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ORIGINAL ARTICLE

Pharmacy-based predictors of non-persistence with and non-adherence to statin treatment among patients on oral diabetes medication in the Netherlands

Sofa D. Alfian^{a,b}, Pawida Worawutputtapong^a, Catharina C. M. Schuiling-Veninga^a, Jurjen van der Schans^a, Jens H. J. Bos^a, Eelko Hak^a and Petra Denig^c

^aUnit of Pharmacotherapy, -Epidemiology, & -Economics, Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands; ^bDepartment of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Indonesia; ^cDepartment of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

ABSTRACT

Aims: To evaluate statin non-persistence and non-adherence as discrete processes in diabetes patients, and identify pharmacy-based predictors of these processes in the first year after statin initiation.

Methods: We conducted a retrospective cohort study of statin initiators using a pharmacy database. Persistence and adherence were measured in the first, second and third year. Non-persistence was defined as a gap >180 days. Non-adherence was calculated in persistent patients and defined as a medication possession ratio <80%. Cox regression hazard ratios (HRs) and logistic regression odds ratios (ORs) were assessed for sociodemographic and medication-related factors as possible predictors.

Results: Of 12,741 initiators, 20.0% were non-persistent in the first year, while 9.0% and 7.5% were non-persistent in the second and third years. Non-adherence in persistent patients increased from 13.4% in the first to 15.6% and 18.1% in the second and third years. Predictors of non-persistence were female gender (HR: 1.10; 95% CI: 1.01–1.19), older age (HR: 1.52; 95% CI: 1.31–1.75), primary prevention (HR: 1.10; 95% CI: 1.00–1.20), initiating on low dose (HR: 1.44; 95% CI: 1.07–1.94) or standard dose (HR: 1.56; 95% CI: 1.16–2.10), and no cardiovascular co-medication (HR: 1.19; 95% CI: 1.07–1.33), while patients with four or more other medications were more likely to be persistent. Age <50 years (OR: 1.47; 95% CI: 1.22–1.77), low socioeconomic status (OR: 1.27; 95% CI: 1.12–1.45) and primary prevention (OR: 1.21; 95% CI: 1.07–1.38) were predictors of non-adherence, while females were more likely to be adherent (OR: 0.87; 95% CI: 0.77–0.98).

Conclusion: Non-persistence was the foremost problem in the first year after statin initiation, while non-adherence in persistent patients increased in the second and third years. Pharmacy-based predictors of statin non-persistence were different from predictors of non-adherence among persistent patients.

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Introduction

Dyslipidemia is a major risk factor for cardiovascular diseases leading to morbidity and mortality in patients with diabetes¹. Therefore, clinical guidelines highlight the importance of lipid-lowering treatment, in particular statins, to reduce cardiovascular risk in both primary and secondary prevention¹. In the Netherlands, guidelines for diabetes and cardiovascular risk management recommend statin treatment for almost all type 2 diabetes patients². However, the use of statins is known to be suboptimal in daily practice³. In their review, Cramer *et al.* estimated that around 47% of patients were non-persistent with and 49% were non-adherent to statin treatment⁴. Statin adherence tends to decline over the years⁵, also in patients with diabetes⁶. Non-persistence with and non-adherence to statins were found to be associated with increased LDL-cholesterol levels, cardiovascular events and mortality^{7,8}. Therefore, guidelines emphasize checking

patients' adherence when lipid-lowering drugs have insufficient effect².

To improve medication persistence and adherence, it is important to identify the patients who are in need of additional support as early as possible. Pharmacists can play an important role in this process, for example, when they talk with the patient during the first or second dispensing visit. Pharmacist-led interventions have shown to improve adherence to lipid-lowering treatment⁹. To target the patients most in need of an intervention, insight into the predictors of non-persistence and non-adherence based on information that is routinely available to pharmacists is required. Several studies have tried to identify possible predictors of statin non-persistence and non-adherence in diabetes patients. Possible predictors of non-persistence included younger age, female gender, urban location and having heart failure¹⁰. Possible predictors of non-adherence were younger age,

CONTACT Sofa D. Alfian sofa.alfian@unpad.ac.id Unit of Pharmacotherapy, -Epidemiology, & -Economics Groningen Research Institute of Pharmacy, University of Groningen, P.O. Box 196, 9700 AD Groningen, The Netherlands

Supplemental data for this article can be accessed [here](#).

higher HbA1c, no history of smoking and no cardiovascular morbidity⁶. Some of these potential predictors, however, are not available for pharmacists. Moreover, overlapping definitions for non-persistence and non-adherence were used in these studies. Non-persistence was defined as a gap of more than 30 days after the last prescription¹⁰, which is likely to include patients who did not discontinue medication but were just taking less medication than prescribed. On the other hand, non-adherence was defined as taking less than 80% of the medication⁶, which includes some patients who may have discontinued treatment. Not making this distinction disregards the notion that factors related to the discontinuation of medication can differ from factors related to not taking the medication as prescribed among patients continuing treatment, that is, non-adherence in persistent patients¹¹. This latter process has also been called the implementation phase, to distinguish it from the discontinuation phase¹¹. Further studies are therefore needed to identify distinct predictors of non-persistence and of non-adherence in persistent patients after statin initiation, which pharmacists can use to provide early interventions for improving statin use among patients with diabetes.

The aims of this study are to gain insight in statin non-persistence and non-adherence patterns as discrete processes in diabetes patients, and to identify pharmacy-based predictors of these processes in the first year after statin initiation.

Methods

Study design and data source

An observational retrospective inception cohort study was performed using data from the University of Groningen pharmacy database IADB.nl. The pharmacy database IADB.nl contains drug dispensing data, which is collected from 60 community pharmacies in the Netherlands covering a population of approximately 600,000 people. The dispensing data gives full information about the drug, the start date, the number of units (e.g. tablets) dispensed as well as the daily prescribed dose (e.g. 1 tablet per day). The IADB.nl database is a useful and valid tool for pharmacoepidemiological and pharmaco-economic research, and has been used in over 70 publications¹².

Study population

The study population consisted of patients on oral diabetes medication aged 40 years and older who initiated statins in the study period anywhere between 1995 and 2014. Patients on oral diabetes medication were defined by the dispensing of at least two prescriptions of non-insulin blood-glucose lowering drugs without or with concurrent use of insulin within one year before the index date. The index date was defined as the first dispensing for a statin. The initiation of statin treatment was defined as a first dispensing of a statin with no dispensing of lipid-lowering drugs in the preceding 365 days. Patients who received cerivastatin were excluded because it was withdrawn from the market in 2001¹³.

Outcome measurements

Persistence and adherence rates were calculated for the first, second and third years after statin initiation. Persistence was defined as time until discontinuation and was assessed by the permissible gap model¹⁴. Patients were considered non-persistent when there was a gap of >180 days after the end of a prescription. In the Netherlands, the average repeat prescription length for statins is 90 days. The gap length of twice the prescription duration was chosen to clearly distinguish patients who discontinued treatment from patients that were taking less or needed less medication than prescribed, for example, because of a period of hospitalization. Medication possession ratios (MPRs) were calculated for persistent patients¹⁵, i.e. without a medication gap of >180 days, and defined as the number of days' supply divided by the number of days between the start of the first and the end of the last prescription in each year. Patients were excluded from MPR calculations in the following years when they were non-persistent. In addition, patients were excluded from the persistence and adherence calculations when they were lost to follow-up. Patients were allowed to switch to another type of statin, whereas patients who switched to another lipid-lowering drug were censored at the moment of switch. Patients were dichotomized into "adherent" defined as a MPR of $\geq 80\%$ and "non-adherent" defined as a MPR of $< 80\%$, since most consistent clinical benefits are seen at adherence levels 80% or greater¹⁶.

Potential predictors

The variables considered as potential predictors of non-persistence and of non-adherence in the first year after statin initiation included sociodemographic factors and medication-related factors that can be measured using a pharmacy database. The potential predictors were assessed at baseline.

The sociodemographic factors were age, gender and socioeconomic status. The patient's age was calculated at the index date. Gender was documented as male or female in the pharmacy database. Socioeconomic status was obtained from neighborhood status scores on four-digit postcode level based on evidence from the Netherlands Institute for Social Research¹⁷. A status score is an indicator to compare social status of districts in the Netherlands which is derived from a number of characteristics of the neighborhood population (education, income and labor market position) where a high score indicates a higher status¹⁸.

Medication-related factors included type of prevention, initiation dose of statin, number of other medications dispensed before statin initiation, and medication for conditions that may affect persistence and adherence. The initiation dose of statin was classified into three categories (low dose, standard dose, and intensive dose, see Table S1 in Supplementary data)¹⁹. Prevention status was defined as primary or secondary by the use of a proxy indicating a previous cardiovascular event. Patients receiving at least two prescriptions of a platelet aggregation inhibitor, organic nitrate and/or a vitamin K antagonist in the year before the index date were categorized as secondary prevention

patients²⁰. The others were considered as primary prevention patients. Direct-acting oral anticoagulants were not included in this medication proxy, because their use was restricted to a few specific indications and very limited in our study period. The total number of other medications dispensed in the last 120 days before statin initiation was categorized into four groups (1–3, 4–6, 7–9, and ≥ 10 medications with distinct ATC codes). The conditions that may affect persistence and adherence were derived from specific medication dispensed in the year before statin initiation (see list of medications and ATC codes in [Table S2](#) in [Supplementary data](#)). Included were: (1) other cardiovascular diseases (antithrombotic agents, cardiac therapy, antihypertensives, diuretics, beta blocking agents, calcium channel blockers, agents acting on the renin–angiotensin system); (2) psychiatric disorders (antipsychotics, anxiolytics, hypnotics and sedatives, antidepressants); and (3) chronic obstructive pneumonia disease (glucocorticoids, anticholinergics, selective beta-2-adrenoreceptor agonists, xanthines).

Data analysis

Patient characteristics were reported using descriptive statistics. Chi-square tests were used to assess univariate associations with the outcomes. The potential predictors found to be associated with the outcome at a significance level of $p \leq .25$ in the univariate analysis ([Tables S3 and S4](#) in [Supplementary data](#)) were included in the initial multivariate models. Since there was little missing data, we conducted full-case analyses. Hazard ratios (HRs) and odds ratios (OR) with a 95% confidence interval were obtained using Cox regression and logistic regression analysis, respectively, using manual backward elimination. Subgroup analysis by period of statin initiation was carried out. The period of statin initiation was defined as before (1995–2007) or after (2008–2014) the implementation of updated Dutch guidelines through new disease management programs that started in 2007. The goodness-of-fit statistic was assessed, that is, the test of proportional hazards assumption for the Cox model and the Hosmer and Lemeshow test for the logistic model. Sensitivity analysis was conducted to assess the impact of the persistence definition by variation in the permissible gap length (120 and 240 days). All statistical analyses were carried out using SPSS software (version 23.0; IBM, Armonk, NY, USA).

Results

In total, 12,741 patients on oral diabetes medication who initiated statin treatment between 1995 and 2014 were identified from the pharmacy database IADB.nl ([Table 1](#)). Of these 74.2% started with simvastatin ([Figure 1](#)). Of all 12,741 patients, 20.0% were non-persistent in the first year, while 9.0% and 7.5% were non-persistent in the second and third years, respectively. Non-adherence rates for statins in persistent patients increased from 13.4% in the first year to 15.6% and 18.1% in the second and third years, respectively. The numbers of non-persistent and non-adherent patients over three years are displayed in [Figure 2](#). Non-persistence rates

Table 1. Characteristics of patients initiating statin treatment ($n = 12,741$).

Characteristic	Number	%
Gender		
Male	6128	48.1
Female	6611	51.9
Missing	2	
Age, mean [SD], years	63.8 [11.2]	
Age group, years		
40–49	1474	11.6
50–59	3227	25.3
60–69	3807	29.9
70–79	3162	24.8
≥ 80	1071	8.4
Socioeconomic status		
Low	2968	23.3
High	9764	76.7
Missing	9	
Prevention type		
Primary prevention	7459	58.5
Secondary prevention	5282	41.5
Initiation dose		
Low dose	5660	44.4
Standard dose	6782	53.2
Intensive dose	299	2.3
Number of other medications dispensed		
1–3	1777	13.9
4–6	4725	37.1
7–9	3364	26.4
≥ 10	2875	22.6
Medication dispensed before statin initiation		
Cardiovascular disease	2259	63.1
Psychiatric disorder	1066	29.8
COPD	254	7.1

Abbreviations. SD, standard deviation; COPD, chronic obstructive pulmonary disease.

during periods of 1995–2007 and 2008–2014 were 19.6% and 20.7%, respectively, whereas the rates for non-adherence were 13.0% and 14.0%, respectively.

Female patients (HR: 1.10; 95% CI: 1.01–1.19), patients aged >70 –79 years (HR: 1.14; 95% CI: 1.03–1.27) or ≥ 80 years (HR: 1.52; 95% CI: 1.31–1.75), primary prevention patients (HR: 1.10; 95% CI: 1.00–1.20), patients initiating on low dose (HR: 1.44; 95% CI: 1.07–1.94) or standard dose (HR: 1.56; 95% CI: 1.16–2.10), and without cardiovascular co-medication (HR: 1.19; 95% CI: 1.07–1.33) were more likely to become non-persistent. Patients with four or more other medications were less likely to become non-persistent (HR <1 ; [Table 2](#)). The goodness of fit of the model was .463. The subgroup analysis showed mostly similar point estimates for both periods but not all remained significant in both periods ([Table 3](#)).

The risk for becoming non-adherent was significantly lower with female gender (OR: 0.87; 95% CI: 0.77–0.98), whereas the risk was higher in patients younger than 50 years (OR: 1.47; 95% CI: 1.22–1.77), patients with low socioeconomic status (OR: 1.27; 95% CI: 1.12–1.45), and primary prevention patients (OR: 1.21; 95% CI: 1.07–1.38). The goodness of fit of the model was .589 ([Table 4](#)). Again, the subgroup analysis showed similar point estimates for both periods, except for gender where the association was lost in the recent period ([Table 3](#)).

Defining non-persistence as a medication gap of at least 240 days resulted in a non-persistence rate of 18.1%, while using a shorter medication gap of 120 days resulted in a

Figure 1. Flowchart of numbers of patients initiating on different statin treatments.
Note: dark grey: intensive dose; grey: standard dose; light grey: low dose.

Figure 2. Flowchart of numbers of non-persistent and non-adherent patients over three years.

non-persistence rate of 23.4%. Sensitivity analyses for predicting non-persistence using this smaller or larger gap length showed that gender and primary prevention were no longer significant predictors, whereas older age and other medication-related predictors remained largely significant. In particular, low or standard initiation dose remained associated with

more non-persistence, whereas using more other medication remained associated with less non-persistence (Tables S5 and S6 in Supplementary data). Using no other cardiovascular medication remained associated with more non-persistence defined as a medication gap of at least 240 days (Table S6 in Supplementary data).

Discussion

Among 12,741 patients on oral diabetes medication who initiated statin treatment, 20.0% were non-persistent in the first year, while 9.0% and 7.5% were non-persistent in the second and third years, respectively. Non-adherence rates of statins

Table 2. Predictors of statin non-persistence in first year after initiation ($n = 12,730$).

Predictors ^a	Hazard ratios ^b (95% CI)
Gender	
Male	Reference
Female	1.10 (1.01–1.19)
Age group, years	
40–49	1.00 (0.87–1.15)
50–59	0.96 (0.86–1.07)
60–69	Reference
70–79	1.14 (1.03–1.27)
≥80	1.52 (1.31–1.75)
Prevention type	
Primary prevention	1.10 (1.00–1.20)
Secondary prevention	Reference
Initiation dose	
Low dose	1.44 (1.07–1.94)
Standard dose	1.56 (1.16–2.10)
Intensive dose	Reference
Number of other medications dispensed	
1–3	Reference
4–6	0.83 (0.73–0.93)
7–9	0.79 (0.69–0.90)
≥10	0.76 (0.66–0.87)
Medication dispensed before statin initiation	
With cardiovascular disease	Reference
Without cardiovascular disease	1.19 (1.07–1.33)

^aGoodness of fit: p -value .463.

^bFinal multivariate model.

in persistent patients increased from 13.4% in the first year to 15.6% and 18.1% in the second and third years, respectively. Predictors of non-persistence in the first year after statin initiation included several sociodemographic and medication-related factors, whereas predictors of non-adherence were mostly sociodemographic factors. Primary prevention patients were more likely to be non-persistent as well as non-adherent but the association with non-persistence was lost in the sensitivity analysis.

A previous study in a Dutch cohort of diabetes patients showed statin non-persistence and non-adherence rates ranging from 25% to 29%¹⁹. Studies assessing statin non-persistence and non-adherence in diabetes patients in other

Table 4. Predictors of statin non-adherence in persistent patients ($n = 10,188$).

Predictors ^a	Odds ratios ^b (95% CI)
Gender	
Male	Reference
Female	0.87 (0.77–0.98)
Age group, years	
40–49	1.47 (1.22–1.77)
50–59	1.06 (0.90–1.24)
60–69	Reference
70–79	1.08 (0.92–1.27)
≥80	1.17 (0.93–1.48)
Socioeconomic status	
Low	1.27 (1.12–1.45)
High	Reference
Prevention type	
Primary prevention	1.21 (1.07–1.38)
Secondary prevention	Reference

^aGoodness of fit: p -value .589.

^bFinal multivariate model.

Table 3. Subgroup analysis of predictors of statin non-persistence and statin non-adherence in persistent patients based on period of statin initiation.

Predictors	Non-persistence		Non-Adherence in persistent patients	
	Hazard ratios (HR) (95% CI)		Odds ratios (OR) (95% CI)	
	1995–2007 ($N = 8498$)	2008–2014 ($N = 4243$)	1995–2007 ($N = 6834$)	2008–2014 ($N = 3364$)
Rate in first year (%)	19.6 ($n = 1664$)	20.7 ($n = 879$)	13.0 ($n = 887$)	14.0 ($n = 471$)
Gender				
Male	Reference	Reference	Reference	Reference
Female	1.05 (0.95–1.16)	1.18 (1.03–1.35)	0.79 (0.68–0.91)	1.05 (0.86–1.28)
Age group, years				
40–49	1.01 (0.85–1.22)	1.04 (0.84–1.28)	1.39 (1.09–1.77)	1.54 (1.15–2.06)
50–59	0.95 (0.83–1.09)	0.99 (0.82–1.19)	1.03 (0.85–1.25)	1.09 (0.83–1.42)
60–69	Reference	Reference	Reference	Reference
70–79	1.16 (1.02–1.32)	1.07 (0.89–1.30)	1.13 (0.93–1.37)	0.98 (0.73–1.31)
≥80	1.48 (1.24–1.76)	1.49 (1.15–1.92)	1.28 (0.96–1.70)	0.98 (0.64–1.51)
Socioeconomic status				
Low	–	–	1.23 (1.04–1.44)	1.36 (1.09–1.69)
High	–	–	Reference	Reference
Prevention type				
Primary prevention	1.11 (0.99–1.24)	1.09 (0.92–1.29)	1.20 (1.03–1.39)	1.24 (0.98–1.57)
Secondary prevention	Reference	Reference	Reference	Reference
Initiation dose				
Low dose	1.46 (1.01–2.12)	1.48 (0.89–2.43)	–	–
Standard dose	1.81 (1.24–2.62)	1.29 (0.79–2.11)	–	–
Intensive dose	Reference	Reference	–	–
Number of other medications dispensed				
1–3	Reference	Reference	–	–
4–6	0.78 (0.67–0.89)	0.91 (0.75–1.11)	–	–
7–9	0.77 (0.66–0.91)	0.79 (0.64–0.99)	–	–
≥10	0.69 (0.57–0.82)	0.89 (0.70–1.13)	–	–
Medication dispensed before statin initiation				
With cardiovascular disease	Reference	Reference	–	–
Without cardiovascular disease	1.23 (1.07–1.41)	1.11 (0.93–1.32)	–	–

countries showed higher rates^{6,10}. The relatively low non-adherence rates in our study can in part be explained by our exclusion of non-persistent patients from the adherence calculation. The low non-persistence rates are in part the result of using a >180 day gap definition. This is a relatively long period compared to some of the other studies^{10,21}. Shorter gap lengths lead to higher discontinuation rates by also including patients who only used or needed less medication than prescribed in the study period. Furthermore, in the Netherlands lower non-persistence and non-adherence rates are expected since patients are obliged to have health insurance, which covers most of the cost for prescribed medication, including statins. Previous studies have reported that medication cost and lack of insurance coverage can decrease medication adherence²². Another reason for low rates in the Netherlands might be the organization of diabetes care, supported with electronic health systems in pharmacies and general practices, which helps to monitor chronic medication use. Especially after the introduction of diabetes management programs in 2007, it was expected that more attention was given to monitor and support adequate treatment with statins. We observed, however, that non-persistence and non-adherence rates were not lower in patients initiating statins after 2007.

We found that some sociodemographic factors may be relevant for predicting non-persistence and, in particular, non-adherence. Low socioeconomic status was a significant predictor of non-adherence. This is partly in line with previous studies showing that low income, which is related to low socioeconomic status, was associated with higher non-adherence and non-persistence rates^{23,24}. We did not see this association with non-persistence. In the previous studies, however, there was no clear differentiation between non-persistence and non-adherence.

Furthermore, we found that older age was associated with more non-persistence, whereas younger age was associated with more non-adherence. U-shaped associations with non-adherence have been noted before, where both older and younger patients were less adherent^{23,24}. These study results underline that it is important to differentiate between non-persistence and non-adherence. Gender was an inconsistent predictor. This is in line with conflicting results regarding gender in previous studies^{6,23,24}. In our study, females were more likely to become non-persistent but less likely to become non-adherent than males. The association of gender with non-persistence, however, was lost in the sensitivity analysis, whereas the association of gender with non-adherence was lost in the subgroup analysis. This indicates that gender is not a robust predictor.

Primary prevention patients were more likely to become both non-persistent and non-adherent in comparison to secondary prevention patients. In addition, patients who initiated with low-dose or standard-dose statins, who received less other medication in addition to statins, and who did not receive other cardiovascular co-medication were more likely to become non-persistent with statin treatment. This is in line with previous findings^{6,19,24,25}. It has been suggested that primary prevention patients may perceive a lower need for statin treatment, and are thus more likely to discontinue

such treatment²⁶. On the other hand, the occurrence of a cardiovascular event was found to avert a decline in statin adherence²⁵. Also, patients initiating on intensive-dose statins may have more serious or advanced disease, leading to more perceived need. This, however, concerns only a limited number of patients that start with intensive-dose treatment. The association between primary prevention and non-persistence was lost in the sensitivity analysis. In the subgroup analyses, some associations lost significance. This may be due to the inclusion of a smaller number of patients, since most point estimates did not change much but the confidence intervals became larger.

It was our objective to identify predictors of statin non-persistence and non-adherence that pharmacists can use to identify patients in need of support to improve medication use. Our finding that the predictors for non-persistence and non-adherence are not the same is important, because it illustrates that different subgroups should be targeted. Based on our study, we suggest that pharmacists need to motivate in particular the relatively healthy patients without other cardiovascular co-medication not to discontinue their statins. Furthermore, they need to give additional support to younger patients and patients with a low socioeconomic status to take statins daily as prescribed. Most of the associations and the overall predictions were not very strong. This indicates that there are other predictors, which are not readily available to a pharmacist, such as the patient's comprehension of the treatment regimen, fear of side effects or level of forgetfulness²². Therefore, pharmacists must address these issues by consulting the patients that can be selected for support using the predictors.

It is important to note that discontinuation of treatment can be initiated by the prescriber or the patient because of side effects or lack of effect without considering a restart with another statin. Still, it seems that in many of such cases patients can restart on another statin^{27,28}. It was not our objective to look at this dynamic process including re-initiations. Future studies are recommended to identify predictors of statin re-initiations.

The strength of our study is the distinction we made between non-persistence and non-adherence. This allows us to identify predictors which are specific for these separate processes. Also, our use of a pharmacy database with good ascertainment of medication coverage is a strong point. This database has complete information on all medication dispensed. Some limitations need to be addressed. First, assessment of non-persistence and non-adherence based on drug dispensing is likely to underestimate true rates, since patients may not take all the medication they collect. On the other hand, we could not correct for patients who were treated in hospitals or nursing homes for longer periods, which can lead to overestimations. We chose a relatively long gap length of 180 days to clearly distinguish patients who discontinued treatment from patients that were taking or needed less medication than prescribed. Second, we lack information to identify discontinuation that was initiated by the prescriber. Third, the use of area-level information to assess socioeconomic status may not accurately represent patients' real socioeconomic status. Fourth, our use of a proxy to

define prevention status can lead to some misclassification, which may have weakened the associations of prevention status with non-persistence and non-adherence.

Conclusions

Non-persistence is the foremost problem in the first year after statin initiation, while non-adherence rates in persistent patients increase in the second and third years. Pharmacy-based predictors of statin non-persistence were different from predictors of statin non-adherence among persistent patients. Useful predictors of non-persistence – taking the sensitivity analysis into account – include older age, not starting on intensive-dose treatment and taking few other medications, and in particular no other cardiovascular medication. Useful predictors of non-adherence in persistent patients include younger age, low socioeconomic status, and primary prevention.

Transparency

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Declaration of financial/other relationships

S.D.A., P.W., C.C.M.S.-V., J.v.d.S., J.H.J.B., E.H. and P.D. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

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