ORIGINAL RESEARCH

Relation of Low-Density Lipoprotein Cholesterol With Microvascular Injury and Clinical Outcome in Revascularized ST-Elevation Myocardial Infarction

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***Background*—**Microvascular injury (MVI) after primary percutaneous coronary intervention for ST-elevation myocardial infarction (STEMI) is a major determinant of adverse clinical outcome. Experimental data indicate an impact of hypercholesterolemia on MVI; however, there is a lack of clinical studies confirming this relation. We aimed to investigate the association of cholesterol concentrations on admission with MVI visualized by cardiac magnetic resonance imaging and clinical outcome in STEMI patients treated by primary percutaneous coronary intervention.

***Methods and Results*—**In this prospective, observational study, we included 235 consecutive revascularized STEMI patients. Cholesterol (total cholesterol, low-density lipoprotein [LDL], and high-density lipoprotein cholesterol) and triglyceride concentrations were determined at presentation. Cardiac magnetic resonance scans were performed 2 (2–4) days after infarction to assess infarct characteristics, including MVI. Clinical end point was the occurrence of major adverse cardiac events (MACE) comprising all-cause mortality, nonfatal reinfarction, and new congestive heart failure. Patients with MVI (n=129; 55%) showed higher levels of total cholesterol (204 [172–226] versus 185 [168–212] mg/dL; *P*=0.01) and LDL cholesterol (142 [113–166] versus 118 [103–149] mg/dL; *P*=0.001), whereas high-density lipoprotein cholesterol and triglycerides did not differ significantly. In multivariable analysis, including all significant clinical and cardiac magnetic resonance determinants of MVI, LDL concentration emerged as an independent predictor of MVI (odds ratio, 1.02 [95% confidence interval, 1.01–1.02]; *P*=0.002). Furthermore, increased LDL cholesterol (>150 mg/dL) significantly predicted the occurrence of major adverse cardiac events (hazard ratio, 3.09 [95% confidence interval, 1.22–7.87]; *P*=0.01).

***Conclusions*—**In STEMI patients undergoing primary percutaneous coronary intervention, baseline LDL cholesterol concentrations were independently associated with MVI, revealing a clinically relevant link between LDL metabolism and MVI in acute STEMI. **(*J Am Heart Assoc*. 2017;6:e006957. DOI: 10.1161/JAHA.117.006957.)**

Key Words: low-density lipoprotein cholesterol • magnetic resonance imaging • microvascular dysfunction • risk stratification • ST-segment elevation myocardial infarction

Hypercholesterolemia is one of the major cardiovascular risk factors and plays a key pathophysiological role in the development of acute ST-elevation myocardial infarction (STEMI).[1] Inflammation, endothelial dysfunction, and increased thrombogenicity as well as plaque vulnerability are crucial underlying mechanisms explaining the complex interplay between cholesterol metabolism and STEMI.[2–4]

However, it is largely unknown whether differences in cholesterol concentrations at presentation are associated with different characteristics of the infarcted myocardium after primary percutaneous coronary intervention (PPCI). Particularly, the role of cholesterol levels for the occurrence of microvascular injury (MVI), the main determinant of clinical outcome after STEMI,[5] is still unclear.[6–8] Golino et al investigated the effects of acute hypercholesterolemia in rabbits during coronary occlusion-reperfusion and detected an association between acute hypercholesterolemia and no-reflow,[6] a phenomenon attributed to MVI.[9] Underlining these findings, a clinical study of 150 STEMI patients found a relation of hypercholesterolemia with ECG signs of no-reflow.[7] In contrast to these data, the investigation by Iwakura et al

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Clinical Perspective

What Is New?

- Admission low-density lipoprotein cholesterol concentration was revealed as an independent predictor of microvascular injury following reperfused ST-elevation myocardial infarction.
- Furthermore, increased admission low-density lipoprotein cholesterol levels were associated with worse long-term clinical outcome after ST-elevation myocardial infarction.

What Are the Clinical Implications?

- Our findings suggest the determination of baseline low-density lipoprotein cholesterol concentration as a simple clinical tool to enable improved microvascular injury prediction and early risk stratification of ST-elevation myocardial infarction survivors.
- Above and beyond these prognostic implications, low-density lipoprotein lowering may represent a promising prophylactic or therapeutic approach against microvascular injury and subsequent cardiovascular complications following ST-elevation myocardial infarction.

could not confirm a relationship between hypercholesterolemia and no-reflow phenomenon assessed by contrast echocardiography.[8] The high spatial and temporal resolution of cardiac magnetic resonance (CMR) imaging has made this modality to the preferred technique for the characterization of infarcted myocardium.[9,10] Indeed, contrast-enhanced CMR is the only method to allow for a direct in vivo assessment of microvascular destruction on a tissue level and therefore is considered as current gold standard for the evaluation of MVI.[9] However, CMR studies investigating an impact of hypercholesterolemia on MVI are lacking so far.

The value of admission cholesterol concentrations for the prediction of hard clinical end points following STEMI is also still a matter of controversy.[11,12] Because of the lack of CMR data, it is further unclear whether infarct characteristics, particularly MVI, represent potential confounders between cholesterol metabolism and postinfarction clinical outcome.

To clarify this controversial issue, we aimed to investigate the relationship of cholesterol status (total cholesterol, low-density lipoprotein [LDL], and high-density lipoprotein [HDL] cholesterol) with CMR-determined MVI and subsequent clinical outcome in STEMI patients undergoing PPCI.

Methods

Study Design, Clinical Assessments, and End Point Definitions

In this prospective, observational study, we included 235 consecutive STEMI patients admitted to the coronary care unit of Innsbruck University Hospital (Innsbruck, Austria). The following inclusion criteria were applied: first STEMI according to the redefined European Society of Cardiology/American College of Cardiology committee criteria,[13] revascularization by PPCI within 24 hours after onset of symptoms, an estimated glomerular filtration rate >30 mL/min per 1.73 m^2, and Killip class <3 at time of CMR. Exclusion criteria were age <18 years, any history of a previous myocardial infarction or coronary intervention, and any contraindication to CMR examination (pacemaker, claustrophobia, orbital foreign body, cerebral aneurysm clip, or known or suggested contrast agent allergy to gadolinium).

Peripheral venous blood samples for cholesterol analyses were drawn at coronary care unit admission. Total cholesterol, HDL, and LDL cholesterol as well as triglyceride concentrations were measured using the cobas 8000 modular analyzer series (Roche Diagnostics, Vienna, Austria). Peak high-sensitivity cardiac troponin T (hs-cTnT) and peak hs-CRP (high-sensitivity C-reactive protein) concentrations were determined according to our standard post-STEMI protocol as described in detail previously.[14] Concentrations of hs-cTnT were determined by using an enzyme immunoassay (hs-cTnT; E170; Roche Diagostics) with the analytical limit of detection and the 99th percentile upper reference limit of 5 and 14 ng/L, respectively. Measurements of hs-CRP were conducted on the c702 module of cobas 8000 (Roche Diagnostics).

The primary end point of the present study was the presence of MVI as determined by CMR imaging. The clinical end point was the occurrence of major adverse cardiac events (MACE) defined as composite of all-cause death, myocardial reinfarction, and new congestive heart failure. Reinfarction was defined in accord with the redefined European Society of Cardiology/American College of Cardiology committee criteria,[13] and new congestive heart failure was defined as the first episode of cardiac decompensation requiring diuretic therapy. Clinical follow-up data were collected by telephone interview using a standardized questionnaire. All interviews were performed by trained personnel blinded to baseline CMR, laboratory, and angiographic findings. The stated end points were checked afterward by carefully reviewing the corresponding medical records.

Before inclusion in the present study, all participants gave their written informed consent. The study was approved by the local research ethics committee and conducted in conformity with the Declaration of Helsinki.

CMR Imaging

CMR examinations were performed 2 (interquartile range [IQR], 2–4) days after infarction. All CMR scans were performed on a 1.5 Tesla Magnetom AVANTO-scanner (Siemens, Erlangen, Germany). The standardized imaging protocol

of our research group was published in detail previously.[15] Briefly, left ventricular (LV) volumes and function were assessed on short-axis (10–12 slices) cine images using breath-hold, retrospective ECG-triggered trueFISP bright-blood sequences. For postprocessing, standard software (ARGUS; Siemens) was applied. Papillary muscles were assigned to the LV volume.[10]

Late gadolinium enhancement images were acquired 15 minutes after application of a 0.1-mmol/kg bolus of contrast agent (Multihance; Bracco, Vienna, Austria) using an ECG-triggered phase-sensitive inversion recovery sequence with consecutive short-axis slices. The late gadolinium enhancement extent of each slice was quantified by using a PACS workstation (IMPAX; Agfa HealthCare, Bonn, Germany). We defined "hyperenhancement" as +5 SDs above the signal intensity of remote myocardium in the opposite myocardial segment of the left ventricle.[16] Infarct size (IS) was expressed as percentage of LV myocardial mass.[17] MVI was defined as persisting area of "hypoenhancement" within the infarcted, hyperenhanced territory.[18,19] All CMR images were analyzed by experienced observers, blinded to clinical and angiographic data.

Statistical Analysis

SPSS Statistics (version 24.0; IBM Corp, Armonk, NY), MedCalc (Version 15.8; MedCalc Software bvba, Ostend, Belgium), and R (version 3.3.0; The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. According to the presence or absence of normal distribution, continuous variables are presented as mean±SD or median with corresponding IQR. Categorical variables are expressed as absolute numbers and percentages. Differences in continuous variables between 2 groups were evaluated by Mann–Whitney *U* test or Student *t* test, as appropriate. Chi-square test was used to assess differences in categorical variables. Spearman test was applied to calculate correlations of continuous variables. For multivariable testing, binary logistic regression analysis was used to disclose independent predictors of MVI. Parameters showing significant associations ($P<0.05$) with MVI in univariable analysis were included into the multivariable model. To assess additive predictive information of LDL cholesterol over established clinical estimators of MVI, reclassification analysis was calculated using R package "PredictABEL." To evaluate the net reclassification improvement, cutoffs for risk categories were defined based on the prevalence of MVI in the present cohort (55%) using steps of 15% as follows: 25%, 40%, 55%, 70%, and 85%. To guarantee statistical reliability of the reclassification improvement independently of these determined cutoffs for risk categories, the integrated discrimination improvement and also the continuous net reclassification improvement were calculated. MACE-free survival was estimated and depicted by the Kaplan–Meier method, and differences were assessed by the log-rank test. The independence of MACE prediction was evaluated by multivariable Cox regression analysis. Because of the relatively small number of events, only 2 variables (LDL cholesterol and 1 further variable) were integrated into 1 Cox regression model. For all statistical tests, a *P* value of <0.05 was defined as significant.

Results

Study Population and Baseline Characteristics

We included 235 consecutive STEMI patients with a pain-to-balloon time of 207 (IQR, 150–352) minutes. Mean age of the overall population was 57 (±11) years. Baseline characteristics and CMR parameters of the overall cohort are listed in Table 1.

Furthermore, Table 1 provides all parameters separately for patients with (n=129; 55%) and without (n=106; 45%) MVI. Regarding lipid status, patients displaying MVI showed significantly higher levels of total cholesterol ($P=0.01$) and LDL cholesterol ($P=0.001$), whereas HDL cholesterol ($P=0.79$) and triglycerides ($P=0.17$) did not differ significantly. No significant association of total cholesterol or LDL cholesterol with other CMR parameters than MVI (IS, LV end-systolic volume, LV ejection fraction, and LV end-diastolic volume) or with clinical MVI determinants (peak hs-cTnT, peak hs-CRP, and preinterventional Thrombolysis in Myocardial Infarction [TIMI] flow) was found (all $P>0.05$).

Statin therapy before PPCI (n=33; 14%) was related to lower LDL concentrations (115 [IQR 86–148] versus 131 [IQR 110–156] mg/dL; $P=0.02$); however, no significant association of statin pretreatment with total cholesterol, HDL cholesterol, triglycerides, or MVI was detected (all $P>0.05$).

LDL Cholesterol and Microvascular Injury

The increase in LDL concentration (tertiles) was associated with a significant ($P=0.01$) and step-wise increase in MVI rates (LDL <113 mg/dL: 43% MVI; LDL 113–150 mg/dL: 55% MVI; LDL >150 mg/dL: 67% MVI; Figure 1).

The multivariable model for the prediction of MVI is provided by Table 2. The association of LDL cholesterol concentration with MVI remained significant (odds ratio, 1.02; 95% confidence interval [CI], 1.01–1.02; $P=0.002$) after adjustment for clinical and CMR parameters.

In reclassification analysis, the addition of LDL cholesterol concentration to the clinical determinants of MVI (peak hs-cTnT, peak hs-CRP, and preinterventional TIMI flow) led to a net reclassification improvement of 0.34 (95% CI, 0.14–0.54; $P<0.001$). In detail, 26% of the cases (n=33) and 8% of the

Table 1. Patient Characteristics

	Total Population (n=235)	MVI (n=129, 55%)	No MVI (n=106, 45%)	*P* Value
Age, y	57 (±11)	57 (±12)	57 (±10)	0.65
Female, n (%)	35 (15)	18 (14)	17 (16)	0.66
Body mass index, kg/m^2	26.2 [24.7–28.4]	26.2 [24.6–28.9]	26.2 [24.7–28.4]	0.85
Current smoker, n (%)	133 (57)	69 (54)	64 (60)	0.29
Diabetes mellitus, n (%)	23 (10)	12 (10)	11 (10)	0.78
Hypertension, n (%)	130 (55)	74 (57)	56 (53)	0.49
Systolic blood pressure, mm Hg	128 [114–145]	125 [115–144]	130 [113–146]	0.37
Diastolic blood pressure, mm Hg	80 [70–90]	79 [70–90]	80 [70–90]	0.48
Total cholesterol, mg/dL	193 [169–219]	204 [172–226]	185 [168–212]	0.01
LDL cholesterol, mg/dL	128 [106–154]	142 [113–166]	118 [103–149]	0.001
HDL cholesterol, mg/dL	44 [37–53]	43 [38–51]	44 [36–55]	0.79
Triglycerides, mg/dL	109 [80–150]	104 [76–147]	114 [83–159]	0.17
Glucose, mg/dL	132 [114–161]	137 [114–167]	130 [112–152]	0.18
Peak hs-cTnT, ng/L	4134 [527–7238]	5748 [2308–11 346]	2063 [109–4708]	<0.001
Peak hs-CRP, mg/L	19.9 [9.5–43.8]	29.8 [15.9–55.9]	13.1 [5.3–24.2]	<0.001
Time from symptom onset to PPCI, min	207 [150–352]	206 [152–330]	209 [148–448]	0.52
Culprit lesion, n (%)				0.46
RCA	102 (43)	50 (39)	52 (49)	
LAD	101 (43)	60 (47)	41 (39)	
LCX	32 (14)	19 (15)	13 (12)	
Preinterventional TIMI flow, n (%)				0.001
0	150 (64)	93 (72)	57 (54)	
1	34 (15)	19 (15)	15 (14)	
2	45 (19)	13 (10)	32 (30)	
3	6 (3)	4 (3)	2 (2)	
Postinterventional TIMI flow, n (%)				0.27
0	1 (0.5)	0 (0)	1 (1)	
1	1 (0.5)	1 (1)	0 (0)	
2	30 (13)	20 (16)	10 (9)	
3	203 (86)	108 (84)	95 (90)	
Concomitant medication, admission				
Statins, n (%)	33 (14)	18 (14)	15 (14)	0.97
Antiplatelet therapy, n (%)	28 (12)	14 (11)	14 (13)	0.58
ACE inhibitor/ARB, n (%)	39 (17)	22 (17)	17 (16)	0.84
β-blockers, n (%)	28 (12)	19 (15)	9 (9)	0.14
CMR parameters				
LVEDV, mL	150 [127–167]	152 [130–168]	145 [118–167]	0.25
LVESV, mL	68 [53–83]	74 [60–87]	61 [48–77]	<0.001
LVEF, %	54 [48–59]	51 [45–56]	57 [52–63]	<0.001
IS, % of LVMM	15 [8–25]	21 [15–30]	10 [5–14]	<0.001

ARB indicates angiotensin receptor blocker; CMR, cardiac magnetic resonance; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IS, infarct size; LAD, left anterior descending artery; LCX, left circumflex artery; LDL, low-density lipoprotein; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMM, left ventricular myocardial mass; MVI, microvascular injury; PPCI, primary percutaneous coronary intervention; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction.

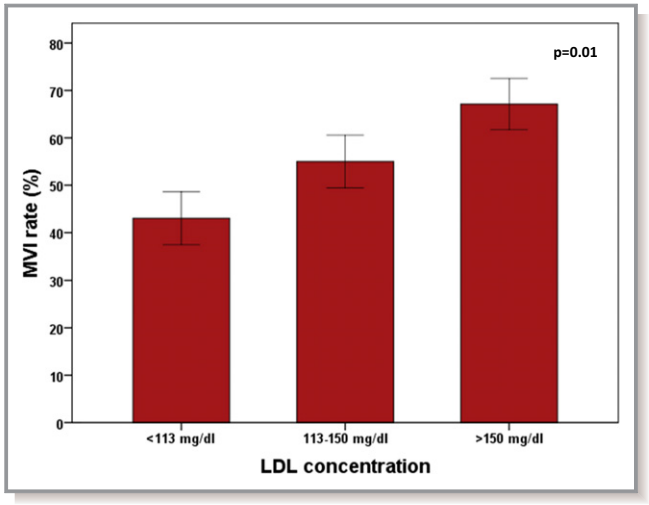

Figure 1. Relation between LDL cholesterol concentration (*x*-axis, tertiles, mg/dL) and rates of MVI (*y*-axis, %). Error bars reflect standard errors (±1 SE). LDL indicates low-density lipoprotein; MVI, microvascular injury.

noncases (n=9) were net correctly reclassified. The continuous net reclassification improvement was 0.38 (95% CI, 0.13–0.63; *P*=0.003), and the integrated discrimination improvement was 0.04 (95% CI, 0.01–0.06; *P*=0.004).

Clinical Outcome

In total, 222 patients (94%) were followed for health outcome. Median follow-up time was 20 (IQR, 12–39) months. Nineteen patients (9%) experienced a MACE event. The area under the curve value of LDL cholesterol concentration for the prediction of MACE was 0.65 (95% CI, 0.52–0.78) with an optimal cut-off value of 150 mg/dL. As depicted by the Kaplan–Meier curve, patients with LDL cholesterol >150 mg/dL showed a significantly lower MACE-free survival (*P*=0.01; Figure 2A). The relation between LDL concentration and MACE rates in more detail: LDL <70 mg/dL: 0% MACE, LDL 70 to 150 mg/dL: 6% MACE, LDL >150 mg/dL: 16% MACE (*P*=0.03). Besides the differences in LDL concentrations, patients with MACE event were older (*P*=0.04), had higher total cholesterol levels (*P*=0.01), lower LV ejection fraction (*P*=0.01), and more frequently MVI (*P*=0.001). MACE-free survival in relation to the presence or absence of MVI is provided by Figure 2B (*P*=0.001). In univariable Cox regression analysis, the hazard ratio of increased LDL cholesterol (>150 mg/dL) for the prediction of MACE was 3.09 (95% CI, 1.22–7.87; *P*=0.01). The association between LDL cholesterol and MACE remained significant after adjustment for age (*P*=0.01), total cholesterol (*P*=0.02), or LV ejection fraction (*P*=0.02), but did not remain significant after adjusting for MVI (*P*=0.07).

Discussion

This is the first comprehensive CMR study investigating the impact of admission lipid status on the occurrence of MVI in STEMI patients revascularized by PPCI. The major findings can be summarized as follows: (1) Patients with MVI showed significantly higher concentrations of LDL cholesterol and total cholesterol, whereas HDL cholesterol or triglyceride concentrations were not significantly associated with MVI. (2) LDL cholesterol concentration remained a significant predictor of MVI after adjustment for major clinical (total cholesterol, preinterventional TIMI flow, peak hs-cTnT, and peak hs-CRP) and CMR determinants (IS, LV ejection fraction, and LV end-systolic volume) of MVI. (3) Moreover, the assessment of LDL cholesterol additionally to MVI-related clinical parameters (preinterventional TIMI flow, peak hs-cTnT, and hs-CRP) provided incremental value for MVI prediction. (4) Finally, LDL cholesterol also predicted clinical outcome post-STEMI, however, not independently from MVI.

Table 2. Binary Logistic Regression Analysis for the Prediction of Microvascular Injury

	Univariable Analysis		Multivariable Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Total cholesterol	1.01 (1.002–1.02)	0.01	…	…
LDL cholesterol	1.01 (1.004–1.02)	0.002	1.02 (1.01–1.02)	0.002
Peak hs-cTnT	1.00 (1.00–1.00)	<0.001	…	…
Peak hs-CRP	1.12 (1.04–1.19)	0.002	…	…
Preinterventional TIMI flow	0.62 (0.46–0.84)	0.002	…	…
LVESV	1.02 (1.01–1.03)	0.001	…	…
LVEF	0.91 (0.88–0.95)	<0.001	0.95 (0.91–0.99)	0.02
IS	1.13 (1.09–1.17)	<0.001	1.11 (1.07–1.16)	<0.001

CI indicates confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; hs-CRP, high-sensitivity C-reactive protein; IS, infarct size; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; OR, odds ratio; TIMI, Thrombolysis in Myocardial Infarction.

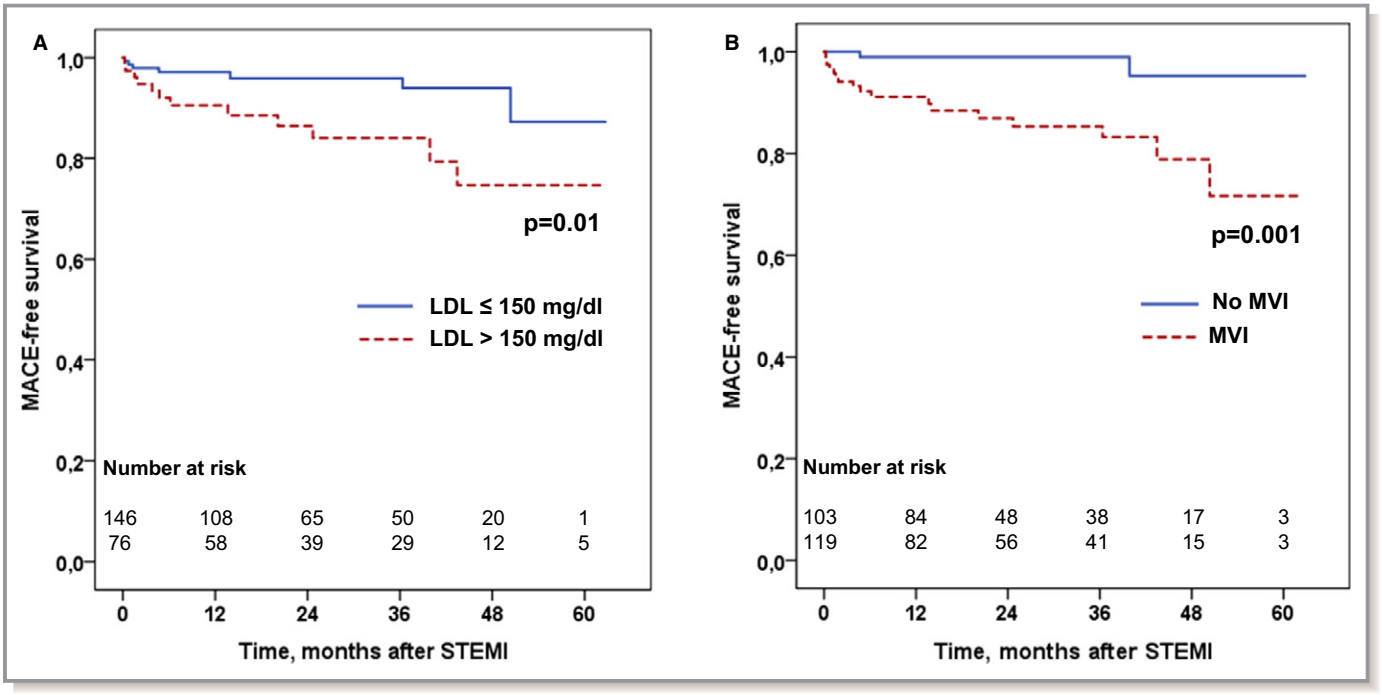

Figure 2. Post-STEMI clinical outcome. A, Kaplan–Meier curve displaying the MACE-free survival in relation to LDL cholesterol concentrations. B, Kaplan–Meier curve displaying the MACE-free survival according to the presence/absence of MVI. LDL indicates low-density lipoprotein; MACE, major adverse cardiac events; MVI, microvascular injury; STEMI, ST-elevation myocardial infarction.

Together, our data revealed LDL cholesterol as an important risk factor for MVI, highlighting a pathophysiological interplay between cholesterol metabolism and MVI in acute STEMI treated with PPCI.

LDL Cholesterol Predicts MVI and Subsequent Clinical Outcome

Occurrence of MVI is a common CMR finding in patients suffering from acute STEMI.[5] In the pooled analysis by van Kranenburg et al including 1025 STEMI patients, MVI was detected in 56%,[5] which is in full agreement with the results of the present study (55% MVI). MVI by CMR has been unequivocally proven to be a marker of major prognostic relevance in patients with revascularized STEMI.[5,20] Accordingly, the detection of clinical risk factors and determinants of MVI has moved into particular focus of cardiovascular research.[21] However, most determinants of MVI detected were not MVI specific, but rather reflectors of more-pronounced overall myocardial damage, explainable by the significant relation between IS and MVI.[22] Three important clinical examples in this context are the preinterventional TIMI flow, enzymatic IS, and inflammatory response (hs-CRP), as demonstrated by previous investigations[22,23] and confirmed by the present data. In contrast to these IS-related MVI indicators, we could reveal LDL cholesterol as an important clinical determinant of MVI independently of the spatial extent of myocardial necrosis. The clinical relevance of this independence was statistically highlighted by demonstrating incremental predictive ability of LDL cholesterol for clinical MVI risk classification. Furthermore, it has to be emphasized that, contrary to the MVI estimators primarily influenced and determined by the acute necrosis, admission LDL concentration indicates a pre-existing metabolic condition. Accordingly, LDL cholesterol concentration seems to act as an actual preinfarction risk factor for the occurrence of MVI, as indicated by previous experimental data.[6]

Despite the convincing evidence regarding hypercholesterolemia and risk for the development of STEMI,[1] it is still debated whether different LDL values in patients presenting with acute infarction are associated with different postinfarction clinical outcomes.[11,12] Interestingly, previous investigations reported even favorable outcomes in patients presenting with hypercholesterolemia,[11,12] which, however, was mainly attributed to important clinical confounders.[11] In our STEMI cohort, we detected a step-wise, direct proportional relationship between admission LDL concentrations and MACE rates, with highest risk in the subgroup showing >150 mg/dL and negligible risk in the group <70 mg/dL LDL cholesterol. These results indicate that STEMI patients with distinct LDL elevation may represent a high-risk population for the development of future cardiovascular events, whereas very low LDL presentation levels seem to be protective. The higher incidence of MVI in patients with increased LDL levels could be 1 important underlying mechanism explaining the relationship between LDL and clinical outcome, as suggested by our

multivariable Cox regression analysis. However, the relatively small number of patients in the present cohort hampers the significance of these findings, requiring further validation by larger trials.

Pathophysiology Between LDL Cholesterol and MVI

The pathophysiological processes leading to MVI in STEMI are sophisticated and not completely elucidated so far.[9] Hypercholesterolemia has been previously discussed as 1 acquired factor potentially increasing individual susceptibility for MVI.[9] Indeed, in this CMR study, we could demonstrate, for the first time, an association between serum hypercholesterolemia and MVI in the clinical setting of acute STEMI. Earlier data of optical coherence tomography and intravascular ultrasound studies may provide a morphological explanation for the relation of LDL with MVI.[24] Soeda et al showed that lipid-rich plaques, defined by greater lipid index and maximal lipid arc, were associated with higher rates of no-reflow.[24] The underlying pathophysiological pathways of LDL-induced plaque formation have been elucidated to a high degree[25]; however, the subsequent mechanisms linking lipid-rich plaques with MVI are largely unclear. One mechanism potentially explaining this relation might be the increased local thrombogenicity.[24] There is good evidence that the lipid core of atherosclerotic plaques provide highest thrombogenicity[3,24,26]; therefore, a higher lipid-load could lead to a higher thrombus burden, which, in turn, would increase the risk of MVI-inducing distal embolization.[27] Besides this aspect regarding thromogenicity, lipoproteins, especially LDL, were shown to cause inflammation as well as endothelial dysfunction,[28] 2 major mechanisms in the pathophysiology of ischemia-reperfusion injury, highlighting another potential link between LDL and MVI.[9] This hypothesis is supported by data from animal studies, in which hypercholesterolemia was shown to aggravate reperfusion injury by enhancing endothelial oxidative stress.[6] Because we could not detect a correlation between LDL and systemic inflammatory response evaluated by hs-CRP concentration, it may be hypothesized that such inflammatory processes of reperfusion injury primarily remain local phenomena in STEMI patients. Taken together, evidence exists that LDL could augment MVI through both mechanisms distal embolization and reperfusion injury; however, the exact underlying processes as well as their pro rata contributions remain to be further elucidated.

Clinical Implications

The present study provides an important new clinical view on the prognostic as well as pathophysiological significance of cholesterol metabolism in survivors of acute STEMI. Our data could, in particular, highlight the prognostic relevance of LDL status in these patients. Indeed, the prognostic value of LDL concentration was independent and incremental to established clinical markers of post-STEMI prognosis, emphasizing the importance of LDL assessment on coronary care unit admission for daily clinical routine. Above and beyond these prognostic implications, the present results suggest LDL lowering as a prophylactic or therapeutic target against the development of MVI and subsequent adverse cardiovascular events. The current literature on the impact of preinfarction statin treatment on MVI, however, is inconclusive.[8,29] Iwakura et al detected an association between statin pretreatment and reduction in no-reflow phenomenon,[8] whereas Fuernau et al as well as our data could not prove an impact of statin pretreatment on MVI.[29] Nevertheless, these investigations were all hampered by insufficient determinations of statin pretreatment, particularly in terms of evaluation of essential therapeutic parameters including exact agent, dose, and duration.[29] Hence, there is a need for a more-comprehensive trial investigating the impact of therapeutic LDL lowering on MVI. This promising prophylactic approach of LDL reduction leading to less MVI and better subsequent outcome would be of high clinical interest, especially in light of the recent data proving beneficial outcome of aggressive LDL-lowering regimes, including proprotein convertase subtilisin/kexin type 9 inhibitors, in patients with high cardiovascular risk profile.[30]

Limitations

The following study limitations have to be declared. First, only established markers of lipid metabolism were investigated, whereas other lipid-related biomarkers (eg, lipoprotein (a), apolipoprotein C3, proprotein convertase subtilisin/kexin type 9, and small dense LDL) were not determined. Second, considering the relatively low number of absolute events the suggested optimal LDL cut-off value for the prediction of MACE (150 mg/dL) should be considered as rather explorative needing validation by larger studies. Moreover, only stable STEMI patients with Killip class <3 were included; therefore, our findings might not pertain to unstable STEMI patients. Finally, we evaluated statin pretreatment just as a binary variable; hence, no information on dose and duration or compliance was ascertained.

Conclusion

In STEMI patients treated by PPCI, admission LDL cholesterol emerged as an independent and incremental predictor of MVI, highlighting a novel pathophysiological perspective on this well-established cardiovascular risk factor. Furthermore, the present data indicate that the determination of admission LDL

may also be useful for early post-STEMI risk stratification in terms of hard clinical end points.

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Disclosures

None.

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