Received: 5 January 2024 | Revised: 17 April 2024 | Accepted: 18 April 2024

DOI: 10.1111/bcpt.14015

ORIGINAL ARTICLE

BCPT Basic & Clinical Pharmacology & Toxicology

Persistence to statin treatment: A cohort study in Lithuania

Karina Kirilova[1] | **Indrė Trečiokienė**[1,2] | **Nomeda Bratčikovienė**[3,4] | **Miriam Qvarnström**[5] | **Björn Wettermark**[1,5]

[1]Pharmacyand Pharmacology Center, Institute of Biomedical Science, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

[2]Unit of PharmacoTherapy, Epidemiology & Economics, Groningen Research Institute of Pharmacy, Faculty of Science and Engineering, University of Groningen, Groningen, Netherlands

[3]Department of Mathematical Statistics, Faculty of Fundamental Sciences, Vilnius Tech, Vilnius, Lithuania

[4]Department of Human and Medical Genetics, Institute of Biomedical Science, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

[5]Department of Pharmacy, Faculty of Pharmacy, Uppsala University, Uppsala, Sweden

Correspondence
Indrė Trečiokienė, Pharmacy and Pharmacology Center, Institute of Biomedical Science, Faculty of Medicine, Vilnius University, Vilnius, Lithuania.
Email: i.treciokiene@rug.nl and indre.treciokiene@mf.vu.lt

Funding information
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Abstract

Cardiovascular diseases are the main causes of death, and statins can reduce the risk of major vascular events. Lithuania is among the European countries with the highest cardiovascular mortality despite a rapidly increasing use of statins. Previous reviews have shown the problem of poor patient adherence, but there are limited studies from Eastern European countries. The aim of this study was to evaluate treatment persistence in new users of statins in Lithuania and to investigate factors associated with persistence. Dispensed prescriptions from patients aged >18 years old initiated on statins in 2018–2019 were included, and data were obtained from a national health insurance fund. Persistence was assessed by the proportion of patients who still had statins dispensed 1 year after the first dispensing. Factors associated with persistence were assessed using logistic regression. A total of 104 726 patients (41.3% men) were initiated on statin treatment. Only 41% of them continued statin use 1 year after initiation. Factors associated with higher persistence rate were older age, higher dose of statin, use of other medicines and use of statins as secondary prevention. Low persistence to statin therapy needs to be recognized by healthcare workers, pharmacists and policy makers to address this problem.

KEYWORDS
adherence, drug utilization, persistence, pharmacoepidemiology, statins

1 | INTRODUCTION

Cardiovascular diseases (CVD) are attributable to more than 3.9 million deaths annually in Europe. CVD is the main cause of death in most European countries.[1] The Baltic states, along with Romania, have the highest mortality rates of CVD in the European Union, comprising 50%–60% of all deaths.[2] For CVD prevention, it is important to lower low-density lipoprotein cholesterol (LDL-C), and for the treatment of dyslipidaemia, statins remain the first-choice therapy, as they have shown to be effective in reducing the risk of major vascular events by lowering LDL-C.[3]

However, large number of studies have shown room for improvement in both physician adherence to guidelines[4] and how statins are being used by the

patients. Many patients have poor adherence to statin therapy and discontinue treatment early after initiation.[5,6] There is also evidence from many observational studies that high adherence and persistence to statin therapy reduce cardiovascular morbidity and mortality.[7,8]

Recently, Makarevicius et al. showed that statin use has increased dramatically in Lithuania during the last decade[9]; still, Lithuania belongs to the countries with the lowest lipid-modifying medication use in European countries.[10] These low rates could be explained by the fact that few patients are initiated with statins or that those patients who are initiated have a low persistence to prescribed medicines. Persistence to statins has not been studied before, thus limiting the recognition of the possible problem affecting cardiovascular mortality. Insights into factors influencing the persistence to statin could identify potential areas for improvement in managing CVD.

The aim of this study was to evaluate treatment persistence in new users of statins in Lithuania and to investigate factors associated with persistence.

2 | MATERIALS AND METHODS

2.1 | Setting

A longitudinal observational retrospective cohort study was conducted assessing the persistence to statins treatment in Lithuania among adult patients (≥18 years) who had their first statin dispensed in 2018–2019. In Lithuania, the national health insurance system is public and covers approximately 97% of the population.[11] The state-provided universal healthcare coverage includes the reimbursement of statins. Prescribed medicines are reimbursed through the National Health Insurance Fund (NHIF). All dispensations of reimbursed medicines are recorded in the information system 'Sveidra'. During the studied period, statins have been reimbursed in hyperlipidaemia, ischaemic attacks, angina pectoris, myocardial or cerebral infarction, occlusion and stenosis of arteries and after cardiac surgery.[12] Reimbursed medicines could be sold outside this system, for example, to foreigners and privately insured patients. Out-of-pocket dispensing in pharmacy is possible without a prescription for a limited 1-month period for those already on treatment. Reimbursed prescriptions could be prescribed for the period from 1 to 6 months. The medicines bought completely out of pocket are not included in the 'Sveidra' dataset, but the medicines that are partly subsidized are included. Personal patient and prescriber information was coded by NHIF.

2.2 | Data sources

Data on dispensed and reimbursed prescription medicines were obtained from the information system 'Sveidra' of the Lithuanian National Health Insurance Fund (NHIF), which contains data on all reimbursed prescriptions and covers up to 100% of the insured population.[13] Only information from the subsystem on reimbursed medicines with some anonymised information about patient and prescriber was used in this study. Patient's sex, age in full years and area of primary care registration were recorded.

The extracted dataset contained all of the filled prescriptions of reimbursed drugs. On each dispensation record, the information on date of prescribing and dispensing, diagnoses by International Classification of Diseases (ICD-10) code, non-proprietary name of the substance, the brand name of the dispensed drug, formulation and strength, WHO Anatomical Therapeutic Chemical classification system (ATC) codes, package size and supply period are recorded. Prescriber qualification was also recorded in the dataset provided.

2.3 | Population

In this study, adult patients (≥18 years) who were initiated on statins during 2018–2019 were included. Patients initiated on statins were selected as having not been dispensed any statin in the previous year, for example, patients were identified as new users if they had no statin prescription from January to December 2017. For the analyses and comparisons in this study, we included all statins (ATC class C10AA).[14] At the time of the study, the following four statins were available on the Lithuanian market: simvastatin (C10AA01), fluvastatin (C10AA04), atorvastatin (C10AA05) and rosuvastatin (C10AA07). Simvastatin was available in two strengths, 10 and 20 mg; fluvastatin in 80 mg; atorvastatin in 10, 20, 30, 40, 60 and 80 mg; and rosuvastatin in 5, 10, 15, 20, 30 and 40 mg. In this study, statin sales were classified by their intensity of treatment as low- (10-mg simvastatin, 20- to 40-mg fluvastatin), moderate- (20- to 40-mg simvastatin, 80-mg fluvastatin, 10- to 30-mg atorvastatin, 5- to 15-mg rosuvastatin) and high-intensity (40- to 80-mg atorvastatin, 20- to 40-mg rosuvastatin) statins.[15,16]

The index date was the date of the first dispensed statin prescription in the years 2018 or 2019. For a patient to be included in the cohort, it was required to have at least 12 months of follow-up time after the index date. Patients were not censored for death or migration as these data were not available in the dataset. Patients were also not censored for being admitted to hospital or home care. In Lithuania, patients admitted to institutions either

used their own chronic medications or could have been prescribed reimbursed medicines that had been administered for at least 1 month before hospitalization.[17]

2.4 | Covariates

Baseline patient characteristics were captured at the index date and include sex, age, first statin prescribed (type and intensity, see below), prescriber (GP, cardiologist or other), cardiovascular risk and which statin substance was dispensed. Previous use of antihypertensive, antithrombotic or antidiabetic drugs was also recorded.

Each patient's cardiovascular risk was assessed using registered diagnoses (ICD-10 codes) on all previous prescriptions during the year before initiation. Based on diagnoses, patients were split into two groups (primary and secondary CVD prevention). No previous diagnoses and diseases such as diabetes mellitus (E10; E11) and hypertension (I10; I11) were considered as a primary CVD prevention, while myocardial infarction (I21; I22; I25.2), stroke and transient ischemic attack (I63) and ischemic coronary heart disease (I20; I25.0; I25.1; I25.5; I25.6; I25.8; I25.9) were considered as secondary CVD prevention. Previous use of other medications such as antidiabetic (ATC A10), antithrombotic (ATC B01) and antihypertensives (ATC C03, C07, C08, C09) was recorded if the drugs were dispensed during the year before initiation.

2.5 | Main outcomes measures

Medication adherence is described as a process that consists of initiation, implementation and discontinuation of medicine use while persistence is described as the length of time between initiation and the last dose, which immediately precedes discontinuation.[18] Persistence with treatment and discontinuation are two related constructs that could be either measured as a time to discontinuation (continues variable) or if the patient is in possession of medicines at a certain time point (dichotomous variable).[19] In this study, persistence (discontinuation) was measured by assessing if the patient had medicine supplies after 1 year of initiation or did not.[20] No considerations were taken into defined daily doses (DDDs) or the number of packages dispensed.

Patients were defined as persistent if they had been dispensed statin in the time interval of 365 ± 90 days starting from their first prescription dispensed (index date). Individual patients were followed from the index date to the end of the study period (2020.12.31). Each patient's dispensing patterns were assessed over time and persistence to statin therapy was calculated within the first year. Patients remaining on statins treatment, but switching between statin types or doses, were considered as persistent.

2.6 | Statistical analysis

Data were analysed using the R environment (version 4.3.1 [2023-06-16]). Descriptive statistics was used to describe baseline characteristics. Continuous non-normally distributed variables were summarized using medians, as a measure of central tendency, and differences were tested using a Mann–Whitney U (Wilcoxon). Frequency distributions between groups are compared with the Chi-square test. We consider the differences to be statistically significant when p-value < 0.05. A multivariate logistic regression was used to explore factors associated with persistence. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) were calculated. The dependent variable was persistence to statins, and independent variables were age group, gender, area of primary care registration, prescriber qualification, type of prevention, diagnosis, previous use of drugs and initiated statin type.

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[21] Ethical approval was issued by the Vilnius Regional Biomedical Research Ethics Committee in 2021. Permission number 2021/2-1314-790.

3 | RESULTS

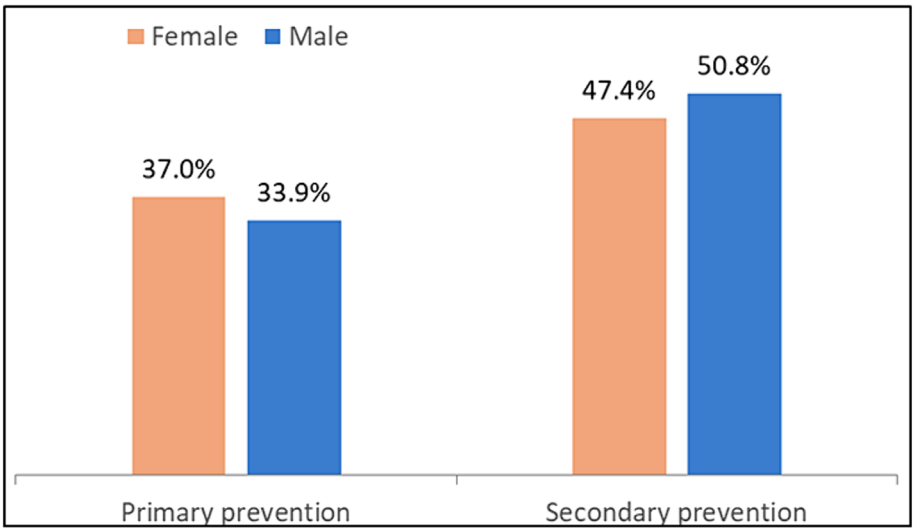
3.1 | Characteristics of patients initiated on the statin treatment

A total of 104 726 patients (41% men, 59% women) were initiated on statin therapy in Lithuania between 2018–2019 and thus included in the study (Table 1). The age group of 45–64 years old accounted for the largest proportion of patients initiated on statins treatments, with men in general being younger than women at initiation on statin treatment (p-value < 0.001). A majority of all women 69% initiated on statin treatment received medication for primary prevention, while the corresponding figure for men was 56% (Table 1). Comorbidity with hypertension and diabetes mellitus were common. The most commonly used other cardiovascular drugs were antihypertensives.

The majority of patients were initiated on moderate-intensity statin treatment (74%), while 26% were on high-intensity statin treatment. Atorvastatin accounted for 60.2% of all prescribed medications, while rosuvastatin constituted 39.6% of the prescriptions. On the other hand, fluvastatin and simvastatin were initiated in fewer than 1% of all patients.

TABLE 1 Characteristics of patients initiated on the statins' treatment in Lithuania 2018–2019.

	Women		Men	
	Total	**%**	**Total**	**%**
Age group				
Total	61 478	100.0%	43 248	100.0%
Age 18–44	380	0.6%	4945	11.4%
Age 45–64	37 369	60.8%	24 499	56.7%
Age 65–74	12 056	19.6%	8128	18.8%
Age 75+	11 673	19.0%	5676	13.1%
Cardiovascular risk (other diagnosis)				
Stroke/TIA	2401	3.9%	2671	6.2%
Heart attack	4110	6.7%	7734	17.9%
Ischemic coronary heart disease	15 679	25.5%	13 260	30.7%
Diabetes mellitus	9430	15.3%	6701	15.5%
Hypertension	50 362	81.9%	34 963	80.8%
Primary prevention	42 354	68.9%	24 166	55.9%
Secondary prevention	19 124	31.1%	19 082	44.1%
Previous use of drugs				
Antidiabetic	7091	11.5%	4675	10.8%
Antithrombotic	3920	6.4%	3363	7.8%
Antihypertensives	39 054	63.5%	23 041	53.3%



Differences were statistically significant in both groups, Chi-Square p-value<0.001

FIGURE 1 Patients persistent to statin treatment by prevention type.

3.2 | Patients' persistence to the treatment

In the study, 41% of all patients remained on the statin therapy after 1 year. Persistence was similar between genders with 40% of women and 41% of men being considered as persistent to the statin treatment. Patients using statins for secondary prevention were more persistent than patients using statins for primary prevention (Figure 1). The proportion of patients persistent to statin treatment increased by age, except for in the oldest age group. The group of patients in 18–44 years age group was the only group where males shared a lower persistence rate than females, respectively 32% for males and 39% for females (Figure 2).

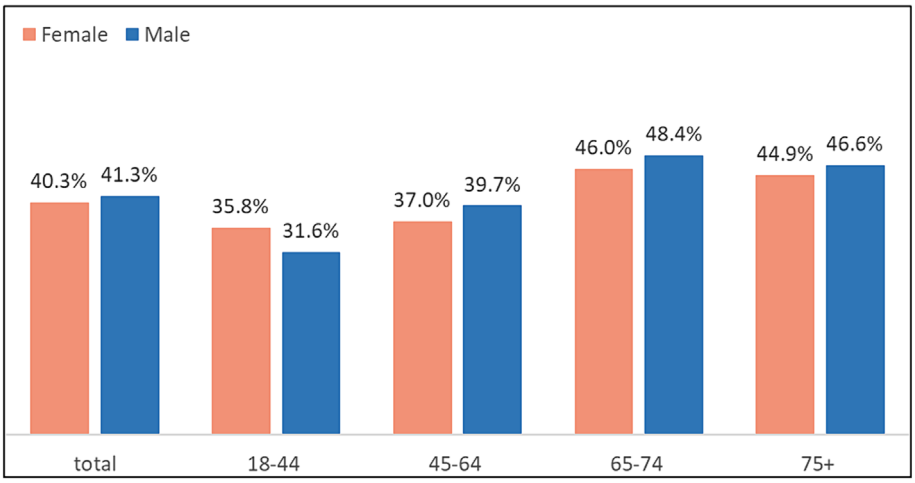
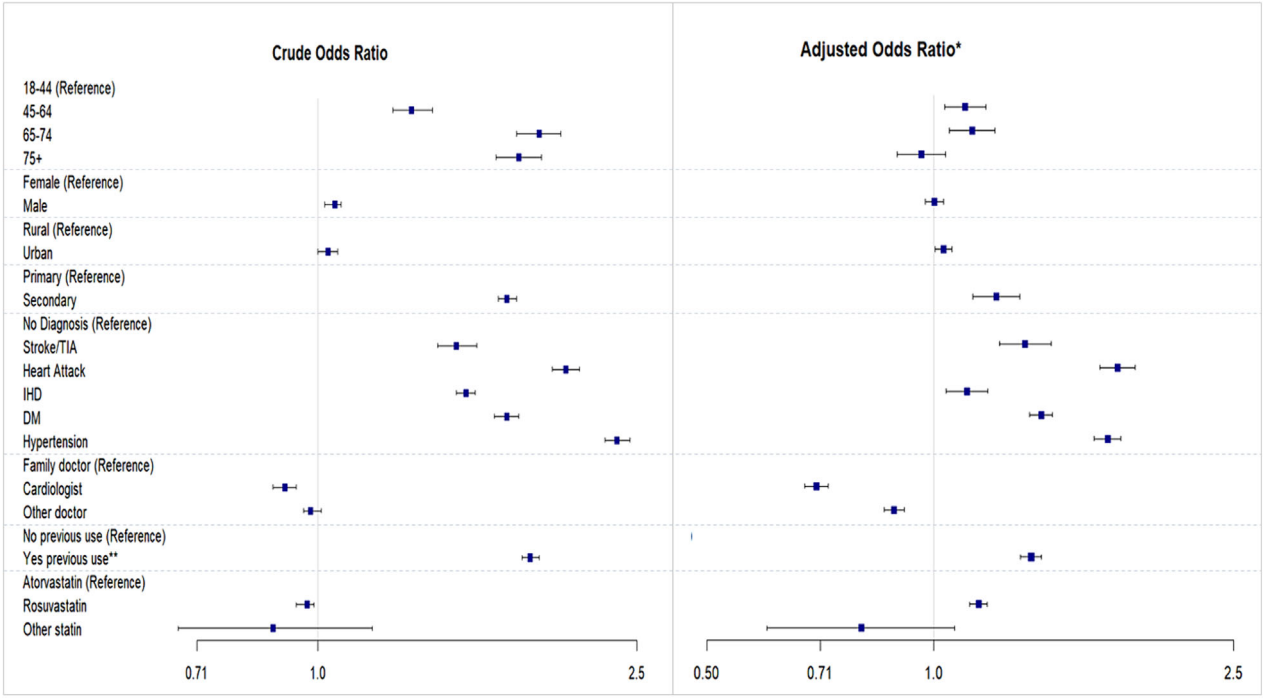


FIGURE 2 Patients persistent to statin treatment by gender and age group.

Differences were statistically significant in all groups, Chi-Square p-value<0.001



** Multivariate stepwise regression model including all covariates studied: age in years, gender, area of primary care registration, prescriber qualification, type of prevention, diagnosis, previous use of drugs and initiated statin type*

*** Previous use of anti-diabetic, antithrombotic, antihypertensive (at least one or all of them)*

95% confidence intervals calculated

IHD - Ischemic coronary heart disease; DM - Diabetes mellitus disease, TIA - Transient ischemic attack

FIGURE 3 Factors associated with persistence to statins.

3.3 | Factors associated with persistence to statins

Patients in the age group of 65–74 years were more likely to stay persistent to the statin treatment (adjusted OR 1.12, CI 1.05–1.21). It was also observed that patients on secondary prevention were more likely to stay persistent to the treatment (adjusted OR 1.21, CI 1.13-1.30). Patients with previous use of anti-diabetic, antithrombotic and antihypertensive were more persistent (adjusted OR 1.35, CI 1.30–1.39) than those who had no previous use of these drugs. Crude and adjusted ORs are presented in Figure 3. Tabular results for the logistic regression are presented in Table A1.

4 | DISCUSSION

In this study of more than 100 000 people in Lithuania initiated on statin treatment in 2018–2019, we found that

only 41% remained on treatment after 1 year. Prior studies have shown a large difference in persistence between different studies. A review of 139 studies showed a variation in 1-year persistence to lipid-lowering therapy between 30% and 85%.[22] Consequently, Lithuania seems to belong to countries with the lowest persistence. High variation between the countries could be explained by differences in health care systems and differences in methods of persistence measurement.[22]

In Lithuania, atorvastatin and rosuvastatin were found to be the leading statins for patients initiated on the treatment. According to a recent study conducted in Croatia, the most commonly used statin was atorvastatin (43%).[23] However, the achievement of LDL-C goals was relatively low at 39%, especially among those considered to be at high cardiovascular risk (37%). The study also revealed that overall adherence to statin medication was suboptimal.[23] In a Spanish study, the most commonly used statin was simvastatin (40.4% of new users), followed by atorvastatin (24.7%), rosuvastatin (24.4%) and other statins.[24] However, it is important to acknowledge that the choice of statin for initiation may vary substantially depending on the time period, since large changes have happened on the market with patent expiries, introduction of new drugs and guideline changes.[25] In this study, it was discovered that in Lithuania, there were relatively more men on secondary prevention than women. The tendency for women generally to experience the onset of CVD 10 years later than men is notable, though the risk for CVD such as ischemic heart disease raised in parallel after age 55 years for women and 45 years for men. In clinical trials, women experience the same low-density lipoprotein (LDL) reductions on statins and possibly greater atherosclerotic regression on statins per unit LDL reduction. However, in practice, it has been shown that women taking statins are less likely to achieve desired LDL goals.[26]

After the adjustment of different covariates, it was found that patients on the secondary prevention had 21% higher odds to stay persistent on the treatment, than patients initiated statins for the primary prevention. This is positive given the higher risk these patients have. A systematic review to assess the effects of adherence and persistence on clinical outcomes in patients treated with statins has shown that good adherence and longer duration of persistence with statins were associated with progressively increasing clinical benefits in secondary prevention and reduction of CVD events.[7] An extensive meta-analysis involving 376 162 patients across 20 studies, which examined prescription refill frequency for seven distinct drug classes, revealed notable patient adherence rates of 57% for statin treatment in primary prevention and 76% in secondary prevention.[5]

The results for patients with secondary prevention are also supported by results on previous medicine use. This study shows that patients who had a record of previous use of other medications had 35% higher adjusted odds of being persistent to statin treatment than those who had no previous use of medications. This might indicate that people have a better understanding of possible disease risk and the importance of treatment. Similar results were found in an observational study conducted on a cohort of 26 768 individuals who experienced a myocardial infarction or underwent revascularization in Stockholm between 2012 and 2018. This study showed that strong adherence to treatment, the utilization of high-intensity statins and the existence of conditions like hypertension or diabetes mellitus were correlated with an increased likelihood of reaching and sustaining LDL-C targets.[27]

In the study, it was found that patients who were initiated with statins by family doctors had higher persistence rates than patients initiated with statins treatment by cardiologist. It might be hypothesized that better persistence to treatment initiated by family doctors can be explained by continuity with follow-up visits to renew prescriptions. However, continuity itself was not measured in this study, and as other studies have found the opposite,[28] this should be studied further. The differences in these studies may rather reflect the difference between primary care practices in different countries. There is variability in the ratio of GPs to population and in the extent to which patients relate to individual physicians in European countries. In some countries, the gatekeeper function of general practice is more highly developed and the use of specialist services varies accordingly.

The main strength of this study is the large number of included patients with complete nationwide coverage of all patients in Lithuania initiated on statin treatment and all drugs dispensed to them. Furthermore, important covariates such as previous cardiovascular diagnoses to distinguish between secondary and primary prevention as well as previous use of other medications were also assessed. In the study, there were also some limitations. One of the limitations is that we could not distinguish the people who died in the study year from the study population and this could contribute to non-persistency rates. It is known that myocardial infarction survivors remain at higher risk of CV death, particularly older individuals and patients with comorbid hypertension, diabetes, peripheral artery disease or history of stroke.[29] In a large Swedish study, an annual risk of death after myocardial infarction ranged from 6.5% (England) to 10.0% (USA) and was more than double those in the general population.[30]

In this study, we used claims data where primary non-adherence, when patients were prescribed statins but never claimed the prescription, could not be detected. As there might have been patients who have not started their treatment, the actual number of patients prescribed statin treatment but not taking medications might be even higher. We used the anniversary method to assess persistence. It is simple and easy to compute, but it is rather unspecific; it only assesses whether or not patients are still in possession of medicines at the given period after initiation, but it is insensitive to discontinuation periods that occur before the treatment initiation anniversary. The other limitation of the persistence measure is that it does not measure true adherence, as it is only assumed that patients in possession of the medicine take the medicines as prescribed. The choice of the follow-up period could have also affected the small number of patients who were initiated statin treatment at the end of 2019. As the data were only available for 2020, some of those might have been assigned to being non-persistent. Statins that were purchased completely out of pocket have not been included in this study.

We also acknowledge the limitation that classifying patients as primary or secondary prevention was based on diagnoses recorded before initiation of the treatment. Some patients might have experienced a cardiovascular event during the study period which could have enhanced their adherence. Cardiovascular events were not recorded in the data used, and we have not checked if new diagnoses occurred during follow-up.

Despite some methodological limitations of the study, this investigation of statin persistence in Lithuania should raise concerns among clinicians, patients and society about the clinical problem. Poor medication adherence has been a healthcare issue for several decades; very few countries measure and report on rates of adherence and persistence at the health system level. CVD could be preventable with initiation and continuation of statins treatment being one of the most critical interventions to decrease cardiovascular morbidity and mortality.

Interventions to increase therapy persistence should be done. In particular, given the high mortality rate due to CVD in Lithuania, such interventions may be focused on the patient, health professionals and the health delivery system. Multifaceted combinations of patient education, patient–physician communication enhancement, extended care through ancillary healthcare providers, simplification of drug regimens, increased patient monitoring and additional follow-ups are likely strategies that can be implemented.[31,32] Although listed interventions could help increase persistence to statin treatment, this would require relatively high investments into healthcare workforce by the government.

5 | CONCLUSION

Less than half of Lithuanian patients initiated on statin therapy remained on treatment after a year later. Low persistence to statin therapy should raise concerns among clinicians and policy makers to address this problem. Special focus and tailored intervention should be focused on younger patients treated for primary prevention, not using any other cardiovascular medicines.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Indrė Trečiokienė https://orcid.org/0000-0001-6583-9999

Björn Wettermark https://orcid.org/0000-0003-0531-2516

REFERENCES

1. Wilkins E, Wilson L, Wickramasinghe K, et al. European Cardiovascular Disease Statistics 2017. Published online February 15, 2017.
2. Cardiovascular diseases statistics - Statistics Explained. Accessed March 13, 2024. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Cardiovascular_diseases_statistics#Deaths_from_cardiovascular_diseases
3. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *The Lancet*. 2005;366(9493):1267-1278. doi:10.1016/S0140-6736(05)67394-1
4. Dixon DL, Sharma G, Sandesara PB, et al. Therapeutic inertia in cardiovascular disease prevention: time to move the bar. *J am Coll Cardiol*. 2019;74(13):1728-1731. doi:10.1016/J.JACC.2019.08.014
5. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. *Am J Med*. 2012;125(9):882-887.e1. doi:10.1016/j.amjmed.2011.12.013
6. Deshpande S, Quek RGW, Forbes CA, et al. A systematic review to assess adherence and persistence with statins. *Curr Med Res Opin*. 2017;33(4):769-778. doi:10.1080/03007995.2017.1281109
7. Simpson RJ, Mendys P. The effects of adherence and persistence on clinical outcomes in patients treated with statins: a systematic review. *J Clin Lipidol*. 2010;4(6):462-471. doi:10.1016/J.JACL.2010.08.026

8. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol*. 2014;78(4):684-698. doi:10.1111/BCP.12339/SUPPINFO
9. Makarevičius G, Rinkūnienė E, Badarienė J. National trends in statin use in Lithuania from 2010 to 2021. *Medicina (Lithuania)*. 2023;59(1):59. doi:10.3390/MEDICINA59010037/S1
10. Blais JE, Wei Y, Yap KK, et al. Trends in lipid-modifying agent use in 83 countries. *Atherosclerosis*. 2021;328:44-51. doi:10.1016/J.ATHEROSCLEROSIS.2021.05.016
11. OECD. *Reviews of Health Systems: Lithuania 2018, OECD Reviews of Health Systems*. OECD Publishing. ISBN 9789264300866; 2018. Accessed June 26, 2020. https://www.oecd.org/countries/lithuania/lithuania-9789264300873-en.htm
12. Health Ministry Order No.49 Regarding Reimbursed Medicines List. Summary editorial 2019. Accessed March 13, 2024. https://www.e-tar.lt/portal/lt/legalAct/TAR.FA9CC3E1430C/ZkTTYWLLQo
13. OECD. *Lithuania: Country Health Profile 2019, State of Health in the EU*. OECD Publishing; 2019. ISBN:9789264340787
14. *WHO Collaborating Centre for Drug Statistic Methodology. Guidelines for ATC Classifi Cation and DDD Assignment, 2015*. World Health Organization; 2014.
15. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/-AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J am Coll Cardiol*. 2014;63(25):2889-2934. doi:10.1016/J.JACC.2013.11.002
16. Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association between intensity of statin therapy and mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2017;2(1):47-54. doi:10.1001/JAMACARDIO.2016.4052
17. Regarding the rules for writing prescriptions and issuing (selling) medicinal products, medical devices (medical devices) and reimbursable medical aids in pharmacies to the population and storing paper prescriptions after dispensing (selling) medicinal pr. Accessed September 15, 2021. https://e-seimas.lrs.lt/portal/legalAct/lt/TAD/TAIS.162242/asr
18. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705. doi:10.1111/j.1365-2125.2012.04167.x
19. Elseviers M. Drug utilization research: methods and applications. Accessed November 8, 2023. https://www.wiley.com/en-us/Drug+Utilization+Research%3A+Methods+and+Applications-p-9781118949788
20. Caetano PA, Lam JMC, Morgan SG. Toward a standard definition and measurement of persistence with drug therapy: examples from research on statin and antihypertensive utilization. *Clin Ther*. 2006;28(9):1411-1424. doi:10.1016/J.CLINTHERA.2006.09.021
21. Tveden-Nyborg P, Bergmann TK, Jessen N, Simonsen U, Lykkesfeldt J. BCPT 2023 policy for experimental and clinical studies. *Basic Clin Pharmacol Toxicol*. 2023;133(4):391-396. doi:10.1111/bcpt.13944
22. Cramer JA, Benedict Á, Muszbek N, Keskinaslan A, Khan ZM. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. *Int J Clin Pract*. 2008;62(1):76-87. doi:10.1111/j.1742-1241.2007.01630.x
23. Tsioufis K, Castellano Vázquez JM, Sykara G, Mondello Malvestiti F, van Vugt J. Real-world evidence for adherence and persistence with atorvastatin therapy. *Cardiol Ther*. 2021;10(2):445-464. doi:10.1007/S40119-021-00240-8
24. Malo S, Aguilar-Palacio I, Feja C, et al. Persistence with statins in primary prevention of cardiovascular disease: findings from a cohort of Spanish workers. *Rev Esp Cardiol (English Edition)*. 2018;71(1):26-32. doi:10.1016/J.REC.2017.04.002
25. Pettersson B, Hoffmann M, Wändell P, Levin LÅ. Utilization and costs of lipid modifying therapies following health technology assessment for the new reimbursement scheme in Sweden. *Health Policy (New York)*. 2012;104(1):84-91. doi:10.1016/J.HEALTHPOL.2011.10.010
26. Goldstein KM, Zullig LL, Bastian LA, Bosworth HB. Statin adherence: does gender matter? *Curr Atheroscler Rep*. 2016;18(11):1-9. doi:10.1007/S11883-016-0619-9/FIGURES/2
27. Mazhar F, Hjemdahl P, Clase CM, Johnell K, Jernberg T, Carrero JJ. Lipid-lowering treatment intensity, persistence, adherence and goal attainment in patients with coronary heart disease. *Am Heart J*. 2022;251:78-90. doi:10.1016/J.AHJ.2022.05.021
28. Citarella A, Kieler H, Sundström A, et al. Family history of cardiovascular disease and influence on statin therapy persistence. *Eur J Clin Pharmacol*. 2014;70(6):701-707. doi:10.1007/S00228-014-1659-0/FIGURES/1
29. Johansson S, Rosengren A, Young K, Jennings E. Mortality and morbidity trends after the first year in survivors of acute myocardial infarction: a systematic review. *BMC Cardiovasc Disord*. 2017;17(1):1-8. doi:10.1186/S12872-017-0482-9/TABLES/5
30. Rapsomaniki E, Thuresson M, Yang E, et al. Using big data from health records from four countries to evaluate chronic disease outcomes: a study in 114 364 survivors of myocardial infarction. *Eur Heart J Qual Care Clin Outcomes*. 2016;2(3):172-183. doi:10.1093/EHJQCCO/QCW004
31. Conn VS, Ruppar TM, Chase JAD, Enriquez M, Cooper PS. Interventions to improve medication adherence in hypertensive patients: systematic review and meta-analysis. *Curr Hypertens Rep*. 2015;17(12):1-15. doi:10.1007/S11906-015-0606-5/TABLES/5
32. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence. *Circulation*. 2009;119(23):3028-3035. doi:10.1161/CIRCULATIONAHA.108.768986

How to cite this article: Kirilova K, Trečiokienė I, Bratčikovienė N, Qvarnström M, Wettermark B. Persistence to statin treatment: A cohort study in Lithuania. *Basic Clin Pharmacol Toxicol*. 2024;135(1):43-51. doi:10.1111/bcpt.14015

APPENDIX A

TABLE A1 Tabular results for logistic regression analyses.

Independent variables	Crude odds ratio	Standard error	*P*-value	Confidence interval (95%)	Adjusted odds ratio	Standard error	*P*-value	Confidence interval (95%)
Age group (years)								
18–44					*reference*			
45–64	1.31	0.040	<0.001	(1.24, 1.39)	1.10	0.036	0.003	(1.03, 1.17)
65–74	1.89	0.062	<0.001	(1.77, 2.01)	1.12	0.040	0.001	(1.05, 1.21)
75+	1.78	0.059	<0.001	(1.67, 1.90)	0.96	0.036	0.311	(0.90, 1.04)
Gender								
Female					*reference*			
Male	1.05	0.013	<0.001	(1.02, 1.07)	1.00	0.014	0.867	(0.98, 1.03)
Area								
Rural					*reference*			
Urban	1.03	0.013	0.021	(1.00, 1.06)	1.03	0.013	0.021	(1.00, 1.06)
Prevention								
Primary					*reference*			
Secondary	1.72	0.022	<0.001	(1.68, 1.77)	1.21	0.045	<0.001	(1.13, 1.30)
Diagnosis								
No diagnosis					*reference*			
Stroke/TIA	1.49	0.042	<0.001	(1.41, 1.58)	1.32	0.053	<0.001	(1.22, 1.43)
Heart Attack	2.04	0.040	<0.001	(1.96, 2.12)	1.75	0.048	<0.001	(1.66, 1.85)
IHD	1.53	0.021	<0.001	(1.49, 1.57)	1.11	0.036	0.002	(1.04, 1.18)
DM	1.72	0.026	<0.001	(1.66, 1.78)	1.39	0.025	<0.001	(1.34, 1.44)
Hypertension	2.36	0.042	<0.001	(2.28, 2.45)	1.70	0.036	<0.001	(1.63, 1.77)
Prescriber								
Family doctor					*reference*			
Cardiologist	0.91	0.015	<0.001	(0.88, 0.94)	0.70	0.013	<0.001	(0.68, 0.72)
Other	0.98	0.014	0.262	(0.96, 1.01)	0.89	0.014	<0.001	(0.86, 0.91)
Previous use of anti-diabetic, antithrombotic, antihypertensive (at least one or all of them)								
No					*reference*			
Yes	1.84	0.024	<0.001	(1.80, 1.89)	1.35	0.022	<0.001	(1.30, 1.39)
Statin								
Atorvastatin					*reference*			
Rosuvastatin	0.97	0.012	0.007	(0.94, 0.99)	1.15	0.016	<0.001	(1.12, 1.18)
Other	0.88	0.126	0.388	(0.67, 1.17)	0.80	0.117	0.131	(0.60, 1.07)