ORIGINAL ARTICLE

Assessment of factors related to statin non-adherence in patients with established coronary artery disease: A single-center observational study

Koroner arter hastalarında statin uyumunu etkileyen faktörlerin incelenmesi: Tek merkez gözlemsel çalışması

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ABSTRACT

Objective: Lifelong statin treatment is recommended in patients with cardiovascular diseases, but drug adherence is a significant problem. The aim of this study was to investigate factors related to statin discontinuation in high-risk patients with coronary artery disease (CAD) diagnosed by coronary angiography.

Methods: A total of 300 consecutive patients who were followed-up with a diagnosis of CAD were recruited. Patients were categorized as statin adherent or statin non-adherent (patients interrupting statin therapy >30 days). Study participants completed a questionnaire regarding demographic characteristics, medical history, knowledge of statin treatment, and factors related to statin discontinuation.

Results: In all, 160 patients (53.3%) were found to be statin adherent. Of those, 122 patients had suffered myocardial infarction, and atorvastatin was the most prescribed statin on discharge. Among the study population, 26% were illiterate and 55% had graduated from primary school. Only 39 cases (13%) cases had a low-density lipoprotein-cholesterol level <70 mg/dL. In 60% of the statin non-adherent patients, the reason for statin discontinuation was physician discontinuation of the statin prescription. In 14%, the patient stopped the therapy after cholesterol parameters had been reduced or reached the normal range. Only 8% of participants reported that negative information received from TV programs and social media was responsible for the decision to terminate drug use.

Conclusion: Our findings demonstrated that the importance of intensive statin treatment in CAD patients has not been recognized by patients or many physicians. Adherence to statin treatment and success of the therapy is low, leading to unnecessarily high cholesterol levels in patients with CAD.

ÖZET

Amaç: Koroner arter hastalarına (KAH) hayat boyu statin tedavisi önerilmesine rağmen, tedaviye uyum ciddi bir problemdir. Bu çalışmada, koroner anjiyografi (KAG) ile KAH tanısı konmuş yüksek riskli hastalarda statin tedavisinin kesilmesine yol açan faktörlerin incelenmesi amaçlandı.

Yöntemler: Çalışmaya KAH tanısıyla takip edilen ardışık 300 hasta alındı. Statin tedavisine devam eden hastalar tedaviye bağlı grubu oluştururken, statin tedavisine 30 günden fazla ara veren hastalar statin tedavisine bağlı olmayan grubu oluşturdu. Hastalara demografik özellikleri, tıbbi geçmişleri, statin tedavisi hakkında bilgi durumları ve statin tedavisini kesme nedenlerini içeren bir anket formu doldurtuldu.

Bulgular: Hastaların 160'ı (%53.3) statin tedavisine bağlı idi. Yüz yirmi iki hastaya miyokart enfarktüsü tanısı konmuştu ve taburcu olurken en sık atorvastatin reçete edilmişti. Hastaların %26'sı okuma-yazma bilmiyordu ve %55'i ilkokul mezunuydu. Tüm hasta popülasyonu değerlendirildiğinde, sadece 39 hastada (%13) LDL-kolesterol <70 mg/dL saptandı. Statin tedavisine bağlı olmayan grupta, %60 oranında statin tedavisinin bırakılmasının sebebinin ilacın doktorlar tarafından kesilmesi olduğu görüldü. Yüzde 14 hasta, kolesterol değerlerinin düşmesi veya normal değerlere inmesi nedeniyle ilacı kendileri bırakmıştı. Televizyon programları veya sosyal medyadan etkilenerek statin tedavisini bırakma oranı ise sadece %8 olarak saptandı.

Sonuç: Bulgularımız, KAH'lı hastalarda yoğun statin tedavisinin öneminin hastalar ve hekimler tarafından tam anlaşılmadığını göstermektedir. KAH'da statin tedavisine devamlılık oranı ve tedavi başarısı düşük olduğundan kolesterol değerleri yüksek kalmıştır.

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Cardiovascular diseases are the most frequent cause of death and about half of the mortality occurs due to coronary artery diseases (CAD).[1] Dyslipidemia, hypertension (HT), diabetes mellitus (DM), smoking, and familial predisposition to CAD are the major risk factors for CAD. The prevalence of dyslipidemia has been reported to be between 35% and 40 % in Turkey.[2,3] Dyslipidemia is a modifiable risk factor and lipid-lowering drugs, namely statins, have been used safely for primary and secondary prevention for about 30 years. Long-term statin treatment decreases the risk of CAD, peripheral arterial disease, stroke, myocardial infarction (MI), cardiovascular mortality and all-cause mortality.[4–7] Accordingly, lifelong statin therapy is recommended by evidence-based guidelines for primary prevention in patients with a high-risk profile for CAD, and for secondary prevention in patients with established CAD.[8,9]

Adherence to once-daily statin treatment for at least 1 to 2 years is critical to gain the clinical benefit of lipid-lowering therapies.[10] However, adherence to cardiovascular drugs, including statins, is inadequate, which increases the risk of adverse cardiac events.[11–15] Recently, the European Action on Secondary and Primary Prevention through Intervention to Reduce Events (EUROASPIRE) IV study showed that statin adherence has increased compared with results from EUROASPIRE III and reached about 90%, but only two-thirds of patients could reach the target low-density lipoprotein cholesterol (LDL-C) levels.[13,16] Insufficient follow-up by physicians, too little education, and misguidance from media programs about statin side-effects are possible factors for the low statin treatment adherence rate.[17] Identification of individual factors in the discontinuation of statin treatment is of paramount importance, especially for patients with established CAD. Thus, in this study, the objective was to investigate the level of knowledge about lifestyle modification and statin treatment, as well as factors prompting cessation of statin treatment in patients in the Turkish population with established CAD.

METHODS

This was a cross-sectional study performed at a cardiology outpatient clinic between December 2014 and February 2015. A total of 300 consecutive patients (53.3% men, 46.7% women) were recruited for the study. The medical records of patients with established CAD were examined for clinical details, angiographic properties, and laboratory parameters. CAD was diagnosed using an angiogram as the presence of coronary stenosis of ≥50% or percutaneous coronary intervention (PCI) performed in at least 1 coronary artery. The medications prescribed on discharge for the index event, including statin dosage, were collected. A questionnaire about the duration of the therapy, general knowledge of CAD, lifestyle modifications, level of physical activity, additional drug or non-drug treatments for hyperlipidemia, and the reason for the discontinuation of medication was completed by the participants. Patients not taking a statin for more than 30 days during the study period were classified as the statin non-adherent group and patients continuing the treatment after coronary angiography (CAG) were classified as the statin adherent group.

Abbreviations:

CAD	*Coronary artery disease*
CAG	*Coronary angiography*
CI	*Confidence interval*
LDL-C	*Low-density lipoprotein cholesterol*
MI	*Myocardial infarction*
OR	*Odds ratio*
PCI	*Percutaneous coronary intervention*

The exclusion criteria were the presence of 1) end stage renal or liver disease; 2) severe co-morbid conditions, such as dementia or terminal-stage malignancy; 3) acute or chronic inflammatory disease; and 4) inability to complete the questionnaire due to communication difficulties. The study protocol was approved by the local ethics committee. Informed consent was provided by all of the participants.

Fasting blood samples were drawn and complete blood count and biochemical parameters were analyzed using automatic analyzers (Coulter LH 780 Hematology Analyzer; Beckman Coulter Inc., Brea, CA, USA) and (Hitachi H7600; Hitachi, Ltd., Tokyo, Japan).

HT was defined as systolic pressure >140 mmHg and/or diastolic pressure >90 mmHg, or if the individual was taking antihypertensive medication. DM was defined as a fasting glucose level >126 mg/dL and/or if the patient was taking anti-diabetic medication. Individuals who reported smoking at least 1 cigarette per day during the year before the examination were classified as smokers. End-stage kidney disease was defined as an estimated glomerular filtration rate below 30 mL/minute/1.73 m^2.

Statistical analysis

Data were presented as mean±SD or median (25%-75%) for continuous variables and the number of cases and percentages were used for categorical variables. The Kolmogorov–Smirnov test was applied to determine if the normal distribution assumption for continuous variables was provided or not. Quantitative data were evaluated using an unpaired t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared with a chi-square test; Fisher's exact test was used if the sample size in a cell was <5. For multivariate analysis, logistic regression was used to assess the effect of study parameters on statin discontinuation with a backward inclusion model. The goodness-of-fit of the models was assessed using the Hosmer-Lemeshow chi-square test, which revealed p=0.492 for the final model. The parameters with p<0.10 in univariate analysis were included in the multivariable model: MI as the initial diagnosis, stent implantation, total cholesterol level on admission, and the total number of medications used. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A p value <0.05 was considered statistically significant. All statistical studies were carried out using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 300 consecutive patients were included in the study, 160 (53.3%) of whom continued statin treat-

Table 1. Demographic and clinical properties of the study groups

	Statin adherent (n=160)			Statin non-adherent (n=140)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age, years			61.2±10.4			62.6±10.7	0.244*
Male gender, n (%)	113	70.6		90	64.3		0.242+
Weight (kg)			79.8±13.5			80.6±14.9	0.625*
Height (cm)			165.8±9.7			165.1±8.4	0.497*
Body mass index (kg/m^2)			29.0±4.3			29.6±5.3	0.295*
Smoking	28	18		26	19		0.810+
Diabetes mellitus	68	42		51	36		0.284+
Hypertension	102	64		87	62		0.813+
Initial diagnosis							
STEMI	41	26		29	21		0.315+
NSTEMI	34	21		18	13		0.055+
Elective CAG	85	53		93	66		0.019+
Angiographic properties							
Duration since CAG (months)			29.6±12.5			30.8±11.3	0.505*
Number of diseased vessels			1.32±0.63			1.24±0.56	0.242*
Stent implantation	105	65		74	53		0.024+
CABG surgery	7	5		8	6		0.566+
Only medical therapy	48	30		58	41		0.038+
Educational status							
Illiterate	37	23		40	29		
Primary school graduate	86	54		79	56		
Secondary school graduate	18	11		11	8		0.311+
High school graduate/postgraduate	19	12		10	7		

*Unpaired t-test; +Chi-square test. CABG: Coronary artery bypass grafting; CAG: Coronary angiography; NSTEMI: Non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction; SD: Standard deviation.

ment after CAG. The mean age in the statin adherent group was 61.2±10.4 years and it was 62.6±10.7 in the statin non-adherent group (p=0.244). The demographic and clinical characteristics of the study groups are summarized in Table 1. The frequency of HT and DM, as well as body mass index results, were similar between the groups. The rate of smoking was 18% and was not significantly different between the groups. Most patients (55%) were primary school graduates (n=165), and the distribution of educational status was not significantly different between the groups (Table 1). In total, 178 (59.3%) of the patients had undergone elective CAG or PCI, and 122 (40.6%) had suffered MI. The total number of diseased arteries (arteries with ≥50% stenosis) was not significantly different between the groups. The frequency of stent implantation was higher in the statin adherent group, whereas the frequency of patients with only medical therapy was higher in the statin non-adherent group (p=0.024 and p=0.038, respectively). When concomitant medications were investigated, the statin adherent patients also used more drugs and had a higher frequency of beta-blocker and clopidogrel use (Table 2). In addition, patients with MI used more medications compared with elective CAG patients (3.43±1.21 vs 2.59±1.12; p<0.001).

After the CAG, the most prescribed statins were atorvastatin (n=187; 62.3%) and rosuvastatin (n=108; 36%) (Table 2). In the statin adherent group, the mean duration of statin treatment was 24 months (range: 11-36 months), and the mean doses of atorvastatin and rosuvastatin were 22.5±13.5 mg and 15±7.5 mg, respectively. In all, 28 patients had atorvastatin treatment with a dose of ≥40 mg and 23 patients had rosuvastatin treatment with a dose of ≥20 mg.

The laboratory parameters of the study population are summarized in Table 3. At discharge, the total cholesterol and LDL-C levels were significantly higher in the statin adherent group. As expected, the recent laboratory results revealed lower total cholesterol and LDL-C levels in the statin adherent group. The mean LDL-C level was 94 mg/dL (range: 71-129 mg/dL) in the statin adherent group. Triglyceride and high-density lipoprotein cholesterol levels were not significantly different between the groups. In the statin adherent group, only 34 (21.2%) of the patients, and in the statin non-adherent group only 5 (3.6%) had an LDL-C level below 70 mg/dL.

The frequency of lifestyle modifications applied in the study groups is summarized in Table 4. About half of the patients reported that they had implement-

Table 2. Medical therapy in the study population

	Statin adherent (n=160)	Statin non-adherent (n=140)	*p*
Angiotensin-converting enzyme inhibitor, n (%)	59 (36.8)	37 (26.4)	0.053
Angiotensin receptor blocker, n (%)	37 (21.2)	37 (26.4)	0.508
Beta-blocker, n (%)	130 (81.2)	93 (66.4)	0.003
Acetylsalicylic acid, n (%)	126 (78.7)	97 (69.3)	0.061
Clopidogrel, n (%)	46 (28.7)	23 (16.4)	0.011
Nitrates, n (%)	16 (10)	11 (7.8)	0.518
Fenofibrate, n (%)	5 (3.1)	2 (1.4)	0.356[+]
Total number of medications	3.60±1.13	2.16±0.92	<0.0001
Statin treatment			
Atorvastatin, n (%)	96 (60)	91 (65)	
Rosuvastatin, n (%)	61 (38.1)	47 (33.5)	0.656
Pravastatin, n (%)	3 (1.9)	2 (1.5)	
Dose of atorvastatin (mg), Mean±SD	22.5±13.5	–	–
Dose of rosuvastatin (mg), Mean±SD	15±7.5	–	–
Duration of therapy (months)	24 [11-36]	–	–

Continuous data are expressed as mean (± standard deviation) or median (interquartile range).

Table 3. Laboratory parameters of the study groups on discharge and during the study period

	Statin adherent (n=160)	Statin non-adherent (n=140)	*p*
On discharge			
Triglycerides (mg/dL)	149 [116–216]	151 [106–286]	0.607
Total cholesterol (mg/dL)	243 [223–265]	209 [182–243]	0.0001
Low-density lipoprotein (mg/dL)	161.1±26.8	134.2±33.9	0.0001
High-density lipoprotein (mg/dL)	45.5±9.1	45.9±11.7	0.896
Recent			
Fasting blood glucose (mg/dL)	107 [96–141]	102 [95–119]	0.061
Aspartate aminotransferase (U/L)	20.4±9.4	20.6±10.2	0.871
Alanine aminotransferase (U/L)	19 [14–30]	16 [12–25]	0.060
Triglycerides (mg/dL)	146 [108–212]	151 [106–234]	0.363
Total cholesterol (mg/dL)	167 [147–208]	207 [170–242]	0.0001
Low-density lipoprotein (mg/dL)	94 [71–129]	128 [107–157]	<0.0001
High-density lipoprotein (mg/dL)	46.3±11.2	46.2±12.7	0.943

Continuous data are expressed as mean (± standard deviation) or median (minimum-maximum).

Table 4. Lifestyle modification and statin usage parameters of the study population

	Statin adherent (n=160)		Statin non-adherent (n=140)		*p*
	n	%	n	%	
Diet change	74	46.2	61	43.6	0.642
Regular physical exercise	55	34.4	44	31.4	0.588
≥10% weight loss after coronary angiography	16	10	12	8.6	0.671
Herbal medicine use	9	5.6	16	11.4	0.070

ed diet changes and one-third reported that they participated in regular physical exercise since the CAG. The frequency of patients with weight loss of ≥10% was not significantly different between the groups. Nine patients in the statin adherent group and 16 in the statin non-adherent group reported that they used herbal medicine (p=0.069).

The study population was also evaluated with regard to the reason for statin therapy discontinuation (Table 5). The most common response was cessation of the prescription for the statins by a physician (60%). In 14% of the cases, the patients stopped the therapy after cholesterol parameters were reduced or in the normal range. Patients stopped taking the medication due to information they obtained from television or social media claiming that long-term statin treatment may be harmful to the liver in 8% of the cases, and in 9% of the statin non-adherent group, personal discretion was reported as the reason the patients terminated use of the medication.

Table 5. The reason for discontinuation of statin therapy in the non-adherent group

Reason for discontinuation	(n=140)	
	n	%
Stopped by the physician during follow-up	84	60
Cholesterol lowered/in normal range	19	14
Misguidance in media broadcasts	11	8
Patient's discretion (does not like taking pills)	13	9
Fear of liver toxicity	7	5
Difficulty obtaining the drug from the pharmacy	6	4

Table 6. Predictors of statin adherence in multivariable regression analysis

	B	SE	Wald	*p*	Exp(B)	95% CI for EXP(B)	
						Lower	Upper
Presence of myocardial infarction	0.45	0.38	1.38	0.240	1.57	0.74	3.35
Stent implantation	0.51	0.37	0.02	0.893	1.05	0.51	2.19
Total cholesterol level on admission	0.022	0.004	28.86	<0.001	1.02	1.01	1.03
Total number of medications used	1.54	0.21	57.13	<0.001	4.89	3.23	7.39

In univariate regression analysis, age, gender, the presence of DM, HT, educational status, and the total number of diseased coronary vessels were not correlated with statin adherence rates. In univariate analysis, the presence of MI as the initial diagnosis (OR: 1.684; 95% CI, 1.054-2.693; p=0.029), stent implantation (OR: 1.703; 95% CI, 1.069-2.712; p=0.025), total cholesterol level on admission (OR: 1.022; 95% CI, 1.016-1.029; p<0.001), and the total number of medications used (OR: 4.308; 95% CI, 3.031-6.125; p<0.01) were correlated with statin adherence. Multivariate analysis using a backward LR method revealed that the total cholesterol level on admission and the total number of medications used were significantly correlated with statin adherence. The other parameters did not remain statistically significant (Table 6).

DISCUSSION

Atherosclerosis is a continuous process and when a patient is diagnosed with CAD, lifelong precautions should be applied in order to decrease the risk of future adverse cardiac events, including mortality. Lifestyle modifications, such as diet and exercise, and medical therapies, such as antiaggregant and cholesterol-lowering therapies, are recommended by recent guidelines.[8,9] Compliance is a major problem in CAD patients, and multiple strategies, including patient-physician communication, frequent follow-ups, patient or relative education, and facilitated dosing schedules play an important role in increasing the adherence rate.[13] In this study, we included a patient population with coronary stenosis and a high frequency of PCI due to acute coronary syndromes. The participants used multiple therapies, such as acetylsalicylic acid, beta-blockers, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and clopidogrel, as these medications were started upon discharge after the index event. Though our study was not a prospective one, and we only included patients who were in follow-up after CAG, we found that only 53.3% of the study participants continued statin treatment after CAG. Since we only included patients who continued to make regular control visits to the outpatient clinic, we could not report the rate of statin discontinuation in patients who did not continue clinical follow-up after the index event.

The EUROASPIRE III study, Turkey arm (338 patients), revealed that compliance of CAD patients with lifestyle modifications and medical therapies is worse in Turkey compared with Europe.17 In that study, the length of time since the coronary intervention was ≥6 months (as an inclusion criterion), which was relatively short, compared with our study. They determined a rate of statin adherence of 65.9%, which is higher than our study result. The authors especially noted that compliance with statin therapy is worse than it is with other medications, such as anti-platelets and anti-hypertensives.

The geographic region, the following physician, the frequency of follow-up visits, and patient-related characteristics, such as age, gender, comorbid conditions, and educational status, are important factors in statin adherence.[15,18–20] In our study, gender and age did not differ significantly between the groups. Patients who had MI and PCI tended to have a higher rate of adherence to statin treatment, and in patients with conservative treatment, the adherence rate was lower. Another important finding in our study was that patients using multiple medications (especially clopidogrel and beta-blockers) also tended to continue statin treatment. These findings indicated that patients with a more severe form of presentation during the index event were more likely to comply with drug therapies, including statin treatment. Initiation of intensive statin treatment at discharge and frequent

follow-ups with cardiologists may be a major underlying reason for higher adherence rates.

Recently, Tokgözoğlu et al.[21] reported factors related to statin discontinuation in 271 patients with primary prophylaxis and in 261 patients with secondary prophylaxis in Turkey. Discontinuation was defined as failure to renew a statin prescription for ≥30 days. The rate of CAD was 49.1% and the smoking rate was 26.5%. They found that in 73.7% of the cases the decision to terminate use of the statin was made by the patient, and that the rate of discontinuation was higher in patients with more formal education. They noted that negative information received from television and radio broadcasts was a major cause of statin use cessation, especially due to the exaggeration of statin side effects and the promotion of non-drug alternatives, such as walnut oil and herbal mixtures. In our study, illiterate and primary school graduates constituted 80% of the study population, and the education level was lower compared with that of Tokgözoğlu et al. We did not find a correlation between education status and statin adherence rate. The proportion of patients who use the Internet or social media was low in our study. The effect of misguidance in media broadcasts or online was the reason for discontinuation of therapy in only 8% of our cases, while Tokgözoğlu et al. found that it was a major reason in their research. The characteristics of the study populations were different, and the frequency of patients who used the Internet was low in our study.

The continuation of the drug prescription by the following physician seems to be the main factor related to statin adherence in our study. In the majority of cases, the reason for stopping statin therapy was due to the following physician. In particular, primary physicians, who prescribe most cardiovascular drugs during follow-up, stop statin therapy mainly due to normalization of the cholesterol level. Another independent predictor for statin adherence is a higher total cholesterol level at discharge. It is important to inform patients that statin treatment should be lifelong for patients with established CAD. Intensive statin treatment should be started during hospitalization, and consultation with a cardiologist before any change or cessation of the medications should be recommended at discharge.

Another important finding of our study is that the dosage of stain therapy was low and many did not reach targeted cholesterol levels. The mean dose of atorvastatin was 22.5±13.5 mg and the mean rosuvastatin dose was 15±7.5 mg. The mean LDL-C level was 102.9±42.9 mg/dL in the statin adherent group. Unfortunately, these findings imply that a large percentage of physicians do not comply with the current guidelines and may indirectly cause an increase in cardiovascular events in this high-risk population. Particularly when the educational status and knowledge of the patients about hyperlipidemia and the benefits of statin treatment is low, frequent follow-ups, especially by specialists such as cardiologists and internal medicine specialists, may be beneficial in increasing the rate of adherence to statins and other cardiovascular drugs.

There are some limitations to our study. First of all, our sample size was relatively small, and as patients were recruited from a single center, our findings may not be representative of the overall population of CAD patients in Turkey. The rate of statin discontinuation may have been lower than would be seen in real life, as we only included patients who continued outpatient clinic follow-ups. When patients without regular follow-up are considered, most likely the rate of statin discontinuation would be higher than 53.3%. A larger prospective study including all of the consecutive patients after CAG is warranted to further support our findings. Second, the reasons for statin discontinuation are highly subjective. This study was conducted in a region with a low socioeconomic status where the level of educational achievement and use of the Internet and social media are low. When compared to study of Tokgözoğlu et al., it is obvious that the district where the study is conducted is an important factor and may affect the results in this type of research.

In conclusion, in this cross-sectional study, even in patients who had undergone CAG, patient knowledge about statin treatment was not adequate, especially due to a low educational status. Negative information obtained from television programs and the Internet further decreased statin adherence rates. However, our primary finding indicated that more physicians need to comply with the current guidelines and encourage lifelong intensive statin treatment in addition to other therapies.

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