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Plasma lipid levels during ACS: Association with 20-year mortality: The ABC-5* Study on Heart Disease

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To assess the association between baseline plasma lipid levels during acute coronary syndrome (ACS) and long-term mortality we examined 589 patients who were admitted to Adria, Bassano and Conegliano General Hospitals in Italy between June 1995 and January 1998 and were discharged alive.

Baseline plasma lipids were evaluated on days 1 and 7 after admission. Criteria for diagnosis and follow-up data were reported following the protocol of the ABC Study on Heart Disease[1] (www.abcheartdiseasestudy.org/en/). The study has been performed in accordance with the Declaration of Helsinki and was approved by the hospitals' ethics committee. Patients were followed for 20 years or until death. The primary clinical outcome was all-cause mortality and the secondary outcomes were modes of death. Results reported as a percentage or median and interquartile range. Log-transformed continuous variables were used for global mortality risk estimation using unadjusted and adjusted Cox regression models as well as competitive risk regressions models with the Fine–Gray method.

All patients completed the follow-up, except for three. Their median age was 67 (58–74) years and 29.2% were women. Comparing patients according to the plasma total cholesterol (TC) level at admission in relation to a median value of 208 mg/dL, the two groups did not differ in most of the clinical characteristics. However, women were more frequently among patients with higher TC levels (36% vs. 22%, $P < 0.001$). In addition, these patients had a higher body mass index (BMI) (26 (24–29) vs. 25 (23–27), $P = 0.0001$), used alcohol less frequently (68% vs. 80%, $P = 0.001$) and had higher blood haemoglobin values (14 (13–15) vs. 13 (12–15), $P = 0.0001$). Patients who had TC greater than 208 mg/dL at admission also had higher low-density lipoprotein (LDL) (157 (144–178) vs. 108 (91–158), $P < 0.0001$), high-density lipoprotein (HDL) (45 (39–52) vs. 42 (36–51), $P = 0.005$) and triglyceride levels (155 (112–218) vs. 109 (81–147), $P < 0.0001$).

By the end of follow-up, 437 (74%) patients had died: 24% due to coronary artery disease/heart failure (CAD/HF), 21% sudden cardiac death (SCD), 16% due to other cardiovascular causes and 39% due to non-cardiac death (CD) causes. The incidence rate (IR) of all-cause mortality was approximately 67 (95% confidence interval (CI) 61–73) cases/1000 person-years. Unexpectedly, the IR was not different among patients with baseline plasma lipids equal to or less than or greater than their median at admission or discharge ($P > 0.05$ for all). The IR of CAD/HF mortality tended to be higher among patients with LDL and triglyceride levels greater than the median values ($P = 0.04$ for both). No difference was found for SCD or other cardiovascular causes. In contrast, the non-CD incidence rate tended to be lower among patients with TC and LDL levels greater than the median values ($P = 0.01$ for both).

The cumulative hazard estimate analysis revealed a slight inverse trend between plasma TC, LDL ($P = 0.07$ for both) and triglyceride ($P = 0.03$) levels and all-cause mortality, and an insignificant positive trend for HDL ($P = 0.21$). In the fully adjusted Cox surviving model including age, gender, smoking, diabetes mellitus, hypertension, HF at admission, ST-segment elevation myocardial infarction, and baseline plasma lipid levels tended to show the same inverse association ($P = 0.01$

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

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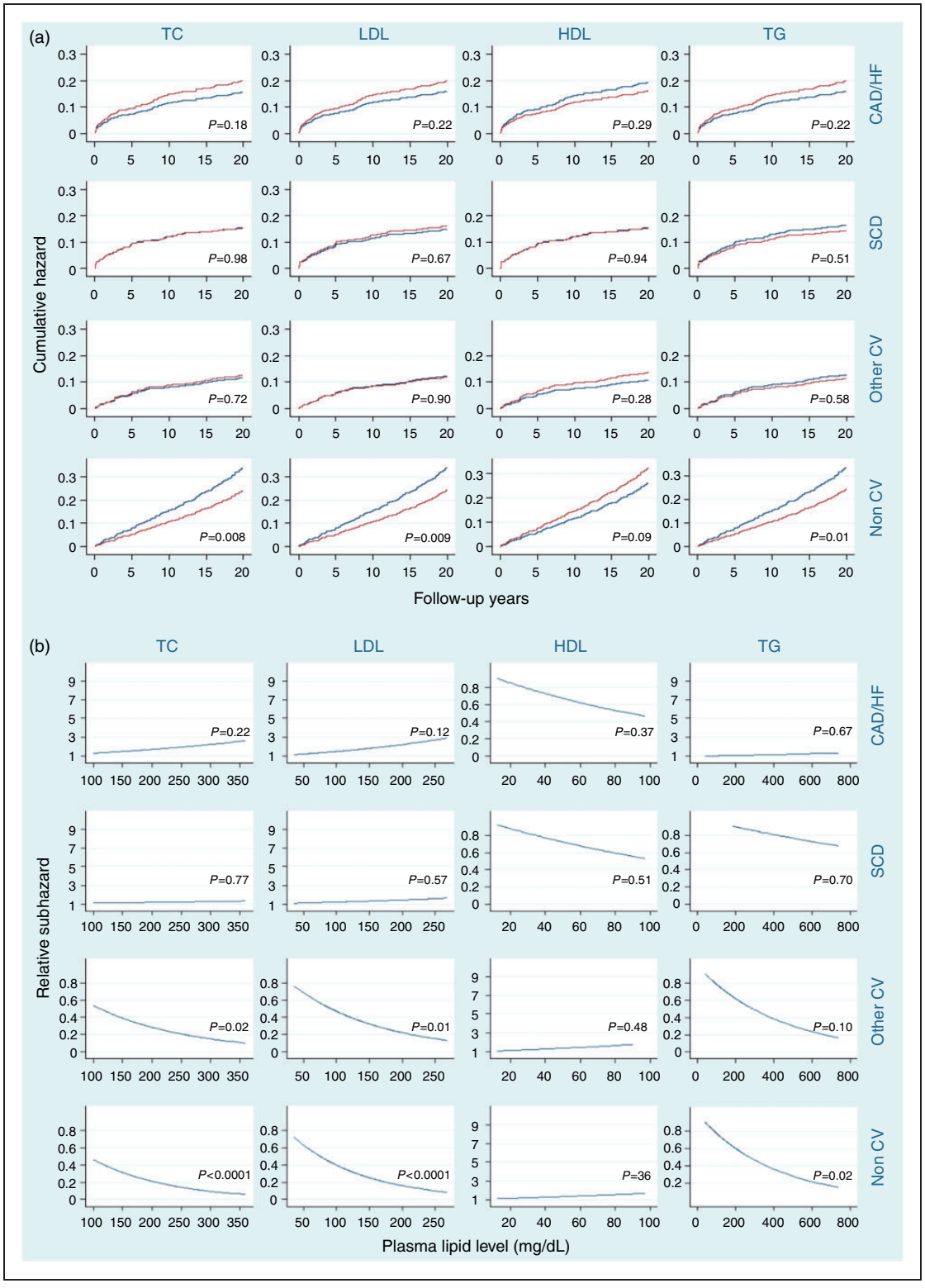

Figure 1. Cumulative hazard estimate curves for 20 years cause-specific mortality risk. (a) Cumulative hazard estimate according to day 1 plasma lipid levels (red line greater than median value and blue line median value or less). (b) Estimated prediction. CAD/HF: coronary artery disease/heart failure; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; non-CD: non-cardiac death; other CV: other cardiovascular causes; SCD: sudden cardiac death; TC: total cholesterol; TG: triglycerides. *P* values were calculated by unadjusted competitive risk regression models using log-transformed continuous variables.

for both TC and LDL). Similar results held even after excluding patients who received statin treatment during follow-up from the analysis.

The survival analysis accounted for competitive risks for each cause of death, revealed that the positive association of baseline TC, LDL and triglyceride levels, and the negative association of HDL level with long-term CAD/HF mortality were not statistically significant either in the unadjusted model (Figure 1), or in the fully adjusted model ($P > 0.05$ for all). The analysis also showed a lack of consistent positive or negative association between TC and LDL and other causes of cardiac mortality ($P > 0.05$ for all). Only the hazard of non-CD mortality was consistently higher among patients with TC or LDL values equal to or less than the median values in all models (hazard ratio (HR) 0.6, 95% CI 0.5–0.9, $P = 0.01$) and (HR 0.6, 95% CI 0.5–0.9, $P = 0.01$) respectively.

This prospective three-centre study of an unselected real-world patient sample showed that baseline plasma TC, LDL, HDL and triglyceride levels at the time of ACS were not associated with long-term global mortality. We observed only an independent inverse association between TC and LDL levels and non-CD death. The results are consistent for lipid measurements at admission or after one week of hospitalisation. Furthermore, the associations we found seem to be mostly independent of anti-lipid treatment, suggesting that the core prognostic issue lies on the lipid levels per se. In the general population, increased serum cholesterol and lipoproteins are associated with a higher risk of total and cardiovascular mortality.[2] However, the absence of an association, or even an inverse association, has been reported,[3,4] especially with increasing age.[5] Prior observational studies have reported paradoxically better outcomes in hypercholesterolemic patients who sustain ACS, the so-called 'cholesterol paradox'. The prognostic value of plasma lipids at admission was investigated in prior studies, and a hypercholesterolemia paradox has also been observed.[6,7] Importantly, the majority of these reports were performed in the short to intermediate term and tended to focus on total mortality. We also observed that non-CD was more prevalent,[8] and an inverse association with plasma lipid levels was observed in concordance with previous reports.[4,9,10] We could assume that the improvement in cardiovascular treatment tends to reduce cardiovascular mortality, allowing non-cardiac disorders and their complications to prevail. The median age of our cohort at the time of admission was approximately 67 (58–74) years, and it is understandable that the prognostic role of plasma lipids changes with the aging of the population.[5] In short, our study provides new clinical insight and perspective into the long-term prognostic significance of admission plasma lipid levels in survivors of ACS.

A major limitation of the study was that, at the time of patient enrollment, percutaneous coronary angioplasty was not yet used. Thus it remains uncertain whether the results may have been altered by early mechanical reperfusion. Yet Al-Mallah et al.[6] reported an inverse association, despite the fact that more than 60% of their patients had been subjected to percutaeous coronary intervention or coronary artery bypass graft surgery. Furthermore, statin treatment was much less commonly used at the beginning of the study period. Finally, as the patients in this study were all Caucasians, we cannot generalise the present findings to other populations.

Declaration of conflicting interests

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