ORIGINAL ARTICLE

Evaluation of perceptions, knowledge and compliance with guidelines in real-life practice: A survey on the under-treatment of hypercholesterolemia

Dislipidemi kılavuzuna uyumun, bilgi ve hasta algı düzeylerinin gerçek yaşamda saptanması

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ABSTRACT

Objective: Few studies have directly assessed suboptimal management of dyslipidemia in Turkey. This study was conducted to assess patients' understanding and perceptions of high cholesterol as well as physicians' knowledge and awareness of lipid management strategies.

Methods: This was a multicenter, observational study (ClinicalTrials.gov identifier: NCT02608645). Consecutive patients admitted to the participating cardiology clinics who were at least 18 years of age and who had been classified in a secondary prevention (SP) group or a high-risk primary prevention (PP) group were enrolled. The study population included 1868 patients from 40 sites in Turkey. Two-thirds (67.5%) of the patients in the SP group had been prescribed a statin, whereas only 30.1% of the PP group patients received statin therapy (p<0.001).

Results: It was determined that 18% of the SP patients and 10.6% of the PP patients had a low-density lipoprotein cholesterol level at the recommended level (p<0.001). A patient survey revealed that almost half of the patients in the PP and in the SP groups were aware that their cholesterol levels were high. Negative information about statin treatment disseminated by media programs was the most common reason (9.4%) given for treatment discontinuation.

Conclusion: Perceptions, knowledge and compliance with the guidelines for PP and SP patients in real-life practice have increased, but it remains far below the desired level. Patients and physicians should have more information about the treatment of hyperlipidemia. More accurate media programming could help to prevent the dissemination of misinformation.

ÖZET

Amaç: Türkiye'de dislipideminin suboptimal yönetimini az sayıda çalışma doğrudan değerlendirmiştir. Bu çalışma, hastaların yüksek kolesterol algısını ve lipit yönetim stratejileri ile ilgili olarak hekimlerin kolesterol hakkındaki bilgi ve farkındalığını değerlendirmek amacıyla yapıldı.

Yöntemler: Çalışma gözlemsel ve çok merkezli bir çalışmadır (ClinicalTrials.gov identifier: NCT02608645). En az 18 yaşında olan, kardiyoloji kliniklerine başvuran ikincil korunma (SK) grubunda ve çok yüksek, yüksek riskli birincil korunma (PK) grubundaki ardışık hastalar çalışmaya alındı. Çalışma popülasyonu, Türkiye'de 40 bölgeden 1868 hasta içermektedir. SK grubunda hastaların üçte ikisine (%67.5) statin verildi, PK hastalarının sadece %30.1'ine statin tedavisi verildi (p<0.001).

Bulgular: Düşük yoğunluklu lipoprotein kolesterol (LDL-C) düzeyi önerilen düzeyde olan hastaların oranı PK'da %10.6, SK'da %18 idi (p<0.001). Hastaya özgü anket, PK ve SK gruplarındaki hastaların neredeyse yarısının kolesterol seviyelerinin yüksek olduğunu bildiğini ortaya koydu. Medya programlarındaki statin tedavisi ile ilgili olumsuz bilgiler (%9.4) tedavinin kesilmesinin en yaygın nedeniydi.

Sonuç: Gerçek yaşam pratiğinde birincil ve ikincil korunma ile ilgili algı, bilgi ve uyum artmıştır, ancak istenen seviyelerin çok altındadır. Hastalar ve hekimler hiperlipideminin tedavisi hakkında daha fazla bilgi sahibi olmalıdır. Ayrıca, medya programlarını kontrollerinin sağlanması, hastaların yanlış bilgilendirilmesini önleyebilir.

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Elevated serum low-density lipoprotein cholesterol (LDL-C) is associated with increased cardiovascular disease morbidity and mortality.[1,2] Statins are the first-line therapy in all disorders of elevated cholesterol, as they have been shown to reduce the number of coronary heart disease (CHD) events and mortality in individuals with severe dyslipidemia.[3–6] The guidelines of the European Society of Cardiology (ESC) recommend a target LDL-C level of <70 mg/dL as a treatment goal.[7] The results of the EUROASPIRE IV (European Action on Secondary and Primary Prevention through Intervention to Reduce Events) survey concerning lipid-lowering therapy (LLT) in CHD patients showed that despite clear evidence of the benefits of lipid-lowering treatment with statins as a secondary prevention (SP) effort, many coronary patients with dyslipidemia are still inadequately treated and a significant number of patients using LLT are still not reaching LDL-C treatment goals.[8]

Turkey has a relatively young population in comparison with many Western societies. CHD has been reported to be the major cause of death and disability.[9] In 2016, 46.8% of deaths in Turkey were due to cardiovascular system diseases, while it was 42% in European Union countries.[10,11] Turkey ranked first among European nations in deaths caused by CHD among those under the age of 50; CHD occurred 10 years earlier compared with other European countries. In the Turkish arm of the EUROASPIRE III and IV studies, 20% and 19.3%, respectively, of the patients who experienced a coronary event were younger than 50 years of age.[12,13] The mean age of these patients was markedly younger than that reported in the EUROASPIRE-IV Europe study (62.5 years). Hyperlipidemia is likely one of the major risk factors for early CHD in the Turkish population. A recent meta-analysis revealed a prevalence of hypercholesterolemia, defined as a LDL-cholesterol level higher than 130 mg/dL, of 29.1%.[14] Furthermore, the incidence of an elevated level of LDL-C was greater among both men and women in Turkey when compared with European data. The EUROASPIRE IV Turkey study found that 49.6% of the Turkish participants had a high total cholesterol level, 53% had a high LDL-C level, 57.5 % had a low high-density lipoprotein cholesterol (HDL-C) level, and targeted LDL-C levels were not attained in 91.7% of the patients, even in the SP group. However, LLT drugs, such as statins, are widely reimbursed and the prices are very low in Turkey compared with other countries. The underlying reasons for such a low rate of LDL goal attainment is not known. There are only a few studies that have considered patients' or caregivers' perceptions of cardiovascular disease prevention in Turkey. The EPHESUS (Evaluation of Perceptions, Knowledge and Compliance with the Guidelines for Secondary Prevention in Real Life Practice: A Survey on the Under-treatment of Hypercholesterolemia) study aimed to evaluate patient adherence to cholesterol treatment recommendations and achievement of LDL-C goals in Turkey, as well as to assess physicians' perceptions and real-world experience with hypercholesterolemia.

Abbreviations:

CHD	*Coronary heart disease*
ESC	*European Society of Cardiology*
EPHESUS	*Evaluation of Perceptions, Knowledge and Compliance with the Guidelines for Secondary Prevention in Real Life Practice: A Survey on the Under-treatment of Hypercholesterolemia*
EUROASPIRE	*European Action on Secondary and Primary Prevention through Intervention to Reduce Events*
HDL-C	*High-density lipoprotein cholesterol*
LDL-C	*Low-density lipoprotein cholesterol*
LLT	*Lipid-lowering treatment*
PP	*Primary prevention*
SCORE	*Systemic Coronary Risk Estimation*
SP	*Secondary prevention*

METHODS

The design and rationale of the EPHESUS trial have been described in detail elsewhere.[15] In brief, the EPHESUS study (Clinical Trials.gov identifier NCT02608645) was designed as a cross-sectional study that created a national, observational, multicenter registry to allow for the inclusion of consecutive patients. This study was approved by the local ethics committees of the participating institutions, and all of the subjects who were included provided written, informed consent and were at least 18 years of age at the time of enrollment. The study was initiated on March 1, 2016 and the last patient was enrolled on January 1, 2018.

The Systemic Coronary Risk Estimation (SCORE) was used in the patient evaluation. The SP group comprised patients with peripheral artery disease, atherosclerotic cerebrovascular disease, or known CHD, including post-myocardial infarction patients or patients who had undergone percutaneous coronary intervention or coronary bypass surgery. The PP group was made up of those at very high risk: presence of diabetes mellitus with a major risk factor such as smoking, hypertension, or dyslipidemia; a SCORE calculation of ≥10% for 10-year risk of fatal cardio-

vascular disease; and those classified as high-risk: patients with type 2 diabetes who had no known prior CHD; markedly elevated single risk factors, in particular, cholesterol >310 mg/dL, blood pressure ≥180/110 mmHg, a SCORE assessment of 5%–10% for 10-year risk of fatal cardiovascular disease. Exclusion criteria were a history of acute coronary syndrome in the previous month, current pregnancy or postpartum status of <6 months, renal failure with a creatinine level of >3 mg/dL and a history of liver or muscle disease.

Demographic and clinical characteristics evaluated included age, gender, educational status, medical history related to cardiovascular disease, classic cardiovascular risk factors (hypertension, type 2 diabetes, smoking status), physical examination data, current treatment for hypercholesterolemia and other risk factors. The use of LLT and the dose of the drug was noted. Fasting venous blood was drawn to estimate the level of total cholesterol, LDL-C, HDL-C, and triglycerides. The prescription and adherence to statin use were analyzed according to the ESC guidelines.[16] Patients and physicians were surveyed to analyze perceptions and awareness of hypercholesterolemia. The patient survey was made up of 10 questions (Supplement 1) and the physician survey comprised 8 questions (Supplement 2).

The cost of statin therapy based on drug prices during the period when the study was conducted was also calculated.

Statistical analysis

The Kolmogorov-Smirnov or Shapiro-Wilk test was used to determine normal distribution. Continuous variables were summarized using the median and interquartile range or mean±SD. The Mann-Whitney U test was used for the comparison of nonparametric variables, and Student's t-test was used for parametric variables. Categorical variables were expressed as frequencies and percentages. Univariate analysis was performed for continuous variables and a chi-square or the Fisher exact test was applied for categorical variables. The Fisher exact test was used if at least 1 cell had a value <5, a chi-square test with continuity correction was applied if the cell value was 5–25, and Pearson's chi-squared test was applied if neither was applicable. A cross table with at least a 3 column or row likelihood ratio was used if at least 1 cell had a value <5, and Pearson's chi-squared test was used if all the values were >5. The correlation between nominal variables was calculated using chi-squared analysis with the phi coefficient. A p value of <0.05 was considered significant. All of the analyses were performed with the statistical package IBM SPSS Statistics for Windows, Version 24.0. (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 1868 consecutive adult patients (61.83±10.93 years; n=713, 38.2% female) were enrolled. Of 1868 patients, 386 (20.7%) had no prior history of atherosclerotic cardiovascular disease (PP group), whereas 1482 (79.3%) had 1 or more atherosclerotic vascular diseases (SP group). Of the 386 patients who were in the high-risk PP group, 286 (74.1%) had a very high risk and 100 (25.9%) were considered to have a high risk for cardiovascular disease (Fig. 1).

Comparison of baseline characteristics and medications in PP and SP groups

Baseline demographics and characteristics were generally different between the 2 groups (Table 1). As ex-

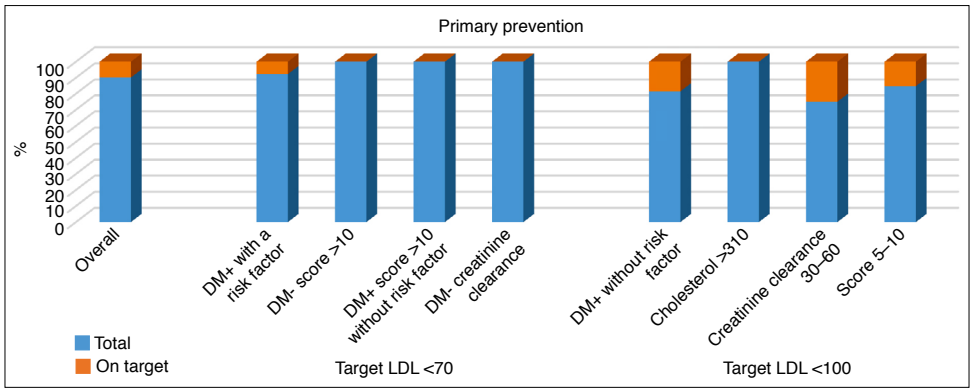

Figure 1. Very high-risk and high-risk primary prevention groups.

Table 1 . Patient demographics, characteristics and comorbid features

	Overall (n=1868)	Primary prevention (n=386)	Secondary prevention (n=1482)	*p*
Age (years), median (Q1–Q3)	61 (56–68)	59 (51–66)	63.5 (55–70)	<0.001
Female n/N (%)	713/1868 (38.2)	250/386 (64.8)	463/1482 (31.2)	<0.001
Body mass index (kg/m^2), median (Q1–Q3)	28.5 (25.5–31.5)	30.1 (26.6–33.8)	28.1 (25.3–31.1)	<0.001
Smoking n/N (%)	471/1868 (25.2)	93/386 (24.1)	378/1482 (25.5)	0.569
Educational status				
Illiterate n/N (%)	348/1864* (18.7)	80/385* (20.8)	268/1479* (18.1)	
Primary school n/N (%)	836/1864* (44.8)	154/385* (40.0)	682/1479* (46.1)	
Secondary school n/N (%)	234/1864* (12.6)	41/385* (10.6)	193/1479* (13.0)	0.038
High school n/N (%)	293/1864* (15.7)	69/385* (17.9)	224/1479* (15.1)	
University or higher n/N (%)	153/1864* (8.2)	41/385* (10.6)	112/1479* (7.6)	
Comorbidities				
Family history of CV disease n/N (%)	744/1844* (40.3)	131/382* (34.3)	613/1462* (41.9)	0.007
Atrial fibrillation n/N (%)	128/1868 (6.9)	30/386 (7.8)	98/1482 (6.6)	0.422
COPD n/N (%)	317/1868 (17)	59/386 (15.3)	258/1482 (17.4)	0.322
Chronic renal disease n/N (%)	130/1868 (7)	24/386 (6.2)	106/1482 (7.2)	0.596
Congestive heart failure n/N (%)	280/1843* (15.2)	18/382* (4.7)	262/1462* (17.9)	<0.001
Hypertension n/N (%)	1294/1868 (69.3)	281/386 (72.8)	1013/1482 (68.4)	0.092
Diabetes mellitus n/N (%)	873/1868 (46.7)	302/386 (78.2)	571/1482 (38.5)	<0.001
Stroke/TIA n/N (%)	101/1843* (5.5)	16/380* (4.2)	85/1463* (5.8)	0.274
Medication				
Antiplatelet therapy n/N (%)	1512/1868 (80.9)	130/386 (33.7)	1382/1482 (93.3)	<0.001
Anticoagulant therapy n/N (%)	109/1868 (5.8)	22/386 (5.7)	87/1482 (5.9)	0.995
Fenofibrate n/N (%)	71/1868 (3.8)	15/386 (3.9)	56/1482 (3.8)	1.000
Statin n/N (%)	1158/1868 (62)	122/386 (31.6)	1036/1482 (69.9)	<0.001
Oral antidiabetic n/N (%)	735/1868 (39.3)	273/386 (70.7)	462/1482 (31.2)	<0.001
Insulin n/N (%)	308/1868 (16.5)	82/386 (21.2)	226/1482 (15.2)	0.005
Beta blocker n/N (%)	1275/1868 (68.3)	112/386 (29.0)	1163/1482 (78.5)	<0.001
ACE inhibitor/ARB n/N (%)	1206/1868 (64.6)	207/386 (53.6)	999/1482 (67.4)	<0.001
Calcium channel blocker n/N (%)	317/1868 (17)	72/386 (18.7)	245/1482 (16.5)	0.323
Digoxin n/N (%)	36/1868 (1.9)	7/386 (1.8)	29/1482 (2.0)	1.000
Laboratory parameters				
Total cholesterol (mg/dL), median (Q1–Q3)	191 (155–229)	221 (188–259)	183 (149–219)	<0.001
LDL cholesterol (mg/dL), median (Q1–Q3)	110 (81–144)	139 (108–168)	103 (77–138)	<0.001
HDL cholesterol (mg/dL), median (Q1–Q3)	43 (36–51)	45 (39–52)	42 (36–50)	<0.001
Triglycerides (mg/dL), median (Q1–Q3)	153 (112–215)	168 (121–230)	150 (110–209)	<0.001
Fasting blood glucose (mg/dL), median (Q1–Q3)	111 (97–148)	131 (105–180)	108 (96–140)	<0.001
Creatinine (mg/dL), median (Q1–Q3)	0.88 (0.75–1.04)	0.8 (0.67–0.95)	0.9 (0.78–1.1)	<0.001
Aspartate aminotransferase UI/L, median (Q1–Q3)	21 (16–27)	20 (16–27)	21 (17–27)	0.485
Alanine transaminase UI/L, median (Q1–Q3)	21 (16–29)	23 (16–32)	20 (15–28)	0.001
Creatine kinase UI/L, median (Q1–Q3)	74 (44–124)	68 (46–108)	75 (44–126)	0.304

ACE inhibitor: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; COPD: Chronic obstructive pulmonary disease; CV: Cardiovascular; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TIA: Transient ischemic attack. *Missing value.

Table 2. Questions about patient perceptions

	Primary prevention	Secondary prevention	*p*
	n/N (%)	n/N (%)	
Is your cholesterol level high? Yes	202/386 (52.3)	703/1482 (47.4)	0.086
Do you know your cholesterol level? Yes	142/386 (36.8)	481/1482 (32.5)	0.108
If the cholesterol level of a patient has normalized, should cholesterol treatment be terminated? Yes	159/386 (41.2)	479/1482 (32.3)	0.001
Are exercise and diet safer and more effective than drugs to reduce cholesterol level? Yes	168/386 (43.5)	556/1482 (37.5)	0.031
Does using cholesterol medication for a long time cause liver or kidney damage? Yes	138/386 (35.8)	486/1482 (32.8)	0.272
Does using cholesterol medication for a long time cause diabetes mellitus or cancer? Yes	57/386 (14.8)	137/1482 (9.2)	0.002
Does using cholesterol medication for a long time cause dementia? Yes	35/386 (9.1)	131/1482 (8.8)	0.889
Do you think you have a healthy diet? Yes	183/386 (47.4)	882/1482 (59.5)	<0.001
Should patients using a statin take it every day? Yes	71/106* (67)	781/999* (78.2)	0.009

*Missing value.

pected, participants in the SP prevention group were older (63.5 vs 59 years; p<0.001) and were more likely to be male (68.8% vs 35%; p<0.001). The mean body mass index was higher in patients in the PP group than in those with documented atherosclerotic vascular disease (30.64±5.52 vs 28.55±2.25, respectively; p<0.001). More patients in the documented atherosclerotic vascular disease group than in the PP population had heart failure (17.9% vs 4.7%; p<0.001) and a family history of premature CHD (41.9% vs 34.3%; p=0.007). However, the prevalence of diabetes mellitus was significantly greater in PP patients than in SP patients. Participants in the SP group were less likely to be taking insulin (15.2% vs 21.2%; p=0.005) and oral antidiabetics (31.2% vs 70.7%; p<0.001). Compared with patients in the PP group, SP patients were more likely to use antiaggregants (93.3% vs 33.7%; p<0.001), anticoagulants (5.9% vs 5.7%; p=0.995), beta blockers (78.5% vs 29%; p<0.001), and angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers (67.4% vs 53.6%; p<0.001). Two-thirds (67.5%) of the patients in the SP group had been prescribed a statin, whereas only 30.1% of the PP patients received statin therapy (p<0.001).

All of the cholesterol parameters and fasting glucose and alanine transaminase levels were lower, but creatinine levels were higher in the SP patients compared with patients in the PP group.

Comparison of patient perceptions in PP and SP groups

The patient survey revealed that almost half of the patients in the PP and in the SP groups were aware that their cholesterol level was high. However, only 37% of the PP patients and 32.5% of the SP patients knew their cholesterol level (Table 2).

Patient knowledge was better in the SP group than the PP group; the percentage of patients who thought that cholesterol treatment should be terminated when the cholesterol level of a patient has normalized was greater in the PP group (41.2 vs 32.3%; p=0.001). The percentage of patients who thought that long-term cholesterol medication use causes diabetes mellitus, cancer, dementia, liver or kidney damage was greater in the PP patient group. Most of the patients (78.2%) in the SP group stated that they took their medication every day, but only 66.7% of the patients in the PP group stated that they took their medication regularly (p=0.008) (Table 3).

Analysis of physician perceptions

The physician survey focused on knowledge of hy-

Table 3. Questions about physician perceptions

	Primary prevention	Secondary prevention	*p*
	n/N (%)	n/N (%)	
Was the target low-density lipoprotein cholesterol level for this patient reached? Yes	102/378* (27)	508/1473* (34.5)	0.06
If the patient is not following statin treatment, was it prescribed? • Yes, but the patient discontinued use	101/252** (40.1)	274/434** (63.1)	<0.001
Does the patient take the statin every day? • Every day, regularly	71/106*** (66.7)	781/999*** (78.2)	0.008

*Missing value; **Missing value for patients not on statin; ***Missing value for patients on statin.

percholesterolemia. Clinicians were asked if the target LDL-C level for patients had been achieved. The patients were not on target and the physician reported that they were not on target in 1220 of 1851 (65.9%) cases, in 285 of 1851 (15.3%) cases, the patients were on target and the physician thought that they were on target, while in 325 of 1851 (17.5%), the patients LDL-C levels were not on target but the physician thought that they were, and in 21 of 1851 (1.1%) cases, the patients were on target but the physician thought that they were not on target.

Comparison of target attainment in PP and SP groups

In the PP group, 10.6% of the patients met the recommended LDL-C level (Fig. 1), and 18% of the patients in the SP group met the goal (p<0.001). However, when physicians were questioned regarding LDL-C targets, 102 (27%) of the PP and 508 (34.5%) of the SP patients were identified as meeting the target (p=0.006) (Table 3). There was a moderate correlation between physician perception and patients who met the target LDL-C (r=0.570; p<0.001).

In this study group, 400 (21.4%) patients used high-density statin therapy (atorvastatin 40–80 mg, rosuvastatin 20–40 mg). Of these, 97 (24.3%) patients were identified as having an LDL-C level that met the target.

Initiation and discontinuation of statin treatment

Statin treatment was initiated most frequently by cardiologists (n=1232, 66.2%), followed by specialists of internal medicine (n=444, 23.8%) and family medicine (n=68, 3.6%). A total of 602 patients (32.2%) had discontinued statin treatment on at least 1 occasion in the past. Negative information about statin treatment disseminated by media programs was the most common reason for treatment discontinuation (n=176, 9.4%), followed by physician recommendation (n=118, 6.3%), and problems related to drug access (n=108, 5.8%) (Fig. 2). Discontinuation of statin therapy was significantly different according to education level: Those with a mid-level formal education (at least secondary: n=248, 44.6%) were more likely to discontinue the medication compared with those with less (illiterate or only primary: n=354, 37.5%) (p=0.007). Discontinuation of medication use was lowest among university graduates (36.7%) and highest in those with a high school-level education

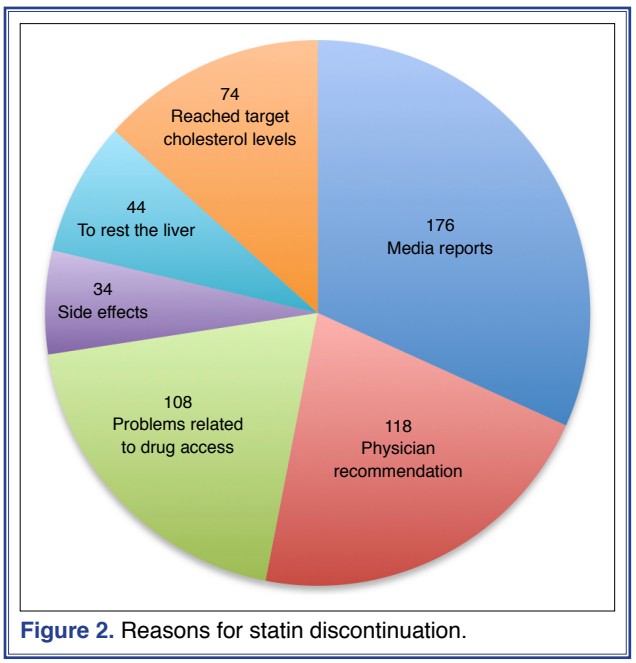

Figure 2. Reasons for statin discontinuation.

(51.5%). Treatment discontinuation was higher in the PP group (n=132, 61.7%) compared with the SP group (n=471, 36.5%) (p<0.001).

Cost of statin therapy

As part of the EPHESUS study, the mean cost of statin therapy for 1 month was calculated at USD 5.772 for the 1128 patients who were on statin therapy. The monthly cost of a high-density statin (atorvastatin 40-80 mg, rosuvastatin 20–40 mg) was calculated at USD 7.50 and the monthly cost of a medium-low-density statin (atorvastatin 10–20 mg, rosuvastatin 5–10 mg, pitavastatin 2–4 mg, pravastatin 10–20–40 mg, fluvastatin 40–80 mg, simvastatin 10–20–40–80 mg) was calculated at USD 4.40.

DISCUSSION

The ESC lipid guidelines focus on the LDL-C level as the primary treatment goal and strongly emphasize the importance of attaining these targets. In our study, a significant proportion of patients in clinical practice did not reach the target LDL-C level according to the guideline recommendations, and lipid parameters were under control in only 30% to 50% of the patients.[17] The results of the EPHESUS study indicated that the percentage of patients who were at the recommended LDL-C level was only 10.6% in the PP group and 18% in the SP group (p<0.001). These values are much lower than those seen elsewhere.

The EUROASPIRE III survey was conducted in 22 countries in Europe. There was a particular decrease in Turkey in the use of lipid-lowering drugs during follow-up compared with other European countries.[18] The EUROASPIRE IV Turkey study indicated that the targeted LDL-C level was attained by 8.3% of the patients. The EPHESUS study results showed that the targeted LDL-C level was reached by 18% of the SP patients.

Yiğiner et al.[19] assessed adherence to statin therapy and LDL-C goal attainment in type 2 diabetes and SP patients. The authors evaluated the data of 194 patients who had been on statin therapy for at least a year with a target LDL-C level of <100 mg/dL and found that the incidence of attaining the target was only 24%, and was lower among diabetic patients compared with SP patients. The rate of reaching the target value in this study was higher than that seen in the EPHESUS study. In both studies, the number reaching the target LDL-C value in the group with a secondary school education was higher, but not significantly sufficient. More patients who were educated to at least a high school level and patients who met the dietitian met the LDL-C goal. Intermittent drug discontinuation was seen in 109 patients (56.2%); the most common reason provided was the reduction of cholesterol levels to normal (35%).

In the EPHESUS study, discontinuation of statin therapy was significantly greater among those with a higher educational status (at least secondary school: n=248, 44.6%) compared with less formal education (illiterate or only primary school: n=354, 37.5%) (p=0.007) and negative information about statin treatment viewed in the media (n=176, 9.4%) was the most common reason cited for treatment discontinuation. In a recently published national, cross-sectional, non-interventional and observational study, Tokgözoğlu et al.[20] analyzed the data of 532 patients who had been diagnosed with hypercholesterolemia and had discontinued statin treatment on at least 1 occasion in the past. The authors found that the decision to discontinue statin treatment was made at the patient's discretion in 74% of the cases, and that patients with a higher education level were more likely to decide to discontinue treatment. They also reported that cardiologists were the physicians most frequently responsible for the initiation of the statin treatment, and that television coverage of several statin side effects and patients' lack of information regarding high cholesterol and the related risks were the leading factors in treatment discontinuation. These findings were similar to those of the EPHESUS study. However, in contrast to our study, Tokgözoğlu et al. investigated only patients who had discontinued statin therapy. We have demonstrated that statins were also underused in high-risk patients and that the LDL-C goal attainment was poor in a larger sample of Turkish population.

Conclusion

The EPHESUS study is the largest study to date in Turkey to evaluate adherence to dyslipidemia guidelines in high-risk PP and SP patients. The perceptions, knowledge, and compliance with the guidelines for PP and SP patients in real-life practice have increased, particularly the use of statins in the SP group, and the percentage of those achieving the target LDL-C is higher than in the PP group, but in a country like

Turkey, which provides broad repayment of conventional therapy, it is still not enough. Patients and physicians should have more information about the treatment of hyperlipidemia. In addition, more accurate media programming could prevent patients from being misinformed.

Limitations

Despite the relatively large sample size, the study population is not representative of all of the treated patients in Turkey. The need to obtain patient consent might have led to the selection of a more motivated population compared with those not willing to participate, inducing a positive selection bias. The same bias could be applied to the participating physicians. This study included patients with or at high risk for atherosclerotic cardiovascular disease, which might also have led to a selection bias and may explain the difference in the prevalence of categorical variables.

The questionnaires used were only for exploratory purposes and were not validated for the general Turkish population. The results of the EPHESUS study only reflect the perspective of cardiologists, as prescriptions from family physicians were not included. It is well known that a significant number of low-dose statins are prescribed by family physicians in Turkey.

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REFERENCES

1. Cui Y, Blumenthal RS, Flaws JA, Whiteman MK, Langenberg P, Bachorik PS, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. Arch Intern Med 2001;161:1413–9. [CrossRef]
2. Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, 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;322:1700–7. [CrossRef]

3. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
4. Besseling J, Hovingh GK, Huijgen R, Kastelein JJP, Hutten BA. Statins in Familial Hypercholesterolemia: Consequences for Coronary Artery Disease and All-Cause Mortality. J Am Coll Cardiol 2016;68:252–60. [CrossRef]
5. Brugts JJ, Yetgin T, Hoeks SE, Gotto AM, Shepherd J, Westendorp RG, 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. [CrossRef]
6. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 1999;282:2340–6. [CrossRef]
7. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al; ESC Scientific Document Group. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J 2016;37:2999–3058. [CrossRef]
8. Reiner Ž, De Backer G, Fras Z, Kotseva K, Tokgözoglu L, Wood D, et al; EUROASPIRE Investigators. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries-Findings from the EUROASPIRE IV survey. Atherosclerosis 2016;246:243–50. [CrossRef]
9. Ünüvar N, Mollahaliloglu S, Yardim N, Refik Saydam. Hygiene Center. School of Public Health, on behalf of The Ministry of Health of Turkey (MoH). Turkey Burden of Disease Study 2004. 1th ed. Ankara: MoH Publication; 2007. p. 4–8.
10. Turkish Statistical Institute. National Health Report of 2014. Turkey in Statistics 2014. Publication No: 4380. Ankara; 2014. Available at: http://www.turkstat.gov.tr/. Accessed Sep 2, 2016.
11. European Commission. Eurostat Death Statistics Report of 2011. Eurostat regional yearbook 2011. Luxemburg: Publications Office of the European Union; 2011. Available at: http://ec.europa.eu/eurostat/. Accessed Sep 2, 2016.
12. Tokgözoğlu L, Kaya EB, Erol C, Ergene O; EUROASPIRE III Turkey Study Group. EUROASPIRE III: a comparison between Turkey and Europe. [Article in Turkish]. Turk Kardiyol Dern Ars 2010;38:164–72.
13. Tokgözoğlu L, Kayıkçıoğlu M, Altay S, Aydoğdu S, Barçın C, Bostan C, et al. EUROASPIRE-IV: European Society of Cardiology study of lifestyle, risk factors, and treatment approaches in patients with coronary artery disease: Data from Turkey. [Article in Turkish]. Turk Kardiyol Dern Ars 2017;45:134–44. [CrossRef]
14. Tokgözoğlu L, Bariş Kaya E. Atherosclerotic vascular disease and risk factors in Turkey: from past to present. J Atheroscler Thromb 2008;15:286–91. [CrossRef]
15. Doğan V, Başaran Ö, Özlek B, Çelik O, Özlek E, Mert KU, 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. [CrossRef]
16. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al; ESC Scientific Document Group. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J 2016;37:2999–3058. [CrossRef]
17. 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;160:459–67. [CrossRef]
18. Catalan VS, LeLorier J. Predictors of long-term persistence on statins in a subsidized clinical population. Value Health 2000;3:417–26. [CrossRef]
19. Yiğiner O, Ozmen N, Ozçelik F, Inanç T, Kardeşoğlu E, Uz O, et al. Adherence to statin therapy and LDL cholesterol goal attainment in type 2 diabetics and secondary prevention patients: the role of education and knowledge. [Article in Turkish]. Turk Kardiyol Dern Ars 2010;38:544–50.
20. Tokgözoğlu L, Özdemir R, Altındağ R, Ceyhan C, Yeter E, Öztürk C, 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. [CrossRef]

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Supplement 1. Patient questionnaire

- What is cholesterol?
- Is your cholesterol level high?
- Do you know your cholesterol level?
- What causes high cholesterol?
- Do cholesterol levels cause symptoms?
- What kind of symptoms does one experience when their cholesterol level is elevated?
- Is high cholesterol dangerous?
- If the cholesterol level of a patient has normalized, should cholesterol treatment be terminated?
- Are there herbal methods to reduce cholesterol more safely and efficiently?
- If you were previously using a statin and stopped, why did you decide to terminate the treatment?
  - What I heard in media reports
  - Doctor recommendation
  - Problem obtaining the medication
  - Allergy or side effects
  - To keep liver healthy
  - Improvement in cholesterol levels

Supplement 2. Physician questionnaire

- What is the highest known low-density lipoprotein cholesterol level of the patient?
- Was the target low-density lipoprotein cholesterol level for this patient reached?
- If the patient did not reach the target cholesterol level, what might be the reason?
  - Not on statin treatment
  - On statin treatment but inadequate (e.g., low dose, non-adherent)
  - Not applying lifestyle changes
- If the patient is not on statin treatment, had he/she been prescribed statin therapy previously?
  - No
  - Yes, but he/she quit
- If the patient is on statin treatment, for how many months has he/she been on the therapy?
- Does the patient take the statin every day?
  - Every day, regularly
  - Not every day
- If the patient stopped the statin treatment, what was the reason?
  - Media reports
  - Physician recommendation
  - Problems related to drug access
  - Side effects
  - To keep liver healthy
  - Reached target cholesterol levels