The use over time of statins in coronary patients in an Italian tertiary referral center

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Coronary artery disease; Statins.

Background. **In the last decade, large-scale clinical trials have consistently shown that therapy with statins is of great benefit to patients with and at risk of developing coronary artery disease. We assessed, in a sample of patients with coronary artery disease in whom coronary angiography was indicated and hospitalized in the last 10 years, the use of statins at admission.**

Methods. **One hundred patients with stable coronary artery disease were randomly selected per year from 1991 to 2000. The final study population consisted of 1000 patients. The prescription of statins for ≥ 6 months before hospital admission was determined from a hospital-wide clinical database.**

Results. **From 1995, the prevalence of patients treated with statins at hospital admission progressively increased. In 1991, only 2% of patients were treated with statins before hospital admission while in the year 2000, 38% of patients were receiving this treatment. The mean prevalence of patients treated with statins before and after 1995 was 3 vs 22% ($p < 0.0001$) respectively. The distribution of the demographic and clinical parameters and the prevalence of conventional cardiovascular risk factors were similar in patients treated or not treated with statins.**

Conclusions. **After 1994, in coincidence with the publication of the results of clinical trials showing the benefit of statins in patients with coronary artery disease, the use of these drugs increased significantly. This finding suggests that the widespread diffusion of the results of the major clinical trials and of guidelines drawn up by medical associations have had a significant impact on statin prescription in patients with coronary artery disease. Nevertheless our data also indicate that, despite overwhelming evidence on the benefits of statin therapy, in current clinical practice cardiologists are not optimally utilizing lipid management and that statins are frequently prescribed without an appropriate analysis of risk factors.**

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In the last decade, controlled large-scale clinical trials investigating statin (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor) therapy in the prevention of ischemic heart disease have consistently shown that lowering plasma cholesterol concentrations is of great benefit to patients with and at risk of developing coronary artery disease[1-5]. On the basis of this strong evidence, guidelines have been disseminated by the major international cardiological associations to assist clinicians in applying the most effective medical strategy in the prevention and cure of coronary heart disease[6-10]. However, despite guideline recommendations and the widespread diffusion of the results of major clinical trials showing the benefit of lipid reduction, recent evidence indicates that, in clinical practice physicians, including cardiologists, are not optimally utilizing lipid management[11-13]. To further explore the impact of clinical trials on the use of statins in the daily clinical management of patients with coronary heart disease, we carried out a retrospective study in selected cohorts of patients admitted in the last 10 years to our institution to undergo coronary angiography. The prevalence of patients treated with statins at the time of hospital admission was investigated. Furthermore, as statins have also been reported to produce non lipid-related benefits associated with an anti-inflammatory effect[14,15], we also had the opportunity to investigate the potential interactions between statin therapy and C-reactive protein. The latter is the prototype of acute phase reactants and increased plasma levels are correlated with a worse cardiovascular prognosis[16,17].

Methods

Study population. The Division of Cardiac Surgery of the "Tor Vergata" Universi-

ty of Rome is a tertiary level care center to which patients are referred to undergo coronary angiography and/or percutaneous or surgical coronary revascularization. With regard to this, the vast majority of patients admitted to our institution are referred by other cardiological centers without invasive/surgical facilities. One hundred patients per year with a diagnosis and objective signs of stable ischemic heart disease before hospital admission were randomly selected from 1991 to 2000. The final study population consisted of 1000 patients. In order to avoid misclassification, great care was taken in the collection of each patient's clinical data; the clinical history was verified through direct examination of case records, clinical notes, disease certificates and results of diagnostic tests. Patients were classified as having suffered from myocardial infarction according to the MONICA criteria[18]. Patients with an acute coronary syndrome, acute inflammatory disease and objective evidence of systemic inflammatory disease within 3 months of hospitalization were excluded.

Cardiovascular risk factors. Conventional cardiovascular risk factors were examined by directly questioning patients and from medical or hospital records. A family history for ischemic heart disease was considered present if any first-degree relative had sustained a documented acute or chronic manifestation of coronary disease before the age of 65 years. Diabetes mellitus was considered present if two fasting plasma glucose values were > 126 mg/dl (> 7.0 mmol) or if the patient was on treatment with oral hypoglycemic agents or insulin because of a previous documented diagnosis of diabetes mellitus. Systemic hypertension required a documented prior diagnosis or a systemic arterial pressure > 160/90 mmHg on at least three separate occasions except during angiography. Patients were considered as smokers if they had been smoking > 10 pack-years until 1 year or less before angiography.

Statin prescription. Prescription of statins at the time of hospital admission was determined from a hospital-wide clinical database. The database query asked for the prescription of any of the following agents: simvastatin, pravastatin, fluvastatin, and atorvastatin. Statin dosages were also recorded. Although drug compliance could not be determined, for the purposes of the present study, only patients in whom the duration of treatment with statins before hospital admission was ≥ 6 months were selected.

Lipid assessment. All fasting biochemical parameters were determined at the time of hospital entry. Serum total cholesterol was measured colorimetrically and serum triglycerides fluorometrically using the Liebermann-Burchard method on an AutoAnalyzer II (Technicon, Tegimenta, Switzerland)[19]. After precipitation by heparin-manganese, high-density lipoprotein (HDL) cholesterol was measured by the Liebermann-Burchard method on an AutoAnalyzer II (Technicon)[19]. Low-density lipoprotein (LDL) cholesterol was calculated as the total cholesterol value minus the HDL cholesterol value minus the values (triglyceride/5)[20]. Performance against reference samples indicates that in our laboratory the bias of the mean HDL cholesterol values was < 1.0%; the coefficient of variation was < 3.0%.

C-reactive protein. Plasma samples were immediately analyzed for the C-reactive protein concentration, which was immunologically determined by the immunoturbidimetric method (Roche Unimate 3 CRP, Milan, Italy)[21]. This assay has a detection limit of 2 mg/l and a measurement range up to 180 mg/l. The normal upper reference value for C-reactive protein with this method is 5 mg/l. C-reactive protein analysis was performed on the 500 patients selected from 1996 to 2000 when C-reactive protein plasma level measurement was routinely performed in our institution.

Statistical analysis. From 1991 to 2000, 100 patients per year were randomly selected on the basis of a standard random table[22]; this number represents about 10% of the annual number of patients with ischemic heart disease admitted to our institution to undergo coronary angiography. Continuous variables are presented as mean ± SD and were analyzed by means of the unpaired Student's t-test or one factor analysis of variance as appropriate; the Scheffe F-test was employed to assess significance when analysis of variance was used. Categorical variables are presented as proportions and analyzed using the coded χ^2 test. A two-tailed p value < 0.05 was considered to be statistically significant.

Results

Patient characteristics. The baseline characteristics of the study population are summarized in table I. Overall, the distribution of demographic and clinical parameters and the prevalence of conventional risk factors were similar in the last 10 years indicating that the cohorts of patients randomly selected did not change during the last decade. The mean values of total cholesterol and of LDL cholesterol progressively decreased from 1997 (p = 0.0001) and from 1999 (p = 0.01) respectively (Table I). HDL cholesterol and triglyceride levels did not change.

Statin prescription. The prevalence of patients on statin treatment at the time of hospital admission progressively increased from 1995 onwards (p = 0.001; Fig. 1). Of note, in 1991, before hospital admission only 2% of patients were treated with statins while in 2000, 38% of patients were receiving this treatment. The mean prevalence of patients treated with statins before and after 1995 was 3 vs 22% respectively (p < 0.0001). The distribution of demographic and clinical parameters and the prevalence of conventional cardio-

Table I. Baseline characteristics of the study population at hospital admission from 1991 to 2000.

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	p
Age (years)	60 ± 9	59 ± 9	59 ± 10	59 ± 10	59 ± 9	60 ± 9	62 ± 9	63 ± 9	63 ± 9	63 ± 10	NS
Diseased vessels (%)											
1 vessel	35	24	21	20	28	17	19	27	17	24	NS
2 vessels	25	31	25	36	28	33	26	19	31	28	NS
3 vessels	36	45	49	44	41	49	54	51	49	47	NS
LMD	4	0	5	0	3	1	1	3	3	1	NS
Diabetes (%)	13	15	23	20	25	25	20	26	26	28	NS
Previous MI (%)	65	73	58	57	52	65	57	50	58	62	NS
Hypertension (%)	26	29	25	28	29	31	26	28	29	30	NS
Family history (%)	42	44	47	40	45	44	41	41	42	45	NS
Total cholesterol (mg/dl)	216 ± 44	225 ± 52	256 ± 52	219 ± 43	233 ± 49	219 ± 42	218 ± 44	213 ± 41	207 ± 49	198 ± 37	0.0001
LDL cholesterol (mg/dl)	135 ± 48	141 ± 49	175 ± 49	144 ± 44	154 ± 45	131 ± 41	134 ± 38	137 ± 34	127 ± 40	127 ± 33	0.0001
HDL cholesterol (mg/dl)	47 ± 8	47 ± 9	46 ± 9	48 ± 6	47 ± 8	47 ± 10	49 ± 10	44 ± 10	42 ± 9	40 ± 9	NS
Triglycerides (mg/dl)	172 ± 98	178 ± 99	162 ± 86	151 ± 64	157 ± 98	188 ± 99	168 ± 73	164 ± 97	184 ± 99	166 ± 92	NS

HDL = high-density lipoprotein; LDL = low-density lipoprotein; LMD = left main disease; MI = myocardial infarction.

Figure 1. *The prevalence of patients receiving statins at the time of hospital admission from 1991 to 2000.*

vascular risk factors were similar in patients treated and in those not treated with statins (Table II). A history of previous myocardial infarction was present in 597 patients (60%); of these, only 87 patients (15%) were on statin therapy at the time of hospital admission. Patients on statin treatment had lower levels of total cholesterol and LDL cholesterol compared to patients not receiving statins. On the other hand, levels of triglycerides and HDL cholesterol were similar (Table II). Overall, 33% of patients treated with statins and 16.5% of those not receiving statins had LDL cholesterol plasma levels 100 mg% ($p < 0.01$). Similar percentages were observed when considering only patients with previous myocardial infarction (31 vs 17%, $p < 0.01$). Of note, LDL cholesterol plasma levels were similar in patients with and without myocardial infarction (142 ± 45 vs 140 ± 44 mg%, $p = 0.2$) and the prevalence of statin prescription in patients with at least three risk factors (family history, diabetes, and hypertension) was lower than that observed in patients with less than three risk factors (17 vs 27%, $p = 0.02$). The global distribution of statin use among the study cohorts was 54% simvastatin, 27% atorvastatin, and 19% for pravastatin and fluvastatin. The median daily dosage of simvastatin, pravastatin and fluvastatin was 20 mg and that of atorvastatin 10 mg. In 1999 and 2000, atorvastatin was the most prescribed statin as more than a half of all patients were treated with this molecule.

Statins and C-reactive protein. At hospital entry, 117 patients (22%) had plasma levels of C-reactive protein above the upper limit of normal. C-reactive protein levels were > 5 mg/l in 11% of patients receiving statins and in 27% of patients not treated with statins ($p < 0.001$). Plasma levels of C-reactive protein were lower in patients receiving statins compared to those observed in patients who were not treated with statins (3.2 ± 2.6 vs 5.3 ± 7.1 mg/l, $p = 0.01$; Fig. 2). Finally, among patients treated with statins, those receiving atorvastatin had lower plasma levels of C-reactive protein compared to patients treated with other statins (2.5 ± 2.2 vs 3.5 ± 2.8 mg/l, $p = 0.01$).

Table II. Baseline characteristics of patients receiving and not receiving statins at hospital admission.

	Statin therapy	No statin therapy	p
No. patients	147	853	
Sex (M/F)	125/22	730/123	NS
Age (years)	60 ± 10	61 ± 9	NS
Diseased vessels (%)	2.3 ± 0.9	2.2 ± 1	NS
Diabetes (%)	17	23	NS
Previous MI (%)	59	60	NS
Hypertension (%)	28	26	NS
Family history (%)	42	40	NS
Total cholesterol (mg/dl)	204 ± 51	223 ± 46	0.0001
LDL cholesterol (mg/dl)	124 ± 47	143 ± 43	0.0001
HDL cholesterol (mg/dl)	44 ± 10	46 ± 9	NS
Triglycerides (mg/dl)	179 ± 99	168 ± 95	NS

Abbreviations as in table I.

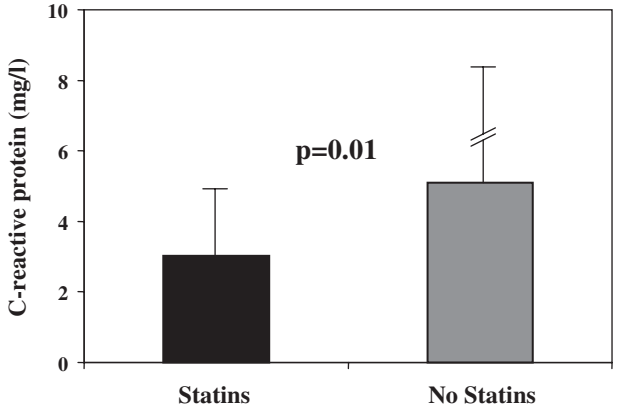

Figure 2. *C-reactive protein plasma levels in patients receiving* (dark bar) *or not receiving* (clear bar) *statins.*

Discussion

The results of the first large scale clinical trials demonstrating the benefit of lipid reduction with statins in patients with coronary artery disease appeared in the mid '90s. Thus, in the present study, we had the opportunity to investigate the prevalence of statin prescription before and after the publication and the diffusion of the results of the major clinical trials demonstrating the value of lipid-lowering therapeutic strategies in the primary and secondary prevention of coronary artery disease. Of note, in Italy, the costs of simvastatin and pravastatin treatment have been, since January 1994, totally covered by the National Health Service for patients aged < 75 years and with a documented myocardial infarction or coronary revascularization and with plasma levels of total cholesterol or LDL cholesterol > 210 and 130 mg% respectively. Since January 1998 and for the same indications, even atorvastatin is provided free of charge. Finally, all statins are free of charge for patients with documented familial hypercholesterolemia.

The present study. Our center is a tertiary level care institution to which patients with documented coronary artery disease are mainly referred for coronary angiography and/or percutaneous or surgical myocardial revascularization. The vast majority of patients are referred by other cardiological centers without invasive/surgical facilities. Our findings indicate that the prevalence of patients treated with statins at the time of hospital admission significantly increased after 1994, i.e. following the publication of the results of large scale clinical trials on statins. In the years 1995-2000 the prevalence of statin prescription increased 7 times compared to that observed in the period 1991-1994. These figures suggest that the results of large clinical trials and their diffusion have had a significant impact on statin prescription in patients with documented coronary artery disease. In 1991, only 2% of patients admitted to our center were treated with statins. In the year 2000, 38% of patients were on statins at the time of hospital admission. Interestingly, the prevalence of statin prescription observed in our population is comparable to that reported in a similar North American population studied in the same period of time[13]. This finding suggests that although the health care systems in these two countries are substantially different, in everyday clinical practice the prevalence of patients treated with statins is rather similar.

Another finding of the present study is that although previous reports clearly identified subgroups of patients who benefit most from lipid-lowering therapeutic strategies such as those with myocardial infarction, diabetes and hypertension[23], we did not find any difference in the prevalence of statin prescription when conventional cardiovascular risk factors were considered. This finding was also observed in a recent study which evaluated data from the US National Registry of Myocardial Infarction 3[13] and suggests that lipid-lowering drugs are often prescribed without having previously performed an appropriate analysis of risk factors. In our study, only 15% of patients with previous myocardial infarction were receiving statins at the time of hospital

admission and a paradoxical inverse relationship was revealed between statin prescription and the global risk of the individual patient. Our findings indicate that at present only one third of patients with documented coronary artery disease receive lipid-lowering drugs. Of note, more than one half of our patients had suffered from a previous myocardial infarction and had at least two-vessel disease thus suggesting that, despite the clear evidence of the benefit of lipid-lowering therapy in high-risk patients and despite national and international guidelines recommendations, a huge treatment gap still persists.

Statins and C-reactive protein. Statins may produce beneficial effects independently of their lipid lowering capability. These potential benefits may be mediated by the prevention of thromboembolism, the improvement of endothelial function, the inhibition of vascular smooth muscle proliferation and through anti-inflammatory effects[24]. Indeed, some studies aimed at evaluating the effects of statins on the incidence of cardiovascular events have shown that the separation in the survival curves begins before a reduction in lipid plasma levels occurs, thus suggesting that other drug-related mechanisms may be responsible for the beneficial effects[17]. A recent report suggests that for patients with elevated C-reactive protein plasma titers, the reduction in the cardiovascular risk produced by statin therapy may be due to a decrease in these levels[25]. In a retrospective substudy of the CARE trial, Ridker et al.[26] have reported that patients with elevated baseline C-reactive protein serum levels who were randomized to pravastatin had a more marked reduction in plasma levels of C-reactive protein and in the incidence of cardiovascular events compared with placebo. This finding has recently been confirmed in a larger prospective observational study on patients with angiographically diagnosed coronary artery disease[17]. Two other recent reports from the 4S study[27] and the AFCAPS/TexCAPS study[28] also showed lower plasma levels of C-reactive protein in patients treated with statins compared with placebo. In the 4S study, however, the risk due to higher levels of C-reactive protein was not eliminated for patients receiving statins while in the AFCAPS/TexCAPS study, statins were effective in the primary prevention of coronary events among persons with relatively low lipid levels but with elevated levels of C-reactive protein. Although our study is a retrospective analysis and in spite of the fact that no survival data are currently available, our findings are in line with the conclusions of these previous studies. This confirms that patients treated with statins have lower plasma levels of C-reactive protein.

Study limitations. The prescription of statins does not necessarily imply that patients were receiving the most appropriate agent or dosage. Indeed, in our study only 33% of patients treated with statins had plasma levels of LDL cholesterol < 100 mg% at the time of hospital admission. Furthermore, although in our study only patients in whom the duration of treatment with statins before hospital admission was ≥ 6 months were selected, we have no data on patient drug compliance before hospital admission. Finally, our study is a single center, retrospective, observational analysis performed on a relatively limited number of patients; however, it approximates real-world clinical practice and thus represents a realistic picture of the use of statins in the last 10 years. These limitations should increase the applicability of our findings to all patients with coronary artery disease.

In conclusion, this study indicates that after 1994, in coincidence with the publication of the results of the major clinical trials on the benefits of lipid-lowering therapeutic strategies in the secondary prevention of coronary heart disease, the prevalence statin treatment among patients with high-risk coronary artery disease significantly increased. This finding suggests that the results of the major clinical trials and the widespread diffusion of guideline recommendations by cardiological associations had a significant impact on statin prescription in patients with coronary artery disease. Nevertheless, our data also indicate that although the increase in statin prescription was relevant, in current clinical practice cardiologists are not optimally utilizing lipid management as only one third of high-risk patients with ischemic heart disease receives statins. Furthermore, the prescription of statins by physicians does not appear to be based on an appropriate evaluation of the most conventional cardiovascular risk factors. Finally, our findings confirm that patients treated with statins present with lower serum levels of C-reactive protein suggesting that these drugs may exert a systemic anti-inflammatory effect, the clinical importance of which deserves further studies.

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