



Short- and Long-Term Statin Persistence and Determinants in Patients Initiating Statin Therapy

Statin Başlanan Hastalarda Kısa ve Uzun Dönem Statin Persistansı ve Belirleyicileri

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ABSTRACT

Objective: Despite the established efficacy of statins in reducing major cardiovascular events and mortality, rates of statin persistence remain low. This study aimed to assess short- and long-term statin persistence rates and identify factors influencing persistence in patients initiating statin therapy.

Methods: A retrospective, observational, clinical study was conducted, enrolling a consecutive total of 903 patients aged 18 years and older (692 female, 211 male, mean age: 60.74 ± 11.70 years) who had initiated statin therapy between January 1, 2016, and January 1, 2017. Short-term (2018) and long-term (2023) statin persistence statuses were determined. Groups persisting and non-persisting with statin therapy were compared for demographic characteristics; presence of cardiometabolic diseases such as diabetes mellitus (DM), coronary artery disease (CAD), and hypertension (HT); statin therapy intensities; and indications for statin initiation (primary or secondary prevention) for both time periods.

Results: The study included 903 patients with a mean age of 60.7±11.7 years and a female predominance of 76.6%. In 2018, 498 (55.1%) patients continued statin therapy, while 405 (44.9%) discontinued. In 2023, excluding 36 cases with death (18 cases were among those continuing statin treatment, and 18 cases were who did not continue). Four hundred and forty-eight (51.7%) patients persisted with statin therapy, while 419 (48.3%) discontinued. Statin non-persistence was more frequent in patients initiated on statins for primary prevention (p<0.01) and more frequent in those under 45 years old (p=0.028 and p=0.036, respectively), while it was less common in patients with HT, DM, and CAD (all p<0.01).

Conclusions: The study reveals the low and declining rates of statin persistence in patients initiating statin therapy, both in the short and long term. Furthermore, persistence rates are lower in younger patients and those initiated on statins for primary prevention compared to those with established cardiovascular risk factors

Keywords: Statin persistence, cardiometabolic disease, statin intensity

ÖZ

Amaç: Randomize kontrollü çalışmalarda statinlerin majör kardiyovasküler olay riskini ve tüm nedenlere bağlı mortaliteyi azalttığı gösterilmiş olmasına ve güncel lipid kılavuzlarının etkin kolesterol tedavî önerilerine rağmen statine devam etme (statin persistansı) oranlarının düşük olduğu gözlenmektedir. Bu çalışmanın amacı statin başlanan hastalarda kısa ve uzun dönem statin persistansı oranlarının ve bunun üzerine etkili faktörlerin belirlenmesidir.

Yöntemler: Retrospektif, gözlemsel, klinik çalışmaya 01.01.2016-01.01.2017 tarihleri arasında statin tedavisi başlanmış 18 yaş ve üzeri toplam 903 hasta (692 kadın, 211 erkek, ortalama yaş: 60.74±11,70 yıl) ardışık olarak alındı. Kısa (2018) ve uzun dönem (2023) statin persistans durumları belirlendi. Her iki dönem için statin tedavisine devam eden ve etmeyen hasta grupları demografik özelliklerine, diabetes mellitus (DM), koroner arter hastalığı (KAH) ve hipertansiyon (HT) gibi kardiyometabolik hastalık varlıklarına, statin tedavi yoğunluklarına (low-intensity, moderate-intensity, high-intensity) ve statin başlama endikasyonlarına (primer veya sekonder koruma) göre karşılaştırıldı.

Bulgular: 2018 yılı kontrollerinde; 903 olgudan statin tedavisine devam eden 498 (%55.1), devam etmeyen 405 (%44.9), 2023 yılı kontrollerinde; eksitus olan 36 olgu (statine devam edenlerde 18, etmeyenlerde 18 olgu) hariç tutulduğunda 867 olgudan statine devam eden 448 (%51.7), devam etmeyen 419 (%48.3) olgu vardı. Her iki kontrolde de statine devam etmeyenlerin sıklığı primer koruma amaçlı statin başlananlarda (ikisi için de p<0.01) ve <45 yaş olanlarda (sırasıyla p=0.028 ve p=0.036) yüksek, HT, DM ve KAH olanlarda düşüktü (tümü için p<0.01).

Sonuçlar: Bu çalışma statin başlanan hastalarda statin persistansının hem kısa hem de uzun dönem takiplerde düşük ve düşme eğiliminde olduğunu ve genç yaştaki hastalar ile kardiyovasküler riski yüksek olmayan ve primer koruma amaçlı statin başlanan hastalarda persistansın diğer hastalara göre daha düşük olduğunu göstermiştir.

Anahtar kelimeler: Statin devamlılığı, kardiyometabolik hastalık, statin yoğunluğu

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INTRODUCTION

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), commonly used in the treatment of hypercholesterolemia, have been shown to reduce the risk of major cardiovascular events and all-cause mortality in both primary and secondary prevention studies¹⁻³. Despite the effective cholesterol treatment recommendations outlined in current lipid guidelines, low rates of statin persistence and adherence are observed in many countries⁴⁻⁶. Factors contributing to this phenomenon include low disease awareness among patients, fear of side effects, biases regarding treatment efficacy, negative experiences with previously used medications, and inadequate disclosure of the benefits and side effects of treatment by healthcare providers⁷⁻⁹. Exaggerated negative media coverage of statin side effects in both visual and written media has also been shown to adversely affect treatment continuation and adherence among both patients initiating statin therapy and those already using statins^{10,11}. Especially in patients at high cardiovascular risk, premature discontinuation of statin therapy has been shown to increase the risk of death from atherosclerotic cardiovascular diseases¹².

The aim of this study was to determine the proportion of patients who continued statin therapy in the short and long term, the changes in this proportion over the years, and the factors thought to influence statin persistence, such as age, sex, cardiometabolic diseases, statin indications, and intensity of statin therapy.

MATERIALS and METHODS

A retrospective, observational, clinical study was conducted at Istanbul Medeniyet University Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Internal Medicine Outpatient Clinics, including consecutive patients aged 18 and above who initiated statin therapy between January 1, 2016, and January 1, 2017, and had regular medical records available. Patients receiving non-statin lipid-lowering therapy and those with missing medical records were excluded from the study. The flow of the study is depicted in Figure 1. Informed consent was obtained from the patients participating in the studies. Local Ethics Committee of Istanbul Medeniyet University approval was obtained for the study (reference number: 2023/0714, date: 25.10.2023), and the study adhered to the principles of the Helsinki Declaration throughout its duration.

The primary endpoint of the study was to evaluate the proportion of patients continuing statin therapy among those who initiated it, and the changes in this proportion

over the years.

The secondary endpoint was aimed at determining whether there were differences in demographic and cardiometabolic disease characteristics, statin intensity, and indications for statin initiation between patients continuing and discontinuing statin therapy.

Study Design

Patients' baseline age, gender, presence of cardiometabolic diseases such as diabetes mellitus (DM), coronary artery disease (CAD), and hypertension (HT), as well as indications for statin initiation (primary or secondary prevention), and statin classification (low-intensity, moderate-intensity, high-intensity) were determined from their medical records. Short-term (2018) and long-term (2023) statin persistence statuses were also determined from the medical records as part of the study flow process. Patient groups persisting, and non-persisting with statin therapy were compared for demographic characteristics, presence of cardiometabolic diseases, statin intensity, and indications for statin initiation for both time periods.

Definitions

Cardiometabolic diseases and mortality

Patients' diagnoses of HT, DM, and CAD were determined from their medical records using International Classification of Diseases (ICD-10) 10th revision ICD-10 codes. Mortality records were obtained from the National Death Notification System.

Statin indication and persistence

Patients who had not experienced a cardiovascular event before starting statin therapy were classified as receiving statin therapy for primary prevention, while those who had experienced an atherosclerotic cardiovascular event were classified as receiving statin therapy for secondary prevention. Among patients initiated on statins for primary prevention, those who experienced an atherosclerotic cardiovascular event between 2018 and 2023 were additionally classified as receiving statin therapy for primary and secondary prevention.

Statin discontinuation was defined as a period of ≥ 90 days without statin therapy.

Statin Intensity

Low-intensity statin therapy was defined as fluvastatin 20-40 mg, lovastatin 20 mg, simvastatin 10 mg, pitavastatin 1 mg, and pravastatin 10-20 mg. Moderate-

intensity statin therapy was defined as atorvastatin 10-20 mg, fluvastatin twice daily 40 mg or once daily 80 mg (extended-release formulation), lovastatin 40 mg, pitavastatin 2-4 mg, pravastatin 40-80 mg, rosuvastatin 5-10 mg, and simvastatin 20-40 mg. High-intensity statin therapy was defined as atorvastatin 40-80 mg or rosuvastatin 20-40 mg.

Statistical Analysis

SPSS 26 (Statistical Package for the Social Sciences) software was used for data analysis. Descriptive statistical methods, such as mean, standard deviation, median, minimum, and maximum values, were used to evaluate quantitative variables, while qualitative variables were presented as frequencies and percentages. The normal distribution of data was assessed using the Shapiro-Wilk test, and box plots. The chi-square test and McNemar test were used to compare qualitative data. Results were evaluated at a significance level of $p < 0.05$ with a 95% confidence interval.

RESULTS

A total of 903 patients, with a mean age of 60.7 ± 11.7 years and a female predominance (76.6%), were included in the study. Of these, 574 (63.6%) were initiated on atorvastatin, 284 (31.5%) on rosuvastatin, 41 (4.5%) on pitavastatin, and 5 (0.5%) on simvastatin.

The majority of patients (90.8%) were prescribed moderate-intensity statin therapy, while 9.2% received high-intensity statin therapy; no patients received low-intensity statin therapy. Among the patients, 88.4% were initiated on statin therapy for primary prevention, while 11.6% were initiated on statin therapy for secondary prevention. HT was the most common comorbid cardiometabolic disease (43.3%). The majority of patients (86.3%) were between the ages of 45 to 79 years (Table 1).

The frequencies of patients continuing and discontinuing statin therapy in the 2018 and 2023 assessments are shown in Table 2. In the 2018 assessment, out of 903 patients, 498 (55.1%) continued statin therapy, while 405 (44.9%) discontinued. In the 2023 assessment (excluding those who were deceased), out of 867 patients, 448 (51.7%) continued statin therapy, while 419 (48.3%) discontinued. Between 2018 and 2023, it was observed that 36 patients (3.9%) died. The mortality rate was 3.6% ($n=18$) among those continuing statin therapy and 4.4% ($n=18$) among those discontinuing statin therapy ($p=0.526$).

In the 2018 assessment, out of 480 patients continuing statin therapy, 325 (67.7%) continued in the

2023 assessment, while 155 (32.3%) discontinued. Among the 387 patients who discontinued statin therapy in the 2018 assessment, 123 (31.8%) restarted statin therapy in the 2023 assessment, while 264 (68.2%) remained discontinued.

In the 2018 assessment, the frequency of statin non-persistence was higher in patients who were initiated on statins for primary prevention compared to those who were initiated for secondary prevention ($p=0.001$). Patients with HT, DM, and CAD, were observed to have a higher rate of statin persistence compared to those without these comorbidities (all $p=0.001$). In terms of age groups, patients aged <45 years, had a higher frequency of statin non-persistence compared to other age groups ($p=0.028$) (Table 3).

Table 1. Baseline characteristics of the patients.		
Age (year)	Mean±Sd	60.74±11.70
	Median (min-max)	61 (19-95)
	<45	79 (8.7)
Age groups (n,%)	45-64	485 (53.7)
	65-79	294 (32.6)
	≥80	45 (5.0)
Gender (n, %)	Female	692 (76.6)
	Male	211 (23.4)
Statin intensity (n, %)	Moderate-intensity	820 (90.8)
	High-intensity	83 (9.2)
Statin indication (n, %)	Primary prevention	798 (88.4)
	Secondary preventiom	105 (11.6)
Cardiometabolic diseases (n, %)	Hypertension	391 (43.3)
	Diabetes mellitus	213 (23.6)
	Coronary artery disease	100 (11.1)
Sd: Standard deviation		

Table 2. Change in statin persistence over the years.			
	Total	Continuing statin therapy	Discontinuing statin therapy
Patient data for the year 2018 (n,%)	903	498 (55.1)	405 (44.9)
Those who exited between 2018 and 2023 (n,%)	36	18 (3.6)	18 (4.4)
Patient data for the year 2023 (n,%)	867	448 (51.7)	419 (48.3)

In the 2023 assessment, patients using moderate-intensity and primary prevention statins had a higher frequency of statin non-persistence compared to those continuing statin therapy (both $p=0.001$). Meanwhile, patients using high-intensity and secondary prevention statins had a higher frequency of statin persistence

compared to those discontinuing statin therapy (both $p=0.001$). Similar to the 2018 assessment, patients with HT, DM, and CAD had a higher rate of statin persistence compared to those without these comorbidities (all $p=0.001$). Patients aged <45 years had a higher frequency of statin non-persistence ($p=0.036$) (Table 4).

Table 3. Clinical characteristics of patients continuing and discontinuing statin therapy based on 2018 data.

		Continuing statin therapy (n=498)	Discontinuing statin therapy (n=405)	p
Gender (n, %)	Female	125 (25.1)	86 (21.2)	0.172
	Male	373 (74.9)	319 (78.8)	
Statin intensity (n, %)	Moderate-intensity	452 (90.8)	368 (90.9)	0.958
	High-intensity	46 (9.2)	37 (9.1)	
Statin indication (n, %)	Primary prevention	416 (83.5)	382 (94.3)	0.001
	Secondary prevention	82 (16.5)	23 (5.7)	
Cardiometabolic disease (n, %)	Hipertansiyon	252 (50.6)	139 (34.3)	0.001
	Diabetes mellitus	147 (29.5)	66 (16.3)	0.001
	Coronary artery disease	79 (15.9)	21 (5.2)	0.001
Age (n, %)	<45	32 (6.4)	47 (11.6)	0.028
	45-64	265 (53.2)	220 (54.3)	
	65-79	174 (34.9)	120 (29.6)	
	≥80	27 (5.4)	18 (4.4)	

Table 4. Clinical characteristics of patients continuing and discontinuing statin therapy based on 2023 data.

		Continuing statin therapy (n=448)	Discontinuing statin therapy (n=419)	p
Gender (n, %)	Female	343 (76.6)	330 (78.8)	0.438
	Male	105 (23.4)	89 (21.2)	
Statin intensity (n, %)	Moderate-intensity	393 (87.7)	397 (94.7)	0.001
	High-intensity	55 (12.3)	22 (5.3)	
Statin indication (n, %)	Primary prevention	348 (77.7)	373 (89.0)	0.001
	Secondary prevention	68 (15.2)	27 (6.4)	
	Primary-secondary prevention	32 (7.1)	19 (4.5)	
Cardiometabolic disease (n, %)	Hypertension	215 (48)	150 (35.8)	0.001
	Diabetes mellitus	128 (28.6)	70 (16.7)	0.001
	Coronary artery disease	65 (14.5)	25 (6)	0.001
Age (n, %)	<45	29 (6.5)	50 (11.9)	0.036
	45-64	250 (55.8)	229 (54.7)	
	65-79	150 (33.5)	126 (30.1)	
	≥80	19 (4.2)	14 (3.3)	

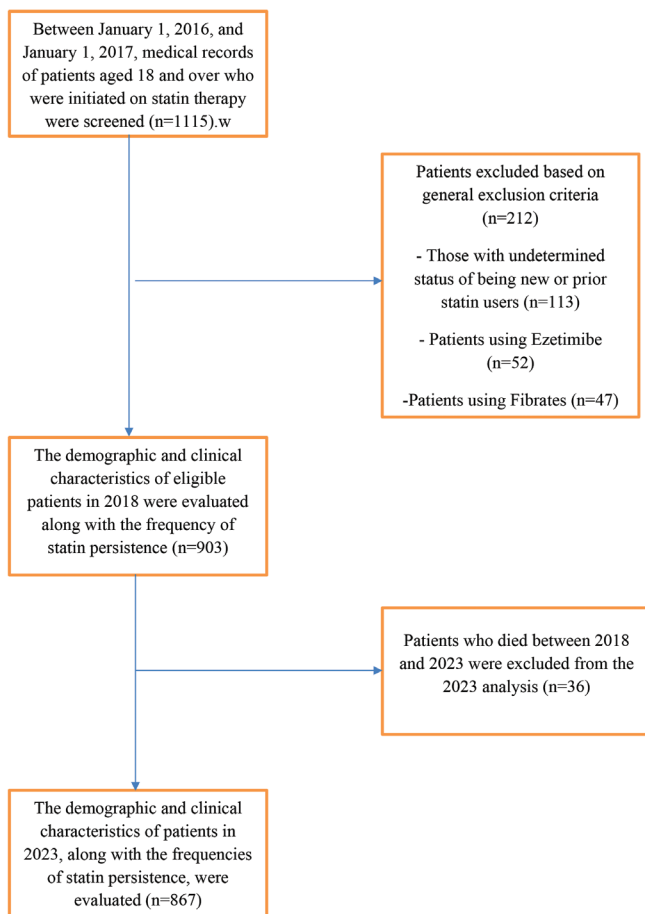


Figure 1. Study flow process.

DISCUSSION

The results of this study have demonstrated that statin persistence is low in both short and long-term follow-ups of patients who initiate statin therapy, with no improvement over time. Particularly, lower statin persistence has been observed in young patients (<45 years), patients with low cardiovascular risk, and patients initiated on statins for primary prevention.

In our cohort, approximately 90% of patients were initiated on statins for primary prevention. This relatively low rate of secondary prevention can be explained by the specific patient profile and departmental context of our study. In our internal medicine clinic, the majority of our patients had comorbidities such as DM and HT, for whom statin therapy was initiated primarily for primary prevention. In contrast, patients with established cardiovascular diseases-such as myocardial infarction, stroke, or peripheral artery disease-are often managed by cardiology, neurology, or cardiovascular surgery departments, where statin initiation typically occurs.

Moreover, real-world studies have also shown that the number of patients initiated on statins for primary prevention is substantially higher than the number of those receiving statins for secondary prevention. This disparity in statin prescriptions appears consistent with the findings of our study¹³.

It has been reported that among therapies aimed at controlling cardiometabolic diseases such as dyslipidemia, DM, and HT, patients using statins exhibit the lowest adherence and persistence rates¹⁴. Similar findings are observed among different lipid-lowering drugs such as statins, ezetimibe, and anti-proprotein convertase subtilisin/kexin type 9 monoclonal antibodies, where statin initiators demonstrate the lowest persistence and adherence rates¹⁵. Cohort studies have reported a decreasing trend in both short and long-term statin persistence and adherence rates^{16,17}. In patients aged 45 and above initiated on statins for DM and/or cardiovascular disease, the likelihood of continuing statin therapy decreases to 47% after one year and 19% after five years; with statin persistence falling below 25% regardless of the presence of revascularization, heart failure, peripheral artery disease, or renal disease at the outset of a 5-year follow-up⁷.

In our study, it was observed that 44.9% of patients initiated on statins, did not continue statin therapy at the first-year evaluation, and this rate increased to 48.3% at the sixth-year evaluation. This finding is in line with existing literature, indicating that nearly half of patients initiated on statins discontinue treatment over time. It can be interpreted as a promising improvement that 31.8% of patients who did not continue statin therapy in the first year resumed statin therapy at the sixth-year evaluation. However, although this is not sufficient.

Various demographic factors such as age and gender, as well as drug-related characteristics such as the indication for statin initiation (primary or secondary prevention), statin intensity, and statin type, are known to play a role in statin persistence and adherence. Clinical trials have reported lower statin persistence and adherence, especially in the youngest and oldest individuals and those without cardiovascular disease or risk factors. In contrast, higher persistence and adherence are observed in patients initiated on statins for secondary prevention, and with high-intensity statins, although the effect of gender remains controversial^{13,17,18}. In our study, it was observed that both in the first and sixth-year evaluations, patients initiated on statins for primary prevention and those under 45 years of age were less likely to continue statin therapy. In contrast, patients initiated on statins for secondary prevention and those

with HT, DM, or CAD were more likely to continue statin therapy. The lower statin persistence in patients under 45 years of age and those initiated on statins for primary prevention can be explained by these individuals being mostly asymptomatic and having a lower awareness of cardiovascular risk due to their relatively good health status and lower prevalence of cardiovascular events.

No significant difference in statin persistence was found in patients initiated on moderate or high-intensity statins at the first-year evaluations. However, at the sixth-year evaluations, statin persistence was lower in patients using moderate-intensity statins compared to those using high-intensity statins. The higher persistence rates observed in patients using high-intensity statins for secondary prevention appear to be consistent with the notion that individuals at high cardiovascular risk are more adherent and responsive to statin therapy. No gender difference in statin persistence was observed in our study.

An increase in exaggerated media reports about statin side effects has been observed to have a negative impact on the statin persistence and adherence¹⁹. Early discontinuation of statins has been reported to increase the risk of myocardial infarction and cardiovascular mortality in these patients. Although the effect of media reports on statin persistence was not evaluated in our study, the fact that approximately one-third of patients discontinued or resumed treatment at the first and sixth follow-ups suggests that patients are still influenced by them.

Study Limitations

Retrospective design is one of the limitations in this study. Firstly, the reasons for discontinuation of statins by patients, whether due to drug characteristics, physician or media influence, or patient factors, were not evaluated. Secondly, due to the intervening COVID-19 pandemic, the relationship between lipid control and statin persistence could not be established because of the lack of regular lipid monitoring in patients. Thirdly, since it was not clearly determined whether mortality causes were cardiovascular, or not, a cause-effect relationship between statin persistence and cardiovascular events and mortality could not be established. Fourth, due to the absence of patients initiated on low-intensity statins, the effect of statin intensity on statin persistence could be limited. Lastly, due to the asymmetric distribution of initiated statin types (mostly atorvastatin), a comparable statistical analysis could not be performed for the relationship between statin type and statin persistence.

CONCLUSION

In conclusion, the results of this study have shown that statin persistence is low for both short- and long-term follow-ups, regardless of the reason for initiation. Although there is no simple way to increase statin adherence, increasing patient awareness and consciousness of cardiovascular risk through listening to patient concerns about treatment, informing about potential side effects, engaging in discussions, and involving patients in the decision-making process for treatment should be the primary approach to improve statin persistence and adherence.

Ethics

Ethics Committee Approval: Local Ethics Committee of Istanbul Medeniyet University approval was obtained for the study (reference number: 2023/0714, date: 25.10.2023).

Informed Consent: This is a retrospective study.

Footnotes

Author Contributions

Surgical and Medical Practices: M.U., E.E., L.C., Concept: M.U., C.T., G.A.U., Design: M.U., C.T., E.E., Data Collection and/or Processing: M.U., C.T., E.E., G.A.U., L.C., Analysis or Interpretation: M.U., C.T., E.E., Literature Search: M.U., C.T., E.E., Writing: M.U., C.T., E.E.

Conflict of Interest: The authors have no conflict of interest to declare.

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