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The Relationship Between Cholesterol and Survival in Patients With Chronic Heart Failure

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OBJECTIVES We sought to describe the relationship between cholesterol and survival in patients with chronic heart failure (CHF).

BACKGROUND Increasing lipoprotein levels are a cardiovascular risk factor. In patients with CHF, the prognostic value of endogenous lipoproteins is not fully clarified.

METHODS A group of 114 patients with CHF recruited to a metabolic study was followed for a minimum of 12 months (derivation study). The results were applied to a second group of 303 unselected patients with CHF (validation study). The relationship between endogenous lipoproteins and survival was explored.

RESULTS In the derivation study, survival at 12 months was 78% (95% confidence interval [CI] 70% to 86%) and 56% (95% CI 51% to 62%) at 36 months. Increasing total serum cholesterol was a predictor of survival (hazard ratio 0.64, 95% CI 0.48 to 0.86), independent of the etiology of CHF, age, left ventricular ejection fraction, and exercise capacity. Receiver-operating characteristic curves demonstrated a best cut-off value of ≤5.2 mmol/l (200.8 mg/dl) as being the best predictor of mortality at 12 months (sensitivity 80.0%, specificity 62.9%). In the validation population, one-year survival was 88% (95% CI 84 to 91%) and three-year survival was 68% (95% CI 63 to 73%). The chance of survival increased 25% for each mmol/l increment in total cholesterol. Survival rates above and below the cut-off value for cholesterol in patients with ischemic heart disease (n = 181) were 92% (95% CI 89 to 94) versus 75% (95% CI 64 to 85%) at one year and 72% (95% CI 67 to 76%) versus 50% (95% CI 43 to 56%) at three years.

CONCLUSIONS In patients with CHF, lower serum total cholesterol is independently associated with a worse prognosis. (J Am Coll Cardiol 2003;42:1933–40) © 2003 by the American College of Cardiology Foundation

Coronary heart disease is a world-wide health care problem. Cholesterol is a major adverse risk factor for the development of coronary heart disease, and cholesterol reduction therapy with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) has been shown to be beneficial in both primary and secondary prevention of coronary heart disease (1,2). The risk of developing chronic heart failure (CHF) is strongly associated with the presence of coronary heart disease (3,4), and the use of a statin has been shown to prevent the development of new-onset CHF (5). There is, however, no evidence of either a benefit or harm with statin therapy in patients who have already developed CHF. There are theoretical concerns about statins in CHF (6), and the presence of CHF was an exclusion criterion in all of the landmark statin studies. The relationship between cholesterol and survival in CHF has not been fully established.

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We have hypothesized that low serum cholesterol may be a marker of impaired prognosis in patients with CHF (7). Patients with CHF have a diffuse increase in indices of immune activity, which is potentially linked to higher than normal levels of endotoxin (8). Lipoproteins are natural nonspecific buffers of endotoxin; binding to endotoxin (lipopolysaccharide [LPS]) leads to reduced LPS bioactivity and to diminished immune activation. Preliminary reports have suggested that there is an increased mortality in CHF patients with low cholesterol (9,10). A more recent article has confirmed these findings in a larger population (11).

The objective of the present study was to explore and validate the relationships between cholesterol and triglyceride levels and all-cause mortality in a large CHF population.

METHODS

Study population. All patients with CHF were recruited from the Royal Brompton Hospital Chronic Heart Failure and Cardiomyopathy Clinic. The studies were approved by the local ethics committee, and all participants had given written, informed consent. The diagnosis of CHF was

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Abbreviations and Acronyms

CHF	= chronic heart failure
CI	= confidence interval
HDL	= high-density lipoprotein
HMG-CoA	= 3-hydroxy-3-methylglutaryl coenzyme A
HR	= hazard ratio
LDL	= low-density lipoprotein
LPS	= lipopolysaccharide
LVEF	= left ventricular ejection fraction
ROC	= receiver-operating characteristics
sTNF-R1	= soluble tumor necrosis factor receptor type 1
V_{O_2}	= oxygen consumption
V_E/V_{CO_2} slope	= slope of the relationship between ventilation and carbon dioxide production

based on standard criteria (12). The duration of CHF was between 6 months and 20 years. Cardiac cachexia was defined as weight loss >7.5% over a period of more than six months, as described previously (13). We first investigated a population of patients who had undergone metabolic evaluation to explore the relationship between cholesterol and mortality (derivation study), and then we applied this to a wider group of patients with CHF (validation study).

Derivation study. Between January 1992 and July 1999, we recruited 114 CHF patients (New York Heart Association [NYHA] functional class I/II/III/IV: 11/34/54/15; 4 females) into our metabolic study programs, aiming at one-third of the patients being cachectic (n = 38). Patients were excluded from the study if they had clinical signs of acute infection, rheumatoid disease, or myocardial infarction within the previous 12 months, or if there was a clinical suspicion of a malignant or primary wasting disorder. Patients with metabolic disorders affecting lipoprotein metabolism (e.g., thyroid disease, severe liver disease) or those with excessive alcohol intake were also excluded. Effectively, no patient was excluded based on a criterion of no myocardial infarction within the previous 12 months. If a patient was not studied in the derivation study, he or she could still have been included in the validation study. If a patient had several metabolic assessments, the earliest available information was used.

All patients performed a maximal treadmill exercise test (modified Bruce protocol, Amis 2000, Odense, Denmark) for measurement of peak oxygen consumption (V_{O_2}, ml/kg per min) and the slope of the relationship between ventilation and carbon dioxide production (V_E/V_{CO_2} slope) (14,15). Left ventricular ejection fraction (LVEF) was measured by radionuclide ventriculography. All patients were treated with medical therapy thought to be optimal for their individual CHF profile at that time. Overall, patients received diuretics (94%), angiotensin-converting enzyme inhibitors (91%), aspirin (53%), digoxin (40%), nitrates (37%), amiodarone (26%), statins (18%), calcium channel antagonists (11%), and beta-blockers (4%) in varying combinations.

On the assessment day, blood samples (25 ml) were collected between 9 and 10 AM, after an overnight fast of at least 12 h. Blood was drawn following supine rest for at least 20 min. Serum samples for the measurement of lipoproteins and routine biochemical variables were analyzed within 1 h. Plasma aliquots, following immediate centrifugation, were stored at −70°C until analysis. Plasma concentrations of soluble tumor necrosis factor receptor type 1 (sTNF-R1, sensitivity 25 pg/ml) were determined by a sandwich ELISA from R&D Systems (Minneapolis, Minnesota) (16). All other biochemical analyses were performed using routine hospital analyses.

Validation study. To assess the validity of our findings, we recruited a second independent population of patients with CHF. This population consisted of outpatients who were not recruited into metabolic studies, but in whom nonfasting serum levels of total cholesterol and high-density lipoprotein (HDL) cholesterol had been determined as part of the routine outpatient procedure between January 1993 and June 1999 (n = 303). If a patient had several assessments, the earliest available information was used. We tested the predictive power of total cholesterol and HDL levels using the results from the derivation study.

Follow-up. Patients in both the derivation and validation studies were followed up by outpatient assessments, by telephone contact between the patient or his or her local physician, or through the Hospital Information System in July 2000. Survival status was also obtained from the Office of National Statistics, where all patients had been flagged for death as part of the Royal Brompton Hospital Chronic Heart Failure Registry. The primary end point of the study was all-cause mortality. Follow-up was censored at 36 months.

Determination of lipoproteins. Serum total cholesterol, HDL cholesterol, and triglyceride levels were measured by routine hospital analyses (SYNCHRON CX Systems CX MULI Calibrator, Beckman Coulter, Inc., Fullerton, California). Low-density lipoprotein (LDL) cholesterol was also calculated (17). Assessments of lipoproteins were performed at the beginning of the follow-up period.

Statistical analysis. Data are expressed as the mean value ± SE. Normality of distribution for continuous variables was tested using the Kolmogorov-Smirnov test. The unpaired Student *t* test was used to compare mean values between groups. Proportions were compared using the chi-square and Fisher exact test. Cox proportional hazards analyses were used to assess prognostic associations. The hazard ratio (HR) with 95% confidence interval (CI) and p values by the likelihood ratio test are presented. Hazard ratios for continuous variables apply per unit of the analyzed variable. Kaplan-Meier cumulative survival plots were constructed to illustrate the results (StatView version 5.0, Abacus Concepts, Berkeley, California).

To compare different predictive values at a particular time

Table 1. Clinical and Biochemical Characteristics of Patients in the Derivation Study

Variable	All Patients (n = 114)	12 Months		36 Months	
		Nonsurvivors (n = 25)	Survivors (n = 89)	Nonsurvivors (n = 39)	Survivors (n = 50)
Age (yrs)	63.0 ± 1.0	66.3 ± 2.2	61.6 ± 1.1	66 ± 1.5¶	58 ± 1.5
BMI (kg/m^2)	24.8 ± 0.4	23.4 ± 0.8	25.2 ± 0.5	23.7 ± 0.6†	25.6 ± 0.6
Mean arterial pressure (mm Hg)	88.4 ± 1.2	88.0 ± 3.0	88.5 ± 1.3	87.8 ± 2.5	88.0 ± 1.7
Sodium (mmol/l)	137.0 ± 0.3	135.7 ± 0.9	137.2 ± 0.3	135.7 ± 0.6§	137.7 ± 0.4
Potassium (mmol/l)	4.0 ± 0.04	4.0 ± 0.12	4.0 ± 0.04	4.1 ± 0.09	3.9 ± 0.04
ESR (mm/h)	22 ± 2	30.7 ± 5.4†	19.6 ± 1.8	29.7 ± 4¶	15.0 ± 1.6
sTNF-R1 (pg/ml)	1,495 ± 90	2,207 ± 196‡	1,295 ± 92	2,081 ± 145‡	992 ± 99
BUN (mmol/l)	4.8 ± 0.3	7.1 ± 0.6‡	4.2 ± 0.3	6.7 ± 0.5‡	3.6 ± 0.3
Peak V_{O_2} (ml/kg per min)	17.0 ± 0.6	11.2 ± 0.8‡	18.1 ± 0.7	12.4 ± 0.6‡	19.7 ± 0.9
V_E/V_{CO_2} slope	39.3 ± 1.4	48.7 ± 3.6§	37.3 ± 1.5	48.6 ± 2.9‡	33.2 ± 1.7
LVEF (%)	29.0 ± 1.0	20.6 ± 2.4§	31.5 ± 1.6	23.2 ± 2.2§	30.2 ± 2.2
Total cholesterol (mmol/l)	5.2 ± 0.1	4.56 ± 0.20¶	5.44 ± 0.12	4.90 ± 0.16§	5.70 ± 0.16
HDL cholesterol (mmol/l)	1.2 ± 0.04	1.2 ± 0.1	1.2 ± 0.0	1.2 ± 0.1	1.2 ± 0.1
LDL cholesterol (mmol/l)	3.3 ± 0.1	2.80 ± 0.16§	3.39 ± 0.11	3.02 ± 0.14§	3.65 ± 0.14
Triglycerides (mmol/l)	1.7 ± 0.1	1.2 ± 0.1§	1.9 ± 0.2	1.5 ± 0.1†	2.0 ± 0.2
NYHA class* (n)					
I	11	0	11	0	9
II	34	3	31	7	16
III	54	14	40	21	22
IV	15	8	7	11	3
Etiology (%)					
IHD	62	56	64	64	56
DCM	38	44	36	36	44
Cachexia (%)	33	60	26*	54	24*
Medication (%)					
Loop diuretic	90	92	90	95	92
ACE inhibitor	91	88	92	90	96
Calcium channel blocker	11	9	11	8	14
Digoxin	40	44	39	51	40
Amiodarone	26	20	28	28	28
Beta-blocker	4	0	4	0	4
Lipid lowering	18	16	19	10	14
Aspirin	53	44	55	44	54

*$p < 0.01$ survivors versus nonsurvivors by the Fisher exact test; †$p < 0.05$, ‡$p < 0.0001$, §$p < 0.01$, ¶$p < 0.001$ survivors versus nonsurvivors. The difference in NYHA class distribution was significant at both time points. Data are presented as the mean value ± SEM or number or percentage of subjects.

ACE = angiotensin-converting enzyme; BMI = body mass index; BUN = blood urea nitrogen; DCM = dilated cardiomyopathy; ESR = erythrocyte sedimentation rate; HDL and LDL = high- and low-density lipoprotein, respectively; IHD = ischemic heart disease; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; V_E/V_{CO_2} = relationship between ventilation and carbon dioxide production; V_{O_2} = oxygen consumption.

point, areas under the curve for sensitivity and specificity were constructed. The best prognostic cut-off value for survival status at a given time point was defined as that which gave the highest product of sensitivity and specificity (MedCalc, version 5.0, MedCalc Software, Mariakerke, Belgium). For both sets of patients, the analysis was retrospective.

RESULTS

Derivation study. The characteristics of the patients at baseline and after subgrouping into survivors and nonsurvivors are given in Table 1. A minimum follow-up of 12 months (mean 31 ± 0.9 months, median 36, range 12 to 36) was achieved for survivors. Survival at 12 months was 78% (95% confidence interval [CI] 70 to 86%) and 56% (95% CI 51 to 62%) at 36 months.

Total cholesterol was normally distributed (range 2.59 to 9.05 mmol/l) and was not related to NYHA class, etiology of CHF (nonischemic: 5.3 ± 0.2 mmol/l [204.6 ± 7.7 mg/dl]; ischemic: 5.2 ± 0.1 mmol/l [200.8 ± 3.9 mg/dl]; $p = 0.7$), the presence of cachexia (cachectic: 5.0 ± 0.2 mmol/l [193.1 ± 7.7 mg/dl]; noncachectic: 5.4 ± 0.1 mmol/l [208.5 ± 3.9 mg/dl]; $p = 0.07$), or age ($r = 0.009$, $p = 0.9$). There were no differences in LDL cholesterol or triglycerides between those with ischemic heart disease and those without ($p > 0.2$), but the patients with ischemic heart disease had a lower HDL cholesterol level (1.2 ± 0.0 mmol/l [46.3 ± 2.1 mg/dl] vs. 1.3 ± 0.1 mmol/l [50.2 ± 3.9 mg/dl]; $p = 0.04$).

Cachectic CHF patients (n = 38) did not differ from noncachectic patients with regard to serum total, LDL, and HDL cholesterol (all $p > 0.07$), but they had lower triglycerides (1.4 ± 0.1 vs. 1.9 ± 0.1 mmol/l [123.9 ± 8.9 vs. 168.2 ± 8.9 mg/dl], $p = 0.02$). Cholesterol was related to body mass index ($r = 0.28$, $p = 0.003$). This relationship was significant only in noncachectic patients ($r = 0.26$, $p =$

Table 2. Predictors of Survival at 36 Months in Chronic Heart Failure Patients Derivation Study

Variable	Hazard Ratio (95% CI)	p Value	Chi-Square Value	Joint Chi-Square Value
Univariate analyses				
Peak V_{O_2}	0.77 (0.70–0.84)	<0.0001	44.6	
V_E/V_{CO_2} slope	1.04 (1.02–1.05)	<0.0001	16.6	
Total cholesterol	0.64 (0.48–0.86)	0.002	9.2	
LDL	0.67 (0.48–0.93)	0.02	5.86	
TG	0.63 (0.42–0.96)	0.02	5.67	
HDL	0.91 (0.42–2.0)	0.82	0.05	
Age	1.04 (1.01–1.08)	0.006	7.47	
Cachexia	3.07 (1.63–5.77)	0.0006	11.83	
LVEF	0.96 (0.94–0.99)	0.001	10.46	
sTNF-R1	1.0006 (1.0004–1.0008)	<0.0001	20.7	
Bivariate analyses				
Peak V_{O_2}	0.79 (0.72–0.86)	<0.0001	27.8	51.6
Cholesterol	0.68 (0.51–0.91)	0.009	6.8	
LVEF	0.95 (0.93–0.98)	0.0004	12.5	24.1
Cholesterol	0.54 (0.39–0.76)	0.0003	12.9	
sTNF-R1	1.0007 (1.0006–1.001)	<0.0001	28.5	32.9
Cholesterol	0.63 (0.48–0.83)	0.0009	11.1	
Multivariate analysis				
sTNFR-1	1.00008 (1.0004–1.001)	<0.0001	21.2	74.1
Peak V_{O_2}	0.83 (0.76–0.90)	<0.0001	17.4	
LVEF	0.96 (0.93–0.99)	0.003	9.0	
Cholesterol	0.61 (0.11–0.85)	0.003	8.6	

CI = confidence interval; TG = triglycerides; other abbreviations as in Table 1.

0.02). An inverse correlation was found between serum cholesterol and sTNF-R1 ($r = -0.27$, $p = 0.005$) and, after subgrouping, in cachectic CHF patients ($r = -0.45$, $p = 0.005$), but not in noncachectic patients. Patients with serum cholesterol below the median value (5.31 mmol/l [205.0 mg/dl]) had significantly higher plasma concentrations of sTNF-R1 (1,585 ± 123 vs. 1,113 ± 91 pg/ml, $p = 0.002$).

Univariate predictors of survival at 36 months are given in Table 2. We confirmed the predictors commonly reported, including high concentrations of sTNF-R1 (16) and the presence of cardiac cachexia (13). Duration of CHF was not a mortality predictor. Low serum cholesterol predicted increased mortality. There was a 36% increase in the risk of death within three years for every mmol/l decrease in serum cholesterol. The survival for quartiles of cholesterol is shown in Figure 1. Triglycerides and LDL cholesterol also predicted survival (Table 2), but not HDL cholesterol ($p > 0.8$).

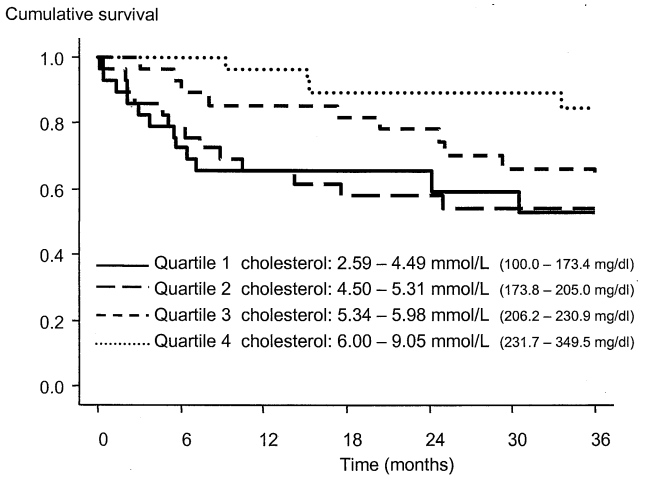

Figure 1. Survival in the derivation study with patients classified into quartiles of total cholesterol (quartile 1 being the lowest; 4 the highest). Log-rank $p = 0.0016$ for the differences between quartiles.

To explore the predictive power of cholesterol independent of established prognostic indicators, bivariate analyses demonstrated that low serum cholesterol predicted increased mortality independent of peak V_{O_2}, LVEF, sTNF-R1, age, and CHF etiology (Table 2). In each of these analyses, cholesterol was a predictor independent of age and etiology of CHF. On multivariate analysis, sTNF-R1, LVEF, peak V_{O_2}, and cholesterol jointly predicted CHF mortality independent of age ($p = 0.7$) and CHF etiology ($p = 0.7$). Triglycerides and LDL cholesterol were not predictors independent of total cholesterol.

The same variables predicted survival to one year (HR [95% CI]): peak V_{O_2} 0.75 (0.66 to 0.85), $p < 0.0001$; sTNFR-1: 1.0006 (1.0003 to 1.0009), $p < 0.0001$; cholesterol: 0.53 (0.37 to 0.76), $p = 0.0005$; and LVEF: 0.95 (0.91 to 0.98), $p = 0.003$. On multivariate analysis, all four variables were independent predictors of survival with a combined chi-square statistic of 60.6 ($p < 0.0001$).

Receiver-operating characteristic (ROC) curve analysis identified a cholesterol level ≤5.20 mmol/l (200.8 mg/dl) as being the best predictor of mortality at both 12 (sensitivity

Table 3. Clinical Details of the Patients in the Validation Study

Variable	All Patients (n = 303)	12 Months		36 Months	
		Nonsurvivors (n = 38)	Survivors (n = 265)	Nonsurvivors (n = 91)	Survivors (n = 162)
Age (yrs)	62.1 ± 0.7	64.7 ± 1.8	61.7 ± 0.7	64.0 ± 1.2	60.6 ± 0.9*
NYHA class (%)					
I	17	6	18	6	24
II	43	37	44	34	46
III	31	31	31	37	27
IV	9	26	7†	23	3‡
Etiology (%)					
IHD	60	68	58	68	59
DCM	40	32	42	34	41
Cachexia (%)	4.4	17	2.6‡	12	0.7‡
Peak Vo_2 (ml/kg/min) (n = 221)	17.3 ± 0.4	15.1 ± 1.1	17.6 ± 0.4*	14.7 ± 0.6	18.8 ± 0.5‡
LVEF (%) (n = 197)	30.4 ± 1.1	21.7 ± 1.8	31.5 ± 1.2†	21.3 ± 1.5	35.0 ± 1.5‡
Total cholesterol (mmol/l)	5.59 ± 0.07	5.01 ± 0.20	5.67 ± 0.08†	5.29 ± 0.13	5.85 ± 0.10‡
HDL cholesterol (mmol/l)	1.10 ± 0.02	0.99 ± 0.05	1.12 ± 0.03	1.00 ± 0.04	1.06 ± 0.03
Medication (%)					
Loop diuretic	81	88	80	85	80
ACE inhibitor	86	82	87	83	86
Calcium channel blocker	19	10	20	11	21
Digoxin	26	36	24	31	21
Amiodarone	17	10	18	13	12
Beta-blocker	8	6	8	2	12
Lipid lowering	20	12	21	11	21
Aspirin	53	61	55	38	60

The p values refer to comparisons between survivors and nonsurvivors at each time point: *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$. Data are presented as the mean value ± SEM or percentage of subjects.

Abbreviations as in Table 1.

80.0%, specificity 62.9%) and 36 months (sensitivity 61.5%, specificity 74%).

Validation study. Clinical data for the 303 CHF patients in the validation study are shown in Table 3. One-year survival was 88% (95% CI 84 to 91%) and three-year survival was 68% (95% CI 63 to 73%). All survivors were followed for a minimum of 12 months (average 33.4, median 36). There were 91 deaths. Serum total cholesterol (5.6 ± 1.2 mmol/l [range 2.4 to 9.0]; 216.0 ± 46.3 mg/dl [range 92.7 to 347.5]) and HDL cholesterol (1.1 ± 0.4 mmol/l [range 0.4 to 3.1]; 42.5 ± 15.0 mg/dl [range 42.5 to 119.7]) were normally distributed. Serum cholesterol was not related to body mass index ($r = 0.01$, $p = 0.44$). Cachectic and noncachectic patients did not differ in total

Table 4. Comparison of Patients Below and Above the Predetermined Cut-Off Value for Cholesterol in the Validation Study

Variable	Cholesterol (mmol/l)		p Value
	<5.2 (n = 126)	≥5.2 (n = 177)	
Age (yrs)	61.2 ± 1.1	62.7 ± 0.8	0.29
NYHA class (%)			0.21
I	16	17	
II	39	46	
III	31	30	
IV	13	6	
Etiology (%)			
IHD	63 (50)	118 (67)	0.004
DCM	63 (50)	59 (33)	
Cachexia (%)	5.4	3.7	0.52
Peak Vo_2 (ml/kg per min) (n = 221)	16.7 ± 0.7	17.7 ± 0.5	0.25
LVEF (%) (n = 197)	29.8 ± 1.8	30.8 ± 1.3	0.64
Total cholesterol (mmol/l)	4.42 ± 0.05	6.41 ± 0.06	—
One-year survival (%)	79 (72–86)	93 (89–97)	0.0013
Three-year survival (%)	59 (50–68)	75 (68–82)	0.0011

The p values refer to the unpaired *t* test for continuous variables and the chi-square test for discontinuous. The survival values are from the log-rank test. The difference in cholesterol is "significant" by definition.

Abbreviations as in Table 1.

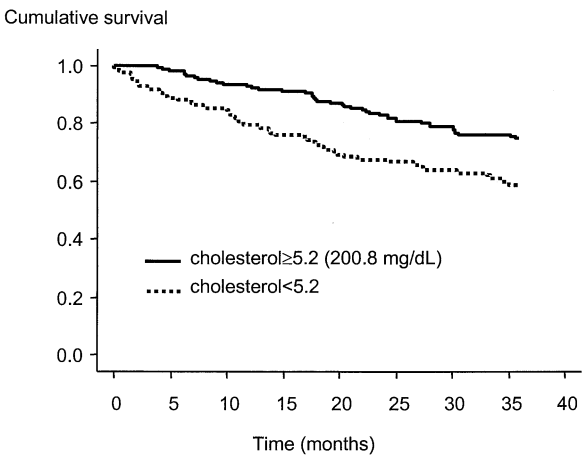

Figure 2. Survival in the validation study related to the best predictive value for serum cholesterol found in the derivation study. Log-rank p = 0.0011 for the difference between groups.

cholesterol (5.3 ± 0.5 vs. 5.6 ± 0.1 mmol/l [204.6 ± 19.0 vs. 216.2 ± 3.9 mg/dl]) and HDL cholesterol levels (1.07 ± 0.11 vs. 1.08 ± 0.02 mmol/l [41.3 ± 19.3 vs. 41.7 ± 0.8 mg/dl], both p > 0.2). Patients who died during follow-up had a lower serum cholesterol level than survivors (Table 3).

Increasing serum cholesterol predicted improved survival at 36 months (chi-square = 10.4, p = 0.001), independent of age. The chance of survival increased ~25% for each mmol/l increment in total cholesterol (relative risk 0.75 [95% CI 0.63 to 0.90]). The patients were classified into groups according to the previously determined best predictor of mortality (<5.20 vs. ≥5.2 mmol/l [200.8 mg/dl]). Comparative data are shown in Table 4, and the Kaplan-Meier survival plots are shown in Figure 2. Lower cholesterol predicted a worse outcome. Cholesterol predicted survival independent of age, LVEF, etiology, NYHA class, and peak Vo_2 (Table 5).

Figure 3 shows the survival times in patients grouped by underlying diagnosis. Although the study was not designed to investigate the influence of lipid-lowering therapy on survival from heart failure and the numbers involved were very small (20% of patients), we did combine the two groups for a single analysis of the effect of lipid-lowering therapy on survival. Treatment was associated with a greater three-year survival (82% [95% CI 77 to 87%] vs. 64% [95% CI 58 to 69%], chi-square = 5.7, p = 0.02). If the patients on statins are removed from the analysis, the relationship between cholesterol and survival is not materially altered (data not shown).

To analyze the relationship between serum cholesterol level and survival in the subgroups of cachectic and noncachectic CHF patients, we combined the two data sets. In 50 cachectic CHF patients, 31 deaths were observed and higher cholesterol levels related to longer survival (HR 0.71 [95% CI 0.53 to 0.91], p = 0.021). Also in the 367 noncachectic patients (99 deaths during follow-up), higher cholesterol levels related to longer survival (HR 0.75 [95% CI 0.63 to 0.89], p = 0.0011).

DISCUSSION

There is a host of factors related to prognosis in CHF. These factors cluster around an index of exercise capacity (such as Vo_2), an index of left ventricular function (such as ejection fraction), and an index of metabolic activity (such as cytokines). We have demonstrated a relationship between cholesterol and survival in patients with CHF. First, we explored the relationship between lipids and other variables and outcome in a smaller group of patients with moderate to severe CHF recruited into a metabolic study, and then we applied the results to a larger cohort of patients with mild to moderate CHF. The chance of survival during 36-month follow-up increased by ~36% for each mmol/l increment in total cholesterol. This finding was independent of the age of the patient, the presence of cachexia, and the etiology of the CHF.

At first sight, it might appear that cholesterol might have a deleterious effect in CHF. Cholesterol is a predictor of increased morbidity and mortality (1,18) from coronary artery disease, and coronary artery disease in the most common cause of CHF in industrialized societies (19). The occurrence of incident heart failure is reduced by long-term treatment with cholesterol-reducing drugs (5).

There are few data on the effects of lipoprotein levels in patients with established CHF. Vredevoe et al. (10) reported lower total, LDL, and HDL cholesterol and triglyceride levels in a group of 109 patients with severe CHF due to dilated cardiomyopathy (but not patients with ischemic heart disease). Richartz et al. (9) showed that low cholesterol levels were associated with increased mortality in 45 patients undergoing left ventricular assist device implantation. In a small pilot study, we demonstrated that a cholesterol level <5.2 mmol/l (200.8 mg/dl), which would conventionally be considered to be a positive feature (20), predicted a worse one-year event-free survival (21). Horwich et al. (11) evaluated follow-up data in over 1,000 patients and found that patients in the lowest quintile of total cholesterol had a twofold increase in relative risk during five-year follow-up. This group also reported a similar best cut-off value from ROC analysis at 4.9 mmol/l (190 mg/dl).

Chronic heart failure is a metabolically demanding condition. Resting energy consumption is increased (22,23), and there is a general shift from anabolic to catabolic processes (24). It may be that a higher cholesterol level represents a greater metabolic reserve to deal with the CHF syndrome. However, we believe that there may a specific protective role for lipoproteins in CHF.

The origins of the immunologic activation seen in CHF are not well understood. We have previously suggested that a possible source is exposure to bacterial LPS or endotoxin (25). Translocation of LPS across the intestinal wall, per-

Table 5. Predictors of Three-Year Survival in the Validation Study

Variable	Hazard Ratio (95% CI)	p Value	Chi-square
Cachexia	5.4 (2.8–10.5)	<0.0001	24.7
LVEF	0.94 (0.92–0.96)	<0.0001	24.5
Peak Vo_2	0.90 (0.85–0.94)	<0.0001	18.9
Etiology	0.67 (0.43–1.03)	0.06	3.4
NYHA class	2.16 (1.67–2.79)	<0.0001	34.6
Age	1.02 (1.00–1.04)	0.06	3.4
Cholesterol	0.75 (0.63–0.90)	0.001	10.4
Total cholesterol <5.2 mmol/l	1.97 (1.30–2.97)	0.001	10.3

NYHA is treated as a continuous variable. Two sets of results for cholesterol are shown: cholesterol as a continuous variable and cholesterol above or below the best predictive value calculated in the derivation study.
Abbreviations as in Tables 1 and 2.

haps due to bowel wall edema, leads to increased tumor necrosis factor production by peripheral blood mononuclear cells. In keeping with this suggestion, LPS is elevated in patients with edematous CHF (25).

In this model, circulating lipoproteins are potentially of beneficial importance by behaving as a sump for LPS at times of increased exposure. Lipoproteins would contribute to a reduction of LPS bioactivity and consequently lead to lower levels of inflammatory cytokines. This may explain the inverse correlation between cholesterol and sTNFR-1 in the derivation study. In vitro (26) and in vivo (27) models of endotoxemia in mice have demonstrated that lipoproteins such as LDL (26), very-low-density lipoprotein (27), HDL (28), lipoprotein(a) (29), triglycerides (30), and chylomicrons (27) can modulate the bioactivity of LPS. Lipoprotein classes bind LPS in direct proportion to their plasma cholesterol concentration (26). Furthermore, LDL receptor-deficient mice with markedly increased plasma cholesterol concentrations are protected against lethal endotoxemia and severe gram-negative infections (29). The most plausible mechanism by which lipoproteins bind to LPS is by the formation of micelles (31).

This model suggests a beneficial role for lipoproteins in patients with CHF and could explain the better survival of patients with higher cholesterol levels. Additionally, cholesterol levels reflect nutritional status, which might also have a prognostic impact. In our studies, lipoprotein levels were no different between patients with and without cachexia, suggesting that cachexia in CHF may not be related major nutritional abnormalities. The relationship between cholesterol and survival was independent of the presence of cachexia.

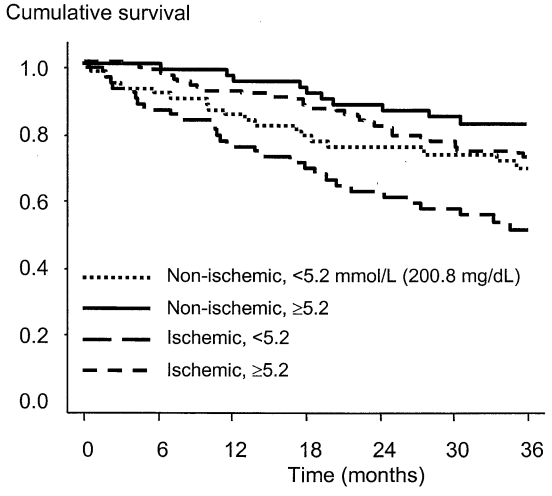

Figure 3. Survival by etiology and cholesterol in the validation study. Log-rank p = 0.05 for comparison between high and low cholesterol in nonischemic etiology and p = 0.001 for ischemic etiology.

Cholesterol predicted survival, independent of the etiology of heart failure. In our view, survival, in general, is a result of a balance of risks. Cholesterol (particularly LDL) is still likely to be a pro-atherosclerotic factor in CHF, but the risk associated with this mechanism is unlikely to affect the prognosis over the relatively short follow-up relevant to heart failure. If cholesterol does limit (LPS-induced) production of cytokines, particularly during phases of clinical deterioration, then high levels of cholesterol may have a strongly positive effect on survival. Thus, the balance of risk attributable to cholesterol favors high levels in patients with CHF, even with an ischemic etiology.

This proposed mechanism depends on the presence of LPS as a pathogen. It is certainly present in patients with severe heart failure, as well as in patients with sepsis and liver cirrhosis (32). In sepsis, at least, higher lipoprotein levels are related to a better outcome (33).

Study limitations. Our study cannot establish that low cholesterol is the *cause* of increased mortality. In larger cohorts of patients with standardized follow-up, it may be possible in the future to analyze the interplay between changes in lipoprotein levels, underlying treatment, changes in body weight, and survival. We have reported on total mortality, which may be the only indisputable and unbiased end point in CHF patients. Our study was underpowered to study the relationship between lipoprotein levels and the frequency of events, such as nonfatal stroke or nonfatal myocardial infarction. Patients with CHF who suffer a stroke or myocardial infarction die earlier. We cannot see how higher cholesterol levels could be related to much better survival and more such events at the same time. The study was not powered to exclude the presence of a U-shaped relationship between cholesterol levels and survival. Interestingly, of 14 CHF patients with cholesterol levels >8 mmol/l (308.9 mg/dl), none died during the first

12 months of follow-up. In this study, statin use seemed to be associated with a lower mortality. We are unable to analyze this finding further due to the small numbers of patients taking statins (18% and 20% in the two patient groups derivation and validation, respectively).

Conclusions. We have demonstrated a relationship between higher levels of cholesterol and increased survival in patients with CHF, independent of age, etiology of CHF, left ventricular function, and exercise capacity. The findings have implications for the treatment of CHF. Many clinicians have applied the results of the clinical trials of HMG-CoA reductase inhibitors to patients with CHF, despite the fact that CHF patients were excluded from these studies by design. The present data suggest the need for caution. Reducing cholesterol may be deleterious in CHF, but HMG-CoA reductase inhibitors may have other, more important beneficial effects that outweigh this possible risk. Controlled trials of statin therapy in patients with CHF are needed.

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