Predictors of Recurrent Ischemic Events in Patients With ST-Segment Elevation Myocardial Infarction

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Little is known about the predictors recurrent ischemic events in patients with ST-segment elevation myocardial infarction (STEMI). This study aimed at investigating the predictors of recurrent myocardial infarction (MI) at long-term follow-up in a real-world STEMI cohort. All consecutive STEMI patients who underwent emergent coronary angiography and primary percutaneous coronary intervention between February 2013 and June 2019 at our institution were included. The primary outcome was recurrent MI; secondary outcomes were all-cause death, target vessel revascularization (TVR), in-stent restenosis, definite stent thrombosis (ST) and non-TVR. The study population included 724 STEMI patients; at median follow-up of 803 (324 to 1,394) days, the primary outcome was reported in 70 patients (10.1%). All-cause death occurred in 6.8%, TVR in 4.2%, in-stent restenosis in 2.5%, and ST in 1.9% of cases. At multivariable analysis, diabetes (hazard ratio [HR] = 1.18), serum level of lipoprotein(a) [Lp(a), HR = 1.01], and angiographic evidence of restenotic lesion (HR = 2.98) resulted independent predictors of recurrent MI. Kaplan-Meier analysis confirmed that diabetes, restenotic lesion, and differential Lp(a) risk range values, identified patients with lower long-term survival free from recurrent MI. Lp(a) level ≥ 30 mg/dL had an incremental prognostic stratification capability in patients with diabetes (HR = 5.34), and in patients with both diabetes and restenotic lesion (HR = 17.07). In conclusion, in this contemporary cohort of STEMI patients, diabetes, Lp(a) serum levels and restenotic lesions were independently associated with recurrent MI at long term. The coexistence of Lp(a) level ≥ 30 mg/dL showed an incremental risk stratification capability, supporting its implementation for long-term prognostic assessment in this high-risk clinical setting. **(Am J Cardiol 2021;159:44–51)**

Despite the advances in preventive strategies, antithrombotic drugs and primary percutaneous coronary intervention (PCI) techniques, ST-segment elevation myocardial infarction (STEMI) is still associated with a high risk of death both in the acute setting and at long term.[1,2] In previous studies, patients who have had a myocardial infarction (MI) were at heightened risk for recurrent ischemic events and death, suggesting the need for better prognostic stratification and prolonged surveillance after the index event.[3,4] Given the wide spectrum of factors involved in acute coronary syndrome (ACS) pathophysiology, novel predictors or multiparametric models are advisable to stratify the prognosis and optimize secondary preventive strategies in patients with a recent history of STEMI. Many clinical, laboratory, angiographical, and PCI parameters are routinely collected by real-world registries, but their prognostic performance at long term is still poorly known. Against this background, we aimed at investigating the predictors of recurrent MI in a contemporary population with STEMI who received primary PCI treatment.

Methods

This was an observational, single-center, cohort study including consecutive patients who underwent primary PCI at our Institution. From February 2014 to June 2019, all consecutive patients with STEMI who underwent urgent/emergent coronary angiography at the University Hospital of Salerno, Italy, were prospectively collected in the institutional ACS register. Only drug-eluting stent (DES) was implanted during the study period. Patients who underwent PCI of venous or arterial graft, those conservatively treated or with an indication for coronary artery bypass graft, were excluded from the analysis.

STEMI was defined, according to current guidelines, by the presence of symptoms consistent with myocardial ischemia (i.e., persistent chest pain) and electrocardiographic criteria: ST-segment elevation (measured at the J-point) ≥ 2.5 mm in men <40 years, ≥2 mm in men ≥40 years, or ≥1.5 mm in women in leads V2 to V3 and/or ≥1 mm in the

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other leads (in the absence of left ventricular hypertrophy or left bundle branch block).[5] Informed consent was obtained from all individual participants at the time of inclusion in the register. The study was approved by the local ethics committee. The investigation conforms to the principles outlined in the Declaration of Helsinki.

During the hospitalization, demographic, clinical, laboratory, echocardiographic, angiographic, and PCI procedural data were prospectively collected. Blood samples were collected in all patients at admission to determine blood count, myocardial biomarkers, and creatinine. Glomerular filtration rate was estimated by using the Chronic Kidney Disease Epidemiology Collaboration equation. After 12 hours from admission, serum levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), triglyceride, lipoprotein (Lp) (a) C-reactive protein, and erythrocyte sedimentation rate were systematically determined. Echocardiography was performed in all patients at admission. Coronary angiography and PCI procedural data were also systematically collected. For each patient, we reported the occurrence of adverse events during hospitalization including ventricular tachycardia, ventricular fibrillation, high-grade atrioventricular block, acute heart failure, cardiogenic shock, and death. Follow-up data were obtained through outpatient clinic visits, medical charts, or telephone interview. For some deceased patients, the information were obtained by telephone interview of the treating physicians or the next of kin. In this study, clinical outcome was assessed at the longest available follow-up. The primary outcome measure was the rate of recurrent nonfatal or fatal MI after discharge. Recurrent MI was defined by the presence of angina symptoms with typical ECG changes and elevated cardiac troponin levels with at least one value above the 99th percentile upper reference limit according to the Fourth Universal Definition of MI.[6] Secondary outcome measures were target vessel revascularization (TVR), in-stent restenosis (ISR), definite stent thrombosis (ST), non-TVR, and all-cause death. TVR was defined as any repeat PCI or coronary artery bypass graft of any segment of the target vessel; any revascularization of a different vessel was defined as non-TVR. ISR was defined as a previously stented lesion with a >50% diameter stenosis. ST was defined as the presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent confirmed by coronary angiography.[7]

The distribution of continuous data was tested with the Kolmogorov-Smirnov and the Shapiro-Wilk test. Normally distributed variables were expressed as mean ± standard deviation, whereas non-normal ones as median and interquartile range. Categorical variables were reported as numbers and percentages. All baseline variables were tested at univariable Cox regression analysis for the primary study outcome; a multivariable stepwise Cox regression was performed to identify a set of independent predictors for recurrent MI at the longest available follow-up. To limit the risk of overfitting, only variables with higher statistical significance at univariable analysis were tested in the multivariable model. Results were presented as hazard ratios (HR) with 95% confidence intervals (CI). The Hosmer-Lemeshow statistic was used to assess the goodness-of-fit of the logistic regression model. The cumulative incidence of the primary study outcome was estimated at various time frame using the Kaplan-Meier method and the log-rank test was used for comparison between groups. For all test, a p value <0.05 was considered statistically significant. Statistical analysis was performed by using SPSS version 25.0 (SPSS Inc., Chicago, IL) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Overall, 724 STEMI patients were included in the analysis. The baseline characteristics of the study population are summarized in Table 1. Missing values for the variable of interest are reported in Supplementary Table S1. The mean age was 62.1 ± 13.3 year; 560 (77.3%) were males. Ninety-two patients (12.7%) had a history of previous MI, and 82 (11.3%) underwent previous PCI. The left ventricle ejection fraction at admission was <35% in 8.8% of patients, between 35% and 45% in 27.6%, between 45% and 55% in

Table 1
Baseline characteristics of the study population

Variable	Overall population (N = 724)
Age (years)	62.1±13.3
Men	560 (77.3%)
Hypertension	456 (63.0%)
Diabetes mellitus	187 (25.8%)
Hyperlipidemia	334 (46.1%)
Active smokers	391 (54.0%)
Obesity	197 (27.2%)
History of CAD	110 (15.2%)
Prior MI	92 (12.7%)
Prior PCI	82 (11.3%)
Left ventricular EF (%)	
<35	64 (8.8%)
35-45	200 (27.6%)
45-55	219 (30.2%)
>55	228 (31.5%)
Hemoglobin (g/dL)	14.5 (13.2-15.6)
eGFR (mL/min)	80.0 (60.5-94.0)
Peak troponin (pg/mL)	31.1 (7.5-75.7)
Total cholesterol (mg/dL)	182.3±47.8
HDL-cholesterol (mg/dL)	45.2±13.5
LDL-cholesterol (mg/dL)	110.2±40.1
Triglycerides (mg/dL)	123.0 (85.0-163.8)
Lipoprotein(a) (mg/dl)	10.0 (6.0-30.0)
C-reactive protein (mg/L)	0.92 (0.36-2.62)
Erythrocyte sedimentation rate (mm/hour)	15.0 (7.0-28.5)

CAD = coronary artery disease; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Continuous normally distributed variables are expressed as mean ± SD. Categorical variables are expressed as N (%). Continuous non-normally distributed variables are expressed as median (interquartile range). Hyperlipidemia was defined by laboratory data showing LDL-C > 160 mg/dL, HDL-C < 40 mg/dL in men or < 50 mg/dL in women, fasting triglycerides > 150 mg/dL, clinical diagnosis of primary hyperlipidemia, or previous lipid lowering therapy. History of CAD was defined as previous acute coronary syndrome, coronary revascularization, or established CAD. Obesity was defined by body mass index value ≥ 30 kg/m^2.

Table 2
Angiographic and procedural features

Variable	Overall population (N = 724)
Time to PCI (hours)	
0-3	325 (45.6%)
3-6	198 (27.8%)
6-12	61 (8.6%)
> 12	128 (18.0%)
Treated coronary artery	
Left main	14 (1.9%)
Left anterior descending	407 (56.2%)
Left circumflex	118 (16.3%)
Right	263 (36.3%)
Multivessel coronary disease	282 (39.0%)
Bifurcation lesion	125 (17.3%)
Chronic occlusion	17 (2.3%)
Restenotic lesion	48 (6.6%)
Stent implantation	684 (94.5%)
Number of stents	1.0 (1.0-2.0)
Minimum stent diameter (mm)	3.00 (2.50-3.50)
Maximum stent diameter (mm)	3.00 (2.75-3.00)
Stents length (mm)	28.0 (18.0-38.0)
TIMI flow after PCI	
0	18 (2.5%)
1	14 (2.0%)
2	79 (11.1%)
3	603 (84.5%)
GP IIb/IIIa inhibitors	204 (28.2%)
Cangrelor	3 (0.4%)

PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction; GP IIb/IIIa inhibitors = glycoprotein IIb/IIIa inhibitors.

Continuous normally distributed variables are expressed as mean ± SD. Categorical variables are expressed as N (%). Continuous non-normally distributed variables are expressed as median (interquartile range).

30.2%, and >55% in 31.5%. Angiographic and procedural features are reported in Table 2. Left anterior descending (56.2%) and right coronary artery (263, 36.3%) were the most treated vessels. DES implantation was reported in 684 (94.5%) patients.

In−hospital and follow-up adverse events are summarized in Supplementary Table S2. The proportion of acute heart failure and cardiogenic shock was 6.2% and 6.6%, respectively. Thirty patients (4.1%) died during the hospitalization.

During a median follow-up of 803 (interquartile range 324 to 1,394) days, the primary study outcome was reported in 70 patients (10.1%). All-cause death occurred in 47 patients (6.8%), TVR in 29 (4.2%), non-TVR in 30 (4.3%), ISR in 17 (2.5%), and ST in 13 patients (1.9%); one patient was lost at follow-up. At univariable Cox regression analysis, age (p = 0.003), male sex (p = 0.040), diabetes (p = 0.006), history of coronary artery disease (CAD, p = 0.039), previous PCI (p = 0.047), Lp(a) (p = 0.004), multivessel disease (p = 0.008), and restenotic lesion (p <0.001) were significantly associated with the risk of recurrent MI. At multivariable model, diabetes (HR = 1.72; 95% CI 1.02 to 2.90), Lp(a) (HR = 1.01; 95% CI 1.00 to 1.02), and restenotic lesion (HR = 2.99; 95% CI 1.59 to 5.59) resulted as independent predictors for the primary outcome (Table 3). Figure 1 shows the Kaplan-Meier curves for survival free from MI recurrence in the overall population and in subsets stratified according to the presence or not of diabetes, type of coronary lesion, and Lp(a) risk range value <30, ≥30 and <50, and ≥50 mg/dL. Noteworthy, each of these conditions was able to identify patients with a lower probability of survival at long-term follow-up. Figure 2 depicts the distribution of the study population according to Lp(a) value and shows the incremental risk for the primary outcome in patients with Lp(a) ≥30 and <50, and in those with Lp(a) ≥50 mg/dL compared with patients with Lp(a) <30 mg/dL. Figure 3 shows the risk for the primary outcome in patients with diabetes (HR = 2.93; 95% CI 1.31 to 6.54), Lp(a) ≥ 30 mg/dL (HR = 3.56; 95% CI 1.78 to 7.10) and/or restenotic lesion (HR = 8.43; 95% CI 2.74 to 25.90) in isolation compared with patients without these conditions set as a reference group. The coexistence of Lp(a) level ≥ 30 mg/dL was associated with a substantially increased risk for recurrent MI in patients with diabetes (HR = 5.34; 95% CI 2.28 to 12.50). Also, the combination of Lp(a) ≥ 30 mg/dL with both diabetes and coronary restenotic lesions, albeit reported in only 5 patients, was associated with a markedly higher risk for recurrent MI (HR = 17.07; 95% CI 3.83 to 76.11).

Discussion

The main findings of the present study enrolling a contemporary population of STEMI patients treated with primary PCI can be summarized as follows: (1) diabetes, restenotic lesions and Lp(a) level were independent predictors of MI recurrence at long-term follow-up; (2) patients with diabetes versus those without, patients with angiographic evidence of restenotic versus de novo coronary lesions, and patients with different Lp(a) risk range values, have a significantly different survival probability in terms of MI recurrence; (3) the coexistence of Lp(a) level ≥ 30 mg/dL with diabetes and/or restenotic lesions was associated with an incremental risk for recurrent MI.

The implementation of local networks to reduce the out-of-hospital delay, the advances in primary PCI techniques, and the adoption of more effective antithrombotic drugs have substantially cut down the rate of in-hospital mortality and improved the expectancy and quality of life after STEMI.[1] The improved survival during the hospitalization has resulted in the progressive growth of stable post-MI patients, who need special care in terms of secondary preventive programs.[3] The percentage of death during the hospitalization in our population was 4.1% and was consistent with previous contemporary STEMI populations from multicenter register cohorts[8]; after discharge, about one in ten patient developed a new MI event during the follow-up. This finding emphasizes the importance of prognostic stratification and strong secondary preventive programs in higher-risk STEMI subjects.

Diabetes and restenotic lesions are established risk factors for recurrent MI. The Framingham study demonstrated a double risk of developing CAD among diabetic compared with nondiabetic subjects.[9] Diabetic patients with ACS had longer lesions, greater plaque burden, smaller lumen area, and larger plaque necrotic core and calcium content compared with nondiabetic patients.[10] Consistently with our

Table 3
Cox regression analysis for the recurrence of MI

Variable	Univariable model			Multivariable model		
	HR	95% CI	p value	HR	95% CI	p value
Age (years)	1.027	1.009-1.045	0.003			n.s.
Male sex	0.589	0.356-0.976	0.040			n.s.
Hypertension	1.466	0.881-2.442	0.141			
Diabetes	1.956	1.211-3.159	0.006	1.718	1.018-2.900	0.043
Hyperlipidemia	0.963	0.603-1.540	0.876			
Active smokers	0.840	0.528-1.338	0.464			
Obesity	1.086	0.652-1.809	0.750			
History of CAD	1.776	1.029-3.067	0.039			n.s.
Prior MI	1.585	0.868-2.895	0.134			
Prior PCI	1.841	1.008-3.362	0.047			
Left ventricular EF (%)	0.839	0.676-1.042	0.112			
Hb (g/dL)	0.990	0.977-1.003	0.118			
eGFR (mL/min)	0.994	0.984-1.003	0.209			
Peak troponin (pg/mL)	1.000	0.997-1.004	0.787			
Total cholesterol (mg/dL)	1.000	0.994-1.005	0.863			
HDL-cholesterol (mg/dL)	1.005	0.987-1.024	0.583			
LDL-cholesterol (mg/dL)	1.000	0.993-1.006	0.908			
Triglicerides (mg/dL)	0.998	0.994-1.002	0.265			
Lipoprotein(a) (mg/dl)*	1.010	1.003-1.016	0.004	1.010	1.003-1.017	0.007
C-reactive protein (mg/L)	1.000	0.999-1.001	0.757			
Erythrocyte sedimentation rate (mm/hour)	1.012	0.999-1.026	0.066			
Left main PCI	2.013	0.492-8.230	0.330			
Left anterior descending PCI	1.083	0.674-1.739	0.742			
Left circumflex PCI	0.973	0.511-1.852	0.934			
Right coronary artery PCI	1.008	0.619-1.641	0.974			
Multivessel disease	1.872	1.175-2.983	0.008			n.s.
Bifurcation lesion	1.199	0.667-2.155	0.545			
Chronic occlusion	0.669	0.093-4.823	0.690			
Restenotic lesion	3.654	1.992-6.703	<0.001	2.985	1.593-5.591	0.001
Stent implantation	1.172	0.472-2.909	0.733			
Number of stents	0.812	0.557-1.183	0.277			
Minimum stent diameter (mm)	0.869	0.513-1.469	0.599			
Maximum stent diameter (mm)	0.773	0.462-1.295	0.328			
Stents length (mm)	0.996	0.979-1.013	0.620			
TIMI flow after PCI	1.226	0.752-2.000	0.414			
GP IIb/IIIa inhibitors	1.176	0.707-1.954	0.533			

CAD = coronary artery disease; CI = confidence interval; EF = ejection fraction; eGFR = estimated glomerular filtration rate; GP IIb/IIIa inhibitors = glycoprotein IIb/IIIa inhibitors; Hb = hemoglobin; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = thrombolysis in myocardial infarction.

* Per 1 mg/dL increase.

finding, diabetes has been strongly associated with new cardiovascular adverse events after the index MI.[11]

Although the implementation of new-generation DES has substantially reduced the entity of neointimal hyperplasia after stent implantation, ISR remains the leading mechanism of PCI failure.[12,13] In a large cohort of 10,000 patients who underwent PCI and routine control angiography at 6 to 8 months, Cassese et al reported ISR as an independent correlate of 4-year mortality.[14] The strongest predictors of ISR were small vessel size, long stented segments, the percentage of residual stenosis after PCI, and the antiproliferative drug released by DES.[15−17] Our study conducted on a contemporary population treated with new-generation DES, confirmed the independent association of restenotic lesion and recurrent MI. This risk was particularly high in patients with coexistent diabetes and Lp(a) level ≥ 30 mg/dL.

The novelty of the present study is the role of Lp(a) as an independent predictor of recurrent MI, suggesting to consider this information for STEMI risk stratification in combination with more conventional prognostic parameters such as diabetes and restenotic lesions. Lp(a) is a cholesterol-rich low-density lipoprotein consisting of an apolipoprotein B100 moiety covalently linked to apolipoprotein(a), and it is characterized by pro-inflammatory, pro-atherogenic, and pro-thrombotic effects.[18] High levels of Lp(a) were found to be associated with major cardiovascular events in large population-based cohort studies.[19,20] Although these data were limited to healthy adults, low-risk, populations, routine one-time screening for Lp(a) has been recommended also for individuals at intermediate or high risk of CV events, including patients with established CAD.[21] However, the clinical utility of Lp(a) as a marker of risk after MI remains uncertain,[22,23] particularly in the high-risk setting of STEMI. A preliminary analysis of three large secondary prevention cohorts of patients with established CAD, showed no significant association between the risk of CV events and levels of

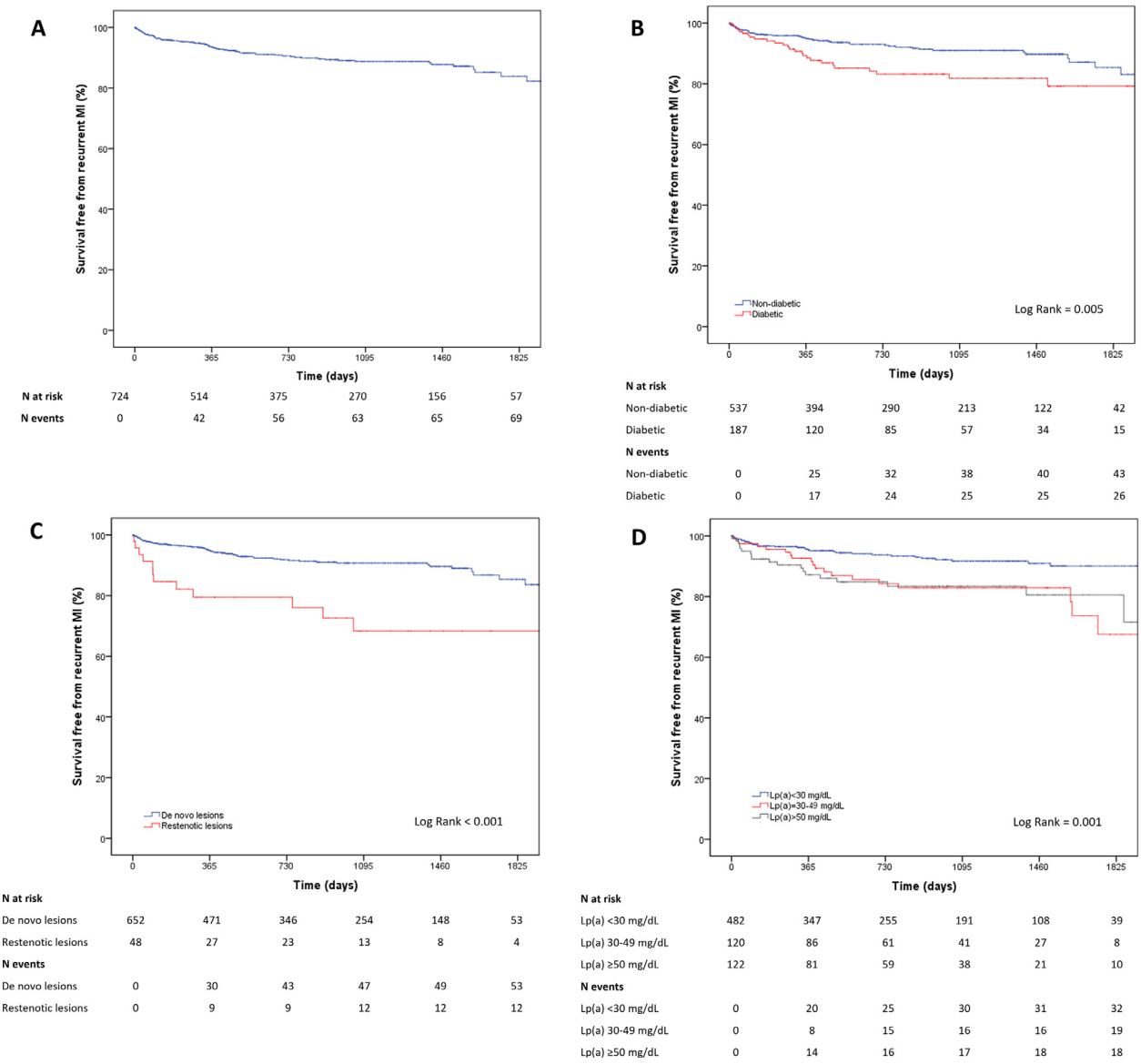


Figure 1. Kaplan-Meier curves of survival free from recurrent MI in the overall population (*A*) and stratified by diabetes (*B*), Lp(a) values (*C*), and type of coronary lesion (*D*). Lp(a) = lipoprotein(a).

Lp(a) analyzed as a continuous variable. However, when data were combined with other 8 secondary prevention studies, patients with Lp(a) levels in the highest quantile showed an increased risk of recurrent events, albeit with significant heterogeneity between studies.[24] Moreover, in a subanalysis of the dal-Outcomes trial, Lp(a) levels did not predict the occurrence of further ischemic events in patients with recent ACS.[23] Nonetheless, given the low median levels of Lp(a) in the observed population, the study was underpowered to clarify the impact of Lp(a) on cardiovascular outcomes. In the present study, we included only patients with STEMI, an ACS subset characterized by the highest thrombotic risk, younger median age, and the need for more aggressive antithrombotic treatment. Therefore, we may hypothesize that Lp(a) may perform better as a prognostic marker due to the characteristics of these very high-risk population. Our results were consistent with a previous single-center study evaluating a historical cohort of 435 STEMI patients admitted from 2000 to 2003.[25] However, in that study half of the patients were treated with fibrinolysis, and the devices adopted for PCI, as well as secondary preventive pharmacotherapy, differed substantially from the current standard of care (i.e., antiplatelet therapy and lipid-lowering therapy). Conversely, we included a larger contemporary population of patients who underwent primary PCI and clinical management according to the most recent and recommended standard of care.

In a recent subanalysis of the ODYSSEY Outcomes trial, baseline Lp(a) predicted the recurrence of major cardiovascular events in patients with an index ACS event, independently from LLDL-C levels. Interestingly, alirocumab produced a median 23% reduction in Lp(a) levels, and the LDL-C and Lp(a) lowering were independently associated with the absolute reduction on cardiovascular events.[26] Similar data were reported in a prespecified analysis of the FOURIER trial, with a 27% reduction of Lp(a) concentration

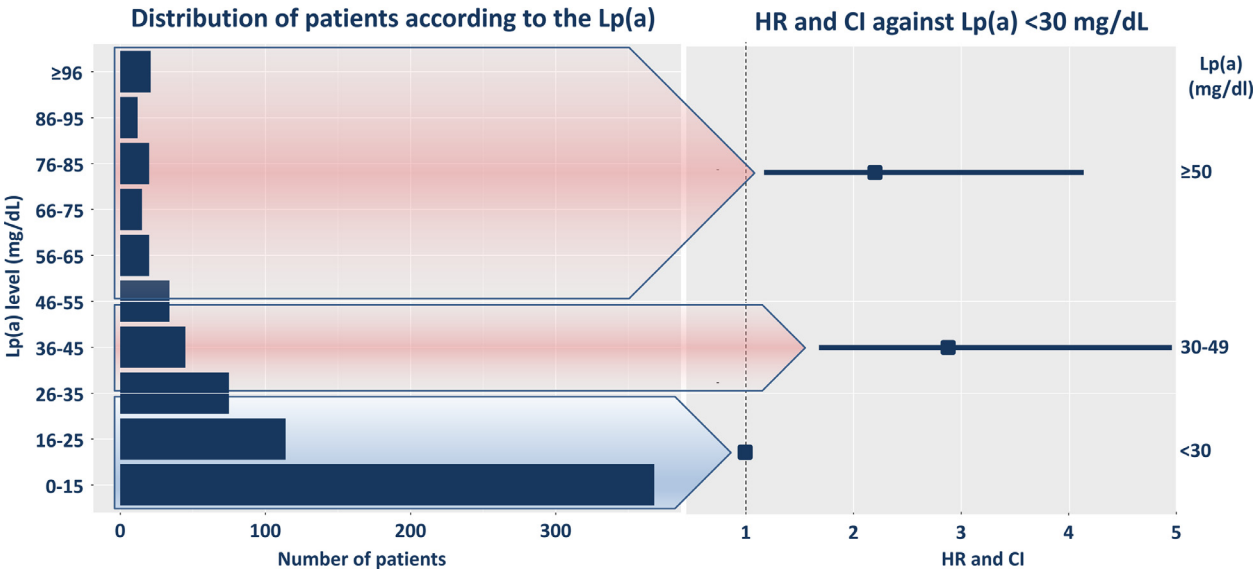
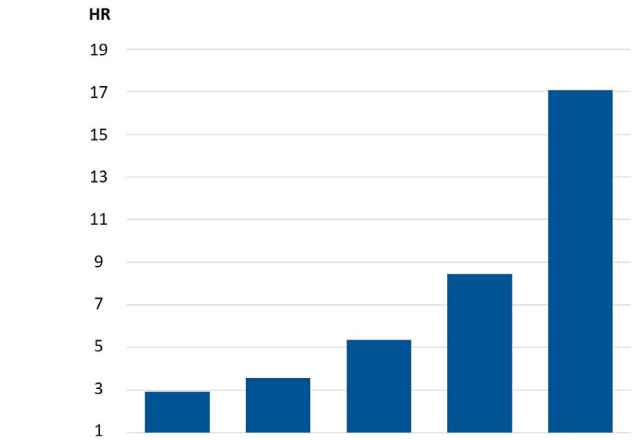


Figure 2. Distribution of patients according to Lp(a) value and risk for recurrent MI. Lp(a) levels < 30 mg/dL was set as reference (HR = 1). CI = confidence interval; HR = hazard ratio; Lp(a) = lipoprotein(a).



	Diabetes	Lp(a)≥30 mg/dl	Diabetes + Lp(a)≥30 mg/dl	Restenotic lesion	Diabetes + Lp(a)≥30 mg/d + Restenotic lesion
N° of patients	112	157	48	15	5
HR* (CI)	2.93 (1.31, 6.54)	3.56 (1.78, 7.10)	5.34 (2.28, 12.50)	8.43 (2.74, 25.90)	17.07 (3.83, 76.11)

Figure 3. Incremental risk for recurrent MI in patients with high Lp(a) levels. Bar graph showing the incremental risk for recurrent MI in patients with diabetes, Lp(a) ≥ 30 mg/dL and/or restenotic lesions, in isolation or combined, against those free from these conditions.
*Patients not affected by diabetes, Lp(a) levels ≥ 30 mg/dL and restenotic lesions were set as reference (HR = 1). The number of patients in the reference group was 335 and the rate of recurrent MI in this group was 1.53 per 100 person-years. CI = confidence interval; HR = hazard ratio; Lp (a) = lipoprotein(a).

produced by evolocumab.[27] These findings derived from RCT populations are confirmed in our real-world STEMI population, suggesting that Lp(a) may influence the patient risk profile after the index event. Moreover, these studies suggest the importance to develop novel therapeutic strategies, including PCSK9 inhibitors, for reducing the residual risk of cardiovascular adverse events through the combined reduction of both LDL-C and Lp(a) levels.[28,29]

The results of this study need to be interpreted considering some limitations. First, the retrospective, observational, single-center study design and the relatively small sample size. However, to the best of our knowledge, this is the largest study investigating the prognostic role of Lp(a) in the high-risk setting of STEMI. Second, we did not provide data on LDL-C control in our study population. It is uncertain whether Lp(a) predicts cardiovascular events in patients with optimal statin therapy and target LDL-C values, and a detailed description of LDL-C control would have enabled us to address this controversial issue. However, these data were not available in our register and, beyond recent evidence on PCSK9 inhibitors, conventional antilipidic drugs are ineffective to reduce the Lp(a) serum concentration. Third, we did not report the Lp(a) values during follow-up. Since Lp(a) may act as an acute-phase protein, its levels may increase during the acute phase and remain high for several weeks after an ACS.[30]

In conclusion, in this real-world cohort of STEMI patients, diabetes, Lp(a) serum levels and restenotic lesions were independently associated with recurrent MI at long term. The coexistence of Lp(a) level ≥ 30 mg/dL showed an incremental risk stratification capability in patients with diabetes and/or restenotic lesions, supporting its implementation for long-term prognostic assessment in this high-risk clinical setting.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.08.019.

1. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, James S, Kellerth T, Lindahl B, Ravn-Fischer A, Rydberg E, Yndigegn T, Jernberg T. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. *Eur Heart J* 2017;38:3056–3065.
2. Chen DY, Li CY, Hsieh MJ, Chen CC, Hsieh IC, Chen TH, Chen SW, Wang CY, Chang SH, Lee CH, Tsai ML, Ho MY, Yeh JK, Chang CJ, Wen MS. Predictors of subsequent myocardial infarction, stroke, and death in stable post-myocardial infarction patients: a nationwide cohort study. *Eur Heart J Acute Cardiovasc Care* 2019;8:634–642.
3. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J* 2015;36:1163–1170.
4. Silverio A, Benvenga RM, Piscione F, Gulizia MM, Meessen J, Colivicchi F, Nardi F, Baldi C, Galasso G, Vecchione C, Di Lenarda A, Gabrielli D, De Luca L. Prevalence and predictors of out-of-target LDL cholesterol 1 to 3 years after myocardial infarction. A subanalysis from the EYESHOT Post-MI Registry. *J Cardiovasc Pharmacol Ther* 2021;26:149–157.
5. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;39:119–177.
6. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Fourth universal definition of myocardial infarction. *Circulation* 2018;138:e618–e651.
7. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344–2351.
8. Montalescot G, Dallongeville J, Van Belle E, Rouanet S, Baulac C, Degrandsart A, Vicaut E. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). *Eur Heart J* 2007;28:1409–1417.
9. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: the Framingham study. *Circulation* 1979;59:8–13.
10. Marso SP, Mercado N, Maehara A, Weisz G, Mintz GS, McPherson J, Schiele F, Dudek D, Fahy M, Xu K, Lansky A, Templin B, Zhang Z, de Bruyne B, Serruys PW, Stone GW. Plaque composition and clinical outcomes in acute coronary syndrome patients with metabolic syndrome or diabetes. *JACC Cardiovasc Imaging* 2012;5:S42–S52.
11. Levantesi G, Macchia A, Marfisi R, Franzosi MG, Maggioni AP, Nicolosi GL, Schweiger C, Tavazzi L, Tognoni G, Valagussa F, Marchioli R. Metabolic syndrome and risk of cardiovascular events after myocardial infarction. *J Am Coll Cardiol* 2005;46:277–283.
12. Bønaa KH, Mannsverk J, Wiseth R, Aaberge L, Myreng Y, Nygård O, Nilsen DW, Kløw NE, Uchto M, Trovik T, Bendz B, Stavnes S, Bjørnerheim R, Larsen AI, Slette M, Steigen T, Jakobsen OJ, Bleie Ø, Fossum E, Hanssen TA, Dahl-Eriksen Ø, Njølstad I, Rasmussen K, Wilsgaard T, Nordrehaug JE. Drug-eluting or bare-metal stents for coronary artery disease. *N Engl J Med* 2016;375:1242–1252.
13. De Rosa R, Silverio A, Varricchio A, De Luca G, Di Maio M, Radano I, Belmonte M, De Angelis MC, Moscarella E, Citro R, Piscione F, Galasso G. Meta-analysis comparing outcomes after everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic stents in patients with acute coronary syndromes. *AM J Cardiol* 2018;122:61–68.
14. Cassese S, Byrne RA, Schulz S, Hoppman P, Kreutzer J, Feuchtenberger A, Ibrahim T, Ott I, Fusaro M, Schunkert H, Laugwitz KL, Kastrati A. Prognostic role of restenosis in 10 004 patients undergoing routine control angiography after coronary stenting. *Eur Heart J* 2015;36:94–99.
15. Lemos PA, Hoye A, Goedhart D, Arampatzis CA, Saia F, van der Giessen WJ, McFadden E, Sianos G, Smits PC, Hofma SH, de Feyter PJ, van Domburg RT, Serruys PW. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) Study. *Circulation* 2004;109:1366–1370.
16. Kastrati A, Dibra A, Mehilli J, Mayer S, Pinieck S, Pache J, Dirschinger J, Schömig A. Predictive factors of restenosis after coronary implantation of sirolimus- or paclitaxel-eluting stents. *Circulation* 2006;113:2293–2300.
17. Cassese S, Byrne RA, Tada T, Pinieck S, Joner M, Ibrahim T, King LA, Fusaro M, Laugwitz KL, Kastrati A. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. *Heart (British Cardiac Society)* 2014;100:153–159.
18. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, Nordestgaard BG. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009;301:2331–2339.
19. Kamstrup PR, Benn M, Tybjaerg-Hansen A, Nordestgaard BG. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation* 2008;117:176–184.
20. Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* 2009;302:412–423.
21. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41:111–188.
22. Zewinger S, Kleber ME, Tragante V, McCubrey RO, Schmidt AF, Direk K, Laufs U, Werner C, Koenig W, Rothenbacher D, Mons U, Breitling LP, Brenner H, Jennings RT, Petrakis I, Triem S, Klug M, Filips A, Blankenberg S, Waldeyer C, Sinning C, Schnabel RB, Lackner KJ, Vlachopoulou E, Nygård O, Svingen GFT, Pedersen ER, Tell GS, Sinisalo J, Nieminen MS, Laaksonen R, Trompet S, Smit RAJ, Sattar N, Jukema JW, Groesdonk HV, Delgado G, Stojakovic T, Pilbrow AP, Cameron VA, Richards AM, Doughty RN, Gong Y, Cooper-DeHoff R, Johnson J, Scholz M, Beutner F, Thiery J, Smith JG, Vilmundarson RO, McPherson R, Stewart AFR, Cresci S, Lenzini PA, Spertus JA, Olivieri O, Girelli D, Martinelli NI, Leiherer A, Saely CH, Drexel H, Mündlein A, Braund PS, Nelson CP, Samani NJ, Kofink D, Hoefer IE, Pasterkamp G, Quyyumi AA, Ko YA, Hartiala JA, Allayee H, Tang WHW, Hazen SL, Eriksson N, Held C, Hagström E, Wallentin L, Åkerblom A, Siegbahn A, Karp I, Labos C, Pilote L, Engert JC, Brophy JM, Thanassoulis G, Bogaty P, Szczeklik W, Kaczor M, Sanak M, Virani SS, Ballantyne CM, Lee VV, Boerwinkle E, Holmes MV, Horne BD, Hingorani A, Asselbergs FW, Patel RS, Krämer BK, Scharnagl H, Fliser D, März W, Speer T. Relations between lipoprotein(a) concentrations, LPA genetic variants, and the risk of mortality in patients with established coronary heart disease: a molecular and genetic association study. *Lancet Diab Endocrinol* 2017;5:534–543.
23. Schwartz GG, Ballantyne CM, Barter PJ, Kallend D, Leiter LA, Leitersdorf E, McMurray JJV, Nicholls SJ, Olsson AG, Shah PK, Tardif JC, Kittelson J. Association of Lipoprotein(a) with risk of recurrent ischemic events following acute coronary syndrome: analysis of the dal-outcomes Randomized Clinical Trial. *JAMA Cardiol* 2018;3:164–168.
24. O'Donoghue ML, Morrow DA, Tsimikas S, Sloan S, Ren AF, Hoffman EB, Desai NR, Solomon SD, Domanski M, Arai K, Chiuve SE, Cannon CP, Sacks FM, Sabatine MS. Lipoprotein(a) for risk assessment in patients with established coronary artery disease. *J Am Coll Cardiol* 2014;63:520–527.
25. Miñana G, Gil-Cayuela C, Bodi V, de la Espriella R, Valero E, Mollar A, Marco M, García-Ballester T, Zorio B, Fernández-Cisnal A, Chorro FJ, Sanchis J, Núñez J. Lipoprotein(a) and long-term recurrent infarction after an episode of ST-segment elevation acute myocardial infarction. *Coron Artery Dis* 2020;31:378–384.
26. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, Fras Z, Goodman SG, Halvorsen S, Hanotin C, Harrington RA, Jukema JW, Loizeau V, Moriarty PM, Moryusef A, Pordy R, Roe MT, Sinnaeve P, Tsimikas S, Vogel R, White HD, Zahger D, Zeiher AM, Steg PG, Schwartz GG. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. *J Am Coll Cardiol* 2020;75:133–144.

27. O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, Im K, Lira Pineda A, Wasserman SM, Češka R, Ezhov MV, Jukema JW, Jensen HK, Tokgözoğlu SL, Mach F, Huber K, Sever PS, Keech AC, Pedersen TR, Sabatine MS. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. *Circulation* 2019;139:1483–1492.
28. Tsimikas S, Viney NJ, Hughes SG, Singleton W, Graham MJ, Baker BF, Burkey JL, Yang Q, Marcovina SM, Geary RS, Crooke RM, Witztum JL. Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study. *Lancet* 2015; 386:1472–1483.
29. Viney NJ, van Capelleveen JC, Geary RS, Xia S, Tami JA, Yu RZ, Marcovina SM, Hughes SG, Graham MJ, Crooke RM, Crooke ST, Witztum JL, Stroes ES, Tsimikas S. Antisense oligonucleotides targeting apolipoprotein(a) in people with raised lipoprotein(a): two randomised, double-blind, placebo-controlled, dose-ranging trials. *Lancet (London, England)* 2016;388:2239–2253.
30. Maeda S, Abe A, Seishima M, Makino K, Noma A, Kawade M. Transient changes of serum lipoprotein(a) as an acute phase protein. *Atherosclerosis* 1989;78:145–150.