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ORIGINAL PAPER

Cardiovascular medicine

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Baseline plasma lipid levels in patients with acute coronary syndrome: Association with 20-year mortality. The ABC-5a* Study on Heart Disease

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Abstract

Background: The relationship between baseline plasma lipid levels during acute coronary syndrome and the outcome has clinical relevance.

Methods: To evaluate their long-term prognostic value, we examined 589 patients admitted with acute coronary syndrome at three hospitals. Baseline plasma lipids were assessed on days 1 and 7. Patients were followed for 20 years or until death.

Results: Virtually, all patients completed follow-up; 437 (74%) had died: 24% from coronary artery disease/heart failure (CAD/HF), 21% sudden cardiac death (SCD), 16% from other cardiovascular causes and 39% had non-cardiac death. The incidence rate (IR) of all-cause mortality was not different among patients with baseline plasma lipids less or greater than the median value. The IR of CAD/HF mortality was not significantly higher among patients with greater than median low-density lipoprotein (LDL) cholesterol and triglyceride (TG) levels. The IR of non-cardiac death tended to be lower among patients with greater than median total cholesterol (TC) and LDL levels. Using three levels of adjusted Cox survival models, baseline plasma lipids had no consistent independent or inverse association with all-cause mortality, even after excluding patients who received statins. Competitive risk survival models for each cause of death revealed that the only hazard of non-cardiac death was consistently higher among patients with less than or equal to median TC and LDL levels.

Conclusion: In the present prospective long-term study, after acute coronary syndrome, baseline plasma lipid levels seem not to be associated with long-term global mortality. Only an independent inverse association between TC and LDL and non-cardiac death has been observed.

1 | INTRODUCTION

Ischaemic heart disease (IHD) is the world's biggest killer, accounting for 9.4 million deaths (16.6% of total deaths) in 2016 and has been the leading cause of death globally over the last 15 years.[1]

High plasma lipid levels, particularly total serum cholesterol (TC) and low-density lipoprotein (LDL), have long been recognised as a major risk factor for atherosclerosis and IHD.[2-4] However, this causal relationship has been debated in recent reports.[5-7] The prognostic value of admission plasma lipid levels in patients presenting with acute coronary syndrome has rarely been discussed in the literature.[8-10] In the present study, we aimed to report the association

*ABC is an acronym for Adria, Bassano, Conegliano, and Padova Hospitals.

between the in-hospital plasma lipid profile and the subsequent long-term mortality risk over 20 years of follow-up in an unselected sample of patients discharged alive from three different centres after an index hospitalisation with acute coronary syndrome.

What's known

- In many studies, increased serum lipids are reported to be associated with a higher risk of mortality.

What's new

- After 20 years of follow-up of acute coronary syndrome survivors, baseline plasma lipid levels were not associated with all-cause mortality.
- Baseline plasma lipid levels were significantly inversely associated with death from non-cardiac causes.

2 | METHODS

2.1 | Patients

The ABC Study on Heart Disease is an ongoing prospective investigation designed to represent, as closely as possible, an unbiased population of patients with acute coronary syndrome (www.abcheartdiseasestudy.org/en/). The cohort includes Caucasian patients with definite acute coronary syndrome, including ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) or unstable angina, who were admitted to the intensive care units of Adria, Bassano, and Conegliano General Hospitals in Italy between June 1995 and January 1998. The original aim of the ABC study was to monitor these patients with regard to natural long-term history, both non-fatal and fatal events, and causes of death. Another study aim was to investigate the prognostic value of multiple baseline clinical variables. Criteria for acute coronary syndrome diagnosis included clinical presentation, electrocardiogram findings and the presence of serum biochemical markers of necrosis.[11,12]

A total of 741 patients were considered eligible upon admission, 84 of whom were excluded because they had diseases other than acute coronary syndrome, and 23 were excluded because of a lack of baseline data. Among the 634 enrolled patients with acute coronary syndrome, 45 died during the index hospitalisation. Therefore, the postdischarge follow-up study included 589 patients (Figure 1). Each patient received an anonymous code, and no personal data or identifiers were included in the baseline or follow-up database. The study has been performed in accordance with the Declaration of Helsinki and it was approved by Adria, Bassano del Grappa and Conegliano General Hospitals ethics committee. All enrolled patients gave their written informed consent.

2.2 | Measurements and follow-up

At enrolment, a thorough patient history was collected from medical records and patient interviews. All presently analysed baseline clinical and laboratory data were obtained during the first 7 days of hospitalisation in the intensive coronary care unit. The acute coronary syndrome diagnosis criteria were the fulfilment of at least two of the following: central chest pain lasting >30 minutes, typical changes in serum enzymes, including total creatine kinase (CK) and creatine kinase MB (CK-MB), and typical electrocardiogram changes with pathological Q waves and/or localised ST-T changes in at least two contiguous leads.[13] Two fasting venous blood samples (12 hours after admission and before discharge) were drawn for TC, LDL, HDL, and triglyceride (TG) measurements. LDL concentrations were estimated using the modified Friedewald formula (MFF): LDL (mg/dL) = non-HDL × 90% − TG × 10%. In all three hospitals, plasma lipid measurements were performed using an enzymatic colorimetric method.[14] Details of the measured variables were published previously.[11,12]

Each patient underwent a clinical check-up 1, 3, 5, 7, 10, 12, 15, 17 and 20 years after recruitment. At each recruitment hospital, two

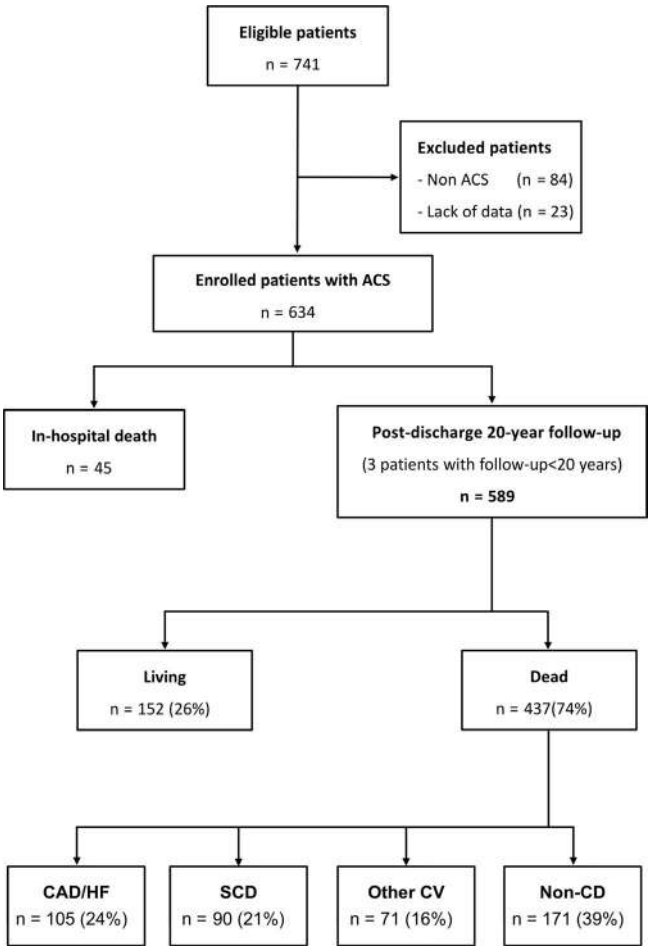

FIGURE 1 Flow diagram of the study population and progress during follow-up. ACS, acute coronary syndrome; CAD/HF, coronary artery disease/heart failure; Other CV, other cardiovascular causes; SCD, sudden cardiac death

cardiologists were responsible for monitoring the cohort of patients throughout the follow-up. Data were obtained from scheduled examinations, public administrations, hospital records, family doctors, postmortem examinations and death certificates. The medications received during index hospitalisation and follow-up treatments were also recorded.

All data after enrolment were recorded prospectively following the protocol of the ABC Study on Heart Disease.[11] According to the protocol, baseline data and follow-up data were recorded in two different datasheets. For the present analysis, the datasheets were merged after completion of 20 years of follow-up.

2.3 | Causes of death

The primary clinical outcome was 20-year all-cause mortality. The secondary outcomes were modes of death, which were classified into the following categories: coronary artery disease and/or heart failure progression (CAD/HF); sudden cardiac death (SCD), defined as witnessed, out-of-hospital death within 1 hour after the onset of acute symptoms or unwitnessed, unexpected death (eg, during sleep) in patients with good health 24 hours before the event[15]; other cardiovascular (other CV) causes; and non-cardiac death causes. The patients were examined and the cause of death was determined by two clinical researchers with no knowledge of the patients' baseline data.

2.4 | Statistical analysis

The accrued variables were analysed as continuous variables or proportions. Log transformations were applied to correct for positively skewed distributions as appropriate. Measured variables were analysed using the unpaired Student's *t* test, and categorical variables using Pearson's χ^2 test. If a patient dropped out prior to 20 years of follow-up, her/his data were censored at that time. Survival curves were constructed using cumulative hazards.[16] We compared incidence rates (IRs) using Mantel-Haenszel estimates of the rate ratio. Interaction analysis for lipid versus age and gender was also performed.[17] The risk ratios (RRs) estimated in the analysis and graphic representations of the mortality were obtained using lipid values as dichotomous variables, with the 50th percentile as a cut-off.

Log-transformed continuous variables were used for global mortality risk estimation using Cox regression models and scaled Schoenfeld residuals were used to test the proportionality assumption with 95% confidence intervals (CIs). Competitive risk regression models with the Fine-Gray method using the same log-transformed continuous variables were set-up to analyse each of the four modes of death. The strength of an association was expressed as β coefficient ± SE. The predictive power of lipid values as continuous variables with regard to mortality was also estimated. Based on survival regression, a postestimation prediction of mortality was carried out and graphically presented along with the appropriate *P*-values calculated by the survival regression. Unless otherwise indicated, two-tailed *P*-values < .05 were considered significant. Statistical analyses were performed using STATA 14.

3 | RESULTS

All enrolled patients completed the follow-up unless pre-empted by death, except three patients for whom survival time was censored before 20 years; two withdrew consent and one moved overseas (Figure 1). Table 1 compares the demographic and baseline clinical characteristics of the patients according to plasma TC level at admission in relation to the median value of 208 mg/dL.

At enrolment, the two groups did not differ in most of the clinical characteristics. However, females were more frequent among patients with higher TC levels. In addition, these patients had higher BMI, used alcohol less frequently and had higher blood haemoglobin values. Patients who had TC >208 mg/dL at admission also had higher LDL and TG levels and lower HDL levels.

By the end of 20 years of follow-up, 437 (74%) of the patients discharged alive had died: 105 (24%) from CAD/HF, 90 (21%) SCD, 71 (16%) other CV causes and 171 (39%) non-cardiac death (Figure 1). The IR of all-cause mortality throughout follow-up after acute coronary syndrome was approximately 66.7 (95% CI 60.7-73.3) cases/1000 person-years. Unexpectedly, the IR was not associated with the baseline plasma lipids (Table S1). Cumulative hazard estimate curves for 20-year all-cause mortality risk according to baseline plasma lipid levels are illustrated in Figure 2 and Figure S1.

The final survival analysis accounted for competitive risks for each of the main four causes of death, revealing that the positive association of baseline TC, LDL and TG levels and the negative association of HDL level with long-term CAD/HF mortality were not statistically significant in the unadjusted model, a model adjusted for age and gender or the fully adjusted model (Table 2). The analysis also showed a lack of consistently positive or negative association between TC and LDL and other causes of cardiac mortality. Only the hazard of non-cardiac death was consistently higher among patients with TC or LDL values less than or equal to median values at admission in all models (Table 2B).

4 | DISCUSSION

This prospective three-centre study of an unselected real-world patient discharged alive after acute coronary syndrome showed that baseline plasma TC, LDL, HDL and TG levels are not associated with long-term global mortality. The association with modes of death showed an independent inverse association between TC and LDL and non-cardiac death. The same findings were reported in our research letter.[18]

The results are consistent for lipid measurements at admission or after 1 week of hospitalisation. Furthermore, the associations were independent of anti-lipid treatment, suggesting that the core prognostic issue lies on the lipid levels per se.

TABLE 1 Baseline characteristics of patients with acute coronary syndrome according to the baseline total cholesterol level

Variable	Overall sample (n = 589)	TC ≤208 mg/dL (n = 295)	TC >208 mg/dL (n = 294)	*P* values
Median age, years	67 (58-74)	67 (59-75)	66 (58-73)	.47
Gender, female	29.2	22	36	<.0001
Education above primary school	26	29	23	.37
Median body mass index, kg/m^2	26 (24-28)	25 (23-27)	26 (24-29)	.0001
Smoking habit[a]	67	71	64	.09
Alcohol use	74	80	68	.001
Hypertension	47	51	44	.08
Diabetes mellitus	22	22	23	.68
Median systolic blood pressure, mm Hg	120 (110-130)	120 (110-130)	120 (110-135)	.19
Median diastolic blood pressure, mm Hg	80 (70-80)	75 (70-80)	80 (70-80)	.50
Median heart rate, beats/min	71 (60-82)	72 (60-81)	70 (61-82)	.54
Non-ST elevation ACS	38	38	39	.79
Killip class >1	33	34	33	.75
LVEF (%) (n = 500)	52 (45-61)	53 (45-60)	52 (45-61)	.73
Hb, g/dL	14 (13-15)	13 (12-15)	14 (13-15)	.0001
Blood glucose level, mg/dL	119 (100-158)	117 (98-153)	122 (103-172)	.06
Serum creatinine level, mg/dL	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	.95
CK-MB peak[b], U/L	102 (43-203)	100 (42-186)	104 (34-214)	.15
Serum lipids[b], mg/dL				
Total cholesterol				
At admission	208 (179-243)	179 (159-193)	243 (225-264)	<.0001
At discharge	198 (174-224)	177 (155-192)	220 (204-245)	<.0001
LDL[c]				
At admission	133 (108-157)	108 (91-158)	157 (144-178)	<.0001
At discharge	125 (106-147)	109 (93-122)	143 (128-163)	<.0001
HDL				
At admission	44 (37-51)	42 (36-51)	45 (39-52)	.005
At discharge	39 (33-47)	37 (32-46)	40 (33-49)	.01
TGs				
At admission	127 (93-178)	109 (81-147)	155 (112-218)	<.0001
At discharge	146 (111-188)	129 (102-162)	162 (124-212)	<.0001

Note: The values are presented as medians and interquartile ranges or percentages.

Abbreviations: ACS, acute coronary syndrome; CK-MB, creatine kinase-MB isoenzyme; Hb, haemoglobin; HDL, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase-1 isoenzyme; LDL-C, low-density lipoprotein-cholesterol; LVEF, left ventricular ejection fraction; TC, total cholesterol; TG, triglyceride.

[a]Previous smokers and currently smoking patients.

[b]*P*-values were calculated using log-transformed data.

[c]Calculated using modified Friedewald formula.

The general view is that an elevated level of plasma of TC and LDL is a major risk factor for developing atherosclerotic cardiovascular disease (CVD).[2-4] Interestingly, our results demonstrated that neither total nor LDL-cholesterol was elevated at the time of admission with acute coronary syndrome as it should be expected according to that view. Low or normal TC and LDL-C in patients

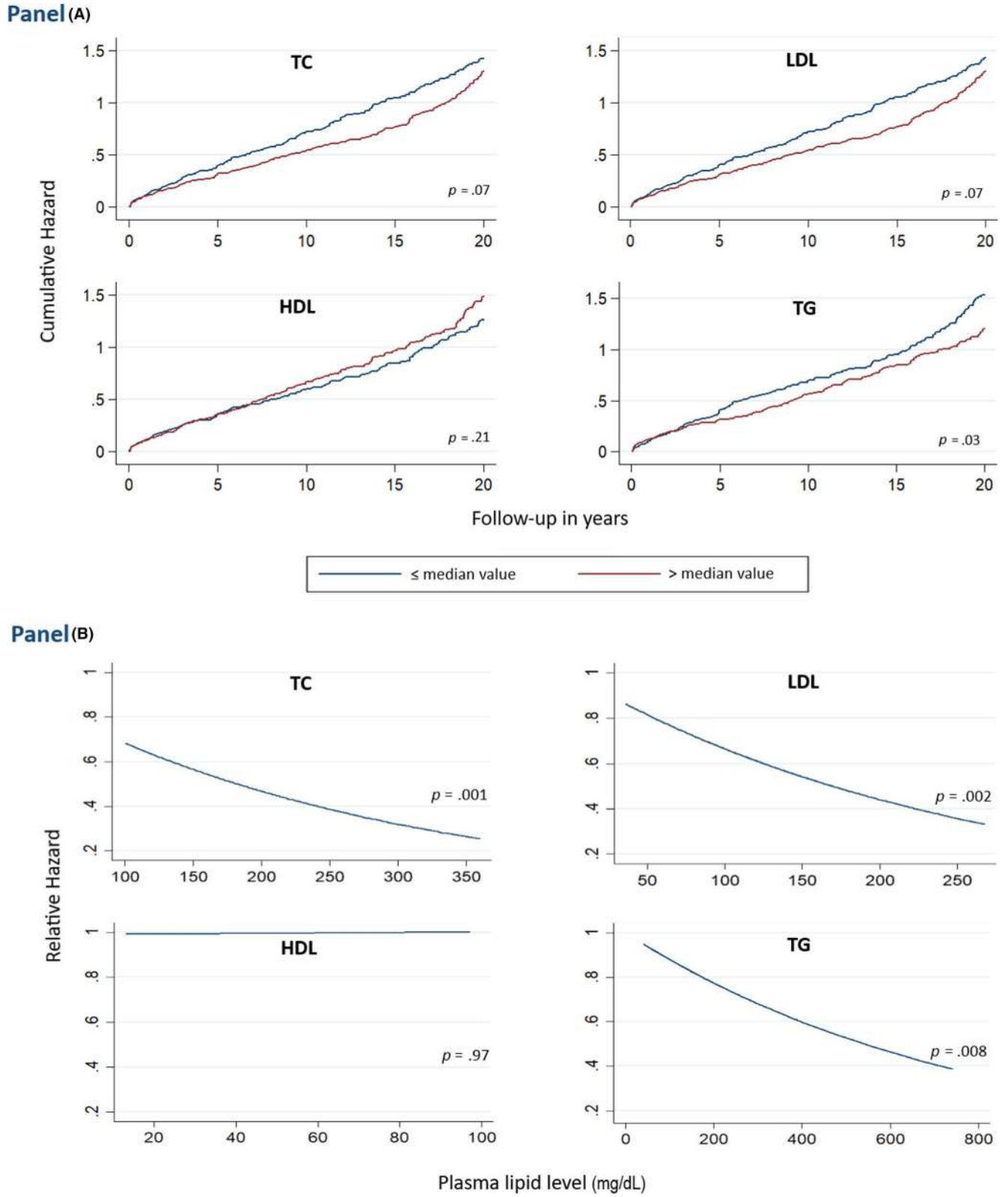

FIGURE 2 Cumulative hazard estimate curves for 20-year all-cause mortality risk. A, Cumulative hazard estimate according to day 1 plasma lipid levels. B, Estimated prediction. HDL, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol; TG, triglyceride. *P*-values were calculated by unadjusted Cox regression models using log-transformed continuous variables

with CVD has been reported by other researchers.[19,20] Recently, the general view has been questioned.[5-7] As reported by Ravnskov et al, [7] there are many observations and experiments contradicting that high TC or LDL-C causes atherosclerosis and CVD, and several recent observations have supported their view. For instance, six recent follow-up studies including almost 700 000 individuals of

TABLE 2 Cox regression analysis of all-cause mortality risk (A) and competing risk regression analysis for the main causes of death (B) according to baseline plasma lipid levels

	Adjusted for age and gender			Fully adjusted[a]			Fully adjusted[b]		
Variable	β ± Robust SE	Z	*P*	β ± Robust SE	Z	*P*	β ± Robust SE	Z	*P*
(A) Cox regression analysis									
All-cause mortality (n = 437)									
Total cholesterol									
At admission	0.46 ± 0.22	−2.07	.04	0.58 ± 0.22	−2.62	.01	0.44 ± 0.24	−1.86	.06
At discharge	0.55 ± 0.27	−2.02	.04	0.50 ± 0.27	−1.86	.06	0.32 ± 0.28	−1.14	.25
LDL									
At admission	0.33 ± 0.16	−2.02	.04	0.43 ± 0.17	−2.58	.01	0.32 ± 0.18	−1.82	.07
At discharge	0.32 ± 0.22	−1.46	.14	0.34 ± 0.22	−1.58	.12	0.20 ± 0.23	−0.86	.39
HDL									
At admission	0.41 ± 0.18	−2.20	.03	0.36 ± 0.19	−1.89	.06	0.35 ± 0.19	−1.87	.06
At discharge	0.64 ± 0.20	−3.22	<.0001	0.46 ± 0.21	−2.21	.03	0.41 ± 0.21	−1.98	.05
TGs									
At admission	0.11 ± 0.10	1.04	.30	0.06 ± 0.11	0.58	.56	0.10 ± 0.11	0.90	.37
At discharge	0.11 ± 0.14	0.81	.42	0.02 ± 0.14	0.16	.87	0.07 ± 0.14	0.49	.62
(B) Competing risk regression									
CAD/HF mortality (n = 105)									
Total cholesterol									
At admission	0.78 ± 0.48	1.63	.10	0.78 ± 0.48	1.63	.10			
At discharge	0.33 ± 0.57	0.57	.57	0.57 ± 0.56	1.01	.31			
LDL									
At admission	0.66 ± 0.37	1.76	.08	0.69 ± 0.39	1.77	.08			
At discharge	0.55 ± 0.46	1.20	.23	0.74 ± 0.46	1.60	.11			
HDL									
At admission	−0.66 ± 0.38	−1.74	.08	−0.51 ± 0.41	−1.24	.22			
At discharge	−0.72 ± 0.39	−1.85	.06	−0.54 ± 0.42	−1.29	.20			
TGs									
At admission	0.41 ± 0.20	2.01	.05	0.33 ± 0.21	1.59	.11			
At discharge	0.19 ± 0.27	0.69	.49	0.05 ± 0.27	0.19	.85			
SCD (n = 90)									
Total cholesterol									
At admission	0.58 ± 0.52	1.12	.26	0.83 ± 0.46	1.83	.07			
At discharge	0.27 ± 0.64	0.42	.67	0.74 ± 0.59	1.25	.21			
LDL									
At admission	0.44 ± 0.41	1.09	.28	0.62 ± 0.38	1.62	.10			
At discharge	0.46 ± 0.52	0.89	.38	0.76 ± 0.50	1.52	.13			
HDL									
At admission	−0.41 ± 0.44	−0.94	.35	−0.35 ± 0.46	−0.76	.45			
At discharge	−1.11 ± 0.44	−2.53	.01	−0.76 ± 0.46	−1.63	.10			
TGs									
At admission	0.10 ± 0.23	0.45	.65	0.25 ± 0.22	1.17	.24			
At discharge	0.06 ± 0.31	0.20	.85	0.12 ± 0.31	0.37	.71			

(Continues)

TABLE 2 (Continued)

	Adjusted for age and gender			Fully adjusted[a]			Fully adjusted[b]		
Variable	β ± Robust SE	Z	*P*	β ± Robust SE	Z	*P*	β ± Robust SE	Z	*P*
Other CV causes (n = 71)									
Total cholesterol									
At admission	−0.63 ± 0.46	−1.35	.18	−0.44 ± 0.50	−0.87	.38			
At discharge	−0.68 ± 0.60	−1.13	.26	−0.56 ± 0.65	−0.87	.39			
LDL									
At admission	−0.38 ± 0.31	−1.21	.23	−0.23 ± 0.36	−0.66	.51			
At discharge	−0.68 ± 0.46	−1.48	.14	−0.62 ± 0.51	−1.22	.22			
HDL									
At admission	0.15 ± 0.50	0.30	.77	0.34 ± 0.49	0.70	.49			
At discharge	0.22 ± 0.48	0.45	.65	0.49 ± 0.57	0.86	.39			
TGs									
At admission	−0.12 ± 0.24	−0.50	.61	−0.30 ± 0.26	−1.16	.25			
At discharge	0.27 ± 0.31	0.89	.37	0.08 ± 0.34	0.24	.81			
Non-cardiac death (n = 171)									
Total cholesterol									
At admission	−0.86 ± 0.36	−2.40	.02	−1.12 ± 0.39	−2.86	<.0001			
At discharge	−0.28 ± 0.42	−0.66	.51	−0.53 ± 0.46	−1.15	.25			
LDL									
At admission	−0.71 ± 0.27	−2.67	.01	−0.88 ± 0.28	−3.11	<.0001			
At discharge	−0.40 ± 0.33	−1.20	.23	−0.55 ± 0.36	−1.54	.12			
HDL									
At admission	0.38 ± 0.28	1.38	.17	0.25 ± 0.29	0.87	.39			
At discharge	0.64 ± 0.31	2.05	.04	0.35 ± 0.33	1.07	.29			
TGs									
At admission	−0.28 ± 0.18	−1.60	.11	−0.32 ± 0.19	−1.64	.10			
At discharge	−0.18 ± 0.22	−0.84	.40	−0.11 ± 0.23	−0.48	.64			

Note: P-values were calculated for log-transformed data.

Abbreviations: CAD, coronary artery disease; CV, cardiovascular; HDL, high-density lipoprotein cholesterol; HF, heart failure; LDL-C, low-density lipoprotein-cholesterol; SCD, sudden cardiac death; SE, standard error; TG, triglyceride.

[a]Adjusted for age, gender, smoking, diabetes mellitus, hypertension, heart failure at admission, STEMI and hospital site.

[b]Adjusted for age, gender, smoking, diabetes mellitus, hypertension, heart failure at admission, STEMI, hospital site and the use of statins.

all ages from various countries have shown that neither TC nor LDL-C is a risk factor of mortality, neither among statin-treated patients nor among untreated individuals.[21-25] In fact, as shown by our results as well, low values are associated with increased total mortality. This finding challenges the view that high cholesterol is the cause of early death from CVD as well because the commonest cause of death in most countries is CVD. Furthermore, in the study by Ravnskov et al,[26] CVD mortality was recorded as well in seven of the 19 studies they had included in their review, and in six of them, LDL-C was not associated with CVD mortality and in one of them, CVD mortality was highest among those with the lowest LDL-C.

In many studies, increased serum lipids and lipoproteins are associated with a higher risk of total and cardiac mortality.[27-35] However, absence of an association, or even an inverse association, has been reported,[5-7] especially with increasing age.[26,36] In accordance, prior observational studies have reported paradoxically better outcomes in hypercholesterolaemic patients who sustain acute coronary syndrome, the so-called 'cholesterol paradox'.[20,37-39]

The occurrence of acute coronary syndrome is accompanied by transient changes in the plasma lipid profile, including decreases in TC, LDL and HDL levels and increases in plasma TG.[40,41] The prognostic value of plasma lipids at admission was investigated in prior studies, and a hypercholesterolaemia paradox has also been observed.[8-10,20,42-45]

Importantly, the majority of these reports were performed in the short- to intermediate term; the longest was approximately 3 years.

Furthermore, a single LDL or TG level at admission was used, accordingly, the effect of the changes in their levels on clinical outcomes could not be assessed. Notably, these reports tended to focus on total mortality.[8-10,20,42-45]

Although it was not significant, we also observed the negative trend (hypercholesterolaemia paradox). Our different prognostic results support the assumption of the presence of other modifiable risk factors, other than cholesterol levels, that deliberates this risk in the majority of patients and may explain why patients develop myocardial infarction despite a low LDL level [19,39] or why a considerable proportion of major adverse events are still not prevented by aggressive lipid-lowering treatment.[46] We also observed during the long-term follow-up that non-cardiac death was more prevalent, and an inverse association with plasma lipid levels was observed in concordance with previous reports.[5,47,48] This observation is clinically relevant if we consider that the non-cardiac mortality rate after acute coronary syndrome has progressively increased in recent years.[49,50] We could assume that the improvement in CV treatment tends to reduce CV mortality, allowing non-cardiac disorders and their complications to prevail. In agreement with our findings, other authors have reported an unexplained absence of an independent association between cholesterol and stroke mortality, especially at older ages or in the presence of higher blood pressures.[32] Age is also a considerable factor, as the median age of our cohort at the time of admission was approximately 67 years, and it is understandable that the prognostic role of plasma lipids changes with the ageing of the population. In a systematic review, Ravnskov et al [26]reported a lack of an association or inverse association between LDL and mortality in elderly people. In short, our study provides new clinical insight and perspective into the long-term prognostic significance of admission plasma lipid levels in survivors of acute coronary syndrome.

The present prospective long-term study revealed that baseline plasma lipid levels during acute coronary syndrome seem not to be associated with long-term global mortality. Only an independent inverse association between TC and LDL and non-cardiac death has been observed.

5 | STUDY LIMITATIONS

A major limitation of the ABC study of acute coronary syndrome was that, at the time of patient enrolment, percutaneous coronary angioplasty was not yet used to reopen coronary arteries in patients with STEMI. Thus, it remains uncertain whether the results may have been altered by early mechanical reperfusion. Although Cho et al[43] reported that admission LDL-cholesterol level was not an independent predictor of mortality at 12 months among 9571 patients with acute myocardial infarction who had a percutaneous coronary intervention (PCI). Pres et al[45] also reported that LDL level at admissions was not associated with increased in-hospital mortality in non-diabetic patients treated with PCI for STEMI, and Al-Mallah et al[8] reported an inverse association, despite that more than 60% of their patients have been subjected to PCI or coronary artery bypass graft surgery. Furthermore, statin treatment was much less commonly used at the beginning of the study period (1995-1998) and steadily increased from the 1st to the 20th year of follow-up in accordance with guideline revisions over that time period. Finally, as the patients in this study were all Caucasians, we cannot generalise the present findings to other populations and ethnic groups.

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DISCLOSURES

None.

AUTHOR CONTRIBUTIONS

Dr G. Berton and Dr F. Cavuto designed the study. Dr R. Cordiano and Dr F. Bagato contributed to the original data collection. Dr F. Cavuto and Dr R. Cordiano contributed to data handling and patient follow-up. Dr G. Berton and Dr HT Mahmoud contributed to the data analysis and interpretation, tables and figures preparation and manuscript preparation. All authors contributed to ensuring the accuracy of the data analysis.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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