ORIGINAL ARTICLE

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

EPHESUS (Kılavuzlara Uyumun, Bilgi ve Algı Düzeylerinin Gerçek Yaşamda Saptanması) çalışmasının temel, tasarım ve metodolojisi

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ABSTRACT

Objective: A wide gap exists between dyslipidemia guidelines and their implementation in the real world, which is primarily attributed to physician and patient compliance. The aim of this study is to determine physician and patient adherence to dyslipidemia guidelines and various influential factors.

Methods: The Evaluation of Perceptions, Knowledge, and Compliance with the Guidelines in Real Life Practice: A Survey on the Under-treatment of Hypercholesterolemia (EPHESUS) trial (ClinicalTrials.gov number NCT02608645) will be an observational, multicenter, non-interventional study. The study targets enrollment of 2000 patients from 50 locations across Turkey. All of the data will be collected in a single visit and current clinical practice will be evaluated. A cross-sectional survey of public perception and knowledge of cholesterol treatment among Turkish adults will be performed. All consecutive patients admitted to cardiology clinics who are in the secondary prevention group (coronary heart disease, peripheral artery disease, atherosclerotic cerebrovascular disease) and who are in the high-risk primary prevention group (type 2 diabetes mellitus with no prior known coronary heart disease; patients who had markedly elevated single risk factors, in particular, cholesterol >8 mmol/L [>310 mg/dL], blood pressure ≥180/110 mmHg, a calculated Systematic Coronary Risk Evaluation [SCORE] ≥5%, or <10% 10-year risk of fatal cardiovascular disease) will be included. Demographic, lifestyle, medical, and therapeutic data will be collected with a survey designed for the study.

Conclusion: The EPHESUS registry will be the largest study conducted in Turkey evaluating the adherence to dyslipidemia guidelines both in secondary and high-risk primary prevention patients.

ÖZET

Amaç: Dislipidemi kılavuzları ile gerçek dünyadaki uygulamalar arasında öncelikle doktor ve hasta uyumundan kaynaklanan geniş bir boşluk bulunmaktadır. Bu çalışma, hekimin ve hastanın dislipidemi kılavuzlarına ve onu etkileyen çeşitli faktörlere bağlılığını belirlemeyi amaçlamaktadır.

Yöntemler: EPHESUS (Kılavuzlara Uyumun, Bilgi ve Algı Düzeylerinin Gerçek Yaşamda Saptanması) çalışmasının temel, tasarım ve metodolojisi) gözlemsel, çok merkezli ve girişimsel olmayan bir çalışmadır. Çalışmada, Türkiye'de 50 birimden 2000 hastanın kayıt edilmesi hedeflenmiştir. Tüm veriler bir noktada toplanacak ve mevcut klinik uygulama değerlendirilecektir (ClinicalTrials.gov numarası NCT02608645). Türk erişkinlerde kolesterol tedavisi ile ilgili halkın algısı ve bilgisine ilişkin kesitsel bir araştırma yapılacaktır. Kardiyoloji kliniklerine başvuran ardışık, ikincil koruma grubunda (koroner kalp hastalığı, periferik arter hastalığı, aterosklerotik serebrovasküler hastalık) ve yüksek riskli birincil korunma grubunda (önceden bilinen koroner kalp hastalığı bulunmayan tip 2 diabetes mellituslu hastalar, belirgin bir şekilde tek risk faktörü artışı olan hastalar; kolesterol >8 mmol/L (>310 mg/dL) veya kan basıncı ≥180/110 mmHg veya hesaplanmış SCORE değeri 10 yıl için ölümcül kardiyovasküler hastalık riski ≥%5 ve <10% olanlar) olan tüm hastalar dahil edilecektir. Demografik, yaşam tarzı, tıbbi ve terapötik veriler bu özel anketle toplanacaktır.

Sonuç: EPHESUS kayıtları, hem ikincil korunma, hem de yüksek riskli hastalarda birincil korunmada dislipidemi kılavuzlarına uyumu değerlendiren en büyük çalışma olacaktır.

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Dyslipidemia is the most common atherosclerosis-associated risk factor.[1] Previous studies have demonstrated that lipid-lowering treatment, predominantly statins, can reduce cardiovascular adverse events in patients with atherosclerotic vascular disease.[1,2] The role of statins in the secondary prevention of cardiovascular morbidity and mortality has resulted in clinical guidelines recommending statin use for all adults with cardiovascular disease.[3,4] Statins are also effective in the primary prevention of cardiovascular disease for those at high risk, including patients with type 2 diabetes who had no known prior coronary artery disease, and those who had markedly elevated single risk factors, in particular cholesterol >8 mmol/L (>310 mg/dL), blood pressure (BP) ≥180/110 mmHg, a calculated Systematic Coronary Risk Evaluation (SCORE) ≥5%, or <10% 10-year risk of fatal cardiovascular disease.[3,4]

The European Society of Cardiology (ESC) lipid guidelines focus on low-density lipoprotein (LDL) cholesterol as the treatment goal and strongly emphasize the importance of attaining these targets. However, a significant proportion of patients in clinical practice could not reach their target LDL cholesterol level, and lipid parameters were under control in only 30% to 50% of patients according to the guideline recommendations.[5] The perception and attitude of general population to the management of dyslipidemia is critical for ensuring the effective translation of guideline-based medicine into real-life practice, but there are limited data on patient's beliefs about hyperlipidemia and adherence to treatment in this country. The European Action on Secondary and Primary Prevention through Intervention to Reduce Events (EUROASPIRE) III survey was conducted in 22 countries in Europe to describe the risk factors, demographic characteristics, lifestyle, and therapeutic management of patients with coronary artery disease and compliance with current guidelines.[6] The data from this survey revealed that the number of patients in follow-up 6 months after the index event was lower in Turkey. And there was a particular decrease in the use of lipid-lowering drugs during follow-up in Turkey compared with other European countries.[7] Hence, the Evaluation of Perceptions, Knowledge and Compliance with the Guidelines in Real Life Practice: A Survey on the Under-treatment of Hypercholesterolemia (EPHESUS) study will be conducted to examine the level of public awareness and to identify areas of misconception with regard to cholesterol management. The main objective of the EPHESUS study is to determine the perceptions of physicians and patients, and will focus on those who are at high risk of being undertreated according to current guidelines. These current guidelines reflect the importance of high cholesterol in cardiovascular outcomes, and also address perceived barriers to treatment of high cholesterol.

Abbreviations:

BP	*Blood pressure*
EPHESUS	*Evaluation of Perceptions, Knowledge, and Compliance with the Guidelines in Real Life Practice: A Survey on the Under-treatment of Hypercholesterolemia*
ESC	*European Society of Cardiology*
EUROASPIRE	*European Action on Secondary and Primary Prevention through Intervention to Reduce Events*
HDL	*High-density lipoprotein*
LDL	*Low-density lipoprotein*
SCORE	*Systematic Coronary Risk Evaluation*

METHODS

Study design

The EPHESUS study (ClinicalTrials.gov identifier NCT02608645) is a national, multicenter registry. This study was approved by the local ethics committee and all eligible consecutive patients who give written informed consent will be included.

Setting

This cross-sectional study will be conducted in outpatient cardiology clinics, and all data will be collected in a single visit. A total of 2000 patients from 50 sites aimed to be enrolled (Table 1). To ensure that there is adequate representation of the geographic diversity of Turkey, a proportional number of patients from the 7 different regions (Fig. 1) are to be included. State, university, education and research, and private hospitals will participate to incorporate patients treated in different healthcare settings. The study was initiated

Table 1. Design of the EPHESUS study

• Number of patients	2000
• Study type	Multicenter, cross-sectional
• Patient population	Secondary prevention
	High risk primary prevention

EPHESUS: Evaluation of Perceptions, Knowledge, and Compliance with the Guidelines in Real Life Practice: A Survey on the Under-treatment of Hypercholesterolemia.

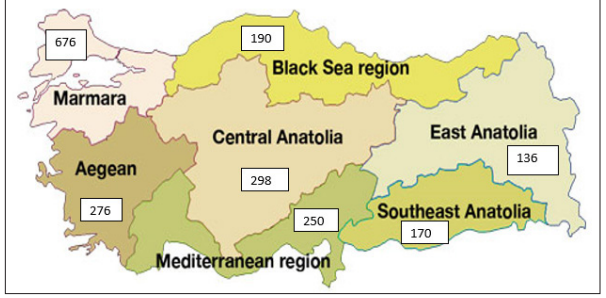

Figure 1. The geographic diversity of Turkey.

on October 1, 2016 and the last patient will be enrolled on October 10, 2017.

Inclusion criteria

The EPHESUS study will enroll both secondary and high-risk primary prevention adult patients aged 18 years or older. The high-risk primary prevention group includes patients with type 2 diabetes who had no known prior coronary artery disease, who had markedly elevated single risk factors, in particular, cholesterol >8 mmol/L [>310 mg/dL], blood pressure ≥180/110 mmHg, a calculated SCORE ≥5%, or <10% 10-year risk of fatal cardiovascular disease. Secondary prevention patients are those with known peripheral artery disease or atherosclerotic cerebrovascular disease, known coronary heart disease, including post myocardial infarction (acute myocardial infarction is defined as cardiomyocyte necrosis in a clinical setting consistent with acute myocardial ischemia) patients, patients who have undergone percutaneous coronary intervention, or who have undergone coronary bypass surgery. Diabetes mellitus will be defined as fasting plasma glucose >126 mg/dL, postprandial plasma glucose >200 mg/dL, or glycated hemoglobin A1c >6.5%, according to the 2012 American Diabetes Association definition. Patients who are diagnosed with diabetes and who are on medication will be included in the study regardless of their plasma glucose level. Imaging methods will determine the presence of coronary artery disease in patients with diabetes mellitus.

Exclusion criteria

The exclusion criteria will be a history of acute coronary syndrome within 1 month, pregnancy or within 6 months of the postpartum period, renal failure with creatinine >3 mg/dL, history of hepatic disease or myopathy, and no measurement within the last 6 months of total cholesterol, LDL-cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides.

Evaluation

Demographic and clinical characteristics of the participants recorded will include: age, gender, educational status, medical history focused on cardiovascular disease, cardiovascular risk factors (hypertension, type 2 diabetes, smoking status), physical examination details, and current treatment for hypercholesterolemia and other risk factors. The use of a statin and the dose of the drug will be noted. For biochemical analysis, routine fasting venous blood results will be assessed within 6 months before the registration date, including total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides. The laboratory parameters to be collected are total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, fasting plasma glucose, creatinine, aspartate aminotransferase, alanine aminotransferase, and creatine kinase. The demographic characteristics of the patients who will be included in EPHESUS study are summarized in Table 2.

Outcomes

The objective of the patient survey is to understand patient perceptions regarding (1) the significance of high cholesterol, (2) the barriers patients face in preventing atherosclerotic adverse events and managing their cholesterol, and (3) the degree to which patients are willing to take an active role in prevention and cholesterol management. The guidelines-based use of statins in eligible patients and reasons for not being on statin therapy will be analyzed based on responses to the questionnaire (Table 3).

The number of statin prescriptions and the level of adherence by patients will be analyzed according to the ESC guidelines (4). Nonadherence will be classified as:

1. Lack of patient understanding of the physician's instructions for taking the medication (use the statins for only a limited time, take the statins on alternate days, stop taking the statin after normalization of cholesterol levels, etc.),

2. Due to side effects, considering all those described for the medication, or

3. Nonutilization of the medication, in spite of having the prescription.

Table 2. Variables measured in the questionnaire

• Demographic information	Date of visit
	Date of birth
	Gender
	Height/weight
	Blood pressure
	Education level
	Occupation
	Marital Status
• Medical history	CV comorbidities
	Cardiac operations/procedures
	Concomitant diseases
	CV risk factors
• Family history	In terms of CV disease
• Laboratory data	Total cholesterol
	LDL-Cholesterol
	HDL-cholesteol
	Triglycerides
	Fasting blood glucose
	Creatinne
	Liver transaminases
	Creatine kinase
• Information on current medication	Whether or not to use antilipid agents and concomitant drugs

CV: Cardiovascular; LDL-Cholesterol: Low-density lipoprotein cholesterol; HDL-Cholesterol: High-density lipoprotein cholesterol.

Table 3. Questions about patient perceptions

• 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 rest my liver
Improvement in cholesterol levels

The perceptions of physicians regarding statin therapy will be also evaluated with the questionnaire (Table 4).

Statistical analyses

Continuous variables will be summarized by median and interquartile range or mean±SD. Categorical variables will be expressed as frequencies and percentages. Univariate analysis will be performed for continuous variables and a chi-square or Fisher's exact test will be applied for categorical variables. Correlation between variables will be assessed with the Pearson or Spearman test. A p value of <0.05 will be considered significant.

DISCUSSION

The EPHESUS registry will be the largest study conducted among Turkish patients examining the public awareness of hyperlipidemia and identifying the areas of misconception with regard to cholesterol management. The main findings will be data regarding statin use for primary and secondary prevention. The results of the EPHESUS study will provide important real-world evidence, as well as potentially providing a better understanding of the burden of hyperlipidemia and variability in disease management in individual units.

Chronic diseases, such as atherosclerotic cardiovascular diseases and diabetes, require prolonged clinical treatment. Despite the common occurrence of hyperlipidemia and the consequent high risk of adverse events, an elevated cholesterol level remains undertreated.[8] Persistence on statin therapy 1 year after initiation varies from 33% to 64.3%.[9] However, a high statin treatment persistence rate has been observed in some European countries.[10] Several factors have been shown to be predictive of poor patient adherence, including age, race, education level, household income, family support, cigarette smoking, patients' beliefs, comorbidities, the number of concurrent medications, and drug side effects. Previous studies revealed that patients aged ≥60 years were

Table 4. Questions about physician perceptions

• 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 life style 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 rest the liver • Reached target cholesterol levels

better adherents, whereas those under 45 or over 75 years of age displayed significantly lower adherence rates.[11] Higher education and household income levels, a cohesive family, positive attitude toward healthy living, and a patient-healthcare provider relationship have also been shown to be associated with increased adherence levels.[12] Poor adherence (often defined as ≤80% adherence) is one of the main factors responsible for failure to achieve treatment goals in hyperlipidemia, resulting in increased cardiovascular mortality and morbidity.[13]

A meta-analysis of adherence studies of patients with hypercholesterolemia revealed that adherence to therapy was associated with a 25% decrease in the risk for a null or poor outcome compared to those who were nonadherent. Furthermore, a decreased level of adherence to hypercholesterolemia medications has been associated with a general increase in medical costs.

Although nonadherence to hypercholesterolemia medications is a prevalent public health issue, the prevalence of nonadherence to statin therapy among patients with diabetes and coronary artery disease and the relationship between adherence and attainment of LDL-cholesterol goals have not been well studied in Turkey. Yiğiner et al.[14] assessed adherence to statin therapy and LDL-cholesterol goal attainment in type 2 diabetic and secondary prevention patients. The authors evaluated the data of 194 patients who had been on statin therapy for at least a year with a target LDL-cholesterol level of <100 mg/dL and found that the incidence of attaining the target LDL-cholesterol level was only 24%, and was lower in diabetics compared with secondary prevention patients. In a recently published national, cross-sectional, non-interventional, and observational study, Tokgözoğlu et al.[15] analyzed the data of 532 patients who had been diagnosed with hypercholesterolemia and had discontinued statin treatment on at least one occasion in the past. The authors found that the decision to discontinue statin treatment was made at the patient's discretion in 74% of cases, and that patients with a higher education level were more likely to decide to discontinue treatment. Furthermore, they reported that cardiologists were the physicians most frequently responsible for the initiation of the statin treatment, and that TV 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.[16]

The Turkish population has a unique lipoprotein profile that would be predicted to be associated with

a greater cardiovascular risk.[17] Several studies have confirmed that HDL- cholesterol levels in Turks are among the lowest in the world and are 10–15 mg/dL lower than that seen in western European or US populations.[18] Therefore, it is very important to attain the recommended cholesterol goals for optimal hyperlipidemia management and to reduce the cardiovascular risk of patients in our country.

Limitations

Despite the relatively large sample size, the study population will not be representative of all treated patients in Turkey. The fact that patient consent is to be obtained might lead to the selection of a more motivated population compared with those not willing to participate, inducing a positive bias. The same bias could apply to the participating physicians.

The EPHESUS study will be a survey without independent verification of the answers provided. The questionnaires will be used only for exploratory purposes.

The EPHESUS study will not include prescriptions written by family doctors. A significant number of low-dose statin prescriptions are written by family physicians in Turkey. This may result in a better reported adherence rate than actually exists.

Conclusion

Patient adherence has been considered to be a major factor in the low rate of LDL-cholesterol target attainment; greater adherence to treatment is linked to larger proportions of patients reaching their targets. Reasons for nonadherence have included patients forgetting to take their medication or terminating the medication when their cholesterol had reached a normal level. Perceptions, knowledge, and compliance with the guidelines for primary and secondary prevention in real-life practice have increased, but it is not enough. This study is designed to evaluate current clinical practice regarding prevention strategies in high-risk patients with hyperlipidemia. The results will help to generate hypotheses to improve prevention strategies.

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Conflict-of-interest: None declared.

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Keywords: Lipid; statin therapy; Turkey.

Anahtar sözcükler: Lipit; statin tedavisi; Türkiye.