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Adherence to Current Dyslipidemia Guideline in Patients Utilizing Statins According to Risk Groups and Gender Differences: The AIZANOI Study

ORIGINAL INVESTIGATION

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ABSTRACT

Background: The aim of this study was to assess the adherence to the current European Society of Cardiology dyslipidemia guidelines, the ratio of reaching target values according to risk groups, and the reasons for not reaching LDL-cholesterol (LDL-C) goals in patients on already statin therapy in a cardiology outpatient population.

Methods: The AIZANOI study is a multi-center, cross-sectional observational study including conducted in 9 cardiology centers between August 1, 2021, and November 1, 2021.

Results: A total of 1225 patients (mean age 62 ± 11 years, 366 female) who were already on statin therapy for at least 3 months were included. More than half (58.2%) of the patients were using high-intensity statin regimens. Only 26.2% of patients had target LDL-C level according to their risk score. Despite 58.4% of very high-risk patients and 44.4% of high-risk patients have been using a high-intensity statin regimen, only 24.5% of very-high-risk patients and only 34.9% of high-risk patients have reached guideline-recommended LDL-C levels. Most prevalent reason for not using target dose statin was physician preference (physician inertia) (40.3%).

Conclusion: The AIZANOI study showed that we achieved a target LDL-C level in only 26.2% of patients using statin therapy. Although 58.4% of patients with a very high SCORE risk and 44.4% of patients with a high SCORE risk were using a target dose statin regimen, we were only able to achieve guideline-recommended LDL-C levels in 24.5% and 34.9% of them, respectively, in cardiology outpatients clinics. Physician inertia is one of the major factors in non-adherence to guidelines. These findings highlight that combination therapy is needed in most of the patients.

Keywords: Low-density lipoprotein cholesterol, statins, SCORE risk

INTRODUCTION

Cardiovascular diseases are the main reason for death among adults in Türkiye, as in many other countries. Overwhelming evidence on atherosclerosis showed that low-density lipoprotein cholesterol (LDL-C) was the primarily responsible cause of the pathogenesis of cardiovascular diseases. Many trials have demonstrated that LDL-C levels were strongly associated with the incidence of atherosclerotic cardiovascular disease (ASCVD).[1-4] And, there was a linear and strong relationship between the time of exposure to high LDL-C and ASCVD risk.[5,6] Although statins are the main drug group for dyslipidemia, many patients require additional drugs like ezetimibe, fibrates, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors to reach target LDL-C level.

The latest Mendelian and PCSK9 trials revealed that there was no LDL-C limit in which beneficial effect of LDL-C lowering drugs was not seen. There is a linear correlation between LDL-C level and ASCVD risk.[7] Therefore, 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidemias updated the target LDL-C levels according to SCORE risk. Patients at very high risk, high risk, moderate risk, and low risk,

LDL-C target levels of <55 mg/dL, 70 mg/dL, 100 mg/dL, and 116 mg/dL are recommended, respectively. The guideline recommends high-intensity statins, which have the power to reduce LDL-C levels by at least 50% for very high versus high-risk groups. If the target LDL-C value cannot be reached in the 8- to 12-week follow-up, it is recommended that the patient switch to the highest tolerated dose of statin therapy and, if necessary, to combine treatment with ezetimibe and PCSK9 inhibitors.[8] Unfortunately, there is insufficient data on the use of statins, drug continuation rates, and treatment success in the treatment of dyslipidemia in Türkiye.

The Objectives of the AIZANOI Study

The AIZANOI study aims to evaluate adherence to current ESC dyslipidemia guidelines, the ratio of usage of guideline-directed intensity statin according to risk group, and the prevalence of reaching target LDL-C values across different risk groups among patients receiving statin therapy in outpatient settings. The study also aims to determine whether there are any gender differences in adherence to guidelines. Specifically, the study seeks to identify the reasons underlying the failure to achieve guideline-directed target LDL-C levels, providing valuable insights into the challenges encountered in real-world dyslipidemia management practices in Türkiye.

METHODS

Methods and Study Population

The AIZANOI study, titled "Adherence to Current Dyslipidemia Guidelines in Patients Utilizing Statins According to Risk Groups," is a multicenter, cross-sectional observational study conducted across 9 cardiology centers in 4 geographical regions in Türkiye. The study aims to evaluate patients' adherence to guidelines regarding statin usage. A total of 1225 patients, who presented to cardiology outpatient clinics between August 1, 2021, and November 1, 2021, and had been on statin therapy for at least 3 months, were consecutively enrolled (Figure 1). Inclusion criteria included patients aged between 40 and 75 years old, who had been using statins for at least 3 months and were diagnosed with dyslipidemia according to ESC guidelines. Exclusion criteria comprised statin therapy duration of less than 3 months, recent acute coronary syndrome history within one month, renal failure with glomerular filtration rate below 30 mg/dL, and triglyceride levels above 400 mg/dL.

HIGHLIGHTS

- Overall, only 26.2% of patients had target LDL-C levels according to their risk score.
- Only 24.5% of very high-risk patients and 34.9% of high-risk patients reached guideline-recommended LDL-C levels.
- One LDL-C lowering drug is not enough to reach guideline targets. There is a need to add second LDL-C-lowering drug.
- Physician inertia is one of the major factors of non-adherence to guidelines.

During outpatient visits, demographic information, statin dosage, indication for statin usage, risk category (very high, high, and medium), and statin adherence were recorded. Risk factors for ASCVD, such as hypertension, diabetes mellitus, family history of premature CAD, and current smoking, were also noted. Definitions of the comorbidities are shown below.

Definitions	
Atherosclerotic cardiovascular disease	Having a history of myocardial infarction or unstable angina, stable angina, percutaneous coronary intervention, coronary artery bypass grafting, CAD, stroke, transient ischemic attack
Coronary artery disease	Documented coronary events (myocardial infarction, stable angina pectoris, unstable angina, percutaneous coronary intervention, and coronary artery bypass grafting) or significant plaque on coronary angiography or computerized tomography
Peripheral artery disease	History of claudication, peripheral vascular surgery, percutaneous peripheral vascular intervention, or significant plaque in peripheral vascular tree on peripheral angiography or computerized tomography.
Chronic kidney disease	Presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min per 1.73 m^2, persisting for 3 months or more.
Cerebrovascular disease	History of transient ischemic attack, or cerebrovascular event, or significant plaque in carotid artery
Heart failure	Having diagnosis of heart failure with reduced ejection fraction symptomatic HF with LVEF ≤40%, heart failure with mildly reduced ejection fraction: symptomatic HF with LVEF 41-49%, HFpEF: symptomatic HF with LVEF ≥50%.
Atrial fibrillation	Having diagnosis paroxysmal or permanent atrial fibrillation with or without oral anticoagulation.
Family history of premature coronary artery disease	Having a primary relative who had been diagnosed with coronary artery disease prior to the age of 55 years in a male relative or 65 years in a female relative

Statin adherence was evaluated by determining the average frequency of statin usage per week, categorized as daily, more than 4 days per week, 3-4 days per week, or less than 3 days per week. It was noted whether the prescribed statin dosage complied with guidelines and whether LDL-C levels reached the target threshold.

Current lipid profiles, including total cholesterol, LDL-C, HDL cholesterol (HDL-C), and triglyceride levels, were collected within the last 2 weeks. Non-HDL cholesterol (non-HDL-C) levels were calculated using the formula (total cholesterol minus HDL-C). The study also investigated whether target LDL-C levels were achieved and explored reasons for failure to meet these goals.

Figure 1. Cities of participating centers.

Reasons for not attaining target LDL-C levels included statin-related adverse events such as intolerance, comorbidities leading to drug-drug interactions, inappropriate statin dosages, patient preferences, physician preferences, and unidentified factors. Statin intolerance could manifest in various forms, including muscle symptoms, myopathy, rhabdomyolysis, liver enzyme elevation, gastrointestinal symptoms, neurological symptoms, and skin reactions.

Physician preference referred to the decision not to escalate statin dosage to the target level despite the absence of contraindications. Patient preference was defined as cases where patients were hesitant to take higher doses of statins. The use of fibrates was not taken into consideration for the current study because fibrates are not the first-choice treatment to lower LDL-C levels, and patients with high triglycerides (>400 mg/dL) were already excluded.

Cardiovascular Risk Evaluation and Low-density Lipoprotein Cholesterol Targets

Patients risk categories according to the SCORE risk model, LDL-C levels according to risk groups, and statin intensity categories consistent with 2019 ESC/EAS Dyslipidemia Guideline definitions are shown in Supplementary Table 1. Patients who had documented ASCVD (myocardial infarction or unstable angina, stable angina, percutaneous coronary intervention, coronary artery bypass grafting, CAD, stroke, and transient ischemic attack), significant plaque on coronary angiography or computerized tomography scan or on carotid ultrasound, diabetics with target organ damage or with at least 3 major risk factors, severe kidney disease or SCORE > 10%, were considered very high risk. Patients who had a single highly elevated risk factor as LDL-C > 190 mg/dL and/or blood pressure >180/110 mm Hg, diabetic patients with additional risk factor, moderate kidney disease or SCORE between 5 and 10% were considered at high risk. Patients with diabetes less than 10-year with an additional risk factors or people who have SCORE risk score between 1% and 5% were considered at moderate risk. Low risk category includes people who have SCORE risk lower than 1%. Target LDL-C levels are 55 mg/dL, 70 mg/dL, 100 mg/dL, and 115 mg/dL for very high, high, moderate and low-risk category, respectively. The guideline recommends high-intensity statin regimens such as atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg for very-high and high-risk groups, whereas it recommends moderate-intensity statin for moderate risk category. According to guideline recommendations, we defined target dose statin as high intensity (atorvastatin 40-80 mg and rosuvastatin 20-40 mg) for very-high risk and high-risk groups and moderate-intensity statin (atorvastatin 10-20 mg, rosuvastatin 5-10 mg, pitavastatin 1-4 mg, and pravastatin 40-80 mg) for moderate-risk group. Both giving guideline-directed intensity statin according to risk group and achieving guideline-recommended LDL-C target levels were accepted as complete adherence to the guidelines.

The AIZANOI study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients gave written informed consent to participate. This study was approved by Non-invasive Studies Ethics Committee (Decision no: 2021/12-17 date: July 8, 2021).

We did not use artificial intelligence-assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) in the production of submitted work.

Statistical Analysis

Continuous variables were summarized using either the median and interquartile range (IQR) for non-normally distributed data or the mean ± standard deviation (SD) for normally distributed data. Normality of the variables was assessed using the Shapiro–Wilk test. The Mann–Whitney *U*-test was employed to analyze non-normally distributed variables. Categorical variables were presented as frequencies and

percentages. Univariate analysis was conducted for continuous variables, while categorical variables were analyzed using either the chi-squared test or Fisher's exact test. Correlations between variables were assessed using either Pearson's or Spearman's correlation tests, depending on the distribution of the data. Additionally, subgroup analyses were performed to examine the association between statin intensity, sex, and LDL-C target achievement. Interaction terms were included to assess effect modification.

MedicReS E-PICOS Version 21.3 Copyright statistical program was used for statistical analysis. A significance level of $P < .05$ was considered statistically significant.

RESULTS

Baseline demographic and clinical characteristics of patients are demonstrated in Table 1. A total of 1225 patients (mean age 62 ± 11 years, 366 female) who were already using statins for at least 3 months were included in this study. The number of male patients was predominantly higher than the number of female patients (859 male [70.1%] vs. 366 female [29.9%]). A comparison of sex differences revealed that female patients exhibited significantly higher rates of hypertension and diabetes than males (75.1% vs. 55.4% and 48.4% vs. 34%, respectively). A higher proportion of men had CAD compared to women (92.8% vs. 72.9%), while more women in our cohort exhibited atrial fibrillation (13.4% vs. 6.1%). Additionally, the proportion of heart failure was higher in men than in women (14.8% vs. 9.8%, respectively). Concomitant medical therapies are also shown in Table 1.

Majority of patients (n = 1112, 90.8%) had very high risk and 4.8%, 3.5%, and 0.3% of patients had high, moderate, and low risk, respectively, according to 2019 ESC/EAS Guidelines for the management of dyslipidemia.[8] The proportion of male patients was higher than females in the very high-risk group. More than half the patients (58.2%) were using high-intensity statin regimens such as atorvastatin 40-80 mg and rosuvastatin 20-40 mg (Figure 2). The ratio of being on high-intensity statins were 72.5% for male patients and 61.9% for female ($P < .001$). But, only 24.7% of female patients and 27.9% of male patients who were using high-dose statin regimen reached guideline-recommended LDL-C target levels. Most of the patients (64.5%) had been using statins for more than 1 year. Statin therapy was initiated mostly by a cardiologist (92.8%) followed by internal medicine (7.2%). Only 26.2% of patients had reached to the target LDL-C level according to their risk score. Less than 30% of men and women were on LDL-C targets (26.9% of male patients and 24.6% of female patients, $P = .43$). Combined use of LDL-C lowering drug was very low, only 2.9% of the patients were using add-on ezetimibe (Table 2).

Table 1. Baseline Demographic and Clinical Characteristics of the Patients

Variables	All Patients	Female	Male	*P*
n (%)	1225	366	859	
Age (years) (± SD)	62.2 ± 10.6	65.1 ± 10.4	60.9 ± 10.5	<.001
Risk factors, n (%)				
Hypertension, n (%)	751 (61.7)	275 (75.1)	476 (55.4)	<.001
Diabetes, n (%)	469 (38.3)	177 (48.4)	292 (34.0)	<.001
Family history of premature coronary artery disease, n (%)	110 (10.6)	33 (9.0)	77 (9.0)	.976
Smoking, n (%)	334 (27.3)	59 (16.1)	275 (32.1)	<.001
Comorbidities				
Coronary artery disease, n (%)	1063 (86.8)	266 (72.9)	797 (92.8)	<.001
Peripheral artery disease, n (%)	57 (4.7)	13 (3.5)	44 (5.1)	.232
Cerebrovascular event, n (%)	54 (4.4)	17 (4.6)	37 (4.3)	.792
Heart failure, n (%)	163 (13.3)	36 (9.8)	127 (14.8)	.019
Chronic kidney disease, n (%)	80 (6.5)	26 (7.1)	54 (6.3)	.596
Atrial fibrillation, n (%)	101 (8.2)	49 (13.4)	52 (6.1)	<.001
Drugs (except statin and ezetimibe)				
Antiplatelets, n (%)	1086 (88.7)	287 (78.4)	799 (93.1)	<.001
ACEi, ARB, ARNI, n (%)	833 (68.1)	243 (66.4)	590 (68.7)	.431
Beta blockers, n (%)	970 (79.2)	271 (74)	699 (81.4)	<.001
Non-DHP calcium channel blockers, n (%)	60 (4.9)	26 (7.1)	34 (4.0)	.019
DHP calcium channel blockers, n (%)	181 (14.8)	77 (21)	104 (12.1)	<.001
Diuretics, n (%)	251 (20.5)	96 (26.2)	155 (18.1)	<.001
Mineralocorticoid receptor antagonists, n (%)	11 1(9.1)	35 (9.6)	76 (8.8)	.689
Oral anticoagulants, n (%)	123 (10)	57 (15.6)	66 (7.7)	<.001
Oral antidiabetics, n (%)	302 (25.2)	115 (31.5)	187 (21.8)	<.001

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin recetor neprilysin inhibitor; DHP, dihydropiridine.

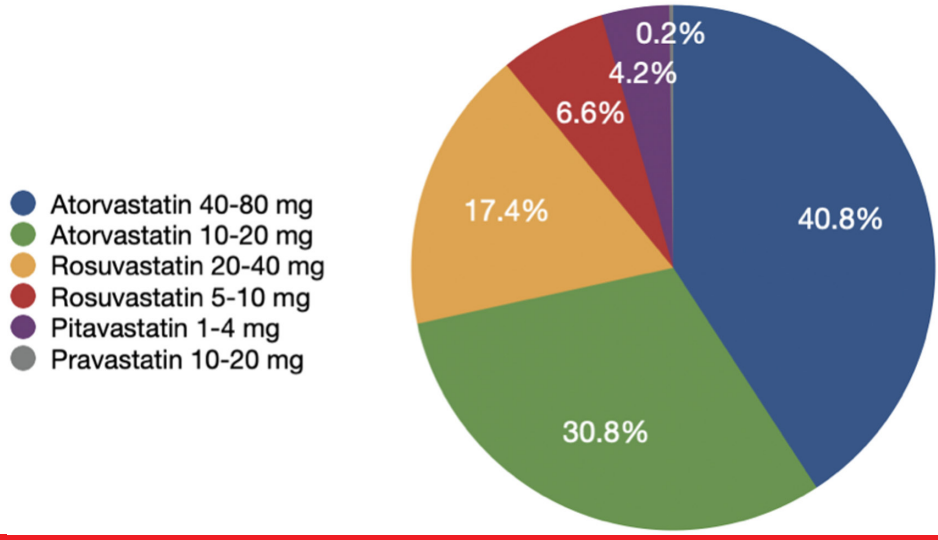

Figure 2. Types and doses of statins.

Table 2. Risk Status, the Intensity of Statin Therapy, Type, and Dose of Statin and Using Target Dose Statin. The Ratio of LDL-C Target Level Achievement in High-Intensity Statin Group, Ezetimibe Usage of the Patients, and Duration of Current Statin Therapy

Risk Level	All Patients	Female	Male	*P*
n (%)	1225	366	859	-
Very high, n (%)	1112 (90.8)	289 (79.2)	823 (96.4)	<.001
High, n (%)	60 (4.9)	40 (11.0)	20 (2.3)	<.001
Moderate, n (%)	43 (3.5)	34 (9.0)	9 (1.1)	<.001
Low, n (%)	4 (0.3)	2 (0.5)	2 (0.2)	.378
Intensity of statin therapy				
High, n (%)	846 (69.3)	226 (61.9)	620 (72.5)	<.001
Moderate, n (%)	370 (30.3)	138 (37.8)	232 (27.1)	<.001
Low, n (%)	4 (0.3)	1 (0.3)	3 (0.4)	.830
Type and dose of statin				
Atorvastatin 40-80 mg, n (%)	498 (40.8)	127 (34.7)	371 (43.3)	<.001
Rosuvastatin 20-40 mg, n (%)	213 (17.4)	62 (16.9)	151 (17.6)	.787
Atorvastatin 10-20 mg, n (%)	376 (30.8)	118 (32.2)	258 (30.1)	.443
Rosuvastatin 5-10 mg, n (%)	80 (6.5)	35 (9.6)	45 (5.3)	<.001
Pitavastatin 1-4 mg, n (%)	51 (4.2)	23 (6.3)	28 (3.3)	.015
Pravastatin 10-20 mg, n (%)	3 (0.2)	0 (0)	3 (0.4)	.257
Using target dose statin				
Yes, n (%)	723 (59.2)	206 (56.3)	517 (60.5)	.203
No, n (%)	498 (40.8)	160 (43.7)	338 (39.4)	.154
The ratio of LDL-C target level achievement				
LDL-C at target, n (%)	320 (26.2)	90 (24.6)	230 (26.9)	.425
The ratio of LDL-C target level achievement in high-dose statin group				
LDL-C at target, n (%)	229 (27.2)	56 (15.3)	173 (20.1)	.046
Ezetimibe, n (%)	36 (2.9)	6 (1.6)	30 (3.5)	.078
Duration of statin therapy				
3 - 6 months, n (%)	201 (16.5)	53 (14.5)	148 (17.3)	.234
6-12 months, n (%)	233 (19.1)	65 (17.8)	168 (19.6)	.462
>1 year, n (%)	787 (64.5)	247 (67.7)	540 (62.8)	.122

The most prevalent reason for not using a guideline-recommended intensity statin was physician preference (for women 22.4% and men 16.5% $P = .01$) (Table 3, Figure 3). The statin adherence of patients was high in the study population. Most of them (78.7%) declared that they receive their statin medication daily (Table 3). Among patients with very high risk, 58.4% of them used guideline-recommended high-intensity statin therapy, while among those with high risk, the percentage was 44.4%. Despite using guideline-recommended intense statin therapy, only 24.5% of patients classified as very high risk and 34.9% of those classified as high risk were able to reach guideline-recommended LDL-C targets. Only 18.3% of patients who did not use a target dose statin had LDL-C level at target. Among patients classified as very high risk, 54.3% of females and 59.8% of males were using target dose statin therapy, while among those classified as high risk, the rates were 40% for females and 55% for males. Female patients with very high risk reached LDL-C target levels at a rate of 20.4%, while male patients in the same risk category achieved this at a rate of 25.9%. In the high-risk category, 27.5% of female patients and 50% of male patients reached LDL-C target levels (Table 4). Baseline laboratory values of the patients are depicted in Table 5.

Table 3. The Reasons for Not Using Target Dose of Statin and Statin Adherence of the Patients

Reasons	All Patients	Female	Male	*P*
n (%)	1225	366 (29.9)	859 (70.1)	–
Adverse events, n (%)	39 (3.2)	9 (2.5)	30 (3.5)	.345
Older age, n (%)	10 (0.8)	4 (1.1)	6 (0.7)	.482
Comorbidities, n (%)	6 (0.5)	3 (0.8)	3 (0.3)	.280
LDL-C at target, n (%)	102 (8.3)	26 (7.1)	76 (8.8)	.311
Patient preference, n (%)	77 (6.3)	17 (4.6)	60 (7.0)	.122
Physician preference, n (%)	224 (18.3)	82 (22.4)	142 (16.5)	.014
Unknown, n (%)	96 (7.8)	27 (7.4)	69 (8.0)	.695
Statin use	**All patients**	**Female**	**Male**	***P***
n (%)	1225	366 (29.9)	859 (70.1)	–
Every day, n (%)	958 (78.7)	286 (79.0)	672 (78.6)	.972
> 4 days in a week, n (%)	118 (9.7)	40 (11.0)	78 (9.1)	.315
3-4 days in a week, n (%)	107 (8.8)	27 (7.4)	80 (9.3)	.271
< 3 days in a week, n (%)	28 (2.3)	8 (2.2)	20 (2.3)	.878

LDL-C, low-density lipoprotein cholesterol.

DISCUSSION

This real-life study showed that most of the patients followed in cardiology outpatient clinics are far from the recommended LDL-C targets. In our observational study, 26.2% of the study population have reached target LDL-C levels according to their risk SCORE. Among patients with very high risk, 58.4% of them used guideline-recommended high-intensity statin therapy, while among those with high risk, the percentage was 44.4%. Only 24.5% of patients who had very high risk and only 34.9% of patients who had high risk reached LDL-C targets, respectively, despite using target dose statin. Most of our patients (64.5%) had been using statins for over 1 year. Furthermore, over half of both female and male patients at very high risk were using a high-intensity statin regimen.

Additionally, even though more than half of both female and male patients at very high risk were using a high-intensity statin regimen, only 20.4% of female patients and 25.9% of male patients at very high risk achieved target LDL-C levels. Female patients tended to be less likely to use high-intensity statins. Compliance with treatment was similar between men and women. Furthermore, the statin adherence of the patients to statin treatment was high in the study population but the most prevalent reason for not using a target dose

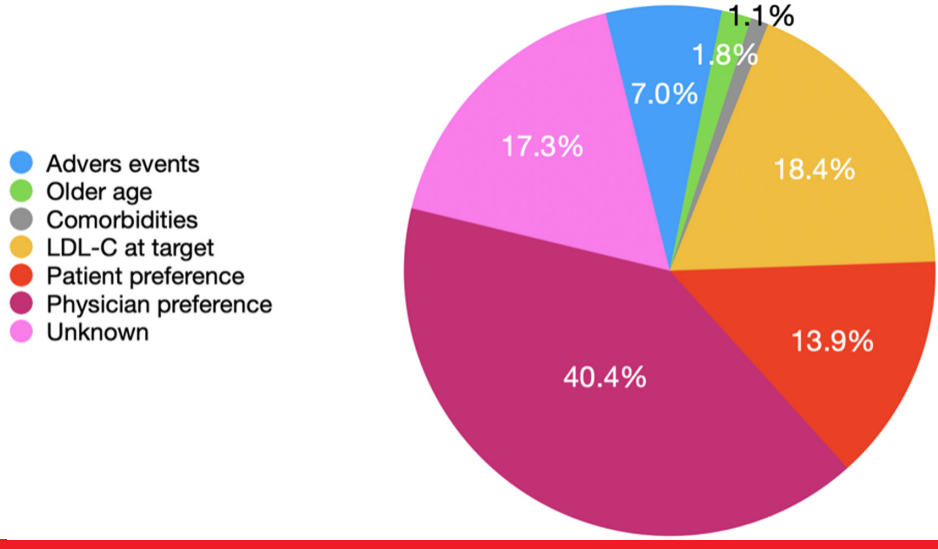

Figure 3. The reasons for not using target dose of statin.

Table 4. Target Dose Statin Usage Ratio of Very High and High-Risk Groups and the Ratio of Achieving Target LDL-C Level in Patients Using Target Dose Statin

SCORE Risk Groups	Target Dose Statin Use Ratio				LDL-C at Target			
	All Patients, n (%)	Female, n (%)	Male, n (%)	*P*	All Patients, n (%)	Female, n (%)	Male, n (%)	*P*
Very high risk	649 (58.4)	157 (54.3)	492 (59.8)	.105	272 (24.5)	59 (20.4)	213 (25.9)	.062
High risk	27 (45)	16 (40)	11 (55.0)	.270	21 (35)	11 (27.5)	10 (50.0)	.084

LDL-C, low-density lipoprotein cholesterol.

statin was physician preference. Physicians were more reluctant to prescribe guideline-directed dose of statin for female patients.

Dyslipidemia is among the most significant risk factors for ASCVD. Current guidelines emphasize maintaining low LDL-C levels, particularly for patients at very high and high cardiovascular risk. In real-world daily clinical practice, most of the patients could not reach target LDL-C levels according to their risk score due to some reasons such as physician inertia, poor patient compliance, some adverse effects, and comorbid conditions.[9]

Most of the patients in the AIZANOI study had very high risk, and we included the patients who had been already on statin treatment for at least 3 months duration. Most of them had been using it for more than 1 year. The aim of this study was to test adherence to dyslipidemia guidelines in patients who were still on statin treatment. The patients who did not use statins were not included in this study,; therefore, evaluation of the reasons for not to start statin medication is out of scope of this study.

Dyslipidemia constitutes a major public health problem in Türkiye. Several national registries and meta-analysis had been conducted to describe the prevalence of major cardiovascular risk factors. These surveys revealed that the prevalence of hypercholesterolemia was 29.1% in Türkiye.[10,11]

In a recent review from Türkiye, Kızılırmak et al[12] investigated the effect of statin therapy on LDL-C levels in Turkish population over published 39 full-text articles in the literature from Türkiye. They concluded that only %15 of the patients reached LDL-C below 70 mg/dL. EUROASPIRE V also showed that only 42.3% of the patients who were started on high-intensity statins at discharge of an acute coronary syndrome continued to use high-dose statins during the follow-up, and the statin dose was reduced or completely discontinued in 20.8% of the patients during the 6-month follow-up. Only 29% of 8261 patients had reached the guideline-recommended LDL-C levels. The main reason for dose reduction was stated as physician preference at 36.8% and the development of drug-related side effects at 15.8%. High-intensity statin therapy was used at a lower rate in Türkiye than in many other countries and only 19.3% of patients had LDL-C <70 mg/dL in secondary prevention.[13,14] These results emphasize the existence of variations between countries for the management of dyslipidemia. Türkiye was among the few countries in which high-intensity statin usage ratio was low. The most important factor for these results might be physician inertia. This underlines that standard of care is crucial issue to achieve targets. We need to implement strong strategies to improve the education and increase the awareness of physicians to reach guideline targets. Given that the AIZANOI study was conducted in cardiology outpatient clinics, this research underscores both the absence of current information regarding LDL-C target levels and the inertia observed among cardiologists in taking appropriate actions.

Table 5. Laboratory Values

Values	Mean ± SD	Minimum	Maximum	Median
Glucose (mg/dL)	130.7 ± 57.4	65	433	110
Total cholesterol (mg/dL)	162.4 ± 46.2	67	391	155
LDL-C (mg/dL)	87.1 ± 39.1	14	259	80
HDL-C (mg/dL)	44.8 ± 11.6	15	118	43
Non-HDL-C (mg/dL)	117.6 ± 34.6	52	273	112
Triglycerides (mg/dL)	162.5 ± 87.3	45	391	140
AST (mg/dL)	22.3 ± 10.4	5	146	20
ALT (mg/dL)	23.4 ±18.2	4	350	20

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-C, high- density lipoprotein; LDL-C, low-density lipoprotein cholesterol.

In the United States, less than 50% of patients who had acute ASCVD were treated according to recommendations of ACC/AHA dyslipidemia guidelines.[15] In the EPHESUS study, Mert et al investigated the reasons for poor lipid target attainment in real life cardiology practice. Of note, Ephesus is a country-wide observational study conducted in 40 cardiology centers in Türkiye between 2016 and 2018. The current guideline was the 2016 European Society of Cardiology (ESC)/European Atherosclerotic (EAS) Guidelines for the Management of Dyslipidemias during EPHESUS when LDL-C targets were <70 mg/dL for very high-risk group and <100 mg/dL for high-risk patients.[16] In the EPHESUS study, only 18% of patients achieved LDL-C levels below guideline targets. In the AIZANOI study, overall 26.2% of patients reached LDL-C targets. Despite using guideline-recommended target doses of statins, only 24.5% of patients classified as very high risk and 34.9% of patients classified as high risk reached LDL-C targets. Achieving the ratio of LDL-C target in the AIZANOI study was higher than the EPHESUS study despite EPHESUS study using previous dyslipidemia guidelines in which the target LDL-C levels were higher than the current dyslipidemia guideline. These results may imply that the LDL-C control is getting better in cardiology practice in Türkiye. As the AIZANOI study was performed during the pandemic, patients might have been more adherent to statin

therapy during the pandemic. Adherence to statin during the pandemic might explain the higher rate of reaching target the LDL-C level despite lower LDL-C target levels in AIZANOI study than in EPHESUS study. In the EPHESUS trial, high-intensity statin usage was 35.7% for LDL-C off target group and 40.4% for LDL-C on target group.[17] In the AIZANOI study, 58.4% of patients who had very high risk and 44.4% of patients who had high risk used guideline-directed intensity statin (high-dose statin). In the AIZANOI study, higher usage of high-intensity statin, especially in patients who had very high risk may explain the higher achievement of target LDL-C levels in our study. However, ezetimibe use was low in both studies, which may indicate that cardiologists' knowledge of ezetimibe needs to be increased.

The most commonly used statin regimen was atorvastatin 40-80 mg (40.8%) followed by atorvastatin 10-20 mg (30.8%) and rosuvastatin 20-40 mg (17.4%). The AIZANOI study showed that 59.2% of patients had been using guideline-directed intensity statin. 58.4% of patients who have very high SCORE risk and 44.4% of patients who have high SCORE risk use guideline-directed intensity statin (high-intensity statin) according to guidelines. Despite 58.4% of very high-risk patients and 44.4% of high-risk patients were using guideline-directed intensity statin regimens, only 24.5% of very high-risk patients and only 34.9% of high-risk patients could reach guideline-recommended LDL-C levels. In our study, the utilization rate of ezetimibe was notably low, with only 2.9% of patients using it. In Türkiye, the Social Security Institution reimburses ezetimibe if the target LDL-C level is above 100 in patients who have been on statins for at least 6 months. This might be a major reason for low ezetimibe use in Türkiye. Moreover, only cardiologists, endocrinologists, cardiovascular surgeons, and neurologists may recipe high-dose statin in Türkiye. Because statin therapy was initiated mostly by a cardiologist in the AIZANOI study, this was not a limitation of this study.

The causes of non-adherence to guidelines are various. Some are related to patients and some are related to physicians. Three main factors take a role in compliance and adherence to guidelines with statin therapy. (1) initiation of statin at the appropriate dose, (2) drug dose titration to reach the target LDL-C level, and when necessary, switching to combination with non-statin cholesterol-lowering drugs, and (3) ensuring continuity of treatment and persistence in treatment.[18]

In our study, the main reason for not using a target dose statin was physician preference. Physician inertia was one of the major factors in non-adherence to guidelines. Physician inertia means physicians' failure to start the treatment or intensify the dose of the medication. Similarly, Krempf et al[19] revealed that physicians tended to prescribe suboptimal doses of statin to most patients, and they gave few patients to high-dose statin, especially when LDL-C was far from target. Generally, we see that physicians are reluctant to prescribe potent statins in real practice. There may be some reasons for this inertia: one reason might be concerns about adverse side effects of statins. Our results also provide information about statin intolerance. The proportion of adverse statin reactions was minimal. In the EPHESUS study, the most important reason for discontinuation of statin therapy was media programs. The other and the most important reason may be to ignore the importance and effect of statins on ASCVD unintentionally due to lack of time during daily practice. Large number of patients and lack of time during daily outpatient clinics do not allow the physician to spare enough time to implement guideline recommendations for each patient. In each visit, physicians should communicate with the patients to inform them about the importance of the statin and the goals to prevent cardiovascular events to improve adherence and prevent treatment discontinuation.

In a retrospective study, investigators included 1360 patients with acute myocardial infarction and collected lipid parameters within 24 hours of admission and within 1 year after discharge. 36.9% and 18.2% of patients reached the LDL-C targets according to 2016 and 2019 ESC /EAS guidelines, respectively. They emphasized the need for combination of statin and non-statin lipid-lowering therapies.[20] Another study of the same investigator group evaluated adherence to guidelines in prescribing statins at discharge and to assess patient adherence to statin therapy during a 1-year follow-up period after hospitalization for acute coronary syndrome. Complete adherence to guideline was only 17.8%. As a result, the compliance with guidelines was low.[21]

A higher proportion of male patients were utilizing a high-intensity statin regimen, with a ratio of 72.5%, compared to 61.9% for females ($P < .001$). Despite the higher rate of reaching the target LDL-C level in males (26.9%) compared to females (24.6%), this difference did not reach statistical significance. Despite the comparable efficacy demonstrated between more-intensive and less-intensive statins for both sexes, systematic analyses consistently reveal a noteworthy disparity: women consistently exhibit a lower likelihood than men of being prescribed statin therapy for the secondary prevention of ASCVD.[22-24] AIZANOI study also emphasized that despite ongoing initiatives to minimize sex-based variations in guideline-recommended therapy, women consistently maintain a lower likelihood than men of complying with a prescription for high-intensity statins. The significant difference of physician preferences between male and female patients supports this result.

Despite clear evidence demonstrating the effectiveness and safety of high-intensity statin therapy for both men and women with clinical ASCVD, there remains a discrepancy in the intensity of statin dosage between the both sexes. Recent findings from a meta-analysis of individual participant data from 5 randomized controlled trials showed that more-intensive statin regimens, compared to less-intensive ones, led to a 29% reduction in the risk of recurrent major vascular events in men and a 25% reduction in women per 38 mg/dL reduction in LDL-C. There was no significant difference in treatment efficacy between men and women.[25]

A meta-analysis including 53 studies showed that females had 10% risk of statin non-adherence.[26] Another study of women demonstrated that women were less adherent to

statin therapy than men.[27] Noteworthy gender-specific factors contributing to statin non-adherence include reduced awareness of ASCVD risk among women, increased risk of statin intolerance among women, and the added burden of family caregiving responsibilities. Similar to limitations observed in the broader literature, there is insufficient incorporation of gender-specific analyses in statin-related trials. Disparities in statin adherence based on gender can be attributed to factors at the physician level, psychosocial influences, and medication intolerance. Interventions aimed at enhancing statin adherence should consider gender-specific challenges, such as women experiencing increased ASCVD risk at older ages, encountering higher rates of statin intolerance, and potentially facing greater caregiving obligations.[28] In Turkish Nationwide SurvEy of Glycemic and Other Metabolic Parameters of Patients with Diabetes Mellitus (TEMD Study), 37% of patients with type 2 diabetes mellitus LDL-C levels are < 100 mg/dL in only 37% of the patients. In TEMD study, there was a female predominance in patients who did not attain target LDL-C levels ($P < .001$).[29] When we compare these results with our study, patient compliance with statin treatment was similar between men and women in AIZANOI study. More than half of both female and male patients at very high risk were using a high-intensity statin regimen, there was statistically significant difference in attaining guideline-directed LDL-C levels between male and female patients (20.4% of female patients and 25.9% of male patients). The most important reason for failure to attain target LDL-C levels in female patients was physician inertia.

Despite widespread statin use, a substantial proportion of patients fail to achieve target LDL-C levels, indicating a discrepancy between guideline-directed therapy and clinical outcomes. Furthermore, our study underscores the importance of addressing physician inertia and gender disparities in statin prescription practices. Physician preference emerged as a prominent barrier to adherence to guideline-recommended therapy, highlighting the need for targeted interventions to overcome this inertia. Healthcare systems should strive to implement gender-sensitive approaches to dyslipidemia management, ensuring equitable access to guideline-directed therapy for all patients.

Strengths and Limitations

The main limitation of our study was that 9 participating centers from 4 different geographical regions were not widely distributed across Türkiye. Despite large sample size, our study captured the western part of the country, therefore it is impossible to generalize the results to the whole country. Also our results cannot be generalized to primary care or internal medicine as we mostly included cardiologists. However, as the cardiologists are expected to be the most aware group of physicians about the association of ASCVD and getting the LDL-C targets, our results could be much better than the other physician's practice. The lack of a validated survey might be accepted as another limitation.

Another limitation of our study was the lack of baseline LDL-C level in our database. We could not evaluate 50% decrease in LDL-C level from baseline with statin therapy.

CONCLUSION

In cardiology practice in Türkiye, despite an improvement in achieving LDL-C targets compared to previous studies, we are still far from aligning with guideline recommendations. Despite the increase in the usage of high-intensity statins, monotherapy continues to impede reaching the target goals. Physician inertia seems to be the major obstacle in the implementation of guideline recommendations in cardiology practice.

Although patient compliance with statin treatment was similar between men and women, there was a difference in attaining guideline-directed LDL-C levels between male and female patients. The most important reason for failure to attain target LDL-C levels in female patients was physician inertia. Physicians tend to prescribe high-intensity statins to female patients at a lower rate compared to male patients.

Ethics Committee Approval: The AIZANOI study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients gave written informed consent to participate. This study was approved by Kütahya Health Sciences University Non-invasive Studies Ethics Committee (decision number: 2021/12-17; date: July 8, 2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Supplementary Table 1. Patient Risk Categories According to SCORE Risk Model, Target LDL-C Levels According to Risk Groups and Statin Intensity Categories

Very high risk	**High risk**	**Moderate risk**	**Low Risk**
Documented ASCVD (MI or unstable angina; stable angina, PCI, CABG, CAD, Stroke, TIA, PAD)	**LDL-C > 190 mg/dL BP > 180/110 mm Hg**	**DM+<10 year duration+no RF and young patient**	**SCORE < 1%**
Significant **plaque** on **coronary angiography** or **CT** scan or on **carotid ultrasound**	**DM+>10 year duration / plus RF**	**SCORE 1-5%**	
DM+OD/3RF/>20 year	**Moderate CKD** (eGFR 30-50 ml/min/1.73 m^2)		
Severe CKD (eGFR < 30ml/min/1.73 m^2)	**SCORE 5-10 %**		
FH+1 RF			
SCORE > 10%			

ASCVD; atherosclerotic cardiovascular disease, PCI; Percutaneous coronary intervention, CABG; coronary artery bypass grefting, CAD; coronary artery disease, TIA; transient, ischemic attack, PAD; Peripheral artery disease, CT; Computerized Tomography, DM; Diabetes mellitus, OD; organ damage, RF; risk factor, CKD; chronic kidney disease, GFR; glomerular filtration rate, FH; familial hypercholesterolemia, LDL-C; low-density lipoprotein cholesterol, BP; blood pressure, SCORE; Systematic Coronary Risk Estimation

Target LDL-C levels according to risk groups

	LDL-C target levels	**Target statin intensity**
Very high risk	55mg /dl and 50%↓	High intensity statin
High risk	<70 mg/dL and 50%↓	High intensity statin
Moderate risk	<100mg/dL	Moderate intensity statin
Low risk	<115 mg/dL	

LDL-C; low-density lipoprotein cholesterol,

Statin intensity categories

	High intensity statin	**Moderate intensity statin**	**Low-intensity statin**
Atorvastatin	40-80 mg	10-20 mg	
Rosuvastatin	20-40 mg	5-10 mg	
Pitavastatin		1-4 mg	
Pravastatin		40-80 mg	10-20 mg
Simvastatin		20-40 mg	10 mg