Original Research

CARDIOLOGY

Cardiology 2014;127:45–50
DOI: 10.1159/000355164

Received: February 16, 2013
Accepted after revision: August 6, 2013
Published online: November 5, 2013

Low Levels of Low-Density Lipoprotein Cholesterol: A Negative Predictor of Survival in Elderly Patients with Advanced Heart Failure

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Key Words
Cholesterol · Low-density lipoprotein · Heart failure

Abstract
Objectives: There are conflicting reports on the role of cholesterol as an adverse prognostic predictor in patients with heart failure (HF). This study aimed to examine the impact of low levels of low-density lipoprotein cholesterol (LDL-c) on cardiac mortality in a cohort of elderly patients with moderate and severe HF. ***Methods:*** Chronic HF patients from the HF Unit at the Tel-Aviv Medical Center (n = 212, 77% males) with an average NYHA classification of 2.8, a mean age of 76.9 ± 7.3 years (range 66–91) and a mean follow-up of 3.7 years were consecutively enrolled. The cohort was divided into tertiles according to LDL-c levels: LDL <90 mg/dl (group 1), LDL 90–115 mg/dl (group 2) and LDL >115 mg/dl (group 3). ***Results:*** The Cox regression analysis revealed that group 3 patients had the best outcome (p = 0.01 vs. groups 2 and 3), with 58% of them surviving longer than 50 months compared to 34% in group 1. The same trend was seen in the group of patients suffering from ischemic cardiomyopathy and in patients who were treated by statins (p = 0.04). ***Conclusion:*** Low LDL-c levels are associated with a reduced survival in elderly patients with clinically controlled moderate and severe HF.

Introduction

Heart failure (HF) affects approximately five million people in the USA, and survival at 5 years is only 50% despite advances in medicine and device technology [1, 2].

For the primary and secondary prevention of coronary events, treatment with statins is well established [3, 4]. Many large clinical and animal studies advocate the use of statins in chronic HF, assuming pleiotropic effects that are irrespective of cholesterol reduction [5–9]. There are, however, insufficient data to show whether or not low cholesterol levels influence outcome in HF patients [8–10].

The findings of the Beta-Blocker Evaluation of Survival Trial (BEST) [11] showed that cholesterol reduction by statins was independently associated with a decrease in all-cause and cardiovascular mortality in patients with nonischemic dilated cardiomyopathy (EF <35, NYHA class 3–4). In contrast, Iwaoka et al. [12] showed that low levels of apolipoprotein A-1 are independently associated with an adverse prognosis in patients with nonischemic HF. Several other studies [13–17] suggested that low total cholesterol levels are associated with increased mortality in patients with systolic nonischemic HF. According to Flammer et al. [17], patients with HF who have intrinsically low cholesterol lev-

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els have double the risk of death within 5 years compared to patients with pharmacologically induced low cholesterol. Horwich et al. [15] concluded that low serum total cholesterol is a detrimental factor in the unfavorable prognosis of HF patients. Somewhat surprisingly, the results of the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study [17] showed no survival or morbidity benefit in a group of patients with ischemic systolic HF who had been given low-dose rosuvastatin.

The aim of this study was to examine the impact of low LDL-c levels on cardiac mortality and to determine whether there is reverse epidemiology in a cohort of elderly patients with moderate and severe controlled HF of different etiologies.

Methods

All the participants in this study were enrolled consecutively between January 2002 and July 2003 from the HF Unit at the Tel-Aviv Medical Center. Follow-up started after blood samples had been obtained for lipid profiles, renal function tests and hemoglobin levels [N-terminal pro-B-type natriuretic peptide B-type natriuretic peptide (NT-pro-BNP)]. Systolic HF was defined as a left ventricular ejection fraction (LVEF) ≤40% by echocardiography or an isotopic Tc 99m ventriculography scan. Diabetes mellitus and hypertension were defined by medical history and according to WHO diagnostic criteria. The patients were examined by a senior cardiologist, and the following information was obtained at the first visit: medical history, medications, physical examination findings, resting blood pressure, heart rate, weight, NYHA classification and results of echocardiography or isotopic ventriculography. Follow-up examinations were carried out at least every 3 months. The exclusion criteria were malignant metastatic disease, severe cerebral vascular disease, being chronically bedridden and severe thyrotoxicosis. To determine the predictive value of LDL levels on mortality, we divided our cohort into tertiles according to their LDL levels: group 1 patients had levels <90 mg/dl, group 2 had levels ranging between 90 and 115 mg/dl and group 3 had levels >115 mg/dl. The end point of this study was mortality. The study was approved by the institutional ethics committee and the Israeli Ministry of Health.

All data were summarized and displayed as mean ± standard deviation (SD) for normally distributed continuous variables, as median and interquartile range for nonnormally distributed continuous variables, and as number of individuals (percentage) in each of the 3 groups for dichotomous variables. In order to evaluate the importance of different levels of the lipid profile, we divided our cohort into tertiles of each of the lipid values, and compared the mortality among those tertiles. The comparison between the basic parameters among the tertiles was done using one-way analysis of variance for the continuous variables, and the χ^2 test for categorical ones. In order to compare mortality among the tertiles, we first constructed Kaplan-Meier curves, with analysis of the statistical difference using the log-rank test. We then compared the age-, gender-, NYHA class-, creatinine clearance test (CCT)- and LVEF-adjusted mortality among the tertiles using the Cox regression. All analyses were considered significant at $p < 0.05$ (two-tailed). The SPSS statistical package was used to perform all of the statistical evaluations (SSPS Inc., Chicago, Ill., USA).

Results

A total of 233 consecutive outpatients with HF-related symptoms met the inclusion criteria and were prospectively entered into this study. Twenty-one of them were excluded for technical reasons, noncompliance or lack of follow-up information, and the remaining 212 patients comprised the study group. Their mean age was 76.9 ± 7.3 years (range 66–91 years), 163 (77%) were males, 193 (91%) had ischemic cardiomyopathy, 19 (9%) had valvular disease, 175 (83.6%) had systolic dysfunction and 37 (17.4%) had diastolic dysfunction. The mean LVEF was 37.4%. The mean number of clinical visits was 15.3. The mean follow-up was 3.7 years. The HF disease duration ranged from 10 months to 6 years. The general characteristics of the patients and the distribution of selected clinical characteristics are shown in table 1. The demographic data demonstrated that patients in group 3 were slightly younger. There were no differences between groups in age or prevalence of diabetes mellitus, hypertension or ischemic heart disease; however, there were slightly more patients with an advanced NYHA class (3.5–4) in group 3. The mean NYHA class for the whole cohort was 2.8. Figure 1 displays the survival according to LDL tertiles.

Table 2 presents the main laboratory data of the patients according to their LDL group. The group 3 patients had significantly higher levels of total cholesterol and triglycerides. The levels of hemoglobin, glucose albumin, creatinine and CCT were approximately equal among the groups. The C-reactive protein level was similar in all 3 groups ($p = 0.402$).

There were no significant group differences in trends for higher total cholesterol and triglyceride levels being associated with increased mortality, even when we applied tertiles. A higher HDL level was associated with longer survival in all groups. There were no between-group differences in the use of most of the medications (table 3). However, the prevalence of angiotensin-converting enzyme inhibitor (ACEI) use was significantly less in group 1, whereas digoxin and antiarrhythmic drugs were used more frequently by the patients in group 3. Only 59% of patients received beta-blockers. Beta-blocker treatment had been prescribed for the majority of the patients, but

Table 1. Characteristics of 212 patients according to LDL-c tertiles

Variable (number of patients)	Lower tertile LDL <90 mg/dl (n = 74)	Middle tertile 90–115 mg/dl (n = 72)	Upper tertile LDL >115 mg/dl (n = 66)	p value
Age, years (n = 212)	77.9±6.3	76.9±7.3	76.1±6.3	>0.005
Male gender (n =163)	79	68	67	
Weight, kg	73.5±15.2	73.6±13.1	75.3±13.8	>0.005
Hypertension (n = 138)	36	32	32	
Hyperlipidemia (n = 127)	35	33	32	
Diabetes mellitus (n = 88)	35	28	37	
Smoker (n = 58)	21	36	43	
IHD/AMI (n = 193)	33	34	23	
Valvular disease (n = 19)	29	39	32	
Atrial fibrillation (n = 60)	36	32	32	
CVA/TIA (n = 33)	46	30	24	
PCI/CABG (n = 111)	33	37	30	
LVEF (n = 212)	36	30	34	
NYHA class				
1–2 (n = 45)	40	42	18	
2.5–3.5 (n = 118)	37	36	27	
3.5–4 (n = 49)	35	37	38	

Values are given as means ± SD or percentages. AMI = Acute myocardial infarction; CABG = coronary artery bypass grafting; CVA = cerebrovascular accident; IHD = ischemic heart disease; PCI = percutaneous coronary intervention; TIA = transient ishemic attack.

some of them discontinued it before and during the enrolment in the study because of the side effects.

The Cox regression curves revealed a significant difference in outcomes: group 3 patients had the best overall (ischemic and valvular) outcome (p = 0.01 vs. groups 2 and 3), with 58% of them surviving longer than 50 months compared to 34% in group 1 (fig. 1a). The same trend was seen in the group of patients suffering from ischemic cardiomyopathy: 63% of the group 3 patients versus 36% of the group 1 patients survived longer (fig. 1b; p = 0.04). Patients who were treated with statins showed a similar tendency: 80% of the group 3 patients survived longer than 50 months compared to 43% of the group 1 patients (fig. 1c; p = 0.04). Patients who were not treated with statins showed no difference in survival according to LDL tertiles. The mean follow-up was 3.7 years, and 78 of the study patients (37%) died during follow-up. The cause of death for these 78 patients was: ischemic cardiomyopathy in 90% (n = 70), nonischemic valvular cardiomyopathy in 10% (n = 8), 85% (n = 66) had systolic dysfunction and 15% (n = 12) had and preserved LVEF. There were no significant differences between the tertiles of the latter three diagnoses. The LDL-c levels of the patients who died were significantly lower (p < 0.05) than the levels of those who were alive at the end of the follow-up period. Both the nonadjusted and the adjusted overall and cardiac mortality rates were markedly elevated in the tertiles with LDL levels <90.

Discussion

The purpose of this study was to investigate the relationship between hypocholesterolemia and outcomes in patients with advanced HF. Our results showed that low initial LDL-c levels were a significant predictor of worse outcome in both ischemic and nonischemic CHF in an elderly CHF cohort. The mortality of patients in the third tertile (LDL >115 mg/dl) was reduced by 24% in spite of the fact that the percent of patients with an NYHA class of 3.5–4 was higher in this group. Even after adjusting for multiple known predictors of HF mortality, high LDL levels remained a significant novel independent predictor of improved survival. Low levels of total cholesterol or triglycerides were not significant in predicting mortality. It has been well documented that higher levels of HDL correlate with longevity. Most of our study patients were taking statins for lowering their LDL levels in order to improve prognosis, but according to the tertiles, there

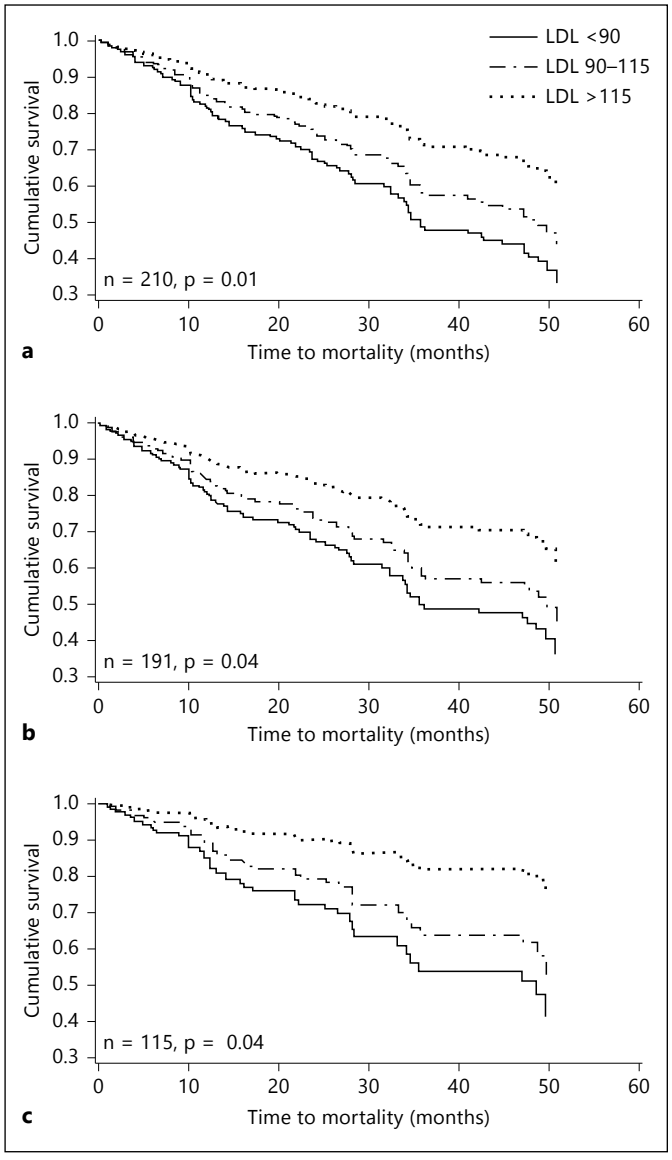

Fig. 1. a Mortality according to LDL tertiles. **b** Survival curves according to LDL-c tertiles in patients with ischemic heart disease (IHD). **c** Survival curves according to LDL-c tertiles in patients treated with statins.

was no difference in survival between the patients who were treated with statins and those who were not.

The relationship between LDL levels and HF outcomes among the elderly, which we document here, seems to be contradictory to the findings in patients with coronary artery disease [5–9] and in patients enrolled in other HF studies [8, 9, 11, 18, 19]. Several studies reported that patients with ischemic and nonischemic HF appear to have an opposite pattern ('reverse epidemiology'), with low levels being associated with a worse prognosis independent of other prognostic factors [13, 20]. Rauchhaus et al. [16] studied 414 patients with HF and found a 36% decreased risk of mortality with each millimole per liter increase in total cholesterol, independent of other risk factors. Horwich et al. [15] showed an adverse relation between total cholesterol and mortality in patients with systolic dysfunction.

An increased mortality risk among individuals with low HDL levels was observed in non-HF patients who had severe advanced diseases, end-stage renal failure on hemodialysis, traumatic renal failure and multiple-organ failure [21–23]. Several studies documented low LDL levels as being associated with all-cause mortality [23–27]. The large, randomized CORONA trial on statins concluded that myocardial infarction and stroke are relatively uncommon in systolic HF patients, and that rosuvastatin had no effect on the mortality rates from cardiovascular causes or sudden death [28].

There are several mechanisms by which high cholesterol levels may actually be protective in severely ill patients. Lipids and lipoproteins may play a protective role in HF by modulating the inflammation markers, such as C-reactive protein, cytokines, oxidized LDL, tumor necrosis factor and interleukin 6 [16, 22–26]. Cholesterol can bind endotoxin and lipopolysaccharides which are more common in severe HF: bacteria enter across the edematous epithelium of the bowels and detoxify them, thus participating in the downregulation of inflammatory process and deactivating cytokines which contribute to myocyte damage [16, 26].

Ubiquinone (Q10), an essential product of cardiac mitochondrial respiration, is reduced in patients with congestive HF [14–17, 20, 26]. Treatment with statins was shown to reduce ubiquinone levels and could thus be potentially harmful [14–17, 20].

Thus, low LDL levels may cause HF patients to be vulnerable to inflammatory processes. On the other hand, a low LDL level may be a marker of disease severity. Advanced HF patients are characterized by a high catabolic state, increased metabolic demands and increased energy consumption. Weight loss (not edematous) and cardiac cachexia are well-known independent risk factors for HF mortality. Unlike the results of other studies [9, 14, 19, 21], our elderly patients with a range of LDL levels had the same normal albumin, creatinine, hemoglobin and body mass index values which are established markers of the nutritional state. They also had normal levels of the inflammatory marker, C-reactive protein. All this indicates that as the main lipid predictor of atherosclerosis, the LDL-c may be considered an independent predictor of mortality and not only a marker of the nutritional state.

Table 2. Mean values of the different laboratory parameters according to LDL-c tertiles

	<90 mg/dl (n = 74)	90–115 mg/dl (n = 72)	>115 mg/dl (n = 66)	ANOVA p value
Hemoglobin, g/dl	12.6±1.62	12.8±1.5	12.9±1.5	NS
Glucose, mg/dl	135.2±56.3	134±66.5	124±60.5	NS
Creatinine clearance test, ml/min	43.4±3.2	42.3±2.6	45.2±4.3	NS
Creatinine	1.93±9.9	1.76±0.8	1.9±1.4	NS
Total cholesterol, mg/dl	150.26±23.1	173±24.2	217±43.5	<0.001
High-density lipoprotein, mg/dl	41.2±11.3	45.1±11.3	46.4±9	<0.002
Triglycerides, mg/dl	145.4±90.2	138.3±49.2	171.2±78.3	0.009
Aspartate amino transferase, mg/dl	23.2±12.1	24±10.3	24±14.4	NS
Alkaline phosphatase, mg/dl	70.85±34.1	68.6±38.1	63.9±27.2	NS
Albumin, g/l	39.4±5.6	39.6±9.4	39.5±8.1	NS
Alanine amino transferase, mg/dl	20.55±12.3	22.06±15.9	23.6±16.5	NS
Total bilirubin, mg/dl	0.7±0.3	0.5±0.1	0.7±0.2	NS
Weight, kg	73.5±15.2	73.6±13.6	75.3±13.8	NS
LVEF, %	36.6±14.3	37.8±13.8	36.4±14.1	NS
N-terminal pro-B-type natriuretic peptide, pg/ml	1,954.8±989.5	1,879.7±1,764.3	1,999.5±1,232.4	NS
High-sensitivity C-reactive protein, mg/dl	8.8±3.1	7.7±3.4	8.3±11.3	NS
Red blood cell count (×1,000,000)	4.3±0.6	4.4±0.6	4.5±0.6	NS
White blood count (×1,000)	7.2±1.8	7.5±2.38	7.1±2.4	NS
Neutrophils (×1,000)	4.5±1.6	4.6±2.2	5.3±2.8	NS
Lymphocytes (×1,000)	1.8±1.1	1.7±2.1	2.2±1.2	NS
Platelets (×1,000)	232.8±75.2	214±62.2	234.6±75.2	NS

Values are means ± SD. NS = Not significant.

Table 3. Frequency of medications as percentages according to LDL-c tertiles

Medication and number of patients	Lower tertile LDL <90 mg/dl (n = 74)	Middle tertile 90–115 mg/dl (n = 72)	Upper tertile LDL >115 mg/dl (n = 66)
Warfarin (n = 43)	37	33	30
Aspirin (n = 122)	36	35	28
Statins (n = 116)	40	41	19
Angiotensin-converting enzyme inhibitors (n = 163)	39	36	25
Angiotensin receptor blocker (n = 23)	32	37	31
Clopidogrel (n = 18)	25	41	39
Nitrates (n = 88)	33	35	31
Calcium-channel blockers (n = 35)	37	43	26
Beta-blockers (n = 124)	37	36	27
Insulin (n = 15)	33	27	40
Oral hypoglycemic drugs (n = 53)	40	36	25
Alpha-blockers (n = 43)	39	37	23
Fibrates (n = 6)	27	27	46
Antiarrhythmics (n = 37)	35	32	33
Digoxin (n = 37)	27	36	38
Spironolactone (n = 37)	34	37	29
Diuretics (n = 170)	36	37	27

Thus, as noted by Rauchaus et al. [16], advanced HF and cardiac cachexia alone may not fully explain the paradoxical association of LDL levels and survival.

Our 6-year longitudinal study confirms that a low LDL level is an adverse prognostic factor in advanced HF in the elderly. Our results indicate that this holds true for patients with both ischemic and nonischemic HF. A low LDL is a predictor of worse outcomes in HF with either a systolic or diastolic etiology. While the relation between cholesterol and atherosclerosis is indisputable, the questions remain unanswered as to whether patients with HF need lipid-lowering treatment and what the optimal LDL levels should be. HF is a very late stage of most forms of cardiovascular disease when many cardiovascular alterations are irreversible. For instance, lowering of LDL levels by HMG coenzyme reductase inhibitors does not reduce the event rates even in patients with ischemic cardiomyopathy [17]. Our observations suggest that levels of LDL between 115 and 135 mg/dl (most of our elderly patients in the third tertile) may be considered as being within acceptable limits for elderly patients with advanced CHF.

Conclusion

Low LDL-c levels are associated with a reduced survival in elderly patients with clinically controlled moderate and severe HF. Statins were independently and significantly associated with a higher risk of mortality.

Acknowledgment

Esther Eshkol is thanked for editorial assistance.

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