Lipid levels achieved after a first myocardial infarction and the prediction of recurrent atherosclerotic cardiovascular disease

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ABSTRACT

Background: Low density lipoprotein cholesterol (LDL-C) goals post-myocardial infarction (MI) are debated, and the significance of achieved blood lipid levels for predicting a first recurrent atherosclerotic cardiovascular disease (rASCVD) event post-MI is unclear.
Methods: This was a cohort study on first-ever MI survivors aged ≤76 years attending 4–14 week revisits throughout Sweden 2005–2013. Personal-level data was collected from SWEDEHEART and linked national registries. Exposures were quintiles of LDL-C, high density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TGs) at the revisit. Group level associations with rASCVD (nonfatal MI or coronary heart disease death or fatal or nonfatal ischemic stroke) were estimated in Cox regression models. Predictive capacity was estimated by differences in C-statistic, integrated discriminatory improvement, and net reclassification improvement when adding each blood lipid to a validated risk prediction model.
Results: 25,643 patients, 96.9% on statin therapy, were followed during a mean of 4.1 years. rASCVD occurred in 2173 patients (8.5%). For LDL-C and TC, moderate associations with rASCVD were observed only in the 5th vs. the lowest (referent) quintiles. For TGs and HDL-C increased risks were observed in quintiles 3–5 vs. the lowest. Minor predictive improvements were observed when lipid fractions were added to the risk model but the discrimination overall was poor (C-statistics <0.6).
Conclusions: Our data question the importance of LDL-C levels achieved at first revisit post-MI for decisions on continued treatment intensity considering the weak association with rASCVD observed in this post-MI cohort.

1. Introduction

Lipid-lowering therapy (LLT) with statins is a cornerstone in the secondary prevention of cardiovascular (CV) events after a myocardial infarction (MI) [1–5]. In order to monitor responses to statin therapy, lipid panels are routinely analyzed post-MI with a strong emphasis on achieving low density lipoprotein cholesterol (LDL-C) target levels [2,3]. Currently, the European guidelines recommend an attained LDL-C <1.8 mmol/L or >50% reduction if baseline LDL-C levels are 1.8–3.5 mmol/L in post-MI patients [1,2].

There has, however, been poor consensus regarding LDL-C based treatment goals as the treatment targets for LDL-C are based on observational post-hoc analyses of the large statin trials [6] and the use of LDL-C as a surrogate variable for outcomes may be questioned [7,8]. Therefore, the 2013 ACC/AHA Guidelines abandoned treatment to target levels of LDL-C in favor of risk guided intensity of statin treatment [3]. In contrast, even lower LDL-C goals have been advocated after the recent proprotein convertase subtilisin/

kexin type 9 inhibitor trials [4,9,10] and non-LDL lipid fractions remain marginalized in secondary prevention risk assessment.

Better residual risk stratification within the post-MI population may further improve outcomes through individualized risk guided treatment intensity, as successfully practiced in primary prevention [5,11]. Blood lipids are established risk factors for CV disease and the risk contribution may be modified by efficient LLT. The importance of LDL-C and other blood lipid levels in post MI patients on effective statin treatment for the risk of suffering a first recurrent athero-sclerotic cardiovascular disease event (rASCVD) [3] remains unclear.

Therefore, we examined the recurrences of ASCVD in a large Swedish cohort of first-ever MI patients in relation to blood lipids routinely measured at an early revisit with special interest in the predictive value of LDL-C over and above a comprehensive risk estimation score [12].

2. Methods

2.1. Study design and data sources

This was a nationwide cohort study on first ever MI patients attending at the standardized follow-up 4–14 weeks post MI in the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) quality registry [13,14]. Patients aged ≤76 years were consecutively enrolled between 2005 and 2013. Data on CV risk factors and therapies were collected at the follow-up visit and enriched with clinical data from the time of the index MI. In 2014, 97% (70/72) of all cardiac emergency care hospitals throughout Sweden reported secondary prevention data to SWEDEHEART [15]. The Swedish Board of Health and Welfare manages the national Cause of Death, Inpatient, and Prescribed Drug Registries from which complementary individual level data was retrieved by linkage through the unique personal identification number assigned to all Swedish residents [16,17]. The validities of the Swedish Inpatient registry and SWEDEHEART are high [14,18]. The study was approved by the Regional Ethical Review Board in Stockholm (EPN 2015/124-31/4). Informed consent was not obtainable but the study involves no infringement of personal integrity and all patients had the right to refuse participation in the quality registry.

2.2. Clinical data

Quality registry data collected at baseline were age (continuous, years), gender (male, female), inclusion year (ordinal, year), pharmacological treatments (yes, no) including acetylsalicylic acid, beta blockers, angiotensin II receptor antagonists or angiotensin converting enzyme inhibitors, insulin treatment or oral antidiabetics, and clinical data on smoking status (never, former, current), body weight (continuous, kg), systolic blood pressure (continuous, mmHg). Data collected from inpatient care at the time of the index MI were hypertension diagnosis (yes, no), history of congestive heart failure (yes, no), height (continuous, centimeters), discharge heart rhythm (sinus, non-sinus), left ventricular ejection fraction (<30, 30–49, or ≥50%), creatinine (continuous, μmol/L), and cardiac injury biomarkers (Troponin T, Troponin I and hsTnT; continuous, μg/L, μg/L, and ng/L, respectively). Oral and/or insulin treatment were merged to a binary diabetes treatment variable. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [19] and categorized according to chronic kidney disease staging (<15, 15–29, 30–59, 60–89, ≥90 mL/min/1.73 m^2). If more than one serum creatinine input was available, the mean was used. Body mass index (BMI) was calculated by dividing patient weight (kg) by squared height (m) and categorized according to World Health Organization cut-offs (<18.5, 18.5–24.9, 25–29.9, ≥30 kg/m^2). Congestive heart failure (CHF) was defined as history of CHF at the index MI or a LVEF measurement <50%. Detailed data on all lipid modifying therapy were obtained from the National Pre-scribed Drug registry, specifying the type by ATC-code and the dosage that had been prescribed and claimed at any Swedish pharmacy most recently before the study baseline visit, i.e., 4–14 weeks after the MI. Dosages were categorized into high (Rosuvastatin 20–40 mg or Atorvastatin 40–80 mg), moderate (Rosuvastatin 5–10 mg, Atorvastatin 10–20 mg, or Simvastatin 20–40 mg) and low (Simvastatin 10 mg) intensity statin therapy according to previous guidelines [3], and a fourth non-statin lipid lowering drug category was added. A peripheral artery disease variable was created from the National Inpatient Registry based on presence of ICD-10 codes (Supplementary Methods) at baseline. For model III, relevant variables were dichotomized and adapted to the TRS2°P risk prediction model [12].

2.3. Definition of exposures and outcomes

Exposures were the levels of the blood lipid fractions LDL-C, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) in mmol/L, measured in conjunction with the post-MI revisit. LDL-C was calculated using the Friedewald formula in all but 164 (0.6%) patients where a direct measurement was used [20]. The four lipid fractions were categorized into quintiles for the main

analyses. In addition, LDL-C was also categorized according to guideline LDL-C treatment goals and usual indications for treatment [2].

All participants were followed up prospectively regarding rASCVD. This composite endpoint was defined as first recurrent event of nonfatal MI or CHD death or fatal or nonfatal ischemic stroke as adopted from the New Pooled Cohort Risk Equations [5]. Secondary endpoints were pre-specified as fatal or nonfatal MI, fatal or nonfatal stroke, and all-cause mortality. Corresponding ICD-10 codes were identified in the National Inpatient [18] and Cause of Death registries. See Supplementary eTable 1 in the Appendix for details. The outcomes were collected from baseline until the first event within the time frame of January 1, 2005 to December 31, 2013.

2.4. Statistical methods

Baseline characteristics of the study population are presented in Table 1. Categorical variables are reported as frequencies and percentages, while continuous variables are reported as medians and interquartile ranges. Missing data are reported and commented on in eTable 2.

Crude rates of rASCVD were calculated as the number of events per 1000 person-years by quintiles of LDL-C, TC, HDL-C and TGs. Two Cox proportional-hazards models were used to assess the group level associations between each of the lipid fractions and rASCVD by estimating hazard ratios (HRs) and 95% confidence intervals (CIs). Model I was crude, thus reflecting the basis for clinical decisions on LLT in current practice. Model II was adjusted for age, gender, and year of baseline revisit, covariates representing confounding related to registry inclusion criteria.

A third model was adopted from an externally validated secondary prevention risk prediction study that had built a risk stratification scheme based on 9 independent predictors identified among numerous clinical indicators of CV risk [12,21]. We then assessed whether the four lipid fractions would increase the predictive power of this model. To do so, we added them one at a time to model III and calculated their predictive power, as measured by differences in Harrell's C statistics [22]. Standard errors for the Harrell's C statistics were calculated using the jackknife estimator [23]. Complementary information on the incremental predictive model performance from adding the four lipid fractions was assessed by estimating integrated discrimination improvement (IDI) and continuous net reclassification improvement (cNRI) [24,25].

The robustness of model II results was assessed in a sensitivity analysis estimating the association between lipid levels and rASCVD in subgroups with and without high statin treatment intensity. In another sensitivity analysis, the potential confounding by intensification of LLT after baseline in patients with high LDL-C levels was evaluated. We did so by adding to model II an adjustment factor accounting for any change in statin treatment intensity (none, decrease, increase) after the baseline visit. In a third sensitivity analysis, covariation between levels of HDL-C and LDL-C was evaluated by entering both lipid fractions into model II. Statistical analyses were performed using Stata version 14.2 (StataCorp, College Station, TX).

3. Results

The study population selection procedure and reasons for non-participation are described in Supplemental Fig. S1.

3.1. Patient characteristics

The final study cohort comprised 25,643 patients with a median (IQR) age of 63.3 (56.4, 68.8) years; 27% were women and 96.7% were on statin therapy. Baseline characteristics stratified by LDL-C quintiles are summarized in Table 1. Patients with LDL-C in the lower range were slightly older, more likely to be men, and non-smoking. They were treated with more intense statin therapy and more often with renin angiotensin system inhibitors. Furthermore, patients in the lowest LDL-C quintile more often had hypertension, diabetes mellitus or obesity. Levels of TGs and especially TC increased by level of LDL-C whereas the correlation with HDL-C was weak.

3.2. Primary outcome analysis

During a mean follow-up of 4.1 years 2173 (8.5%) of the study participants experienced rASCVD. Recurrence rates by quintiles of the lipid fractions are reported in eTable 3. No consistent pattern in relation to LDL-C quintiles were observed whereas they increased across all quintiles of TGs, from 17.6 (95% CI 16.0–19.4) to 24.1 (95% CI 22.1–26.3) events per 1000 person-years. Kaplan-Meier estimates of the rASCVD-free proportions during follow-up by lipid fraction quintiles are presented in supplemental Fig. S2, panels A-E. Crude and multivariable adjusted HRs with 95% CIs for rASCVD by

Table 1
Patient characteristics by quintiles of LDL-C.

Characteristic	Quintiles of LDL-C, mmol/L				
	<1.58	1.58–1.91	1.92–2.24	2.25–2.66	≥2.67
No. (%) with data	5161	5103	5194	5057	5128
HDL-C, median (IQR), mmol/L	1.10 (0.90, 1.40)	1.10 (1.00, 1.40)	1.20 (1.00, 1.40)	1.20 (1.00, 1.40)	1.20 (1.00, 1.40)
TC, median (IQR), mmol/L	3.10 (2.80, 3.40)	3.50 (3.30, 3.80)	3.90 (3.60, 4.20)	4.30 (4.00, 4.60)	5.10 (4.70, 5.60)
TGs, median (IQR), mmol/L	1.15 (0.83, 1.60)	1.12 (0.90, 1.60)	1.20 (0.90, 1.64)	1.30 (1.00, 1.70)	1.47 (1.10, 1.90)
Age, median (IQR), years	63.9 (56.6, 69.4)	63.8 (56.8, 69.2)	63.4 (56.5, 68.7)	62.7 (56.1, 68.4)	62.7 (56.0, 68.3)
Female sex, No. (%)	1232 (23.9)	1303 (25.5)	1399 (26.9)	1442 (28.5)	1567 (30.6)
Follow-up year, No. (%)					
2005	198 (3.8)	193 (3.8)	193 (3.7)	224 (4.4)	207 (4.0)
2006	385 (7.5)	317 (6.2)	296 (5.7)	293 (5.8)	269 (5.2)
2007	440 (8.5)	449 (8.8)	444 (8.5)	430 (8.5)	440 (8.6)
2008	449 (8.7)	475 (9.3)	537 (10.3)	485 (9.6)	497 (9.7)
2009	385 (7.5)	541 (10.6)	551 (10.6)	626 (12.4)	671 (13.1)
2010	479 (9.3)	604 (11.8)	677 (13.0)	728 (14.4)	763 (14.9)
2011	610 (11.8)	678 (13.3)	797 (15.3)	875 (17.3)	920 (17.9)
2012	848 (16.4)	763 (15.0)	811 (15.6)	732 (14.5)	746 (14.5)
2013	1367 (26.5)	1083 (21.2)	888 (17.1)	664 (13.1)	615 (12.0)
Evidence-based treatment, No. (%)					
Statins intensity[a, b] No. (%)					
No statin	47 (0.9)	72 (1.4)	96 (1.8)	129 (2.6)	458 (8.9)
Low	13 (0.3)	29 (0.6)	26 (0.5)	36 (0.7)	67 (1.3)
Moderate	3113 (60.3)	3510 (68.8)	3730 (71.8)	3825 (75.6)	3585 (69.9)
High	1988 (38.5)	1492 (29.2)	1342 (25.8)	1067 (21.1)	1018 (19.9)
Low-dose aspirin	4937 (95.7)	4924 (96.6)	5000 (96.3)	4868 (96.4)	4848 (94.6)
Beta blockers	4702 (91.2)	4613 (90.5)	4757 (91.7)	4613 (91.3)	4613 (90.0)
ACEi/ARB	4178 (81.0)	4042 (79.2)	4074 (78.5)	3860 (76.4)	3884 (75.8)
Cardiovascular risk factors and comorbidities					
Persistent smoking, No. (%)	574 (11.2)	555 (10.9)	585 (11.3)	619 (12.3)	688 (13.4)
SBP, median (IQR), mm Hg	130.0 (120.0, 140.0)	130.0 (120.0, 140.0)	130.0 (120.0, 140.0)	130.0 (120.0, 140.0)	130.0 (120.0, 140.0)
Hypertension[c], No. (%)	2120 (41.3)	1994 (39.3)	1946 (37.7)	1809 (36.0)	1854 (36.4)
Diabetes, No. (%)	972 (18.9)	698 (13.7)	582 (11.2)	469 (9.3)	495 (9.7)
eGFR[c] < 60 ml/min/1.73 m^2, No. (%)	498 (10.1)	377 (7.7)	376 (7.5)	408 (8.4)	449 (9.1)
BMI > 30 kg/m^2 No. (%)	1037 (25.3)	959 (24.5)	922 (23.3)	849 (21.9)	862 (22.3)
Peripheral Artery Disease[d]	32 (0.6)	26 (0.5)	28 (0.5)	25 (0.5)	54 (1.1)
Index infarction severity					
Discharge heart rhythm[c] (non-sinus), No. (%)	142 (2.8)	115 (2.3)	96 (1.9)	115 (2.3)	112 (2.2)
Cardiac injury biomarker quintiles[c, e], No. (%)					
1 (min)	728 (15.4)	757 (16.0)	768 (15.9)	770 (16.2)	809 (16.8)
2	864 (18.3)	858 (18.2)	896 (18.5)	831 (17.5)	911 (18.9)
3	916 (19.4)	928 (19.6)	918 (18.9)	951 (20.0)	977 (20.2)
4	1004 (21.3)	1024 (21.7)	1066 (22.0)	1031 (21.7)	1041 (21.6)
5 (max)	1212 (25.7)	1159 (24.5)	1197 (24.7)	1164 (24.5)	1091 (22.6)
Congestive heart failure[c]	1442 (28.0)	1369 (27.0)	1374 (26.6)	1377 (27.4)	1394 (27.3)

Abbreviations: LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; IQR, inter quartile range; TC, total cholesterol; TGs, triglycerides; ASA, acetylic salicylic acid; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; BMI, body mass index;

To convert LDL-C, TC, or HDL-C values to mg/dL, multiply by 38.67. To convert TG values to mg/dL, multiply by 88.57.

[a] ATC-code and daily dosage data stratified according to the 2013 ACC/AHA Blood Cholesterol Guideline (High: Rosuvastatin 20–40 mg, Atorvastatin 40–80 mg, or; Moderate: Rosuvastatin 5–10 mg, Atorvatstatin 10–20 mg, or Simvastatin 20–40 mg; Low: Simvastatin 10 mg).

[b] Data from the Swedish Pharmaceutical Registry.

[c] Data collection during inpatient care of indexing myocardial infarction.

[d] Data from national inpatient registry at baseline.

[e] Cardiac injury biomarker maximum level regardless of troponin subtype measured.

blood lipid quintiles are reported in Table 2 and Fig. 1, panels A-D. Supplemental Fig. S3 illustrates the associations in model II between the lipid fractions modelled with restricted cubic splines and the primary outcome. Using the lowest LDL-C quintile as referent, no significant associations with the outcome were observed among increasing quintiles of LDL-C apart from moderate risk increases in the highest quintile in models I-II. For TC there was an association in the highest vs. the lowest quintile that was unaffected by model II adjustments, but the risk was not elevated in quintiles 2–4. For HDL-C the 3rd vs. the lowest quintile was associated with less rASCVD in both models. The crude risk decrease was moderate, gaining importance in model II in which associations were also observed in the 4th–5th quintiles. For TGs the risk was elevated in the 3rd compared to the lowest quintile, with further increases in quintiles 4–5. Associations with rASCVD in these top quintiles of TGs were strong in models I-II.

In a complementary analysis using Guideline based cut-offs with a referent category for LDL-C of <1.8 mmol/L ($n = 8329$), only the top 4th category with LDL-C ≥ 4.0 mmol/L ($n = 621$) was associated with an increased risk of rASCVD in models I-II (Fig. 1E).

3.3. Predictive value of blood lipid fractions

The TRS2°P risk model performed poorly with regard to discrimination of rASCVD. Additions of LDL-C, TC, or TGs improved the discrimination slightly but significantly when added to the model (C-index difference $p < 0.02$ for all), whereas HDL-C did not. (Table 3) The integrated discrimination improvement (IDI) was improved by adding LDL-C, TC, or HDL-C, but not TGs. The continuous net reclassification improvement (cNRI) was improved from adding LDL-C, but neither of the other blood lipid fractions. The C-statistics remained low (<0.6) in all analyses.

3.4. Sensitivity analyses

Results by subgroups of patients treated with high or low-moderate statin intensity are reported in Supplemental eTable 4. In the high statin intensity subgroup ($n = 6907$ for LDL-C) no statistically significant associations with rASCVD were observed for LDL-C or TC. For HDL-C, the association with the outcome remained in 3rd vs the lowest quintile (HR 0.52, 95% CI 0.36−0.74) and for TGs, the risk in the 5th vs the lowest quintile remained high (HR 2.09, 95% CI 1.50−2.91).

A new statin prescription was claimed by 10,880/25,643 patients during a 6-month period after the baseline visit. Statin intensity was assumed unchanged in patients with no new claim. Associations were similar after adding statin intensity change as a covariate to model II (supplemental eTable 5). For LDL-C, however, this rendered non-significance also in the highest vs. the lowest quintile of LDL-C compared model II associations.

Entering both HDL-C and TGs into model II attenuated associations between HDL-C and rASCVD but they remained significant in quintiles 3 (HR 0.77 (95% CI 0.68−0.88) and 4 (HR 0.86, 95% CI 0.74−1.00) compared to the lowest. The associations between TGs and rASCVD did not change.

3.5. Secondary endpoints

HRs for secondary outcomes are reported in eTables 6−8. There were 1740 MIs, 507 ischemic strokes, and 1566 all cause deaths

Table 2
rASCVD HRs with 95% CIs by quintiles of lipid fractions and analysis model.

Lipid fraction (mmol/L)	Model I[a] HR (95% CI)	Model II[b] HR (95% CI)	Model III[c] HR (95% CI)
LDL-C			
Q1 (<1.58)	1.00	1.00	1.00
Q2 (1.58−1.91)	1.02 (0.89−1.17)	1.02 (0.89−1.17)	1.07 (0.93−1-23)
Q3 (1.92−2.24)	0.93 (0.81−1.06)	0.94 (0.82−1.08)	1.00 (0.87−1.16)
Q4 (2.25−2.66)	1.05 (0.92−1.20)	1.07 (0.93−1.22)	1.14 (0.99−1.31)
Q5 (≥2.67)	1.15 (1.01−1.31)	1.17 (1.03−1.34)	1.22 (1.06−1.39)
TC			
Q1 (<3.30)	1.00	1.00	1.00
Q2 (3.30−3.69)	1.05 (0.92−1.21)	1.05 (0.91−1.21)	1.11 (0.96−1.28)
Q3 (3.70−4.19)	0.98 (0.86−1.12)	0.98 (0.86−1.12)	1.04 (0.91−1.19)
Q4 (4.20−4.69)	1.08 (0.94−1.24)	1.07 (0.93−1.23)	1.13 (0.98−1.30)
Q5 (≥4.70)	1.30 (1.14−1.48)	1.31 (1.14−1.49)	1.35 (1.18−1.55)
HDL-C			
Q1 (<0.90)	1.00	1.00	1.00
Q2 (0.90−1.09)	0.95 (0.84−1.08)	0.91 (0.81−1.03)	1.03 (0.91−1.16)
Q3 (1.10−1.29)	0.78 (0.69−0.89)	0.72 (0.64−0.83)	0.87 (0.76−1.00)
Q4 (1.30−1.49)	0.87 (0.76−1.01)	0.79 (0.68−0.91)	0.94 (0.81−1.09)
Q5 (≥1.50)	0.98 (0.86−1.11)	0.85 (0.74−0.98)	1.11 (0.97−1.28)
TGs			
Q1 (<0.90)	1.00	1.00	1.00
Q2 (0.90−1.09)	1.06 (0.92−1.22)	1.06 (0.92−1.22)	1.03 (0.89−1.19)
Q3 (1.10−1.39)	1.15 (1.01−1.31)	1.15 (1.01−1.32)	1.10 (0.96−1.26)
Q4 (1.40−1.89)	1.33 (1.17−1.52)	1.36 (1.19−1.55)	1.26 (1.10−1.44)
Q5 (≥1.90)	1.38 (1.22−1.57)	1.46 (1.29−1.66)	1.18 (1.04−1.35)

Abbreviations: rASCVD, first recurrent event of atherosclerotic cardiovascular disease; HR, hazard ratio; CI, confidence interval; Q, quintile; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TGs, triglycerides.
To convert LDL-C, TC, or HDL-C values to mg/dL, multiply by 38.67. To convert TG values to mg/dL, multiply by 88.57.
[a] Unadjusted model.
[b] Multivariable model adjusted for age, gender and study inclusion year (2005−2013).
[c] Multivariable model adjusted for predictors of the TRS2°P model (age, history of congestive heart failure, diabetes, peripheral artery disease, chronic kidney disease and smoking).

during mean follow-ups of 4.1, 4.3, and 4.3 years, respectively. The risk for fatal or nonfatal MI by lipid fraction quintiles was very similar to that for rASCVD, but without any crude association observed for LDL-C. For fatal or nonfatal ischemic stroke, there were no associations with LDL-C in model I or II. The risks for stroke associated with TGs, TC, and HDL-C were comparable to the associations with rASCVD but without crude association with TGs. For all cause death, higher quintiles of LDL-C were associated with a risk reduction compared to the lowest quintile. The 4th quintile of TC was also associated with a lower risk of death. Third quintile associations, as in the analysis for rASCVD, were observed between HDL-C and all cause death. The top quintiles of TGs were associated with increased all cause death.

4. Discussion

4.1. Findings/meaning

The main finding of this nationwide cohort study with early revisit data in post-MI patients was that LDL-C was the lipid fraction with the weakest association with rASCVD. Stronger associations were observed for TC, HDL-C or, especially, TGs. Adding LDL-C to a validated secondary prevention risk model yielded a small improvement of risk prediction which, however, was still poor (C-index 0.589). At the first revisit post MI, the LDL-C levels achieved are a major concern in current clinical practice. Regardless of whether a further reduction of LDL-C might benefit the patient, the present data indicate that achieved LDL-C levels at an early revisit post-MI are of limited value for identifying high-risk patients. This is, to our knowledge, the first study that examines the value of routine lipid panel measurements at an early revisit post MI for the prediction of rASCVD.

4.2. Comparison with related studies

We observed poor predictive values of routinely measured lipid fractions, including LDL-C, at the early revisit post MI. Among recent secondary prevention risk prediction studies, LDL-C has rarely qualified to the final model or score when considered as a candidate risk factor [26,27]. Compared to these previous studies, our sample was much larger, recruited nationwide and included only patients with a recent MI. Although there is currently no established method for predicting long-term risk of recurrence post-MI, we made an effort by adopting predictors of an externally validated model developed for patients with recent MI and a matching primary composite outcome [12]. Our results support the contention that the well documented predictive role of lipid levels for the risk of a first occurrence of ASCVD cannot be extrapolated to the secondary prevention setting post-MI [28,29].

We report the weakest association with outcomes for LDL-C. In related studies, differences in important aspects of study design contribute to non-consistent results. In a study on residual CV mortality risk in patients with coronary heart disease, De Baquer et al. reported significantly increased HRs for low HDL-C and top levels of TC and LDL-C, whereas TGs were not reported [30]. TC was reported as the only predictive lipid fraction. Recruitment to the study was between 1995 and 1996 and 1999−2000 for cohort subsets and only 44.2% were on LLT as compared to 96.9% in our cohort. Consequently, the range of the lipid level categories was shifted upwards compared to our cohort. For instance, 28% of the cohort ($n = 5216$) had TC levels ≥6.0 mmol/L, and the referent lowest category for LDL-C was <2.5 mmol/L.

In our study, the strongest association with rASCVD was observed for TGs, independently of HDL-C. A study from the bezafibrate infarction prevention registry observed a similar but
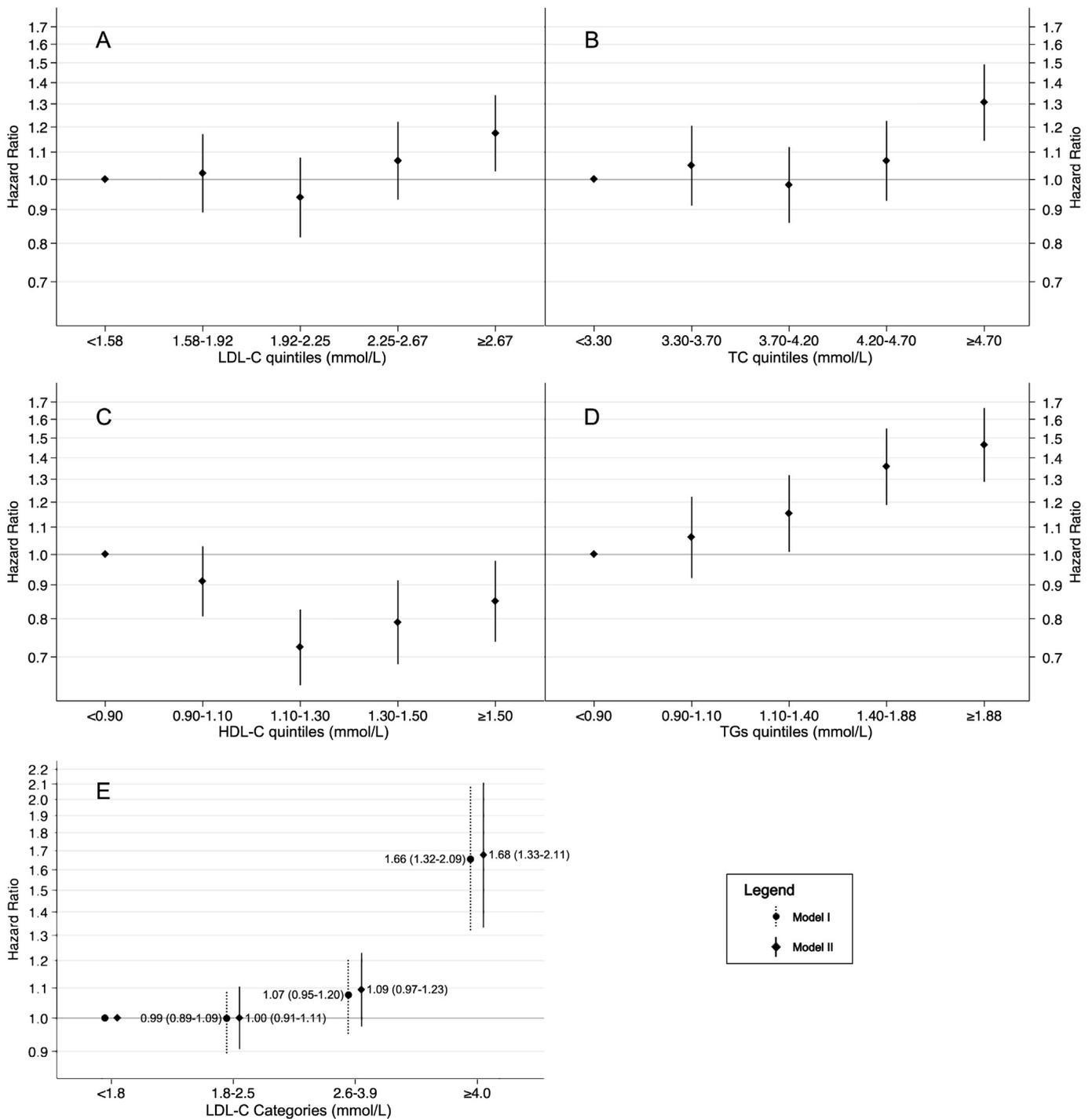
Fig. 1. Forest plots depicting group-level hazard ratios with 95% confidence intervals for rASCVD by quintiles of LDL-C (panel A), TC (panel B), HDL-C (panel C), and TGs (panel D). Panel E depicts model I-II hazard ratios by categories of LDL-C. Abbreviations: LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; TGs, triglycerides. To convert LDL-C, TC, or HDL-C values to mg/dL, multiply by 38.67. To convert TG values to mg/dL, multiply by 88.57. Model I was crude. Model II was adjusted for age, gender, and year of baseline revisit.

smaller stepwise risk increase when evaluating the mortality outcomes associated with high TGs in 11,532 patients with established coronary heart disease, before the statin era. The predictive value of TGs was enhanced by elevated levels of LDL-C or TC but attenuated by adjustment for HDL-C [31]. The study did not report LLT and only 65% had suffered an MI at baseline. Another study from this cohort found strong associations between TC and LDL-C and recurrent stroke but reported that only 5% of the participants were on LLT at baseline [32].

Our data question the importance of LDL-C levels achieved at the first revisit post-MI for identifying high-risk patients and for decisions on continued treatment intensity. Our results are challenging in an era when LDL-C levels are the main lipid management concern post-MI [1,2,4]. The positive results from the FOURIER trial evaluating CV outcomes in high-risk patients treated with evolocumab on top of statin therapy [33] have been interpreted as support for a direct relationship between the surrogate marker LDL-C and CV outcomes and an impetus to achieve as low LDL-C

Table 3
Incremental predictive performance by difference in Harrell's C-statistic, integrated discrimination improvement (IDI), and continuous net reclassification improvement (cNRI) from adding a lipid fraction to prediction model III[a].

Model	C-index (95% CI)	C-index difference from base model (95% CI)	IDI difference	cNRI difference
Model III	0.583 (0.569–0.596)			
Model III + LDL-C	0.589 (0.575–0.603)	0.006 (0.001–0.012), $P = 0.012$	0.002 (0.001–0.004), $P < 0.001$	0.074 (0.026–0.104), $P < 0.001$
Model III + HDL-C	0.585 (0.571–0.600)	0.003 (−0.003–0.009), $P = 0.366$	0.002 (0.000–0.004), $P = 0.032$	0.098 (−0.017–0.134), $P = 0.216$
Model III + TC	0.592 (0.578–0.606)	0.010 (0.003–0.016), $P = 0.016$	0.002 (0.000–0.004), $P = 0.012$	0.026 (−0.009–0.084), $P = 0.172$
Model III + TGs	0.590 (0.576–0.604)	0.007 (0.001–0.014), $P = 0.019$	0.000 (0.000–0.002), $P = 0.216$	0.027 (−0.021–0.060), $P = 0.287$

Abbreviations: CI, confidence interval; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TC, total cholesterol; TGs, triglycerides.

[a] multivariable Cox regression model based on the validated TRS2°P risk prediction model adjusted for age, history of congestive heart failure, diabetes, peripheral artery disease, chronic kidney disease and smoking.

levels as possible [10]. In a recent meta-analysis, intensive compared to less intensive LLT was associated with a reduction in risk only when baseline LDL-C levels were above 2.6 mmol/L. [34] Similar findings were reported in the ODYSSEY trial with alirocumab vs. placebo on top of high-dose statin treatment in patients with a relatively recent acute coronary syndrome [35]. For many MI patients with proper evidence-based secondary preventive therapy the current European LDL-C goal of <1.8 mmol/L may be unnecessarily aggressive. Most importantly, however, clinical decision making should be based on empirical predictors, regardless of pathogenesis [7], and in the secondary preventive setting other factors may be of interest, such as socioeconomic status [36].

4.3. Study limitations

A registry-based design entails that the data was not specifically collected for our study question. Exposures were objective continuous variables analyzed by hospital laboratories throughout Sweden but rely on single measurements which may reduce accuracy. However, decisions on continued LLT are based on these measurements at the first revisit post-MI in clinical practice. Decreased blood lipid levels during the first 6 weeks after a MI [37] may have resulted in misclassification of a few study participants with post-MI revisits prior to the standard time frame of 6–12 weeks but this is unlikely to have influenced the results.

4.4. Implications for research and clinical practice

The aims of secondary prevention post-MI are to counteract or delay the progression of atherosclerosis, to manage and prevent conditions secondary to the MI, and to prevent recurrent CV events through actions based on global risk assessments. The first revisit after cardiac care unit discharge is an important opportunity to reinforce treatment given thus far in high risk patients. With new, potent and very expensive treatments this requires accurate risk assessments. In a pooled analysis of patients from several trials the prognostic value of a 50% reduction of LDL-C levels, equivalent to high-intensity statin therapy, outperformed the prognostic value of attaining a static LDL treatment goal of <1.8 mmol/L with regard to outcomes [38]. Although LDL-C improved the prediction of rASCVD slightly more than TC, HDL-C or TGs in this study, the predictive performance of the TRS2°P-based model was still poor. LDL-C was the lipid fraction with the weakest association with rASCVD and our results do not support the use of achieved LDL-C at the first revisit post-MI for identification of high-risk patients [1,5].

5. Conclusions

LDL-C was the lipid fraction with the weakest association with rASCVD and provided little guidance for identifying high-risk patients at the early routine revisit post-MI. The incremental

predictive value of LDL-C was minor when assessed together with other CV risk factors. LDL-C was not superior to levels of TC, HDL-C, or TGs for risk assessment in this nationwide cohort of first ever MI patients.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.07.001.

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