

Gender differences in total cholesterol levels in patients with acute heart failure and its importance for short and long time prognosis

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Aim. The purpose of this study was to evaluate whether there are gender differences in total cholesterol levels in patients with acute heart failure and if there is an association of this parameter with short and long time mortality.

Methods. The AHEAD MAIN registry is a database conducted in 7 university hospitals, all with 24 h cath lab service, in 4 cities in the Czech Republic. The database included 4 153 patients hospitalised for acute heart failure in the period 2006–2009. 2 384 patients had a complete record of their total cholesterol levels. 946 females and 1437 males were included in this analysis. According to the admission total cholesterol levels, patients were divided into 5 groups: < 4.50 mmol/l (group A), 4.50–4.99 mmol/l (group B), 5.0–5.49 mmol/l (group C), 5.50–5.99 mmol/l (group D) and > 6.0 mmol/l (group E). The median total cholesterol levels were 4.24 in males and 4.60 in females ($P < 0.001$). There were differences in the distribution of total cholesterol levels between men and women: group A 57.6 vs 45.0%, group B 13.8 vs 16.3%, group C 9.8 vs 12.5%, group D 7.7 vs 11.4%, group E 11.1 vs 14.8% respectively (all $P < 0.001$). The median age of men was 68.7 vs 77.3 years in women ($P < 0.001$). In all total cholesterol categories women were older than men: group A 77.7 vs 69.5 years, group B 78.6 vs 69.1 years, group C 77.3 vs 68.8 years, group D 76.8 vs 64.2 years, group E 75.6 vs 64.4 years (all $P < 0.001$). For the calculation of long term mortality, the cohort was divided into three groups: total cholesterol levels below 4.50 mmol/l, 4.50–5.49 mmol/l and above 5.50 mmol/l. The log rank test was used for the analysis.

Results. There were no differences in hospital mortality between male and female in general (9.2 vs 10.8%, $P < 0.202$), or in total cholesterol levels in subgroups. Total cholesterol levels were associated with in-hospital mortality ($P < 0.002$). In the long-term follow up (78 months) patients with total cholesterol levels below 4.5 mmol/l had the worst prognosis ($P < 0.001$). An independent influence of total cholesterol level on mortality and survival was confirmed in the multivariate model as well.

Conclusions. Women with acute heart failure had higher total cholesterol levels than men in all ages. There was a higher percentage of women with total cholesterol levels above 6 mmol/l and lower percentage in the group below 4.5 mmol/l than in men. In all, total cholesterol categories women were older than men. Total cholesterol levels are important for in-hospital mortality and long term survival of patients admitted for acute heart failure.

Key words: acute heart failure, AHEAD, cholesterol, gender, in-hospital mortality, prognosis

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INTRODUCTION

Acute heart failure (AHF) is a major and rapidly growing problem responsible for millions of hospitalisations worldwide^{1,2}.

A prevalence of in-hospital mortality as high as 10% and re-hospitalisations >50% within 1 year have been reported³. In a prospective cohort of hospitalised patients with AHF (ADHERE), in-hospital mortality was 4%

(ref.⁴); the Second EuroHeart Failure Survey (EHFS II) had an in-hospital mortality of 6.7% (ref.¹).

The aetiology of AHF is mainly ischemic heart disease (IHD). More than 95% of patients with myocardial infarction with ST elevation are treated in the Czech Republic by primary percutaneous coronary intervention. Cholesterol is a risk factor for the development of atherosclerosis.

We hypothesised that total cholesterol levels in acute

heart failure were significant in short and long term prognosis and that there were possible gender differences in this regard.

MATERIAL AND METHODS

The Acute Heart Failure Database (AHEAD) registry consisted of two independent parts. The AHEAD main registry includes consecutive patients in seven centres with a 24 h Cath Lab service and centralised care for patients with acute coronary syndromes (ACS) from a region of about 3 million inhabitants. The AHEAD network also includes five regional hospitals without a Cath Lab service.

The inclusion criteria for the database adhere to the European guidelines for HF. Hence, there must be signs and symptoms of HF; confirmed left-ventricular dysfunction (systolic or diastolic); and/or positive response to therapy⁵. The data were collated by experienced physicians – cardiologists.

In the majority of patients the laboratory data were available: minerals, urea, creatinine, glycaemia, transaminases, total cholesterol levels, triacylglycerols and blood count. Laboratory samples were collected on admission or on the 2nd day of hospitalization in the morning on an empty stomach.

The AHEAD main registry included 4 153 patients hospitalised at seven Cardiology Departments with Cath Lab facilities in four cities. The data were collected prospectively from September 2006 to October 2009 using a database accessible via the Internet website www.ahead.registry.cz, and were evaluated continuously (including in-hospital mortality). The long-term mortality was followed using the centralised database of the Ministry of Health of the Czech Republic and recent data from the year 2010. Written informed consent was obtained from all subjects. The study protocol complied with the Declaration of Helsinki, and was approved by the local

Ethics Committee of the Faculty Hospital Brno (Brno, Czech Republic).

Statistical analyses

Statistical analyses were done by the Institute of Biostatistics and Analyses of Masaryk University (Brno, Czech Republic). Standard summary statistics were used to describe primary data, absolute and relative frequencies, medians, the 5th-95th percentile range, arithmetic means, and standard deviation. The statistical significance of differences between groups of patients for continuous parameters was tested using the Mann-Whitney U test. The Fisher exact test and maximum likelihood χ^2 test were applied for analyses of differences in categorical data. The log rank test was used for the analysis of long term survival. The independent influence of total cholesterol level on mortality and survival was assessed using multivariate logistic regression and Cox proportional hazards model respectively.

Due to the large sample size, all statistical results were interpreted with respect to their clinical significance. Statistical analyses were undertaken using the SPSS 18.0.3 statistical package (SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics

Of 4 153 patients, 526 (12.7%) patients died during hospitalisation. The median length of hospitalisation was 7.1 days (5.5 days for those patients who died and 9.7 days for those who were discharged home) and was identical for males and females. Their baseline clinical characteristics and causes of acute heart failure is described in Table 1.

2 384 patients had complete records for total cholesterol levels – 946 females and 1437 males were included in this analysis.

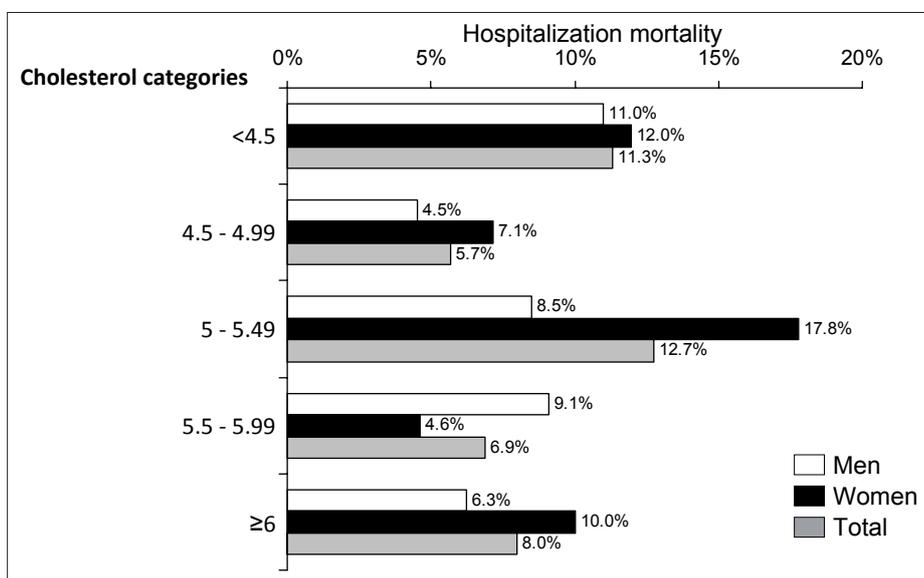


Fig. 1. Hospitalization mortality according to total cholesterol level.

According to the admission total cholesterol levels, the patients were divided into 5 groups: < 4.50 mmol/l (group A), 4.50-4.99 mmol/l (group B), 5.00-5.49 mmol/l (group C), 5.50-5.99 mmol/l (group D) and > 6.0 mmol/l (group E).

The median total cholesterol levels was 4.24 mmol/l in males and 4.60 mmol/l in females ($P<0.001$). There were differences in the distribution of total cholesterol levels between men and women with more men in group A with the lowest level of total cholesterol and with more women in groups B, C, D, E (all $P<0.001$) (Table 2). The median age of men was 68.7 vs 77.3 years in women ($P<0.001$). In all total cholesterol categories women were older than men ($P<0.001$) (Table 3).

For calculation of long-term mortality the cohort was divided into the three groups according to total chole-

sterol levels: below 4.500 mmol/l, 4.50-5.40 mmol/l and above 5.40 mmol/l. Log rank test was used for the analysis.

There were no differences in hospital mortality according to total cholesterol categories between men and women (9.2 vs 10.8%, $P<0.202$), but total cholesterol levels were important for hospital mortality for both genders ($P<0.002$) (Table 4) (Fig.1). In the long-term follow up (78 months) patients with total cholesterol level below 4.5 mmol/l had the worst prognosis ($P<0.001$) (Fig.2), men as well as women ($P<0.001$) (Fig.3).

The independent influence of total cholesterol on mortality and survival was confirmed for both men and women also in the multivariate analysis when total cholesterol level below 4.5 mmol/l was combined with other predictors revealed in the univariate analysis (Table 5).

Table 1. Baseline characteristics of patients according to syndromes of acute heart failure.

Patients characteristics	Total ¹ (N=4153)	ADHF (N=2241)	Hypertensive AHF (N=179)	Pulmonary oedema (N=748)	Cardiogenic shock (N=600)	AHF with high output (N=132)	Right AHF (N=156)	<i>P</i> ²
Female	42.4%	40.4%	65.4%	44.1%	39.0%	53.0%	43.6%	<0.001
Age	73.8 (49.3; 87.9)	73.8 (48.5; 87.6)	74.8 (49.3; 88.7)	73.8 (53.8; 88.3)	74.3 (50.3; 87.9)	76.2 (51.0; 91.1)	65.8 (35.3; 84.9)	<0.001
>70 years	60.0%	59.9%	61.5%	62.6%	60.0%	70.5%	41.0%	<0.001
De-novo HF	58.3%	52.6%	74.3%	58.4%	68.7%	63.6%	77.6%	<0.001
ACS at admission	36.2%	33.1%	0.0%	40.8%	61.3%	7.6%	25.6%	<0.001
NYHA III+IV	43.2%	48.8%	34.0%	43.2%	27.2%	37.2%	29.5%	<0.001
Insignificant CAD	13.9%	15.8%	22.3%	12.4%	5.5%	13.6%	15.4%	<0.001
Significant CAD	51.0%	51.5%	16.2%	55.0%	65.0%	20.6%	32.1%	<0.001
CAD - unknown	35.1	32.7%	61.5%	32.6%	29.5%	65.8%	52.5%	<0.001
Hypertension	73.1%	70.4%	94.3%	80.8%	72.1%	68.0%	60.7%	<0.001
Diabetes mellitus	42.6%	41.1%	43.1%	51.0%	44.0%	36.2%	24.5%	<0.001
Previous MI	32.1%	31.6%	26.4%	36.8%	36.0%	23.6%	11.3%	<0.001
Previous PCI or CABG	29.5%	29.0%	3.4%	28.7%	45.2%	9.1%	25.0%	<0.001
PM/ICD/CRT	12.2%	14.5%	8.4%	11.6%	7.5%	9.8%	6.4%	<0.001
COPD	16.2%	16.7%	17.8%	16.5%	14.4%	20.5%	8.0%	0.027
Stroke or TIA in history	16.5%	16.0%	26.4%	18.0%	15.7%	13.4%	9.9%	0.002
Atrial fibrillation	26.5%	28.3%	19.0%	21.4%	19.7%	73.5%	19.2%	<0.001
Coronary angiography	17.5%	19.7%	11.7%	18.5%	11.6%	12.1%	12.3%	<0.001
Systolic BP	135 (80; 200)	136 (95; 195)	198 (140; 260)	145 (95; 218)	110 (55; 170)	140 (90; 180)	110 (60; 160)	<0.001
Systolic BP ≤ 100	15.6%	10.0%	0.0%	8.7%	44.4%	15.2%	36.1%	<0.001
Diastolic BP	80 (50; 110)	80 (60; 110)	100 (70; 150)	80 (60; 120)	65 (30; 95)	80 (58; 112)	70 (34; 100)	<0.001
Heart rate	90 (54; 142)	85 (52; 140)	93 (55; 140)	98 (63; 141)	90 (45; 136)	130 (70; 170)	90 (49; 146)	<0.001
Ejection fraction (%)	37 (16; 65)	36 (15; 65)	55 (30; 70)	35 (18; 60)	30 (12; 60)	52 (25; 70)	57 (25; 74)	<0.001
Ejection fraction ≤ 30%	37.9%	38.3%	5.6%	42.8%	52.6%	10.1%	12.2%	<0.001

¹ Syndromes are not known for 97 patients. ACS - acute coronary syndrome, CAD - coronary artery disease, MI - myocardial infarction, PCI - percutaneous coronary intervention; CABG - coronary artery bypass graft, PM - pacemaker; ICD - Implantable cardiac defibrillator; CRT - Cardiac resynchronisation therapy; COPD - Chronic obstructive pulmonary disease; TIA - transient ischemic attack, BP - Blood pressure

DISCUSSION

Predictors of mortality

AHEAD main registry is one of the largest national observational prospective databases of AHF. The register was suggested as a multicentre, prospective with long term follow-up of mortality⁶.

In previous analyses (not yet published) using univariate logistic regression analyses we defined all parameters that were related to hospital and long-term mortality in patients without cardiogenic shock. After exclusion of cardiopulmonary resuscitation and use of adrenalin, according to the multivariate analyses, low levels of total cholesterol (< 3 mmol/l) were an independent predictive factor of higher in-hospital mortality (OR (95% CI) 2.4 (1.4-4.2); $P < 0.002$). In the OPTIMIZE HF registry⁷, the strongest predictors of mortality in 48.612 patients were low SBP, hyponatraemia, high levels of creatinine and left-ventricular dysfunction⁸.

In the study of Arques, patients admitted for acute heart failure were prospectively included. By multivariate analysis, albumin ($P = 0.0017$), BNP ($P = 0.016$) and age ($P = 0.03$) were independent predictors of in-hospital death. Serum troponin I was predictive of in-hospital

death ($P = 0.01$), as well as serum total cholesterol measured after stabilization ($P = 0.004$). However, these two variables no longer predicted outcome in multivariate models, unlike serum albumin and BNP (ref.⁹).

The study of Horwich investigated a relationship between lipid levels and in-hospital mortality in patients with acute HF. Baseline patient characteristics, treatment regimens, and in-hospital mortality were examined by total cholesterol (TC) levels (mg/dl) quartiles (Q) as follows: Q1 (TC ≤ 118), Q2 (TC 119-145), Q3 (TC 146-179), and Q4 (TC ≥ 180). Patients with lower TC were older and had a higher prevalence of ischemic heart disease. In-hospital mortality in TC Q1 to Q4 was 3.3%, 2.5%, 2.0%, and 1.3%, respectively ($P < 0.0001$). On multivariable adjusted analyses, each 10-mg/dl (0.26 mmol/l) increase in TC level was associated with 4% decreased risk of in-hospital mortality (odds ratio 0.96, 95% CI 0.93-0.98).

In patients hospitalized with HF, lower TC levels independently predicted increased in-hospital mortality risk¹⁰. Similar results as in our study were confirmed in the prospective study of Rauchaus et al. They studied the relationship between total cholesterol and survival in patients with chronic heart failure. Increasing total cholesterol was a predictor of survival, independent of age, etiology of

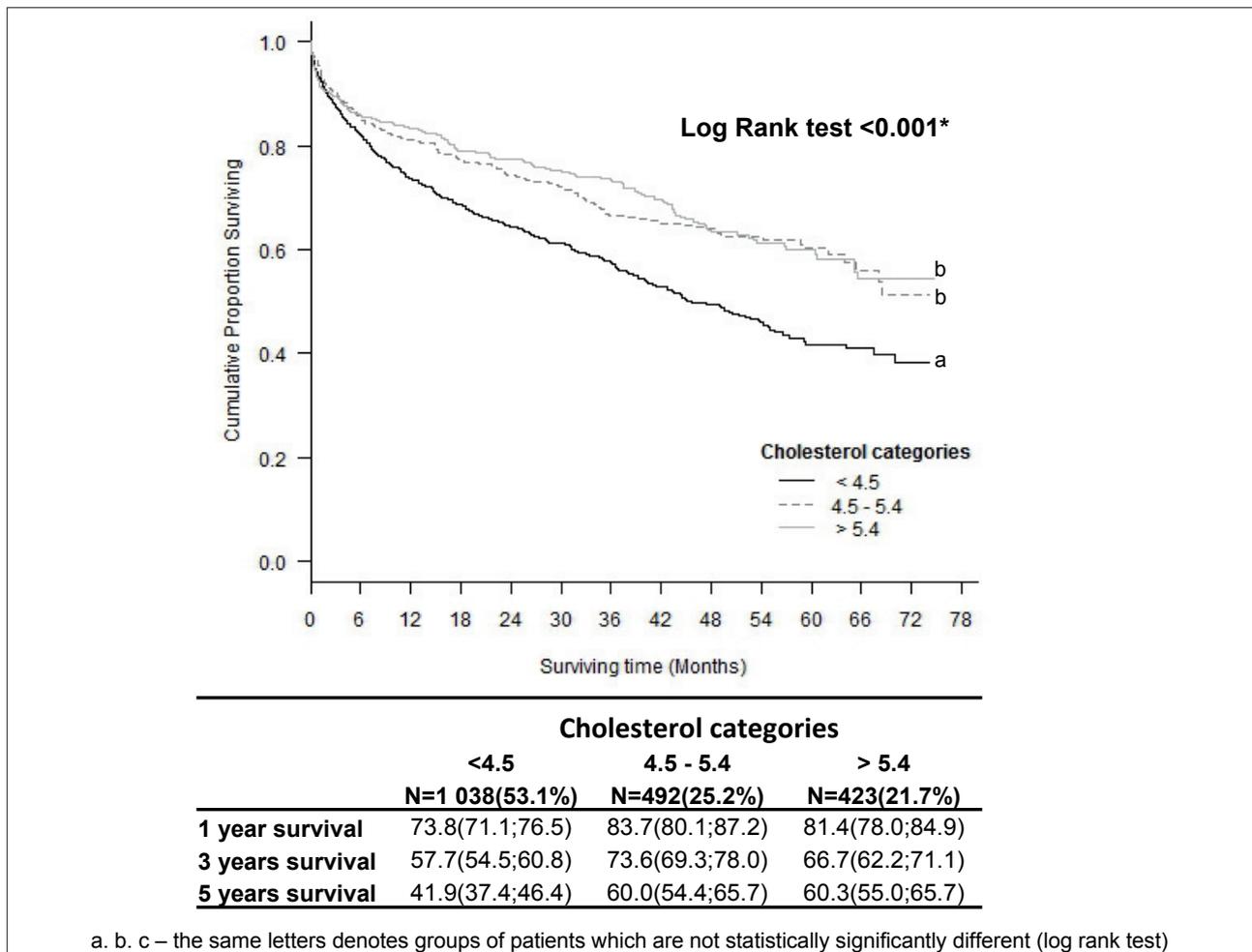


Fig. 2. Long-term survival for discharged patients according to total cholesterol level.

heart failure, ejection fraction of left ventricle or exercise capacity. Receiver-operating characteristic curves demonstrated the cut-off value < 5.2 mmol/l as being the best predictor of 12 month mortality. The chance of survival increased 25% for each mmol/l increment in total cholesterol¹¹.

It may be that higher total cholesterol represents a greater metabolic reserve to deal with heart failure syndrome. There might be a specific protective role for lipoproteins in chronic heart failure and also in long-term follow up of acute heart failure patients. Total cholesterol is still likely to be proatherogenic, but the risk associated with this mechanism is unlikely to affect prognosis over the relatively short follow up. If total cholesterol limits the production of harmful cytokines (TNFR-1), then the higher levels of total cholesterol might have a strongly positive effect on survival¹¹.

Conventional risk factors such as obesity, hypertension and hypercholesterolemia are associated with increased risk of developing chronic heart failure and mortality in the general population. In marked contrast to the general population, a higher body mass index, increased serum total cholesterol level and higher blood pressure are strongly correlated with decreased morbidity and mortality in heart failure^{12,13}. These paradoxical observations have been referred to as reverse epidemiology¹⁴. As the heart failure population has a greater mortality risk than that in general population, the long-term effects of these factors may be overwhelmed by the short-term effects of other factors on heart failure. Another phenomenon

should be taken in account, known as reverse causation. This indicates that low blood pressure, BMI or total serum cholesterol are not etiologically linked to a higher mortality in heart failure patients, but they are merely the markers of poor outcome¹⁴.

Gender differences in cholesterol level

In the study of Spinar total cholesterol levels were measured at public places (mostly department stores) from 2005 to 2008. No significant difference between genders in total cholesterol levels were found. A smaller proportion of women than men had total cholesterol below 5 mmol/l (45.2 vs 53.0 %). Total cholesterol levels rise with age in both genders, stagnate at a certain point and subsequently decline. There was a significant difference in this between men and women – the levels start to stagnate at the age of 50 in men and beyond the age 65-70 in women. The levels fall with increasing age in both genders after the age of 65. Total cholesterol levels were statistically significantly higher in women over 55 years. This difference was retained to the advanced age of >75 years¹⁵. It is generally accepted that menopause leads to hormonal, metabolic and lipid profiles changes. Agrinier et al. conducted a meta-analysis of 10 cross-over and 9 long-term clinical trials examining lipid levels in postmenopausal women and showed that these women have higher total cholesterol, LDL cholesterol and triglycerides and that these changes persist even after adjustment for age. Interestingly, these differences did not affect hormonal treatment for estrogen¹⁶.

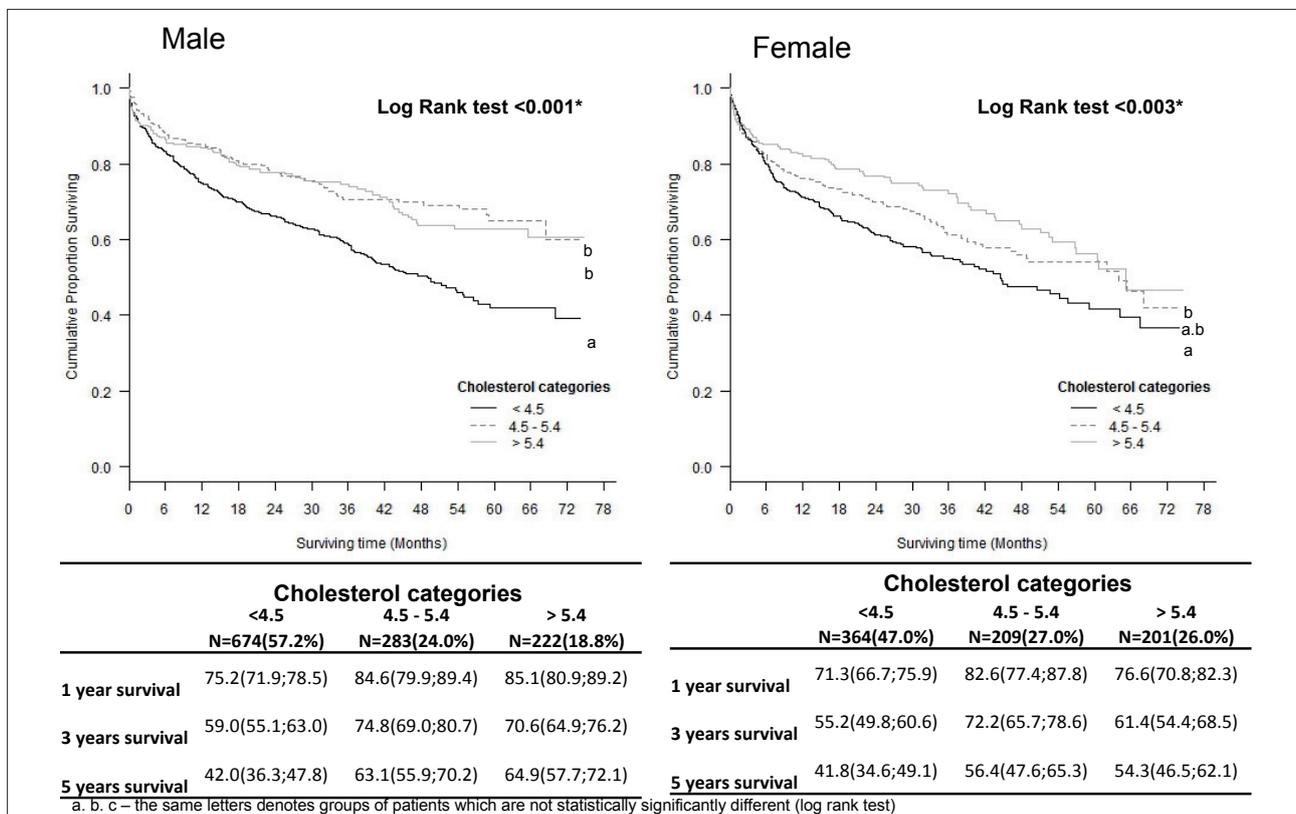


Fig. 3. Long-term survival for discharged patients according to the total cholesterol level and gender.

WHILA - The Womens Health in the Lund Area (in Sweden) study examined 6908 women aged 50-59 years. These women were divided into premenopausal (PM), postmenopausal without hormone therapy (PM0) and postmenopausal with hormone therapy (PMT). Total cholesterol increased with age both in PM0 ($P<0.001$) and the PMT ($P<0.001$), similarly increased LDL cholesterol in the PM0 ($P<0.001$) and slightly less for PMT ($P<0.007$). The number of women with total cholesterol > 7.0 mmol/l and triglycerides > 2.0 mmol/l decreased with age in PM, but significantly increased both the PM0 and PMT. Total cholesterol increased with age in all groups, but due to the rise in HDL cholesterol in PM and due to LDL cholesterol in PM0 and PMT (ref.¹⁷). In an multiethnic population of 2556 persons aged 65-103 years there was observed a relationship between total cholesterol and overall mortality. People in the lowest total cholesterol quartile had a 2-fold higher risk of death than those in the highest quartile, and this was expressed most in whites and less in Hispanics. High total cholesterol seems not

to be a cardiovascular risk factor for persons > 65 years and conversely low total cholesterol is associated with higher mortality¹⁸.

Our study confirms the same results: older women have higher total cholesterol than men of same age but lower risk of mortality.

Study limitation

Our presented results are only from hospitals with Cath Lab service (AHEAD main), results from regional hospitals participating in AHEAD network were not included. This could lead to a higher contribution of patients with ACS and high percentage of patients with performed coronary angiography and PCI during hospitalization.

Table 2. Proportion of patients according to the total cholesterol categories and gender.

	All patients ¹ (N = 2384)	Women ¹ (N = 946)	Men ¹ (N = 1437)	<i>p</i> ²
Total cholesterol level	4.40 (2.50;6.80)	4.60 (2.70;6.95)	4.24 (2.37;6.67)	$<0.001^*$
Total cholesterol categories				
Group A: <4.50	1 253 (52.6%)	426 (45.0%)	827 (57.6%)	$<0.001^*$
Group B: 4.50–4.99	353 (14.8%)	154 (16.3%)	199 (13.8%)	
Group C: 5.00–5.49	259 (10.9%)	118 (12.5%)	141 (9.8%)	
Group D: 5.50–5.99	218 (9.1%)	108 (11.4%)	110 (7.7%)	
Group E: ≥ 6.00	300 (12.6%)	140 (14.8%)	160 (11.1%)	

¹ Continuous variables are expressed as median, 5th and 95th percentile, categorical variables as percentage proportion within gender group

² Mann-Whitney U test for total cholesterol level and Chi-square test for total cholesterol categories for testing differences between genders; *statistically significant

Table 3. Age of patients according to the total cholesterol level and gender.

Age	All patients ¹	Women ¹	Men ¹	<i>p</i> ²
Total cholesterol categories				
Group A: <4.50	72.8 (47.4;87.0)	77.7 (53.8;89.5)	69.5 (44.4;85.1)	$<0.001^*$
Group B: 4.50 – 4.99	72.6 (53.5;87.3)	78.6 (55.9;88.4)	69.1 (48.7;84.8)	$<0.001^*$
Group C: 5.00 – 5.49	72.8 (52.3;85.3)	77.3 (54.3;86.3)	68.8 (51.8;83.1)	$<0.001^*$
Group D: 5.50 – 5.99	70.9 (45.5;85.9)	76.8 (50.0;87.8)	64.2 (43.2;83.9)	0.004*
Group E: ≥ 6.00	69.4 (47.4;85.8)	75.6 (54.8;86.9)	64.4 (43.6;83.6)	$<0.001^*$
Together	72.0 (48.9;86.4)	77.3 (54.4;88.2)	68.7 (45.3;84.8)	$<0.001^*$

¹ Age is expressed by median, 5th and 95th percentile.

² Mann-Whitney U test for testing differences in age between men and women within total cholesterol level group; *statistically significant

CONCLUSION

The AHEAD main registry provides up-to-date information on demographic characteristics and the underlying conditions of AHF patients as well as the aetiology, investigation, treatment and prognosis of AHF in a country with centralized care for ACS and with a high percentage of patients with performed angiography and coronary revascularization.

Women with acute heart failure have higher total cholesterol levels than men. There is a higher percentage of

women with total cholesterol above 6 mmol/l and lower percentage in the group below 4.5 mmol/l than in men. In all total cholesterol categories women were older than men. Total cholesterol levels influence the in-hospital mortality and are predictive for long term mortality of patients admitted for acute heart failure. The independent influence of total cholesterol level on mortality and survival was confirmed in the multivariate model. Patients with cholesterol below 4.50 mmol/l, irrespective of gender, have the worst prognosis.

Table 4. Hospitalization mortality according to the total cholesterol categories and gender.

	All patients ¹	Women ¹	Men ¹	<i>P</i> ²
Total cholesterol categories				
Group A: <4.50	142 (11.3%)	51 (12.0%)	91 (11.0%)	0.610
Group B: 4.50 – 4.99	20 (5.7%)	11 (7.1%)	9 (4.5%)	0.293
Group C: 5.00 – 5.49	33 (12.7%)	21 (17.8%)	12 (8.5%)	0.026*
Group D: 5.50 – 5.99	15 (6.9%)	5 (4.6%)	10 (9.1%)	0.189
Group E: ≥ 6.00	24 (8.0%)	14 (10.0%)	10 (6.3%)	0.233
Together	234 (9.8%)	102 (10.8%)	132 (9.2%)	0.202
<i>P</i> ³	0.002*	0.009*	0.023*	

¹ Mortality is expressed by number and percentage proportion within gender-total cholesterol level-group.

² Chi-square test for total cholesterol categories for testing differences in proportion of deceased patients between genders; *statistically significant

³ Chi-square test for testing differences in proportion of deceased patients between total cholesterol categories within men and women; *statistically significant

Table 5. Total cholesterol level in multivariate model for mortality or long term survival prediction.

	Women		Men	
Hospitalization mortality ¹				
	OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
Total cholesterol < 4.5mmol/l	1.82 (1.01; 3.28)	0.045	1.57 (1.03; 2.38)	0.036
Age > 70 yrs	2.20 (1.09; 4.44)	0.028	2.35 (1.57; 3.50)	<0.001
Cardiogenic shock	7.83 (4.26; 14.39)	<0.001	1.96 (1.73; 2.22)	<0.001
Invasive ventilation	6.79 (3.65; 12.61)	<0.001	-	
Creatinine > 120 umol/l	1.58 (0.88; 2.83)	0.122	-	
Na > 130 mmol/l	-		3.06 (1.60; 5.87)	<0.001
Long term survival ²				
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Total cholesterol < 4.5mmol/l	1.30 (1.02; 1.66)	0.037	1.43 (1.14; 1.80)	0.002
Age > 70 yrs	1.54 (1.15; 2.07)	0.004	1.82 (1.44; 2.28)	<0.001
Creatinine max. > 145 umol/l	-		2.16 (1.73; 2.71)	<0.001
Haemoglobin: ≤ 120/130 g/dl	-		1.43 (1.14; 1.80)	0.002
Diabetes mellitus	1.58 (1.23; 2.04)	<0.001	1.21 (0.97; 1.50)	0.094
Previous stroke or TIA	1.35 (0.99; 1.84)	0.054	1.46 (1.11; 1.94)	0.008

¹ odds ratio supplemented by 95% confidence interval and its significance is based on logistic regression

² hazard ratio supplemented by 95% confidence interval and its significance is based on Cox proportional hazards model

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CONFLICT OF INTEREST STATEMENT

Author's conflict of interest disclosure: None of the authors has any proprietary interest.

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