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Rev Invest Clin. 2021;73(6):371-8 ORIGINAL ARTICLE

Evaluation of Low-density Lipoprotein Cholesterol Target Attainment Rates According to the 2016 and 2019 European Society of Cardiology/ European Atherosclerosis Society Dyslipidemia Guidelines for Secondary Prevention in Patients with Acute Myocardial Infarction

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ABSTRACT

Background: High-intensity statin (HIS) therapy is widely recommended for secondary prevention after an acute myocardial infarction (AMI). The 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) dyslipidemia guidelines have lowered the target low-density lipoprotein cholesterol (LDL-C) level, which necessitates a more frequent use of non-statin therapies. **Objectives:** The objectives of the study were to investigate the rate of LDL-C target attainment for secondary prevention in AMI patients. **Methods:** This retrospective investigation included 1360 patients diagnosed with AMI in a tertiary heart center. Lipid parameters were collected within 24 h of admission and within 1 year after discharge. The medications used were retrieved from medical records, and the lowest LDL-C levels after statin treatment were used to assess the effectiveness of the therapy. LDL-C target attainment was defined according to the 2016 ESC/EAS dyslipidemia guidelines as an LDL-C level of < 70 mg/dL and a ≥ 50% reduction from baseline. In addition, the rate of LDL-C target attainment according to the 2019 ESC/EAS guidelines was defined as an LDL-C level of < 55 mg/dL and a ≥ 50% reduction from baseline. **Results:** In total, 502 (36.9%) and 247 (18.2%) patients reached the LDL-C targets according to the 2016 and 2019 ESC/EAS guidelines, respectively. The admission LDL-C levels were significantly lower and HIS treatment was used more frequently in patients who subsequently attained the LDL-C goal. Remarkably, 461 (34%) patients failed to reach the LDL-C goals despite HIS treatment. Only 27 (1.9%) patients were prescribed ezetimibe. **Conclusion:** The rate of LDL-C goal attainment in AMI patients was low, which indicates the need for combination statin and non-statin lipid-lowering therapies. (REV INVEST CLIN. 2021;73(6):371-8)

Key words: Statin. Low-density lipoprotein. European Society of Cardiology. Acute myocardial infarction.

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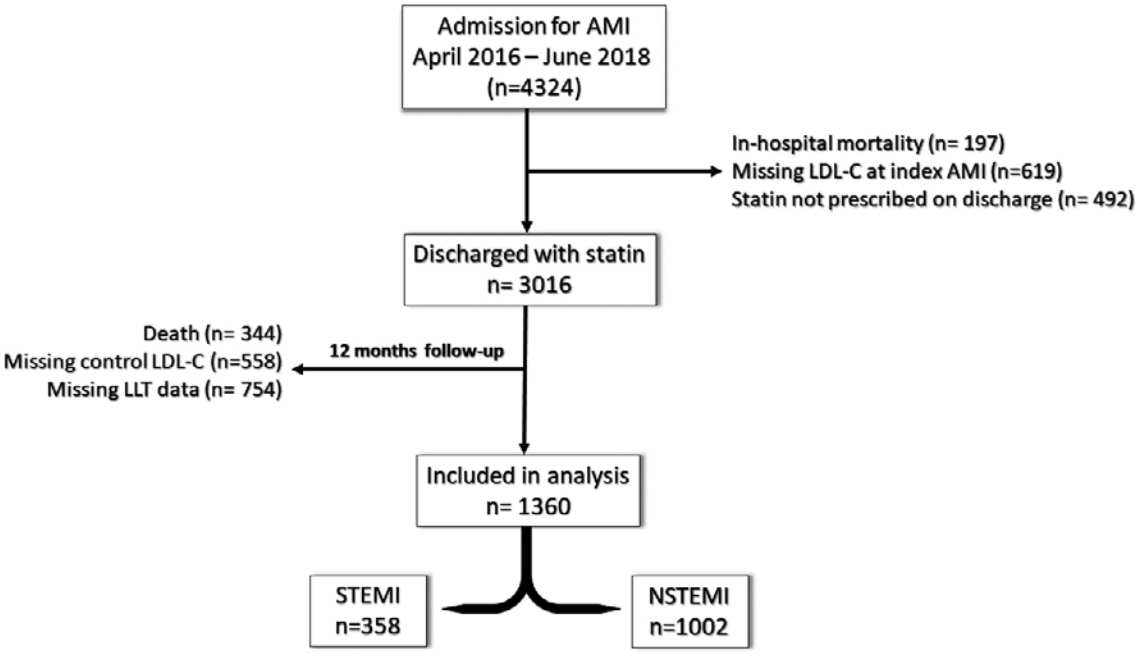
Figure 1. Flowchart of the study participants. AMI: acute myocardial infarction; LDC-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction.



INTRODUCTION

Acute myocardial infarction (AMI), which includes ST-segment elevation myocardial infarction (STEMI) and non-STEMI, remains one of the most common causes of death worldwide despite significant advancements in diagnosis and treatment methods[1]. Dyslipidemia is a major modifiable risk factor in AMI patients, and the reduction of low-density lipoprotein cholesterol (LDL-C) with statin treatment reduces the risk of recurrent cardiovascular events[1,2]. High-intensity statin (HIS) therapy is widely recommended for secondary prevention after an AMI[3,4]. The previous edition (2016) of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines on the management of dyslipidemia recommended a serum LDL-C level of 70 mg/dL for patients at a very high total cardiovascular risk[5]. The current (2019) ESC/EAS guidelines have lowered the target LDL-C treatment goal to < 55 mg/dL, which necessitates a more frequent use of non-statin therapies for very high-risk patients[6]. In this retrospective study, we investigated the rates of LDL-C target attainment to highlight the need for statin dose intensification and statin and non-statin lipid-lowering therapy (LLT) combinations.

METHODS

Study population

This was a cross-sectional, observational, and single-center study that included patients treated for AMI between April 2016 and June 2018. A total of 33,08 patients were discharged with statin treatment during the study period. After the exclusion of patients without follow-up LDL-C measurements and LLT data and patients who died during a 12-month follow-up, 1,360 patients (358 STEMI and 1,002 non-STEMI) were included in the analysis (Fig. 1). Baseline demographic features and laboratory and angiographic findings were retrieved from the hospital's electronic database. Data on medications at admission, in-hospital treatments, discharge medications, and LLT at follow-up were collected from hospital records or telephone interviews with patients if necessary.

Laboratory measurements

In all patients, fasting blood samples were collected from the antecubital vein within 24 h of admission. Complete blood count parameters were measured

using an ABX Pentra DX 120 hematology analyzer immediately after sampling. Biochemical parameters, including creatinine, aspartate transaminase, alanine transaminase (ALT), and lipid levels, were measured using a Roche Cobas Integra 800 device (Roche Diagnostics, Switzerland). Total cholesterol, high-density lipoprotein cholesterol, and LDL-C levels were recorded. The LDL-C levels were calculated using the Friedewald formula. Follow-up laboratory results were collected from an electronic database to investigate statin-associated laboratory changes in selected patients. For all patients, it was confirmed that lipid parameters were measured within 30 days of statin refill using medical records or telephone interviews.

Definitions

STEMI and non-STEMI were defined according to the 2017 and 2020 universal definitions of the ESC myocardial infarction guidelines[1,7]. The diagnosis of non-STEMI was confirmed based on clinical evidence of myocardial ischemia with a rise and/or fall in troponin values with at least one value above the 99th percentile upper limit of the range and at least one of the following criteria: symptoms of myocardial ischemia, new ischemic electrocardiogram changes, development of pathological Q waves, imaging evidence of new loss of viable myocardium, and identification of a coronary thrombus. LDL-C target attainment was defined according to the 2016 ESC/EAS dyslipidemia guidelines as an LDL-C level of < 70 mg/dL and a ≥ 50% reduction from baseline. In addition, the rate of LDL-C target attainment according to the 2019 ESC/EAS guidelines, defined as an LDL-C level of < 55 mg/dL and a ≥ 50% reduction from the baseline, was calculated[5,6]. Liver function abnormality was defined as an ALT level more than 3 times higher than the upper limit of normal (ULN). An ALT level above the ULN but < 3 times higher was considered borderline elevation. A creatinine kinase level 4 times higher than the ULN was considered abnormal[6].

Categorization of lipid-lowering therapies and follow-up targets

A baseline LDL-C level is required to assess the target attainment levels. Thus, in patients receiving LLT during inclusion (n = 197, 15%), baseline LDL-C was confirmed from prior laboratory analyses or extrapolated using the admission LDL-C levels and the reduction achieved by the administered LLTs. The patients were divided into two groups according to their LDL-C levels at a 1-year follow-up. Group 1 included the patients who reached the target LDL-C level according to the 2016 ECS/EAS guidelines, and Group 2 included those who did not. Lipid-lowering medications were classified according to the type and dose as HIS therapy (expected LDL-C decrease of ≥ 50%, that is, 40-80 mg of atorvastatin or 20-40 mg of rosuvastatin daily), moderate-intensity statin therapy (expected LDL-C decrease of 30-49%, that is, 10-20 mg of atorvastatin, 5-10 mg of rosuvastatin, 20-40 mg of simvastatin, 40-80 mg of pravastatin, 40-80 mg of lovastatin, 1-4 mg of pitavastatin, or 80 mg of fluvastatin XL daily), and low-intensity statin therapy (all other statins and doses)[8].

Statistical analysis

Continuous variables were expressed as means ± standard deviations or medians (25th-75th percentiles), and categorical variables were expressed as numbers and percentages. The Kolmogorov–Smirnov test was used to evaluate the normal distribution of continuous variables. Quantitative data were evaluated using an unpaired *t*-test or the Mann–Whitney *U* test as appropriate. Categorical variables were compared using the chi-squared test. Fisher's exact test was used if the sample size in a cell was <5. Univariate and multivariate logistic regression analyses were performed to identify independent factors for the failure to attain the 2016 and 2019 LDL-C goals. Clinically relevant variables were included in the univariate analysis to identify baseline features associated with the failure to achieve the LDL-C goal at the time of enrollment and follow-up. Variables with values of $p < 0.05$ in the univariate analysis were selected for the multivariate analysis. The results of both regression analyses were expressed as odds ratios (OR) with 95% confidence intervals (CI). A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

A total of 502 (36.9%) patients attained the LDL-C target defined by the 2016 ESC/EAS (< 70 mg/dL and ≥ 50% reduction from baseline) dyslipidemia

Table 1. Clinical and demographic properties of all cases according to ESC 2016 dyslipidemia guidelines

	All patients (n = 1360)	Group 1* (LDL-C target reached (n = 502)	Group 2* (LDL- C target not reached) (n = 858)	p value
Age, year	61.5 ± 11.9	60.9 ± 11.7	61.7 ± 12.1	0.19
Gender (male), n (%)	958 (70)	380 (76)	578 (67)	< 0.01
History				
Hypertension, n (%)	801 (59)	284 (57)	517 (60)	0.27
Diabetes mellitus, n (%)	496 (36)	191 (38)	305 (36)	0.36
Ex-smoker, n (%)	50 (4)	23 (5)	27 (3)	0.17
Current smoker, n (%)	514 (38)	191(38)	323 (38)	0.88
Prior MI, n (%)	341 (25)	121 (24)	220 (26)	0.52
Prior PCI, n (%)	214 (16)	73 (15)	141 (16)	0.36
Prior ACBG operation, n (%)	129 (9)	45 (9)	84 (10)	0.61
Renal failure, n (%)	66 (5)	25 (5)	41 (5)	0.73
Prior medication				
Antiplatelet, n (%)	383 (28)	144 (29)	239 (28)	0.74
Statin therapy, n (%)	197 (14)	70 (14)	127 (15)	0.75
Ezetimibe therapy, n (%)	7 (1)	3 (1)	4 (0)	0.74
ACE inh., n (%)	457 (34)	170 (34)	287 (34)	0.81
Beta-blocker, n (%)	344 (25)	118 (24)	226 (26)	0.29
Index diagnosis				
ST-elevation MI, n (%)	358 (26)	142 (28)	216 (25)	0.22
Non-ST elevation MI, n (%)	1002 (74)	360 (72)	642 (75)	0.22

*LDL-C target attainment was defined according to ESC/EAS 2016 dyslipidemia guidelines, which was LDL-C < 70 mg/dL and ≥ 50% reduction from baseline.
MI: myocardial infarction; PCI: percutaneous coronary intervention; ACBG: aorta-coronary bypass grafting; ACE: angiotensinogen converting enzyme.

guidelines (Group 1), and 858 (63.1%) patients failed to reach it (> 70 mg/dL and < 50% reduction from baseline) (Group 2) (Table 1). More male than female patients reached the target. The distribution of clinical characteristics, including AMI type, prior AMI, percutaneous coronary intervention or aorta-coronary bypass grafting, and previous medications, did not differ significantly between the two groups.

The baseline total cholesterol and LDL-C levels were significantly higher in Group 2 (Table 2). The mean LDL-C level decreased from 104 ± 36 to 52 ± 11 mg/dL in Group 1 and from 122 ± 41 to 84 ± 21 mg/dL in Group 2. The use of HIS was significantly higher in Group 1 than Group 2 (n = 339 cases [67%] vs. n = 461 cases [54%], p < 0.01, respectively). Importantly, in 461 patients (33.8%), HIS therapy was not adequate to reach the LDL-C goal. Atorvastatin was the most prescribed statin and ezetimibe combination was used only in 27 patients (1.9%). Remarkably, 662 (48.7%) patients reached the LDL-C < 70 mg/dL; however, 160 (19%) patients did not have ≥ 50% LDL-C reduction from baseline. Consequently, only 502 (36.9%) patients attained the LDL-C target defined by the 2016 ESC/EAS dyslipidemia guidelines. Similarly, even though 286 (21%) patients reached the LDL-C target < 55 mg/dL, 39 (5%) patients did not have ≥ 50% LDL-C reduction from baseline. As a result, only 247 (18.2%) patients reached the LDL-C target recommended by the 2019 ESC/EAS guidelines. Among 800 patients receiving HIS, the LDL-C target attainment rate was 42.3% according

Table 2. Lipid-lowering therapies and LDL-C target attainment rates of all cases according to ESC 2016 and 2019 lipid guidelines

	All patients (n = 1360)	Group 1* (LDL-C target reached) (n = 502)	Group 2* (LDL-C target not reached) (n = 858)	p value
Cholesterol level on admission				
Total cholesterol, mg/dL	185 ± 46	174 ± 43	193 ± 46	< 0.01
LDL-C, mg/dL	116 ± 40	104 ± 36	122 ± 41	< 0.01
HDL-C, mg/dL	36 ± 9	35 ± 9	37 ± 11	< 0.01
Lipid-lowering therapy at follow-up, n (%)				
Low-intensity statin	115 (8)	27 (5)	88 (10)	< 0.01
Moderate-intensity statin	445 (33)	136 (27)	309 (36)	< 0.01
High-intensity statin	800 (59)	339 (67)	461 (54)	< 0.01
Statin with ezetimibe	27 (2)	7 (1)	20 (2)	0.23
Statin type, n (%)				
Atorvastatin	1241 (91)	466 (93)	775 (90)	0.10
Rosuvastatin	34 (3)	12 (2)	22 (3)	0.62
Others	85 (6)	24 (5)	61 (7)	0.08
Cholesterol level at follow-up				
Total cholesterol, mg/dL	139 ± 32	118 ± 23	151 ± 32	< 0.01
LDL-C, mg/dL	72 ± 23	52 ± 11	84 ± 21	< 0.01
HDL-C, mg/dL	41 ± 9	40 ± 9	41 ± 9	0.11
LDL decrease percentage, mg/dL	49 ± 13	61 ± 7	42 ± 11	< 0.01
LDL-C < 70, n (%)	662 (49)	502 (100)	160 (19)	< 0.01
LDL-C < 55, n (%)	286 (21)	247 (49)	39 (5)	< 0.01
LDL-C decrease ≥ %50, n (%)	724 (53)	502 (100)	222 (26)	< 0.01
LDL-C >70 and LDL-C decrease < %50, n (%)	476 (35)	0 (0)	476 (55)	< 0.01

*LDL-C target attainment was defined according to ESC/EAS 2016 dyslipidemia guidelines, which was LDL-C < 70 mg /dl and ≥50% reduction from baseline.
LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

to the 2016 guidelines and only 22% according to the 2019 guidelines.

The logistic regression analysis results of the predictors of the inability to reach the 2016 ESC/EAS LDL-C target are displayed in table 3. Higher baseline LDL-C levels (OR: 1.013, 95% CI: 1.010–1.016; p < 0.01) and HIS use (OR: 0.550, 95% CI: 0.431–0.703; p < 0.01) were found to predict LDL-C goal attainment. Age, gender, AMI type, and comorbidities were not significant predictors.

DISCUSSION

The main findings of this study can be summarized as follows: (I) the LDL-C goal recommended by the 2016 ESC/EAS guidelines was achieved by only one-third of the study population. (II) The LDL-C goal recommended by the 2019 ESC/EAS guidelines was achieved by less than one-fifth of the study population. (III) The HIS treatment rate was very low. (IV) Despite the use of HIS therapy in patients with high baseline LDL-C levels, both 2016 and 2019 ESC/EAS

Table 3. Univariate and multivariate predictors of not reaching the 2016 ESC/EAS dyslipidemia guideline target

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Age	1.006	(0.997-1.015)	0.196			
Male gender	0.663	(0.517-0.850)	< 0.01	0.777	(0.596-1.011)	0.060
Hypertension	1.163	(0.930-1.454)	0.183	–	–	–
Diabetes mellitus	0.898	(0.714-1.128)	0.355	–	–	–
Current smoker	0.983	(0.783-1.233)	0.882	–	–	–
STEMI versus Non-STEMI	0.853	(0.666-1.093)	0.209	–	–	–
Previous MI	1.071	(0.829-1.384)	0.599	–	–	–
Previous statin therapy	1.061	(0.774-1.455)	0.713	–	–	–
Baseline LDL	1.012	(1.009-1.015)	< 0.01	0.013	(1.010-1.016)	< 0.01
Intensive statin versus others	0.558	(0.444-0.703)	< 0.01	0.550	(0.431-0.703)	< 0.01

STEMI: ST-elevation myocardial infarction; Non-STEMI: non-ST-elevation myocardial infarction, tables 1 and 2.

LDL-C target attainment rates were low in such patients. (V) A higher baseline LDL-C level and statin therapy intensity were predictors of the failure to achieve the 2016 ESC/EAS LDL-C goal.

The current guidelines recommend statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors for AMI patients with dyslipidemia to reach the LDL-C target[6,9-12]. A recent meta-analysis of 26 randomized trials including data of 170,000 participants found that each 1-mmol/L (38.67 mg/dL) reduction in LDL-C correlates with a 22% lower 5-year incidence of major cardiovascular events, with a major benefit for AMI patients[13]. However, the reality of lipid management in routine clinical practice differs. The European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) studies I, II, III, IV, and V are pivotal studies that describe the lifestyles, risk factors, and treatment goals, including LDL-C target attainment rates, in patients with coronary heart disease in Europe. The latest study (EUROASPIRE V) found that 32% of patients reached the LDL-C goal of < 1.8 mmol/L (< 70 mg/dL)[14]. Similarly, the target LDL-C values defined by the 2016 ESC/EAS dyslipidemia guidelines (LDL-C < 70 mg/dl and ≥50% reduction from baseline) were achieved by 36.9% of the patients in our study. Possible explanations include generally low initial statin doses, little or no up-titration following treatment initiation, with only half of patients on high-intensity LLT at interview, and infrequent use of combination therapies with other drugs, such as ezetimibe[14,15].

Lifestyle modifications play a major role in the prevention of cardiovascular events and the treatment of dyslipidemia. The EUROASPIRE V trial reported that the implementation of lifestyle interventions is low and is associated with inadequate control of hypertension and dyslipidemia in secondary prevention[16,17]. Moreover, a prior multi-center and prospective study did not investigate the impact of lifestyle interventions[18]. Unfortunately, we could not collect data on lifestyle changes such as smoking cessation, healthy diet habits, and regular exercise. Thus, we cannot estimate the impact of such factors on LDL-C target attainment rates.

Insufficient use of statin treatment and insufficient reduction of LDL-C levels remain a common problem in clinical practice. In the Translational Research Investigating Underlying disparities in AMI Patients' Health Status (TRIUMPH) registry, it was observed that LDL-C declines greatly depend on the intensity of statin therapy at hospital discharge[19]. It was found that patients discharged with low-potency statins showed no significant changes in LDL-C levels over time, and those discharged with moderate statins had modest declines (14 and 10 mg/dL at 1 and 6 months, respectively), whereas those discharged with intensive statins showed decreases of 25 and 14 mg/dL at 1 and 6 months, respectively[19,20]. In our study, the

LDL-C reductions achieved during the 1-year follow-up period were much higher in patients receiving HIS therapy compared to those receiving medium- and low-density statin therapy. These findings demonstrate the importance of intensive statin therapy at hospital discharge and during the follow-up period for lowering the LDL-C levels, and they provide the expected changes in LDL-C levels.

A prior study that evaluated the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry data found that even with HIS and ezetimibe therapy, around 70% of patients could not reach LDL-C targets within 6-10 weeks of an AMI, thus requiring a combination with PCSK9 inhibitors[21]. In our country, statin and ezetimibe treatments are reimbursed by the government, but PCSK9 inhibitors are not. In our study, among 800 patients receiving HIS, LDL-C target attainment according to the 2019 ESC/EAS dyslipidemia guidelines was only 22%. The use of ezetimibe combinations was rare, and the use of PCSK-9 inhibitors was nonexistent. Undoubtedly, combinations with non-statin LLTs in secondary prevention should be used more frequently to reduce recurrent events and mortality rates.

The EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care (DA VINCI) study, which included 5888 patients (3000 primary prevention and 2888 secondary prevention patients) from 18 European countries, aimed to determine how the revised guidelines can be applied to routine practice[18]. In line with our findings, statin monotherapy was the dominant mode of LLT (84%), while combination therapies were limited, with 9% of patients receiving ezetimibe with a medium or HIS and 1% receiving a PCSK9 inhibitor combined with a statin and/or ezetimibe. Furthermore, like in our study, the risk-based LDL-C goal achievement was suboptimal, with only 54% of patients reaching the 2016 ESC/EAS guideline targets and 33% reaching the 2019 guideline targets. In our study, we observed no effects of age, history of cardiovascular disease, or type of index AMI on the LDL-C target attainment rates. In terms of gender, male gender was a determinant for LDL-C target achievement in univariate analysis; however, it was not an independent predictor of LDL-C target achievement according to the multivariate analysis. Baseline LDL-C levels and the use of HIS were the only independent predictors of LDL-C target attainment in the multivariate analysis.

Our study has certain limitations. First, it was a single-center retrospective study with limited sample size. Second, follow-up LDL-C levels after statin exposure were collected from medical records. Thus, we cannot ascertain the effectiveness of the treatment in some patients. Third, in statin-naïve patients, we extrapolated the baseline LDL-C from measured levels and the intensity of LLT to calculate the LDL-C reduction. Fourth, we did not consider the effects of lifestyle interventions on LDL-C target attainment. Although we performed a multivariate regression analysis to determine the reasons for LDL-C target attainment failure, it is possible that unmeasured variables may have produced different results.

In conclusion, this observational study once again demonstrates that LDL-C target attainment only with statin treatment may not be possible for most secondary prevention patients despite its limitations. Based on the results of the study, HIS treatment should be administered to every patient with established cardiovascular disease, and combination therapies with ezetimibe and/or PCSK9 inhibitors should be administered to patients who fail to reach LDL-C targets.

ACKNOWLEDGMENTS

The study was approved by the local ethics committee (decision number: 2021/KK/61-3188) and was conducted in accordance with the Good Clinical Practice guidelines of the Declaration of Helsinki. Informed consent was waived due to the retrospective design of the study.

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