QJM: An International Journal of Medicine, 2018, 319–325

doi: 10.1093/qjmed/hcy043
Advance Access Publication Date: 23 February 2018
Original paper

ORIGINAL PAPER

A longitudinal 20 years of follow up showed a decrease in the survival of heart failure patients who maintained low LDL cholesterol levels

G. Charach, O. Argov, H. Nochomovitz, O. Rogowski, L. Charach and I. Grosskopf

From the Department of Cardiology, Tel Aviv Sourasky Medical Center, Sackler School of Medicine, Tel Aviv University, Tel Aviv 64239, Israel

Address correspondence to Dr G. Charach, The Department of Cardiology and Internal Medicine 'C', Tel Aviv Sourasky Medical Center, Sackler Medical School, Tel Aviv University, 6 Weizman Street, Tel Aviv 64239, Israel. email: drcharach@012.net.il

Summary

Background: Treatment by statins is well established for primary and secondary prevention of cardiac events but may be hazardous for patients with heart failure (HF).
Aim: We studied the long-term (20 years) association between baseline low-density lipoprotein cholesterol (LDL-c) levels and clinical outcome in patients with severe HF.
Design: Patients were divided into those with plasma LDL-c levels 110 mg/dl (Group 1) or >110 mg/dl (Group 2).
Methods: The mean follow-up of 305 study patients with advanced HF who had an average NYHA score of 2.7 was 11.3 years (range 15 months to 20 years). Mortality during follow-up was 43%.
Results: Patients with the highest baseline LDL-c levels had significantly improved outcome, whereas those with the lowest LDL-c levels had the highest mortality. This paradoxical effect was prominent in patients <70 years old. The negative association of LDL-c levels and mortality was most conspicuous among the HF patients who were treated with statins.
Discussion and Conclusion: Long-term follow-up findings showed that low LDL-c levels may predict a less favorable outcome in advanced HF, particularly in patients <70 years old and those taking statins. This negates the protocol of following an aggressive LDL-c-lowering strategy in younger patients with HF.

Background

Low-density lipoprotein cholesterol (LDL-c) is an established major cardiovascular risk factor and one that is associated with increased mortality in adult populations.[1,2] Treatment by statins is well established for primary and secondary prevention of coronary events.[3–5] There is conflicting data regarding reduction of LDL-c. Many clinical investigations showed that high concentrations of LDL-c were associated with increased mortality.[6] Several pre-clinical and clinical studies recommended the use of statins in HF[7–9] for lowering cholesterol levels. Statins induce an improvement in endothelial dysfunction and down-regulation of inflammation, both of which are involved in the pathophysiology of HF.[8–10] However, many controlled studies showed opposite results for the reduction of cholesterol by statins, pointing to the possibility that they may be hazardous in HF patients. Ubiquinone (Q10), which is well known as a vital product of the cardiac mitochondrial respiration chain, participates in ATP

Received: 1 January 2018; **Revised (in revised form):** 2 February 2018

production harboring anti-oxidant effects and it is reduced in patients with congestive HF (CHF).[11] Treatment with statins has been shown to reduce ubiquinone levels and thus could be potentially harmful. Moreover, according to the endotoxin-lipoprotein hypothesis, LDL-c and triglyceride-rich particles are capable of buffering endotoxins that are powerful promoters of inflammatory cytokine release.[10,11] Reduction of LDL-c may lead to increased susceptibility to infections that are common among patients with CHF.[6–8] In contrast, many clinical studies[5–9,12–15] as well as anecdotal studies[11,16–22] have shown that treatment with statins is associated with improved outcome in patients with HF. The large CORONA study[17] reported that rosuvastatin treatment did not reduce cardiovascular death from different etiologies, such as non-fatal myocardial infarction and non-fatal stroke in older patients with systolic HF. Although autopsy studies suggested that acute coronary disease can be found in 33% of patients who died from pump failure, rosuvastatin did not have any effect on mortality from HF.[17]

In the current longitudinal 20-year follow-up study, we examined the baseline LDL-c levels as an unfavorable prognostic factor in patients with advanced but clinically controlled HF who were or were not managed by statin treatment.

Materials and methods

The participants in this prospective study were enrolled from the specialized outpatient HF clinic at Tel-Aviv Sourasky Medical Center. Initial baseline blood samples for lipid profiles, kidney function tests and hemoglobin levels were obtained between January 1998 and July 2001. All compliant consecutive HF patients were recruited. Systolic HF was defined as a left ventricular ejection fraction (LVEF) <40% by echocardiography or Tc99 scan ventriculography. At the first visit, all patients were examined by a cardiologist and data of the following were obtained: medical history, medications, physical examination including blood pressure, pulse, weight, New York Heart Association (NYHA) class, echocardiography and Tc99scan ventriculography. They were followed-up by a cardiologist from the HF unit every 3 months or more as needed. Exclusion criteria were cancerous disease with metastases, advanced dementia, acute inflammatory disease, end-stage renal failure or severe cerebrovascular disease. The endpoint of the study was all-cause mortality. The study was approved by the institutional ethics committee (No- 0554-17-TLV) and each subject provided informed consent to participate.

Statistical analyses

Categorical variables were described using frequency and percentage. Continuous variables were evaluated for normal distribution using histograms and Q-Q plots. Normally distributed continuous variables were described as mean and standard deviation, and skewed variables were expressed as median and interquartile range. The length of follow-up was described using a reverse censoring method. **LDL was divided into tertiles, and the lower tertile value was used as cut-off value. Patients with LDL under that value were compared to those above this value. We compared the lower tertile to the two upper ones using a single threshold value since we believe that low LDL (<110) is a strong predictor of mortality even when it is compared to patients with LDL > 110.**

The mean age was used to divide the age into categories, above and under the mean age. The independent samples t-test and the Mann–Whitney test were used to compare continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test. Kaplan Meier curves were used to describe mortality over time, and the log-rank test was used to compare between categories. The multivariate cox regression was used to evaluate associations between LDL categories and all-cause mortality. The multivariate cox regression was comprised of three blocks: the first block included the LDL category to describe the crude association, the second block included age and gender to describe the association after controlling for age and gender, and the third block included variables that were selected using a backward stepwise method (likelihood ratio as criteria). Hypertension (HTN), diabetes mellitus (DM), ischemic heart disease or myocardial infarction (IHD/MI), left ventricular ejection fraction (LVEF), valve disease, chronic atrial fibrillation(CAF), transient ischemic attack or cerebrovascular accident (TIA/CVA), percutaneous transluminal coronary angioplasty or coronary aortic bypass graft (PTCA/CABG), smoking status, New York Heart Association (NYHA) class, creatinine, albumin, CRP, **Triglycerides** and Nt-proBNP were considered for inclusion in the third block. We repeated the regression separately in patients under 70 years of age and in older patients. All statistical tests were two-tailed. A P level < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

Results

A total of 334 consecutive outpatients diagnosed as having HF, and treated in the heart failure unit, were found suitable to be enrolled in the study according to the exclusion and inclusion criteria. Of them, 29 were excluded because of noncompliance or absence of follow-up information. The remaining 305 patients comprised the study cohort. Their mean follow-up was 11.3 years. The duration of HF ranged from 15 months to 20.5 years. Table 1 describes the general patient characteristics, including their demographic and clinical data, comorbidities, mediations and functional NYHA class. The patients' mean age was 70.3 **years (range 38–90), 73.8% were males, 74% had ischemic cardiomyopathy, 18.4 had valvular disease: (9% had aortic stenosis, 5.4% had mitral regurgitation due to left ventricular dilatation, 3% had tricuspid insufficiency due to left heart failure and 1% had calcified mitral stenosis)** and 72% had systolic dysfunction. The mean LVEF was 35% and their mean NYHA was 2.7. The mean number of clinical visits during follow-up was 24.3. Forty percent of the patients had a confirmed diagnosis of type 2 diabetes mellitus, 60.2% had HTN and 30.5% were smokers. To determine the predictive value of LDL on mortality, we divided the study patients into two groups according to LDL-c levels: levels: ≤110 mg/dl for Group 1 and > 110 mg/dl for Group 2. The demographic data demonstrated that the Group 1 patients were slightly younger than those in Group 2 (69 vs. 72 years old, respectively), but that they did not differ in any of the clinical or laboratory characteristics except for lipid profile, monocytes and diuretic treatment. There were no differences in the prevalence of NIDDM, HTN, IHD, C-reactive protein and or even in N- terminal pro b- type natriuretic peptide (Nt-proBNP). Table 2 lists the patients' characteristics according to LDL cholesterol (≤110 mg/dl and >110 mg/dl).

Figure 1 displays the Kaplan–Meier survival curves which showed significant differences according to LDL cholesterol levels below and above 110 mg/dl in all of the patients during the 20 years of follow-up: patients with higher LDL-c survived 21% more than those with LDL less than 110 mg/dl. In addition, there were more prominent differences in the Kaplan–Meier survival

Table 1. General demographic, clinical and laboratory data

Characteristics	($n = 305$)
Demographic	
Age (y)	70.3 (10.6)
≤70	122 (40.0%)
>70	183 (60.0%)
Male	225 (73.8%)
Weight (kg)	77.3 (15.8)
Smoker	93 (30.5%)
Functional status	
NYHA Class	2.7 (2–3)
Echocardiogram	
LVEF %	35 (25–49.5)
Comorbidities	
Hyperlipidemia	187 (61.3%)
Hypertension	183 (60.2%)
Diabetes mellitus	122 (40.0%)
IHD/MI	231 (75.7%)
Valve disease	56 (18.4%)
Atrial fibrillation	73 (23.9%)
TIA/CVA	39 (12.8%)
PTCA/CABG	151 (49.5%)
Medications	
Coumadin	60 (19.7%)
Aspirin	180 (59.0%)
Statin	167 (54.8%)
ACEi	148 (48.5%)
ARb	67 (22.0%)
Plavix	26 (8.5%)
Nitrate	109 (35.7%)
Calcium-blocker	49 (16.1%)
Beta-blocker	185 (60.7%)
Insulin	21 (6.9%)
Oral hypoglycemic drugs	71 (23.3%)
Alpha blocker	53 (17.4%)
Bezafibrate	18 (5.9%)
Anti-arrhythmic	52 (17.0%)
Digoxin	68 (22.3%)
Aldactone	163 (53.4%)
Diuretic	245 (80.3%)
Blood tests	
Cholesterol	179 (159–203)
LDL mg/dl	127.2 (38.2)
≤110	98 (32.1%)
>110	207 (67.9%)
HDL mg/dl	44.6 (11.2)
Triglycerides mg/dl	131 (95–194)
Creatinine mg/dl	1.5 (1.2–2.0)
Albumin mg/l	41.1 (4.4)
C- reactive protein mg/dl	3.9 (1.5–9.0)
Hemoglobin g%	12.9 (1.7)
Monocytes %	9 (6–14)
NT-proBNP	1560 (657–4328)

Categorical variables are presented as n(%) and continuous variables are presented as mean (SD) or median (IQR).

NYHA, New York Heart Association; IHD/MI, Ischemic Heart Disease/Myocardial Infarction; TIA/CVA, Transient Ischemic Attack/Cerebrovascular Accident; ACE I, angiotensine converting enzyme Inhibitor; NT-proBNP, N-terminal prohormone brain natriuretic peptide.

curves for patients under 70 years old or younger as **compared to those above 70 where the differences were not significant (Figure 2a and b) during a period of** 6 years survival of patients ≤70 years with LDL ≤110 was 88% as compared to 68% in mixed patients group.

Table 2. Patients demographic, clinical and laboratory data according to LDL-c

	LDL mg/dl		
	≤110 ($n = 98$)	>110 ($n = 207$)	*P*-value
Demographic			
Age (year)	72.6 (10.02)	69.2 (10.7)	0.009
Male	77 (78.6%)	148 (71.5%)	0.190
Weight	77.8 (16.64)	77.07 (15.41)	0.711
Smoker	29 (29.6%)	64 (30.9%)	0.814
Functional status			
NYHA	3 (2–3)	3 (2–3)	0.741
LVEF	35 (25–50.25)	35 (25–46)	0.657
Comorbidities			
Hyperlipidemia	60 (61.2%)	127 (61.4%)	0.983
HTN	61 (62.2%)	122 (59.2%)	0.615
DM	36 (36.7%)	86 (41.5%)	0.423
IHD/MI	76 (77.6%)	155 (74.9%)	0.611
Valve disease	17 (17.3%)	39 (18.8%)	0.753
CAF	26 (26.5%)	47 (22.7%)	0.465
TIA/CVA	15 (15.3%)	24 (11.6%)	0.365
PTCA/CABG	44 (44.9%)	107 (51.7%)	0.268
Medications			
Coumadin	18 (18.4%)	42 (20.3%)	0.693
Aspirin	64 (65.3%)	116 (56.0%)	0.124
Statin	61 (62.2%)	106 (51.2%)	0.071
Acein	52 (53.1%)	96 (46.4%)	0.275
ARB	20 (20.4%)	47 (22.7%)	0.651
Plavix	9 (9.2%)	17 (8.2%)	0.777
Nitrate	36 (36.7%)	73 (35.3%)	0.803
Ca-blocker	13 (13.3%)	36 (17.4%)	0.359
Beta-blocker	62 (63.3%)	123 (59.4%)	0.521
Insulin	8 (8.2%)	13 (6.3%)	0.544
Oral hypoglycemic	23 (23.5%)	48 (23.2%)	0.957
Alpha blocker	17 (17.3%)	36 (17.4%)	0.992
Bezafibrate	5 (5.1%)	13 (6.3%)	0.683
Anti-arrhythmic	18 (18.4%)	34 (16.4%)	0.674
Digoxin	17 (17.3%)	51 (24.6%)	0.153
Aldactone	56 (57.1%)	107 (51.7%)	0.373
Diuretic	86 (87.8%)	159 (76.8%)	0.025
Blood tests			
LDL mg/dl	87.1 (17.4)	146.1 (29.7)	
Cholesterol mg/dl	166 (144–187)	184 (165–214)	<0.001
HDL mg/dl	42.7 (12.1)	45.5 (10.6)	0.039
Triglycerides	120 (91–189)	138 (100–199)	0.061
Creatinine mg/dl	1.5 (1.2–2.0)	1.5 (1.2–2.0)	0.598
Albumin mg/l	41.7 (3.7)	40.8 (4.6)	0.083
CRP mg/dl	4.1 (1.4–8.3)	3.9 (1.5–9.0)	0.802
Hgb g/%	12.9 (1.6)	13.0 (1.7)	0.649
Monocytes%	8.0 (5.0–11.0)	10.5 (6.4–16.0)	<0.001
NT Pro-BNP (pg/ml)	1439 (565–4168)	1620 (704–4374)	0.443

Categorical variables are presented as *n* (%) and continuous variables are presented as mean (SD) or median (IQR).

NYHA, New York Heart Association; IHD/MI, Ischemic Heart Disease/Myocardial Infarction, TIA/CVA, Transient Ischemic Attack/Cerebrovascular Accident; ACE I, angiotensine converting enzyme Inhibitor, NT-proBNP, N-terminal prohormone brain natriuretic peptide.

Regarding the patients with valvular disease there were no differences in survival according to LDL-c: survival of the patients with LDL ≤ 110 mg/dl was 53% at the 20 years follow up, and survival of those with LDL> 110 mg/dl was 55% (P > 0.24).

Table 3 displays the univariate and multivariate analysis of the association between LDL-c and mortality in both study

groups. The adjusted (for different clinical and demographic parameters) hazard ratio (HR) **of 1.479** ($P = 0.037$) was the highest between LDL and mortality. The LVEF and NYHA class for Group 2 had lower HRs (0.985 and 1.516, respectively, $P < 0.03$) than for Group 1. The univariate and multivariate analyses of the association between LDL-c and mortality for the patients ≤70 years of age revealed that the HR for LDL-c was even higher, reaching a value of 4.475 ($P = 0.002$) (Table 4) in comparison to older patients –aged above 70 were HR did not reach significance ($P > 0.05$). Other significant HR in this group was seen only in pro BNP –1.009, $P = 0.015$, NYHA class 2.650, $P = 0.032$ and CAF-HR –3.780, $P = 0.027$.

There were no significant differences with respect to mortality in association with total cholesterol levels**, triglycerides** and HDL-c levels which are associated with longer survival in ischemic heart disease.[3,4,9,13]

To determine group differences in survival, we separately examined patients who were treated with statins separately according to the age (≤ 70 and> 70 years old) from those who were not: the former showed the same pattern as the entire cohort taken together (adjusted to risk factor-related diseases, revascularization procedures and NYHA class). Thirty two percent of patients ≤ 70 years old who were treated with statins(LDL ≤ 110) showed 32% 20 years survival (Figure 3a), whereas patients > 70 years old and a higher LDL > 110 level was associated with better prognosis- 63% 20 years survival (Figure 3b).

Forty-three percent of the patients died during the 20-year follow-up. The LDL-c levels of the patients who died were significantly lower ($P < 0.002$) compared to the levels of those who were alive at the end of the follow-up period.

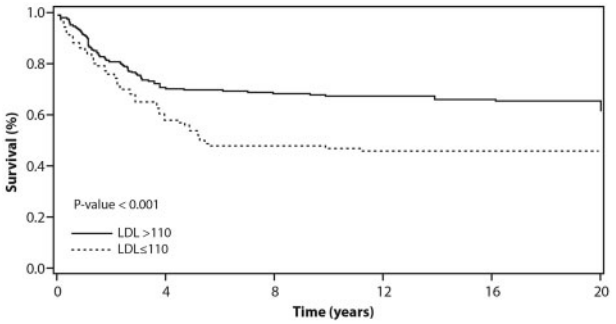

Figure 1. Cox regression curves comparing the survival of patients with LDL ≤ 110 and >110 mg/dl, adjusted for age, gender, LVEF, NYHA FC and CCT (entire cohort, $n = 305$).

Discussion

Similarly to short-term reports on patients with HF,[8,10–13,17–19] the results of the current long-term study showed that low

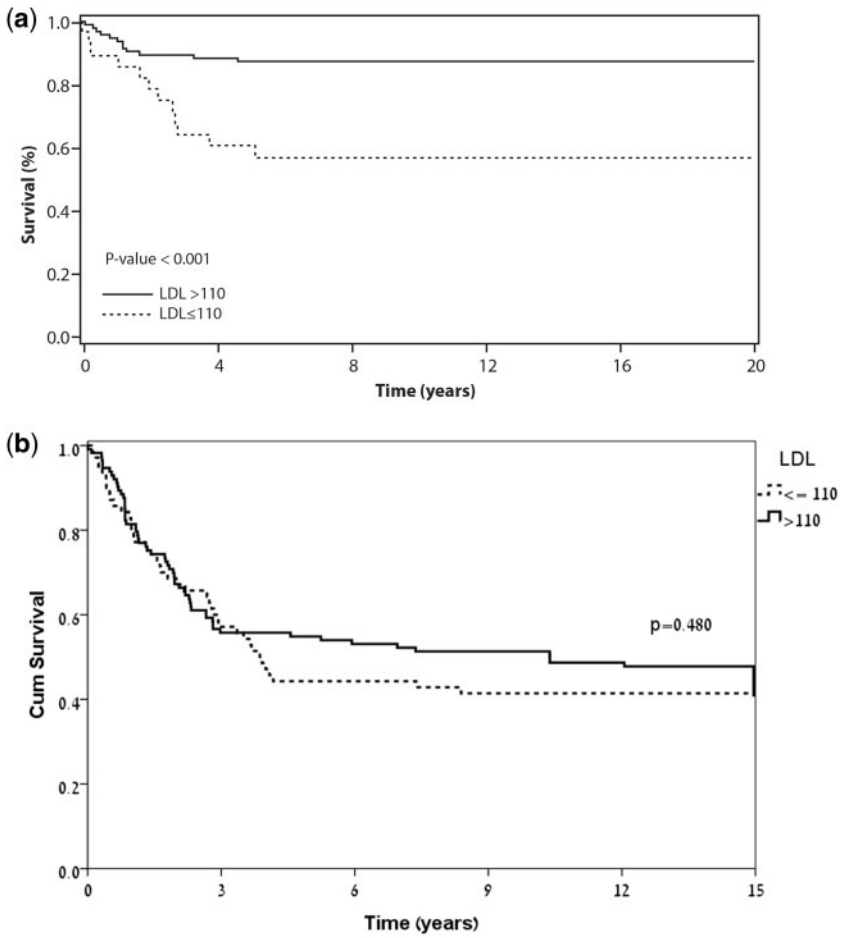

Figure 2. (**a**) Cox regression curves comparing the survival of patients aged 70 and under, with LDL ≤ 110 and >110 mg/dl, adjusted for age, gender, LVEF, NYHA class, and CCT (IHD cohort, $n = 142$). (**b**) Cox regression curves comparing the survival of patients above 70 years of age with LDL ≤ 110 and LDL >110 mg/dl, adjusted for age, gender, LVEF, NYHA class and CCT (IHD cohort, $n = 163$).

Table 3. Univariate and multivariate analysis of the association between LDL cholesterol and mortality for the entire cohort

Type of analysis	Parameter	HR (95% CI)	*P*-value
Crude	LDL ≤110 mg/dl	1.784 (1.243–2.559)	0.002
Multivariate[a]	LDL mg/dl ≤110	1.377 (0.957–1.983)	0.085
	Age	1.094 (1.070–1.118)	<0.001
	Male	1.290 (0.844–1.972)	0.239
Multivariate[b]	LDL ≤110	1.479 (1.024–2.137)	0.037
	Age	1.066 (1.061–1.115)	<0.001
	Male	1.206 (0.783–1.858)	0.395
	NYHA	1.516 (1.072–2.145)	0.019
	LVEF	0.985 (0.971–0.998)	0.026
	DM	1.683 (1.161–2.439)	0.006
	CAF	1.548 (1.048–2.288)	0.028
	Nt pro-BNP/ 1000 pg/ml	1.004 (1.001–1.007)	0.004

[a]Enter method: age, gender, LDL.
[b]Enter method: age, gender, LDL and backward stepwise using all other variables as potential for inclusion in the final model.
NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CAF, chronic atrial fibrillation; NT-pro BNP, N-terminal prohormone brain natriuretic peptide.

Table 4. Univariate and multivariate analysis of the association between LDL cholesterol and mortality in patients aged ≤70 years

Type of analysis	Parameter	HR (95% CI)	*P*-value
Crude	LDL (mg/dl) ≤ 110	3.729 (1.643–8.464)	0.002
Multivariate[a]	LDL(mg/dl) ≤ 110	4.046 (1.752–9.344)	0.001
	Age	1.069 (0.997–1.146)	0.059
	Male	0.940 (0.315–2.810)	0.912
Multivariate[b]	LDL ≤ 110	4.475 (1.748–11.458)	0.002
	Age	1.016 (0.939–1.099)	0.692
	Male	0.602 (0.179–2.022)	0.411
	NYHA	2.650 (1.087–6.460)	0.032
	DM	2.480 (0.916–6.711)	0.074
	Valve disease	0.160 (0.015–1.651)	0.124
	CAF	3.780 (1.168–12.238)	0.027
	Nt Pro BNP/ 100 (pg/ml)	1.009 (1.002–1.016)	0.015

[a]Enter method: age, gender, LDL.
[b]Enter method: age, gender, LDL and backward stepwise using all other variables as potential for inclusion in the final model.
NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CAF, chronic atrial fibrillation; NT-pro BNP, N-terminal prohormone brain natriuretic peptide.

baseline LDL-c levels (of patients who were and were not treated by statins) are a significant predictor of worse outcome in both ischemic and nonischemic HF patients. This effect was also consistently found after adjusting for multiple established clinical and laboratory predictors of HF mortality, such as Nt- proBNP, CRP albumin, creatinine, history of diabetes and others. Moderately elevated LDL-c levels remained the most significant independent predictor of better long-term survival, while low total cholesterol and was not significant in predicting mortality. Statin therapy for patients with HF who maintained lower LDL-c levels showed a similar trend of increased mortality over the entire study follow-up period as it was reported previously.[5–9,12–15,23–27]

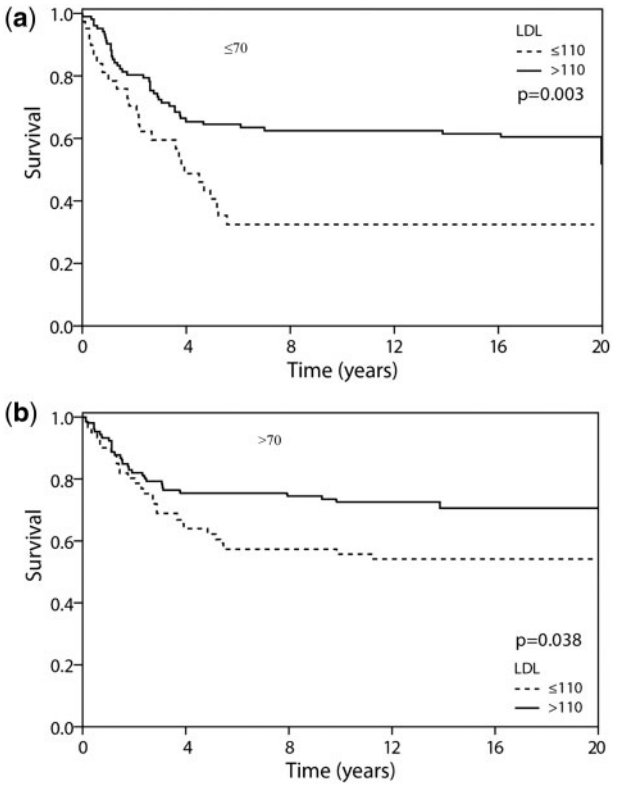

Figure 3. (**a**) Cox regression curves comparing the survival of patients treated by statins with the survival of patients who did not receive statins aged≤ 70 years ($n = 139$) adjusted with adjustment for age, gender, LVEF, NYHA FC, CCT. (**b**) Cox regression curves comparing the survival of patients treated by statins with the survival of those patients who did not receive statins aged >70 years ($n = 166$), adjusted with adjustment for age, gender, LVEF, NYHA FC, CCT.

Horwich *et al.*[19] showed an inverse relation between total cholesterol and mortality in patients with HF and systolic dysfunction. Several studies on elderly populations demonstrated that lower LDL-c levels were associated with an increase in all-cause mortality.[28,29]

Lipids and lipoproteins may play a protective role in HF by modulating the inflammatory markers, such as CRP, cytokines, oxidized LDL, TNF-alpha and interleukin 6.[18,25,30,31] Earlier reported pleiotropic effects of LDL cholesterol can bind the endotoxin and liposaccharide components of infectious agents which are more common in severe HF (e.g. bacteria that enter across the edematous epithelium of the bowel) and neutralize them by detoxification, thus inducing down-regulation of an inflammatory process, and deactivate these destructive leukotrienes and cytokines.[18,32] Overall, these studies suggest that LDL-c has protective functions against all different kinds of infections.

In contrast to other similar studies,[9,26,27,32,33] while patients in the current study had various levels of LDL–c, they tested as having similar and normal levels of albumin, creatinine, hemoglobin and body mass index, all of which are established markers of the nutritional state and normal CRP levels. These factors are thus not likely to have biased our findings. Cardiac cachexia alone as result of advanced HF may not fully explain the paradoxical association of LDL-c and survival.[18]

We believe that the main mechanism that predicts survival in HF patients is not ischemic but pump failure, which is the final stage of coronary artery disease. Our longitudinal study

confirms that low LDL-c levels are an adverse prognostic factor in advanced HF, and it also extends these findings to include ischemic and non-ischemic patients as well as those with decreased, as well as preserved, LVEF. These findings are especially relevant to the guidelines which suggest that patients with a low LVEF due to severe coronary atherosclerosis require an aggressive lipid-lowering pharmacological approach. Further studies will be needed to resolve this apparent paradox, but such research will be difficult to perform because of the current widespread use of statins for the treatment of patients with atherosclerosis.

Conclusion

The long-term results of the current study showed that lower levels of LDL-c were associated not only with unfavorable prognosis, as had been widely reported, but also with worse long-term outcome in a population of patients with advanced and clinically controlled HF. They were particularly prominent for the group of patients under 70 years of age and the patients taking statins. Our findings oppose the use of an aggressive LDL-c-lowering strategy in patients with HF.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Tel Aviv Medical Center. It is registered at Clinical Trials.gov, registration number NCT01601444. All participants provided written informed consent prior to data collection.

Competing interests

The authors declare that they have no competing interests whatsoever.

Availability of data and materials statement

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Acknowledgements

Esther Eshkol, MA, the institutional medical and scientific copyeditor, is being thanked for editorial assistance. This study was funded by internal departmental resources.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest: None declared.

References

1. Lenfant C. Report of the task force on research in heart failure. *Circulation* 1994; **90**:1118–23.
2. Cowie MR, Mosterd A, Wood DA, Deckers JW, Poole-Wilson PA, Sutton GC, *et al*. The epidemiology of heart failure. *Eur Heart J* 1997; **18**:208–25.
3. Ford I, Murray H, Packard CJ, Shepherd J, Macfarlane PW, Cobbe SM. Long-term follow-up of the west of Scotland coronary prevention study. *N Engl J Med* 2007; **357**:1477–86.
4. Pedersen TR, Kjekshus J, Berg K, Haghfelt T, Faergeman O, Faergeman G, *et al*. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. *Atheroscler Suppl* 2004; **5**:81–7.
5. Raina A, Pickering T, Shimbo D. Statin use in heart failure: a cause for concern? *Am Heart J* 2006; **152**:39–49.
6. Song XJ, Yang CY, Liu B, Wei Q, Korkor MT, Liu JY, *et al*. Atorvastatin inhibits myocardial cell apoptosis in a rat model with post-myocardial infarction heart failure by downregulating ER stress response. *Int J Med Sci* 2011; **8**:564–72.
7. Tousoulis D, Charakida M, Stefanadi E, Siasos G, Latsios G, Stefanadis C. Statins in heart failure. Beyond the lipid lowering effect. *Int J Cardiol* 2007; **115**:144–50.
8. Khush KK, Waters DD. Effects of statin therapy on the development and progression of heart failure: mechanisms and clinical trials. *J Card Fail* 2006; **12**:664–74.
9. Sakatani T, Shirayama T, Suzaki Y, Yamamoto T, Mani H, Kawasaki T, *et al*. The association between cholesterol and mortality in heart failure. Comparison between patients with and without coronary artery disease. *Int Heart J* 2005; **46**: 619–29.
10. von Haehling S, Okonko DO, Anker SD. Statins: a treatment option for chronic heart failure? *Heart Fail Monit* 2004; **4**:90–7.
11. Silva S, Lourenço P, Paulo C, Ferreira E, Lebreiro A, Sousa A, *et al*. Statin-induced low cholesterol is not associated with poor outcome in chronic heart failure. *J Cardiovasc Pharmacol Ther* 2012; **17**:284–90.
12. Krum H, Latini R, Maggioni AP, Anand I, Masson S, Carretta E, *et al*. Statins and symptomatic chronic systolic heart failure: a post-hoc analysis of 5010 patients enrolled in Val-HeFT. *Int J Cardiol* 2007; **119**:48–53.
13. Go AS, Lee WY, Yang J, Lo JC, Gurwitz JH. Statin therapy and risks for death and hospitalization in chronic heart failure. *JAMA* 2006; **296**:2105–11.
14. Martin JH, Krum H. Statins and clinical outcomes in heart failure. *Clin Sci* 2007; **113**:119–27.
15. Krum H, Ashton E, Reid C, Kalff V, Rogers J, Amarena J, *et al*. Double-blind, randomized, placebo-controlled study of high-dose HMG CoA reductase inhibitor therapy on ventricular remodeling, pro-inflammatory cytokines and neurohormonal parameters in patients with chronic systolic heart failure. *J Card Fail* 2007; **13**:1–7.
16. Böhm M, Hjalmarson A, Kjekshus J, Laufs U, McMurray J, van Veldhuisen DJ. Heart failure and statins–why do we need a clinical trial? *Z Kardiol* 2005; **94**:223–30.
17. Clearfield M. Rosuvastatin in older patients with systolic heart failure. *Curr Atheroscler Rep* 2009; **11**:5–6.
18. Lv Y-B, Yin Z-X, Chei C-L, Qian H-Z, Kraus VB, Zhang J, *et al*. Low-density lipoprotein cholesterol was inversely associated with 3-year all-cause mortality among Chinese oldest old: data from the Chinese Longitudinal Healthy Longevity Survey. *Atherosclerosis* 2015; **239**:137–42.
19. Horwich TB, Hamilton MA, Maclellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. *J Card Fail* 2002; **8**:216–24.
20. Cleland JGF, Loh H, Windram J, Goode K, Clark AL. Threats, opportunities, and statins in the modern management of heart failure. *Eur Heart J* 2006; **27**:641–3.
21. Domanski M, Coady S, Fleg J, Tian X, Sachdev V. Effect of statin therapy on survival in patients with nonischemic dilated cardiomyopathy (from the Beta-blocker Evaluation of Survival Trial [BEST]). *Am J Cardiol* 2007; **99**:1448–50.

22. Iwaoka M, Obata J, Abe M, Nakamura T, Kitta Y, Kodama Y, *et al*. Association of low serum levels of apolipoprotein A-I with adverse outcomes in patients with nonischemic heart failure. *J Card Fail* 2007; **13**:247–53.
23. Aronow WS, Ahn C. Frequency of congestive heart failure in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol > or = 125 mg/dl treated with statins versus no lipid-lowering drug. *Am J Cardiol* 2002; **90**:147–9.
24. Afsarmanesh N, Horwich TB, Fonarow GC. Total cholesterol levels and mortality risk in nonischemic systolic heart failure. *Am Heart J* 2006; **152**:1077–83.
25. Richartz BM, Radovancevic B, Frazier OH, Vaughn WK, Taegtmeyer H. Low serum cholesterol levels predict high perioperative mortality in patients supported by a left-ventricular assist system. *Cardiology* 1998; **89**:184–8.
26. Fraunberger P, Nagel D, Walli AK, Seidel D. Serum cholesterol and mortality in patients with multiple organ failure. *Crit Care Med* 2000; **28**:3574–5.
27. Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, *et al*. Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA* 2004; **291**:451–9.
28. Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet* 2001; **358**: 351–5.
29. Tikhonoff V, Casiglia E, Mazza A, Scarpa R, Thijs L, Pessina AC, *et al*. Low-density lipoprotein cholesterol and mortality in older people. *J Am Geriatr Soc* 2005; **53**:2159–64.
30. Anand IS, Latini R, Florea VG, Kuskowski MA, Rector T, Masson S, *et al*. C-reactive protein in heart failure: prognostic value and the effect of valsartan. *Circulation* 2005; **112**: 1428–34.
31. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL. Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). *Circulation* 2001; **103**:2055–9.
32. Harris HW, Grunfeld C, Feingold KR, Rapp JH. Human very low density lipoproteins and chylomicrons can protect against endotoxin-induced death in mice. *J Clin Invest* 1990; **86**:696–702.
33. Christ M, Klima T, Grimm W, Mueller H-H, Maisch B. Prognostic significance of serum cholesterol levels in patients with idiopathic dilated cardiomyopathy. *Eur Heart J* 2006; **27**: 691–9.