1 **Detailed Lipid Profiles and Lipid-related Residual Risk after 12-week 10 mg**

2 **Rosuvastatin Treatment for Acute Myocardial Infarction**

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Abstract

Objective: We aimed to reveal detailed on-treatment lipid profiles, lipid-related surrogate markers, and factors predicting failure to achieve the guideline-recommended lipid management goal following guideline-recommended statin treatment in Japanese patients with acute myocardial infarction (AMI).

Methods and Results: Sixty AMI patients who underwent coronary intervention and had received rosuvastatin 10 mg/day since the start of their hospitalization were assessed for on-treatment lipid-related profiles, including high-sensitivity C-reactive protein, small dense low-density lipoprotein cholesterol (sd LDL-C), and lipoprotein (a), at the 12-week follow-up. Patients who failed to achieve the guideline-recommended lipid management at 12 weeks were defined as the "unachieved group." Univariate and multivariate logistic regression analyses were performed to evaluate the predictors of inclusion in the unachieved group after high-dose statin treatment. Despite the use of high-dose rosuvastatin, 61.7% of the enrolled AMI patients were included in the unachieved group. In addition, the unachieved group had higher sd LDL-C and lipoprotein (a) levels than the achieved group. Logistic regression analyses demonstrated that low baseline high-density lipoprotein cholesterol (HDL-C) levels and the absence of diabetes were predictors of inclusion in the unachieved group.

Conclusion: More than half of the Japanese AMI patients treated with rosuvastatin 10 mg/day did not achieve the guideline-recommended goal of lipid management and still had lipid-related residual risk at 12 weeks. Particular attention should be paid to patients with low baseline HDL-C levels and those without diabetes with regard to their on-treatment lipid profiles.

Key words: acute myocardial infarction, lipoproteins, guidelines, statin

Introduction

It is widely acknowledged that high-dose statin therapy in cases after acute myocardial infarction (AMI) or acute coronary syndrome (ACS) effectively reduces cardiovascular risks, including mortality and myocardial infarction[1, 2]. Based on this evidence, a recent guideline reported by the Japanese Circulation Society (JCS) recommends the initial administration of tolerable maximum doses of strong statins to AMI in Japan[3]. In addition, the Japan Atherosclerosis Society (JAS) guidelines recommend that the goal of lipid management be as follows: low-density lipoprotein cholesterol (LDL-C) <70 mg/dL, triglyceride (TG) <150 mg/dL (fasting) or TG <175 mg/dL (non-fasting), and high-density lipoprotein cholesterol (HDL-C) ≥40 mg/dL[4]. Thus, achievement of lipid-lowering goals can be reasonably expected when guideline-recommended statin treatment is administered after AMI.

However, data regarding whether or not Japanese AMI patients without homozygous familial hypercholesterolemia (FH) can achieve lipid management goals after receiving the maximum approved doses of strong statins, such as rosuvastatin 10 mg/day, atorvastatin 40 mg/day, and pitavastatin 4 mg/day, are lacking. Furthermore, a recent registry study showed that elevated high-sensitivity C-reactive protein (hs-CRP) levels (>0.2 mg/dL) are associated with increased cardiovascular events, even among groups with LDL levels ≤70 mg/dL, suggesting the potential linkage of some surrogate markers with lipid-related residual risk[5].

Therefore, in the present study, we sought to reveal the following: the frequency of patients who failed to achieve all and each lipid management goal after receiving high-dose strong statins following AMI, relative surrogate markers of lipid-related residual risk, and the characteristics of patients who were unable to achieve these goals after high-dose strong statin treatment for secondary prevention of AMI.

Methods

Study design and population

This was a single-arm interventional study of AMI patients who underwent rosuvastatin 10 mg monotherapy without the concomitant use of other lipid-lowering agents, such as ezetimibe or fibrates. Between April 2021 and December 2021, we enrolled eligible patients with AMI who underwent percutaneous coronary intervention (PCI) at Iwate Medical University Hospital or affiliated hospitals (Iwate Prefectural Chubu Hospital, Hachinohe Red Cross Hospital, Iwate Prefectural Kuji Hospital, Iwate Prefectural Miyako Hospital, and Iwate Prefectural Ofunato Hospital). AMI was diagnosed based on the fourth universal definition of myocardial infarction[6]. Regarding the patients enrolled in this study, PCI was performed under an expert consensus document published by the Japanese Association of Cardiovascular Intervention and Therapeutics[7]. After patients became capable of oral intake, those with AMI received rosuvastatin 10 mg/day, in addition to lifestyle modification therapy, regardless of the baseline LDL-C level. Because this study was exploratory, the target number of cases was set at 60, which was achievable within a limited budget. The exclusion criteria were as follows: (1) patients with homozygous FH in whom the use of other cholesterol-lowering agents (evolocumab or ezetimibe) during the observation period was planned, (2) those who were contraindicated for rosuvastatin treatment or with a poor tolerance to rosuvastatin due to myalgia, (3) those with chronic inflammatory diseases with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or ongoing cancer treatment, (4) those with an impaired consciousness or severe mental illness makes obtaining consent difficult, and (5) those with difficulty in attending follow-up visits.

The research protocol was developed according to the guidelines of the Ethics Committee of Iwate Medical University (MH2020174) and conducted according to the principles of the Helsinki Declaration. Written informed consent was obtained from all patients after PCI. This study was registered with the UMIN Clinical Trial Registry (UMIN-CTR ID: UMIN000051955).

Study endpoints and the definition of the "unachievement" of the treatment goal

The primary endpoint of the present study was the prevalence of residual lipid-related risks, defined as the unachievement of ≥1 of the following JAS guideline-recommended treatment goals at 12 weeks: levels of LDL-C ≥70 mg/dL and/or HDL <40 mg/dL and/or TG ≥175 mg/dL. The secondary endpoints were the levels of lipid-related surrogate markers at 12 weeks, including small-dense LDL-C (sd LDL-C), lipoprotein (Lp) (a), and high-sensitivity C-reactive protein. SRL Inc. (Tokyo, Japan) measured the sd LDL-C and Lp (a) levels in this study; in contrast, other laboratory data were measured at each hospital. Baseline blood samples were collected within 24 h of admission, either in the emergency department or the intensive-care unit. Due to limitations in the Japanese healthcare system, we collected lipid profile data for LDL-C, HDL-C, and TG but not total cholesterol. Therefore, a direct LDL-C measurement method was used for both the baseline and 12-week LDL-C assessments. As most patients were admitted during off-hours and some data could not be collected during this time period in some hospitals, baseline sd LDL-C and hs-CRP levels were unavailable in this study. This study categorized patients with ≥1 residual lipid-related risks at 12 weeks as the "unachieved group," while patients with no residual lipid-related risk at 12 weeks were categorized as the "achieved group."

Statistical analyses

Because most of the continuous values were not normally distributed, data are presented as the median (interquartile range) or number (%). Group comparisons of categorical data were performed using the appropriate chi-square contingency test or Fisher's exact test. Intergroup comparisons of medians were performed using the Mann–Whitney U test. Univariate and multivariate logistic regression analyses were used to evaluate the factors associated with residual lipid-related risks. Statistically significant variables in the univariate analysis were incorporated into the multivariate analysis to evaluate the relative factors of failure to achieve the lipid management goals. Differences were considered statistically significant at P <0.05.

All statistical analyses were performed using the SPSS software program for Windows (version 21.0; IBM Corp., Armonk, NY, USA).

Results

Among the 90 consecutive live AMI cases reported at related facilities during the study period, 28 were excluded from this study due to difficulty in attending 12-week follow-up visits. During the study period, there were no cases of poor tolerance to rosuvastatin, chronic inflammatory diseases, ongoing cancer, or homozygous FH. Informed consent was obtained from all 62 remaining patients for study inclusion. However, two patients were excluded because they could not provide blood samples for follow-up at the 12-week mark. Thus, 60 patients with AMI were analyzed for baseline and 12-week data.

Among these patients, 9 (15%) had already received statin therapy at admission. None of the registered patients experienced side effects such as myalgia or liver dysfunction, requiring discontinuation or alteration of rosuvastatin treatment during the study period.

Baseline patient background, laboratory data and medications

Table 1 shows the baseline patient background and laboratory data of the unachieved and achieved groups. The median age tended to be younger (63 vs. 72 years old, p = 0.07), and the prevalence of ST-elevation myocardial infarction (STEMI) tended to be higher (84% vs. 61%, p=0.07) in the unachieved group than in the achieved group. While the patient backgrounds were mostly similar between the two groups, the unachieved group had a significantly lower prevalence of diabetes mellitus than the achieved group (24% vs. 52%, p <0.05). The unachieved group showed significantly lower median HDL-C levels (46 mg/dL vs. 53 mg/dL, p = 0.03), higher median TG levels (110 mg/dL vs. 76 mg/dL, p = 0.03), and a lower median eicosapentaenoic acid (EPA)-to-arachidonic acid (AA) ratio (0.21 vs. 0.31, p = 0.02) than the achieved group.

Serial changes in each lipid profile between 0 and 12 weeks

Figure 1 shows the continuous changes in various lipid levels from week 0 to week 12. After 12 weeks of 10 mg/day rosuvastatin administration, the median LDL-C level significantly decreased from 121 to 66 mg/dL (p <0.001). However, no significant changes were observed in other lipid values over 12 weeks. The EPA/AA ratio showed no improvement, with a median value of 0.24 at 12 weeks compared to 0.25 at the start of rosuvastatin 10 mg/day administration.

Frequency and detail of residual lipid-related risks at 12 weeks (primary endpoint)

Figure 2 shows the frequency distribution of each lipid value after 12 weeks of rosuvastatin administration (10 mg/day). The percentages of cases that did not achieve the lipid level management goals of LDL-C <70 mg/dL, HDL-C ≥40 mg/dL, and TG <175 mg/dL were 40.0%, 18.3%, and 16.7%, respectively. However, 5% of cases did not achieve an LDL-C level <100 mg/dL goal. Among all patients, 23 (38.3%) achieved all lipid management goals, forming the achieved group. In contrast, there were 37 (61.7%) patients in the unachieved group; among them, the most common unachieved goal was the LDL-C level, with 24 (64.9%) patients not achieving this target (Figure 3). In this study, none of the lipid management goals were achieved.

Serum levels of sd LDL-C, Lp (a), and hs-CRP at 12 weeks

Figure 4 shows the sd LDL-C, Lp (a), and hs-CRP levels after 12 weeks of rosuvastatin administration. When comparing the unachieved and achieved groups, the sd LDL-C levels (22.0 vs. 17.0 mg/dL, p <0.01) and Lp (a) levels (19.0 vs. 10.0 mg/dL, p = 0.02) were significantly higher in the unachieved group than in the achieved group. However,

although these values were numerically higher in the unachieved group, there was no statistically significant difference in hs-CRP levels between the unachieved and achieved groups (0.053 vs. 0.038 mg/dL, p = 0.15).

Relative factors associated with not achieving the therapeutic goal at 12 weeks

Using baseline data, a logistic regression analysis was performed to explore the factors associated with failure to achieve lipid management goals (Table 2). The results of the univariate analysis showed that non-diabetes, low baseline HDL-C levels, and low baseline EPA/AA ratios were associated with the unachieved group. Furthermore, a multivariate logistic regression analysis including these factors revealed that non-diabetes (odds ratio [OR] 0.19, 95% confidence interval [CI] 0.05–0.74, p = 0.02) and low baseline HDL-C levels (OR 0.95, 95% CI 0.90–0.99, p = 0.02) were independent relative factors of failure to achieve lipid management goals. However, focusing on the achievement rate of lipid management goals in patients with diabetes mellitus versus those without diabetes mellitus, there was no significant difference, as follows: levels of LDL-C <70 mg/dL (71.4% vs. 53.8%, p = 0.19), HDL-C ≥40 mg/dL (85.7% vs. 79.5%, p = 0.55), and TG <175 mg/dL (85.7% vs. 82.1%, p = 0.72).

Discussion

In the present single-arm interventional study, we investigated the achievement rate of lipid management goals in 60 Japanese patients who received rosuvastatin 10 mg/day after PCI. The main results were as follows: (1) The median LDL-C level improved significantly from 121 to 66 mg/dL (p <0.001); however, there were no significant changes in the TG or HDL-C levels. (2) The overall achievement rate of lipid management goals was 38.3%. (3) The main contributing factor to the inability to achieve lipid management goals was the failure to achieve LDL-C targets. (4) The unachieved group showed significantly higher sd LDL-C and Lp (a) values than the achieved group. (5) The relative factors for residual lipid-related risk based on information obtained at admission were non-diabetes and low baseline HDL-C levels.

This study suggests that many Japanese patients have residual lipid-related risks even after undergoing treatment with the recommended initial dose of strong statins according to the JCS and JAS guidelines. One possible reason is that the approved statin dosages in Japan are lower than those in the United States[8]. Focusing on racial differences in the cholesterol-lowering effect of statins, LDL-C reduction with rosuvastatin 10 mg/day treatment in Eastern Asian patients was significantly greater than that in Western patients. However, 14 mg/day rosuvastatin treatment for Eastern Asians and 40 mg/day rosuvastatin treatment for Westerners had a similar LDL-C-lowering effect (<70 mg/dL)[9]. The plasma level of statins in Asians is higher than that in Caucasians, and systemic exposure to rosuvastatin is 1.7- to 2-fold higher in Asian patients than in Caucasian patients[10]. Therefore, if the frequency and severity of side effects are acceptable for Japanese patients, rosuvastatin 20 mg/day may be a viable therapeutic option for lowering lipid levels in Japanese patients with AMI. A recent study in South Korea demonstrated that adding ezetimibe 10 mg to rosuvastatin 10

mg provided equivalent preventive effects to rosuvastatin 20 mg/day in patients with coronary artery risk[11]. In Japanese patients with AMI, early co-administration of ezetimibe or PCSK-9 inhibitors may also be a practical option for treatment intensification.

This study also found that the residual lipid risk at 12 weeks was correlated with on-treatment sd LDL-C and Lp (a) levels; however, there was no correlation with hs-CRP levels. Among Japanese patients who underwent strong statin treatment, baseline sd LDL-C levels had an impact on the long-term clinical outcomes[12]. In addition, sd LDL-C levels are generally considered to have a stronger association with the prognosis than LDL-C alone[13]. Given that our data show a strong relationship between on-treatment LDL-C levels and residual lipid risk, on-treatment sd LDL-C may be a better predictive marker than on-treatment LDL-C and other classical surrogate markers in some AMI patients. During statin treatment, Lp (a) levels strongly predict cardiovascular events[14]. Since Lp (a) levels remain unchanged before and after statin treatment[15], combining on-treatment Lp (a) with LDL-C, HDL-C, and TG levels may also help stratify patients who require more intensive lipid management to reduce residual risk. However, this study demonstrated no significant difference in the on-treatment hs-CRP levels between the unachieved and achieved groups. This was probably because strong statins were able to substantially reduce hs-CRP levels within 1 month after ACS[16], resulting in an hs-CRP level of <0.2 mg/dL in most of our patients. Looking back at the baseline data, the unachieved group had a significantly higher prevalence of statin pre-treatment and a numerically higher LDL-C level than the achieved group. These results suggest that the unachieved group may have included patients with more severe hypercholesterolemia or heterozygous FH, possibly with a high baseline Lp (a) level.

This study identified low baseline HDL-C levels on admission and non-diabetes as relative risk factors in the unachieved group. In patients with coronary artery disease (CAD), low pretreatment HDL-C levels are limited even after high-dose statin treatment and are strongly associated with CAD[17, 18]. Thus, it is reasonable to conclude that a low baseline HDL-C level predicts lipid-related residual risk after rosuvastatin treatment. However, the association between lipid-related residual risk and patients without diabetes has yet to be established. In a pooled data analysis of 21 randomized control trials comparing combined ezetimibe/statin therapy with statins alone, patients with diabetes had lower on-treatment LDL-C levels and LDL-C improvement rates and a higher rate of achieving treatment goals than those without diabetes, regardless of statin pretreatment[19]. In addition, a recent observational study on patients with COVID-19 demonstrated that patients with diabetes taking statins had significantly lower hs-CRP levels on admission and in-hospital mortality than those not taking statins. In contrast, there was no marked difference in hs-CRP levels between patients without diabetes who used statins and who did not use statins[20]. These findings suggest that patients without diabetes may have a reduced response to statin therapy in terms of improvement in lipid profiles and anti-inflammatory effects compared to patients with diabetes.

Limitations

Several limitations associated with the present study warrant mention. First, the sample size was relatively small, which may limit the generalizability of the findings. Furthermore, we could not assess sex-related differences in lipid-related residual risk. Second, this study did not focus on clinical endpoints; therefore, its association with the long-term prognosis remains unclear. Third, non-fasting blood samples for lipid

measurements, particularly TG levels, may have influenced our results. Fourth, the absence of baseline data for sd LDL-C, Lp (a), and hs-CRP levels upon admission made it difficult to assess changes or improvements during the study period. Fifth, because this study lacked data on total cholesterol levels, the residual risk related to non-HDL-C might have been underestimated. Further research with larger sample sizes, clinical endpoint evaluations, and standardized fasting blood sampling is warranted to address these limitations and provide a more comprehensive understanding of lipid management in patients with ACS.

Conclusion

This study suggests that the initial administration of rosuvastatin 10 mg/day for Japanese patients with AMI, as recommended by the Japanese guidelines, frequently fails to achieve patients' lipid management goals with high on-treatment Lp (a) and sd LDL-C levels. Particular attention should be paid to patients without diabetes and/or with low baseline HDL-C levels, even after high-dose, strong statin treatment.

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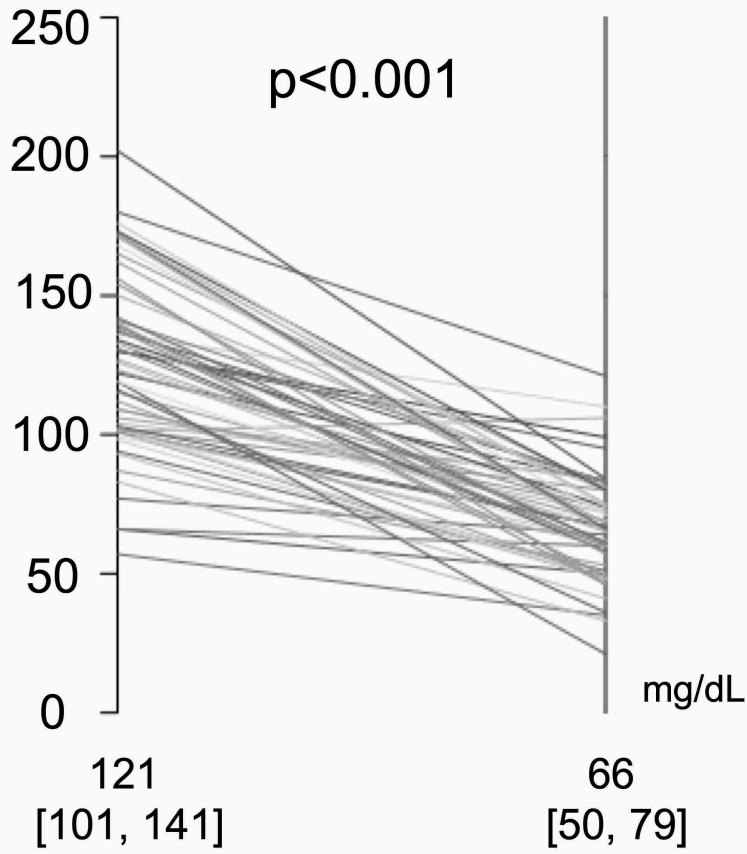1   *Am Heart Assoc* 2020;**9**:e018475.

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Figure legends

Figure 1: Serial changes in each lipid profile between 0 and 12 weeks. The LDL-C level was significantly decreased after high-dose strong statin treatment. In contrast, regarding TG and HDL-C levels and the EPA/AA ratio, there was no marked difference between values at baseline and 12 weeks. EPA/AA, eicosapentaenoic acid-to-arachidonic acid ratio; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride

Figure 2: Each lipid profile at 12 weeks. Forty percent of patients had not achieved therapeutic goals for LDL-C. However, most patients achieved the therapeutic goals for TG and HDL-C. Abbreviations as in Figure 1.
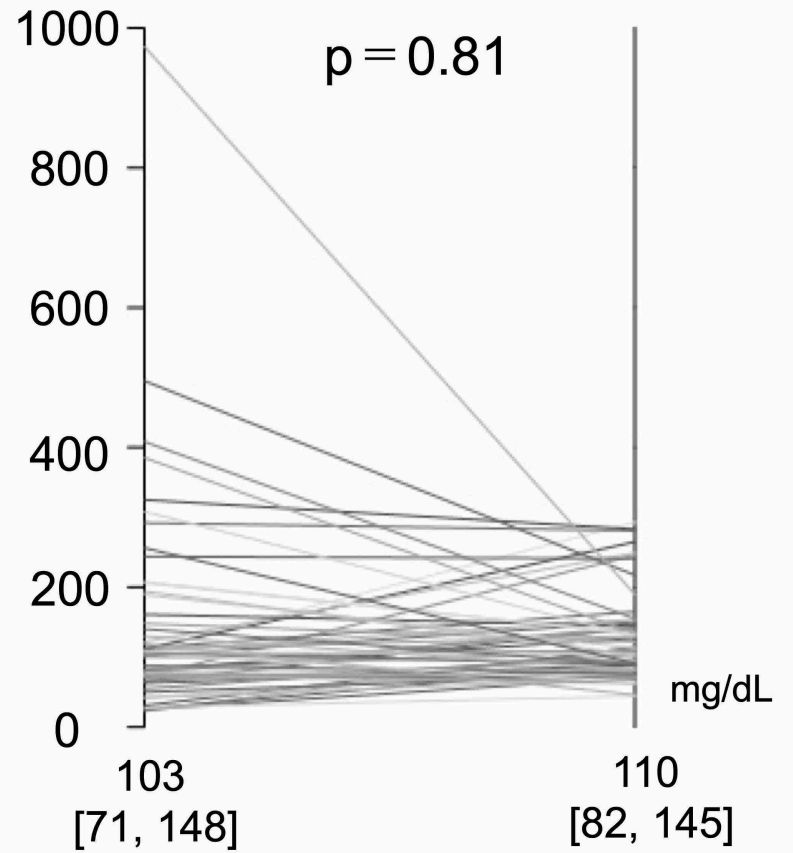
Figure 3: Detail of residual lipid-related risks. The most common residual risk factor was LDL-C. No patients had all three residual risk factors. Abbreviations as in Figure 1.

Figure 4: Secondary endpoints at 12 weeks. sd LDL-C and Lp (a) levels in the unachieved group were significantly higher than in the achieved group, while there was no statistically significant difference in hs-CRP levels. Hs-CRP, high-sensitivity C-reactive protein; Lp (a), lipoprotein (a); sd LDL-C, small dense low-density lipoprotein cholesterol.
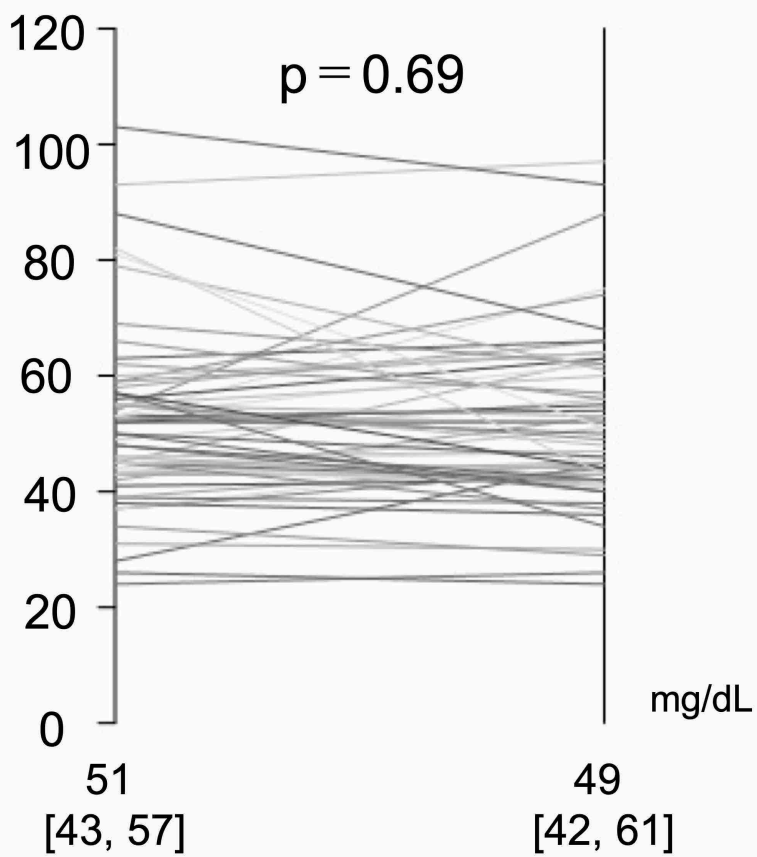
(A) LDL-C

p<0.001

mg/dL

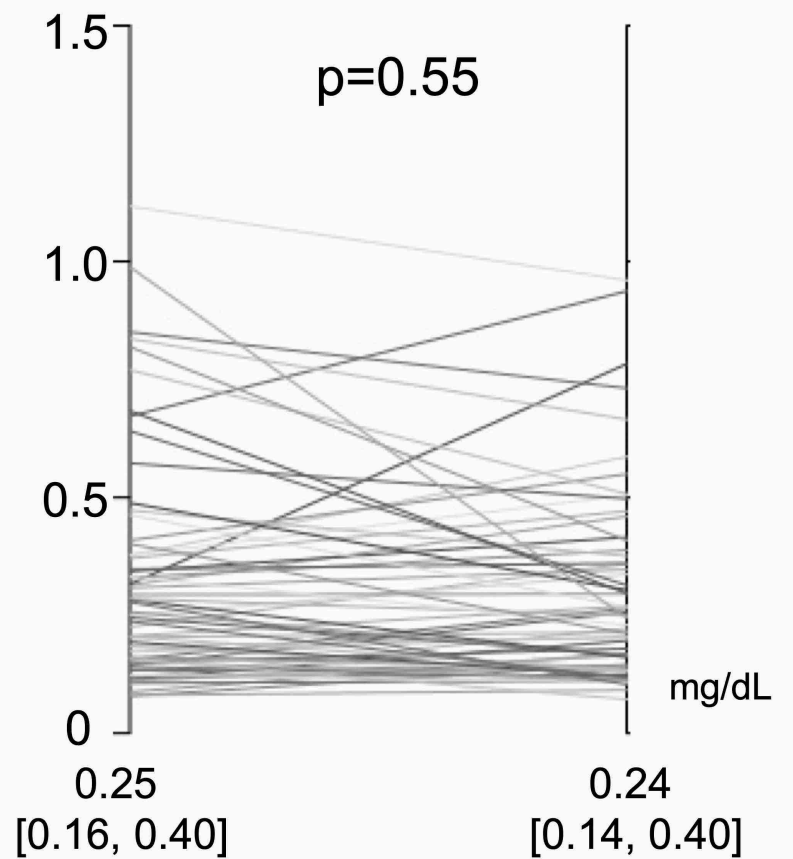121
[101, 141]

66
[50, 79]

(B) TG

p = 0.81

mg/dL

103
[71, 148]

110
[82, 145]

(C) HDL-C

p = 0.69

mg/dL

51
[43, 57]

49
[42, 61]

(D) EPA/AA

p=0.55

mg/dL

0.25
[0.16, 0.40]

0.24
[0.14, 0.40]

(A) LDL-C
(B) TG
(C) HDL-C

(A) sd LDL-C

mg/dL

p < 0.001

(B) Lp(a)

mg/dL

p = 0.02

(C) hs-CRP

mg/dL

p = 0.15

Unachieved group   Achieved group
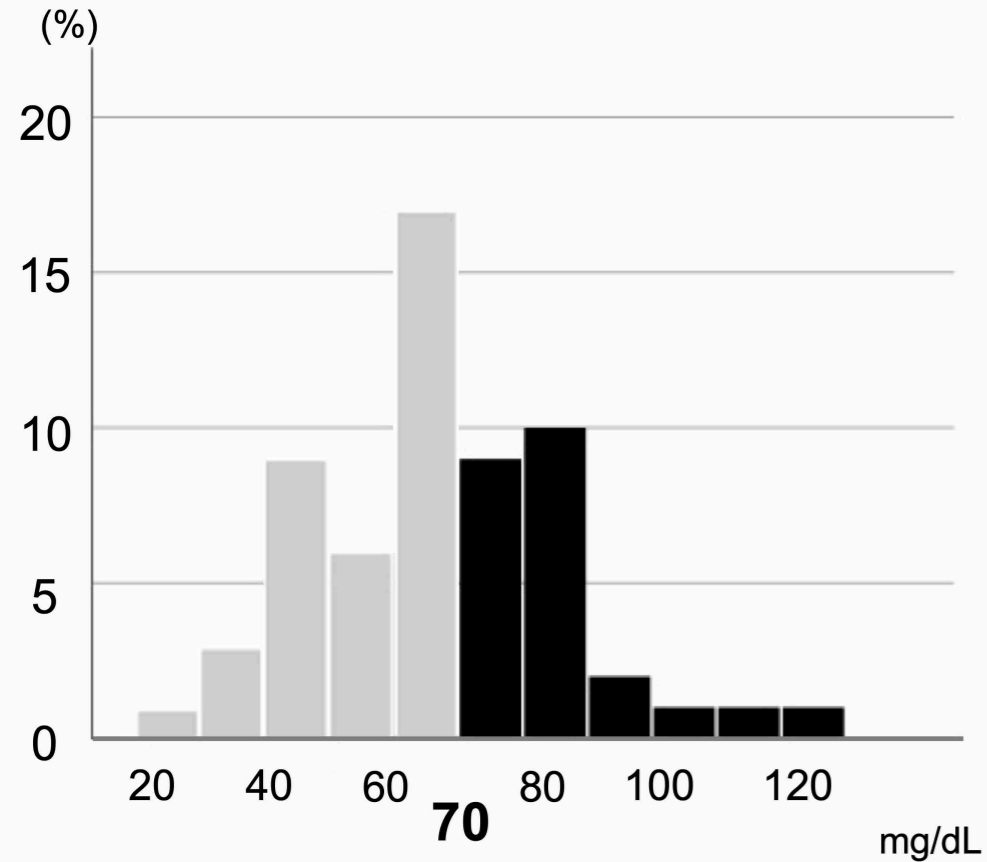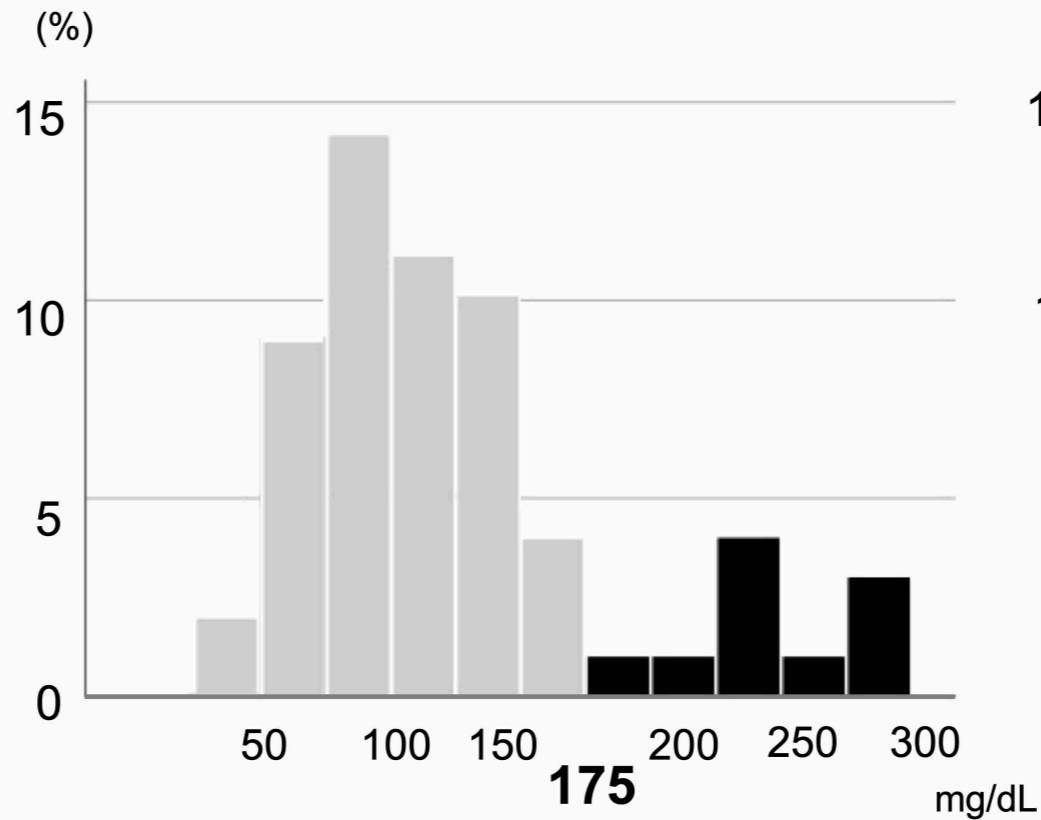
Table 1: Baseline patient background, laboratory data and medications

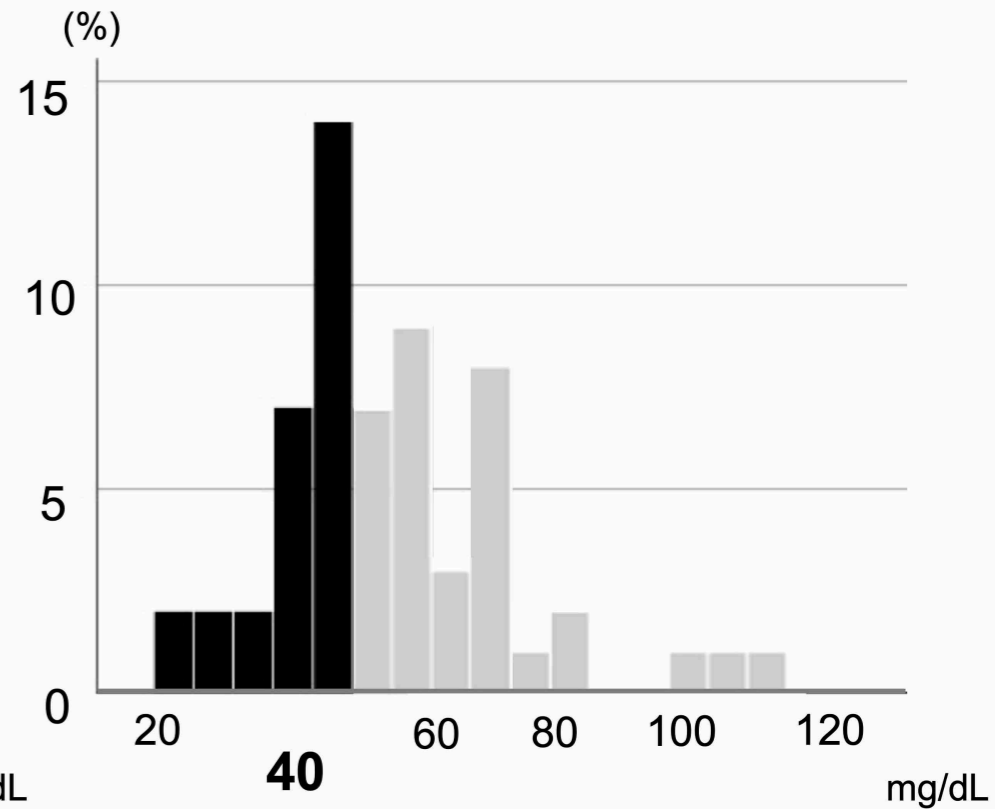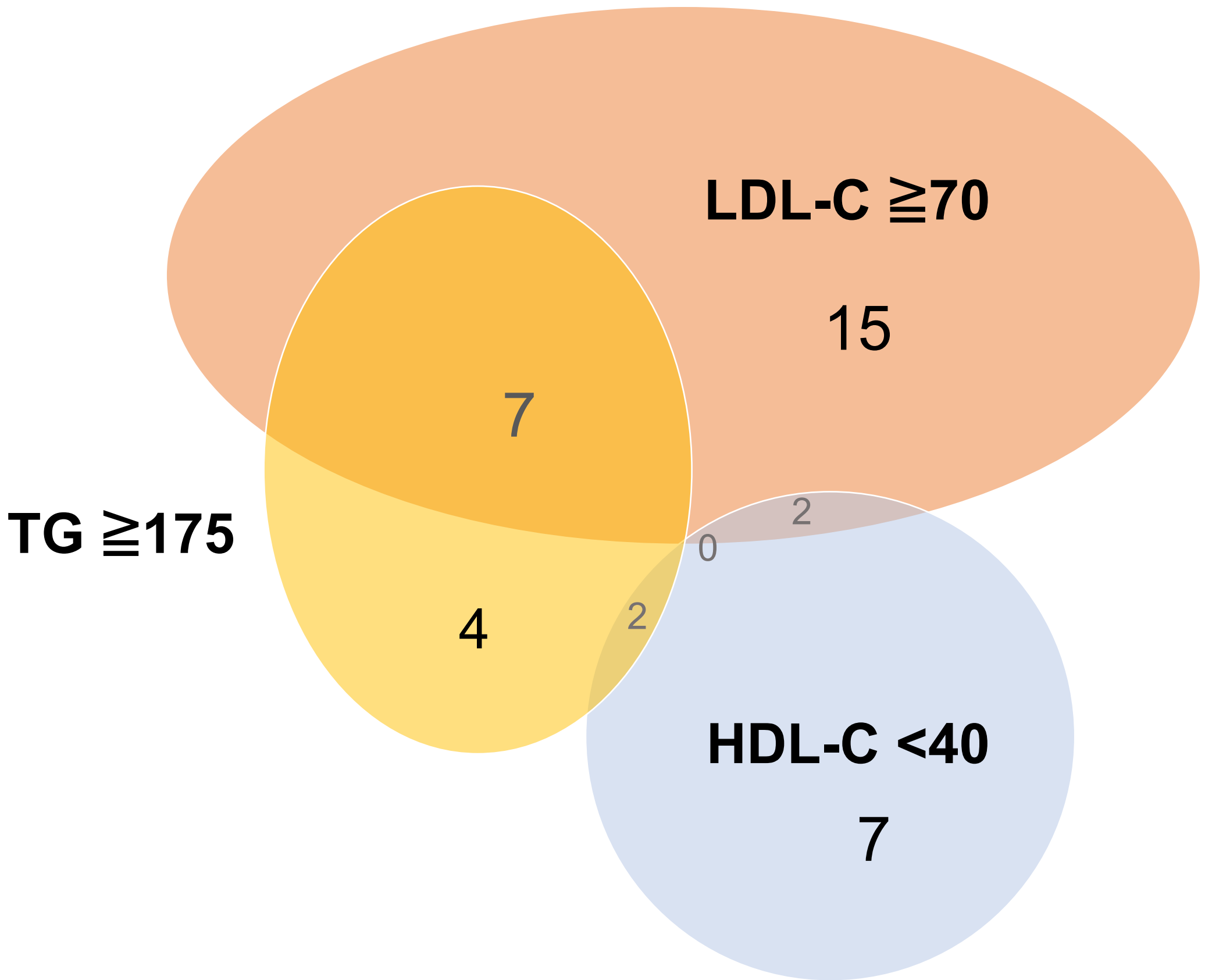|	Unachieved group (n=37)	Achieved group (n=23)	P value
Age, years	63 [53, 73]	72 [60, 77]	0.07
Male sex, n (%)	31 (84)	19 (83)	1.00
Body length, cm	167 [160, 171]	161 [158, 170]	0.13
Body weight, kg	66.0 [56.1, 77.7]	61.0 [55.8, 73.2]	0.27
Body mass index	24.0 [21.2, 27.5]	23.2 [21.6, 27.3]	0.77
STEMI, n (%)	31 (84)	14 (61)	0.07
Hypertension, n (%)	23 (62)	14 (61)	1.00
Dyslipidemia, n (%)	21 (57)	11 (48)	0.60
Diabetes mellitus, n (%)	9 (24)	12 (52)	0.04998
Current smoking, n (%)	28 (78)	17 (74)	0.73
Renal deficiency, n (%)	18 (49)	15 (65)	0.21
Prior PCI	1 (3)	1 (4)	1.00
Statin pretreatment, n (%)	8 / 22 (36)	1 / 12 (8)	0.11
LDL-C, mg/dL	130 [106, 142]	103 [101, 139]	0.12
HDL-C, mg/dL	46 [39, 56]	53 [46, 66]	0.03
TG, mg/dL	110 [77, 207]	76 [65, 112]	0.03
EPA/AA	0.21 [0.14, 0.36]	0.31 [0.19, 0.82]	0.02
HbA1c, %	6.5 [5.7, 7.4]	5.7 [6.0, 6.5]	0.21
Anti-thrombotic agents, n (%)	37 (100)	23 (100)	1.00
Rosuvastatin 10 mg/day, n (%)	37 (100)	23 (100)	1.00
Fibrate, n (%)	0 (0)	1 (4)	0.20
Ezetimibe, n (%)	0 (0)	0 (0)	N/A
Beta blocker, n (%)	28 (76)	28 (76)	0.82
ACE-I, ARB or ARNI, n (%)	24 (65)	15 (65)	0.98
MRA, n (%)	6 (16)	3 (13)	0.74
SGLT-2 inhibitor, n (%)	4 (11)	5 (22)	0.25

Data are presented as median [1st quartile, 3rd quartile], or n (%).

Renal deficiency was defined as an eGFR of < 30 mL/min/1.73 m^2.

Anti-thrombotic agents included aspirin, P2Y12 inhibitors and anticoagulants.

AA, arachidonic acid; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; EPA,

eicosapentaenoic acid; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MRA, mineralocorticoid receptor antagonist; N/A, not available; PCI, percutaneous coronary intervention; SGLT-2, Sodium-glucose cotransporter-2; STEMI, ST-elevation myocardial infarction; TG, triglyceride

Table 2: Relative factors associated with unachievement of lipid profile goals at 12 weeks (Logistic regression analysis using baseline data)

	Univariate model			Multivariate model		
	OR	95%CI	P value	OR	95%CI	P value
Age	0.96	0.91-1.00	0.07			
Male gender	1.09	0.27-4.36	0.91			
STEMI	3.32	0.99-11.1	0.05			
Hypertension	1.06	0.36-3.08	0.92			
Diabetes mellitus	0.30	0.10-0.90	0.03	0.19	0.05-0.74	0.02
Dyslipidemia	1.43	0.50-4.07	0.50			
Current smoking	1.24	0.37-4.18	0.73			
Renal deficiency	0.51	0.17-1.48	0.21			
Statin pretreatment	6.07	0.71-52.18	0.10			
Baseline LDL-C	1.01	0.99-1.03	0.23			
Baseline TG	1.01	1.00-1.01	0.11			
Baseline HDL-C	0.95	0.91-0.99	0.02	0.95	0.90-0.99	0.02
Baseline EPA/AA	0.03	0.003-0.41	0.01	0.13	0.01-1.74	0.12
Baseline HbA1c	0.84	0.58-1.23	0.37			

AA; arachidonic acid, CI; Confidence interval, EPA; eicosapentaenoic acid, HbA1c; hemoglobin A1c, HDL-C; high density lipoprotein cholesterol, LDL-C; low density lipoprotein cholesterol, OR; odds ratio, STEMI; ST-elevation myocardial infarction, TG; triglyceride