Received: 16 March 2019 | Revised: 9 April 2019 | Accepted: 26 April 2019

DOI: 10.1111/ijcp.13358

ORIGINAL PAPER

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE WILEY

The reasons of poor lipid target attainment for secondary prevention in real life practice: Results from EPHESUS

Gurbet Özge Mert[1] | Özcan Başaran[2] | Kadir Uğur Mert[3] | Volkan Doğan[2] | Bülent Özlek[2] | Oğuzhan Çelik[2] | Eda Özlek[2] | Cem Çil[2] | İbrahim Halil Özdemir[4] | İbrahim Rencüzoğulları[5] | Fatma Özpamuk Karadeniz[6] | Lütfü Bekar[7] | Müjdat Aktaş[8] | Mübariz Murat Resulzade[9] | Macit Kalçık[7] | Gökhan Aksan[10] | Göksel Çinier[11] | Kadriye Akay[12] | Nihat Pekel[13] | Utku Şenol[14] | Murat Biteker[2] | Meral Kayıkçıoğlu[15]

[1]Department of Cardiology, Eskişehir Yunus Emre State Hospital, Eskişehir, Turkey

[2]Department of Cardiology, Faculty of Medicine, Muğla Sıtkı Koçman University, Muğla, Turkey

[3]Department of Cardiology, Faculty of Medicine, Eskişehir Osmangazi University, Eskişehir, Turkey

[4]Department of Cardiology, Nizip State Hospital, Gaziantep, Turkey

[5]Department of Cardiology, Faculty of Medicine, Kafkas University, Kars, Turkey

[6]Department of Cardiology, Erzurum Regional Training and Research Hospital, Erzurum, Turkey

[7]Department of Cardiology, Faculty of Medicine, Hitit University, Çorum, Turkey

[8]Department of Cardiology, Faculty of Medicine Regional Training and Research Hospital, Kocaeli University, Kocaeli, Turkey

[9]Department of Cardiology, Private Hospitalpark Hospital, Kocaeli, Turkey

[10]Department of Cardiology, Sıslı Hamıdıye Etfal Research and Training Hospital, İstanbul, Turkey

[11]Department of Cardiology, Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Center, İstanbul, Turkey

[12]Department of Cardiology, Kocaeli State Hospital, Kocaeli, Turkey

[13]Department of Cardiology, Tekden Private Hospital, Denizli, Turkey

[14]Department of Cardiology, Eskisehir Acıbadem Hospital, Eskişehir, Turkey

[15]Department of Cardiology, Ege University Faculty of Medicine, İzmir, Turkey

Abstract

Objective: There are lack of studies considering the suboptimal management of dyslipidemia especially in cardiology outpatient clinics. This study was conducted to assess the patient adherence to cholesterol treatment recommendations and attainment of low-density-lipoprotein cholesterol (LDL-C) goals.

Methods: EPHESUS (NCT02608645) is a national, observational and multicenter registry which has been designed as a cross-sectional study to allow inclusion of all consecutive patients with hypercholesterolemia in cardiology outpatient clinics. The present subgroup analyses of the EPHESUS trial included patients with known peripheral artery disease or atherosclerotic cerebrovascular disease, and coronary heart disease namely secondary prevention.

Results: The present analysis of the EPHESUS study included 1482 patients (62.79 ± 10.4 years, 38.2% female) with secondary prevention from 40 sites in Turkey. Regarding recommended lipid targets for LDL-C, only 267 patients (18%) were below the target of 70 mg/dL. Females were significantly more off-target when compared with male patients (396, 85.5% vs 67, 14.5%; $P = 0.017$). Moreover, the achievement of LDL-C goal was significantly decreased with illiteracy (233, 19.2% vs 35, 13.1%; $P = 0.02$). Patients who think that the cholesterol treatment should be terminated when the cholesterol level of a patient has normalised were higher in the off-target group (34.0% vs 24.7%, $P < 0.001$). Besides, physician perceptions about LDL-C goal for secondary prevention were significantly related with LDL-C target attainment.

Conclusions: EPHESUS is an important study with large population in terms of representing real-life practice of the adherence to dyslipidemia guidelines in secondary prevention patients in Turkey. Perceptions, knowledge, and compliance with the guidelines for secondary prevention have increased, but it is far below from the

Correspondence
Gurbet Özge Mert, Department of Cardiology, Eskişehir Yunus Emre State Hospital, Uluönder Mah., Salih Bozok Cd. No: 23, 26190 Tepebaşı/Eskişehir, Turkey.
Email: gozgeyun@gmail.com

desired levels even in cardiology outpatient clinics. There is a need for patients' and physicians' education regarding the treatment of hyperlipidemia.

1 | INTRODUCTION

A strong and direct association between low-density-lipoprotein cholesterol (LDL-C) and cardiovascular morbidity and mortality has been demonstrated.[1,2] Statins are the first-line therapy in individuals with elevated cholesterol levels,[3-6] based on their efficacy in reducing coronary heart disease (CHD) and mortality.

In Turkey, CHD and stroke are the leading causes of death and disability for both males and females, together causing 35%–38% of all deaths.[7] Despite Turkey having the largest young population among European countries, prevalence of atherosclerotic vascular disease is comparable to the rest of Western Europe.[8] Furthermore, median age of index coronary events was markedly lower for the Turkish arm of the EUROASPIRE IV survey.[9] In addition, when compared with European data on patients with CHD, incidence of elevated levels of LDL-C above the guideline target was higher in Turkey.[9] Dyslipidemia is the leading cause of early atherosclerotic vascular disease in Turkey.[10,11]

The majority of multicentre studies and surveys of guideline-based LDL-C goal attainment in Turkey have been performed in academic centres.[9,12,13] Standard of care in these tertiary centres is probably higher than in the rest of Turkey. The Evaluation of Perceptions, Knowledge and Compliance with the Guidelines for Secondary Prevention in Real Life Practice: A Survey on the Undertreatment of hypercholeSterolemia (EPHESUS) trial evaluated patient adherence to cholesterol treatment and attainment of LDL-C goals in Turkey. We included both secondary and tertiary outpatient clinics in our analysis of data from this study in order to provide a better representation of daily clinical practice. In addition, only a few studies that consider the perceptions of patients or care-givers regarding cardiovascular prevention. Therefore, we sought to reveal the underlying reasons for failure to attain LDL-C goal levels by evaluating perceptions of patients and physicians.

What's already known

- A strong and direct association between low-density-lipoprotein cholesterol (LDL-C) and cardiovascular morbidity and mortality. However, there is limited data regarding LDL-C goal attainment for secondary prevention patients in Turkey.
- Hyperlipidemia is the leading cause of early atherosclerotic vascular diseases. Statins are the first-line therapy in individuals with elevated cholesterol levels.
- LDL-C levels are far above desired levels, even in cardiology outpatient clinics, and despite guidelines for intensive LDL-C reduction in secondary prevention to levels of 0.8-1.8 mmol/l.

What's new

- Despite extensive evidence demonstrating a clear benefit from statin therapy, LDL-C target levels were only obtained in 18% of our secondary prevention patients.
- The major parameters associated with a failure to achieve LDL-C target levels in secondary prevention were female gender and illiteracy.
- The study demonstrated there was a need for further education of patients and physicians regarding the treatment of hyperlipidemia.

2 | MATERIALS AND METHODS

The EPHESUS study (Clinical Trials.gov identifier NCT02608645) was a national, observational and multicentre study. It was designed as a cross-sectional study, including all patients with hypercholesterolemia in cardiology outpatient clinics from 40 centres. The rationale and design of the EPHESUS trial was described previously.[14] The local ethics committee approved the study protocol and all participants gave written informed consent. Inclusion criteria included being ≥18 years of age at the time of enrollment, willing to participate and provide written informed consent, and were patients in very high-risk primary and secondary prevention of peripheral artery disease, atherosclerotic cerebrovascular disease and CHD.

Exclusion criteria included a history of acute coronary syndrome within the last 30 days, current pregnancy or those 0-6 months postpartum, renal failure with creatinine levels >265 μmol/L, history of liver or muscle disease and those who had not had a lipid profile measured within the last 6 months.

Demographic and clinical characteristics were recorded, including age, gender, educational status, medical history relating to cardiovascular disease, and classic cardiovascular risk factors, such as hypertension, type 2 diabetes and smoking status. Physical examination and current treatment for hypercholesterolemia of participants were also reported. The use of lipid lowering treatment (LLT) and its dose were noted. Atorvastatin at 40 and 80 mg, and rosuvastatin at 20 and 40 mg daily were considered high-intensity statin therapies.

Fasting venous blood was drawn to determine total cholesterol, and LDL-C, HDL-C and triglyceride levels.

A survey was conducted on the perception and awareness of both patients and physicians. The patient-specific and physicians-specific surveys included 10 and 7 questions on hypercholesterolaemia, respectively (Data S1 and S2).

Subgroup analyses in this study used data from the EPHESUS trial that included patients with known peripheral artery disease, atherosclerotic cerebrovascular disease and CHD, namely those requiring secondary prevention. CHD was defined as a history of myocardial infarction, coronary revascularisation or angiographic evidence of stenosis in one or more coronary arteries >50% of the luminal diameter. LDL-C<1.8 mmol/l (<70 mg/dL) was adopted as the treatment goal for patients under secondary prevention, aligned with the 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidaemias.[15] The perceptions, laboratory findings, demographics and clinical characteristics of patients, and the perceptions of physicians, were compared with attainment of this LDL-C goal.

2.1 | Turkey's healthcare system

The healthcare system in Turkey consisted of a mixture of public and private health services. Turkey provided national healthcare under the National Health Insurance system. All residents registered with the Social Security Institution received medical care free of charge from allied hospitals. Statin treatment was effectively free to a substantial proportion of patients for secondary prevention. Statin therapy could be initiated by primary care physicians; however, more complex patients and those requiring secondary prevention dealt with a cardiologist.

2.2 | Statistical analysis

Continuous variables were summarised by median and interquartile range, or mean ± standard deviation (SD). The variables were tested for normal distribution by the normality test of Shapiro-Wilk. The Mann-Whitney *U* test was used for the analysis of non-normally distributed variables. Categorical variables were expressed as frequencies and percentages. Univariate analysis was performed for continuous variables, and chi-squared or Fisher exact tests were applied for categorical variables. Correlation between variables was assessed by Pearson or Spearman tests. IBM SPSS Statistics, Version 21.0 (IBM Corp., Armonk, NY) was used for analyses, and a $P < 0.05$ was considered significant.

3 | RESULTS

A total of 267 (18%) out of 1482 patients had LDL-C levels below the 1.8 mmol/l target set for this study. Four hundred and fifteen patients (28%) had LDL-C levels ranging from 1.8 to 2.6 mmol/L (70-100 mg/dL), while 800 patients (54%) had levels >2.6 mmol/L (>100 mg/dL; Figure 1). Mean age of the population was 62.79 ± 10.4 years. Table 1 compares patients below the LDL-C target level (on-target group) with those who have not attained this goal (off-target group). Baseline demographics and characteristics were similar between the two groups, except for gender and educational status. Male patients were significantly more on-target with regard to LDL-C levels than female patients, with 200 males (19.6%) compared to 67 females (14.5%; $P = 0.017$). In addition, achievement of the LDL-C goal was significantly decreased by illiteracy, with 233 19.2% patients with higher education attaining the required level compared to 35 (13.1%; $P = 0.02$) from the lesser educated grouping (Table 1). Moreover, a significant correlation between illiteracy and female gender was demonstrated ($r = 0.366$, $P < 0.001$; Figure 2). All lipid parameters were lower, and statin use was higher in the on-target group compared to patients in the off-target group ($P < 0.001$; Figure 3). High-intensity statin therapy (atorvastatin 40-80 mg, rosuvastatin 20-40 mg) was similar for the two groups (282, 35.7% and 95, 40.4%, respectively; $P = 0.191$).

Statin treatment was most often initiated by cardiologists (1103, 74%), followed by internists (251, 16.9%), family practitioners (57, 3.8%) and specialists and neurologist (19, 1.3%). However, 428 patients (28.9%) had discontinued statin treatment at least once in the past. Negative media information about statins (138, 9.3%) was the most common reason for treatment discontinuation, followed by problems of drug access (95, 6.5%) and physician recommendations (83, 5.6%; Table 2).

3.1 | Comparison of patients' perceptions in attaining the LDL-C target

The patient-specific survey revealed that approximately half of the patients in the LDL-C off-target group (624, 51.4%) were aware that

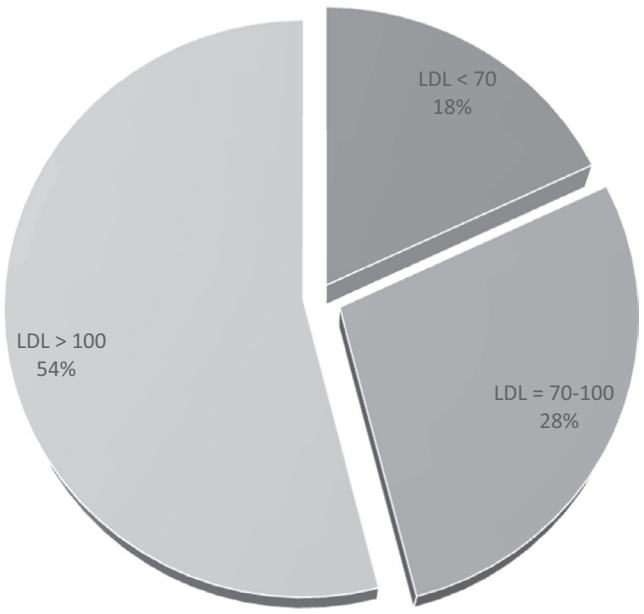

FIGURE 1 Low-density-lipoprotein cholesterol (LDL-C) target attainment of the patients

TABLE 1 Patient demographics, characteristics and comorbid features

Demographic properties, n = 1482	LDL off-target, n = 1215	LDL on-target, n = 267	*P* value
Age, y	63.2 ± 10.6	63.6 ± 10.8	0.783
Female	396 (32.6)	67 (25.1)	0.007
Body mass index (kg/m^2)	28.0 (25.4-30.9)	27.7 (24.9-30.4)	0.126
Smoking (%)	316 (26.0)	62 (23.2)	0.344
Place of residence, rural	357 (29.5)	74 (27.7)	0.555
Family history for coronary heart disease	501 (41.9)	112 (42.3)	0.903
Educational status			
Illiterate	233 (19.2)	35 (13.1)	0.02
Primary school	544 (44.8)	138 (51.7)	0.04
Secondary school	162 (13.3)	31 (11.6)	0.449
High school	185 (15.2)	39 (14.6)	0.798
University or higher	89 (7.3)	23 (8.6)	0.471
Comorbidities			
Atrial fibrillation	79 (6.5)	19 (7.1)	0.715
Chronic obstructive pulmonary disease	205 (16.9)	53 (19.9)	0.245
Chronic renal disease	81 (6.7)	25 (9.4)	0.122
Diabetes Mellitus	471 (38.8)	100 (37.5)	0.690
Hypertension	837 (68.9)	176 (65.9)	0.345
Coronary heart disease	1170 (96.3)	263 (98.5)	0.068
Coronary bypass	307 (25.3)	63 (23.6)	0.568
Congestive heart failure	218 (18.2)	44 (16.7)	0.554
Peripheral vascular disease	66 (5.4)	8 (3.0)	0.098
Carotid arterial disease	120 (9.9)	17 (6.4)	0.073
Stroke/Transient ischemic attack	75 (6.2)	10 (3.8)	0.128
Medication			
Asetilsalisilic asid	1017 (83.7)	235 (88)	0.078
Anticoagulant therapy	76 (6.3)	11 (4.1)	0.179
High density statin	282 (35.7)	95 (40.4)	0.191
Statins	799 (65.8)	237 (88.8)	<0.001
Fenofibrate	44 (3.6)	12 (4.5)	0.498
Oral antidiabetics	381 (31.4)	81 (30.3)	0.744
Insulin	187 (15.4)	39 (14.6)	0.747
Beta blocker	944 (77.7)	219 (82.0)	0.119
ACE inhibitors/ARBs	818 (67.3)	181 (67.8)	0.883
Calcium channel blockers	197 (16.2)	48 (18.0)	0.482
Digoxin	23 (1.9)	6 (2.2)	0.705
Bio-chemical parameters			
Total cholesterol (mmol/L)	5.02 (4.30-5.85)	3.34 (2.95-3.60)	<0.001
LDL cholesterol (mmol/L)	2.90 (2.38-3.68)	1.5 (1.27-1.68)	<0.001
HDL cholesterol (mmol/L)	1.11 (0.96-1.32)	1.06 (0.88-1.27)	<0.001
Triglycerides (mmol/L)	1.76 (1.29-2.43)	1.46 (1.07-1.94)	<0.001
Fasting blood glucose (mmol/L)	5.94 (5.33-7.77)	5.94 (5.33-7.27)	0.993
Aspartate aminotransferase (μkat/L)	0.35 (0.28-0.47)	0.35 (0.28-0.43)	0.563
Alanine transaminase (μkat/L)	0.33 (0.25-0.48)	0.35 (0.27-0.48)	0.625
Creatinine Kinase (μkat/L)	1.27 (0.75-2.1)	1.2 (0.65-2.05)	0.201

Abbreviations: Ace inhibitor, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; CV, Cardiovascular; HDL, High Density Lipoprotein; LDL, Low Density Lipoprotein.

their cholesterol levels were high; however, only 26.6% (79) were aware in on-target group, with the difference between the groups being statistically significant ($P < 0.001$). Even so, only 31.4% of the off-target patients and 37.5% of the on-target patients knew their cholesterol levels. (Table 3).

Patients' knowledge was better in the on-target group compared to those in the off-target group. The percentage of patients who thought that treatment should be terminated when the cholesterol level of a patient has normalised was higher in the off-target group (34.0% vs 24.7%, $P < 0.001$). The percentage of the patients who thought that long-term cholesterol medication caused diabetes mellitus, cancer, dementia, liver or kidney damage was similar for both groups. Most of the patients (94.8%) in the on-target group stated that they took their medication every day, compared to 73.1% of the off-target group ($P < 0.001$; Table 4). Notably, there was a correlation between taking the medicine regularly as prescribed and LDL-C target attainment ($r = 0.223$, $P < 0.001$).

3.2 | Comparison of the perceptions of physicians

One question focused on hypercholesterolaemia on the physician-specific survey asked, "Was the target LDL-C level for this patient reached?" Of 1473 patients, 260 (21.5%) were not on-target when

TABLE 2 Reasons of the discontinuation statin treatment on at least one occasion in the past (n = 428, 28.9%)

	n	%
Media programs	138	32.2
Physician recommendations	83	19.4
Problems related to drug access	97	22.7
Adverse effects	28	6.5
Resting liver	35	8.2
Reached LDL-C target	47	11.0

Abbreviation: LDL-C, low-density-lipoprotein cholesterol.

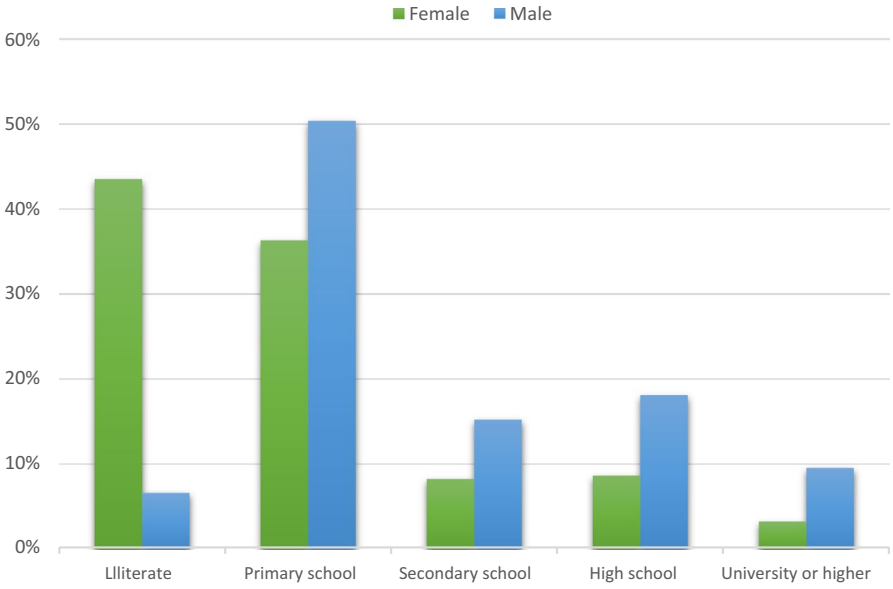

FIGURE 2 Educational status among gender

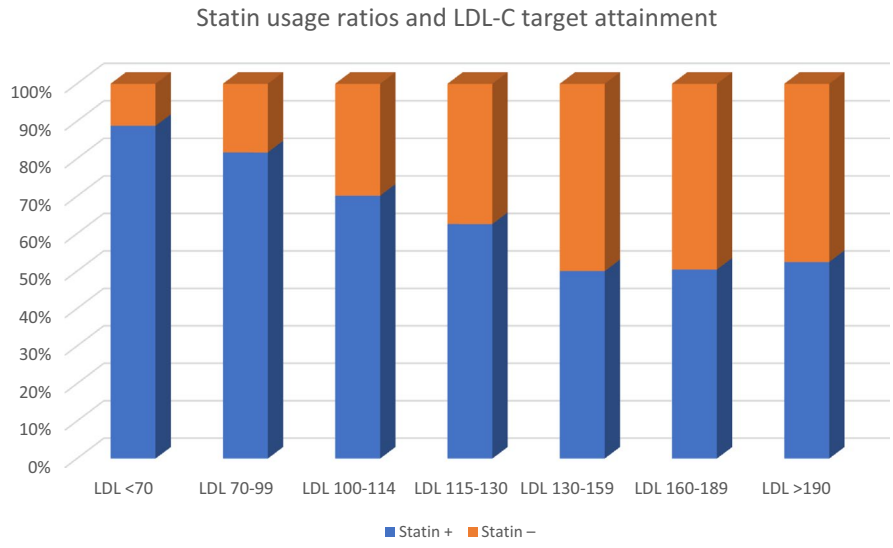

FIGURE 3 Statin usage ratios and LDL-C target attainment

TABLE 3 Questions about patient perceptions

Questions	LDL off-target	LDL on-target	*P*
• Is your cholesterol level high? yes[a]	624 (51.4)	79 (29.6)	<0.001
• Do you know your cholesterol level? yes	381 (31.4)	100 (37.5)	0.054
• If the cholesterol level of a patient has normalised, should cholesterol treatment be terminated? yes	413 (34.0)	66 (24.7)	<0.001
• Are exercise and diet safer and more effective than drugs to reduce cholesterol level? yes	453 (37.3)	103 (38.6)	0.907
• Does receiving cholesterol medication for a long-time cause liver or kidney damage? yes	401 (33.0)	85 (31.8)	0.509
• Does receiving cholesterol medication for a long-time cause diabetes mellitus or cancer? yes	117 (9.6)	20 (7.5)	0.427
• Does receiving cholesterol medication for a long-time cause dementia? yes	104 (8.6)	27 (10.1)	0.451
• Do you think you have a healthy diet? yes	704 (57.9)	178 (66.7)	0.009

[a]Sensitivity 29.6%, Specifity 48.6%.

TABLE 4 Questions about physician perceptions

Questions	LDL off-target	LDL on-target	*P*
Was the target low-density lipoprotein cholesterol level for this patient reached? Yes[a]	260 (21.5)	248 (93.6)	<0.001
If the patient is not on statin treatment, had he/she been prescribed statin • Yes, but he/she quit.	403 (33.2)	25 (9.4)	<0.001
Does the patient take the statin every day? • Every day, regularly	560 (73.1)	221 (94.8)	<0.001

[a]Specifity 78.5%, Sensitivity 93.6%.

their physicians thought that they had LDL-C levels < 1.8 mmol/l. Conversely, 17 (6.4%) of the patients were on-target when their physicians thought they had LDL-C levels > 1.8 mmol/l. Even so, physician perceptions were significantly related with LDL-C target attainment ($r = 0.582$, $P < 0.001$).

4 | DISCUSSION

Despite extensive evidence demonstrating a clear benefit from statin therapy, the LDL-C target was achieved in only 18% of our secondary prevention patients. The major factors correlating with a failure to achieve the LDL-C goal in secondary prevention patients were female gender and illiteracy. In our population, nearly two-fifths of female patients were illiterate and three-quarters of illiterate patients were women. Similar to these findings, two-thirds of the world's illiterate adults are women, according to a United Nations' global report.[16] While literacy rates have improved globally, 30% of women and 19% of men over the age of 65 were found to be illiterate, with those affected not getting the support they need later in life to improve this component of quality of life. There is a strong relationship between increased literacy rates and better health and healthy behaviours.

Treatment of LDL-C to <1.8 mmol/L (<70 mg/dL) can be expected to confer protection against future cardiovascular disease. Therefore, intensive LDL-C reduction in levels of 0.8-1.8 mmol/L (30-70 mg/dL) should be pursued in subjects with or at high risk of CHD.[17] The ESC lipid guidelines focus on LDL-C as the primary treatment goal for CHD and emphasise the importance of attaining these targets.[15] However, a significant proportion of patients in clinical practice do not reach target LDL-C levels.[18-22] For example, in the lipid treatment assessment project (L-TAP), consisting of 4888 patients from five regions of the United States, target LDL-C levels and lipid parameters were only reached in 18% of patients with CHD.[23] Of patients at very high risk of CHD in the Centralised Pan-Middle East Survey on the Undertreatment of Hypercholesterolemia (CEPHEUS), conducted in 29 countries,, only 22.8% of participants were found to have attained the LDL-C goal of <1.8 mmol/L (<70 mg/

dL).[24] The results of the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV survey concerning LLT in 7998 CHD patients similarly revealed that only a fifth of patients had achieved the LDL-C treatment goals.[25] In addition, in the recently published EUROASPIRE V, which was a survey of secondary prevention in Europe, only 29% of 8261 patients had achieved the LDL-C target, despite four-fifths of the patients being on LLT, mainly statins.[26] We demonstrated similar levels of LDL-C target attainment levels in EPHESUS, with similar patient characteristics as the aforementioned studies, namely those requiring secondary prevention. However, results from the Turkish arm of EUROASPIRE IV showed that targeted LDL-C levels were not attained in 91.7% of the patients,[9] which was lower than for the full Europe arm of EUROASPIRE-IV and for our study. The differences in target attainment in this study compared to the Turkish arm of EUROASPIRE IV could be due to the four-fold higher sample size in our study, which might represent a more complete representation of daily practice in Turkey.

Failure to achieve the LDL-C target was high in the female population in EUROASPIRE IV Europe (female, 84.4% vs male, 79.2%), as well as for the EUROASPIRE IV Turkish arm (female, 100% vs male, 90.1%).[9,25] These findings were consistent with results in the current study (female, 85.5% vs male, 80.4%). The basis for these results needs further assessment. For example, perceptions and adherence to the guidelines for secondary prevention might be improved by disease-specific and population-based educational policies.

It has been demonstrated by recent meta-analysis of epidemiological studies on cardiovascular risk factors that mean LDL-C levels and the prevalence of hypercholesterolemia in the Turkish population are lower than for many western populations.[11] Despite the lower LDL-C levels in the Turkish population, the majority of highly treatment-adherent cohorts failed to achieve adequate LDL-C reduction. In spite of high adherence to therapy, the failure to achieve the recommended LDL-C levels might be due to insufficient dosing, and the use of low to standard efficacy statins.[24] The cohort of Dyslipidemia International Study II (DYSIS II) also showed a high prevalence of hyperlipidemia in patients admitted to hospital with acute coronary syndrome.[27] In addition, achievement of the recommended LDL-C goal was found to be unsatisfactory. However, the mean statin dosage was low for individuals at very high cardiovascular risk.[27] Even so, high dose statin therapy was not related to LDL-C target level attainment in this study. High dose statin therapy could be detrimental for patient adherence due to a higher frequency of side effects.[20]

In Turkey, CHD mortality rates fell by 31% between 1995 and 2008, which was similar to falls reported in Western countries. Small mortality reductions were also explained by the treatment of hypertension (5%), by statin use in primary prevention (4%) and by heart failure treatment in hospitals (3%).[28] Mortality reductions were mostly attributed to a decrease in the prevalence of smoking, also explaining approximately 9725 fewer CHD deaths overall.[28] Otherwise, population mean cholesterol did not change significantly in Turkey between 1995 and 2008, a 0.02% increase in the population mean cholesterol level resulting in 355 more deaths.[28] Stable trends or slight decreases in cholesterol levels were also observed in several other Eastern European countries, including Tunisia and Iran, where statin treatments for primary prevention in people with high cholesterol reduced the number of deaths by 725.[28] Furthermore, Tokgözoğlu et al recently analysed patients with hypercholesterolaemia who had previously discontinued statin treatment on at least one occasion.[12] They revealed that approximately three quarters of patients made their decision to stop statin treatment based on misinformation from traditional broadcasts about statin side effects, and also because they got inadequate information from physicians about higher cholesterol levels and related risks. It was shown that patients with a higher educational status were more prone to discontinue statin therapy.[12] Similarly in the EPHESUS study, negative information about statin treatment disseminated by media programs and problems related to drug access were the most common reasons for discontinuing treatment. Awareness of physicians of the LDL-C target clearly helped patients attain this level, though specificity in the communication should be increased. Patients in the off-target group knew that their LDL-C level was high; however, the majority also believed that treatment should be terminated after cholesterol levels normalised. In addition, on-target patients thought that they had a healthy diet.

A possible reason for the LDL-C target attainment being so low might be that Turkey lacks nurse and physician-based prevention clinics for patients after myocardial infarction or revascularisation. It was shown that specialised prevention clinics were most effective for the management of cardiovascular risk factors after acute coronary syndromes.[29] The data of EUROASPIRE III for the Turkish subgroup revealed that more than half of the patients showed increased physical activity, and only 7.3% were involved in the cardiac rehabilitation program after the index event. In comparison with European results, these levels were markedly low.[13] More closely monitored and regular follow-up in outpatient clinics, which specialised in secondary prevention, would likely be more successful compared with standard clinics.

4.1 | Limitations

Despite the relatively large sample size, this study only provided a snapshot of patient characteristics; therefore, it did not provide information regarding the course of hyperlipidemia and outcomes. However, it provided clinical data regarding LDL-C target attainment during secondary prevention. The study was conducted in cardiology outpatient clinics because it was expected that the frequency of follow-up and those reaching the LDL-C target level would be greater than in primary care and internal medicine clinics, which might have limited coverage in Turkey. However, participating institutions were geographically widely distributed across Turkey, and both secondary and tertiary centres were represented. The fact that patient consent was obtained, might lead to the selection of a more motivated population, inducing a positive selection bias. This same

bias might also be applied to the participating physicians. The questionnaires used in this study were only for exploratory purposes, and were not validated for the Turkish population. There are no data on the use of proprotein convertase subtilisin/kexin type 9 serine protease (PCSK9) inhibitors, because of problems with reimbursement and approval for use in Turkey.

5 | CONCLUSION

EPHESUS, besides its large population, was an important study in assessing adherence to dyslipidemia guidelines in secondary prevention patients in Turkish outpatient clinics. Even though LDL-C levels <1.8 mmol/L (<70 mg/dL) have been shown to confer protection against future cardiovascular events, this target was achieved in only 18% of our study population. Female gender and illiteracy were major obstacles to LDL-C target attainment in secondary prevention patients. Negative information about statins, disseminated by the media and problems related to drug access were the most common reasons for discontinuing treatment. Health care policies, including accurate media coverage, should aim to improve awareness of the reasons why patients and physicians are not currently able to achieve recommended LDL-C levels. Educational strategies are more efficient and cheaper than new drug development. In addition, governments with an interest in removing barriers to health-related target attainment should make reducing illiteracy a priority.

ACKNOWLEDGEMENTS

The authors would like to thank participating centers and participants for their contribution to the study: Participating centers: Gaziemir State Hospital, Department of Cardiology, İzmir Medikal Park Hospital, Department of Cardiology, Aydın State Hospital, Department of Cardiology, Fethiye State Hospital, Department of Cardiology, Uşak State Hospital, Department of Cardiology, Burdur State Hospital, Department of Cardiology, Antalya Memorial Hospital, Department of Cardiology, Mersin University, Faculty of Medicine, Department of Cardiology, Mersin State Hospital, Department of Cardiology, Mut State Hospital, Department of Cardiology, Hatay İskenderun State Hospital, Department of Cardiology, Adana Numune Research and Training Hospital, Department of Cardiology, Eskisehir Acibadem Hospital, Department of Cardiology, Ankara Kecioren Research and Training Hospital, Department of Cardiology, Konya Research and Training Hospital, Department of Cardiology, Sivas Cumhuriyet University, Faculty of Medicine, Department of Cardiology, Samsun Research and Training Hospital, Department of Cardiology, İskilip Atıf Hoca State Hospital, Department of Cardiology, Trabzon Ahi Evran Thoracic and Cardiovascular Surgery Hospital, Department of Cardiology , Malatya State Hospital, Department of Cardiology, Luleburgaz State Hospital, Department of Cardiology, Kartal Kosuyolu Research and Training Hospital, Department of Cardiology, İstanbul Private Liv Hospital, Department of Cardiology, İstanbul Haydarpasa Research and Training Hospital, Department of Cardiology, Bagcilar Research and Training Hospital, Department of Cardiology, Gebze Fatih State Hospital, Department of Cardiology, Şanlıurfa Balıklıgöl State Hospital, Department of Cardiology, Diyarbakır Gazi Yaşargil Research and Training Hospital, Department of Cardiology. Participants: Mehmet Tekinalp, Ahmet Çağrı Aykan, Ezgi Kalaycıoğlu,İsmail Bolat,Onur Taşar,Özgen Şafak, Mehmet Yaman,,Sinan İnci,Bernas Altıntaş,Sedat Kalkan, Ahmet İlker Tekkesin, Yasin Çakıllı, Ceyhan Türkkan, Mehmet Hamidi, Vahit Demir, Mustafa Ozan Gürsoy, Müjgan Tek, Sabri Seyis, Mehmet Ballı, Mehmet Hayri Alıcı, Serdar Bozyel, Feyza Çalık, Oğuz Karaca, Füsun Helvacı, Yiğit Çanga, Savaş Çelebi, Emine Altuntaş, Mehmet Aytürk, Tahir Bezgin, Aytekin Aksakal, Beytullah Çakal, Ayşe Çolak, Özgür Kaplan, Adem Tatlısu, Gökhan Gözübüyük, Selami Demirelli, Adnan Kaya, Zübeyde Bayram, Zeki Şimşek, Murat Civan, Ali Ekber Ata, Gökhan Göl, Özkan Candan, Cem Doğan, Şeref Ulucan, Arif Arısoy, Nihat Pekel, Kerem Temel, Vehip Keskin, Erkan Gencer, Ahmet Doksöz, Mehrek Bahramişad, Utku Şenol, Lütfü Aşkın.

DISCLOSURES

None declared.

ORCID

Gurbet Özge Mert https://orcid.org/0000-0001-8350-9758

REFERENCES

1. Pekkanen J, Linn S, Heiss G, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Engl J Med*. 1990;322:1700-1707.
2. Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. *Arch Intern Med*. 2001;161:1413-1419.
3. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA*. 1999;282:2340-2346.
4. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267-1278.
5. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ*. 2009;338:b2376.
6. Besseling J, Hovingh GK, Huijgen R, Kastelein J, Hutten BA. Statins in familial hypercholesterolemia: consequences for coronary artery disease and all-cause mortality. *J Am Coll Cardiol*. 2016;68:252-260.
7. Akgun S, Rao C, Yardim N, et al. Estimating mortality and causes of death in Turkey: methods, results and policy implications. *Eur J Pub Health*. 2007;17:593-599.
8. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med*. 2006;3:e442.
9. Tokgozoglu L, Kayikcioglu M, Altay S, et al. European Society of Cardiology study of lifestyle, risk factors, and treatment approaches in patients with coronary artery disease: Data from Turkey]. *Turk Kardiyol Dern Ars*. 2017;45:134-144.

10. Tokgozoglu L, Baris KE. Atherosclerotic vascular disease and risk factors in Turkey: from past to present. *J Atheroscler Thromb*. 2008;15:286-291.
11. Kayikcioglu M, Tokgozoglu L, Kilickap M, et al. Data on prevalence of dyslipidemia and lipid values in Turkey: Systematic review and meta-analysis of epidemiological studies on cardiovascular risk factors. *Turk Kardiyol Dern Ars*. 2018;46:556-574.
12. Tokgozoglu L, Ozdemir R, Altindag R, et al. Patient characteristics and statin discontinuation-related factors during treatment of hypercholesterolemia: an observational non-interventional study in patients with statin discontinuation (STAY study). *Turk Kardiyol Dern Ars*. 2016;44:53-64.
13. Tokgozoglu L, Kaya EB, Erol C, Ergene O. [EUROASPIRE III: a comparison between Turkey and Europe]. *Turk Kardiyol Dern Ars*. 2010;38:164-172.
14. Dogan V, Basaran O, Ozlek B, et al. Rationale, design, and methodology of the evaluation of perceptions, knowledge, and compliance with the guidelines in real life practice: a survey on the under-treatment of hypercholesterolemia. *Turk Kardiyol Dern Ars*. 2018;46:47-53.
15. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J*. 2016;37:2999-3058.
16. Nations U. The World's Women 2015: Trends and Statistics. In: United Nations DoEaSA, Statistics Division, ed. New York; 2015.
17. O'Keefe JH, Cordain L, Jones PG, Abuissa H. Coronary artery disease prognosis and C-reactive protein levels improve in proportion to percent lowering of low-density lipoprotein. *Am J Cardiol*. 2006;98:135-139.
18. Kitkungvan D, Lynn Fillipon NM, Dani SS, Downey BC. Low-density lipoprotein cholesterol target achievement in patients at high risk for coronary heart disease. *J Clin Lipidol*. 2010;4:293-297.
19. Dopheide JF, Papac L, Schindewolf M, Baumgartner I, Drexel H. Poor attainment of lipid targets in patients with symptomatic peripheral artery disease. *J Clin Lipidol*. 2018;12:711-717.
20. Guglielmi V, Bellia A, Pecchioli S, et al. Effectiveness of adherence to lipid lowering therapy on LDL-cholesterol in patients with very high cardiovascular risk: a real-world evidence study in primary care. *Atherosclerosis*. 2017;263:36-41.
21. Yeh Y-T, Yin W-H, Tseng W-K, et al. Lipid lowering therapy in patients with atherosclerotic cardiovascular diseases: Which matters in the real world? statin intensity or low-density lipoprotein cholesterol level? data from a multicenter registry cohort study in Taiwan. *PLoS ONE*. 2017;12:e0186861.
22. Gotto AM Jr, Moon JE. Management of cardiovascular risk: the importance of meeting lipid targets. *Am J Cardiol*. 2012;110:3a–14a.
23. Pearson TA, Laurora I, Chu H, Kafonek S. The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med*. 2000;160:459-467.
24. Chiang C-E, Ferrières J, Gotcheva NN, et al. Suboptimal control of lipid levels: results from 29 countries participating in the centralized pan-regional surveys on the undertreatment of hypercholesterolaemia (CEPHEUS). *J Atheroscler Thromb*. 2016;23:567-587.
25. Reiner Ž, De Backer G, Fras Z, et al. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries–findings from the EUROASPIRE IV survey. *Atherosclerosis*. 2016;246:243-250.
26. Kotseva K, De Backer G, De Bacquer D, et al. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. *Eur J Prev Cardiol*. 2019;10:2047487318825350.
27. Yan BP, Chiang F-T, Ambegaonkar B, et al. Low-density lipoprotein cholesterol target achievement in patients surviving an acute coronary syndrome in Hong Kong and Taiwan - findings from the Dyslipidemia International Study II. *Int J Cardiol*. 2018;265:1-5.
28. Unal B, Sözmen K, Arık H, et al. Explaining the decline in coronary heart disease mortality in Turkey between 1995. *BMC Public Health*. 2013;13:1135.
29. Kilic S, Simsek E, Soner Kemal H, Yuce EI, Turkoglu C, Kayikcioglu M. The role of specialized prevention clinics for the short term follow-up of acute coronary syndromes. *Turk Kardiyol Dern Ars*. 2017;45:498-505.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Mert GÖ, Başaran Ö, Mert KU, et al. The reasons of poor lipid target attainment for secondary prevention in real life practice: Results from EPHESUS. *Int J Clin Pract*. 2019;73:e13358. https://doi.org/10.1111/ijcp.13358