Variations in lipoprotein levels after myocardial infarction and unstable angina: the LATIN trial

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Key words:
Cholesterol; Myocardial infarction; Unstable angina.

Background. **The aim of this study was to prospectively evaluate the magnitude of the variations in lipid levels in a large population of patients admitted for acute myocardial infarction (MI) and unstable angina (UA). Clinical data and blood samples were prospectively collected from consecutive patients with MI and UA.**

Methods. **The study population consisted of patients with symptoms lasting ≤ 12 hours (for MI) or with the last episode of rest pain within 12 hours and associated with ECG changes (for UA). The exclusion criteria were recent hospitalization for any reason or current treatment with lipid-lowering drugs. Blood samples were obtained at admission, the following morning, at discharge and after 3 months. Samples were centrifuged immediately and 4 aliquots of serum were stored at -20°C. The measurements were performed centrally.**

Results. **We enrolled 1864 patients (1275 with MI and 589 with UA). Serum levels of total and LDL-cholesterol decreased significantly after admission, both in MI and UA patients. After 3 months, serum levels of total cholesterol returned to baseline, while those of LDL-cholesterol were still significantly lower. Between admission and the following morning, total and LDL-cholesterol decreased significantly by 7 and 10% respectively for MI and by 5 and 6% for UA. Lipid measurements not performed at admission accounted for a significant decrease in the number of patients identifiable as hyperlipidemic and suitable for lipid-lowering treatment (18% of MI patients and 11% of UA patients).**

Conclusions. **Serum cholesterol concentrations drop significantly during hospitalization for an acute coronary syndrome after a few hours from admission to the coronary care unit. Lipid profile assessment should be scheduled at admission in order to correctly identify hyperlipidemic patients.**

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Introduction

The variations in the cholesterol levels during acute myocardial infarction (MI) have been extensively studied since the early '60[1-3]. Several studies prospectively evaluated the issue finding a reduction in total and HDL-cholesterol and an increase in triglycerides during hospitalization. These variations contributed to a marked decrease in LDL-cholesterol levels, which returned to pre-infarction levels after 2 or 3 months. However, all the studies that prospectively tested this hypothesis were conducted mainly in a single center and included small samples of patients. For this reason their results were, although coherent in direction, widely variable with regard to the magnitude of the modifications. A comprehensive review published in 1993 by Rosenson[4] showed that the changes detected in different studies ranged from 7 to 47%. In addition, all these studies recruited only patients with acute MI, while scarce data have been published on unstable angina (UA) patients. The explanation for the fall in plasma lipid levels lies in the activation of the acute phase response, during which the levels of lipoproteins and of several other proteins fluctuate significantly. This activation has been shown to occur not only after major events such as surgery, infection and MI but also after minor disorders. In the CARDIA study, patients who stated they have been "ill with cold, flu, fever or vomiting" in the 24 hours preceding blood sampling had significantly lower serum levels of total cholesterol (by 5 mg/dl; $p < 0.006$) compared to those who

did not report such minor disorders[5]. The demonstration of the efficacy of statin therapy[6] confirmed by subsequent studies[7,8] boosted the interest in cholesterol variations during MI. The direct consequence of the transient decrease in lipoprotein levels is that a certain percentage of patients may be mistakenly identified as normolipidemic while they are actually hyperlipidemic. Misdiagnosed patients will thus not be exposed to the proven benefits of statins. International guidelines suggest that sampling for lipid testing should be delayed for at least 4 to 8 weeks if it is not performed at admission or within the first 24 hours of hospitalization.

The aim of this study was to prospectively evaluate the magnitude of the variations in lipid levels in a large population of patients admitted for acute coronary syndromes, either MI or UA.

Methods

Fifty-nine coronary care units agreed to participate in the study. The protocol was approved by the Ethical Committee of each participating hospital. Written informed consent was obtained before inclusion in the study. Patients were eligible if they presented with ST segment elevation within 12 hours of the onset of symptoms or if they had had a typical episode of chest pain at rest associated with any kind of ischemic ECG changes in the preceding 12 hours. Exclusion criteria were a history of hospital admission for any reason in the 2 preceding months and current treatment with a lipid-lowering drug. Four blood samples for the measurement of the total cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride serum levels were scheduled at admission, the following morning, at discharge and after 3 months. The study was started in April 1998 and was terminated in January 1999.

The primary endpoint was to evaluate the variations in lipid values between the time of admission and subsequent time points. The secondary endpoint was to calculate the percentage of patients meeting the criteria for pharmacological intervention at each time point, in order to determine whether a different timing of lipid panel sampling could cause a failure to identify patients with lipid levels indicating lipid-lowering therapy. Two separate criteria were identified to recommend lipid-lowering intervention: total cholesterol levels > 200 mg/dl or LDL-cholesterol levels > 130 mg/dl.

The sample size was calculated in such a way as to have a 90% power to detect a 10% variation in total cholesterol serum levels between admission and subsequent samples. Differences between continuous variables, given as the mean value ± SD, were compared using unpaired Student's t testing and the frequency of parameters using the Pearson χ^2 test.

Lipid parameters were analyzed in terms of the within- and between-patient changes over time using a repeated measure analysis of variance. McNemar's test was performed to compare paired observations. A p value of < 0.05 was considered as statistically significant.

In accordance with previous trial results and with the recommendations of the Italian National Health System, investigators were encouraged to start statin therapy whenever appropriate 3 months after the index myocardial infarction. All patients received usual dietary counseling.

In order to eliminate inter-laboratory variability, biochemical analyses were all performed at the University Department of Laboratory Medicine (Hospital of Desio-MI). All the four serum samples (corresponding to those taken at hospital admission, the following morning, at discharge and at 3 months after the event) of each patient were analyzed in the same run in order to eliminate interassay analytical variability. Total cholesterol, HDL-cholesterol, triglyceride and glucose levels were measured using the appropriate reagents from Roche Diagnostics (Mannheim, Germany), according to the manufacturer's specifications, on a Hitachi 917 automated analyzer. Total cholesterol was measured by enzymatic colorimetric assay (CHOD-PAP) with a procedure certified by the Cholesterol Reference Method Laboratory Network (the comparison was performed with the Cholesterol Reference Method Laboratory Network Laboratory of the San Raffaele Hospital, Milan). HDL-cholesterol, and triglyceride levels were determined by enzymatic colorimetric assay (HDL-cholesterol+ and GPO-PAP respectively). The LDL-cholesterol was measured by a homogeneous enzymatic colorimetric assay (LDL-cholesterol+, Roche Diagnostics).

Blood samples were collected, immediately centrifuged, and the serum was divided into 4 aliquots and stored immediately at -20°C. The aliquots were shipped monthly to the central lab via a specific courier.

Study population. During the whole period of recruitment, the 59 participating centers evaluated 6498 patients. Of these patients, 1864 (28.7%) were included in the LATIN trial (Lipid Assessment Trial-Italian Network; 1275 patients admitted for MI and 589 patients admitted for UA) and 4634 were excluded according to the following criteria: symptom onset > 12 hours or lack of ECG criteria (22.8%), current treatment with lipid-lowering agents (11.4%), recent hospital admission (12.5%), administrative or technical reasons (53.3%). Excluded patients were older and more likely to be females. With regard to the excluded patients, the in-hospital mortality was 9.2% for MI patients (vs 4.2% in the study group) and 0.8% for UA patients (vs 2.0% in the study group). Three-month follow-up data were available for 98.8% of the patients.

Results

The baseline characteristics of the whole population are reported in table I. Thrombolysis was resorted to in

Table I. Baseline characteristics of the study population.

	MI patients (n = 1275)	UA patients (n = 589)	p
Males (%)	77.0	69.4	0.001
Age (years)	63 ± 12	65 ± 11	0.0003
Diabetes (%)	17.4	18.9	NS
Current or former smokers (%)	62.5	53.7	0.001
History of hypercholesterolemia (%)	19.7	22.8	NS
Previous MI (%)	12.2	30.2	0.001
Hypertension (%)	49.8	54.7	0.001
Anterior MI (%)	39.1	–	NA
Killip class > 1 (%)	21.1	–	NA

MI = myocardial infarction; NA = not applicable; UA = unstable angina.

62.5% of MI patients (tissue-type plasminogen activator in 67.5%) and primary percutaneous coronary angioplasty in 2.9%. During the first 24 hours intravenous beta-blockers were used in 30.4%, ACE-inhibitors in 38.8%, and aspirin in 89% of these patients. At discharge beta-blockers, aspirin and ACE-inhibitors were prescribed to 59, 91 and 63% respectively. The in-hospital and 3-month mortality rates were 4.2 and 6.5% respectively in MI patients and 2.0 and 3.8% in UA patients. The in-hospital and 3-month reinfarction rates were 2.7 and 4.1% respectively in MI patients and 4.1 and 6.0% in UA patients. The median hospital stay was 9 and 6 days for MI and UA patients respectively.

The main results of the study are reported in table II. In order to have a "clean" dataset, we decided to analyze lipid changes in the subset of patients who had all four blood samples collected and did not have a new MI or a reinfarction, or undergo a revascularization procedure, or receive a lipid-lowering agent during the 3 months of the study. Lipid profile modifications are therefore presented for 565 patients with MI and for 266 patients with UA. However, it is important to emphasize that the results remained unchanged when all patients were included in the analysis (data not shown).

LDL-cholesterol concentrations showed a statistically significant decrease throughout the period between admission and the 3-month follow-up, while total cholesterol levels returned to baseline values at 3 months. The average decreases in total cholesterol and LDL-cholesterol between admission and the following morning were 7 and 10% respectively for MI and 5 and 6% for UA. HDL-cholesterol serum levels did not vary between admission and the following morning, decreased significantly at discharge and returned to baseline values at 3 months. Triglyceride serum levels decreased slightly (5% decrease between admission and the following morning, probably due to the fasting state) both in patients with MI or with UA.

International guidelines are concordant in suggesting a pharmacological intervention with a lipid-lowering drug in all patients with LDL-cholesterol levels > 130 mg/dl after an acute coronary event. Treatment should be started at least 3 months after the acute phase. Table III reports the percentage of patients who met the criteria for drug treatment at the different time points. If we measure lipid levels at admission we can identify 55.8% of MI patients as candidates for pharmacological intervention. If we do not take the blood sample for lipid testing at admission but wait until the following morning we will find only 38.1% of our population with LDL-cholesterol levels < 130 mg/dl. A similar pattern was observed in UA patients. Our data suggest

Table II. Variations in total, HDL and LDL-cholesterol and triglycerides in 565 patients with myocardial infarction and in 266 patients with unstable angina.

	On admission	Day 1	At discharge	After 3 months
MI patients				
Total cholesterol (mg/dl)	211 ± 40	197 ± 36	197 ± 36	212 ± 37
HDL-cholesterol (mg/dl)	48 ± 14	48 ± 13	41 ± 12	50 ± 14
LDL-cholesterol (mg/dl)	136 ± 36	123 ± 32	120 ± 32	132 ± 33
Triglycerides (mg/dl)	150 ± 98	143 ± 84	159 ± 65	172 ± 96
UA patients				
Total cholesterol (mg/dl)	206 ± 42	196 ± 41	199 ± 39	207 ± 38
HDL-cholesterol (mg/dl)	49 ± 15	47 ± 14	46 ± 14	53 ± 17
LDL-cholesterol (mg/dl)	129 ± 37	121 ± 36	121 ± 33	125 ± 32
Triglycerides (mg/dl)	158 ± 99	150 ± 75	155 ± 67	158 ± 99

Values are expressed as mean ± SD. Abbreviations as in table I.

Table III. Percentage of patients meeting, at different time points, criteria for lipid-lowering therapy according to international guidelines.

	On admission	Day 1	At discharge	After 3 months
MI patients (n=565)				
Total cholesterol > 200 mg/dl (%)	61.1	46.0*	44.2*	61.3§§
LDL-cholesterol > 130 mg/dl (%)	55.8	38.1*	33.8*	48.7§
UA patients (n=266)				
Total cholesterol > 200 mg/dl (%)	54.7	43.0*	44.5**	57.0§§
LDL-cholesterol > 130 mg/dl (%)	48.7	37.7*	35.1*	44.5§§

Abbreviations as in table I. * = $p < 0.001$; ** = $p < 0.005$; § = $p < 0.01$; §§ = p = NS.

that not determining the lipid concentrations at admission can result in a significant decrease in the number of patients identifiable as potential candidates for a lipid-lowering therapy. The magnitude of this underestimation can be quantified as 18% of patients with acute MI and 11% of patients with UA.

Discussion

Our study showed that total cholesterol and LDL-cholesterol levels significantly decrease during the acute phase of hospitalization in patients with both MI and UA. HDL-cholesterol levels decreased (slightly) only in patients with MI but not in patients with UA. Triglyceride levels decreased only between the time of admission and the following morning, probably due to the fasting state. After 3 months total cholesterol and HDL-cholesterol levels returned to baseline values, while LDL-cholesterol concentrations were still significantly lower compared to baseline. Our results have significant clinical and practical implications. The reduction in LDL-cholesterol that occurred between admission and the following morning (median time 10 hours) was sufficiently large to cause a significant decrease in our diagnostic capability of identifying those patients eligible for lipid-lowering treatment. On the basis of the criterion of LDL levels > 130 mg/dl as a cut-off for the prescription of a lipid-lowering drug, almost 18% of patients with MI would not be recognized as potential candidates for lipid-lowering therapy, with the consequent potential loss of the long-term benefits that are associated with statin therapy. The corresponding figure for UA patients is 11%. Similar results were reported by Fattore et al.[9] for 1051 patients with MI and UA. In that study, total cholesterol levels decreased by 10.7% in the first 24 hours and by 16.2% after 4 days. However, in that study variations in LDL-cholesterol levels were not reported.

The magnitude of the cholesterol decrease was lower than previously reported and slightly greater in MI patients compared to UA patients. Given the large sample size of our study, the larger decreases found in the smaller previous studies should be interpreted bearing the regression to the mean phenomenon in mind. In addition, the mean cholesterol concentrations of our population at admission were lower than the mean cholesterol levels of the populations of previous studies. This may also in part explain the smaller variations detected in our study. Another possible explanation for the morning fall in total and LDL-cholesterol levels found in our study may be the presence of a circadian rhythm leading to a morning nadir in the concentration of lipoproteins. However, a recent elegant study by Bremner et al.[10] showed that HDL and LDL-cholesterol in healthy subjects peak in the early morning, while total cholesterol peaks in the afternoon. Therefore, it is unlikely that a circadian rhythm might have significantly influenced our results. We are unable to explain why the decrease in LDL-cholesterol levels was slightly greater in MI than in UA patients. It is possible that myocardial necrosis and neutrophil migration might induce a more powerful response of the liver and that, in turn, this might lead to a stronger activation of the acute phase reaction.

To date, international guidelines recommend that a lipid-lowering therapy should be reserved only to patients who are unresponsive to a 3-month dietary regimen. After the publication of the 4S, CARE and LIPID studies these recommendations have been emended suggesting that such a delay was useless in patients with particularly elevated LDL levels[11]. This modification has been suggested with the aim of broadening the use of statins in those patients who could potentially benefit, but not on the basis of definite evidences, since all the trials included data of patients who had had an MI several months previously. The third report, the National Cholesterol Education Program (Adult Treatment), has recommended that a complete blood lipid profile should be taken in all patients with established coronary heart disease[12]. In the infarct patient, this determination should be obtained at the time of admission or no later than the first 24 hours; otherwise, it would be necessary to wait for a minimum period of 4 weeks after the onset of the infarct in order to allow lipid fractions to stabilize and thus ensure accuracy. During this *interim* period all patients should be treated with a low-cholesterol, low-saturated fat diet such as the American Heart Association step II diet. If plasma LDL-cholesterol concentrations remain > 130 mg/dl, drug therapy should be initiated with the goal of achieving an LDL

level < 100 mg/dl[12]. According to our results, these guidelines should be further modified suggesting that every effort should be taken in order to collect blood samples for the determination of the lipid profile at admission, because a delay of just a few hours could result in a significant loss of diagnostic accuracy. Furthermore, the early recognition and early initiation of an appropriate lipid-lowering regimen would avoid the risk, consequent to an unclear understanding of who (the hospital-based cardiologist or the general practitioner) should be responsible for the secondary prevention strategies to be employed in ischemic patients, of leaving the patients without a life-saving treatment. However, the most suitable time for starting statin therapy has not yet been fully established. Available trials started cholesterol-lowering therapy a few months after MI. In the 4S trial[6] patients with a recent (< 6 months) MI were excluded. The CARE trial included patients who had recovered from an earlier MI and the minimum accepted delay was 3 months[7]. In the LIPID study 9014 patients with a previous MI or with UA were randomized to either 40 mg of pravastatin or placebo. The minimum delay accepted was 3 months[8]. The results of these studies firmly establish the desirability of lowering atherogenic serum lipids among patients who have recovered from MI. A prospective, placebo-controlled, randomized trial testing the safety and the efficacy of a high dose of atorvastatin initiated between 24 and 96 hours after admission for UA or a non-Q wave MI showed a significant reduction in the cumulative endpoint of mortality, reinfarction and hospitalization for angina in the atorvastatin treated patients. However, the effect was negligible for the first two components of the endpoint (death and reinfarction)[13]. A non-randomized, *post hoc* analysis of the PURSUIT study showed that patients admitted for UA or for a non-Q wave MI who initiated statin therapy at discharge had a significantly lower mortality, after adjusting for confounding variables, compared to patients who were discharged without such drugs (relative risk 0.47, 95% confidence interval 0.32-0.70)[14]. Similarly, the RIKS-HIA showed that early (at discharge) initiation of statin treatment in patients with MI was associated with reduced 1-year mortality after adjusting for confounding variables (relative risk 0.75, 95% confidence interval 0.63-0.89, $p < 0.001$)[15]. It is likely that, in the near future, lipid-lowering drugs will be used extensively in patients with acute coronary syndromes and therefore cardiologists should not run the risk of underestimating the fraction of patients who will derive significant long-term benefits from the use of these drugs.

In conclusion, total, HDL and LDL-cholesterol concentrations drop significantly following an acute coronary syndrome (MI and UA). Our study shows that the fall in lipid levels is significant after just a few hours from admission to the coronary care unit. The magnitude of the decrease is lower than previously reported, but large enough to significantly reduce our diagnostic accuracy. On the basis of these results, international guidelines should be implemented with a strong recommendation to collect the blood sample for lipid profile assessment at the time of admission of the patients, in order to correctly identify hyperlipidemic patients.

Appendix

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