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► **To cite this version:**

Heli Halava, Arja Helin-Salmivaara, Jouni Junnila, Risto Huupponen. Selective prescribing of simvastatin and atorvastatin by patient characteristics at treatment initiation over a 7-year period in Finland. *European Journal of Clinical Pharmacology*, 2009, 65 (9), pp.927-933. 10.1007/s00228-009-0664-1 . hal-00534964

HAL Id: hal-00534964

<https://hal.science/hal-00534964>

Submitted on 11 Nov 2010

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Selective prescribing of simvastatin and atorvastatin by patient characteristics at treatment initiation over a 7-year period in Finland

Heli Halava · Arja Helin-Salmivaara · Jouni Junnila · Risto Huupponen

Received: 7 November 2008 / Accepted: 11 May 2009 / Published online: 27 May 2009
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Abstract

Purpose The aim of the study was to investigate preferential initiation with the two most frequently used statins, simvastatin and atorvastatin, by patient characteristics over time.

Methods Statin initiators without a statin prescription during the 365 days preceding the initiation from 1 January 1998 through 31 December 2004 were captured from the nation-wide Prescription Register in Finland. Associations of demographic factors and morbidities with atorvastatin versus simvastatin at initiation of statin treatment were analysed by a logistic regression model adjusted for significant covariates separately for each year.

Results Of all new statin users in 1998, atorvastatin was chosen for 18% and simvastatin for 39%. In 2004, the corresponding figures were 32 and 38%. Atorvastatin was more likely than simvastatin to be initiated in younger age groups than in persons older than 74 years (reference group). Initiation with atorvastatin was less likely for people with than without coronary artery disease; adjusted odds ratios ranged from 0.62 to 0.73 over the years 1998–2003.

Conclusion Channelling of atorvastatin over simvastatin toward the younger and healthier population was found during the first 4 years after its launch in Finland. Channelling may lead to confounding by indication, which must be taken into account when designing pharmacoepidemiology studies on statins.

Keywords Statins · Atorvastatin · Simvastatin · Channelling · Prescribing

Introduction

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are recommended for secondary prevention in coronary artery disease (CAD), and in some situations for primary prevention. Consequently, utilisation of statins has increased markedly over the last decade [1–4]. Publication in 1994 of the Scandinavian Simvastatin Survival Study [5], the first major statin trial, boosted the use of simvastatin. From 2000 to 2005 two statins, simvastatin and atorvastatin, were among the three best-selling drugs worldwide [6].

The dose-response curves of simvastatin and atorvastatin on low-density lipoprotein (LDL) cholesterol are parallel, but based on a meta-analysis published in 2003, greater maximum reductions in LDL cholesterol can be achieved with atorvastatin compared with simvastatin [7]. To detect significant differences in efficacy on clinical outcomes, head-to-head comparisons between various statins would require large randomised clinical trials. Therefore, observational designs have been applied [8–10]. In observational studies on comparative effectiveness of statins, however, confounding bias is of particular concern as perceived

H. Halava · A. Helin-Salmivaara (✉) · R. Huupponen
Dept. of Pharmacology, Drug Development and Therapeutics,
University of Turku,
FI-20014 Turku, Finland
e-mail: arja.helin-salmivaara@utu.fi

J. Junnila
Dept. of Statistics, University of Turku,
Turku, Finland

R. Huupponen
Tykslab, Health Care District of Southwest Finland,
Turku, Finland

benefits affect prescribing decisions. The factors governing the prescribing decision differ by physician and over time, and frequently involve clinical, functional, and behavioural characteristics of patients [11].

Selective prescribing according to patient characteristics, known as channelling and leading to confounding by indication, takes place for example when a newly introduced drug is promoted as more potent than its predecessors. The phenomenon was clearly seen after the introduction of cyclo-oxygenase-2 selective non-steroidal anti-inflammatory drugs; their use was found to be channelled toward females and older patients [12, 13], and those with prior gastropathy or with greater number of other medications [14, 15].

We set out to investigate whether patient-related factors are associated with channelling of atorvastatin or simvastatin, the most frequently used statins worldwide, and if there was any change in the preferred statin at initiation over time. Simvastatin represents a statin introduced among the first of its class, and atorvastatin a newer formulation claimed to have greater LDL-lowering potency than simvastatin.

Methods

Data sources

New statin users from 1 January 1998 through 31 December 2004 were captured from the nation-wide Prescription Register managed by the Social Insurance Institution (SII) of Finland. The reimbursement system covers all permanent residents living in the country, and a unique identifier number is given to each person [16]. The drugs are classified in the register according to the Anatomical Therapeutic Chemical (ATC) classification presented by the WHO [17]. Statins and other cardiovascular drugs are available in Finland by prescription only. During 1998–2004, the register coverage of the total statin consumption outside institutions ranged from 94 to 96% (J. Martikainen, the SII, personal communication). Part of the medications funded directly by sick funds of some employers and prescriptions reimbursed by the local offices of the SII, instead of the direct reimbursement in a pharmacy, were not recorded in the register.

The Prescription Register includes data on dispense date and patient's birth date, gender and residential area, among other things [16]. Morbidities cannot be comprehensively identified since the purpose of the medication is recorded non-systematically. However, patients with certain severe and chronic diseases, such as coronary artery disease (CAD), hypertension, and familial hypercholesterolemia, are entitled to a higher rate of refund and are covered by the

special register also operated by the SII. To be eligible for special reimbursements, a patient's condition must meet explicit predefined criteria, and a written certificate is required from the treating physician.

In Finland, simvastatin was introduced in 1992 and has been the most used statin since 1997. In 2004, it accounted for 38% of total statin consumption as expressed in defined daily doses (DDD) [16]. Use of atorvastatin steadily increased following its introduction in 1998, and in 2004 it accounted for 36% of statin consumption. Fluvastatin, lovastatin, pravastatin and rosuvastatin were markedly smaller players on the Finnish market over the period 1998–2004 with an approximate share of 6, 3, 9 and 7%, respectively, of total statin consumption in 2004. Likewise, the use of cerivastatin was small prior to its withdrawal. During the study period, about 45% of the costs of statin purchases were reimbursed by the SII. In 1992, persons with familiar hyperlipidemia, and in 2000 patients with dyslipidemia associated with CAD, became entitled to higher reimbursement of about 75%. Generic substitution was introduced in April 2003.

Socio-economic status as used here was registered in the 2000 census by Statistics Finland, a governmental agency. The nine-category classification takes account of occupation and employment status (farmers, entrepreneurs, blue-collar workers, white-collar workers, workers, students, pensioners, unemployed and unknown). The variable was available for 99% of new statin users [18].

New users

A new statin user was defined as a person who had not redeemed a statin prescription (ATC code C10AA) during the 365 days prior to their first statin prescription recorded during the study period. The dispense date of the prescription was the index date. The new users identified for each year were treated as distinct cohorts.

Potential user-related explanatory factors

Age, gender, socio-economic status in 2000, and place of residence were considered as potential explanatory factors for the preferred statin at initiation. Place of residence was divided into five geographical areas according to the catchment areas of the tertiary-care hospitals. Furthermore, CAD, hypertension, and familial hypercholesterolemia verified from the Special Reimbursement register of the SII as valid at the index date were analysed as potential covariates. Diabetes was defined here as at least one dispensed antidiabetic drug (ATC code A10) during the 365 days prior to the index date. Since the register for special reimbursements does not cover milder forms of

diseases or risk factors, we used the number of cardiovascular (CV) medicines dispensed during the 365 days prior to the index date as a surrogate for CV morbidity. Presence of at least one prescription from the following classes was taken into account when tallying the number of dispensed drugs: antithrombotics (ATC code B01), cardiac glycosides, antiarrhythmics and nitrates (C01), miscellaneous antihypertensives (C02), diuretics (C03), peripheral vasodilators (C04), beta-blocking agents (C07), calcium antagonists (C08) and agents acting on the renin-angiotensin system (C09). Persons without CV medicines during the 365 days prior to the index date were defined as the low-risk population if they were younger than 40 years (men) and 50 years (women).

Data analysis

Binomial logistic regression analyses were performed to assess associations among the dichotomous outcome variable (initiation with atorvastatin vs. simvastatin), covariates (see above), and year of initiation. The logistic regression analyses were performed in the following steps. First, all covariates were modelled separately. In this stage, the explanatory variables consisted of the covariate, the year, and an interaction term between the year and the covariate. Second, covariates were classified into two subgroups (demographic and disease-related). Covariates for these models were selected based on the results of the previous stage. The year was also included in these models, but the interaction terms were only included if they were statistically significant in the first stage. Third, the subgroups were entered into a final model, where the explanatory variables consisted of a year and the covariates which were found to be significant in the subgroups. However, because many of the interactions

between a year and a covariate were significant ($P < 0.001$) in the subgroups, the final model could not be based on the combined data of years. Therefore, the three-stage modelling was done separately for each year, now using only the covariates as explanatory variables.

Hypertension remained in the final logistic regression model only in 2004, familial hypercholesterolemia only in 1999, diabetes in 1998 and gender in 2004. Low-risk status of a person did not remain statistically significant in any of the years. Final models for each year were adjusted for socioeconomic status.

In all models, associations were quantified with odds ratios (OR) and their 95% confidence intervals (CI). P values < 0.001 were interpreted as statistically significant.

The statistical computation was performed with SAS system for Windows, release 9.1.

Results

New users

Statin therapy was initiated for 39,486 persons in Finland in 1998 (Table 1). During the follow-up, the number of persons starting statin therapy increased by 93% and included 76,300 persons in 2004. Of the new statin users in 1998, atorvastatin was chosen for 18% ($n=6,931$) and simvastatin for 39% ($n=15,487$). In 2004, the corresponding figures were 32% ($n=24,681$) and 38% ($n=29,006$).

The share of simvastatin initiations among all statin initiations varied over the years from 35 to 45%, and that of atorvastatin from 18 to 38% (Table 1). With the exception of 2001, simvastatin was initiated more frequently than atorvastatin. The mean age of new users was 61.8 years and remained stable over the study period. The share of persons

Table 1 Statin initiations in Finland 1998–2004

Year	New statin users	Share of women (%)	Age (years) mean, SD	New users, n (% of all)			Without prior CV medication ^b , n (%)
				Atorvastatin	Simvastatin	Other statins ^a	
1998	39,486	50.9	61.8, 10.6	6,931 (17.6)	15,487 (39.2)	17,068 (43.2)	10,374 (26.3)
1999	50,570	52.0	61.9, 10.9	13,537 (26.8)	19,881 (39.3)	17,152 (33.9)	14,147 (28.0)
2000	58,842	52.7	61.9, 11.3	17,283 (29.4)	22,351 (38.0)	19,208 (32.6)	17,804 (30.3)
2001	58,892	51.8	61.8, 11.5	22,297 (37.9)	20,768 (35.2)	15,827 (26.9)	18,807 (31.9)
2002	60,789	51.3	61.8, 11.8	21,650 (35.6)	27,367 (45.0)	11,772 (19.4)	19,453 (32.0)
2003	63,515	50.8	61.6, 11.8	20,269 (31.9)	26,664 (42.0)	16,582 (26.1)	20,780 (32.7)
2004	76,300	51.8	61.2, 11.7	24,681 (32.4)	29,006 (38.0)	22,613 (29.6)	26,639 (34.9)

CV Cardiovascular

^a Fluva-, lova-, prava-, rosuva- or cervastatin

^b No cardiovascular medicines dispensed during the 365 days prior to the index date

without prior CV medication increased to 35 from 26% over the period (Table 1). Among those older than 74 years, simvastatin was the most preferred statin at initiation in every year (from 42 to 44% of all initiations among the group) (not shown in the table).

During the observation period, the share of patients with CAD clearly decreased among the new users of both statins (Fig. 1). In 1998, the share of patients with CAD was larger among persons starting with simvastatin than with atorvastatin (34 versus 22%), but the difference had disappeared by 2004. Patients with diabetes were more frequent among new users of atorvastatin than simvastatin in 1998 (19 and 14%) and in 1999 (17 and 16%), but from 2000 no difference was observed.

Atorvastatin vs. simvastatin at initiation

In younger age groups, atorvastatin was more likely than simvastatin to be initiated when compared with the reference group (Table 2). The younger the patients were, the greater was the difference from the reference group. After 2001, the differences between age groups were not significant. Region of residence predicted the preferred statin at initiation statistically significantly and consistently: in the east and north, initiation with atorvastatin was less likely than simvastatin compared to the southern parts (reference) of the country (AOR 0.36–0.84). Simvastatin was preferred over atorvastatin at initiation in the reference region in all years except 2001.

The adjusted odds ratios for the effect of CAD ranged from 0.62 to 0.73 over the years 1998–2003 (Table 2). During these years, initiation with atorvastatin was less likely for people with CAD than for those without CAD when compared to simvastatin initiation, indicating channelling of atorvastatin to persons without CAD. In 2004, the difference no longer remained significant. In line with these findings, persons without CV medicines prior to initiation were more likely to be atorvastatin than simvastatin initiators (AOR ranged from 1.14 to 1.18) in 1999–

2003. In 1998, patients with diabetes were more likely to be initiated with atorvastatin than simvastatin (AOR 1.45, 95% CI 1.34–1.58), but thereafter no significant difference was found (data not shown in the table).

Discussion

Channelling, if unrecognised or unmeasured, may introduce an important source of bias in pharmacoepidemiology studies. Here we demonstrate how demographic factors and co-morbidity affected preferences of statin prescribing at initiation and how their impact changed over time. In Finland, during the 4 years after its introduction, atorvastatin was channelled to persons younger than 65 years and those without CAD. The effect of age decreased during the follow-up and the differences between atorvastatin and simvastatin had almost disappeared by the end of the observation in 2004.

Since atorvastatin was promoted as a potent statin [19], we assumed it would be preferred for patients with prior CV morbidity, but the opposite was found. However, as the efficacy of atorvastatin on CV morbidity and mortality was not available until the early 2000s (MIRACL study in 2001 [20], ASCOT-LLA in 2003 [21] and CARDS in 2004 [22]), the channelling of atorvastatin toward patients with lower morbidity in the first years after its launch and the similar initiation models to simvastatin later are understandable. Furthermore, atorvastatin may have been promoted for primary prevention as its introduction coincided with the publication of two large primary prevention trials, WOSCOPS on pravastatin and TexCAPS on lovastatin, in 1995 and 1998 [23, 24].

The effect of patients' expectations for medications and doctors' perceptions of patients' expectations on prescribing are generally strong predictors for prescribing [25, 26]. In a Swedish survey, statin users with only a few CV risk factors tended to expect greater benefits from statins than those with several risk factors [27]. This may

Fig. 1 Share of persons with coronary artery disease (a) and diabetes (b) among patients initiated with atorvastatin (white) and simvastatin (black)

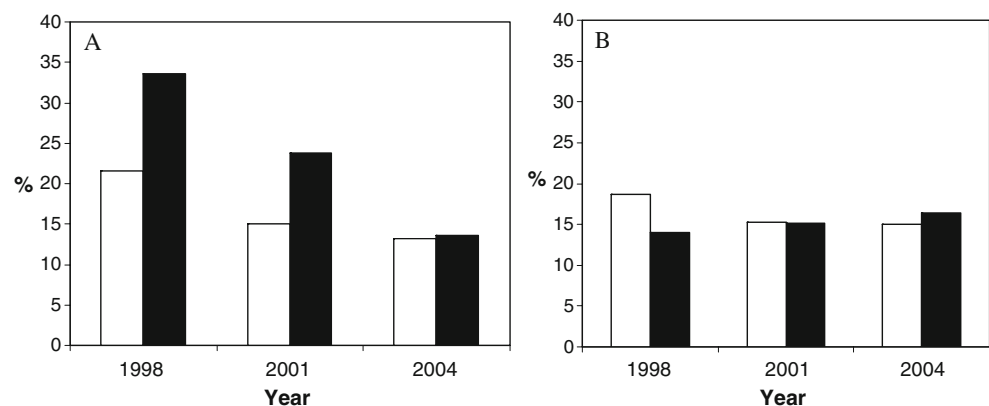


Table 2 Associations of explanatory factors with atorvastatin versus simvastatin at initiation

Age (years)	1998		1999		2001		2003		2004	
	AOR	(95% CI)	AOR	(95% CI)	AOR	(95% CI)	AOR	(95% CI)	AOR	(95% CI)
>74 (reference)	1.00		1.00		1.00		1.00		1.00	
65–74	1.05	(0.93–1.17)	0.96	(0.89–1.04)	1.05	(0.99–1.12)	0.92	(0.87–0.98)	0.93	(0.88–0.98)
55–64	1.20	(1.07–1.35)	1.16	(1.03–1.21)	1.11	(1.03–1.20)	0.91	(0.84–0.98)	1.00	(0.94–1.07)
45–54	1.54	(1.34–1.76)	1.38	(1.25–1.53)	1.20	(1.10–1.31)	1.01	(0.93–1.10)	1.05	(0.97–1.14)
<45	1.75	(1.48–2.07)	1.53	(1.34–1.75)	1.44	(1.29–1.60)	0.97	(0.87–1.07)	1.07	(0.97–1.18)
Region of residence										
Southern (reference)	1.00		1.00		1.00		1.00		1.00	
Mid–west	1.05	(0.97–1.14)	1.05	(0.99–1.12)	0.96	(0.91–1.02)	0.99	(0.94–1.04)	1.02	(0.98–1.08)
Western	0.65	(0.59–0.71)	0.57	(0.53–0.61)	0.60	(0.57–0.64)	0.98	(0.92–1.04)	1.10	(1.04–1.17)
Eastern	0.54	(0.50–0.59)	0.63	(0.59–0.67)	0.53	(0.50–0.55)	0.84	(0.79–0.88)	0.81	(0.77–0.85)
Northern	0.39	(0.34–0.43)	0.36	(0.33–0.39)	0.43	(0.40–0.46)	0.62	(0.58–0.66)	0.83	(0.78–0.87)
CAD (yes vs. no)	0.62	(0.58–0.67)	0.66	(0.62–0.70)	0.69	(0.66–0.73)	0.73	(0.69–0.77)	na	
Number of CV medicines during the 365 days prior to the initiation ^a										
>2 (reference)	na		1.00		1.00		1.00		na	
1–2	na		1.05	(0.99–1.11)	1.05	(0.99–1.10)	1.07	(1.02–1.13)	na	
None	na		1.15	(1.07–1.23)	1.21	(1.14–1.29)	1.18	(1.12–1.26)	na	

The binomial logistic regression model was applied separately for each year. Analyses were adjusted for socioeconomic status, and in the 1998 analysis for diabetes, in the 1999 analysis for eligibility for special reimbursement for drugs used for familial hypercholesterolemia, and in the 2004 analysis for gender and for eligibility for special reimbursement for drugs used to treat hypertension

AOR Adjusted odds ratio, CI confidence interval, CAD coronary artery disease, CV cardiovascular, na not available due to insignificance in the univariate analyses

^a At least one prescription from the following categories during the 365 days prior to the index date was taken into account when tallying the number of drugs: antithrombotics (ATC code B01), cardiac glucosides, antiarrhythmics and nitrates (all C01), miscellaneous antihypertensives (C02), diuretics (C03), peripheral vasodilators (C04), beta-blocking agents (C07), calcium antagonists (C08), agents acting on the renin-angiotensin system (C09)

partly explain why younger and wealthier patients tended to receive a potentially more effective atorvastatin. The region of residence clearly had an influence on the preferred statin at initiation. This may be a reflection of different marketing efforts but also differences in patient demography, such as age, in different parts of the country. As the prices of simvastatin and atorvastatin were at the same level up to 2003, cost is an unlikely explanation for the channelling.

The strength of our study is that all dispensed prescriptions of statins in the entire Finnish population in 1998–2004 were used in the analysis which eliminates the possibility of selection and recall bias. We were also able to analyse the impact of various patient-related factors potentially explaining initiation with a distinct statin. However, we were unable to capture data on cholesterol concentrations and on some relevant CV risk factors such as smoking, family history or obesity.

The utilisation of statins is increasing in many societies. In line with our results, other recent studies from Nordic countries [28, 29] demonstrate channelling of statin initiations, especially with newer preparations, toward

healthier populations. These trends are assumed to continue as evidence for beneficial effects of statin are accumulating also among populations with low cardiovascular risk. The cardiovascular benefit of statin therapy is approximately linearly related to the reduction in LDL cholesterol even among persons with low baseline lipid levels [30, 31].

However, the number of persons that must be treated to prevent one cardiovascular complication is remarkably larger among persons with a low cardiovascular risk profile compared to persons with a higher risk level [30]. As a consequence, the present trend tends to reduce the cost-effectiveness of statin therapy. In monetary terms, the impact of this trend is alleviated by generic substitution and reference pricing applied by many insurance and reimbursement systems.

Conclusion

In comparison with simvastatin, atorvastatin was channelled to younger patients with less CV morbidity following its launch in Finland. The channelling effect gradually

vanished over the study period. Channelling may lead to confounding by indication, a bias that must be handled carefully in pharmacoepidemiology studies.

Funding This study was funded by grant 10/26/2007 from the Social Insurance Institution of Finland (SII).

Role of the funding source The SII had no role in the design, analyses, interpretation of data, writing the report, or in the decision to submit the manuscript.

Conflict of interests Arja Helin-Salmivaara: No conflict of interests. Heli Halava: No conflict of interests. Jouni Junnila: No conflict of interests. Risto Huupponen: No conflict of interests.

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