

## Is Blood Cholesterol Level a Marker of Cardiovascular Event in Primary Prevention? A Long-Term Observational Study

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### Abstract

**Introduction:** The association of coronary risk factors and cardiovascular events does not necessarily imply a causal relationship. Dyslipidemia is such a coronary risk factor and the role of cholesterol in the pathophysiology of cardiovascular disease remains controversial.

**Aim:** To evaluate in the long term the incidence of cardiovascular events in patients with and without dyslipidemia.

**Methods and Results:** 1142 patients admitted to a nuclear medicine center who presented normal effort myocardial perfusion test with SPECT, were enrolled in the study. Population were split into two groups; patients without dyslipidemia (n = 486) and patients with dyslipidemia without statins treatment (n = 656). Follow-up of 15.9 years was carried out with the following end-points: cardiac mortality, non-fatal myocardial infarction and unstable angina that required myocardial revascularization procedures. During follow-up, 44 patients experienced at least one cardiovascular event. The most frequent cardiovascular event was unstable angina that required some myocardial revascularization procedure. Surprisingly, 91.5% of patients with dyslipidemia remained free of cardiovascular events, showing a similar survival function as those patients without dyslipidemia (p = 0.31).

**Conclusion:** Patients with and without dyslipidemia in primary prevention presented similar survival functions, therefore both sorts of patients would belong to the group of low cardiovascular risk. Therefore, blood cholesterol level was not a marker of cardiovascular events in our study population.

**Keywords:** LDL-Cholesterol; Dyslipidemia; Cardiovascular Events; Primary Prevention

### Introduction

In the Frammingham studies, conditions such as dyslipidemia, arterial hypertension (AHT), smoking and diabetes were found to present a strong association with the incidence of cardiovascular disease (CVD). These variables were given the name of coronary risk factors.

However, it is common to see in medical practice patients with dyslipidemia who do not evolve to cardiovascular disease while others with normal or below normal cholesterol levels progress to coronary heart disease. Therefore, the jointly occurrence of dyslipidemia and CVD does not necessarily imply a causal relationship.

LDL-cholesterol (LDL-C) plays a fundamental role in the formation of cell membranes, so it is essential in any type of cell repair. In addition, cholesterol is a biosynthetic precursor of vitamin D and bile acids and it is an ancestor of steroid hormones.

It is also well known that coronary heart disease is associated with arterial wall damage, mainly expressed by a chronic inflammatory process. The LDL-C in contact with the injured arterial wall would undergo oxidation processes and generate products with chemotactic activity for monocytes and smooth muscle cells. This is how they transform into foam cells by installing the chronic inflammatory process and whose accumulation causes the production of fatty streaks. By continuing the proliferative process, they evolve to the formation of a more complex atheroma plaque [1].

American and European guidelines present cholesterol as the main responsible for cardiovascular disease [2,3]. Nevertheless, in 2009 Sachdeva, *et al.* reported an analysis of 136905 patients admitted to 541 hospitals for coronary heart disease showing that almost half of the patients had normal or below normal cholesterol levels at the time of admission [4] and more recently, Ravnskov, *et al.* found an inverse relationship between LDL-C and mortality in the elderly [5]. These observations remain controversial, showing disagreement about the role of cholesterol in the pathophysiology of cardiovascular disease.

As a result, we address the following question; are blood cholesterol levels responsible for the onset of arteriosclerotic processes that occur so frequently in our population? The main aim of this work was to address the incidence of cardiovascular events on patients with and without dyslipidemia in a cohort of 1142 low risk patients.

### Materials and Methods

Between January 2001 and December 2016, 1142 patients (aged  $59 \pm 11$  years with a male prevalence of 52%) were enrolled in the protocol. These patients were referred by their general practitioners to perform a myocardial perfusion study for diagnostic purposes in accordance with the guidelines of the "American College of Cardiology", the "American Heart Association" and the "American Society of Nuclear Cardiology" [6] and all of them showed a uniform radiotracer uptake, indicating a preserved myocardial perfusion.

Patients were older than 21 years, presented an ejection fraction  $\geq 50\%$  and had normal ventricular volumes. None of these patients had a history of myocardial infarction, revascularization surgery, coronary angioplasty, stroke, intermittent claudication, left bundle branch block or atrial fibrillation. All patients and in agreement with their GPs, agreed to participate in this observational, prospective cohort study.

A clinical history was prepared for all of them, including cardiovascular symptoms, coronary risk factors and complementary studies previously carried out.

Following the established criteria, we considered the coronary risk factors as follows:

1. Diabetes: Fasting blood glucose  $> 126$  mg/dl in at least two determinations or with indication of oral hypoglycemic agents or insulin.
2. Obesity: when reached a body mass index  $\geq 30$
3. Dyslipidemia: Total cholesterol  $> 200$  mg/dl, HDL-cholesterol  $< 40$  mg/dl, LDL-cholesterol  $> 130$  mg/dl, triglycerides  $> 150$  mg/dl and/or total cholesterol / HDL-cholesterol ratio  $> 4.5$ . It is known that the absolute value of cholesterol is very variable since it depends on several factors, including diet and fasting performed by the patient prior to blood draw. As, in addition, these patients are referred by their general practitioners, the results of the clinical analysis come from different institutions, which further determines their variability. This is the reason why we have not considered in this study the absolute value of blood cholesterol. The incorporation of individuals with and without dyslipidemia was established with the last two laboratory results following the stated parameters. When there was controversy in these values, the patient was excluded from the study.
4. Hypertension: Systolic pressure  $\geq 140$  mm Hg or diastolic  $\geq 90$  mmHg or those under antihypertensive treatment.
5. Smoking.

**Myocardial perfusion**

The ergometric protocol used was continuous and scalariform on a cycle ergometer with blood pressure control and continuous ECG monitoring. The effort was stopped when the subject reached the desired heart rate according to the Robinson table [7,8] or when there were clinical or electrocardiographic criteria to interrupt the exercise. One minute before the end of the maximum effort, 20 mCi of Tc 99m-mibi was injected intravenously. The dose administered had a cardiac biodistribution according to the coronary flow obtained during the effort. After thirty minutes, the cardiac images were acquired in a gamma camera (General Electric) with the SPECT system triggered and they were processed and interpreted following the classic criteria reported [9]. The resting study was performed between 24 and 72 hours after the effort, with the same conditions of radiotracer dose and image acquisition as in the effort stage.

**Demographic characteristics**

Table 1 shows the baseline characteristics of the study population. Two groups were defined as follows; Group 1: 486 patients without dyslipidemia (42.5%) and Group 2: 656 patients with dyslipidemia without statins indication (57.5%).

	<b>Group 1 (n = 486)</b>	<b>Group 2 (n = 656)</b>	<b>p</b>
Age	57,9 ± 12		0.008
AFT	2192	2090	0.242
Male	264 (54,3%)	330 (50,3%)	0.170
Diabetes	38 (7,8%)	75 (11,4%)	0.051
Smoker	75(15,4%)	122(18,5%)	0.201
Ex smoker	178(36,6%)	259(39,4%)	0.473
Hypertension	256(52,6%)	385(58,6%)	0.098
Obesity	149(30,6%)	241(36,7%)	0.051
Angina	20(4,1%)	39(5,9%)	0.163
Arrhythmia	67(13,7%)	98(14,9%)	0.587
ARBs	81(16,6%)	118(17,9%)	0.554
ACEI	75(15,4%)	99(15%)	0.887
Aspirin	86(17,6%)	152(23,1%)	0.021
BB	118(24,2%)	158(24%)	0.937

**Table 1:** Baseline characteristics of the study population.

AFT: Average Follow-Up Time; ARBs: Angiotensine II Receptor Blockers;  
 ACEI: Angiotensin-Converting Enzyme Inhibitor; BB: Beta Blockers;  
 Quantitative Variables: Mean ± SD; Qualitative variable: N (%).

**Follow up**

Follow-up extended to 15.9 years and the following primary outcomes were considered: a) cardiac mortality; b) non-fatal myocardial infarction and c) myocardial revascularization procedures by either surgery or angioplasty.

ardiac death was defined as any death caused by myocardial infarction or sudden death of documented cardiac origin. Myocardial infarction was defined as an elevation of the enzyme CPK and CPK MB of double the upper limit accompanied by a ST-T supra-level greater than 0.1 mV in at least two electrocardiographic leads. The myocardial revascularization procedures were considered as events,

in those patients who were admitted for unstable angina and who needed revascularization treatment, either by angioplasty or by revascularization surgery. In asymptomatic patients who were studied and then revascularized, the revascularization procedure was not regarded as an event.

After inclusion, general practitioners informed about symptoms, hospitalizations, cardiovascular events, medication indications, date of the event and date of last contact with the patient. In the analysis of the event-free survival curve, performed by the Kaplan Meier method, only the first cardiovascular event of the patients was taken into account. The adherence to the study was of 73.8%. Mean follow-up was 71.4 months with a range spanning from 6.1 to 191.1 months.

**Statistical analysis**

T-student test was utilized to compare quantitative variables. Results are expressed as Mean ± SD. Qualitative data were compared with the Chi square test. The strength of association was evaluated with OR (odd ratio). It was considered that an association was statistically significant when the null hypothesis was rejected at the level of  $p < 0.05$ . The event-free survival curve was analyzed with the Kaplan Meier method and the statistical significance between curves with the Logrank test. The time between events was associated with several independent variables. For this purpose, the Cox proportional hazards regression model was used.

**Results**

**Cardiovascular events**

During follow-up, 43 patients experienced one cardiovascular event, while 1 patient presented two events. Consequently, 45 cardiovascular events were observed in 44 patients.

Table 2 shows the incidence of cardiovascular events. Notice that the most frequent cardiovascular event in this population was the unstable angina that required a procedure of myocardial revascularization as an angioplasty in 19 individuals. Myocardial revascularization surgery was performed in 9 patients. The incidence of non-fatal acute myocardial infarction was observed in 11 patients, while cardiac death in 5 patients. Thirty three non-cardiac deaths occurred during the study and they were not considered as events for the purposes of the present analysis (Table 3).

Cardiovascular events	Occurrence
Acute myocardial infarction	11
Cardiac death	5
Angioplasty	19
Myocardial revascularization surgery	9

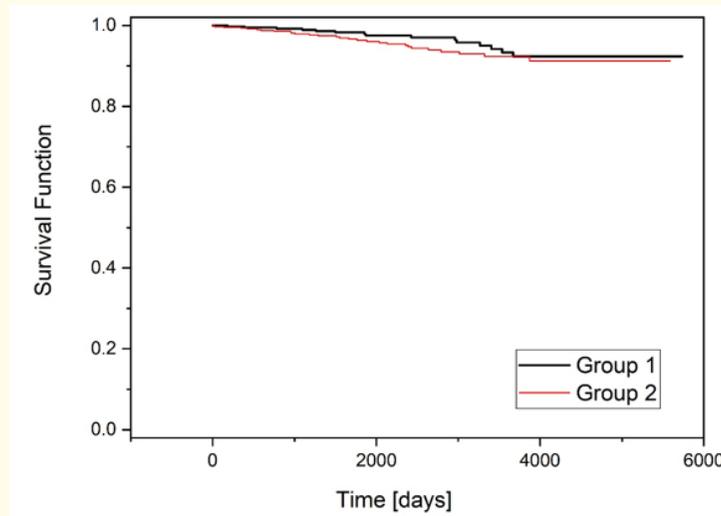
**Table 2:** Incidence of cardiovascular events in 15.9 years.

Non cardiac death causes	Cantidad
Neoplasia	22
Accident	2
Neumopatía	4
Others	5

**Table 3:** Incidence of non-cardiac cause mortality in 15.9 years.

**Survival analysis**

Figure 1 shows the cumulative proportion of individuals free of cardiovascular events for Group 1 and Group 2. Patients without dyslipidemia had an event-free survival of 92.3%, while those with dyslipidemia patients remained free of cardiovascular events in 91.5% of the cases, presenting no significant differences in their survival functions according to the Logrank test ( $p = 0.31$ ). Therefore, patients with and without dyslipidemia presented the same evolution. Thus, in 15.9 years both groups still belonged to the group of low cardiovascular risk.



**Figure 1:** Survival curves for patients with (red) and without (black) dyslipidemia.

In order to determine if dyslipidemia was a predictor of cardiovascular event, the proportional hazards model was utilized (Table 4). Dyslipidemia was not predictive of cardiac events, as seen in the proportional hazards regression when analyzing the following covariates: dyslipidemia, coronary risk factors, age and gender. In such analysis, diabetes resulted the only predictive covariate ( $p = 0.0002$ , RR = 3.75).

Variable	STD Error	Coefficient	Z	P	Risk Ratio
Age	0.03012	0.01610	1.87	0.0614	1.03
Diabetes	1.32308	0.34907	3.79	0.0002	3.75
Hypertension	-0.05716	0.30016	-0.19	0.8490	0.94
Smoking	0.30122	0.39153	0.77	0.4417	1.35
Obesity	0.36144	0.32458	1.11	0.2655	1.44
Gender	0.63375	0.34955	1.81	0.0698	1.88
Dyslipidemia	0.21679	0.33663	0.64	0.5196	1.24

**Table 4:** Cox proportional or regression risk model in patients without dyslipidemia and dyslipidemia. The time to an event is the response variable and there are several predictor variables analyzed, such as coronary risk factors, sex and age.

### Discussion

Some publications claim that dyslipidemia is associated with an increase in cardiovascular risk, even in the absence of other coronary risk factors.

A recent analysis of the WOSCOPS study [10] provides, for the first time, evidence of a randomized trial that supports the benefit of LDL-C reduction in the incidence of cardiovascular events in primary prevention. However, not all publications coincide with this statement.

The concept that the elevated level of LDL-C in blood causes endothelial dysfunction is unlikely because there is no association between the concentration of LDL-C and the degree of endothelial dysfunction [11]. On the other hand, most studies have found no correlation between the level of LDL-C or total cholesterol and the degree of atherosclerosis at autopsies [12].

In studies of women and the elderly, hypercholesterolemia is a very weak risk factor for cardiovascular disease since most cardiac deaths occur in individuals over 65 years of age [13].

In individuals with familial hypercholesterolemia there is no association between LDL-C and the prevalence or progression of cardiovascular disease [14-19].

### Oxidized LDL cholesterol

Lately, special attention has been paid to modified LDL cholesterol and especially to oxidized LDL-C, as a factor that promotes the development of atherogenesis [20-26]. The accumulation of low density lipoproteins (LDL) in the subendothelial space seems to be one of the first episodes associated with the development of atherosclerotic lesions. The LDL-C retained in the wall undergo oxidation processes and generate products with chemotactic activity for monocytes and smooth muscle cells. Monocytes cross the endothelium, differentiate to macrophages, take up the oxidized LDL-C massively and transform them into foam cells whose accumulation in the intima results in the formation of fatty streak [27].

It is thought that most of the oxidation of LDL-C occurs in the subendothelial space of the arteries, where these particles can be retained by the proteoglycans. However, small amounts of oxidized LDL-C can be detected in normal plasma and its concentration increases in some diseases such as diabetes, kidney disease and coronary heart disease [28].

Researchers Satchell and Leake showed that LDL-C can be oxidized intracellularly in the lysosomes of macrophages [29]. The oxidation of LDL-C could take place in the sites of inflammation due to the infiltration of macrophages and monocytes. In the arterial wall, due to the effect of the chronic inflammatory state, free radicals and non-radical oxidants are generated that could be involved in the oxidation of LDL-C.

Oxidation of LDL-C is a very complex process during which both the protein and lipid fraction undergo oxidative changes and thus produce very complex products.

These data that arise from the medical literature and leads us to think that:

- Would the higher concentration of LDL cholesterol in plasma promote a higher production of oxidized LDL cholesterol and consequently the development of atherogenesis?
- If the oxidized LDL cholesterol cannot be measured in blood, we must assume that the increase in LDL native cholesterol is the trigger of coronary heart disease. Are these fractions homologable?
- On the other hand, the oxidized fraction of LDL cholesterol could be formed in the subendothelium of the arterial wall from the presence of free radicals and non-radical oxidants, thus generating the process of arteriosclerosis. However, if this were the mechanism, it should not depend on the concentration of LDL cholesterol in the blood.

### Myocardial perfusion

Beller and Zaret [30] performed a meta-analysis of 14 studies whose objective was to determine the prognostic value of myocardial perfusion images acquired after exercise in more than 12,000 patients. The outcomes analyzed in this study were cardiac death and non-fatal myocardial infarction. Their incidence in the group of patients with a normal perfusion was 0.6% per year, being twelve times more (7.4%) in those with abnormal perfusion images. This suggests that patients with normal perfusion studies integrate a very low risk population.

The population of our study only comprised subjects with normal perfusion and the incidence of events was 0.7% per year in a follow-up of 15.9 years. Although in this work, we included unstable angina that required myocardial revascularization procedures, in addition to the events mentioned above. The low incidence of cardiovascular events suggests the low probability that our population has significant obstruction in any of the arteries of the coronary tree when they entered our protocol.

### Coronary risk factors

Observational data in a number of reports claim that dyslipidemia is associated with an increased cardiovascular risk, even in the absence of other coronary risk factors [2,3]. Indeed, a recent analysis of the WOSCOPS study [9] provides evidence from a randomized trial that supports the benefit of LDL-C reduction in the incidence of cardiovascular events in primary prevention.

Despite this low incidence of cardiovascular events, the prevalence of coronary risk factors in our work was high, with 57.4% of patients with dyslipidemia, 56.8% of hypertensive patients, 34.6% of obese patients, 17.7% of smokers and 10% of diabetics.

This suggests that myocardial perfusion studies, which presented normal myocardial perfusion for all patients, would stratify coronary risk better than the prevalence of risk factors, as stated by Beller and Zaret [20]. This might explain the poor risk stratification obtained from scores based on the prevalence of these risk factors.

As shown in table 1, patients with dyslipidemia are older. The recommendations of the guidelines based on different published studies indicate that the decrease in blood cholesterol levels in the elderly reduces the incidence of cardiovascular events. However, we observed no significant difference in the cardiovascular events in individuals with and without dyslipidemia, with both groups remaining at low cardiovascular risk. This finding is consistent with Ravnskov, *et al.* who showed an inverse relationship between LDL cholesterol levels and the incidence of all-cause and cardiovascular mortality in individuals over 60 years of age [5].

Finally, the fact that patients with and without dyslipidemia presented the same survival function in this piece of work, is in accordance with Sachdeva, *et al.* who found a ratio of 50% of patients with normal cholesterol levels at the time of admission to 541 hospitals for coronary heart disease [4].

These findings support the idea that oxidized LDL-C and not blood LDL-C would cause a cardiovascular event, although further studies should be accomplished in order to elucidate this conception.

### Conclusion

Patients with and without dyslipidemia in primary prevention showed the same survival at 15.9 years, meaning that both groups still belong to the group of low cardiovascular risk. Therefore, blood cholesterol level was not a marker of cardiovascular events in our study population.

### Funding

None declared.

### Conflict of Interest

None declared.

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