

## ORIGINAL ARTICLE

## Cardiovascular Lipid Risk Factors and Rate of Cardiovascular Events After Myocardial Revascularization

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### Abstract

**Background:** Coronary heart disease is a public health problem, and the leading cause of premature death in Europe and worldwide. There is epidemiological evidence that the control of cardiovascular risk factors following myocardial revascularization remains suboptimal.

**Objectives:** Analyze the incidence of cardiovascular events in patients receiving secondary prevention therapies after myocardial revascularization.

**Methods:** Single-center study on consecutive coronary patients retrospectively identified, conducted at the Institute of Cardiovascular Diseases in Timisoara, Romania. Patients with diagnosis of revascularization for coronary artery disease (percutaneous coronary intervention, PCI or coronary artery bypass grafting, CABG) were included, following the inclusion criteria of the EuroAspire IV study. Outcome measures were assessed at three time points– at T0, when myocardial revascularization was performed; at T1 (interview with patients who had undergone revascularization for more than 6 months and less than 5 years), and T2 (interview with patients who had undergone revascularization for more than 5 years). Associations of primary and secondary lipid targets with the rates of adverse cardiovascular events (MACE) were assessed at T2.

**Results:** Of 375 coronary patients, 341 were included in the study. At T1, 5% and 34.9% of patients reached the LDL-c and non-HDL-c target respectively. MACE rate at T2 was 7.9% in a median of 4.33 years of follow-up. We found a positive, statically significant association between MACE rate and LDL-c at T1 ( $p = 0.039$ ). There were significant differences in mean non-HDLc levels between MACE categories at T1 ( $p = 0.02$ ). There was a significant association between mean non-HDL with the incidence of heart failure ( $p = 0.007$ ), newly diagnosed diabetes ( $p = 0.017$ ) and restenosis rate ( $p = 0.004$ ).

**Conclusion:** The study highlights the need to control lipid risk factors after myocardial revascularization procedures, even at long-term, to minimize the risk of cardiovascular events in patients with coronary diseases. (Int J Cardiovasc Sci. 2017;30(1):4-10)

**Keywords:** Coronary Artery Disease; Risk Factors; Lipid; Metabolism; Myocardial Revascularization; Epidemiology.

### Introduction

Coronary heart disease remains "the scourge of the modern world" despite advances made in the field. It is a public health problem, and the leading cause of premature death in Europe and worldwide.<sup>1</sup>

In this study, we focused on understanding the evolution of the atherothrombotic process in coronary

symptomatic patients who underwent coronary revascularization: percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

The relationship between low-density lipoprotein cholesterol (LDL-c) and the incidence of cardiovascular events has been demonstrated by numerous epidemiological studies: CARDS<sup>2</sup> ASPEN<sup>3</sup> ASCOT.<sup>4</sup> The New European Society of Cardiology (ESC) Guidelines for Cardiovascular Disease Prevention recommended LDL-c target levels of lower than 70 mg/dL for coronary patients at high risk and very high risk<sup>5</sup>. In addition, patients under statin therapy may also be at very high cardiovascular risk.<sup>5-6</sup>

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The EuroAspire III and IV trials represent the epidemiological evidence that the control of modifiable cardiovascular risk factors among coronary patients remains suboptimal.<sup>6-7</sup>

The hypothesis of our research was that an inefficient control of cardiovascular risk factors would have a long-term effect on the incidence of fatal and non-fatal cardiovascular events. In this context, our study aimed to analyze the incidence of fatal and non-fatal cardiovascular events in coronary patients under statin therapy years after coronary revascularization, following the ESC prevention of cardiovascular disease program criteria.<sup>5</sup>

## Methods

This is a single-center study conducted at the Institute of Cardiovascular Disease, Timisoara, Romania. The inclusion criteria followed the EUROASPIRE IV protocol. A total of 375 consecutive coronary patients aged 18-80 years with definite diagnosis of revascularization for coronary artery disease (PCI, CABG) were retrospectively identified. Of them, 341 were considered eligible and 341 were included in the study (Figure 1). Clinical data of patients were assessed at three time points – at T0, when successful revascularization was identified, at T1 (from 6 months to 3 years post-myocardial revascularization), and at T2 (from 3 to 5 years post-myocardial revascularization).

The following data was collected on an electronic database: lipid profile data – total cholesterol (TC); triglycerides, (TG); high-density lipoprotein cholesterol (HDL-c); LDL-c; non-HDL-c calculated as TC minus HDL-c<sup>8</sup> – number of fatal / non-fatal cardiovascular events; major adverse cardiovascular events (MACE): cardiovascular death, noncardiovascular death,

restenosis, stroke / transient ischemic attack (TIA) – electrostimulation by pacemaker, hospitalization for reintervention – percutaneous transluminal coronary angioplasty (PTCA) or CABG, hospitalization for heart failure, diagnosis of diabetes mellitus. New lipid risk was evaluated at T0 and T1, following the European Cardiovascular Prevention criteria (5). The rate of fatal and nonfatal cardiovascular events was analyzed based on the potential cardioplipidic risk.

Patients' follow-up was conducted by a questionnaire validated for the countries that participated in the EUROASPIRE IV study.<sup>6</sup> At inclusion, we used the post-revascularization protocols specified in the ESC guidelines for secondary cardiovascular prevention (2012)<sup>9</sup>, adopted by the Romanian Society of Cardiology.

## Statistical analysis

Statistical analysis was performed with SPSS 17.0 statistics, including 31 statistical variables (numerical and categorical). Time variable was calculated from the date the patient underwent coronary revascularization until January 2015, when MACE events were detected as present or absent. Normality of the variables was tested by the Shapiro- Wilk test. Differences between variables with only two categories were assessed by the non-parametric Mann-Whitney test. A p-value < 0.05 was set as statistically significant.

## Results

Of 375 consecutive coronary patients, 341 patients (64.22 ± 8.90 years, 81.52% male) were included in our study. Baseline characteristics of patients are presented in Table 1.

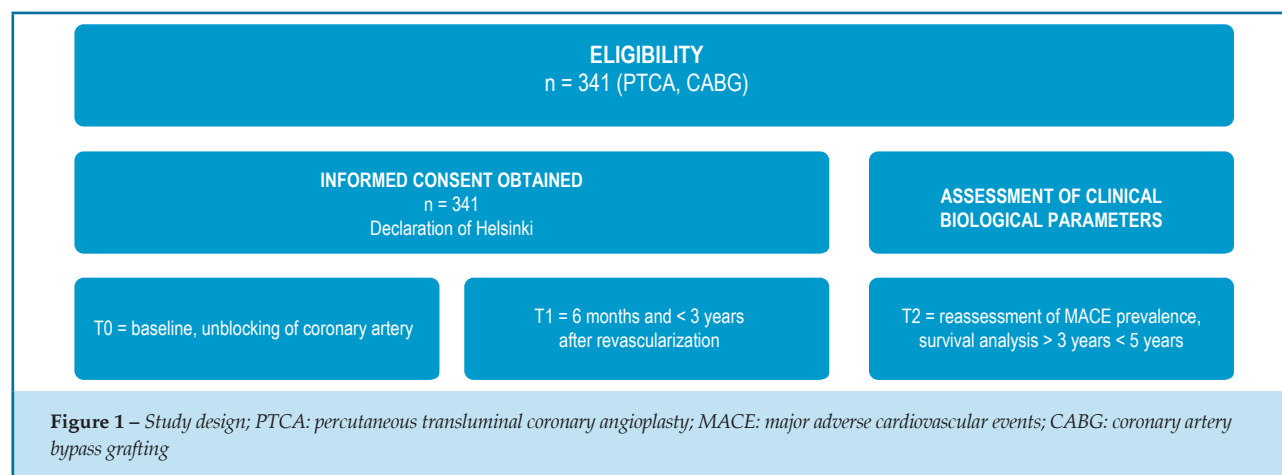


Table 1 – Baseline characteristics of patients (n = 341)	
Characteristics	
Age (years) (mean ± SD)	64.22 ± 8.90
Male (%)	81.52
Body mass index, kg/m <sup>2</sup>	30.47 ± 7.41
Cardiovascular events (%)	
– Death for cardiovascular disease	0
– Death for other causes	1.17
– Restenosis	0.9
– AVC/AIT	0.29
– Pacemaker Implant	0.87
– New By-pass	1.46
– New stent	0.87
– Heart failure	1.46
– Newly diagnosed diabetes	0.87
Ejection fraction (mean ± SD)	47.56 ± 8.8
AVC: stroke; TIA: transient ischemic attack	

At T0, 52.5% of patients had undergone CABG, 43.1% PCI, and 4.4% had undergone both procedures.

At inclusion in the study, there was a high prevalence of modifiable cardiovascular risk factors (Table 1.1).

### Statin therapy for LDL-c control remains a pertinent therapeutic target (Table 2)

At T1, 76.2% of participants had LDL-c values  $\geq 80$  mg/dL. In fact, only 5% of revascularized patients receiving statins that reached the target LDL-c value recommended by the ESC guidelines.<sup>5,10,11</sup>

**Non-HDLc or secondary lipid target and residual risk:** using a non-HDL-c target < 110 mg/dL, we found that 30.8% of patients at T0 and 34.9% at T1 achieved these levels (p = NS) dL. There was no statistically significant differences between mean non-HDL-c at T0 (135.2 ± 44.95 mg/dL) and T1 (129.13 ± 40.9 mg/dL).

**MACE rates and post-revascularization cardiovascular risk:** the MACE rate at T2 was 7.9% in a median follow-up time of 4.33 years.

Table 1.1 – Evaluation of cardiovascular risk factors atT0 (n = 341)	
Variable	%
Arteial hypertension/ medication	27.56/54.25
Body mass index > 30 kg/m <sup>2</sup>	36.07
Hypercholesterolemia / medication	59.82/94.8
Diabetes / medication	78.59/82.23
Smoking	48

Table 2 – Lipid target levels and number of patients in whom these levels were reached at T1		
Variable		n = 341
LDLc < 80	mg/dL	23.8 %
Non HDL < 110	mg/dL	30.8%

There was a positive and statistically significant association between primary lipid target of LDL-c at T1 and MACE (p = 0.039, chi test, 95% CI) (Table 3). In addition, there was a significant difference in mean non-HDL-c between the MACE categories at T1 (p = 0.02, Kruskal Wallis test, 95% CI) (Figure 2).

Restenosis rate was 0.9% and was significantly influenced by average non-HDLc (p=0.04, Mann-Whitney test, 95% CI).

The incidence of heart failure, defined by the value of ejection fraction was significantly higher in patients with increased non-HDL-c, not responsive to medications at T1 (p = 0.007, Mann-Whitney test, 95% CI).

Newly diagnosed cases of diabetes were significantly more frequent in patients with increased non-HDL-c at T1 (p = 0.017, Mann-Whitney test, 95% CI).

There was no significant difference between the incidence of MACE and the type of revascularization procedures.

## Discussion

Our study demonstrates a high cardiovascular risk among coronary patients after 4.33 years of myocardial revascularization.

**Table 3** – Relationship between LDL-c and major adverse cardiovascular events (MACE) at T1

Crosstab				
Count	LDLc_T1categ		Total	
	.00	1.00		
	0	225	89	314
	2	2	2	4
	3	0	3	3
	4	1	0	1
MACE_T2	5	1	2	3
	6	5	0	5
	7	2	1	3
	8	2	3	5
	9	3	0	3
Total		241	100	341

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	16.247 <sup>a</sup>	8	.039
Likelihood Ratio	18.328	8	.019
Linear-by-Linear Association	.394	1	.530
N of Valid Cases	341		

a. 16 cells (88.9%) had expected count less than 5. The minimum expected count was 0.29

The drugs prescribed to be used in association with statins were platelet aggregators, beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers, in accordance with the ESC guidelines for secondary cardiovascular prevention.

Analysis of the relationship between the medications and achievement of target values of modifiable risk factors was previously published by our group.<sup>9</sup> Reduction in systolic blood pressure under medication was achieved in 39.58% of subjects enrolled in this study; cardiometabolic risk was reduced under the maximum

dose of statin. Although the primary lipid target was reached in only 5% of patients, better outcomes were found in the secondary lipid target, non-HDL-c.

The high metabolic risk in these coronary patients is supported by dyslipidemia and high incidence of diabetes at T1, which justifies the implementation of energetic approaches toward lifestyle changes associated with the use of proper medication in revascularized patients.

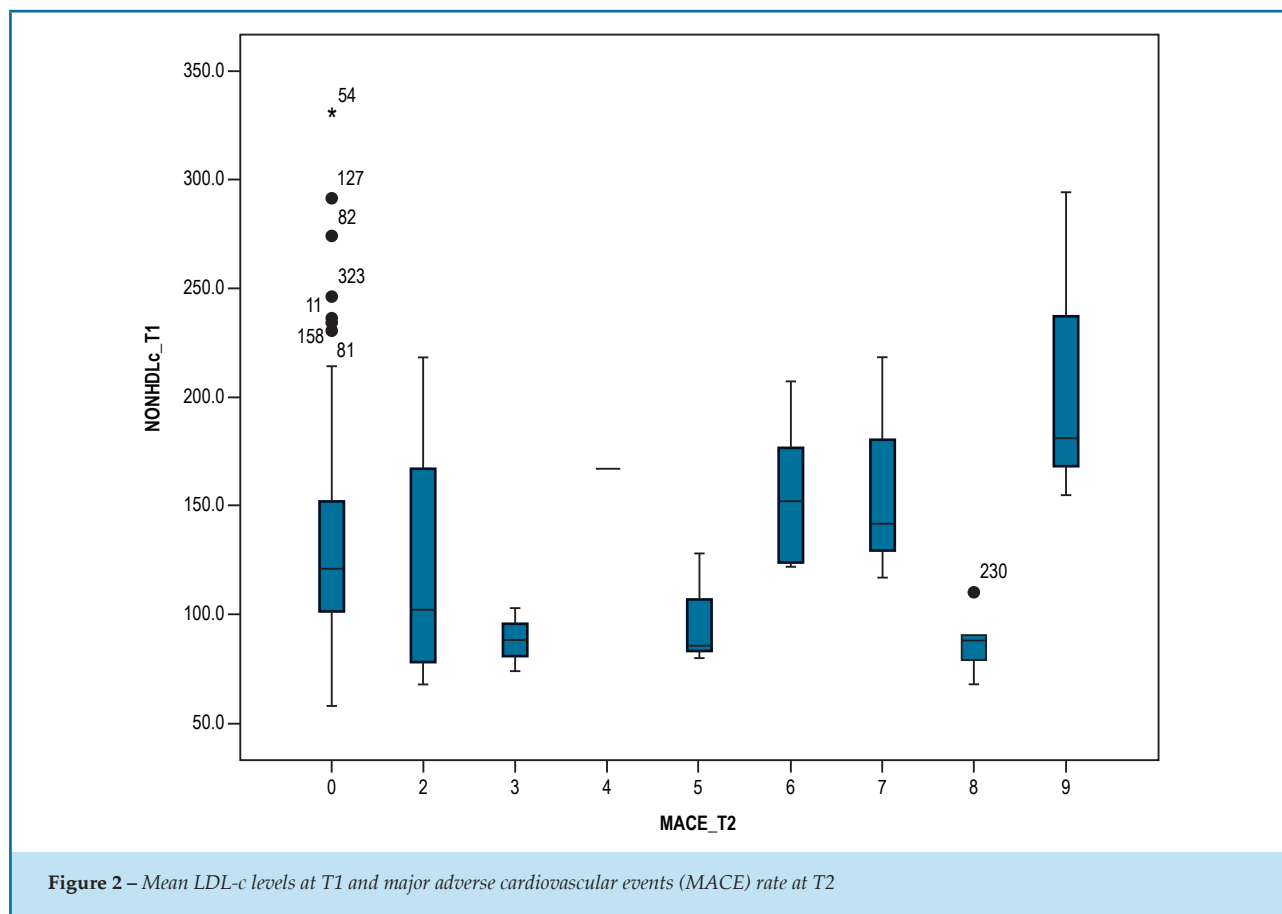
Our study did not set out to analyze the compliance of patients to post-revascularization recovery programs, which would have contributed to interpretation of our results. A low compliance to these programs and cardiovascular preventive approaches may be related to the development of atherothrombosis in coronary patients, and might explain the prevalence of cardiovascular events (7.9%) at T2 and a median survival time of 4.33 years in our study group. Further studies to evaluate the compliance of patients to these approaches would be helpful.

Our study corroborates the need for strategies to control modifiable cardiovascular risk factors.<sup>9,12,13</sup> Despite the use of medications, patients undergoing myocardial revascularization remain at risk of cardiovascular events related to atherosclerosis progression and other metabolic diseases.<sup>9,11</sup>

Results from the EUROASPIRE IV<sup>6</sup> pointed out that the Joint European Societies Guidelines on Cardiovascular Prevention recommendations are achieved in a still low proportion of coronary patients across Europe. In our study, only a modest percentage of revascularized coronary patients met the ESC Guidelines recommendations for LDLc -targets.<sup>10,11</sup> Although statin was prescribed to nearly 95% of patients at T1, the LDL-c levels were not reached by most of them.

Reiner et al.<sup>13</sup> emphasized the need to reduce LDL-c levels after a cardiovascular event to reduce coronary heart disease mortality and morbidity.<sup>13</sup> Other authors suggested several reasons for the mediocre response during statin therapy: inadequate dose, non-adherence to prescribed dose, statin resistance and / or intolerance, and side effects.<sup>14,15</sup> However, our results confirm the association between increased LDL-c levels with cardiovascular event rates.

We wonder if we can predict residual lipid risk in revascularized, coronary patients in use of statins. In our study group, there were significant differences in mean HDL-c and MACE rates at T2 as compared with other time points. Furthermore, they were correlated with the rate of restenosis, prevalence of heart failure and incidence of



**Figure 2** – Mean LDL-c levels at T1 and major adverse cardiovascular events (MACE) rate at T2

diabetes. In ESC / European Atherosclerosis Society (EAS) guidelines recommend the use of non-HDL-c as secondary target, especially among diabetic coronary patients.<sup>11,14-16</sup> It seems that non-HDL would be a better predictor than LDLc of unstable atherosclerotic plaque.<sup>17</sup>

Reiner et al. reported that 12.2% of coronary patients in whom the LDLc target value was reached had pathological levels of non-HDL-c. In our sample, only 7.33% patients had non-HDL-c levels > 110 mg/dL and LDL-c < 80 mg/dL after myocardial revascularization.

The ESC/EAS guidelines recommend that patients with such changes in the lipid profile should be identified and treated as appropriate.<sup>18-20</sup>

Our study has some limitations. First, baseline characteristics of participants were defined in a relatively late stage of coronary artery disease, i.e. at the time of myocardial revascularization. In addition, our sample was somewhat biased, since it was composed exclusively of patients treated at Timisoara Institute of Cardiovascular Diseases, which is a specialized treatment

center, and therefore, the results cannot be to all patients with coronary revascularization. However, there were relatively small differences between our results with those of previous studies conducted in Europe.<sup>16-21</sup>

## Conclusions

The study highlights the need to control lipid risk factors after myocardial revascularization procedures, even at long-term, to minimize the risk of cardiovascular events in patients with coronary diseases.

## Author contributions

Conception and design of the research: Catalina CO, Silvia M. Acquisition of data: Catalina CO, Smarandita BED. Analysis and interpretation of the data: Catalina CO, Adina B. Statistical analysis: Angela D. Obtaining financing: Dan G. Writing of the manuscript: Catalina CO, Silvia M. Critical revision of the manuscript for intellectual content: Dan G, Silvia M.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## Study Association

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