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Enigma of the cholesterol paradox in acute myocardial infarction: lessons from an 8-year follow-up of all-cause mortality in an age-matched and sex-matched case–control study with controls from the patients' recruitment area

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ABSTRACT

Objective To assess the impact of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) on long-term all-cause mortality (ACM) in patients with acute myocardial infarction (AMI) and controls.

Design Matched case–control study with 8-year follow-up.

Setting Vastmanland County Hospital, Vasteras, Sweden.

Participants Consecutive patients with AMI admitted to the coronary care unit from March 2005 to May 2010 and age-matched and sex-matched controls from the general population.

Outcome measures ACM.

Results Person-year at risk among patients with AMI and controls was 11 667 (cases: 5780 and controls: 5887). During follow-up, 199 patients and 84 controls died, implying 3.4 deaths among patients and 1.4 among controls per 100 person-years at risk. Unadjusted Cox analyses showed significantly increasing mortality by decreasing TC and LDL-C levels in both patients (HR=0.70, 95% CI 0.62 to 0.79, p<0.001, and HR=0.64, 95% CI 0.56 to 0.74, p<0.001) and controls (HR=0.73, 95% CI 0.60 to 0.89, p=0.002, and HR=0.74, 95% CI 0.59 to 0.93, p=0.010). After adjusting for clinical variables, the results for the patients remained significant. Cox analyses of the relations between mortality and TC and LDL-C below and above their respective medians revealed the following pattern. Patients: below medians were TC and LDL-C levels significantly inversely related to mortality; above medians there were no relations with mortality. Controls: below medians were TC and LDL-C levels significantly inversely related to mortality; above medians were LDL-C levels significantly positively related to mortality. Mean LDL-C level in patients with blood sampled >12 hours after symptom onset was 0.41 mmol/L lower than that in patients with blood sampled ≤12 hours (p=0.030). This LDL-C decrease was reasonably caused by ongoing AMI and reflects the difference in LDL-C levels between patients and controls.

Conclusions In patients with AMI, lower TC and LDL-C levels independently predict higher ACM. In their controls, LDL-C levels above the median independently predict higher ACM. This study adds to the body of evidence supporting the existence of a cholesterol paradox.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The restriction to one centre serving a defined geographical area and two research nurses taking care of the participants reasonably reduces several sources of bias.
⇒ This strength is partly offset by the difficulty in generalising our findings to those from other geographical areas, although it seems likely that our results are applicable to North Europeans and white North Americans of Caucasian origin.
⇒ All-cause mortality, which is more unambiguously defined than cause-specific mortality and rules out the problem with concomitant endpoints, is a clinically relevant and easily understandable outcome measure for both clinicians and interested patients.
⇒ An inevitable limitation of the case–control design in the present setting is that data from patients dying before hospitalisation are unobtainable, which might cause a minor bias.
⇒ Modern high-sensitivity troponin I assays, which enable identification of an increased number of patients with non-ST-elevation myocardial infarction or acute coronary syndromes, were not clinical practice in Region Vastmanland during the recruitment period of the present study.

INTRODUCTION

High lipid levels are known risk factors for atherosclerotic cardiovascular events, and the blood levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C)

are often routinely determined in patients with acute myocardial infarction (AMI). It is important to extract all clinically useful information, including prognostic information from such a routine. Several reports paradoxically describe low levels of TC and LDL-C as predictors of higher mortality in patients with AMI. Al-Mallah *et al*[1] described in a pioneer report increased 3-year all-cause mortality (ACM) in non-ST segment elevation patients with AMI with LDL-C levels of <2.7 mmol/L (105 mg/dL). Cho *et al*[2] reported better clinical outcome and survival 12 months after percutaneous coronary interventions in patients with AMI as LDL-C increased except for patients with LDL-C levels of ≥4.13 mmol/L (160 mg/dL). However, after adjusting for clinical characteristics, the impact of LDL-C on 12 months' survival diminished. Reddy *et al*[3] reported higher in-hospital ACM by lower LDL-C among 115 492 hospitalised patients with AMI. Budzyński *et al*[4] reported similar observations in 34 191 patients with AMI. Due to observations that a high cholesterol level is a risk marker in the general population for all-cause and cardiovascular mortality as well as for future coronary artery disease,[5–9] the aforementioned findings among patients with AMI are usually interpreted as cholesterol paradoxes.

The primary aim was to investigate the possible existence of a cholesterol paradox in patients with AMI by assessing the strength and direction of the relation between the TC and LDL-C levels and long-term ACM in consecutive patients with AMI and their matched control subjects without previous MI. Subgroup analyses were performed to explore the relations between TC and LDL-C levels below and above their respective median levels and ACM.

To better understand the variation in the TC and LDL-C levels during the AMI phase, we studied, as a secondary aim, the relation between TC and LDL-C levels and the time from onset of AMI symptoms to blood sampling for lipid analyses.

METHODS

Study design

Consecutive patients with AMI admitted to the coronary care unit of the Vastmanland County Hospital Vasteras Sweden were eligible for the study. This hospital is referral centre for a geographical area with about 180 000 inhabitants. The patients were recruited from November 2005 to May 2010. ECG and biomarker criteria recommended by the European and American Societies of Cardiology[10] were used for diagnosing AMI with troponin I ≥0.4 µg/L as diagnostic limit. The patients were categorised by time intervals between symptom onset and blood sampling for TC and LDL-C analyses.

For every patient with AMI, we selected as control subject the individual of the same sex and with the nearest date of birth in the population registry of the hospital's catchment area, provided that this individual had no medical history of MI. Great difficulties in recruiting control subjects above 80 years of age became apparent early in the study. Therefore, patients with AMI >80 years of age were not included in the study. Out of 1015 eligible patients, 737 (73%) were included in the study (figure 1). The patients and their controls were followed up until 9 May 2017 or death, whichever happened first. Age was measured by computing the difference in years, retaining fractional parts, between birthday and date of inclusion in the study. The cases and controls were part of the database of the Vastmanland Myocardial Infarction Study (ClinicalTrials.gov identifier: NCT 01452178).

Previous myocardial infarction (MI), angina pectoris, stroke, diabetes, hypertension and hypercholesterolaemia were defined as a doctor's diagnosis reported by the study participants and verified from available medical records. Current smoking was defined as daily smoking during the month before the AMI.

Blood was sampled by venipuncture when the patient was included in the study, usually after overnight fasting. In control subjects, blood was usually sampled in the morning after overnight fasting. Notably, a joint consensus document from the European Atherosclerosis Society and the European Federation of Clinical Chemistry and Laboratory Medicine[11] states that the difference between fasting and non-fasting lipid profiles is too small to be clinically significant.

Blood TC concentrations were determined in serum by UniCel DxC 800 or Synchron LX20 Analyzer (Beckman Coulter, USA). The coefficient of variation (CV) for TC was 1.5% and 1.6% at 3.2 and 7.7 mmol/L, respectively. CV for high-density lipoprotein cholesterol (HDL-C) analyses was 2.7% at 0.89 mmol/L and 2.4% at 2.4 mmol/L. CV for triglyceride analyses was 3.8% at 0.99 mmol/L and 2.1% at 2.2 mmol/L. LDL-C was calculated from TC, HDL-C and triglycerides by the Friedewald equation: (LDL-C=TC–HDL-C–triglycerides×0.45). Application of this formula presupposes triglyceride levels of <4.5 mmol/L, which reduced the number of LDL-C pairs from 737 to 703. The conversion factor for TC and LDL-C from mmol/L to mg/dL is 38.7.

Troponin I was analysed by a radial partition immunoassay using the sandwich immunoassay principle (Stratus CS STAT, Dade Behring, Germany). CV for troponin I was 8.0% and 7.1% at 0.41 and 1.46 µg/L, respectively.

Patient and public involvement

There was no patient and public involvement in the study.

Statistics

Continuous variables were summarised by mean and SD or, in case of markedly skewed distribution, by median and IQR. Categorical variables were summarised by frequency counts and percentage (%). Tests for differences between cases and controls were performed by paired t-test for continuous variables and McNemar's exact test for categorical variables. Tests for differences between survivors and non-survivors among cases and controls for lipid variables were performed by two-sample t-test. The

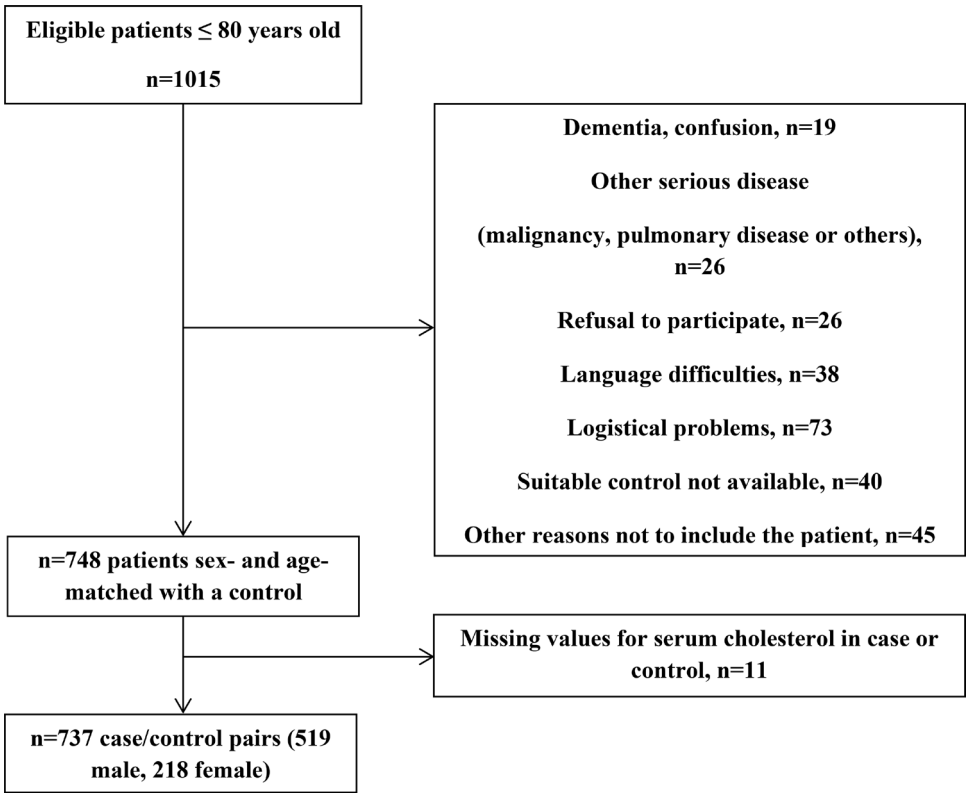

Figure 1 Flowchart of patients with acute myocardial infarction.

difference between TC and LDL-C levels categorised by dichotomised time (<12 hours /≥12 hours) from onset of AMI symptoms to blood sampling for lipid analyses was assessed by Wilcoxon Mann-Whitney rank-sum test. Spearman's rank correlation was used to assess monotone associations.

Crude and adjusted prospective associations between TC, LDL-C and ACM were assessed, separately for patients and controls, by HRs and corresponding 95% CIs using univariable and multivariable Cox proportional hazards regression (PHREG) models. For continuous variables, the assumption of proportional hazards was assessed by examining their interaction with time to death in the Cox PHREG models. The proportional hazard assumption for categorical variables was assessed by visual inspection of the log [−log (cumulative survival)]. Cumulative survival was estimated by means of the Kaplan-Meier method.

A two-sided p value of <0.05 was regarded as statistically significant in all analyses. IBM SPSS Statistics V.26 was used for all statistical analyses.

RESULTS

The number of person-years at risk among patients with MI and control subjects taken together (n=1474) was 11 667 (cases 5780 and controls 5887). The median follow-up time for AMI cases was 8.5 (IQR 7.0–9.9) years and for controls 8.0 (IQR 6.8–9.5). During follow-up, 199 patients with MI and 84 control subjects died, implying 3.4 deaths among patients and 1.4 deaths among controls per 100 person-years at risk (p value for case–control difference <0.001). Kaplan-Meier curves for survival of patients with MI and controls are shown in figure 2.

The median age was 67.2 (IQR 59.6–73.8) years for patients and 68.0 (IQR 60.3–74.6) years for controls. Notably, only 46 (6.2%) of the patients were younger than 50 years. The case–control age difference of 0.8 years implies a 1.2% higher median age of the controls.

Pertinent baseline characteristics of the study population are shown in table 1. Notably, the proportion of patients with AMI on statin treatment increased from 31% at admission to 98% at discharge from the hospital. This reflects good adherence to the guidelines of the European Society of Cardiology,[12] which recommend start of high intensity, long-term statin therapy of patients with AMI at hospitalisation.

Blood levels of TC and LDL-C in case–control pairs are shown in table 2. The mean TC and LDL-C levels were significantly lower in patients than in controls. Further, this case–control difference of TC and LDL-C remained largely unchanged even in analyses restricted to pairs with neither case nor control on statin treatment at recruitment. The size of the case–control differences corresponds well to the decrease in TC and LDL-C levels associated with increasing time between symptom onset and blood sampling (see table 3).

Table 2 also shows the blood levels of TC and LDL-C categorised into survivors and non-survivors within cases and controls. The mean TC and LDL-C levels were significantly lower in survivors than in non-survivors among both the patients with AMI and the

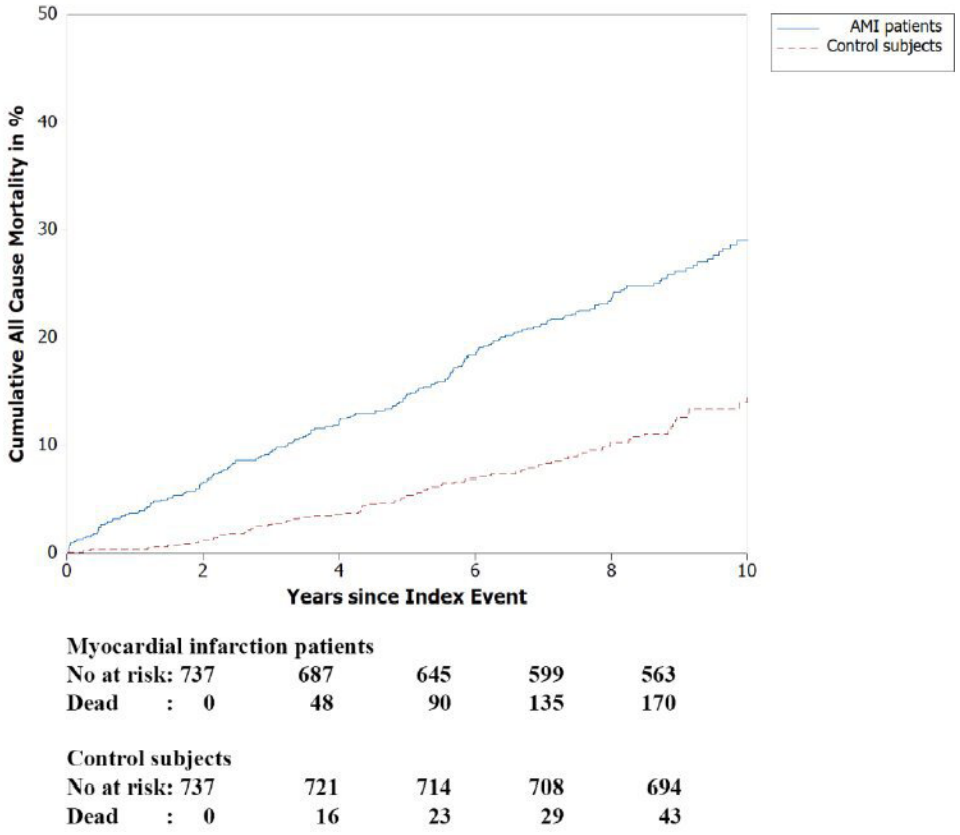

Figure 2 Cumulative mortality stratified by status (patients with AMI/control subjects). AMI, acute myocardial infarction.

control subjects. After further categorising for age (≤65 years/≥66 years), the results remain significant for the patients while they became non-significant for the controls, probably due to low power especially in the category ≤65 years.

Table 1 Basic characteristics among 737 age-matched and sex-matched case–control pairs

	Cases, n (%)	Controls, n (%)	P value
First-time MI	581 (79)	NA	NA
ST elevation AMI	267 (36)	NA	NA
Hypertension	410 (56)	338 (46)	<0.001
Hypercholesterolaemia, n=734	247 (34)	206 (28)	0.021
Diabetes	129 (18)	68 (9)	<0.001
Angina pectoris	172 (23)	42 (6)	<0.001
Heart failure, n=733	48 (7)	14 (2)	<0.001
Stroke	49 (7)	48 (7)	1.000
Current smokers	177 (24)	77 (10)	<0.001
Ever smokers	508 (69)	413 (56)	<0.001
In-hospital death	4 (1)	NA	NA
On statin medication at admission/inclusion, n=731	227 (31)	136 (19)	<0.001
On statin medication at living discharge, n=722	706 (98)	NA	NA
Non-statin lipid lowering drugs, n=733	4 (1)	4 (1)	1.000
BMI, mean (SD), n=731	27.5 (4.9)	26.7 (3.8)	0.002
Estimated glomerular filtration rate, mL/min/1.73 m^2 body surface area, mean (SD), n=725	68.4 (21.4)	72.4 (17.9)	<0.001
Hours from symptom onset to blood sampling, median (IQR), n=579	32 (23–52)	NA	NA

BMI, body mass index; MI, myocardial linfarction; NA, not applicable.

Table 2 TC and LDL-C (mmol/L) in case–control pairs

	Mean (SD)	Mean difference (95% CI)	P value
	Cases/controls		
All pairs			
TC, n=737	5.04 (1.35)/5.61 (1.15)	−0.57 (−0.45 to −0.69)	<0.001
LDL-C, n=703	3.17 (1.16)/3.66 (0.99)	−0.49 (−0.38 to −0.60)	<0.001
Sex*			
Men			
TC, n=519	4.96 (1.32)/5.46 (1.12)	−0.50 (−0.36 to −0.65)	<0.001
LDL-C, n=491	3.15 (1.14)/3.62 (0.98)	−0.46 (−0.33 to −0.59)	<0.001
Women			
TC, n=218	5.23 (1.40)/5.96/1.16)	−0.73 (−0.49 to −0.96)	<0.001
LDL-C, n=212	3.21 (1.21)/3.77 (1.02)	−0.56 (−0.35 to −0.77)	<0.001
Age groups†			
Age ≤65			
TC, n=342	5.26 (1.44)/5.75 (1.07)	−0.49 (−0.29 to −0.68)	<0.001
LDL-C, n=314	3.35 (1.29)/3.78 (0.92)	−0.43 (−0.25 to −0.61)	<0.001
Age ≥66			
TC, n=395	4.85 (1.23)/5.49 (1.20)	−0.64 (−0.48 to −0.80)	<0.001
LDL-C, n=389	3.03 (1.03)/3.57 (1.04)	−0.54 (−0.40 to −0.68)	<0.001
Pairs with first-time MI patients with neither case nor control on statin treatment			
TC, n=397	5.42 (1.33)/5.90 (1.03)	−0.48 (−0.32 to −0.64)	<0.001
LDL-C, n=381	3.56 (1.15)/3.93 (0.85)	−0.37 (−0.23 to −0.52)	<0.001
	Survivors/non-survivors		
All pairs survivors/non-survivors			
TC cases, n=538/199	5.20 (1.34)/4.61 (1.27)	0.60 (0.38 to 0.81)	<0.001
TC controls, n=653/84	5.65 (1.11)/5.26 (1.37)	0.40 (0.14 to 0.66)	0.003
LDL-C cases, n=507/196	3.32 (1.17)/2.79 (1.06)	0.53 (0.34 to 0.72)	<0.001
LDL-C controls, n=622/81	3.70 (0.96)/3.41 (1.19)	0.29 (0.06 to 0.52)	0.015
Age groups			
Age ≤65			
TC cases, n=295/47	5.33 (1.47)/4.81 (1.21)	0.52 (0.08 to 0.96)	0.022
TC controls, n=331/11	5.77 (1.06)/5.20 (1.45)	0.57 (−0.08 to 1.21)	0.086
LDL-C cases, n=270/44	3.41 (1.30)/2.96 (1.11)	0.45 (0.04 to 0.86)	0.030
LDL-C controls, n=304/10	3.79 (0.90)/3.26 (1.22)	0.53 (−0.05 to 1.11)	0.071
Age ≥66			
TC cases, n=243/152	5.04 (1.15)/4.54 (1.29)	0.50 (0.25 to 0.74)	<0.001
TC controls, n=322/73	5.54 (1.16)/5.27 (1.36)	0.27 (−0.03 to 0.58)	0.080
LDL-C cases, n=237/152	3.21 (0.98)/2.75 (1.04)	0.47 (0.26 to 0.67)	<0.001
LDL-C controls, n=318/71	3.60 (1.01)/3.43 (1.20)	0.17 (−0.10 to 0.44)	0.209

*The p values for sex difference of TC were for cases 0.014 and for controls <0.001. The corresponding figures for LDL-C were 0.51 and 0.026.
†The p values for age group differences of TC were for cases <0.001 and for controls 0.003. The corresponding figures for LDL-C were <0.001 and 0.002.
LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TC, total cholesterol.

ACM of patients and controls

As shown in table 4 decreasing levels of TC and LDL-C were significantly associated with increasing long-term mortality in both patients and controls. After adjusting for age, sex and further diabetes, hypertension and previously diagnosed angina pectoris, only the results for the patients remained significant. No interactions between TC and LDL-C levels and the adjusting variables were

Table 3 Mean (95% CI) for TC and LDL-C (mmol/L) categorised in hour groups from symptom onset to blood sampling

Hours	n	Mean (95% CI) (mmol/L)
TC		
≤12	37	5.43 (5.01 to 5.84)
13–24	132	5.13 (4.89 to 5.37)
25–48	236	5.04 (4.85 to 5.22)
>48	174	4.96 (4.78 to 5.14)
Total	579	5.06 (4.95 to 5.17)
LDL-C		
≤12	35	3.59 (3.21 to 3.97)
13–24	128	3.23 (3.04 to 3.43)
25–48	229	3.16 (2.99 to 3.34)
>48	170	3.14 (2.98 to 3.29)
Total	562	3.20 (3.10 to 3.30)

Mean difference between the groups ≤12 and >12 hours were for TC 0.39 mmol/L (p=0.066) and for LDL-C 0.41 mmol/L (p=0.030).
LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

found in the multivariable Cox analyses in either patients or controls.

We also performed separate Cox PHREG analyses of survival below and above the medians of the TC and LDL-C distributions. Among the patients with AMI, both TC and LDL-C levels were significantly negatively related to mortality below their respective median. These findings remained significant after adjusting for age, sex and further diabetes, hypertension and previously diagnosed angina pectoris. Above their respective median, they were unrelated to mortality. Among the controls, LDL-C levels above the median were significantly positively related to higher mortality, whereas LDL-C levels below the median were significantly negatively related to higher mortality. The findings for LDL-C levels above the median remained significant after adjusting for age, sex and further diabetes, hypertension and previously diagnosed angina pectoris, while the results for LDL-C levels below the median became non-significant after adjustments. Similar result patterns, although mostly non-significant, were found for TC.

Figure 3 shows cumulative ACM for TC and LDL-C quartiles for the patients with AMI and their controls.

Table 4 Cox regression analyses of all-cause mortality according to TC and LDL-C levels in cases and controls

	Beta value	HR (95% CI) per 1 mmol/L	P value
	Case/control	Case/control	Case/control
TC, n=737/737	−0.36/−0.31	0.70 (0.62 to 0.79)/0.73 (0.60 to 0.89)	<0.001/0.002
TC*	−0.29/−0.20	0.75 (0.66 to 0.85)/0.86 (0.71 to 1.04)	<0.001/0.13
TC†	−0.19/−0.13	0.83 (0.73 to 0.95)/0.94 (0.76 to 1.16)	0.005/0.57
TC <median‡	−0.54/−0.60	0.58 (0.45 to 0.75)/0.55 (0.37 to 0.82)	<0.001/0.003
TC <median*	−0.50/−0.40	0.61 (0.47 to 0.79)/0.67 (0.45 to 1.01)	<0.001/0.054
TC <median†	−0.39/−0.32	0.68 (0.53 to 0.89)/0.72 (0.46 to 1.13)	0.004/0.15
TC ≥median‡	−0.22/0.39	0.80 (0.60 to 1.08)/1.48 (0.99 to 2.21)	0.14/0.058
TC ≥median*	−0.13/0.38	0.87 (0.65 to 1.17)/1.46 (0.94 to 2.28)	0.37/0.095
TC ≥median†	−0.11/0.44	0.90 (0.67 to 1.20)/1.56 (0.96 to 2.52)	0.47/0.073
LDL-C, n=703/703	−0.44/−0.33	0.64 (0.56 to 0.74)/0.74 (0.59 to 0.93)	<0.001/0.010
LDL-C*	−0.37/−0.21	0.69 (0.60 to 0.80)/0.87 (0.70 to 1.08)	<0.001/0.21
LDL-C†	−0.24/−0.07	0.79 (0.67 to 0.92)/0.96 (0.75 to 1.22)	0.003/0.71
LDL-C <median‡	−0.47/−0.48	0.64 (0.46 to 0.87)/0.62 (0.41 to 0.95)	0.002/0.027
LDL-C <median*	−0.45/−0.29	0.64 (0.47 to 0.86)/0.75 (0.49 to 1.16)	0.004/0.20
LDL-C <median†	−0.32/−0.22	0.73 (0.53 to 1.00)/0.79 (0.48 to 1.28)	0.052/0.34
LDL-C ≥median‡	−0.01/0.61	0.99 (0.75 to 1.30)/1.83 (1.14 to 2.95)	0.93/0.013
LDL-C ≥median*	0.08/0.57	1.09 (0.81 to 1.45)/1.77 (1.08 to 2.91)	0.58/0.024
LDL-C ≥median†	0.11/0.64	1.11 (0.83 to 1.49)/1.89 (1.09 to 3.28)	0.48/0.023

The median follow-up time for cases and controls taken together was 8.2 years.
*Adjusted for age and sex.
†Adjusted for age, sex, diabetes, hypertension and previously diagnosed angina pectoris.
‡Medians for TC cases, TC controls, LDL-C cases and LDL-C controls were 5.0, 5.6, 3.2 and 3.7 mmol/L, respectively.
LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

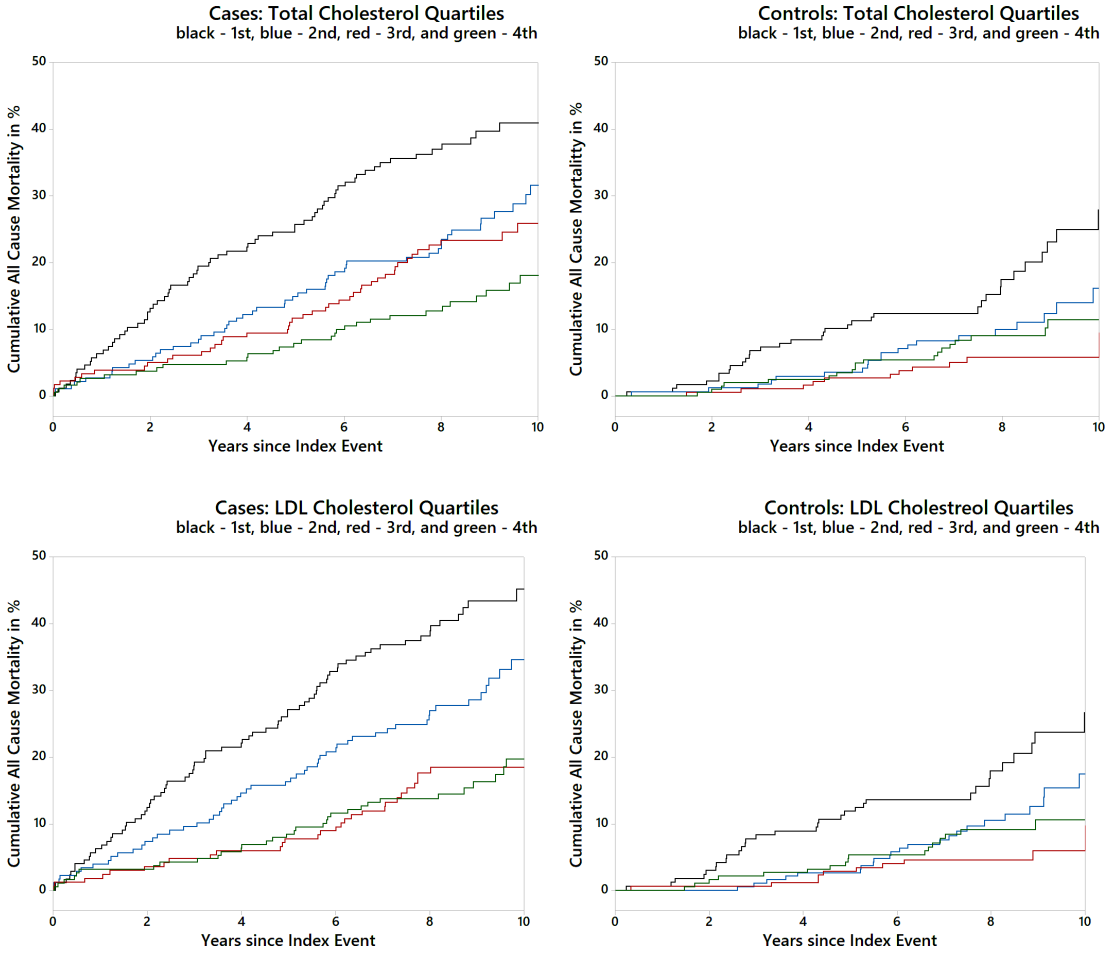

Figure 3 Cumulative mortality by quartiles. Upper left: cases categorised by TC quartiles (<4.1, 4.1–5.0, 5.0–5.9 and ≥5.9). Upper right: controls categorised by TC quartiles (<4.8, 4.8–5.6, 5.6–6.4 and ≥6.4). Lower left: cases categorised by LDL cholesterol quartiles (<2.4, 2.4–3.2, 3.2–3.9 and ≥3.9). Lower right: controls categorised by LDL cholesterol quartiles (<2.9, 2.9–3.7, 3.7–4.4 and ≥4.4). LDL, low-density lipoprotein; TC, total cholesterol.

For the patients, the mortality rate is monotonically decreasing with increasing quartile for both TC and LDL-C, while for controls, the mortality rate is decreasing with increasing quartile for the three lower quartiles and then increases in the upper quartile (TC ≥6.4 mmol/L and LDL-C ≥4.4 mmol/L). Time-dependent Cox regression analyses showed no significant HR changes over time for TC and LDL-C in patients or controls (data not shown).

TC and LDL-C levels related to time from symptom onset to blood sampling

The time intervals between symptom onset and blood sampling for TC and LDL-C analyses could be determined with reasonable certainty by the medical history in 579 (79%) of the patients with AMI. The median for these intervals was 32 (IQR 23–52) hours. The mean TC and LDL-C levels by time interval groups are shown in table 3. Patients with blood sampled within 12 hours from symptom onset stand out with clearly higher TC and LDL-C levels than patients with longer time from symptom onset to blood sampling. The mean LDL-C level in patients with blood sampled >12 hours after symptom onset was 0.41 mmol/L lower than in patients with blood sampled ≤12 hours (Wilcoxon-Mann-Whitney test Z=2.17, p=0.030). This LDL-C decrease was reasonably caused by the ongoing AMI and corresponds relatively well with the difference in LDL-C levels between patients and controls (=0.49 mmol/L). For TC, the corresponding result was 0.39 mmol/L (Wilcoxon-Mann-Whitney test Z=1.84, p=0.066).

The numbers of deaths per 100 person-years at risk among patients with MI with blood sampled ≤12 and >12 hours from symptom onset were 0.95 and 3.35, respectively. A Cox analysis showed a significantly lower mortality in the patients with AMI, which came under coronary care within 12 hours from symptom onset (HR=0.28, 95% CI 0.09 to 0.87, p=0.028).

DISCUSSION

Lower TC and LDL-C levels were associated with higher mortality in the patients but not in the controls after adjustment for clinical variables (age, sex, diabetes, hypertension and previously diagnosed angina). Furthermore, among the controls, LDL-C values above their median

were positively associated with mortality after adjustment for clinical variables. For TC values above their median, there is a trend towards positive association with mortality after adjustment for clinical variables. Consequently, our findings support a cholesterol paradox in patients with AMI, since such a paradox presupposes that higher TC and LDL-C levels increase the risk of death in the general population. Higher mortality by lower TC and LDL-C levels, interpreted as a cholesterol paradox, has been observed in patients with AMI[1–3] as well as in several chronic and acute diseases, for instance, chronic kidney disease, malignancy, chronic obstructive pulmonary diseases and rheumatoid arthritis.[13 14]

Interestingly, a study by Postmus *et al*[15] reported that a genetic predisposition to high LDL-C, as reflected by a high genetic risk score (GRS), predicted high mortality throughout life, including the oldest old. Even high familial longevity was predicted by low GRS. The importance of such a genetic predisposition for high mortality also among elderly people is illustrated by the high mortality rate among the control subjects with relatively high TC and LDL-C levels above their medians in the present study (table 4).

We used ACM as primary outcome since it is more unambiguously defined than cause-specific death. ACM as outcome measure enables comparisons of high validity with other studies using ACM as outcome measure. Moreover, we considered ACM to be a highly relevant and easily understood measure for clinicians and interested patients.

Reverse causation

Because low TC and LDL-C levels sometimes are assumed to be caused by AMI, frailty or other diseases per se, the cholesterol paradox is often referred to as 'reverse causation'. This implies that the high TC and LDL-C levels causing MI are lowered by reverse causation. Thus, our finding of an approximately 10% decrease of the mean TC and LDL-levels between patients with early and later blood sampling for lipid analysis during the acute MI phase (table 3) probably reflects reverse causation due to acute MI during the early MI phase. A possible scenario could be that high genetically determined TC and LDL-C levels cause MI, which in turn lowers these levels by reverse causation. Thus, the lower levels of TC and LDL-C in cases than in controls (table 2) are reasonably related to lowering of the lipid levels by reverse causation due to the AMI per se during the acute MI phase (table 3). This lowering may be added to previous TC and LDL-C lowering by reverse causation due to other factors such as non-AMI diseases, frailty and older age.

Age issues

Notably, only 6% of the present MI cohort was <50 years of age. The corresponding figure for the whole Sweden during the recruitment period of the patients with AMI was 5% according to the registry of the Swedish National Board of Health and Welfare (personal communication). Interestingly, the landmark Framingham pioneer study of a general population,[5] comprising 4374 individuals aged 31–65 years, identified high TC as a risk factor for all-cause and cardiovascular death up to 50 years of age. After age 50, no associations between mortality and TC levels were reported. The findings were related to particularly high mortality among individuals with decreasing TC levels during the observation period. Among younger people, Stamler *et al*[8] presented a study involving 81 488 men aged 18–39 years. An increasing long-term mortality by increasing TC levels was found. This confirms that high TC is a risk factor for death in this age range. Pekkanen *et al*[6] reported that high TC and LDL-C levels predicted high 10-year mortality in 2541 men aged 40–69 years at baseline.

Our finding of an association between low TC and increased long-term ACM in control subjects in unadjusted analyses is consistent with the findings in the Honolulu Heart cohort study[16] involving 3572 elderly men, aged 71–93 years, from the general population. Notably, the Honolulu study population showed decreasing TC before inclusion in the survival study.

A systematic review comprising 30 cohorts with a total of 68 094 people above 60 years of age by Ravnskov *et al*[17] found no or inverse association between LDL-C levels and mortality.

In view of the aforementioned evidence, our finding that lower levels of TC and LDL-C were associated with higher ACM in AMI cases and to a lesser degree in control subjects is not surprising.

Selection of control population in case–control MI studies

Our use of controls of the same sex and with the nearest birthdate in the population registry differs from the methods of selecting controls in other case–control studies of blood lipids in AMI. Two large multicentre case–control studies stand out: the INTERHEART study,[18] which is a global study of risk factors in AMI and the International Studies of Infarct Survival (ISIS) collaborators.[19] The main aim of these studies was to compare various blood lipids as indices of AMI risk in case–control pairs. This differs from the main aim of the present study, which was to determine the strength and direction of the association between the TC and LDL-C levels and ACM in matched case–control pairs, thereby reducing variations due to differences in age, sex and coronary care units, when comparing the results for patients and controls. The case–control age difference of 0.8 years in our study was mainly due to refusals by some selected control subjects, necessitating selection of another control, or delayed examination of controls for logistical reasons. The Spearman's rank correlation between TC case–control differences and time interval case–control differences of inclusion in the study was −0.043 (p=0.243). The corresponding figure for LDL-C was 0.056 (p=0.139). Thus, we considered the impact of the case–control age difference on TC and LDL-C levels to as negligible.

The control population of the worldwide INTERHEART study comprised mainly age-matched and sex-matched patients without cardiovascular diseases from the same hospital as the patients with AMI. Additionally, age-matched and sex-matched attendants and relatives of patients from a non-cardiac ward or unrelated attendants of cardiac patients were recruited as controls. The mean case/control TC levels in this study were 5.13/5.00 mmol/L.

The ISIS study concerned patients with AMI aged 30–79 years recruited in the UK in 1989–1990. In this study, first degree relatives of cases or spouses of such relatives were used as controls. Mean case–control TC and LDL-C, reported adjusted for age, sex, smoking and body mass index, were 5.86/5.60 and 3.64/3.36 mmol/L, respectively. As a comparison, the unadjusted figures for TC and LDL-C in the present study were 5.04/5.61 and 3.17/3.66 mmol/L (table 2).

Determinants of TC and LDL-C levels among cases and controls

Some possible explanations of TC and LDL-C case–control differences deserve consideration.

Pro primo

A decrease of TC and LDL-C levels from symptom onset to blood sampling for lipid analyses in patients with AMI should be considered. Notably, the blood in the ISIS study[19] described previously was sampled already at a mean time of 6 hours after symptom onset. In our study cohort, only 1% of the patients with AMI had their blood sampled within 6 hours. In the INTERHEART study,[18] recruitment of patients with AMI was restricted to those with blood sampled within 24 hours from symptom onset. The aforementioned time intervals between symptom onset and blood sampling were much shorter than those in our study with a median of 32 (IQR 23–52) hours from symptom onset. Consequently, the low TC and LDL-C levels in the patients with AMI of our study cohort, compared with those in the ISIS and INTERHEART cohorts, are reasonably related to longer time intervals between symptom onset and blood sampling as shown in table 3.

Rott *et al*[20] reported a literature review of TC and LDL-C changes during the acute MI phase and presented their own data from the day of hospitalisation to day 4 in 67 patients with AMI. They found a similar early decline of TC and LDL-C levels as found in our study. Moreover, older small studies of patients with AMI showed an even greater decline of TC levels during the acute MI phase.[21] The decline of TC and LDL-C levels in patients with AMI seems to be part of the acute phase reaction associated with acute diseases involving tissue injuries.[21]

Pro secundo

The possibility that lower TC and LDL-C levels in patients with AMI than in the control subjects reflect pre-AMI decrease in future patients with AMI deserves consideration. Manolio *et al*[22] reported a mean decline of TC with 0.16 mmol/L determined 4 years apart in a population-based sample of 2837 individuals above 65 years of age. The size of the TC decline was associated with advanced age, male gender, weight loss, high baseline TC and classification as having poor health. In our study cohort, various non-AMI diseases were more common among cases than among controls (table 1). Such non-AMI diseases, diagnosed or undiagnosed, may contribute to poorer health and frailty associated with lower TC and LDL-C levels in patients with AMI than in their controls.

Pro tertio

Secular trends may be of importance. In the Northern Swedish MONICA (monitoring trends and determinants in cardiovascular disease) study, Eriksson *et al*[23] reported a decrease in the mean TC level from 6.2 mmol/L to 5.5 mmol/L in five population surveys randomly selected from the population register in Northern Sweden between 1994 and 2014. The survey samples were independent of each other. The decrease was strongest (1.0 mmol/L) in the oldest age group, 65–74 years. This age group is in good agreement with the age of our study cohort.

CONCLUSIONS

This study shows that low TC and LDL-C levels are risk markers for ACM in patients with AMI and their age-matched and sex-matched control subjects. However, multivariable Cox PHREG analyses reveal that low TC and LDL-C levels only are independent risk factors for ACM in the patients with AMI. For the control subjects, a high LDL-C level is an independent risk factor for ACM. Thus, this study adds to the body of evidence, which suggests an inverse relation between TC and LDL-C levels and ACM in patients with AMI.

Clinical implications

Current European guidelines for care of patients with AMI[12] recommend high-intensity long-term statin treatment of patients with AMI regardless of TC and LDL-C levels. As target values of statin treatment, LDL-C <1.8 mmol/L or at least a 50% reduction of LDL-C if the baseline LDL-C level is within 1.8–3.5 mmol/L are recommended. The present study indicates that low TC and LDL-C levels predict poor survival in patients with AMI, probably due to reverse causation by the acute MI per se. Other reasons could be that low TC and LDL-C levels are proxies for frailty and/or non-AMI diseases. This complicates the evaluation of target TC and LDL-C values for statin treatment in patients with MI and may indicate that low TC and LDL-C levels in the acute MI phase identifies a patient population requiring special attention due to frailty and/or non-AMI diseases. Future research on this clinically very important topic is warranted.

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Data availability statement Data are available upon reasonable request. Qualified researchers may request access to patient-level data and related study documents, including the study protocol with any amendments, and dataset specifications. Patient-level data will be anonymised and study documents will be redacted to protect the privacy of trial participants.

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