


BMJ Open Association between hyperlipidemia and mortality after incident acute myocardial infarction or acute decompensated heart failure: a propensity score matched cohort study and a meta-analysis

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ABSTRACT

Objective To examine the effect of HLP, defined as having a pre-existing or a new in-hospital diagnosis based on low density lipoprotein cholesterol (LDL-C) level ≥ 100 mg/dL during index hospitalisation or within the preceding 6 months, on all-cause mortality after hospitalisation for acute myocardial infarction (AMI) or acute decompensated heart failure (ADHF) and to determine whether HLP modifies mortality associations of other competing comorbidities. A systematic review and meta-analysis to place the current findings in the context of published literature.

Design Retrospective study, 1:1 propensity-score matching cohorts; a meta-analysis.

Setting Large academic centre, 1996–2015.

Participants Hospitalised patients with AMI or ADHF.

Main outcomes and measures All-cause mortality and meta-analysis of relative risks (RR).

Results Unmatched cohorts: 13 680 patients with AMI (age (mean) $68.5 \pm$ (SD) 13.7 years; 7894 (58%) with HLP) and 9717 patients with ADHF (age, 73.1 ± 13.7 years; 3668 (38%) with HLP). In matched cohorts, the mortality was lower in AMI patients ($n=4348$ pairs) with HLP versus no HLP, 5.9 versus 8.6/100 person-years of follow-up, respectively (HR 0.76, 95% CI 0.72 to 0.80). A similar mortality reduction occurred in matched ADHF patients ($n=2879$ pairs) with or without HLP (12.4 vs 16.3 deaths/100 person-years; HR 0.80, 95% CI 0.75 to 0.86). HRs showed modest reductions when HLP occurred concurrently with other comorbidities. Meta-analyses of nine observational studies showed that HLP was associated with a lower mortality at ≥ 2 years after incident AMI or ADHF (AMI: RR 0.72, 95% CI 0.69 to 0.76; heart failure (HF): RR 0.67, 95% CI 0.55 to 0.81).

Conclusions Among matched AMI and ADHF cohorts, concurrent HLP, compared with no HLP, was associated with a lower mortality and attenuation of mortality associations with other competing comorbidities. These findings were supported by a systematic review and meta-analysis.

Strengths and limitations of this study

- Cohort study comprised of patients with cardiologist-confirmed diagnoses, high rates of case ascertainties and prompt mortality updates.
- Meta-analysis portion of the study adhered to the Preferred Reporting Items for Systematic Review and Meta-analyses Protocols.
- Large sample size and event rates and longer-term follow-up allowed detailed assessment of the association of hyperlipidemia (HLP) with mortality across multiple categories.
- 1:1 propensity scoring was used to match pairs of patients with concurrent HLP and those with no HLP for potential confounders.
- Limitations were inherent disadvantages of retrospective cohort studies, potential unmeasured confounders, *International Classification of Diseases, Ninth Revision, Clinical Modification* to identify study cohorts, ascertainment of comorbid conditions during index hospitalisation and lack of data on subsequent acquisition of these conditions during the follow-up.

INTRODUCTION

Early epidemiological studies of 1970s and 1980s including Framingham Heart Study,¹ Multiple Risk Factor Intervention Trial,² Coronary Primary Prevention Study,³ and Helsinki Heart Study,⁴ all provided substantial evidence for the epidemiological relationship between cholesterol levels and incident coronary artery disease in general population. In 2007, a meta-analysis of individual data from 61 prospective studies suggested that total cholesterol was positively associated with cardiovascular mortality.⁵ However,

contemporary studies largely examined the effect of statins and other cholesterol lowering interventions on cardiovascular events.^{6,7} A similar relationship between hyperlipidemia (HLP) and incident heart failure (HF) has been reported.⁶⁻⁹ Surprisingly, several recent studies found an inverse association where HLP, counterintuitively, conferred an overall survival benefit in patients with established acute myocardial infarction (AMI)¹⁰⁻¹³ and HF.¹⁴ Although cholesterol levels in general population predict new cardiovascular events, it is unclear whether a positive association persists after incident AMI or HF. Furthermore, the effect of HLP on the association of other competing conditions with mortality is unknown.

Systematic reviews and meta-analyses on the association of HLP with new AMI have already been published,⁵ but the clinical trials evaluating this relationship after the incident AMI have not been systematically reviewed. Additionally, the data are limited on the association between HLP and incident HF and subsequent mortality. A comprehensive review of published data on the association of HLP with mortality after incident AMI or HF would clarify these issues.

We postulated that if a diagnosis of HLP decreases the mortality after AMI or HF, then, it also lessens the magnitude of mortality risks associated with other competing comorbidities. We tested this hypothesis, separately, in large cohorts of patients hospitalised for incident AMI and acute decompensated HF (ADHF). To compare patients with and with no HLP, we assembled 1:1 balanced groups using propensity score-matching for each study condition. Our objectives were three-fold: (1) to estimate the association of HLP with all-cause mortality among patients with AMI or ADHF, (2) to determine the extent to which the association between other competing comorbidities¹⁵ and mortality is modified by HLP (3) and to provide risk estimates for mortality associated with HLP after incident AMI or HF through systematic review and meta-analyses of published and current study data to place the current findings in the context of published literature.

METHODS

Cohort study

Study population and data collection

The study cohorts were comprised of adults aged ≥18 years, hospitalised at Mayo Clinic from August 1, 1996 to September 17, 2015 with primary discharge diagnoses of AMI or ADHF with follow-up completed through August 17, 2016. AMI included both ST-elevation myocardial infarction (STEMI) and non-STEMI. ADHF comprised of HF with both reduced and preserved ejection fractions. Discharge diagnoses were identified by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes (presented in online supplementary table 1). Mayo Clinic has one of the oldest and most advanced medical record systems in the USA. Patient provided information is constantly updated at every clinic or hospital visit at its main Rochester campus and

at a network of clinics and hospitals across more than 60 communities in states of Iowa, Wisconsin and Minnesota. Strengthening The Reporting of Observational studies in Epidemiology (STROBE) flow diagram of study cohorts' selection of is presented in online supplementary figure 1. Further details of data extraction are published elsewhere.¹⁶ The study was approved by the Mayo Clinic Institutional Review Board and need for patient consent was waived.

Ascertainment of AMI and ADHF

For each patient the primary discharge diagnosis, AMI or ADHF, was documented by the attending physician at the time of discharge, assigned ICD-9-CM code, and subsequently captured by the abstractors.

Ascertainment of comorbid conditions

We focused on a panel of 20 comorbid conditions CCs defined by Department of Health and Human Services¹⁵ and identified by Clinical Classifications Software codes of US Healthcare Cost Utilization Project. CCs with prevalence <3% were excluded from analysis. To ascertain the comorbid effect of HLP on other concurrent condition, we paired HLP with other competing comorbidities within an individual patient.

Ascertainment of HLP and statin use

HLP was defined as having a pre-existing or a new in-hospital diagnosis based on low density lipoprotein cholesterol (LDL-C) level ≥100mg/dL as clinically measured during index hospitalisation or within the preceding 6months. LDL-C was measured indirectly by Friedewald method.¹⁷ Published reports suggest that lipid panel measured during the first 24hours after an acute cardiovascular event reliably represents baseline level.¹⁸ Statin use was based on discharge medication reconciliation.

Ascertainment of mortality

All deaths occurring from admission to censoring date of August 17, 2016 were abstracted from medical records. The mortality data is updated regardless of the cause of death, including death due to murders, suicides, or accidents. At the time of drafting the manuscript, Minnesota all-cause (including suicide, murder, misadventures and natural) Electronic Death Certificate Data is current to December 31, 2018,

Patient follow-up

All patients were followed from index hospitalisation until death or censoring date of August 17, 2016 whichever occurred first.

Patient and public involvement

Patients and public were not involved in this study

Systematic review and meta-analysis

Data source and searches

This systematic review and meta-analysis was conducted in accordance with the established methods¹⁹ and followed

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.²⁰ We searched of MEDLINE, EMBASE, Cochrane Library, Web of Science databases for eligible trials from inception through September 2017 with continued surveillance through February 2018 for trials examining the associations of HLP with mortality. We identified clinical studies with the same population, condition/disease, intervention, control and at least one outcome and objectives. Studies with incomplete data were excluded. Methodological details of the meta-analysis are published elsewhere.²¹ The search strategy is presented in the supplement.

Study selection

Eligibility criteria included: (1) randomised or non-randomised clinical trials of adults with AMI or HF, (2) comparator groups HLP or hypercholesterolemia versus no HLP or no hypercholesterolemia as defined by individual study investigators and (3) mortality as the primary outcome or one of the outcomes.

Data extraction and risk of bias assessment

From the results of initial search, two investigators (EA and HA), working independently reviewed articles for eligibility on the basis of titles and abstracts. Studies that satisfied the inclusion and exclusion criteria were retrieved for full text review. Disagreements were resolved by consensus and retained conflicts were adjudicated by a third investigator (MY). We extracted the following data from each study: type of study, number of participants, age, gender, presence and absence of HLP, length of follow-up and outcome measures. Measure of association with clinical outcomes (HR, OR), or relative risk (RR)) were abstracted. Risk of bias was assessed using the Newcastle-Ottawa Scale for cohort studies.²²

Statistical analysis

ALL Statistical analyses were performed using SAS V.9.4.

The cohort study

*Propensity score analysis*²³: We assembled 1:1 propensity score-matched pairs of patients with AMI or ADHF to balance the differences in baseline variables between patients with and without concurrent HLP. Propensity scores were estimated using logistic regression (PROC PS MATCH in SAS) based on age, gender, length of stay, race, comorbidities, statin prescription on discharge and time period (1996–2005 vs 2006–2016). Standardised differences in the matched cohort ranged from 0.122 to 0.004. One-to-one nearest neighbour calliper matching was used to match patients based on the propensity score using a calliper equal to 0.2 of the SD of the logit of the propensity score. We performed C-statistic as a measure of the ability of the propensity score to control confounders.²⁴ C-statistic for the model was 0.752 for AMI patients and 0.755 for HF patients. Patients were of exact match on gender, race and enrollment period. Patients without HLP were matched to one with HLP generating a quasi-randomised design whereby study groups (HLP

vs no HLP) have had similar propensity for allocation to either group.

Kaplan-Meier estimates: Kaplan-Meier estimates were performed using propensity-score matched cohorts and stratified log-rank tests were used to compare survival curves.

Multivariable Cox models: Cox proportional hazards models were performed on the matched samples using a robust variance estimator to account for matching. Multiple models were constructed for estimating HR for mortality. Model 1 estimated HR and 95% CI for mortality associated with HLP and other CCs. Model 2 was extended to fit Model 1 plus statin therapy. Model 3 examined the comorbid effect of HLP in combination with other competing comorbidities.

Sensitivity analysis: We performed several sensitivity analyses to ascertain the degree of bias that might explain significant associations between HLP and mortality and to confirm the robustness of our findings. From propensity-score matched AMI and HF patients, we identified patients with available data related to body mass index (BMI), LDL-C, left ventricular ejection fraction (LVEF) and serum concentrations of sodium, blood urea nitrogen (BUN), and creatinine. We conducted sensitivity analyses using separate Cox proportional regression models by excluding (1) patients with no LDL-C data, (2) patients with no available data on levels of sodium, BUN and creatinine, (3) patients with no available data on BMI and (4) patients with no available data on LVEF.

The meta-analysis

The DerSimonian and Laird random-effects model was used to pool estimates across studies.²⁵ The results were expressed as RR and 95% CI. Heterogeneity was assessed using I^2 to reflect proportion of heterogeneity not attributable to chance.²⁶ The number of studies was insufficient to statistically evaluate publication bias. Characteristics of included studies (online supplementary table 2), assessment of risk of bias (online supplementary table 3) and PRISMA flow diagram (online supplementary figure 2) are presented in supplement. PRISMA check list is presented in online supplementary table 4. We pooled the effect sizes (in this case, HR) reported by the studies. We did not pool the intercept of the models as most were not reported. Additionally, the methods to generate the pooled intercept are not well developed either.

RESULTS

The cohort study

Cohort study population

The online supplementary figure 1 illustrates the STROBE flow diagram for selection of final study cohorts: AMI (initial cohort n=13 680; propensity score-matched cohort n=8696, pairs 4348) and ADHF (Initial cohort n=9717; propensity score-matched cohort n=5758, pairs 2879). STROBE checklist is presented in online supplementary table 5.

Baseline characteristics

Baseline characteristics for each study cohort, before and after propensity score-matching by HLP, are presented in [table 1](#). Baseline characteristics for matched patients in each cohort were balanced. Before matching, patients with HLP were younger, more likely to be males, and had lower rates of chronic obstructive pulmonary disease (COPD) and HF and high prevalence of chronic kidney disease (CKD) and hypertension in the AMI cohort. As these variables were balanced in propensity score-matching, a balanced cohort with standardised differences of <10% for baseline characteristics was created for final analysis. online supplementary figure 3 illustrates a love plot of standardised differences before and after propensity-score matching to allow visualisation of improvement in prognostic balance. Of 20 CCs, only eight were included in final analysis for frequency $\geq 3\%$. Online supplementary tables 4 and 5 represent PRISMA

Mortality

AMI: In matched patients, mortality was significantly lower among patients with HLP versus those with no HLP (overall mortality 2182 (50.2%) vs 2718 (62.5%) or 5.9 vs 8.6 deaths/100 person-years of follow-up, $p<0.0001$). Median and person-years of follow-up was greater in matched patients with HLP (median 8.8 years, IQ 3.2–13.1 years, 37068 person-years of follow-up) versus those with no HLP (median 6.3 years, IQ 1.4–12.4 years, 31569 person-years of follow-up).

ADHF: In matched patients, mortality was significantly lower among patients with HLP versus those with no HLP (overall mortality 1687 (58.6%) vs 1948 (67.7%) or 12.4 vs 16.3 deaths/100 person-years of follow-up, $p<0.0001$). Median and person-years of follow-up was greater in matched patients with HLP (Follow-up: median 3.2 years, IQ 1.0–6.9 years, 13577 person-years of follow-up) versus those with no HLP (median 2.5 years, IQ 0.7–6.2 years, 11951 person-years of follow-up).

Kaplan-Meier estimates

[Figure 1](#) displays Kaplan-Meier estimates of all-cause mortality by HLP in propensity-score matched samples of AMI or ADHF patients. Kaplan-Meier survival curves diverged immediately after hospitalisation and then remained parallel during the follow-up in both AMI and ADHF cohorts. Log-rank p value for patients with and with no HLP remained <0.0001 for each index condition. In multiple subanalyses, risk differences in mortality between patients with and without HLP persisted in age <65 and ≥ 65 years, male and female, white and non-White with log-rank $p<0.0001$ for all sub-groups.

Cox proportional regression model 1

The results are presented in [figure 2](#). HLP as compared with no HLP, was associated with a lower risk of death from any cause after AMI (HR 0.76, 95% CI (CI) 0.72–0.80, $n=8696$) or ADHF (HR 0.80, 95% CI 0.75 to 0.86, $n=5758$). Findings did not change significantly with

exclusion of patients with a new in-hospital HLP diagnosis in sensitivity analysis. Co-occurrence of cancer, CKD, COPD, diabetes mellitus, HF, or stroke independently increased mortality following AMI or ADHF. While hypertension reduced mortality by 8% (95% CI 0.87 to 0.98) after AMI, neither hypertension nor coronary artery disease influenced mortality after ADHF hospitalisation.

Cox proportional regression model 2

In separate analysis, adjustment of Cox proportional model for statin treatment did not change results for baseline HLP in predicting the all-cause mortality (AMI: HR 0.69, 95% CI 0.65 to 0.73; ADHF: HR 0.78, 95% CI 0.73 to 0.83).

Cox proportional regression model 3

The results of Cox model 3 are shown in [figure 2](#). Magnitude of HRs for mortality associated with cancer, COPD, CKD, diabetes, HF and stroke were all modestly attenuated with concurrent HLP across study cohorts. By comparison, protective effect of HLP on mortality was enhanced when paired with hypertension (HTN) in both AMI (HR 0.77, 95% CI 0.72 to 0.83) and ADHF (HR 0.86, 95% CI 0.78 to 0.94).

Sensitivity analysis with available data on following covariates

1. **BMI:** Of 8646 patients with AMI 6092, and of 5758 patients with HF, 5311 have data for BMI. The association of HLP with mortality remained unchanged when multivariable model accounted for BMI. BMI was inversely related to mortality with one unit increase in BMI resulting in 1% reduction in mortality in both AMI (HR 0.99, 95% CI 0.98 to 0.99, $p=0.0130$) and HF (HR 0.99, 95% CI 0.98 to 0.99, $p<0.0001$) cohorts ([table 2](#)).
2. **LDL-C on or within 6 months preceding admission:** Overall, 7268 patients (84%) in AMI cohort and 4562 patients (79%) in HF cohort had LDL-C clinically measured on or within 6 months preceding hospitalisation. We stratified patients into quartiles according to levels of LDL-C, <70 mg/dL, 70–99 mg/dL, 100–129 mg/dL and ≥ 130 mg/dL. There was a graded reduction in mortality from highest to the lowest LDL-C quartile in both AMI and HF ([table 2](#)).
3. **Levels of sodium, BUN and creatinine.** AMI: 7603 (87%), 6609 (70%) and 7812 (90%) had data available on sodium, BUN and creatinine respectively. HLP remained an independent predictor of lower mortality compared with no HLP when accounted for levels of sodium (≤ 135 vs >135 mmol/L), BUN (≤ 19 vs >19) and creatinine (≤ 1.5 vs >1.5) ([table 2](#)). HF: 7603 (87%), 6609 (70%) and 7812 (90%) had data available on sodium, BUN and creatinine respectively. HLP remains an independent predictor of lower mortality compared with no HLP when accounted for levels of sodium (≤ 135 vs >135 mmol/L), BUN (≤ 19 vs >19) and creatinine (≤ 1.5 vs >1.5) ([table 2](#)).

Table 1 Patient characteristics and standardised differences before and after propensity score-matching

Acute myocardial infarction							
Variables		All patients (n=13680)			Propensity score-matched cohort (n=8696)		
		With hyperlipidemia n=8929	With no hyperlipidemia n=4751	Absolute standardised difference	With hyperlipidemia n=4348	With no hyperlipidemia n=4348	Absolute standardised difference
Demographics	Age, years, mean±SD	67.0±13.6	71.3±13.5	0.315	68.9±13.3	70.6±13.6	0.122
	Male n (%)	6035 (68)	2938 (62)	0.121	2761 (64)	2761 (64)	0
	White n (%)	8108 (91)	3963 (83)	0.222	3744 (86)	3744 (86)	0
Anthropometric measurements	BMI kg/m ²	30.1±6.2	28.8±6.3	–	29.8±6.3	28.9±6.3	–
	BMI, missing n = (%)	1556 (17)	1520 (32)	–	1274 (29)	1330 (31)	–
Clinical characteristics	LOS, days, median (quartiles 25%–75%)	3 (2–5)	4 (3–8)	0.275	4 (3–6)	4 (3–7)	0.086
Year of hospital admission	1996–2005 n (%)	3886 (44)	3732 (79)	0.770	3341 (77)	3341 (77)	0
	2006–2016 n (%)	5043 (57)	1019 (21)		1007 (23)	1007 (23)	
Comorbid conditions	CAD, n (%)	–	–	–	–	–	–
	Cancer, n (%)	744 (8)	342 (7)	0.042	279 (6)	313 (7)	0.029
	CKD, n (%)	885 (12)	380 (8)	0.067	348 (18)	353 (8)	0.004
	COPD, n (%)	820 (9)	640 (14)	0.136	482 (11)	543 (13)	0.044
	Diabetes, n (%)	2567 (29)	1249 (26)	0.055	1091 (295)	1149 (26)	0.030
	Heart failure, n (%)	1762 (20)	1376 (29)	0.216	1033 (24)	1173 (27)	0.075
	Hypertension, n (%)	6049 (68)	2584 (54)	0.277	2530 (58)	2453 (56)	0.037
	Stroke, n (%)	359 (4)	168 (4)	0.025	151 (4)	148 (3)	0.004
Lipid levels	LDL-C mg/dl	110.9±39.2	78.7±25.0	–	118.4±37.6	78.8±25.1	–
	LDL-C, missing n (%)	483 (5)	1356 (29)	–	251 (6)	1177 (27)	–
Drug treatment	Statin	4665 (52)	1431 (30)	0.461	1566 (36)	1412 (33)	0.074
Heart failure							
Variables		All patients (n=9717)			Propensity score-matched cohort (n=5758)		
		With hyperlipidemia n=3941	With no hyperlipidemia n=5776	Absolute standardised difference	With hyperlipidemia n=2879	With no hyperlipidemia n=2879	Absolute standardised difference
Demographics	Age, years, mean±SD	73.2±12.4	73.0±14.5	0.020	72.6±12.6	73.1±14.1	0.040
	Male n (%)	2342 (59)	3266 (57)	0.058	1682 (54)	1682 (54)	0
	White n (%)	3574 (91)	4896 (85)	0.181	2588 (90)	2588 (90)	0
Anthropometric measurements	BMI kg/m ²	31.1±7.6	29.7±7.5	–	31.0±7.6	30.0±7.5	–
	BMI, missing n (%)	193 (5)	780 (13)	–	185 (6)	262 (9)	–
Clinical characteristics	LOS, days, median (quartiles 25%–75%)	4 (2–6)	4 (2–7)	0.183	4 (2–6)	4 (2–7)	0.018
Year of hospital admission	1996–2005 n (%)	1221 (31)	3510 (61)	0.626	1197 (42)	1197 (42)	0
	2006–2016 n (%)	2720 (69)	2266 (39)		1682 (58)	1682 (58)	
Comorbid conditions	CAD, n (%)	2482 (63)	2309 (40)	0.472	1580 (55)	1537 (53)	0.031
	Cancer, n (%)	595 (15)	736 (13)	0.068	419 (15)	420 (15)	0.001
	CKD, n (%)	1286 (33)	1299 (23)	0.228	802 (28)	819 (28)	0.013
	COPD, n (%)	813 (21)	1152 (20)	0.017	567 (20)	584 (20)	0.015
	Diabetes, n (%)	1617 (41)	1660 (29)	0.260	1117 (39)	1015 (35)	0.075
	Heart failure, n (%)	–	–	–	–	–	–
	Hypertension, n (%)	2911 (74)	2930 (51)	0.492	1931 (67)	1869 (65)	0.046

Continued

Table 1 Continued

Heart failure		All patients (n=9717)			Propensity score-matched cohort (n=5758)		
Variables		With hyperlipidemia n=3941	With no hyperlipidemia n=5776	Absolute standardised difference	With hyperlipidemia n=2879	With no hyperlipidemia n=2879	Absolute standardised difference
	Stroke, n (%)	160 (4)	106 (2)	0.132	94 (3)	75 (3)	0.039
Lipid levels	LDL-C mg/dl	92.8±39.9	75.5±28.5	–	98.5±41.0	74.0±28.5	–
	LDL-C, missing n (%)	517 (13)	2130 (37)	–	268 (13)	928 (32)	–
Drug treatment	Statin	1731 (44)	963 (17)	0.621	906 (32)	800 (28)	0.084

BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; LDL-C, low-density lipoprotein cholesterol; LOS, length of stay.

4. *LVEF*: A total of 5408 patients (62%) with AMI and 3869 patients (67%) patients with ADHF had data available on LVEF, measured clinically during or within 6 months preceding hospitalisation. HLP remained an independent predictor of lower mortality compared with no HLP when adjusted for LVEF in AMI and ADHF (table 2).

Meta-analysis

HLP was associated with lower all-cause mortality after AMI (≤ 30 day mortality: 4 studies,^{10 27 28} n=1 24 912, RR 0.74, 95% CI 0.56 to 0.98; long-term mortality (≥ 2 years): 2 studies,²⁹ n=11 161, RR 0.76, 95% CI 0.72 to 0.80) and ADHF (long-term mortality (≥ 2 years): 6 studies,^{30–34}

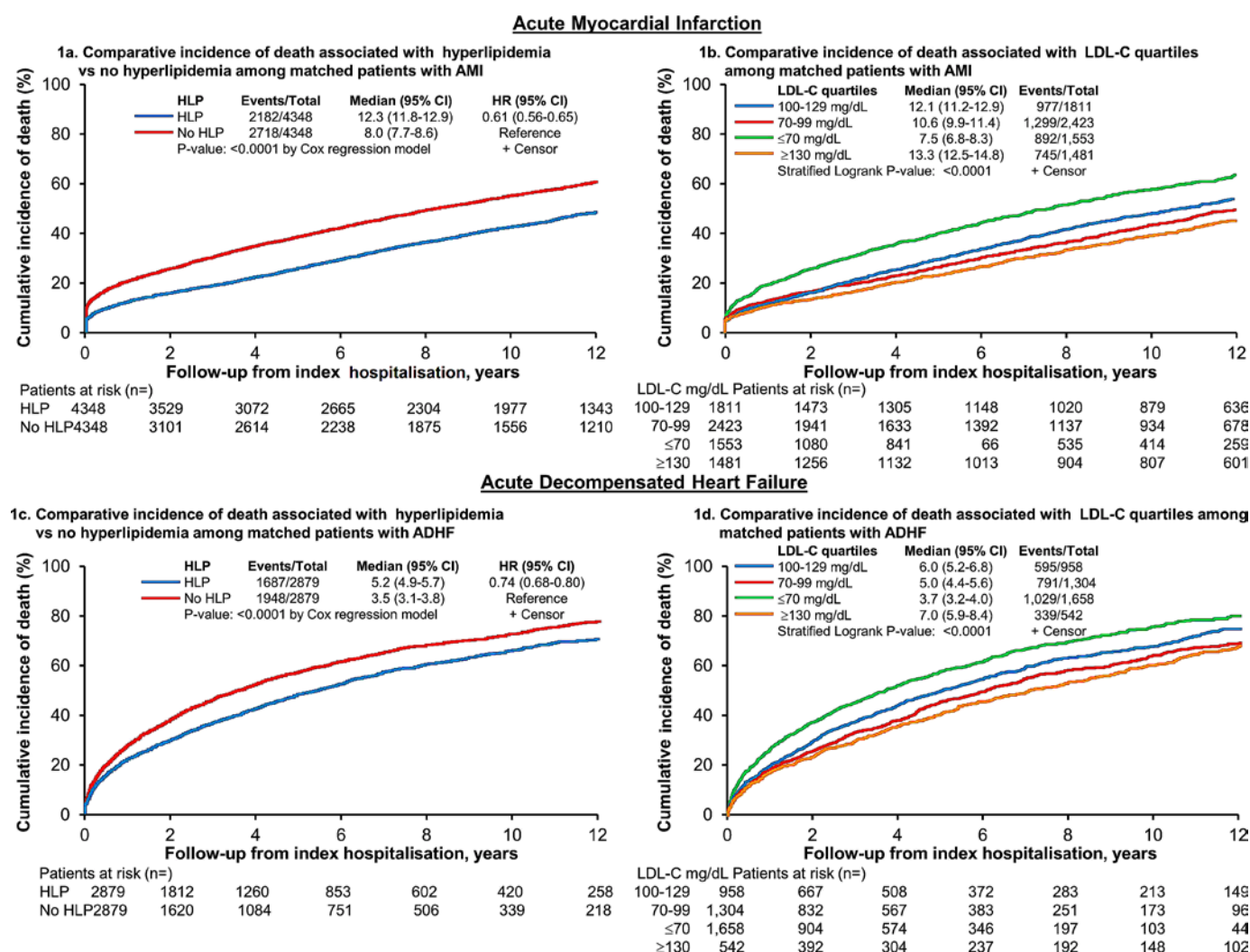


Figure 1 Kaplan-Meier estimates, cumulative incidence of death in propensity-score matched patients. ADHF, acute decompensated heart failure; AMI, acute myocardial infarction; HLP, hyperlipidemia; LDL-C, low density lipoprotein cholesterol.

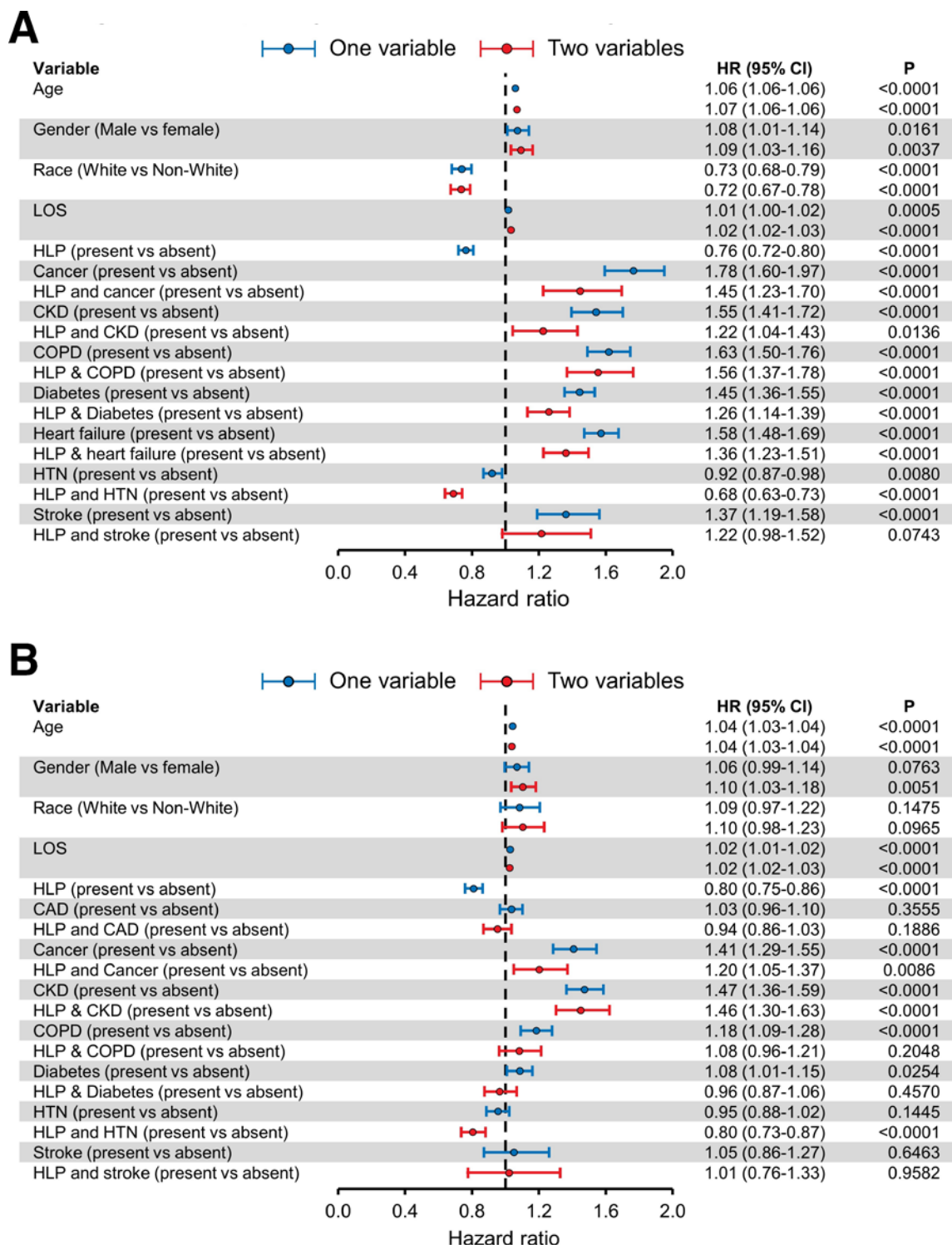


Figure 2 Cox proportional hazard regression models and forest plot. HR and 95% CI for all-cause mortality. CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HLP, hyperlipidemia; HTN, hypertension; LOS, length of stay.

n=11 166, RR 0.67, 95% CI 0.55 to 0.81). Meta-analysis of AMI was homogenous (I^2 0%), however, substantial heterogeneity was noted in HF meta-analysis reflecting different settings in the observational studies. The results of meta-analysis are presented as forest plots (figure 3).

DISCUSSION

Main findings

This propensity-score matched study of large cohorts of patients hospitalised for AMI or ADHF and a systematic review with meta-analysis provided a rigorous assessment of the association between HLP and long-term all-cause

Table 2 Results of four sensitivity analysis by separate COX proportional regression models among patients with acute myocardial infarction or heart failure in whom the relevant data point were available. Model 1, propensity-score matched patients with available data on BMI; model 2, propensity-score matched patients with available data on LVEF; model 3, propensity-score matched patients with available data on LDL-C measured on admission or within the preceding 6 months; model 4, propensity-score matched patients with available data on sodium, BUN and creatinine levels measured on admission.

Acute myocardial infarction				
Variables	Model 1 HR (95% CI) p value	Model 2 HR (95% CI) p value	Model 3 HR (95% CI) p value	Model 4 HR (95% CI) p value
Age	1.06 (1.05 to 1.06)<0.0001	1.07 (1.06 to 1.07)<0.0001	1.06 (1.05 to 1.06)<0.0001	1.06 (1.05 to 1.06)<0.0001
Gender	1.06 (0.99 to 1.14) 0.1123	1.04 (0.96 to 1.13) 0.3128	1.07 (0.99 to 1.14) 0.0650	1.07 (0.96 to 1.11) 0.3931
Ethnicity	0.79 (0.71 to 0.89) 0.0001	0.76 (0.65 to 0.89) 0.0006	0.735 (0.67 to 0.87) 0.9286	0.83 (0.75 to 0.92) 0.0003
Length of stay	1.01 (1.01 to 1.02)<0.0001	1.01 (1.01 to 1.02)<0.0001	1.02 (1.01 to 1.02)<0.0001	1.00 (0.99 to 1.01) 0.1374
Cancer versus no cancer	1.82 (1.62 to 2.05)<0.0001	2.08 (1.82 to 2.39)<0.0001	1.77 (1.57 to 1.99)<0.0001	1.76 (1.56 to 1.99)<0.0001
CKD versus no CKD	1.67 (1.49 to 1.86)<0.0001	1.88 (1.66 to 2.13)<0.0001	1.47 (1.31 to 1.64)<0.0001	
COPD versus no COPD	1.64 (1.50 to 1.81)<0.0001	1.78 (1.60 to 1.98)<0.0001	1.75 (1.60 to 1.91)<0.0001	1.58 (1.44 to 1.74)<0.0001
DM versus no DM	1.48 (1.37 to 1.60)<0.0001	1.51 (1.51 to 1.39)<0.0001	1.45 (1.35 to 1.56)<0.0001	1.38 (1.28 to 1.49)<0.0001
HLP versus no HLP	0.74 (0.70 to 0.80)<0.0001	0.77 (0.72 to 0.83)<0.0001		0.76 (0.71 to 0.82)<0.0001
HF versus no HF	1.65 (1.52 to 1.78)<0.0001	1.54 (1.40 to 1.69)<0.0001	1.65 (1.54 to 1.78)<0.0001	1.55 (1.43 to 1.68)<0.0001
HTN versus no HTN	0.96 (0.89 to 1.03) 0.3022	1.01 (0.93 to 1.09) 0.8735	0.95 (0.89 to 1.02) 0.1532	0.85 (0.79 to 0.91)<0.0001
Stroke versus no stroke	1.32 (1.12 to 1.57) 0.0004	1.20 (0.98 to 1.46) 0.0735	1.28 (1.09 to 1.51) 0.0060	1.45 (1.23 to 1.71)<0.0001
BMI	0.99 (0.98 to 0.99) 0.0130			
LVEF <50% versus ≥50%		1.36 (1.26 to 1.48)<0.0001		
Sodium, ≤135 versus >135 mmol/L				1.12 (1.03 to 1.22) 0.0055
BUN ≤19 versus ≥20 mg/dL				0.79 (0.73 to 0.85)<0.0001
Creatinine ≤1.5 versus >1.5 mg/dL				0.66 (0.55 to 0.66)<0.0001
LDL-C, Q2 versus Q1			0.90 (0.83 to 0.99) 0.0240	
LDL-C, Q3 versus Q1			0.87 (0.79 to 0.95)<0.0033	
LDL-C, Q4 versus Q1			0.83 (0.75 to 0.92)<0.0003	
HF				
Variables	Model 1 HR (95% CI) p value	Model 2 HR (95% CI) p value	Model 3 HR (95% CI) p value	Model 4 HR (95% CI) p value
Age	1.03 (1.03 to 1.04)<0.0001	1.04 (1.04 to 1.05)<0.0001	1.03 (1.03 to 1.04)<0.0001	1.04 (1.03 to 1.04)<0.0001
Gender	1.10 (1.03 to 1.19) 0.0010	1.11 (1.01 to 1.21) 0.0264	1.07 (0.98 to 1.15) 0.1144	1.02 (0.93 to 1.11)<0.0001
Ethnicity	1.18 (1.04 to 1.35) 0.0119	1.05 (0.87 to 1.25) 0.6243	1.14 (1.00 to 1.31)<0.0462	1.13 (0.97 to 1.32) 0.1155
Length of stay	1.02 (1.01 to 1.02)<0.0001	1.02 (1.01 to 1.02)<0.0001	1.02 (1.01 to 1.02)<0.0001	1.04 (1.01 to 1.02) 0.0005
Cancer versus no cancer	1.43 (1.30 to 1.57)<0.0001	1.44 (1.28 to 1.62)<0.0001	1.34 (1.19 to 1.49)<0.0001	1.41 (1.25 to 1.59)<0.0001
CKD versus no CKD	1.50 (1.39 to 1.62)<0.0001	1.72 (1.56 to 1.89)<0.0001	1.48 (1.36 to 1.62)<0.0001	
COPD versus no COPD	1.16 (1.07 to 1.26) 0.0004	1.25 (1.13 to 1.39)<0.0001	1.19 (1.08 to 1.30) 0.0002	1.23 (1.11 to 1.36)<0.0001
DM versus no DM	1.14 (1.06 to 1.23) 0.0005	1.13 (1.03 to 1.23) 0.0068	1.08 (1.00 to 1.17) 0.0450	1.08 (0.99 to 1.18) 0.0769
HLP versus no HLP	0.81 (0.76 to 0.87)<0.0001	0.83 (0.76 to 0.90)<0.0001		0.78 (0.72 to 0.85)<0.0001
CAD versus no CAD	1.03 (0.96 to 1.10) 0.4144	1.04 (0.96 to 1.14) 0.3457	1.02 (0.94 to 1.11) 0.5854	1.05 (0.96 to 1.14) 0.2684
HTN versus no HTN	0.97 (0.90 to 1.05) 0.4229	0.99 (0.90 to 1.08) 0.8029	0.95 (0.87 to 1.03) 0.2073	0.83 (0.85 to 1.02) 0.1386
Stroke versus no stroke	1.05 (0.86 to 1.28) 0.6273	1.17 (0.94 to 1.46) 0.1605	1.06 (0.86 to 1.30) 0.5812	1.01 (0.80 to 1.28) 0.9253
BMI	0.99 (0.98 to 0.99)<0.0001			

Continued

Table 2 Continued

HF				
Variables	Model 1 HR (95% CI) p value	Model 2 HR (95% CI) p value	Model 3 HR (95% CI) p value	Model 4 HR (95% CI) p value
LVEF <50% versus ≥50%		1.07 (0.98 to 1.17) 0.1328		
Sodium, ≤135 versus >135 mmol/L				1.35 (1.23 to 1.48) <0.0001
BUN ≤19 versus ≥20 mg/dL				0.83 (0.74 to 0.92) 0.0007
Creatinine <1.5 versus ≥1.5 mg/dL				0.76 (0.70 to 0.84) <0.0001
LDL-C, Q2 versus Q1			0.89 (0.81 to 0.98) 0.0197	
LDL-C, Q3 versus Q1			0.82 (0.74 to 0.92) <0.0003	
LDL-C, Q4 versus Q1			0.77 (0.68 to 0.87) <0.0001	

BMI, body mass index; BUN, blood urea nitrogen; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF, heart failure; HLP, hyperlipidemia; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; Q, quartile.

mortality. First, a diagnosis of HLP, compared with no HLP, was associated with 24% and 20% relative risk reduction in all-cause mortality corresponding to 27 and 39 fewer deaths per 1000 person-years after incident AMI and ADHF, respectively. The reduced mortality associated with HLP was robust to adjustment for potential confounder including demographics, clinical characteristics and key CCs. The association was consistent across the following subsets: young and old, male and female, white and non-white, and prevailed across both study cohorts. The reductions in mortality were independent of benefit attributable to statin therapy. Kaplan-Meier estimates suggest that the

reduction in cumulative incidence of death from HLP begins immediately after hospitalisation and is maintained into follow-up both in AMI and HF cohorts. Second, we found that cancer, COPD, CKD, diabetes mellitus, HF, or stroke, were all significantly associated with increased long-term mortality. This increased risk was offset by the lower mortality from HLP resulting in attenuation or even a null effect on mortality in patients with AMI or ADHF who had HLP concurrent with other CCs. By comparison, hypertension, while having no effect in HF, was inversely associated with mortality in AMI similar to HLP. The magnitude of mortality reduction associated HLP was enhanced in the

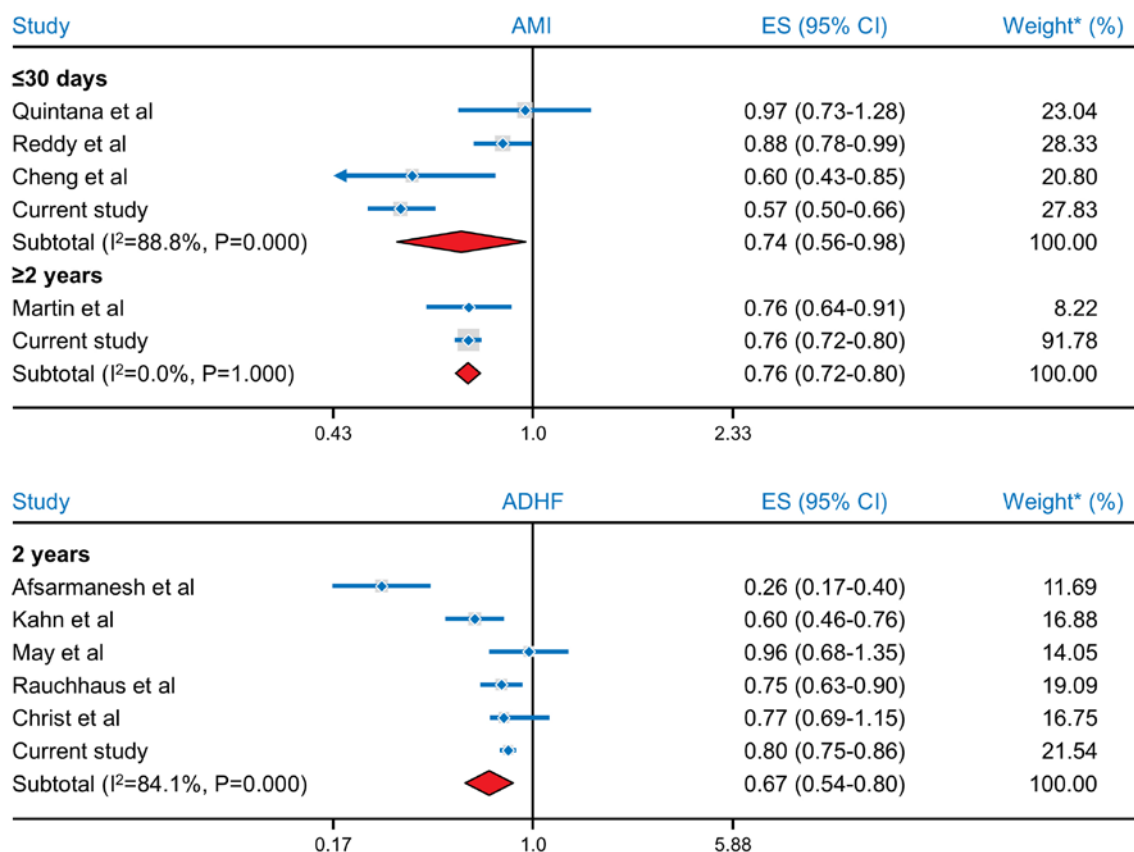


Figure 3 Results of meta-analysis for all-cause mortality. *Weights are from random effects analysis. ADHF, acute decompensated heart failure; AMI, acute myocardial infarction; ES, effect size.

presence of HTN after incident AMI and ADHF. Third, the complementary meta-analysis of published observational studies and current study data demonstrated consistent results and provide further evidence that HLP is associated with decreased mortality following incident AMI or ADHF. Multiple sensitivity analyses among patients with available data on BMI, LDL-C, LVEF, levels of sodium, BUN and creatinine all yielded similar results and the association between HLP and mortality remained robust in AMI and ADHF.

Comparative studies

The association of HLP with atherosclerotic cardiovascular disease is largely based on epidemiological studies^{1–4} and randomised clinical trials of LDL-C lowering therapy. These studies have important limitations and do not ascertain causal relationship. Although genetic studies are promising and have the potential to address causal relationship of LDL-C with atherosclerotic cardiovascular disease,³⁵ the co-inheritance of other pro-atherogenic factors that affect atherosclerotic cardiovascular disease may not be determined.³⁶ Findings of this study dispute general assumption that HLP is associated with increased mortality. However, several community-based and hospital-based population studies contradict this notion and support our findings. A number of large community-based population studies from Scandinavian countries showed that HLP is inversely related to mortality, particularly in older adults.^{37–40} These observations were reproduced in large community-based prospective cohort studies from Japan.⁴¹ A prospective observational study found that low LDL-C on admission was associated with a lower 3-year survival after hospitalisation for non-ST elevation myocardial infarction.⁴² An earlier systematic review found that the mortality risk from HLP decreased with increasing age.⁵ By comparison, we found that HLP maintained its survival benefit even in older adults, a finding supported by a meta-analysis of 19 cohort studies that showed inverse association between elevated cholesterol and mortality.⁴³ These observations were reinforced by widely used risk-prediction models for AMI and HF in which HLP did not make into the final prediction models^{12 13 44–46} suggesting a weaker or no association with mortality. An inverse relationship between HLP and mortality was reported for a number of other conditions not the focus of this study.^{47–49} Similarly, numerous other conditions such as hypertension, cigarette smoking and factor V Leiden exhibit epidemiological paradox.^{50–52} According to epidemiologists, these paradoxes may exemplify collider or index event bias where established risk factor for first occurrence of a disease becomes inversely related after the occurrence of an event.^{53–55} The effect of HLP might be concealed in the presence of stronger competing risk factors for mortality.⁵⁶ Other potential mechanisms include a progressive increase in proportion of deaths from non-cardiovascular conditions with differential association with baseline cholesterol⁵⁷ and a reverse causation, whereby underlying disease lowers

the cholesterol level and increases the risk of death. Numerous investigators argued that low cholesterol represents a biological marker for concurrent cachexia, malnutrition, cancer and other chronic diseases with proven adverse impact on survival.^{58 59} However, HLP remained a predictor of lower mortality in several studies that even excluded terminal diseases.⁴³ Our results support the concept of obesity paradox among patients with HF and AMI and findings were consistent with several published studies. Previous studies reported that even healthy subjects with low cholesterol are especially predisposed to infectious diseases.^{60–62} Although our findings were adjusted for cancer and numerous other CCs, the potential confounding by undiagnosed cachexia or malnutrition cannot be excluded. Our findings were contradicted by a number of randomised clinical trials and meta-analyses of statin therapy in AMI that demonstrated a dose dependent decrease in the risk of cardiovascular events with reduction in LDL-C level, even down to <70 mg/dL.⁶ These discrepant findings are attributable to demographic differences, patient population with lower rates of CCs, shorter follow-up intervals and focus on cardiovascular events including cardiovascular mortality rather than all-cause mortality as the outcome.

Clinical implications

The findings of this study, if validated, should reinforce the importance of HLP in predicting long-term mortality after index AMI or ADHF and potentially provide guidance for subsequent management. HLP can readily be diagnosed and help recognise AMI and HF patients with lower long-term mortality. In these patients, clinical care should not focus on certain lipid targets; rather evidence-based secondary prevention strategies should be initiated. Conversely, patients with AMI and ADHF without HLP may be considered to have increased risk for early mortality and potentially alert providers for close monitoring during hospitalisation and after discharge. Both categories of patients would profit from thoughtful tailored programme with distinctive goals of care for existing CCs.

STRENGTHS AND LIMITATIONS

This study has several strengths. First, large study cohorts, high level of case ascertainment for incident events and prompt mortality update⁶³ allowed precise estimation of mortality risks. Broader range of patient population, long follow-up extending to 20 years, and all-cause rather than cardiovascular mortality as the primary outcome are additional advantages over randomised controlled trials. Second, propensity-score matching to balance observed patient-characteristics enabled further control of potential differences. Third, we conducted a systematic review and meta-analysis to place the findings of this study in the larger context of existing literature with consistent findings. The study also has a number of important limitations. These included possibility of unmeasured confounders, reliance on ICD-9-CM codes to identify study cohort, Clinical Classifications Software codes to assess coexisting CCs,

ascertainment of CCs during index hospitalisation, and lack of data on subsequent acquisition of these conditions during the follow-up. Our study cohorts were homogenous with respect to race and substantially older than those observed in most clinical trials, but, similar to those in many epidemiological studies. The pre-existing HLP and CCs were physician-diagnosed during index hospitalisation rather than being assigned by study investigators. Meta-analysis of ADHF was associated with heterogeneity; nevertheless, the results from all the included studies suggested a reduction in mortality with HLP. Despite some limitations, the findings of the present study may be extended to hospital-based, AMI and ADHF population at large.

CONCLUSIONS

The current findings, based on large unselected hospital-based patient-populations, provide strong evidence that after incident AMI or ADHF, a diagnosis of HLP, compared with no HLP, was associated with reduced long-term mortality, a longer median survival and modest attenuation of the magnitude of mortality risk associated with other competing CCs. Our data support a protective role for HLP against all-cause mortality following incident AMI and ADHF. Further studies are needed to understand the complex relationship between HLP and mortality, especially in the presence of other competing comorbidities and to define appropriate HLP targets to maximise the benefits.

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REFERENCES

- Kannel WB, Castelli WP, Gordon T, *et al*. Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham study. *Ann Intern Med* 1971;74:1-12.
- Multiple risk factor intervention trial. Risk factor changes and mortality results. *JAMA* 1982;248:1465-77.
- The lipid research clinics coronary primary prevention trial results. I. reduction in incidence of coronary heart disease. *JAMA* 1984;251:351-64.
- Frick MH, Elo O, Haapa K, *et al*. Helsinki heart study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237-45.
- Lewington S, Whitlock G, Clarke R, *et al*. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 2007;370:1829-39.
- Baigent C, Blackwell L, Emberson J, *et al*. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:1670-81.
- Silverman MG, Ference BA, Im K, *et al*. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA* 2016;316:1289-97.
- Kjekshus J, Pedersen TR, Olsson AG, *et al*. The effects of simvastatin on the incidence of heart failure in patients with coronary heart disease. *J Card Fail* 1997;3:249-54.
- Velagaleti RS, Massaro J, Vasan RS, *et al*. Relations of lipid concentrations to heart failure incidence: the Framingham heart study. *Circulation* 2009;120:2345-51.
- Reddy VS, Bui QT, Jacobs JR, *et al*. Relationship between serum low-density lipoprotein cholesterol and in-hospital mortality following acute myocardial infarction (the lipid paradox). *Am J Cardiol* 2015;115:557-62.
- Wang TY, Newby LK, Chen AY, *et al*. Hypercholesterolemia paradox in relation to mortality in acute coronary syndrome. *Clin Cardiol* 2009;32:E22-8.
- Granger CB, Goldberg RJ, Dabbous O, *et al*. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;163:2345-53.
- Krumholz HM, Seeman TE, Merrill SS, *et al*. Lack of association between cholesterol and coronary heart disease mortality and morbidity and all-cause mortality in persons older than 70 years. *JAMA* 1994;272:1335-40.
- Kalantar-Zadeh K, Block G, Horwich T, *et al*. Reverse epidemiology of conventional cardiovascular risk factors in patients with chronic heart failure. *J Am Coll Cardiol* 2004;43:1439-44.
- Goodman RA, Posner SF, Huang ES, *et al*. Defining and measuring chronic conditions: imperatives for research, policy, program, and practice. *Prev Chronic Dis* 2013;10:E66.
- Yousufuddin M, Bartley AC, Alsawas M, *et al*. Impact of multiple chronic conditions in patients hospitalized with stroke and transient ischemic attack. *J Stroke Cerebrovasc Dis* 2017;26:1239-48.
- Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499-502.
- Ryder RE, Hayes TM, Mulligan IP, *et al*. How soon after myocardial infarction should plasma lipid values be assessed? *Br Med J* 1984;289:1651-3.
- Stroup DF, Berlin JA, Morton SC, *et al*. Meta-Analysis of observational studies in epidemiology: a proposal for reporting. meta-analysis of observational studies in epidemiology (moose) group. *JAMA* 2000;283:2008-12.
- Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
- Yousufuddin M, Abdalrhim AD, Wang Z, *et al*. Cardiac troponin in patients hospitalized with acute decompensated heart failure: a systematic review and meta-analysis. *J Hosp Med* 2016;11:446-54.
- Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603-5.
- Heinze G, Jüni P. An overview of the objectives of and the approaches to propensity score analyses. *Eur Heart J* 2011;32:1704-8.
- Westreich D, Cole SR, Funk MJ, *et al*. The role of the c-statistic in variable selection for propensity score models. *Pharmacoepidemiol Drug Saf* 2011;20:317-20.
- DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials* 2007;28:105-14.
- Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

- 27 Cheng K-H, Chu C-S, Lin T-H, *et al.* Lipid paradox in acute myocardial infarction-the association with 30-day in-hospital mortality. *Crit Care Med* 2015;43:1255-64.
- 28 Janszky I, Janszky I, Gigante B, *et al.* Diabetes, hypertension, overweight and hyperlipidemia and 7-day case-fatality in first myocardial infarction. *IJC Metab Endocr* 2016;12:30-5.
- 29 Martin SS, Faridi KF, Joshi PH, *et al.* Remnant lipoprotein cholesterol and mortality after acute myocardial infarction: further evidence for a hypercholesterolemia paradox from the triumph registry. *Clin Cardiol* 2015;38:660-7.
- 30 Afsarmanesh N, Horwich TB, Fonarow GC. Total cholesterol levels and mortality risk in nonischemic systolic heart failure. *Am Heart J* 2006;152:1077-83.
- 31 Christ M, Klima T, Grimm W, *et al.* Prognostic significance of serum cholesterol levels in patients with idiopathic dilated cardiomyopathy. *Eur Heart J* 2006;27:691-9.
- 32 Kahn MR, Kosmas CE, Wagman G, *et al.* Low-Density lipoprotein levels in patients with acute heart failure. *Congest Heart Fail* 2013;19:85-91.
- 33 May HT, Muhlestein JB, Carlquist JF, *et al.* Relation of serum total cholesterol, C-reactive protein levels, and statin therapy to survival in heart failure. *Am J Cardiol* 2006;98:653-8.
- 34 Rauchhaus M, Clark AL, Doehner W, *et al.* The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol* 2003;42:1933-40.
- 35 Ference BA, Ginsberg HN, Graham I, *et al.* Low-Density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European atherosclerosis Society consensus panel. *Eur Heart J* 2017;38:2459-72.
- 36 Ravnkov U, de Lorgeril M, Kendrick M, *et al.* Inborn coagulation factors are more important cardiovascular risk factors than high LDL-cholesterol in familial hypercholesterolemia. *Med Hypotheses* 2018;121:60-3.
- 37 Petursson H, Sigurdsson JA, Bengtsson C, *et al.* Is the use of cholesterol in mortality risk algorithms in clinical guidelines valid? ten years prospective data from the Norwegian Hunt 2 study. *J Eval Clin Pract* 2012;18:159-68.
- 38 Bathum L, Depont Christensen R, Engers Pedersen L, *et al.* Association of lipoprotein levels with mortality in subjects aged 50 + without previous diabetes or cardiovascular disease: a population-based register study. *Scand J Prim Health Care* 2013;31:172-80.
- 39 Newson RS, Felix JF, Heeringa J, *et al.* Association between serum cholesterol and noncardiovascular mortality in older age. *J Am Geriatr Soc* 2011;59:1779-85.
- 40 Tuikkala P, Hartikainen S, Korhonen MJ, *et al.* Serum total cholesterol levels and all-cause mortality in a home-dwelling elderly population: a six-year follow-up. *Scand J Prim Health Care* 2010;28:121-7.
- 41 Hamazaki T, Okuyama H, Ogushi Y, *et al.* Towards a paradigm shift in cholesterol treatment. A re-examination of the cholesterol issue in Japan. *Ann Nutr Metab* 2015;66:1-116.
- 42 Al-Mallah MH, Hatahet H, Cavalcante JL, *et al.* Low admission LDL-cholesterol is associated with increased 3-year all-cause mortality in patients with non ST segment elevation myocardial infarction. *Cardiol J* 2009;16:227-33.
- 43 Ravnkov U, Diamond DM, Hama R, *et al.* Lack of an association or an inverse association between low-density-lipoprotein cholesterol and mortality in the elderly: a systematic review. *BMJ Open* 2016;6:e010401.
- 44 Antman EM, Cohen M, Bernink PJ, *et al.* The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835-42.
- 45 Fine MJ, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997;336:243-50.
- 46 Fonarow GC, Adams KF, Abraham WT, *et al.* Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA* 2005;293:572-80.
- 47 Amezcaga Urruela M, Suarez-Almazor ME. Lipid paradox in rheumatoid arthritis: changes with rheumatoid arthritis therapies. *Curr Rheumatol Rep* 2012;14:428-37.
- 48 Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Inverse association between lipid levels and mortality in men with chronic kidney disease who are not yet on dialysis: effects of case mix and the malnutrition-inflammation-cachexia syndrome. *J Am Soc Nephrol* 2007;18:304-11.
- 49 Yermaneni S, Kleindorfer DO, Sucharew H, *et al.* Hyperlipidemia is associated with lower risk of poststroke mortality independent of statin use: a population-based study. *Int J Stroke* 2017;12:152-60.
- 50 Baglin T. Unraveling the thrombophilia paradox: from hypercoagulability to the prothrombotic state. *J Thromb Haemost* 2010;8:228-33.
- 51 Barbash GI, Reiner J, White HD, *et al.* Evaluation of paradoxical beneficial effects of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: mechanism of the "smoker's paradox" from the GUSTO-I trial, with angiographic insights. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol* 1995;26:1222-9.
- 52 Curtis JP, Selter JG, Wang Y, *et al.* The obesity paradox: body mass index and outcomes in patients with heart failure. *Arch Intern Med* 2005;165:55-61.
- 53 Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. *JAMA* 2011;305:822-3.
- 54 Flanders WD, Eldridge RC, McClellan W. A nearly unavoidable mechanism for collider bias with index-event studies. *Epidemiology* 2014;25:762-4.
- 55 Smits LJM, van Kuijk SMJ, Leffers P, *et al.* Index event bias-a numerical example. *J Clin Epidemiol* 2013;66:192-6.
- 56 Ridker PM, Rifai N, Rose L, *et al.* Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347:1557-65.
- 57 Sharma A, de Souza Brito F, Sun J-L, *et al.* Noncardiovascular deaths are more common than cardiovascular deaths in patients with cardiovascular disease or cardiovascular risk factors and impaired glucose tolerance: insights from the nateglinide and valsartan in impaired glucose tolerance outcomes research (navigator) trial. *Am Heart J* 2017;186:73-82.
- 58 Knudtson MD, Klein BEK, Klein R, *et al.* Associations with weight loss and subsequent mortality risk. *Ann Epidemiol* 2005;15:483-91.
- 59 Liu Y, Coresh J, Eustace JA, *et al.* Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. *JAMA* 2004;291:451-9.
- 60 Iribarren C, Jacobs DR, Sidney S, *et al.* Cohort study of serum total cholesterol and in-hospital incidence of infectious diseases. *Epidemiol Infect* 1998;121:335-47.
- 61 Jacobs D, Blackburn H, Higgins M, *et al.* Report of the conference on low blood cholesterol: mortality associations. *Circulation* 1992;86:1046-60.
- 62 Ravnkov U. High cholesterol may protect against infections and atherosclerosis. *QJM* 2003;96:927-34.
- 63 Whisnant JP, Melton LJ, Davis PH, *et al.* Comparison of case ascertainment by medical record linkage and cohort follow-up to determine incidence rates for transient ischemic attacks and stroke. *J Clin Epidemiol* 1990;43:791-7.