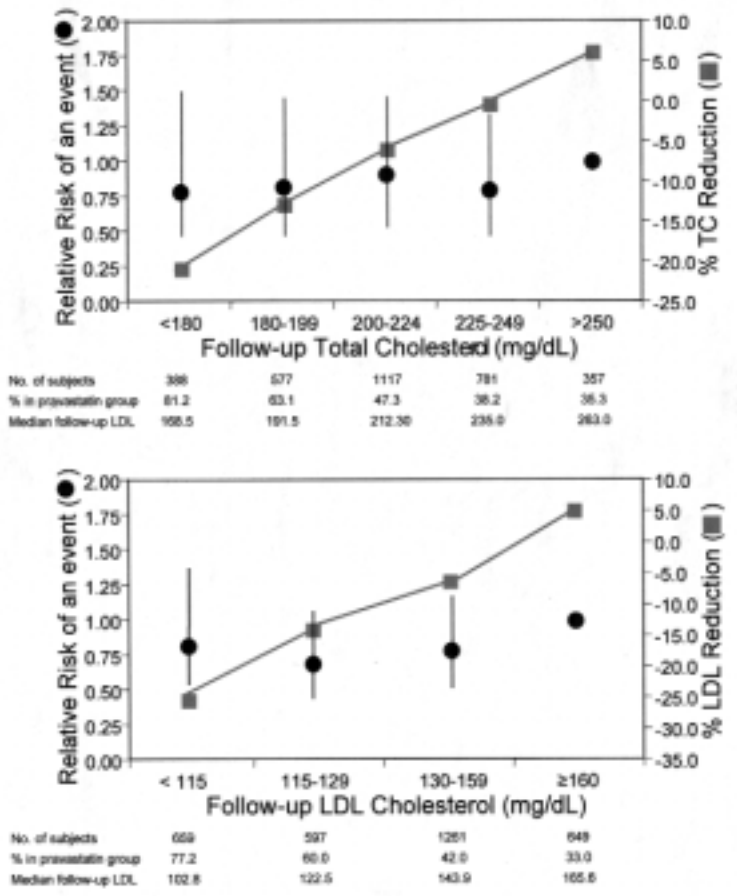

Figure 5. *Reduction in risk of death and non-fatal major cardiovascular events according to the concentrations of blood lipids during follow-up (by-treatment analysis).*

cholesterol-lowering studies (e.g., women and older subjects). However, because of the important policy (cultural as well as economic) implications, any additional in-depth information produced by the Cholesterol Treatment Trialists' Collaboration will be useful for these groups, as well as for those whose baseline cholesterol is lower[25].

An interesting point can be made on the absence in the GISSI-P population of any suggestive trend on the morbidity endpoints which have been so decisive in providing enough statistical power to the efficacy analyses of 4S, CARE, and LIPID. In fact, a significant reduction of non-fatal myocardial infarction was found in CARE and 4S (23 and 37%). The absence of effect over non-fatal myocardial infarction in GISSI-P could be explained either by the short follow-up period (as divergence of survival curves at 2 years in CARE and 4S could suggest) or by the existence in a population with Mediterranean dietary habits of protective mechanisms overlapping those of statins, accompanied by a satisfactory use of protective interventions of well-known efficacy. Interestingly, a different incidence rate of non-fatal myocardial infarction was observed in the non-active treatment groups of these studies (GISSI-P: 10.1 per 1000 patient/years; CARE: 16.7 per 1000 patient/years; 4S: 34.8 per 1000 patient/years).

Due to the publication of the results of 4S in November 1994, the DSMB and the SC agreed to modify the study protocol by allowing the randomization of patients whose total blood cholesterol was < 200 mg/dl, by forbidding the randomization of patients whose total blood cholesterol was > 250 mg/dl, and by recommending the start of a cholesterol-lowering treatment in patients already randomized whose total blood cholesterol was > 250 mg/dl. After the implementation of such recommendations, the recruitment rate slightly decreased. A further decrease in the recruitment rate was apparent after the publication of the results of the WOSCOPS study. After the presentation of the results of the CARE study the unwillingness of the investigators to randomize more patients in a clinical trial with a no treatment arm as control group became apparent, thus the DSMB and the SC decided to close the study in late 1996. The reasons for stopping the trial are consistent with the tradition of the GISSI group of closely monitoring whether the testing of new pharmacological hypotheses respects what is becoming a standard of care. After the presentation of the CARE results and their wide circulation among GISSI-P investigators, the relationship between active cholesterol-lowering strategies and the decrease in cardiovascular risk was also established by the investigators. In fact, they were unwilling

to further randomize patients in a trial with a no treatment control arm, as the discussion of the issue during *ad hoc* meetings and the flattening of the recruitment rate clearly showed. The SC decided to close the cholesterol-lowering part of the GISSI-P study, as it was assumed to be unethical as well as futile to continue the study. The decision of stopping the GISSI-P study on pravastatin is clearly at variance with the choice of other trialists[8,26]. The results of LIPID and other subsequent trials, however, confirmed the reasonability of the position adopted by our SC and DSMB.

In conclusion, the premature stopping of the pravastatin trial hampered its statistical power. The results of the GISSI-P study, however, suggest that a low-dose treatment with pravastatin (20 mg daily) is effective in reducing blood lipids, and underline the importance of long-term compliance with treatments in the search for a maximal effective dosage. Furthermore, the effects of a statin on total and coronary mortality, quantified for the first time in a population of post-infarction patients exposed to Mediterranean dietary and lifestyle habits, are markedly consistent with those obtained in different settings.

References

1. Vaugham CJ, Murphy MB, Buckley BM. Statins do more than just lowering cholesterol. Lancet 1996; 348: 1079-82.
2. La Rosa JC, Pearson TA. Cholesterol screening guidelines: consensus, evidence, and departure from common sense. Circulation 1997; 95: 1651-3.
3. Cleeman JI, Grundy SM. National Cholesterol Education Program recommendations for cholesterol testing in young adults: a science-based approach. Circulation 1997; 95: 1646-50.
4. Grundy SM, Balady GJ, Criqui MH, et al. When to start cholesterol-lowering therapy in patients with coronary heart disease: a statement for healthcare professionals from the American Heart Association Task Force on Risk Reduction. Circulation 1997; 95: 1683-5.
5. Oliver MF, Pyorala K, Shepherd J. Management of hyperlipidaemia: why, when and how to treat. Eur Heart J 1997; 18: 371-5.
6. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383-9.
7. Sacks FM, Pfeffer MA, Moye LA, et al, for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996; 335: 1001-9.
8. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 339: 1349-54.
9. Marchioli R, Di Pasquale A, per i Ricercatori GISSI Prevenzione. Il quadro di riferimento biochimico, farmacologico, epidemiologico del GISSI Prevenzione. G Ital Cardiol 1993; 23: 933-64.
10. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI). Il protocollo dello studio GISSI Prevenzione: studio di intervento preventivo sulle componenti aterosclerotica e trombotica del rischio post-infarto. G Ital Cardiol 1993; 23: 1053-61.
11. Marchioli R, Bomba E, Tognoni G. Sheffield risk and treatment table for cholesterol lowering in prevention of coronary heart disease. GISSI-Prevenzione Investigators. Lancet 1996; 347: 467-8.
12. Marchioli R, Tognoni G. Beneficial effects of statins. GISSI-Prevenzione Investigators. Lancet 1996; 348: 1542.
13. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 1999; 354: 447-55.
14. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction - ISIS-2. Lancet 1988; 2: 349-60.
15. Graziani MS, Ceriotti F, Carobene A, et al. Accuracy of cholesterol measurements in Italian clinical laboratories. Joint project GISSI Prevention-Italian Society of Clinical Biochemistry. SIBioC Prevenzione Group. Eur J Clin Chem Clin Biochem 1997; 35: 311-5.
16. Bachorik PS, Ross JW. National Cholesterol Education Program recommendations for measurement of low-density lipoprotein cholesterol: executive summary. Clin Chem 1988; 34: 193-201.
17. Marchioli R, Marfisi RM, Carinci F, Tognoni G. Meta-analysis, clinical trials, and transferability of research results into practice: the case of cholesterol-lowering interventions in secondary prevention of coronary heart disease. Arch Intern Med 1996; 156: 1158-72.
18. Shepherd J, Cobbe SM, Ford I, et al, for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333: 1301-7.
19. Schectman G, Hiatt J. Dose-response characteristics of cholesterol-lowering drug therapies: implications for treatment. Arch Intern Med 1996; 125: 990-1000.
20. EUROASPIRE Study Group. A European Society of Cardiology survey of secondary prevention of coronary heart disease: principal results. European Action on Secondary Prevention through Intervention to Reduce Events. Eur Heart J 1997; 18: 1569-92.
21. Grundy SM. Statin trials and goals of cholesterol-lowering therapy. Circulation 1998; 97: 1436-9.
22. West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation 1988; 97: 1440-5.
23. Sacks FM, Moyè LA, Davis BR, et al. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events Trial. Circulation 1998; 97: 1446-52.
24. Pedersen TJ, Olsson AG, Faergerman O, et al, for the Scandinavian Simvastatin Survival Study Group. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). Circulation 1998; 97: 1453-60.
25. Cholesterol Treatment Trialists' (CTT) Collaboration. Protocol for a prospective overview of all current and planned randomized trials of cholesterol treatment regimens. Am J Cardiol 1995; 75: 1130-4.
26. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998; 279: 1615-22.