Lower low density lipoprotein cholesterol associates to higher mortality in non-diabetic heart failure patients

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ABSTRACT

Background: In patients with established heart failure (HF) low total cholesterol levels associate with worse prognosis. Evidence concerning the impact of Low-density lipoprotein cholesterol (LDL-c) in HF is scarce. We aimed to evaluate the prognostic impact of LDL-c in patients with HF, both with and without diabetes *mellitus* (DM).
Methods: We retrospectively analyzed outpatients with chronic HF with systolic dysfunction followed in our HF clinic from January/2012 to May/2018. LDL-c was calculated using the Friedewald's formula. Patients without a complete lipid profile were excluded. The endpoint under analysis was all-cause mortality. Patients were followed until January/2021. A Cox-regression analysis was used to study the prognostic impact of LDL-c. The LDL-c cut-off used was 100 mg/dL (mean value). Analysis was stratified according to the coexistence of DM. Multivariate models were built adjusting for age, sex, coronary artery disease, atherosclerotic non-coronary artery disease, arterial hypertension, smoking status, statin use, severity of systolic dysfunction, creatinine clearance and evidence-based therapy.
Results: We studied 522 chronic HF patients, mean age was 70 years, 66.5% males. Severe systolic dysfunction was present in 42.7%, 30.5% had coronary heart disease, 60.5% had arterial hypertension, 41.6% had DM. A total of 92.0% were treated with beta blocker, 87.5% with an ACEi/ARB and 29.1% with a MRA. During a median follow-up of 53 (interquartile range 33–73) months, 235 (45%) patients died. Patients with LDL-c $\leq$100 mg/dL presented increased multivariate-adjusted risk of all-cause mortality: HR = 1.58 (95% CI: 1.08–2.30), p = 0.02. When patients were stratified according to DM, LDL-c $\leq$100 mg/dL was independently associated with increased death risk – HR = 1.55 (95% CI:1.05–2.30), p = 0.03 in patients without DM; in patients with DM no association was detected – multivariate-adjusted HR = 1.18 (95% CI: 0.77–1.80), p = 0.44.
Conclusion: Non-DM HF patients with LDL-c>100 mg/dL have a 35% reduction in the mortality risk when compared with those with lower values. The "cholesterol paradox" in HF also applies to LDL-c in non-DM patients.

1. Background

Heart failure (HF) is a common and serious condition frequently caused by coronary artery disease [1]. Hypercholesterolemia is a major risk factor for coronary artery disease and, therefore, is thought to contribute to incident HF. Low density lipoprotein cholesterol (LDL-c) is highly atherogenic and considered the major effector of plaque building [2]. Puzzlingly, patients with advanced HF often develop wasting and cachexia [3,4], and is not uncommon for them to present hypocholesterolemia [5]. Low total cholesterol levels have been consistently associated with increased mortality in patients with established HF [6–8]. A strange, and yet to fully understand, *reverse epidemiology*

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phenomenon regarding essential cardiovascular risk factors, occurs once HF establishes [3,9–11]. The so-called cholesterol paradox has been mainly reported for total cholesterol. Total cholesterol is an amalgamation of lipoproteins that includes cholesterol transported by high-density lipoprotein (HDL-c), very-low density lipoprotein (VLDL-c) and LDL-c. LDL-c, as mentioned, is highly atherogenic and a widely recognized major cardiovascular risk factor. Evidence concerning the impact of LDL-c or if a similar paradox occurs in HF is scarce, even though evidence suggests LDL-c levels should be lowered as much as possible to prevent cardiovascular disease, especially in high and very high-risk patients [12]. Most HF patients are amongst these risk profile groups, however clear evidence of the benefits of applying such stringent LDL-c limits to high-risk groups who have already developed HF is lacking [13].

There is robust evidence showing that aggressive statin treatment in patients with known coronary artery disease reduces the risk of incident HF [14]. It has also been suggested that statins, through their pleotropic effects of cholesterol lowering, impact on cell death and decrease in oxidative stress, could have beneficial effects among HF patients both ischemic and non-ischemic [15]. Despite the insightful mechanistical anticipated effects of lowering cholesterol levels in HF patients, studies concerning treatment of hypercholesterolemia have had varied results [16], and randomized controlled trials of statin use in HF have not shown a definite mortality benefit in HF populations [17,18]. Meta-analysis of randomized controlled trials and prospective cohort registries have reached different results both beneficial [19] and not beneficial [20] with respect to statin use and all-cause mortality, cardiovascular mortality, and cardiovascular hospitalizations in patients with established HF. This uncertainty is reflected in the most recent HF guidelines [21]; however, the use of statins and a somehow aggressive lipid profile control, namely regarding LDL-c, is still a common approach for the treatment of hypercholesterolemia even in patients with HF. Nonetheless, the evidence concerning the impact of LDL-c in HF is scarce.

We aimed to evaluate the association of LDL-c with mortality in patients with HF. We hypothesized that the prognostic impact of LDL-c would differ in patients with DM and with no coexistent DM.

2. Methods

We retrospectively analyzed outpatients with chronic HF with left ventricular systolic dysfunction (ejection fraction <50%) followed between January/2012 and May/2018 in our specialized HF clinic of the Internal Medicine Department of Centro Hospitalar Universitário São João (CHUSJ). CHUSJ is a Portuguese tertiary care academic hospital that provides direct assistance to an area of more than 320 thousand inhabitants. Patients followed in the HF clinic of the Internal Medicine Department are mainly patients with HF with reduced ejection fraction (ejection fraction≤40%) but patients with HF with mildly reduced ejection fraction are also followed. Referral is basically from the internal medicine ward and from primary care; a small proportion of patients is referred from other specialties, including cardiology, for patients with multiple and complex comorbidities.

Adult patients (>18 years old) with history of HF and left ventricular systolic dysfunction observed in our HF clinic between the above-mentioned time frame were included. Demographic data, comorbidities, clinical and laboratory parameters, as well as medication in use in the index visit were recorded. The index visit was considered the first patients' evaluation since January 2012. We excluded patients with HF with preserved ejection fraction and patients with no complete lipid profile – total cholesterol, high density lipoprotein cholesterol (HDL-c) and triglycerides - in the index visit. LDL-c was calculated using the Friedewald's formula [22].

Comorbidities were defined as follows: Diabetes *mellitus* (DM) was defined as either a known previous diagnosis, current prescription of hypoglycaemic agents, a fasting venous blood glucose above 126 mg/dL,

or a random glucose >200 mg/dL; patients with a glycosylated haemoglobin ≥6.5% were also considered diabetic. Arterial hypertension was defined as systolic blood pressure record ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg in at least 2 separate measurements, the presence of previous diagnosis or record of antihypertensive pharmacological treatment. Patients were considered to have chronic kidney disease if the index estimated glomerular filtration rate (GFR) according to the Modification diet and renal disease formula was <60 mL/min/m2. Patients with current or past tabaco use were considered smokers. Coronary heart disease was defined as history of acute myocardial infarction or significant coronary heart disease image confirmed. Cerebrovascular disease was considered when patients presented history of previous stroke or cerebral hemorrhage or in case of cerebral vascular lesion image confirmed. Peripheral artery disease was considered in case of previous known and reported diagnosis, or ankle brachial index measurement <0.9 or a significant arterial narrowing due to atherosclerosis image documented. Non-coronary atherosclerotic disease was considered when patients presented cerebrovascular disease and/or peripheral artery disease.

The endpoint under analysis was all-cause mortality and patients were followed since the 1st medical appointment from 2012 until January 2021. We determined the patients' vital status by consulting hospital registries and by telephone contact with the patients or their relatives. When no information was obtained, we consulted the Registo Nacional de Utentes platform, a national platform that provides information on patient mortality; cause of death is not disclosed in this platform.

The registry's protocol conformed to the ethical guidelines of the declaration of Helsinki, and it was approved by the local ethics committee. Because of the retrospective nature of the study design informed consent was waived.

2.1. Statistical analysis

Mean ± standard deviation was used for continuous variables with a normal distribution and median (interquartile range) for non-normally distributed continuous variables. Categorical variables were described as counts and proportions. LDL-c presented a roughly normal distribution and the value of 100 mg/dL corresponded to the mean. Patients were categorized according to LDL-c in those with LDL-c≤100 mg/dL and those with values > 100 mg/dL. Patients in both groups were compared: Chi square test for categorical variables, the students *t*-test and Mann-Whitney-U test for variables with normal and skewed distribution, respectively.

The Kaplan-Meier method was used to study the survival curves according to LDL-c. A Cox-regression analysis was used to assess the impact of LDL-c≤100 mg/dL with mortality. A multivariate analysis was performed to adjust for potential confounders. Adjustments were made considering age, sex, coronary artery disease and atherosclerotic non-coronary artery disease, arterial hypertension, DM, smoking status, renal function, severity of systolic dysfunction, evidence-based HF therapy and statin use. Interaction between DM and LDL-c and between statin use and LDL-c in mortality risk was tested. The analysis was further stratified according to the coexistence of DM because there was a significant interaction between DM and LDL-c.

3. Results

From a total of 934 eligible patients, 64 had no baseline analysis. From the remaining 870, 348 had no lipid profile or an incomplete lipid profile that precluded the calculation of LDL-c. We therefore studied 522 chronic HF patients, patients' mean age was 70 years, 66.5% were males. Severe systolic dysfunction was present in 42.7%, 30.5% had coronary artery disease, 60.5% had arterial hypertension, 41.6% had DM. A total of 92.0% were treated with beta blocker, 87.5% with an angiotensin converting enzyme inhibitor (ACEi)/angiotensin receptor

blocker (ARB) and 29.1% with an aldosterone receptor antagonist (MRA); 68.4% of the patients were medicated with a statin. During a median follow-up of 53 (interquartile range 33–73) months, 235 (45%) patients died. Patients' characteristics are shown in Table 1. Mean (SD) LDL-c was of approximately 100 (39) mg/dL. There was a significantly higher male predominance among patients with LDL-c ≤ 100 mg/dL, Patients with lower LDL-c also presented significantly lower total cholesterol and worse renal function. DM and coronary artery disease were more prevalent among patients with lower LDL-c and statin use was significantly higher in the group of patients presenting lower LDL-c: 79.1% against 56.6% in those with LDL-c>100 mg/dL. Importantly body mass index, lymphocyte counts, and serum albumin were similar between groups.

Patients with lower LDL-c showed significantly higher all-cause mortality (51.6 vs 37.8 in the remaining, p = 0.001). Kaplan-Meier survival curves according to basal LDL-c are depicted in Fig. 1.

Table 1
Patients characteristic and comparison between those with LDL-c≤100 mg/dL and those with LDL-c>100 mg/dL.

Characteristic	All (n = 522)	LDL-c > 100 mg/dL (n = 249)	LDL-c ≤ 100 mg/dL (n = 273)	p-value
Age (years), mean (SD)	70 (12)	69 (12)	71 (12)	0.33
Male sex, n (%)	347 (66.5)	147 (59)	200 (73)	<0.001
Arterial hypertension, n (%)	316 (66.5)	146 (68.6)	170 (62.3)	0.40
Diabetes mellitus, n (%)	217 (41.6)	85 (34.1)	132 (48.4)	<0.001
CAD, n (%)	159 (30.5)	52 (20.9)	107 (39.2)	<0.001
non-CAD atherosclerotic disease, n (%)	116 (22.2)	48 (19.3)	68 (24.9)	0.12
Severe LVSD n (%)	223 (42.7)	108 (42.7)	115 (42.1)	0.77
NYHA class I	195 (37.4)	96 (38.6)	99 (36.3)	0.66
NYHA class II	233 (44.6)	112 (45.0)	121 (44.3)	
NYHA class III/ IV	94 (18.0)	41 (16.5)	53 (19.4)	
BMI (kg/m2), mean (SD)	27.4 (5.3)	27.3 (5.5)	27.4 (5.1)	0.77
Total cholesterol (mg/dL), mean (SD)	173 (47)	211 (35)	139 (25)	<0.001
LDL-c (mg/dL), mean (SD)	101 (39)			
Estimated GFR (mL/min/ 1.73m2)	57 (43–75)	61 (46–79)	53 (46–68)	<0.001
Hemoglobin (g/ dL)	13.5 (1.9)	13.5 (1.7)	13.3 (1.9)	0.12
Lymphocytes (/mL)	2027 (891)	2089 (859)	1970 (918)	0.13
Albumin (g/L)	40.8 (4.0)	41.0 (4.3)	40.6 (3.8)	0.42
BNP (pg/mL), median (IQR)	248.9 (99.6–501.3)	226.1 (101.1–439.3)	258.3 (97.0–625.1)	0.41
ACEi/ARB, n (%)	457 (87.5)	225 (90.4)	232 (85.0)	0.06
MRA, n (%)	152 (29.1)	171 (31.3)	74 (27.1)	0.29
Beta blockers, n (%)	480 (92.0)	227 (91.2)	253 (92.7)	0.57
Statin, n (%)	357 (68.4)	141 (56.6)	216 (79.1)	<0.001
Follow-up (months), median (IQR)	53 (33–87)	58 (35–93)	48 (32–82)	0.02
Mortality, n (%)	235 (45.0)	94 (37.8)	141 (51.6)	0.001

ACEi: angiotensin receptor inhibitors; ARB: angiotensin receptor blockers; BNP: B-type natriuretic peptide, CAD: coronary artery disease, GFR: glomerular filtration rate, IQR: interquartile range; LDL-c: low density lipoprotein cholesterol, LVSD: left ventricular systolic dysfunction, MRA: mineralocorticoid receptor antagonist, NYHA: New York Heart Association class, SD: standard deviation.
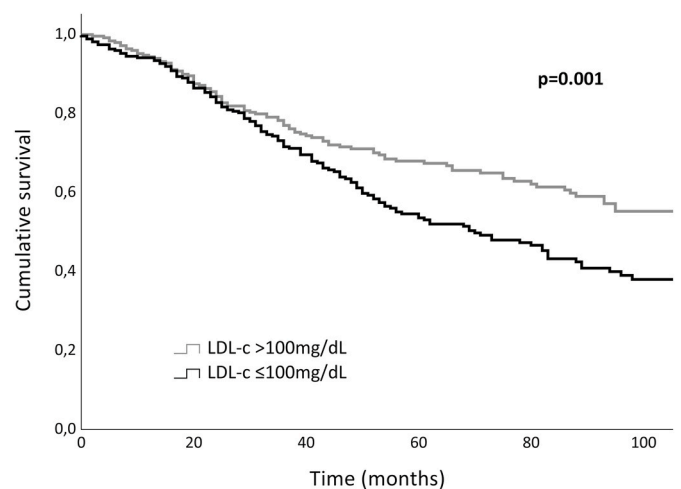

Fig. 1. Kaplan-Meier survival curves according to LDL-c in the whole group of 522 patients.

Patients with elevated LDL-c presented a clear survival advantage when compared to those with LDL-c≤100 mg/dL. Patients with LDL-c≤100 mg/dL presented a crude hazard ratio of all-cause mortality of 1.52 (95% CI: 1.17–1.98), p = 0.002. When multivariate adjustment was performed the hazard ratio was of 1.58 (1.08–2.30), p = 0.02. There was no interaction of statin use in the prognostic impact of LDL-c (p for the interaction term between statin use and LDL-c was of 0.2); however, there was significant interaction between DM and LDL-c (p-value for DM*LDL-c = 0.03). When the analysis was stratified according to DM coexistence, Fig. 2, LDL-c had no prognostic impact in diabetic HF patients; however, among non-diabetic patients' lower LDL-c levels clearly portend an ominous outcome. This differential association between lower LDL-c and mortality in HF patients with and without DM sustained after multivariate adjustment for potential confounders. Table 2 shows the crude and multivariate adjusted hazard ratios of LDL-c≤100 mg/dL and all-cause death in HF patients with coexistent DM and no coexistent DM. In HF patients with no DM, LDL-c ≤100 mg/dL have an independent HR of all-cause mortality of 1.55 (1.05–2.30); in HF patients with DM LDL-c had no prognostic impact.

4. Discussion

LDL-c is the most atherogenic cholesterol lipoprotein and is an established cardiovascular risk factor [23]. Dyslipidemia guidelines have become progressively more demanding regarding LDL-c targets. In very high-risk patients, a 55 mg/dL goal is suggested [12]. Such a demanding objective makes it necessary to use high intensity cholesterol lowering therapy. Coronary artery disease is one of the most common HF etiologies and, not-surprisingly, most patients with established HF can be considered high and very-high risk patients [12,13]. Nevertheless, statin therapies have not been clearly associated with improved outcomes in HF patients [17,20,24] and LDL-c goals cannot be directly extrapolated to HF patients.

In our cohort of chronic HF patients, lower LDL-c levels were not associated with survival benefit and, in the subgroup of patients without DM, LDL-c levels of 100 mg/dL and below were even associated with an independent 55% increased risk of all-cause mortality. This means that in patients with established HF, irrespective of cardiovascular risk factors and atherosclerotic disease, a lower LDL-c is not associated with a survival benefit. This is particularly true for non-DM patients, in whom lower LDL-c even associates to survival disadvantage. Additionally, this non-survival benefit does not appear to be attributable to nutritional status because LDL-c was not correlated with body mass index, lymphocyte counts, and serum albumin. Our findings further question
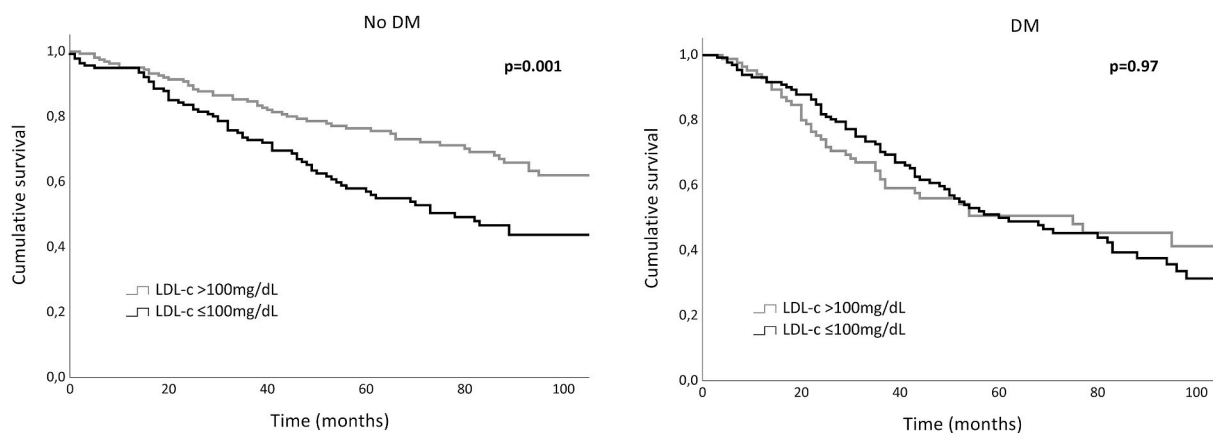
Fig. 2. Kaplan-Meier survival curves according to LDL-c separately in-non DM (left) and DM (right) patients.

Table 2
Crude and multivariate adjusted association between LDL-c ≤100 mg/dL and all-cause mortality. Analysis stratified according to coexistence of Diabetes mellitus.

LDL-c ≤100 mg/dL	Patients without DM HR (95% CI)	p value	Patients with DM HR (95%CI)	p-value
Crude	1.81 (1.26–2.60)	0.001	1.01 (0.69–1.47)	0.97
Multivariate-adjusted	1.55 (1.05–2.30)	0.03	1.18 (0.77–1.80)	0.44

Adjustments to age, sex, coronary artery disease, atherosclerotic non-coronary artery disease, arterial hypertension, smoking status, severity of left ventricular dysfunction, renal function (estimated glomerular filtration rate based on the MDRD formula), evidence-based therapy (renin-angiotensin system inhibitors, beta blockers and mineralocorticoid receptor antagonists), and statin use.
CI: DM: *Diabetes mellitus,* HR: Hazard ratio, LDL-c: low-density lipoprotein-cholesterol.

the use of statins in HF patients, particularly in non-diabetic patients.

For reasons not yet fully understood, there is evidence that, although traditional cardiovascular risk factors, such as obesity or hypercholesterolemia, that are most of the times associated with an independently increased risk of developing HF and mortality in the general population [25], in patients with HF increased total serum cholesterol concentration is strongly correlated with decreased morbidity and mortality [7, 10]. This cholesterol paradox was shown in multiple reports. In a small, early study, Vredevoe et al. [26] concluded that lower cholesterol, HDL-c, LDL-c, and triglycerides were predictors of mortality in non-ischemic HF. Rauchhaus et al. [27] found that total serum cholesterol levels below 200 mg/dl were predictive of impaired 12-month event-free survival in HF patients, independent of the cause of HF and the presence of cachexia. The largest epidemiologic study in this regard was conducted by Horwich et al. [7] whose results showed that in a cohort of over one thousand patients with HF, those with lower total cholesterol levels had a significantly lower albumin level, left ventricular ejection fraction, and cardiac output; and total cholesterol was the only lipid or lipoprotein that remained a significant independent predictor of mortality or need for urgent transplant on multivariate analysis.

In accordance, surviving patients with HF have been shown to present higher prevalence of hyperlipidemia than non-surviving counterparts [28]. It is important to reinforce the fact that previous studies addressed mainly total cholesterol. Lipoproteins consist of a triglyceride and cholesterol core surrounded by a phospholipid outer shell with embedded apolipoproteins. Major lipoproteins in blood are chylomicrons, VLDL, intermediate-density lipoprotein (IDL), LDL, and HDL. Total cholesterol represents the cholesterol transported by all these lipoproteins. Therefore, evidence concerning this paradox or *reverse epidemiology* as it can be called applies only to total cholesterol and specific evidence concerning LDL-c, the main atherogenic agent, remains unknown. Does this paradox also apply to LDL-c? Can an atherogenic effector cease to be atherogenic once HF establishes? Most importantly, can an atherogenic effector become protective in the HF context? All these questions are pertinent in an era in which progressively stringent targets for LDL-c are aimed. Also, despite no straightforward guidelines exist regarding statins in HF, the high prevalence of statin therapy in chronic HF has been widely documented with most studies reporting that more than half of the patients are treated with statins [29–32].

We cannot assume that the low LDL-c levels are causally implicated in the higher mortality and therefore, we cannot argue against the use of statins in non-DM HF patients. Nevertheless, we believe our results raise the possibility that, in terms of clinical practice, a different LDL-c target or therapeutic approach can be reasonable whether we are treating diabetic or nondiabetic HF patients; Should we keep using statins in nondiabetic HF patients? Considering the *reverse epidemiology*, it seemed reasonable to believe that we should not aim to lower LDL-c in all patients with HF. Bearing in mind our results, that principle seems to be valid only in HF patients with no concomitant DM, with diabetic HF patients remaining a subgroup in which we could still consider the use lipid lowering therapy. Definitely, the role of LDL-c in HF should be better clarified, so that clinicians can prescribe lipid lowering therapy more safely in this growing group of patients.

Several limitations to our study should be pointed. The single center nature precludes generalizability to the whole HF population, moreover we only studied patients with ejection fraction <50%, therefore inferences concerning patients with HF with preserved ejection fraction are not possible. The retrospective design makes it impossible to establish cause-effect relationships; still, we documented that lower LDL-c was not associated with better prognosis in HF patients and that, particularly in non-diabetics, lower LDL-c levels associated with higher mortality. Only basal LDL-c measurements were considered, and LDL-c levels might have changed over time due to dietary factors or medications; this is a major limitation that must be stated. Also, only all-cause mortality was considered as an endpoint and we recognize that several other outcomes such as HF hospitalizations, and cardiovascular mortality would have been interesting. We followed patients for a long period of time, over 4 years, and for such a long period the analysis of HF hospitalization or a combined endpoint seemed less useful; however, HF hospitalizations in the first months would have been an interesting outcome to analyze and that is clearly a limitation of our study. Additionally, most deaths occurred outside the hospital and the cause of death could not be fully established in many patients, that was the reason why only all-cause mortality was studied. It would be interesting

to understand if results were similar for cardiovascular and non-cardiovascular deaths and that is an important pitfall of our study. Another setback is the fact that, despite being a real-world HF population, patients were still not under drugs that are currently recognized as clear prognostic-modifying in HF with reduced ejection fraction such as Sodium-glucose cotransporter 2 inhibitors and angiotensin-receptor neprilysin inhibitors.

Despite all these limitations, this is the largest and with longest follow-up study addressing the prognostic implications of LDL-c in HF. Our results suggest that the previously described cholesterol paradox in established HF also applies to its most atherogenic component LDL-c. We further cast doubt on the utility of statin therapy particularly in the subgroup on non-diabetic HF patients and reinforce the notion that an LDL-c target is not established in HF. The interaction between DM and LDL-c suggests that the coexistence of DM influences the impact of LDL-c in HF outcome. Diabetics are a very particular subgroup of HF patients with yet to be established specificities to consider.

5. Conclusions

Lower LDL-c does not associate with survival benefit in HF patients. By the contrary, non-DM HF patients with LDL-c>100 mg/dL have a 34% reduction in the mortality risk when compared with those with lower values. The cholesterol paradox in HF also applies to LDL-c in non-DM patients.

Credit author statement

R. Gouveia: Data curation, Conceptualization, Methodology, Writing- Original draft preparation, **P. Lourenço**: Methodology, Supervision, Writing- Reviewing and Editing, **S. Madureira, C. Elias**: Software., **A. Neves, P. Ribeirinho-Soares**: Visualization, Investigation, **M. Soares-Carreira, J. Pereira**: Supervision, **M. Amorim, A. Ribeiro**: Software, Validation, **J. Almeida, J. P. Araújo**: Writing-Reviewing and Editing.

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