

Pattern of Statin Use Among 10 Cohorts of New Users From 1995 to 2004: A Register-Based Nationwide Study

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Objective: To analyze differences in the pattern of statin use among 10 consecutive yearly cohorts of new users in Finland.

Study Design: Retrospective cohort study based on administrative claims data.

Methods: New users of statins from January 1, 1995, to December 31, 2004, were captured from a nationwide prescription register, and the pattern of statin use was observed until December 31, 2005. The association between year of statin initiation and persistence with statin therapy during the first year of statin use was modeled using Cox proportional hazards regression analysis with multivariable adjustment. The median adherence (proportion of days covered) was computed among patients who discontinued therapy during each 365-day interval since statin initiation.

Results: In total, 490,024 new users of statins were identified. In the multivariable-adjusted model, discontinuation during the first year among initiators of statin use in 1996 and 1997 was similar to that in 1995 (hazard ratio [HR], 0.99; 95% confidence interval [CI], 0.95-1.03 in 1996; and HR, 1.01; 95% CI, 0.98-1.05 in 1997). Compared with the 1995 cohort, the 1998, 1999, 2000, 2001, 2002, 2003, and 2004 cohorts were less likely to discontinue statin use. Hazard ratios of discontinuation for the cohorts ranged from 0.91 (95% CI, 0.88-0.94) in 1998 to 0.80 (95% CI, 0.78-0.83) in 2004. There were no differences in adherence with respect to the duration of therapy among the yearly cohorts.

Conclusions: Compared with the 1995 cohort, 1-year persistence with statin therapy in Finland improved among new users of statins in 1998, and the improvement persisted up to 2004. Adherence to statin therapy remained stable among initiators from 1995 to 2004.

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For author information and disclosures, see end of text.

Modification of cardiovascular (CV) risk factors has top public health priority in industrialized countries. Risk modification with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) has gained popularity, as indicated by a more than 10-fold increase since 1995 in the prevalence of their use.^{1,2}

The efficacy of statins as demonstrated in clinical trials is challenged in real life, as 30% to 40% of initiators stop taking the drugs during the first year.³⁻⁷ In Finland, approximately 40% of statin initiators in 1995 continued therapy for 10 years or longer.⁸ Patients with CV or other preexisting morbidities have better adherence.^{3,9} Decreased out-of-pocket costs enhance the continuity of statin use,¹⁰ and adherence is better among middle-aged and older patients.^{3,7,9} In general, complexity and duration of treatment, adverse effects, costs, characteristics of the health service provision, patient-provider interaction, sociodemographic variables of the patient, and characteristics of the illness may predict adherence to drug therapy.¹¹ All of these factors may change over time.

Attitudes toward hypercholesterolemia as a CV risk factor and the role of statins in risk modification have changed. After the mid-1990s, measurement of cholesterol levels became routine practice,¹² and the number of patients eligible for statin treatment increased as target cholesterol levels decreased in clinical guidelines.¹³⁻¹⁵ Compared with the 1990s, current users of statins are older and more often female.¹ Statin use seems to be channeled to healthier patients than was previously the case.^{15,16} Patent expirations and the development of generic products markedly lowered patients' copayments for statins in many countries.

Most studies on adherence and persistence with statin therapy during the 1990s and 2000s were cross-sectional, were conducted in different settings, and applied diverse definitions for the measures. Based on drug reimbursement data, we compared persistence and adherence with statin therapy across yearly cohorts of new users of statins from 1995 to 2004 in Finland. There was no requirement for approval of the study by an ethics committee, as only deidentified patient data were available to the researchers and the patients were not contacted.

METHODS

Data Source

The Finnish prescription register includes data on reimbursed purchas-

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es of drugs used outside of institutions. It is maintained by the Social Insurance Institution (SII) of Finland and covers all permanent residents living in the community. The drug purchases of patients in public nursing homes or hospitals are not registered. The dispensing date of the prescription, the number of dispensed tablets, the patient's birth (and death) dates, sex, and residential area are also available.

In the prescription register, drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification.¹⁷ Between 1995 and 1997, the prescription register covered 85% to 92% of total statin consumption outside of institutions (JEM, unpublished data, March 31, 2009). From 1998 to 2005, the coverage varied between 94% and 96%.

The purpose of the medication is not recorded in the prescription register. However, patients with certain chronic diseases such as coronary artery disease (CAD), dyslipidemia associated with CAD, and diabetes mellitus are entitled to a higher refund of drug costs and are recorded in a separate register held by the SII. To be eligible for higher reimbursement, a patient's condition must meet explicit predefined criteria.

Statins in Finland

Simvastatin was introduced on the Finnish market in 1992 and has been the most used statin since 1997. In 2004, it accounted for 38% of total statin consumption.¹⁸ The use of atorvastatin calcium increased rapidly after its introduction in 1998, accounting for 36% of total statin consumption in 2004. Cerivastatin sodium (withdrawn in 2001), fluvastatin sodium, lovastatin, pravastatin sodium, and rosuvastatin calcium have been smaller players on the market. In 1995, 0.8% of the population used statins, while the proportion was 8.9% 10 years later.¹

Statins are available by prescription only. During the study period, about 45% of the costs of statin purchases were reimbursed by the SII. In 1992, patients with familial hyperlipidemia became entitled to higher reimbursement (about 75%), and patients with dyslipidemia associated with CAD became entitled to higher reimbursement in 2000. Generic substitution, introduced in April 2003, induced price competition, and the mean yearly cost per simvastatin user decreased within 2 years from €351 (approximately \$397) to €133 (approximately \$137) according to the statistics of the SII.

Definitions

A new user of statins was defined as a patient who had not purchased statins (ATC code B04AB in 1994 and 1995 and code C10AA thereafter) during 365 days before the first

Take-Away Points

New users of statins (n = 490,024) from 1995 to 2004 were captured from the Finnish nationwide prescription register, and the pattern of statin use was observed until December 31, 2005.

- Compared with the 1995 cohort, the risk of discontinuation during the first year of statin use was lower among the 1998 cohort and subsequent cohorts up to 2004, despite notable changes in the prevalence of statin use.
- There were no differences in adherence with respect to the duration of therapy among the yearly cohorts.

prescription from January 1, 1995, to December 31, 2004. The date of a patient's first statin purchase was defined as the index date.

Treatment was considered discontinued if the tablet-free gap between 2 consecutive prescriptions exceeded 270 days. The rationale for choosing this window for primary analyses was that, because of reimbursement rules at the time of the study, patients typically purchased a 3-month supply of chronic medications. Sensitivity analyses were performed using 180-day and 90-day gaps. The supply of a prescription was based on an assumed dosage of 1 tablet per day (Figure). The discontinuation date was based on the period covered by the last prescription. Statins were analyzed as a group, and switches between statins were considered continuation of therapy. Purchasing a single statin prescription was considered extremely poor persistence (no further statins dispensed during 270 days after the end of the supply of the index prescription).

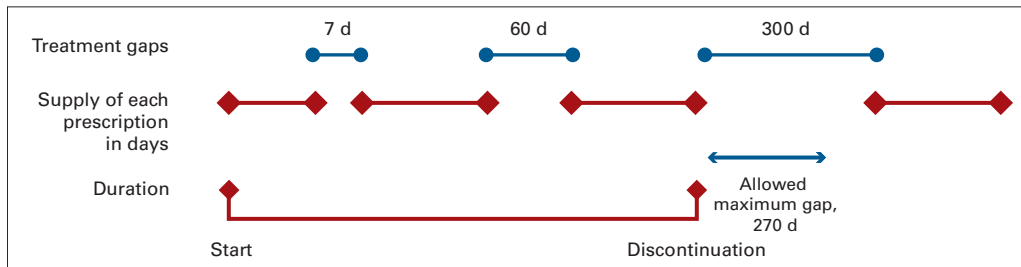
Adherence (percentage) was defined as the proportion of days covered by the tablets dispensed during the treatment period multiplied by 100. Double counting of the tablets was possible, because during switches a patient may have had extra tablets unused from the previous prescription. To avoid bias introduced by tablet supply extending beyond the end of follow-up of the study, only the number of tablets covering the time from the dispense date to December 31 were taken into account during the last quarter of 2005.

Data Analysis

Persistence. The association between year of statin initiation and persistence with statin therapy during the first year of statin use was analyzed using Cox proportional hazards regression. Person-time was observed since the dispensing day of the index prescription until discontinuation, and observation periods were censored at death, when a patient first became ineligible for reimbursement because of long-term institutionalization, or when the first year of statin use was exceeded.

The following covariates were included in the model: sex, age at statin initiation (<45, 45-54, 55-64, 65-74, or

■ **Figure.** Schematic for Calculating Duration of the First Statin Treatment Period



The figure is not drawn to scale.

>74 years), region of residence (geographic areas according to catchment areas of the tertiary care hospitals), socioeconomic status (9-category classification based on a patient's occupation and employment status), use of antidiabetics (ATC code A10), use of hormone therapy among women (ATC codes G03C and G03F), number of different CV medications dispensed during 365 days before the index date, and eligibility for higher reimbursement of CAD drugs at the index date. The following were defined as CV medications: antithrombotics (ATC code B01), cardiac glycosides, antiarrhythmics, nitrates (code C01), miscellaneous antihypertensives (code C02), diuretics (code C03), peripheral vasodilators (code C04), β -blocking agents (code C07), calcium channel blockers (code C08), and agents acting on the renin-angiotensin system (code C09). The use of hormone therapy among women was considered an indicator of health-seeking behavior.

We initially included the presence of asthma (entitlement for special reimbursement), depression (use of antidepressants in the year before statin initiation), and psychotic diseases (entitlement for special reimbursement) in the analyses. Backward stepwise elimination of nonsignificant variables was performed at a significance level of $P \leq .01$, and none of the aforementioned variables remained significant; therefore, they were excluded from the final model.

We tested for possible interaction between age at statin initiation and year of statin initiation by including product terms between dummy variables for these factors in the model. Inclusion of the product terms did not significantly improve the model fit ($P > .01$, log-likelihood ratio test); therefore, only the main effects are reported. The analyses were performed using SAS (version 9.1; SAS Institute Inc, Cary, NC).

Adherence. The median adherence was computed among patients who discontinued therapy during each 365-day interval since statin initiation (from statin initiation to the 365th day constituted during the first year, and from the 366th day to the 730th day constituted during the second year, etc). Pa-

tients with only a single prescription (100% adherence) were excluded from the first 365-day stratum.

RESULTS

In total, 490,024 new users of statins were identified in 10 successive yearly cohorts (Table 1). The mean age at statin initiation did not change, but the proportion of women increased from 45% in the 1995 cohort to 52% in the 2004 cohort. In 1995, 22% of the initiators had no prior CV medications compared with 35% of the initiators 10 years later.

The risk of discontinuation during the first year of statin use remained stable between 1995 and 1997; thereafter, initiators had adjusted hazard ratios (HRs) less than 1.00 (multivariable-adjusted model) versus 1995 initiators (Table 2). Age at statin initiation was associated with persistence; patients aged 65 to 74 years at statin initiation were most unlikely to discontinue compared with patients younger than 45 years. Increased CV risk or comorbidity (ie, the presence of diabetes or CAD), concurrent use of several CV medications, and the use of hormone therapy among women were positively associated with continuation of statin therapy, whereas sex had no effect. Performing a sensitivity analysis with a 180-day gap did not essentially change the results. The adjusted HR of discontinuation for year of statin initiation decreased from 0.90 (95% confidence interval [CI], 0.87-0.93) in 1998 to 0.75 (95% CI, 0.73-0.78) in 2004 (data not shown). Performing a sensitivity analysis with a 90-day gap resulted in adjusted HRs less than 1.00 for subsequent yearly cohorts versus the 1995 cohort. The adjusted HRs ranged from 0.94 (95% CI, 0.91-0.97) in 1996 to 0.71 (95% CI, 0.69-0.73) in 2004 (data not shown).

Among discontinuers of statins, the pattern of adherence was similar across all yearly cohorts (Table 3), as indicated by the overlap of interquartile ranges of adherence (data not shown) in each category of duration of statin therapy. In all cohorts, patients who discontinued during the second, third, and fourth years were less adherent than patients who discontinued later.

Pattern of Statin Use Among New Users From 1995 to 2004

Table 1. Characteristics of New Users of Statins in Finland^a

Year of Statin Initiation	No. of New Users of Statins	Female Sex, %	Age at Statin Initiation, Mean (SD), y	Presence of Coronary Artery Disease, No. (%)	Presence of Diabetes, No. (%)	New Users of Statins, %					Use of Hormone Therapy Among Women, No. (%)
						No. of Different Cardiovascular Medications Used ^b					
						0	1	2	3	≥4	
1995	18,072	45.2	60.3 (10.1)	7863 (43.5)	2391 (13.2)	22.0	15.5	23.6	19.6	19.2	2018 (24.7)
1996	28,681	49.4	61.2 (10.2)	10,083 (35.2)	3801 (13.3)	24.4	18.9	24.0	18.0	14.8	3736 (26.4)
1997	34,877	51.0	61.7 (10.3)	10,952 (31.4)	4726 (13.6)	25.6	19.9	23.5	17.0	14.0	4542 (25.5)
1998	39,486	50.9	61.7 (10.6)	10,914 (27.6)	5628 (14.3)	26.3	20.6	23.4	16.4	13.3	5292 (26.4)
1999	50,570	52.0	61.9 (10.9)	11,224 (22.2)	7729 (15.3)	28.0	22.3	23.9	14.8	11.1	7229 (27.5)
2000	58,842	52.7	61.9 (11.3)	12,091 (20.5)	9478 (16.1)	30.3	23.1	23.2	13.8	9.6	8915 (28.7)
2001	58,892	51.8	61.8 (11.5)	11,434 (19.4)	8873 (15.1)	32.0	23.0	22.5	13.1	9.5	9012 (29.5)
2002	60,789	51.3	61.8 (11.8)	10,810 (17.8)	9324 (15.3)	32.0	23.3	21.1	12.9	10.7	9647 (30.9)
2003	63,515	50.8	61.6 (11.8)	9800 (15.4)	9525 (15.0)	32.7	23.8	20.4	12.6	10.5	9793 (30.4)
2004	76,300	51.8	61.2 (11.7)	9512 (12.5)	11,596 (15.2)	34.9	24.2	19.5	11.7	9.8	11,575 (29.3)
Total	490,024	51.2	61.6 (11.5)	104,683 (21.4)	73,071 (14.9)	30.2	22.3	22.1	14.1	11.3	71,759 (28.6)

^aNew users had no statins dispensed during 365 days before the index statin prescription.

^bThe following were defined as cardiovascular medications: antithrombotics (Anatomical Therapeutic Chemical code B01), cardiac glycosides, antiarrhythmics, nitrates (code C01), miscellaneous antihypertensives (code C02), diuretics (code C03), peripheral vasodilators (code C04), β -blocking agents (code C07), calcium channel blockers (code C08), and agents acting on the renin-angiotensin system (code C09).

A total of 55,750 statin initiators (11%) purchased only a single statin prescription. The proportion of patients with a single prescription varied between 12% and 13% during the 1990s but declined to 11% at the end of the study period. The mean age at statin initiation of these patients varied between 59.0 and 60.8 years among the yearly cohorts. The proportion of men decreased from 58% to 51%, and the proportion of patients without prior CV medication increased from 31% to 43% during the study period.

DISCUSSION

Compared with the 1995 cohort of new users of statins, patients who started using statins in 1998 and thereafter were more likely to continue therapy during the first year. The median adherence among patients who discontinued statin therapy did not vary across the yearly cohorts of initiators.

The stable pattern of statin use may be explained by a stable healthcare sector in Finland during the study period. However, notable changes in drug pricing and in the reimbursement system took place. In 2000, statins on the market before 2000 were approved for reimbursement higher than basic level to patients with established CAD. Generic substitutions became available in 2003. Atorvastatin was introduced in 1998 and rosuvastatin in 2003.¹ Compared with 1995, the improvement in 1-year persistence since 1998 may be attributable to the launch of atorvastatin and to the subsequent public discussions about statin therapy.

The persistence observed herein is in line with the results of previous studies.³⁻⁷ In a 10-year follow-up study⁸ in Finland of

patients who began statin therapy in 1995, the presence of CV morbidity increased the likelihood of longer persistence. Patients without prior CV medication and patients younger than 45 years were less persistent among all cohorts. Poor persistence may be clinically justified if the target lipid level is achieved by lifestyle modification, especially in primary prevention.

As demonstrated by Ho et al,¹⁹ poor adherence to preventive CV medication may reduce the effectiveness of therapy, which could have a negative effect on the cost-effectiveness of therapy. In contrast, good adherence is associated with health-seeking behavior.²⁰ Therefore, associations between patterns of statin use and health outcomes reported in observational studies should be interpreted with caution.

Various interventions purported to improve adherence to various therapies have been studied, with variable results. A summary of 38 review articles capturing 1373 studies found that effective interventions have been performed but that they typically lack theory explaining the underlying mechanisms.²¹ Furthermore, few studies evaluated the effects of interventions beyond 6 months. Based on 8 randomized controlled trials, the authors of a Cochrane review about adherence to lipid-lowering drugs came to a similar conclusion that no specific intervention improving adherence to lipid-lowering drugs can be recommended.²² To be implemented and effective at the population level, an intervention has to be simple and affordable and must have a sound theoretical base. Such a theory has yet to be reported.

To further clarify the patterns of use and attitudes toward statins among different risk populations, qualitative approaches rather than quantitative approaches should be applied.

■ **Table 2.** Hazard Ratios for Discontinuation of Therapy During the First Year of Statin Use Among New Users in Finland^a

Variable	No. (%)	Hazard Ratio (95% Confidence Interval)	
		Unadjusted	Adjusted
Female sex	250,985 (51.2)	0.94 (0.93-0.95)	0.98 (0.97-1.00)
Age at statin initiation, y			
<45	32,375 (6.6)	1.00 [Reference]	1.00 [Reference]
45-54	99,042 (20.2)	0.79 (0.77-0.81)	0.84 (0.82-0.86)
55-64	153,078 (31.2)	0.65 (0.63-0.66)	0.72 (0.71-0.74)
65-74	141,706 (28.9)	0.59 (0.56-0.61)	0.69 (0.67-0.71)
>74	63,823 (13.0)	0.68 (0.66-0.70)	0.86 (0.84-0.89)
Year of statin initiation			
1995	18,072 (3.7)	1.00 [Reference]	1.00 [Reference]
1996	28,681 (5.9)	1.02 (0.98-1.05)	0.99 (0.95-1.03)
1997	34,877 (7.1)	1.05 (1.01-1.09)	1.01 (0.98-1.05)
1998	39,486 (8.1)	0.95 (0.92-0.99)	0.91 (0.88-0.94)
1999	50,570 (10.3)	0.90 (0.87-0.93)	0.84 (0.81-0.87)
2000	58,842 (12.0)	0.89 (0.86-0.92)	0.84 (0.81-0.87)
2001	58,892 (12.0)	0.97 (0.94-1.00)	0.90 (0.87-0.93)
2002	60,789 (12.4)	0.89 (0.86-0.92)	0.83 (0.80-0.86)
2003	63,515 (13.0)	0.83 (0.80-0.85)	0.76 (0.73-0.78)
2004	76,300 (15.6)	0.89 (0.86-0.92)	0.80 (0.78-0.83)
Use of hormone therapy among women	71,759 (28.6)	0.87 (0.86-0.89)	0.88 (0.87-0.90)
Presence of diabetes	73,071 (14.9)	0.85 (0.83-0.86)	0.86 (0.85-0.88)
Presence of coronary artery disease	104,683 (21.4)	0.74 (0.73-0.75)	0.81 (0.80-0.83)
No. of different cardiovascular medications used^b			
0	147,892 (30.2)	1.00 [Reference]	1.00 [Reference]
1	109,439 (22.3)	0.83 (0.81-0.84)	0.86 (0.85-0.87)
2	108,188 (22.1)	0.73 (0.72-0.74)	0.79 (0.77-0.80)
3	69,192 (14.1)	0.68 (0.67-0.70)	0.75 (0.73-0.77)
≥4	55,313 (11.3)	0.63 (0.62-0.63)	0.70 (0.68-0.71)

^aNew users had no statins dispensed during 365 days before the index statin prescription.

^bThe following were defined as cardiovascular medications: antithrombotics (Anatomical Therapeutic Chemical code B01), cardiac glycosides, antiarrhythmics, nitrates (code C01), miscellaneous antihypertensives (code C02), diuretics (code C03), peripheral vasodilators (code C04), β-blocking agents (code C07), calcium channel blockers (code C08), and agents acting on the renin-angiotensin system (code C09). Adjusted for the variables listed in the table plus for the socioeconomic status in 2000 and the place of residence at statin initiation categorized by the catchment area of the tertiary hospitals in the country.

Qualitative approaches may also increase our understanding about primary compliance (ie, whether a patient purchases the first statin prescription issued).

The present study has strengths and limitations. Our study has good external validity, as the prescription register covers all community-dwelling permanent residents in the country irrespective of income or employment status. According to rules in Finland, patients may receive reimbursement for a maximum of 90 days' supply of medications. This

has to be taken into account when interpreting the results herein, as longer refill intervals may improve persistence and adherence compared with shorter refill intervals.²³

We may have underestimated persistence and adherence for 3 reasons. First, patients in permanent institutional care are not entitled to drug reimbursement; therefore, the drugs dispensed for them were not registered. Second, the retrospective filling of gaps between 2 consecutive prescriptions as used in our study (Figure) underestimates persistence.²⁴

Pattern of Statin Use Among New Users From 1995 to 2004

Table 3. Median Percentage Adherence to Statin Use (Proportion of Days Covered) According to the Year of Statin Initiation and the Timing of Discontinuation Among New Users of Statins Between 1995 and 2004 in Finland^a

Year of Statin Initiation	% Adherence (No. of Patients Who Discontinued Therapy)									
	No. of 365-Day Periods Since Statin Initiation									
	1 ^b	2	3	4	5	6	7	8	9	10
1995 (n = 18,072)	87.0 (2431)	71.7 (1443)	73.4 (941)	79.8 (625)	82.9 (429)	84.4 (391)	87.3 (378)	88.7 (413)	89.8 (323)	86.8 (382)
1996 (n = 28,681)	87.5 (4101)	73.5 (2565)	75.7 (1319)	78.8 (945)	83.3 (734)	83.7 (672)	88.3 (636)	88.9 (581)	87.3 (772)	
1997 (n = 34,877)	88.6 (5003)	73.5 (2763)	77.3 (1505)	79.7 (1089)	83.0 (924)	84.7 (869)	87.6 (769)	87.2 (971)		
1998 (n = 39,486)	88.9 (5018)	73.7 (2942)	76.5 (1748)	80.1 (1408)	83.5 (1151)	87.1 (1016)	86.4 (1277)			
1999 (n = 50,570)	88.9 (6244)	74.3 (3939)	77.2 (2559)	81.4 (1816)	82.8 (1473)	83.3 (1845)				
2000 (n = 58,842)	87.8 (7639)	76.6 (4802)	78.3 (2825)	81.6 (2145)	81.1 (2438)					
2001 (n = 58,892)	89.4 (7872)	75.9 (4603)	78.2 (2702)	80.4 (2750)						
2002 (n = 60,789)	87.9 (7598)	76.9 (4704)	76.3 (3823)							
2003 (n = 63,515)	90.0 (7392)	76.0 (6020)								
2004 (n = 76,300)	90.0 (10,405)									

^aFor example, among new users of statins in 1996, the median adherence was 73.5% among patients who discontinued statin therapy 365 to 730 days after statin initiation, and the respective adherence for the 1997 cohort was exactly the same.

^bPatients with a single statin prescription (100.0% adherence) were excluded from the discontinuers during the first year.

Third, contrary to our assumption, tablets may have been split. However, a Canadian study²⁵ found instructions to split statin tablets in only 2.6% of 7.2 million statin prescriptions between 1996 and 2006.

The allowance of a 270-day gap between prescriptions may be too long. The rationale for choosing the 270-day window for the primary analysis is the long-term duration of statin therapy. By using a 270-day gap, we did not lose users who temporarily discontinued therapy. Furthermore, based on a meta-analysis²⁶ of randomized clinical trials studying the prevention of CV diseases, the benefits of statin therapy clearly increase with the duration of therapy. We used more conservative definitions for the gap in sensitivity analyses. Differences among yearly cohorts of statin initiators did not change substantially when using the 180-day gap, and a trend toward greater continuation of statin therapy was observed since 1996 when using the 90-day gap.

In conclusion, patients in Finland initiating statin therapy between 1998 and 2004 had a higher probability of continu-

ing therapy during the first year of statin use than patients initiating therapy in 1995. No substantial differences in adherence were found across yearly cohorts of new users of statins from 1995 to 2004.

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PTL, MJK, JEM, LV, TK); drafting of the manuscript (AH-S, HH, JEM, RH); critical revision of the manuscript for important intellectual content (PTL, MJK, HH, JEM, LKS, LV, TK, RH); statistical analysis (AH-S, PTL, MJK); obtaining funding (AH-S, LV); administrative, technical, or logistic support (LKS, LV, RH); and supervision (RH).

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