

Patient characteristics and statin discontinuation-related factors during treatment of hypercholesterolemia: an observational non-interventional study in patients with statin discontinuation (STAY study)

Hiperkolesterolemide statin tedavisinin kesilmesi ile ilişkili hasta özellikleri ve sorumlu faktörler: Statin tedavisini bırakmış hastalarla yürütülmüş müdahalesiz gözlem çalışması (STAY Çalışması)

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ABSTRACT

Objective: The purpose of this study was to identify patient characteristics and statin discontinuation-related factors in patients with hypercholesterolemia.

Methods: A total of 532 patients (age mean±SD: 57.4±11.5 years; 52.4% women, 47.6% men) with hypercholesterolemia and statin discontinuation were included in this national cross-sectional non-interventional observational study. Data on socio-demographic characteristics of patients, cardiovascular risk factors, past treatment with and discontinuation of statin treatment were collected in one visit.

Results: Mean±SD duration of hypercholesterolemia was 4.9±4.2 years at time of discontinuation of statin treatment. Statin treatment was initiated by cardiologists in the majority of cases (55.8%), whereas discontinuation of statin treatment was decided by patients in the majority of cases (73.7%), with patients with higher (at least secondary education, 80.4%) more likely than those with lower (only primary education, 69.7%) to decide to discontinue treatment (p=0.022). Negative information about statin treatment disseminated by TV programs-mostly regarding coverage of hepatic (38.0%), renal (33.8%), and muscular (32.9%) side effects (32.9%)-was the most common reason for treatment discontinuation.

Conclusion: The decision to discontinue statin treatment was made at the patient's discretion in 74% of cases, with higher likelihood of patients with higher educational status deciding to discontinue treatment and switch to non-drug lipid-lowering alternatives. Cardiologists were the physicians most frequently responsible for the initiation of the statin treatment; coverage of several non-life-threatening statin side effects by TV programs and patients' lack of information regarding high cholesterol and related risks were the leading factors predisposing to treatment discontinuation.

ÖZET

Amaç: Hiperkolesterolemi tanısı ile izlenen statin kullanmakta olan hastalarda statin tedavisinin kesilmesi ile ilişkili hasta özellikleri ve sorumlu faktörlerin belirlenmesi.

Yöntemler: Bu ulusal müdahalesiz gözlem çalışmasına statin tedavisini bırakmış toplam 532 (ort. yaş±SS 57.4±11.5 yıl; %52.4 kadın, %47.6 erkek) hiperkolesterolemili hasta dahil edildi. Hastaların sosyodemografik özellikleri kardiyovasküler risk faktörleri, geçmiş statin tedavisi ve tedavinin kesilmesine yönelik veriler tek ziyarette kaydedildi.

Bulgular: Hastalara statin tedavisini bıraktıklarında ort.±SS 4.9±4.2 yıld, hiperkolesterolemi tanısı konulmuş olduğu tespit edildi. Statin tedavisi hekim grupları içinde en sık kardiyologlar (%55.8) tarafından başlatılırken, tedaviyi bırakma kararının büyük çoğunlukla hastalar (%73.7) tarafından alındığı; hastanın bu kararı kendi inisiyatifinde almasının daha yüksek eğitim düzeylerinde (%80.4), düşük eğitim düzeylerine (%69.7) göre belirgin olarak daha yaygın (p=0.022) olduğu saptandı. TV programlarında statin hakkında yapılan olumsuz haberler (%32.9); ilacın hepatik (%38.0), renal (%33.8) ve musküler (%32.9) yan etkilerinden çekinilmesi statin tedavisinin bırakılması ile ilişkili en sık oranda saptanan faktörler idi.

Sonuç: Sonuç olarak, bu müdahalesiz gözlemsel çalışmada, statin tedavisinin %74 oranda hastaların kendi kendine ilacı bırakma kararı doğrultusunda gerçekleştiği saptanmıştır. Tedavi bırakma ve ilaç dışı alternatif tedavilere yönelme kararının daha yüksek eğitim düzeyine sahip hastalarca daha sıklıkla alındığı görülmüştür. Statin tedavisinin en sık kardiyologlar tarafından başlatıldığı ve TV programlarında statin hakkında özellikle ilacın yaşamı tehdit etmeyen yan etkilerine yönelik yapılan olumsuz haberlerin yanı sıra, hastaların hiperkolesterolemi ve ilgili riskleri konusunda yeterli bilgi düzeyinden yoksun olmalarının statin tedavisinin bırakılmasında öne çıkan sorumlu faktörler olduğu anlaşılmaktadır.

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Hypercholesterolemia is a common treatable condition^[1] that has been recognized as a strong predictor of cardiovascular (CV) disease.^[2,3] Available in clinical practice for more than 20 years, long-term statin therapy has been considered to be generally well tolerated and associated with a substantial decline in CV events, based on large-scale trials as well as extensive post-marketing experience.^[4,5] Statins were documented to reduce clinical end points, achieving a 12% decrease in all-cause mortality, 19% decrease in coronary heart disease (CHD) mortality, and 23% decrease in CHD or myocardial infarction in patients with preexisting CHD.^[6,7] Accordingly, lifelong statin therapy has been recommended in evidence-based clinical guidelines for secondary prevention of coronary artery disease and as an adjunct to lifestyle modification for primary prevention in high-risk persons;^[8,9] patients typically are required to continue with once-daily statin treatment indefinitely.^[9–11]

Data from clinical trials indicate that long-term persistence with treatment is required in order to obtain the therapeutic benefits, with necessity of at least 1 to 2 years of continuous treatment to realize the overall benefits of statin therapy.^[12–14] However, unlike the high adherence rates reported in landmark statin clinical trials,^[15–18] data from observational studies revealed that the long-term use of statins in actual clinical practice settings is far from optimal.^[7,19–22]

Hence, the full benefit of lipid-lowering agents has frequently not been realized, owing to poor patient adherence,^[23] ranging from 30% to 70% of treated patients, depending on measurement methods and definitions used.^[24,25] Continuation to take medication after 5 years was reported in <25% of patients who initiated statin therapy.^[20]

Suboptimal adherence to statin therapy has been associated with inferior clinical outcome, escalated health care costs, and otherwise avoidable CV hospitalizations and deaths due to suboptimal low-density lipoprotein cholesterol (LDL-C) control. Therefore, early identification of patients who are more likely to discontinue their medications is important in clinical practice.^[12,26–29] This may allow timely adherence-promoting interventions and potentially reduce the risk of negative health outcomes.^[12]

The EUROASPIRE III survey^[30] was conducted between 2006 and 2007 in 22 countries in Europe

(76 centers) to describe risk factors, lifestyle and therapeutic management of patients with CHD, and compliance with current guidelines, as well as to document changes over time. The data from the survey^[31] indicated that efforts for CV disease prevention in Turkey fell short of the targets, similar to Europe. Compared with other European countries, less frequent follow-ups by physicians for patients with risk factors and lack of patient education in Turkey were notable factors for the failure to achieve the disease prevention goals.

Given the poor patient adherence to statin therapy among patients with hypercholesterolemia in Turkey, along with the Turkish EUROASPIRE III data^[31] indicating certain handicaps in efforts for CV disease prevention, clarification of the factors responsible for the discontinuation of statin treatment is of paramount importance. Therefore, the present study was designed to identify patient characteristics and factors related to statin discontinuation in patients with hypercholesterolemia.

Abbreviations:

| | |
|-------|-------------------------------------|
| CHD | Coronary heart disease |
| CV | Cardiovascular |
| LDL-C | Low-density lipoprotein cholesterol |

METHODS

Study design and patients

A total of 532 patients aged >18 years (age mean±SD: 57.4±11.5 years; 52.4% women, 47.6% men) who were diagnosed with hypercholesterolemia according to ICD-10 classification and had discontinued statin treatment on at least one occasion in the past were included in this national cross-sectional non-interventional observational study conducted between June and December 2012 at 14 centers of family medicine/general practice and cardiology clinics across Turkey. Study centers included the Diyarbakır Training and Research Hospital (n=108), 1 private clinic in Aydın (n=100), 1 private clinic in Kayseri (n=30), Dışkapı Training and Research Hospital (n=95), Kahramanmaraş Pazarcık Private Middle East Medical Center (n=35), İnönü University Faculty of Medicine (n=25), Bağcılar Training and Research Hospital (n=23), Yeditepe University Faculty of Medicine (n=23), İstanbul University Cerrahpaşa Faculty of Medicine (n=22), İstanbul Academic Hospital (n=21), Turkish High Specialty Research and Training Hospital (n=18), Yedikule Chest Disease and Thoracic Sur-

gery Training and Research Hospital (n=15), Hacettepe University (n=9), and Memorial Ataşehir Hospital (n=8).

Female and male outpatients aged >18 years and diagnosed with ICD-10 classification-based hypercholesterolemia (E78.0, E78.1, E78.2, E78.3, E78.4, E78.5) who had at least 1 statin-related prescription within the last 12 months and gave written informed consent were included in the study. Pregnancy, inability to read/comprehend the study questionnaire, being under statin treatment on admission, current participation in another clinical study, or prior participation in the present study were the exclusion criteria.

Written informed consent was obtained from each subject following a detailed explanation of the objectives and protocol of the study, which was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the institutional ethics committee.

Data collection

When inclusion criteria was met and informed consent was obtained, patient data regarding socio-demographic characteristics, CV risk factors, past treatment with statins (duration of treatment, additional drug or non-drug treatments for hypercholesterolemia, specialty and institution of the prescribing physicians), and discontinuation of statin treatment (decision maker, reasons for discontinuation, and treatments applied after discontinuation of statins) were collected in one visit at time of study enrollment, based on medical records, physical examination and patients' statements.

Discontinuation and duration of statin therapy

Discontinuation of statin therapy is defined as failure to renew a statin prescription with a ≥ 30 -day gap between the end of a prescription and the start of the next prescription. A gap of ≥ 30 days was chosen to represent a period between doses that would lead to a decline in therapeutic effectiveness. Duration of statin therapy was defined as the period from the index dispensing date to first discontinuation.^[12]

Statistical analysis

Sample size was calculated to constitute a minimum of 300–400 patients, based on 95% confidence interval and 2.4–5.7% error. Statistical analysis was performed using SPSS software (version 12.0; SPSS Inc., Chicago, IL, USA). Data were expressed as mean \pm SD

and/or percent (%). Descriptive statistics for numerical variables (mean, median, standard deviation, minimum and maximum) and frequency tables are given for categorical variables. Comparison of categorical variables was performed using chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

Socio-demographic and baseline characteristics of patients

Mean \pm SD age of patients (n=532) was 57.4 \pm 11.5 years, while patients aged <60 and ≥ 60 years composed 59.5% and 40.5% of the study population, respectively. Women composed 52.4% (n=279) of the study population, while men composed 47.6% (n=253). Most patients (62.6%) were primary school graduates (n=333), while at least secondary education was evident in 37.4% (n=199). Location of residence was urban in 81.6% (n=434) of patients and rural in 18.4% (n=98).

Mann-Whitney U test was used to calculate mean \pm SD waist circumference, which was found to be 98.3 \pm 14.5 cm in the study population, with no difference with respect to gender (98.3 \pm 12.1 cm in men, 98.4 \pm 16.7 cm in women, $p=0.523$).

Cardiovascular risk factors, hypercholesterolemia, and related treatment

Hypertension (67.7%) and physical inactivity (67.1%) were the most common CV risk factors identified in the study population (Table 1).

Table 1. Cardiovascular risk factors at study enrollment

| Risk factor | Present | |
|--------------------------------|---------|------|
| | n | % |
| Hypertension | 360 | 67.7 |
| Physical inactivity | 357 | 67.1 |
| Hypertriglyceridemia | 283 | 53.2 |
| Diabetes mellitus | 268 | 50.4 |
| Coronary heart disease | 261 | 49.1 |
| Obesity | 189 | 35.5 |
| Smoking | 141 | 26.5 |
| Peripheral artery disease | 15 | 2.8 |
| Cerebrovascular disease/stroke | 10 | 1.9 |

Mean±SD duration of hypercholesterolemia (n=480) was 4.9±4.2 years, while patients (n=470) were on statin therapy for 3.8±3.9 years (Table 2). Fibrates (7.1%) were the most common lipid-lowering drugs used in combination with statin treatment (Table 2). LDL-C and high-density lipoprotein cholesterol levels in relation to statin treatment are also presented in Table 2.

Dietary modification (61.3%) and physical exercise (56.8%) were the most common non-drug recommendations, followed by smoking cessation (27.1%) (Table 2).

Decisions on the initiation and discontinuation of statin treatment

Statin treatment was initiated most frequently by cardiologists (55.8%), followed by internal medicine (29.1%) and endocrinology (7.9%) specialists (Table 3).

The decision for discontinuation of statin treatment was made by patients in 392 cases (73.7%), by family physicians in 48 (9.0%), and by specialists in 92 (17.3%) of the total 532 cases. Notably, the likelihood of patient-derived decision of discontinuation

Table 2. Data on hypercholesterolemia and related treatment

| | n | % | Mean±SD |
|---|-----|-------|------------|
| Duration of hypercholesterolemia (year) | 480 | | 4.9±4.2 |
| Low-density lipoprotein cholesterol (mg/dL) | | | |
| Prior to statin therapy | 245 | | 153.6±43.5 |
| Discontinuation period | 124 | | 126.1±41.1 |
| At the time of study enrollment | 491 | | 159.8±44.7 |
| High-density lipoprotein cholesterol (mg/dL) | | | |
| Prior to statin therapy | 161 | | 44.6±10.5 |
| Discontinuation period | 119 | | 44.0±10.3 |
| At the time of study enrollment | 395 | | 45.2±11.6 |
| Duration of statin therapy (years) | 470 | | 3.8±3.9 |
| Other lipid-lowering drugs used in combination | | | |
| Fibrate | 38 | 7.1 | |
| Resin | – | – | |
| Ezetimibe | 1 | 0.2 | |
| Niacin | – | – | |
| Other | 6 | 1.1 | |
| Non-drug therapeutic recommendations and awareness activities | | Yes | |
| | n | % | |
| Dietary modification | 326 | 61.3 | |
| Physical exercise | 302 | 56.8 | |
| Smoking cessation | 144 | 27.1 | |
| Additional information (verbal) | 86 | 16.2 | |
| Additional information (written) | 65 | 12.2 | |
| Modification of alcohol consumption | 33 | 6.2 | |
| Information meetings | 14 | 2.6 | |
| Alternative treatments | 7 | 1.3 | |
| Patient education meetings | 3 | 0.6 | |
| Patient support groups | 1 | 0.2 | |
| Total (yes+no) | 532 | 100.0 | |

Table 3. Specialty of the physician who initiated statin treatment (n=532)

| Specialty area | n | % |
|---------------------------|-----|-------|
| Cardiology | 297 | 55.8 |
| Internal medicine | 155 | 29.1 |
| Endocrinology | 42 | 7.9 |
| Gastroenterology | 11 | 2.1 |
| Family physician | 9 | 1.7 |
| Cardiovascular surgery | 4 | 0.8 |
| Nephrology | 4 | 0.8 |
| Neurology | 3 | 0.6 |
| General practitioner | 2 | 0.4 |
| Pediatrics | 1 | 0.2 |
| Chest diseases | 1 | 0.2 |
| Obstetrics and gynecology | 1 | 0.2 |
| Cannot remember | 2 | 0.4 |
| Total | 532 | 100.0 |

was significantly greater with higher (at least secondary, 80.4%) compared to lower (only primary, 69.7%) educational status (p=0.022) (Figure 1). Similar percentages of patients were on primary or secondary statin prophylaxis during treatment discontinuation, regardless of the decision maker (Table 4).

Negative information about statin treatment disseminated by TV programs (32.9%) was the most common reason for treatment discontinuation, and mostly in relation to coverage of hepatic (38.0%), re-

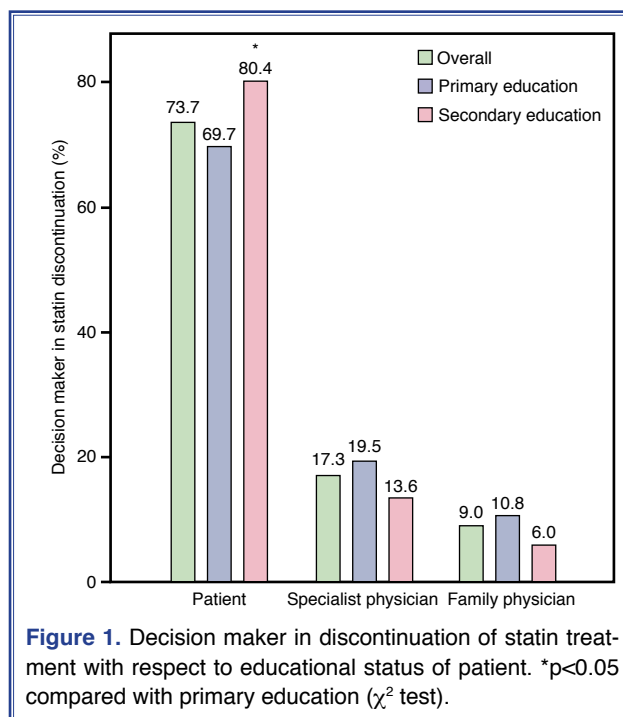


Figure 1. Decision maker in discontinuation of statin treatment with respect to educational status of patient. *p<0.05 compared with primary education (χ^2 test).

nal (33.8%), and muscular (32.9%) side effects of the drug (Tables 5 and 6).

Non-drug alternatives

Walnut oil (48.2%) and herbal mixtures (40.3%) were the 2 leading non-drug alternatives used by patients in the present study. Compared with patients with lower educational status, use of herbal mixtures was more prevalent in patients with higher educational status (32.5%, 51.8%, respectively, p=0.023) (Table 7).

Table 4. Distribution of statin discontinuation decision with respect to type of prophylaxis (n=532)

| Statin discontinuation | Prophylaxis type | | | p |
|-------------------------|---------------------|------------------------------|--------------------------------|--|
| | | Primary ¹ (n=271) | Secondary ² (n=261) | |
| Decision maker | | | | |
| Patient (n=392) | n | 196 | 196 | |
| | % in decision maker | 50.0 | 50.0 | |
| | % in prophylaxis | 72.3 | 75.1 | |
| Family physician (n=48) | n | 28 | 20 | 0.5518 ³ (overall) |
| | % in decision maker | 58.3 | 41.7 | 0.3053 ⁴ (family physician vs other specialist) |
| | % in prophylaxis | 10.3 | 7.7 | |
| Other specialist (n=92) | n | 47 | 45 | |
| | % in decision maker | 51.1 | 48.9 | |
| | % in prophylaxis | 17.3 | 17.2 | |

Patients ¹without or ²with coronary artery disease.

Table 5. Factors contributing to the decision of statin treatment discontinuation (n=532)

| Treatment discontinuation reason | Yes | |
|---|-----|------|
| | n | % |
| Negative information about statin treatment | 213 | 40.0 |
| Negative information about statin treatment in TV programs | 175 | 32.9 |
| Patients' lack of sufficient information on high cholesterol and related risks | 163 | 30.6 |
| Negative information about statin treatment heard from the relatives of the patient | 155 | 29.1 |
| Completion of the treatment as considered by the patient | 149 | 28.0 |
| Switching to non-drug alternatives | 139 | 26.1 |
| Negative information about statin treatment in newspapers | 117 | 22.0 |
| Disbelief in long-term treatment | 87 | 16.4 |
| Not considering high cholesterol as a disease that needs treatment | 78 | 14.7 |
| Considering treatment to be inefficient | 74 | 13.9 |
| Chronically forgetting to take the medicine | 61 | 11.5 |
| Patient copayment contribution | 30 | 5.6 |
| Lack of complete reimbursement by Social Security Institute | 14 | 2.6 |
| High drug costs | 13 | 2.4 |
| Difficulty in payment | 13 | 2.4 |

Table 6. The content of negative information about statins in patients who discontinue medications due to negative information about the drugs (n=213)

| Negative information about statins related to | Yes | |
|---|-----|------|
| | n | % |
| Hepatic side effects of the drug | 81 | 38.0 |
| Renal side effects of the drug | 72 | 33.8 |
| Muscular side effects of the drug | 70 | 32.9 |
| Risk of diabetes | 35 | 16.4 |
| Other | 64 | 30.0 |

DISCUSSION

Maintaining adherence to statin treatment has been considered critical in achieving long-term cholesterol control and overall effectiveness in the secondary prevention of CHD.^[9] Early prediction and identification of those who are at high risk for non-persistence have been emphasized^[12] in overcoming this treatment shortfall.^[32] Additionally, multifaceted strategies combining patient education, simplified dosing schedules, patient-physician communication, increased follow-up and monitoring, and clinic

Table 7. Non-drug alternatives switched to from statin therapy in relation to educational status

| | Non-drug alternatives (yes) | | | | | |
|-----------------|-----------------------------|-------|---------------------|-------|-----------------------|-------|
| | Total | | ≤ Primary education | | ≥ Secondary education | |
| | n | % | n | % | n | % |
| Walnut oil | 67 | 48.2 | 41 | 49.4 | 26 | 46.4 |
| Herbal mixtures | 56 | 40.3 | 27 | 32.5 | 29 | 51.8* |
| Cholesterol tea | 12 | 8.6 | 4 | 4.8 | 8 | 14.3 |
| Other | 42 | 30.2 | 29 | 34.9 | 13 | 23.2 |
| Total (yes+no) | 139 | 100.0 | 83 | 100.0 | 56 | 100.0 |

*p=0.023; compared to primary education, χ^2 test.

schedules that improve medication access have been emphasized.^[33]

Our findings on statin discontinuation in Turkish patients with hypercholesterolemia revealed that discontinuation in the majority of cases was resultant of the patient's (73.7%) rather than physician's discretion. Patients with higher educational status were more likely to choose to discontinue statin treatment and switch to non-drug lipid-lowering alternatives. Cardiologists were responsible for the initiation of statin treatment in 55.8% of cases. Negative information about statin treatment disseminated by TV programs (32.9%) in relation to hepatic (38.0%), renal (33.8%), and muscular (32.9%) side effects of the drug was the leading factor responsible for treatment discontinuation. Patients' lack of sufficient information regarding high cholesterol and its related risks (30.6%) was the most commonly identified patient-related factor predisposing to treatment discontinuation. Several studies in the literature indicate that elderly persons under statin treatment for secondary prevention of coronary artery disease^[34,35] or those who have several comorbid conditions^[22,34,35] were more likely than others to persist with statin therapy.

In this respect, our findings that the majority of patients with statin discontinuation in the present study (59.5%) were aged <60 years is consistent with the poorer compliance reported in patients <50 years.^[36,37] In contrast, given the substantial rate of comorbid disorders in our study population composed of hypercholesterolemia patients with statin discontinuation, our findings do not support the presence of better compliance in patients who have a comorbidity.^[19,22,34–37]

The Turkish data from the EUROASPIRE III survey indicated that in comparison to the European population, Turkish patients with CHD and myocardial infarction were younger (<50 years: 20%, 12.7%, respectively), had higher persistence in smoking (23.1%, 17.2%, respectively), higher immobility, lower high-density lipoprotein cholesterol (50.2%, 36.7%, respectively), increased likelihood of insufficient follow-up by physicians after the index event (12%, 2.2% [overall average value for all countries excluding Turkey], respectively), and insufficient patient education.^[31]

Stressing the importance of risk communication and inaccurate risk perception, young individuals are known to be less compliant with long-term preventive treatment, resultant of perceiving themselves as being at low risk for serious consequences.^[32] Notably, patients aged <60 years comprised 59.5% of our study population, which is consistent with the data on the poorer adherence to statins among younger patients.^[32,34,36,37] In this regard, younger age distribution in Turkish patients with CHD compared with European patients seems to confer a specific risk for higher likelihood of statin non-adherence. Nevertheless, our findings related to age distribution should be interpreted cautiously, given that a substantial portion (40.5%) of our patients with statin discontinuation were aged >60 years and thus expected to show better persistence with statin therapy. Similarly, studies have reported poorer persistence with statin therapy was reported among patients aged >65 years.^[38,39]

Presence of concomitant chronic medical conditions was reported to be associated with a higher likelihood of long-term medication disruption in previous studies.^[29] The decrease in risk of treatment discontinuation was reported when a cardiologist initiates treatment, an effect that persists even when accounting for patient comorbidities and CV disease.^[33,40] Notably, cardiologists were the physicians primarily responsible for the initial prescription of statins in more than half of our patients with statin discontinuation. In only 1.7% of patients with statin discontinuation, initiation of treatment was decided by a family physician, consistent with the data on better compliance with statin treatment when prescribed by family physicians.^[33]

Physician-patient relationship with continuity of providers at each visit has been recognized as a potential facilitator of adherence.^[29,41] In this regard, our data on the positive effect of a family physician, not a cardiologist, prescribing the statin emphasize the role of a good physician-patient relationship or better practice-wide coordination rather than expertise for patient understanding and trust.^[32]

While insufficient patient education was reported in the EUROASPIRE III study for patients with CHD in Turkey,^[31] information meetings, patient education meetings, and patient support groups were evident in <3.0% of our patients.

Usual care settings are generally considered to lack the educational context and frequent reinforcement seen in clinical trials; hence, patients outside of such trials do not always continue with expected regimens.^[40] Thus, identification of information meetings, patient education meetings, and patient support groups in <3.0% of patients with statin discontinuation in the present observational non-interventional study is relevant. The majority of patients in the present study lived in urban areas and practiced modern lifestyles. The likelihood of patients to decide to discontinue statin treatment and switch to non-drug alternatives was higher in patients with higher educational status. Consequently, media debate on statin side effects appears to have remarkable influence on statin adherence in our patients, given the lack of reliable patient education regarding the appropriate management of hypercholesterolemia.

Media coverage of several non-life-threatening statin side effects was reported to be likely to modify the general attitude toward preventive medication and to change prescribing/purchasing behavior.^[42] Supporting this finding, the media debate on statin side effects—mostly seen in TV programs (32.9%)—played a substantial role in patients' decisions about statin discontinuation, with emphasis on hepatic (38.0%), renal (33.8%), and muscular (32.9%) side effects in most of cases.

Safety issues related to any type of chronic treatment and to statins in particular in clinical practice led to the development of other types of lipid-lowering agents derived from botanic materials.^[43] Accordingly, walnut oil (48.2%) and herbal mixtures (40.3%) were the leading non-drug alternatives our patients chose to switch to from statin therapy. A higher likelihood of switching to non-drug alternatives was noted in patients with higher (51.8%) rather than lower (32.5%) educational status.

Patients' lack of belief in the benefits of therapy or polypharmacy has been suggested amongst the explanatory factors in statin non-adherence,^[44] while concomitant use of medication reminders has been considered to enhance adherence.^[29,41] In accordance with these findings, disbelief in long-term treatment (16.4%) and chronically forgetting to take the prescribed medicine (11.5%) were amongst the factors related to the decision to discontinue treatment in the present cohort.

It was indicated that there is a threshold for copayment being a barrier to adherence to statin treatment, with similar likelihood of being adherent to statins between prescription copayments of \$10–\$20 and <\$10 after adjustment for other factors.^[7] Concurrently, lack of a substantial role of copayment and reimbursement-related factors was noted in statin discontinuation in our study population. This appears consistent with the finding that while patent expiry and lower prices likely boosted the general increase in statin utilization, the gradually altered indication and age pattern seem to be driven by dyslipidemia management guidelines, influencing both reimbursement rules and general healthcare policies.^[42]

The predictive role of history of medication non-persistence in future medication-taking behavior has been considered difficult to apply to patients newly started on chronic medications such as statins for asymptomatic diseases.^[45] This emphasizes the essential role of the ability to target high-risk populations at an early stage in achieving cost-effective interventions to improve persistence.^[12] Mean levels of LDL-C (153.6±43.5 mg/dL) prior to statin therapy in our study population is notable, given that high LDL-C (≥190 mg/dL) before statin therapy was considered to be a predictor of statin discontinuation and an indicator of poor compliance with previous medication regimens or lifestyle recommendations.^[32]

Discontinuing beneficial drugs can lead to avoidable morbidity and burden on the public health system.^[46] For subjects at high risk for medication discontinuation, careful monitoring of drug utilization behavior by physicians during clinical consultations and implementation of more innovative adherence-enhancing strategies for lipid-lowering therapies have been recommended.^[29,41]

Inaccurate conception of and disproportionate anxiety over statin side effects have been suggested to contribute to the nonstandard use of statins, resulting in the consideration of statin therapy to consistently have the poorest compliance among cardiovascular therapies.^[47,48] Physicians' reluctance to titrate high-dose statins for high-risk patients^[49,50] and their high awareness of the side effects of the medicine which likely result in withdrawing statin treatment even in cases of slightly elevated transaminase levels, rather than dynamically monitoring biochemical indicators,^[47] have been associated with shortfall in achieving targeted LDL-C levels.

Prejudice and beliefs regarding side effects of statin therapy, as well as the continuation of package inserts containing warnings about possible though remote toxic effects such as hepatotoxicity, seem to manifest disproportionate anxiety over statin side effects.^[51] Considering the balance between visible harms and invisible benefits, this seems to not only harm patients who are in need of the drugs but also binds physicians in a dilemma.^[51] Albeit based on a subjective assessment, lack of sufficient information on high cholesterol and related risks was identified to be the reason of treatment discontinuation in one-third of our patients. Accordingly, our findings emphasize that improved physician awareness of potential risks and benefits of statins, as well as patient education, are warranted to fully achieve the therapeutic benefits of statin therapy in real-world clinical practice.

Data from a recent study on the prevalence of dyslipidemia and associated risk factors in Turkish adults revealed that of 4309 subjects, at least 1 lipid abnormality was diagnosed in 78.7% of men and 80.4% of women.^[52] Given that dyslipidemia was shown to be highly correlated with hypertension, abdominal obesity, and metabolic syndrome in Turkish adults, implementation of more aggressive nationwide public health measures has been emphasized to better diagnose and comprehensively treat dyslipidemia in Turkey.^[52]

Certain limitations to this study should be considered. First, our database of 532 patients from 14 centers in Turkey may not be a representative sample of the overall patient population in Turkey; thus, our findings may not be generalizable. Second, the present cohort was comprised of only patients who discontinued statin therapy, and therefore it is not possible from our findings to consider all possible reasons for discontinuation, such as polypharmacy. Third, data on factors contributing to the decision to discontinue statin treatment are highly subjective, while bias and confounding factors are likely due to non-randomized allocation, consistent with the observational design. Fourth, given that no data are available to accurately estimate the overall rate of statin discontinuation across Turkey, it should be noted that the present cohort was comprised of only patients admitted to outpatient clinics on a voluntary basis. Therefore, one must remain prudent when in-

terpreting our findings, given the likelihood of a significant number of patients who discontinue statin therapy at their own discretion and do not attend outpatient clinics afterwards. Finally, lack of long-term follow-up to observe clinical consequences of statin discontinuation is another important limitation of the study. Nevertheless, despite these certain limitations, considering the paucity of solid information available on this topic, our findings represent a valuable contribution to the literature.

In conclusion, our findings related to factors contributing to discontinuation of statin treatment in patients with hypercholesterolemia revealed that statin discontinuation was primarily at the discretion of patients rather than physicians. We found a higher likelihood of patients with higher educational status to decide for themselves to discontinue treatment and switch to non-drug lipid-lowering alternatives. Cardiologists were the primary physicians responsible for the initiation of statin treatment. Coverage of several non-life-threatening statin side effects by TV programs and patients' lack of sufficient knowledge regarding high cholesterol and related risks were the leading factors predisposing to discontinuation of treatment. By providing data on factors responsible for statin discontinuation in patients with hypercholesterolemia, our findings contribute to the available knowledge on how to optimize statin use in real-world clinical practice in order to fully achieve therapeutic benefits.

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