



HAL
open science

Therapeutic traditions, patient socioeconomic characteristics and physicians' early new drug prescribing—a multilevel analysis of rosuvastatin prescription in south Sweden

Henrik Ohlsson, Basile Chaix, Juan Merlo

► **To cite this version:**

Henrik Ohlsson, Basile Chaix, Juan Merlo. Therapeutic traditions, patient socioeconomic characteristics and physicians' early new drug prescribing—a multilevel analysis of rosuvastatin prescription in south Sweden. *European Journal of Clinical Pharmacology*, 2008, 65 (2), pp.141-150. 10.1007/s00228-008-0569-4 . hal-00477929

HAL Id: hal-00477929

<https://hal.science/hal-00477929>

Submitted on 30 Apr 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Therapeutic traditions, patient socioeconomic characteristics and physicians' early new drug prescribing—a multilevel analysis of rosuvastatin prescription in south Sweden

Henrik Ohlsson · Basile Chaix · Juan Merlo

Received: 16 July 2008 / Accepted: 3 September 2008 / Published online: 4 October 2008
© Springer-Verlag 2008

Abstract

Purpose To investigate the role that both patient and outpatient factors related to health care practice (HCP) play in physicians' early adoption of rosuvastatin.

Materials and methods Generalized estimation equations (GEEs) and alternating logistic regression (ALR) with pairwise odds ratios (PWORs) were used to measure similarities in rosuvastatin prescription within HCPs for all individuals with statin prescriptions in Skåne region, Sweden.

Results After 12 months, 53% of the HCPs had adopted the new statin. Rosuvastatin prescriptions co-occurred within certain HCPs 3.56 times more often than one would have expected based on a random distribution. Private HCPs had four times higher probability of prescribing rosuvastatin than public HCPs.

Conclusion Contextual characteristics of the HCP seem to be relevant for understanding physicians' motivation to

adopt rosuvastatin. Moreover, our study reveals inequity in health care as the socioeconomic status of the patients appears to influence the prescribing behavior of the physicians irrespective of medical reasons.

Keywords Therapeutic traditions · Alternating logistic regression · Early adopter · Rosuvastatin

Background

In many countries drug expenditure is increasing rapidly in relation to overall health care costs, and a greater variety and availability of new, expensive drugs is one of the key factors influencing this phenomenon. Adopting a new drug could be appropriate for the health of the patient and cost-effective for the community, but in some cases newly marketed drugs only bring a marginal or insignificant contribution to the conventional therapeutic arsenal. Previous studies have shown considerable variation among prescribers regarding early adoption of newly marketed drugs [1–9], and it is known that the decision to adopt a new drug reflects differences in information and attitudes among prescribers [10, 11]. However, research on determinants of early adoption of new drugs is still very scarce. Understanding the mechanisms leading to physicians' early adoption of new drugs is, therefore, highly relevant for promoting cost-effective prescription.

Rosuvastatin was marketed as Crestor (AstraZeneca Pharmaceuticals, Wilmington, DE, USA) and incorporated within the Swedish health reimbursement system in July 2003, when it became the fifth available cholesterol-lowering drug from the class of HMG-CoA reductase inhibitors (statins) [12]. However, simultaneously and in concordance with an editorial in *The Lancet* [13], rosuvastatin

H. Ohlsson · B. Chaix · J. Merlo
Social Epidemiology, Department of Clinical Sciences in Malmö,
Faculty of Medicine, Lund University,
Malmö, Sweden

H. Ohlsson · J. Merlo
Department of Social Medicine, Skåne Region,
Malmö, Sweden

B. Chaix
UMR-S 707 Inserm, Université Pierre et Marie Curie-Paris 6,
Faculté de Médecine,
Paris, France

H. Ohlsson (✉)
Social Epidemiology, Department of Clinical Sciences,
Faculty of Medicine, Lund University,
205 02 Malmö, Sweden
e-mail: Henrik.Ohlsson@med.lu.se

tatin was not included in the Skåne region guidelines for rational drug prescription because this drug, despite being effective in lowering total and low-density lipoprotein (LDL) cholesterol, has unstipulated effects on morbidity and mortality and only scarce evidence concerning its safety. Moreover, rosuvastatin was approximately 20 times more expensive than the cheapest alternative statin [14].

The introduction of rosuvastatin on the Swedish market and the fact that there are no solid therapeutic reasons for prescribing the new, more expensive brand instead of the cheaper, recommended ones provide a unique opportunity to investigate determinants of (inappropriate) early adoption of new drugs in general, and of rosuvastatin in particular [15–17]. Therefore, we aimed to elaborate a previous theory that considers measures of variance and clustering to quantify therapeutic traditions [18–21]. For this purpose, we developed an innovative analytical approach using generalized estimation equations (GEE), alternating logistic regression (ALR), and pair-wise odds ratios (PWORs) [22]. Simultaneously, we aimed to investigate the role that both patient characteristics [(i.e., sex, age, socioeconomic status (SES), marital status, country of birth)] and factors related to outpatient health care practice (HCP) (e.g., public vs. private administration, proximity to specialized care, rural vs. urban setting, total prescription volume) played in physicians' propensity to prescribe rosuvastatin after its introduction to the market.

Materials and methods

The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register (SPDR) [23] is administered by the Centre for Epidemiology at the Swedish National Board of Health and Welfare and records information on sales of prescribed pharmaceutical agents by the Swedish Corporation of Pharmacies. The SPDR was launched in January 1999, and since July 2005, it has been using the Swedish personal identification number system rather than an arbitrary number for each prescription, which allows record linkage with other health care registers at the individual level. Among other data, the SPDR contains the brand name and anatomical therapeutic chemical classification (ATC) code for both prescribed and dispensed drugs, whether the prescription is repeated or not, and the HCP where the prescription was issued (identifiable by barcodes on the prescriptions). Information on prescribers is, however, not available.

At the time rosuvastatin was introduced in the Swedish reimbursement system (July 2003) there was not information in the SPDR at the individual level. This information was only available from July 2005, and therefore we used

two different data sets. The first data set included all 84,822 initial prescriptions of statins issued at HCPs in the Skåne region between July 2003 and June 2004. We excluded HCPs with sporadic prescription (i.e., <30 statin prescriptions during the entire observation period), as well as those prescriptions issued from unidentified places or places outside Skåne [13% (11,275/84,822)]. Also, since according to the Swedish reimbursement system, a prescription that covers a whole year must be dispensed in three increments, we only considered first dispensations within the study period. In total we analyzed 73,547 prescriptions (32,641 for women and 40,906 for men) from 170 HCPs. In the second data set, we included all 32,011 individuals (14,316 women and 17,695 men) in Skåne region who were issued at least one prescription for statins between July and December 2005 at the same 159 HCPs (eleven HCPs out of the original 170 gave no prescriptions during this period).

Data from the Longitudinal Multilevel Analysis in Skåne (LOMAS) were used to establish demographic variables and the SES of the individuals [24].

This project was performed with the approval of and assistance from Statistics Sweden and the Centre for Epidemiology at the Swedish National Board of Health and Welfare, as well as approval by the Regional Ethical Review Board in Lund. In order to protect the identity of the individuals, the research database does not contain the real personal identification number but rather an arbitrary number. The link between these two numbers is kept at Statistics Sweden.

Individual-level variables

Statins were defined according to the ATC code C10AA [25]. At the individual level, the outcome variable was prescription (yes vs. no) of rosuvastatin (ATC code C10AA07). In the analyses we included the sex (male vs. female) and age (centered on the overall mean of 66 years) of the patients.

As described elsewhere [26], the SES of the patients seemed to influence the prescribing behavior. Therefore, in the second phase of our analyses we also considered each patient's disposable family income, measured at the end of 2004. We divided income into quartiles and used the highest quartile as reference in the comparisons.

Adopting an exploratory approach we also included the marital and immigrant status of the patients as we hypothesized that these characteristics could influence physicians' prescribing behavior. Marital status was dichotomized into married/cohabiting vs. living alone (i.e., single, divorced, or widowed), with married/cohabiting as reference category. Immigrant status/ethnicity was measured by the country of birth of the patients and the number of years that the patient had resided in Sweden. We categorized this

last variable into (1) always lived in Sweden, (2) ≥ 10 years in Sweden, and (3) 0–9 years in Sweden. The first category was used as a reference in the analysis. The country of birth of the patients was categorized according the World Bank Classification of Country Economies (i.e., low, lower-middle, upper-middle, and high income) [27]. In the analysis, we merged the first two into a single category designated “low-income country”, and used the high-income country category as a reference in the comparisons. Number of years in Sweden and country of birth, according to the World Bank classification, offered an appropriate alternative for measuring immigrant status/ethnicity as this combination considers the acculturation process of immigrants who have resided in Sweden for many years and focuses not on geographic but on economic criteria for classifying country of birth.

Area-level variables

Of the 170 (159) HCPs included in the first (and second) data set, 129 (127) were under public administration as public primary health care centers and hospital outpatient care clinics, and 41 (32) were private primary health care centers employing general practitioners (GPs) and other specialists. The health services in Sweden are largely tax-financed, and even private HCPs are primarily funded by contract between the public health care authorities and the private companies [28]. Private physicians are, however, less influenced by the public health care administration, and we have previously shown that privately managed HCPs have a lower adherence to official guidelines for statin prescription than public HCPs [21]. Therefore, we included this variable (private vs. public) in the analyses since it was possible that the administrative condition of the HCP also influenced early adoption of rosuvastatin.

Given that proximity to specialized care may influence prescription patterns, we also identified those HCPs that employed specialist physicians other than GPs. In the analyses, HCPs employing GPs only were used as reference.

It is probable that several factors that could influence prescription of newly marketed drugs, such as distribution of information, marketing forces, and patient demands and expectations, may be influenced by the population density of the area. Therefore, we considered whether the HCP was located in a rural or an urban area, according to the definition provided by the Swedish Association of Local Authorities and Regions. The definition is based on structural characteristics such as population size, commuting patterns, and the structure of businesses in the municipality [29]. Of the 33 municipalities in Skåne region, those municipalities that were classified as a metropolitan area (1), suburban municipality (6), large town (3), or

medium-sized town (7) were classified as urban areas. Sixteen municipalities were classified as rural areas and were used as reference in the analysis.

The total prescribing volume of the HCP where the prescriber works has been shown in previous studies to affect the likelihood that a physician will adopt a new drug, where a larger prescribing volume is associated with higher probability of early adoption of a new drug [30]. Consequently, we included a variable where the number of statin prescriptions at the HCPs during the entire observation period was divided into three categories: T1 (≤ 234 prescriptions), T2 (235–441 prescriptions), and T3 (> 441 prescriptions). We used T3 as reference in the comparisons.

Statistical and epidemiological analysis

Our hypothesis was that the HCP environment (i.e., therapeutic traditions) had an independent influence on physicians' prescribing behavior in general and on early adoption of rosuvastatin in particular. To investigate this hypothesis we applied a previous theory [18–21] that considers measures of variance and clustering to quantify therapeutic traditions, and we measured clustering of rosuvastatin prescription at the HCP level across time, categorized into four consecutive trimesters from July 2003 to June 2004.

In previous studies we employed multilevel regression analyses [20, 21], a suitable analytical approach when the data have a hierarchical structure as in the present case (i.e., prescriptions were nested within different time periods, which in turn were nested within HCPs). However, since the distribution of the prevalence of rosuvastatin prescription at the HCP level was skewed, we applied ALR. Similarly to multilevel regression analyses, the ALR model accounts for the dependence of the outcome within different levels/categories and thereby allows accurate statistical estimations. Also, the ALR methodology allowed us to quantify the clustering of prescriptions of rosuvastatin within HCPs with an index in the form of an odds ratio (OR), the PWOR [22].

In order to compute PWORs, the model considers all the pairs involving two prescriptions from the same HCP. Using p_{11} to denote the probability that both prescriptions in a pair are for rosuvastatin, p_{00} to denote the probability that neither of the prescriptions in a pair is for rosuvastatin, and p_{10} and p_{01} to denote the probabilities that only one of the prescriptions in a pair is for rosuvastatin, the PWOR can be calculated as follows:

$$\text{PWOR} = \frac{p_{00} \cdot p_{11}}{p_{10} \cdot p_{01}} \quad (1)$$

The PWOR reflects the increase in the odds of a prescription being for rosuvastatin given that another

prescription randomly selected from the same HCP may also be for rosuvastatin. By quantifying the context dependence of the rosuvastatin prescription, PWORs can be used as a measure of “therapeutic traditions.” The higher the PWOR, the stronger the therapeutic traditions. The PWOR is equal to 1 in the absence of clustering, and in this case it indicates that rosuvastatin prescriptions within the same HCP were more frequent than could be expected if prescriptions were distributed randomly across HCPs.

In practice, PWORs are calculated from the ALR model, which simultaneously estimates the following two equations:

$$\log(\text{PWOR}_{kl}) = \alpha Z_{kl} \quad (2)$$

$$\text{logit}(p_k) = \beta_0 \quad (3)$$

Equation 2 expresses the logarithm of PWORs as a function of a dummy variable Z , which simply indicates whether two patients (or two prescriptions), k and l , in a pair belong to the same category or not (the variable Z is equal to 0, and the PWOR to 1, for prescriptions from different HCPs). The ALR model simultaneously estimates a logistic regression by a GEE for the outcome (Eq. 3); in this equation, p_k refers to the expected probability of prescribing rosuvastatin for the patient k .

We specified several different models. Model A was an empty model without any covariates, which only included time as a second level and HCPs as the third level. This model allowed separate PWORs to be calculated within and across different time periods. Models B and C included individual, and individual and contextual variables, respectively.

Applying an established procedure [31], we used the PWORs obtained in the empty model as reference ($\text{PWOR}_{\text{reference}}$) to calculate the percentage of change in the magnitude of clustering, which was explained by including individual or contextual characteristics in the model with more variables ($\text{PWOR}_{\text{more}}$).

Percentage of change

$$= ((\text{PWOR}_{\text{reference}} - \text{PWOR}_{\text{more}}) / (\text{PWOR}_{\text{reference}} - 1)) \times 100 \quad (4)$$

We used this percentage for estimating the relevance of patient characteristics (i.e., the patient composition of the HCPs) as well as the relevance of contextual characteristics of the HCPs for understanding a possible clustering of rosuvastatin prescriptions.

In order to investigate the influence of the SES of patients on the prescription of rosuvastatin, we applied

GEE-ALR on the data from July to December 2005 (i.e., the second data set). Model D was an empty model without any covariates, which only included HCPs as a second level, while models E and F further included individual and contextual variables that could explain a possible clustering of rosuvastatin prescriptions.

We performed a survival analysis at the HCP level, in which we followed the HCPs from baseline until the first prescription of rosuvastatin or the end of the first observation period, and performed a Cox regression to investigate the association between the administrative condition (private vs. public) of the HCP and early adoption of rosuvastatin.

To study associations we calculated ORs and their 95% confidence intervals (95% CIs) from the regression coefficients [(standard errors (SEs)].

The calculations were made using the GENMOD procedure in SAS software, version 9.1 (SAS Institute, Cary, NC, USA), to fit the ALR models, and SPSS, version 15 (SPSS, Chicago, IL, USA).

Results

For the period July 2003 to June 2004, there was a decreasing trend in the prevalence of rosuvastatin prescriptions ranging from 2.6% (410/16,073) in the first trimester to 1.5% (283/18,273) in the last.

Table 1 shows that, on average, patients receiving rosuvastatin were younger than patients receiving other statins. More men than women received a statin prescription, and the same was true for rosuvastatin. Throughout the whole study period, private HCPs, HCPs employing specialists as well as GPs, and HCPs located in an urban area more frequently prescribed rosuvastatin than public HCPs, HCPs with only GPs, and HCPs located in rural areas. The lower the amount of total statin prescribed at the HCP, the higher the percentage of rosuvastatin prescription. However, this phenomenon was only apparent in the early phase of the observation period.

A descriptive analysis of the HCPs shows that 90 of the 170 HCPs prescribed at least one prescription for rosuvastatin during the entire study period. Moreover, in three HCPs the prescription of rosuvastatin was considerably higher than in the rest of the HCPs (>15%). Those three HCPs accounted for 13% of all rosuvastatin prescriptions but only for 1% of all statin prescriptions throughout the study period.

Figure 1 shows that private HCPs seem to have adopted rosuvastatin faster than public HCPs. In addition, the Cox regression showed that private HCPs had a 1.82 (95% CI 1.16–2.84) times higher hazard of adopting rosuvastatin than public HCPs. Moreover, at the end of the observation

Table 1 Characteristics of the 73,547 prescriptions for statins issued to 32,641 women and 40,906 men at 170 health care practices (HCPs)

	Jul–Sept 2003		Oct–Dec 2003		Jan–Mar 2004		Apr–Jun 2004	
	Other statin	Rosuvastatin	Other statin	Rosuvastatin	Other statin	Rosuvastatin	Other statin	Rosuvastatin
Prescriptions	15,663	410 (2.6%)	20,143	444 (2.2%)	18,270	344 (1.9%)	17,990	283 (1.6%)
Mean age (years)	66	61	66	58	67	61	67	61
Men (%)	57	50	56	56	55	51	56	54
HCP								
Private	5,073	268 (5.3%)	6,079	264 (4.3%)	4,402	161 (3.7%)	4,447	156 (3.5%)
Public	10,590	142 (1.3%)	14,064	180 (1.3%)	13,868	183 (1.3%)	13,543	127 (0.9%)
Only GPs	9,565	236 (2.5%)	12,861	219 (1.7%)	12,656	230 (1.8%)	12,614	199 (1.6%)
Other specialists	6,098	174 (2.9%)	7,282	225 (3.1%)	5,614	114 (2.0%)	5,376	84 (1.6%)
Rural	1,946	27 (1.4%)	2,548	29 (1.1%)	2,456	32 (1.3%)	2,476	41 (1.7%)
Urban	13,717	383 (2.8%)	17,595	415 (2.4%)	15,814	312 (2.0%)	15,514	242 (1.6%)
Size ^a								
≤234	1,621	69 (4.3%)	1,999	44 (2.2%)	1,536	23 (1.5%)	1,650	19 (1.2%)
235–441	3,961	62 (1.6%)	5,359	89 (1.7%)	5,027	56 (1.1%)	4,996	54 (1.1%)
>441	10,081	279 (2.8%)	12,785	311 (2.4%)	11,707	265 (2.3%)	11,344	210 (1.9%)

Unless otherwise indicated, values are *n*

^a Size of HCP in terms of number of prescriptions during the observation period

period almost 70% of private HCPs had given at least one prescription of rosuvastatin compared with 45% of public HCPs.

Table 2 (model A) shows that, during the first trimester of the observation period, rosuvastatin prescriptions co-occurred within certain HCPs more frequently than one would had expect if prescriptions were distributed randomly, i.e., PWOR=3.56 (95% CI 1.95–6.51), and this clustering continued to be high in the following trimesters. The between-time clustering was also high (values above

the diagonal for model A in Table 2), indicating that those HCPs with a higher level of rosuvastatin prescription during one trimester were also more likely to prescribe rosuvastatin in the other trimesters. Accounting for the age and gender composition (model B) of the HCPs did not attenuate the magnitude of clustering. However, age was conclusively associated with the prescription of rosuvastatin, with a lower probability for older people. When including the contextual variables (model C), the PWOR was reduced by approximately 40% in the first and second trimesters but only by 9% in the third trimester.

The probability of prescribing rosuvastatin was approximately four times higher in private than in public HCPs (Table 3). In this model, neither the presence of specialist physicians nor the rural vs. urban location of the HCP was associated with rosuvastatin prescription.

Table 4 shows that from July to December 2005, 366 individuals (1.3% of all individuals with statin prescriptions) were prescribed rosuvastatin. The prevalence of rosuvastatin prescriptions was higher among individuals who were married/cohabiting and also showed a socioeconomic gradient with a higher share of rosuvastatin prescriptions among both men and women with high income. However, there was no association between country of birth of patients and rosuvastatin prescription.

Table 5 shows that individuals in the highest income quartile had higher odds of being prescribed rosuvastatin than individuals in the lowest income quartile. In models D–F we did not find any conclusive association between rosuvastatin prescription and number of years in Sweden, country of birth, or marital status. The clustering of rosuvastatin prescriptions at the HCP level was high for

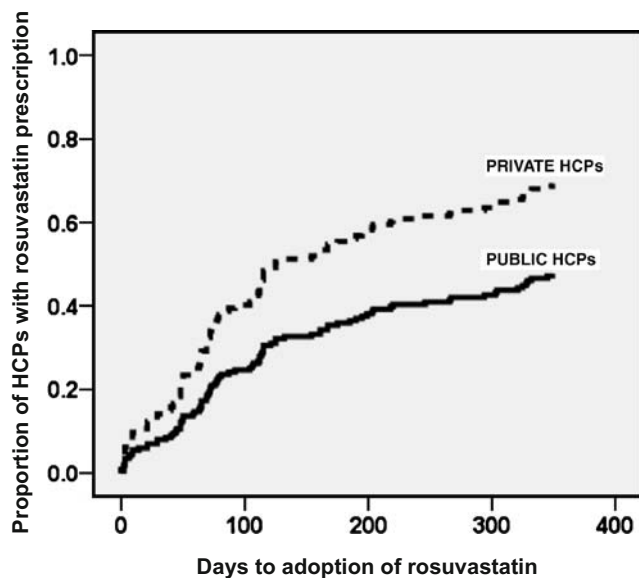


Fig. 1 Prescribing of rosuvastatin in private vs. public health care practices (HCPs) during the observation period July 2003 to June 2004

Table 2 Pair-wise odds ratios and odds ratios (with 95% confidence intervals *in parentheses*) obtained by alternating logistic regression (ALR) analysis of early adoption of rosuvastatin in the county of Skåne, Sweden

Model A	Trimester 1	Trimester 2	Trimester 3	Trimester 4
Trimester 1	3.56 (1.95–6.51)	2.75 (1.87–4.05)	2.18 (1.39–3.43)	2.47 (1.31–4.66)
Trimester 2		2.59 (1.81–3.71)	2.01 (1.42–2.84)	2.41 (1.63–3.58)
Trimester 3			2.71 (1.69–4.35)	2.55 (1.51–4.32)
Trimester 4				3.44 (2.14–5.51)
Model B	Trimester 1	Trimester 2	Trimester 3	Trimester 4
Trimester 1	3.78 (2.08–6.88)	2.88 (1.96–4.25)	2.19 (1.38–3.47)	2.51 (1.30–4.83)
Trimester 2		2.70 (1.86–3.91)	2.00 (1.40–2.86)	2.44 (1.62–3.68)
Trimester 3			2.67 (1.65–4.31)	2.50 (1.47–4.24)
Trimester 4				3.28 (2.01–5.35)
Model C	Trimester 1	Trimester 2	Trimester 3	Trimester 4
Trimester 1	2.05 (1.06–3.93)	1.56 (0.97–2.53)	1.63 (1.11–2.39)	1.61 (1.19–2.17)
Trimester 2		1.59 (0.98–2.58)	1.70 (1.15–2.51)	1.70 (1.14–2.54)
Trimester 3			2.44 (1.51–3.93)	2.08 (1.52–2.85)
Trimester 4				2.47 (1.56–3.92)

both men (PWOR=2.99) and women (PWOR=2.58). Adjustment for the patient characteristics studied attenuated the magnitude of clustering to a small extent. However, the inclusion of contextual variables decreased the magnitude of clustering by approximately 20%.

Discussion

The present study shows that early adoption of rosuvastatin was highly clustered in certain HCPs, and that this clustering remained across the whole observation period. Therefore, our results suggest the existence of strong therapeutic traditions that, at the HCP level, influence prescribing behavior of individual physicians. We also observed that private HCPs prescribed rosuvastatin four times more frequently than public HCPs. However, even if this contextual characteristic appeared to be relevant for understanding physicians' motivation to adopt rosuvastatin, it could not completely explain the observed variance in

rosuvastatin prescription. Moreover, our study reveals some inequity in health care as rosuvastatin was prescribed more frequently to younger patients and to those with a high SES than to elderly patients or to those with a low income. In other words, both contextual and patient characteristics seem to have influenced the behavior of the physicians, independently of medical reasons. Our study supports previous findings [6, 7, 32], indicating that a wide range of factors at different levels may influence the diffusion of innovations [33].

It is important to consider that the context, i.e., the HCP where the physicians worked, seems to have affected both early adoption and the subsequent prescription of rosuvastatin. In fact, those HCPs that prescribed one prescription of rosuvastatin were almost four times more likely to prescribe one more prescription during the same trimester, and almost three times more likely to prescribe rosuvastatin during the following trimester. This observation suggests that local therapeutic traditions remain over time, and that prescription of rosuvastatin was not an occasional early phenom-

Table 3 Fixed effects (odds ratios with 95% confidence intervals *in parentheses*) of the generalized estimation equations (GEE)-ALR methodology

	Model A	Model B	Model C
Age (1 year's increase)		0.96 (0.94–0.97)	0.96 (0.94–0.97)
Sex (male vs. female)		0.87 (0.65–1.15)	0.87 (0.67–1.14)
Private vs. public			4.31 (1.93–9.62)
Size ^a			
≤234			0.64 (0.21–1.96)
235–441			0.67 (0.36–1.23)
>441			Reference
Specialist vs. general practitioner ^b			0.97 (0.58–1.62)
Urban vs. rural ^b			0.98 (0.50–1.90)

^a Size of HCP in terms of number of prescriptions during the observation period

^b Estimated in a model with the same PWOR for all time periods, and time included as a fixed effect

Table 4 Characteristics of the 32,011 individuals (14,316 women and 17,695 men) who were prescribed at least one statin between July and December 2005

	Total		Men		Women	
	Other statin	Rosuvastatin	Other statin	Rosuvastatin	Other statin	Rosuvastatin
Number of individuals	31,645	366 (1.2%)	17,479	216 (1.2%)	14,166	150 (1.1%)
Mean age (years)	68	61	66	60	69	63
Men	55.2%	59.0%				
Income						
Low	8,248	59 (0.7%)	4,171	32 (0.8%)	4,077	27 (0.7%)
Middle-low	8,101	63 (0.8%)	3,893	35 (0.9%)	4,208	28 (0.7%)
Middle-high	7,788	105(1.3%)	4,553	56(1.2%)	3,235	49(1.5%)
High	7,508	139 (1.9%)	4,862	93 (1.9%)	2,646	46 (1.7%)
Marital status						
Living alone	12,033	105 (0.9%)	5,251	56 (1.1%)	6,782	49 (0.7%)
Married/cohabiting	19,612	261 (1.3%)	12,228	160 (1.3%)	7,384	101 (1.4%)
Country of birth						
High-income country	29,009	335 (1.2%)	16,049	196 (1.2%)	12,960	139 (1.1%)
Middle-income country	1,016	15 (1.5%)	527	10 (1.9%)	489	5 (1.0%)
Low-middle income country	1,486	15 (1.0%)	821	10 (1.2%)	665	5 (0.8%)
Low-income country	134	1 (0.7%)	82	0 (0.0%)	52	1 (1.9%)
Number of years in Sweden						
Always	26,695	301 (1.1%)	14,752	178 (1.2%)	11,943	123 (1.0%)
≥10	4,268	56 (1.3%)	2,316	32 (1.4%)	1,952	24 (1.2%)
0–9	682	6 (1.0%)	411	6 (1.5%)	271	3 (1.1%)

enon. When analyzing trends in rosuvastatin prescription, it is relevant to realize that this drug was the subject of safety concerns [12–14] during the observation period. These warnings possibly influenced the patterns of drug utilization, as evidenced by an overall reduction in the prevalence of rosuvastatin prescriptions in the last trimester of observation. However, the clustering of rosuvastatin prescriptions was not substantially affected.

Earlier studies also suggest that a high volume of prescribing at an HCP may affect physicians' adoption of new drugs since the likelihood of seeing a patient as a candidate for the new drug would be higher [30]. However, there are no specific indications that should make one patient more suitable than another for receiving a rosuvastatin prescription, and, in fact, the present analysis shows no association between rosuvastatin prescription and prescription volume at the HCP. Previous studies have shown that medical innovations are more likely to be adopted earlier in urban areas than in rural areas [30]. However, in this study we did not find support for this association.

Based on the actual evidence there is no patient characteristic that could motivate the preferential prescription of rosuvastatin before any other statin. Therefore the individual-level variables in the analysis are included, not because of the need for adjustment for confounding, but rather because we wanted to gain an understanding of the prescribing process. In the present investigation we ob-

served that women were prescribed less rosuvastatin than men. Also, rosuvastatin was more frequently prescribed to patients with higher SES.

Even though the present analysis confirms previous reports indicating that practice-level factors are relevant for understanding prescribing behavior [18–21, 34, 35], part of the prescribing behavior in the present study could in fact have been due to individual physicians rather than to the characteristics of the HCP. In a previous study [36] we showed that approximately 50% of the variation among practices is in fact due to variations among physicians. However, we did not have access to physician-level information in the current database.

Practice variation is a common phenomenon that is not necessarily inappropriate but rather may reflect different therapeutic approaches to confronting a similar health problem [37, 38]. However, since all statins have homogeneous indication and similar efficacy, statins are an ideal medication group for investigating inappropriate practice variation. At the time of this study, rosuvastatin 40 mg was approximately 20 times more expensive than the cheapest recommended statin. Subsequently, when a pharmacological agent is used in an unsuitable way, which could lead to undesirable inequalities in drug use for the population and have important cost implications, it is relevant to investigate determinants of prescription disparities in order to launch interventions promoting appropriate prescription.

Table 5 Pair-wise odds ratios (PWORs) and odds ratios (ORs) (with 95% confidence intervals *in parentheses*), obtained by alternating logistic regression (ALR) analysis of patients who were prescribed rosuvastatin in the region of Skåne, Sweden, from July to December 2005

	Model D		Model E		Model F	
	Men	Women	Men	Women	Men	Women
PWOR (95% CI)	2.99 (1.63–5.49)	2.58 (1.79–3.73)	2.83 (1.58–5.09)	2.46 (1.73–3.50)	1.89 (1.35–2.63)	1.72 (1.27–2.33)
Individual variables			OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (1-year increase)			0.96 (0.94–0.97)	0.96 (0.95–0.98)	0.94 (0.92–0.95)	0.96 (0.95–0.98)
Income						
Low			Reference	Reference	Reference	Reference
Middle-low			1.22 (0.64–2.33)	1.00 (0.58–1.74)	1.22 (0.67–2.22)	1.00 (0.58–1.73)
Middle-high			1.38 (0.85–2.23)	1.68 (0.93–3.03)	1.35 (0.87–2.10)	1.66 (0.93–2.95)
High			1.80 (1.05–3.11)	1.62 (0.93–2.81)	1.74 (1.07–2.85)	1.58 (0.91–2.72)
Marital status						
Living alone			0.78 (0.53–1.13)	0.65 (0.42–1.02)	0.79 (0.56–1.11)	0.66 (0.44–1.01)
Married/cohabiting			Reference	Reference	Reference	Reference
Country of birth						
High-income country			Reference	Reference	Reference	Reference
Middle-income country			1.34 (0.57–3.15)	0.83 (0.25–2.77)	1.33 (0.62–2.83)	0.85 (0.27–2.72)
Low-income country			1.06 (0.38–2.94)	0.54 (0.18–1.65)	1.08 (0.43–2.75)	1.82 (0.63–5.25)
Number of years in Sweden						
Always			Reference	Reference	Reference	Reference
≥10			0.31 (0.05–1.93)	1.46 (0.37–5.86)	0.32 (0.06–1.67)	1.46 (0.40–5.41)
0–9			0.86 (0.19–3.87)	1.31 (0.33–5.86)	0.88 (0.23–3.32)	1.36 (0.36–5.15)
Contextual variables						
Private vs. public HCP					3.41 (1.95–5.95)	3.09 (1.58–6.05)
Size of HCP						
Small					0.86 (0.42–1.79)	0.97 (0.40–2.36)
Medium					0.71 (0.36–1.39)	1.02 (0.51–2.03)
Large					Reference	Reference
Specialist vs. general practitioner					1.62 (0.88–3.00)	1.19 (0.62–2.29)
Urban v. rural					1.14 (0.45–2.84)	0.93 (0.44–1.99)

HCP Health care practice

In previous studies we measured therapeutic traditions using analysis of variance and multilevel logistic regression techniques [20, 21]. In the present investigation we applied the ALR-PWOR approach. Both methods provide analogous, but not identical, information. While the ALR-PWOR approach provides information on the magnitude of clustering of similar behavior within different HCPs, the multilevel logistic regression approach measures the heterogeneity across HCPs. Pair-wise odds ratios appear to be a very suitable measure for interpreting clustering in the well-known OR scale. Also, the ALR-PWOR is appropriate for investigating outcomes with a very skewed distribution [22], as in the present study. The PWOR is also a flexible measure that allows investigation of clustering in arbitrary categories such as different time periods. Alternating logistic regression has been successfully employed in a number of previous epidemiological studies [39–46] and appears to be a relevant measure for investigating and quantifying medical practice variation.

In conclusion, the GEE-ALR and PWOR methodology seems to be a useful tool for investigating determinants of prescription at different levels of analysis. Applying this methodology we observed that contextual factors (e.g., therapeutic traditions) at the HCP may be relevant for understanding physicians' propensity to early adopt and prescribe a new statin (i.e., rosuvastatin), especially in the private sector. Additionally, the age and SES of the patients appeared to influence the prescribing behavior of the physicians, as rosuvastatin was more frequently prescribed to both younger men and younger women with high income. When the same pharmacological therapy is available as different brands at different prices and the prescriber selects the new, more expensive brand based on socioeconomic constructs rather than on medical grounds there are reasons to question the suitability of the observed prescribing process. Our study indicates the existence of inefficient therapeutic traditions and suggests that interventions may be necessary to promote rational prescription guidelines for pharmacologic treatment in the context of a limited health care budget.

References

- Coleman J, Menzel H, Katz E (1959) Social processes in physicians' adoption of a new drug. *J Chronic Dis* 9(1):1–19
- Dybdahl T, Andersen M, Kragstrup J, Kristiansen IS, Sondergaard J (2005) General practitioners' adoption of new drugs and previous prescribing of drugs belonging to the same therapeutic class: a pharmacoepidemiological study. *Br J Clin Pharmacol* 60(5):526–533
- Dybdahl T, Andersen M, Sondergaard J, Kragstrup J, Kristiansen IS (2004) Does the early adopter of drugs exist? A population-based study of general practitioners' prescribing of new drugs. *Eur J Clin Pharmacol* 60(9):667–672
- Greving JP, Denig P, Van der Veen WJ, Beltman FW, Sturkenboom MC, Haaijer-Ruskamp FM (2006) Determinants for the adoption of angiotensin II receptor blockers by general practitioners. *Soc Sci Med* 63(11):2890–2898
- Jones MI, Greenfield SM, Bradley CP (2001) Prescribing new drugs: qualitative study of influences on consultants and general practitioners. *Brit Med J* 323(7309):378–381
- Steffensen FH, Sørensen H, Olesen F (1999) Diffusion of new drugs in Danish general practice. *Fam Prac* 16:407–413
- Tamblyn R, McLeod P, Hanley JA, Girard N, Hurley J (2003) Physician and practice characteristics associated with the early utilization of new prescription drugs. *Med Care* 41(8):895–908
- Florentinus SR, Nielsen MW, van Dijk L, Leufkens HG, Hansen EH, Heerdink ER (2005) Patient characteristics associated with prescribing of a newly introduced drug: the case of rofecoxib. *Eur J Clin Pharmacol* 61(2):157–159
- Kozyrskij A, Raymond C, Racher A (2007) Characterizing early prescribers of newly marketed drugs in Canada: a population-based study. *Eur J Clin Pharmacol* 63(6):597–604
- Haaijer-Ruskamp FM, Hemminki E (1993) The social aspects of drug use. *WHO Reg Publ Eur Ser* 45:97–124
- Merlo J, Lynch JW, Yang M, Lindstrom M, Ostergren PO, Rasmussen NK, Rastam L (2003) Effect of neighborhood social participation on individual use of hormone replacement therapy and antihypertensive medication: a multilevel analysis. *Am J Epidemiol* 157(9):774–783
- Läkemedelsverket (2004) Produktresumén revideras för Crestor (Product resume for Crestor is revised) (in Swedish). http://www.lakemedelsverket.se/Tpl/NewsPage_1166.aspx. Accessed 18 Sept 2008
- Editors (2003) The statin wars: why AstraZeneca must retreat. *Lancet* 362(9393):1341
- Ohlsson O, Kjellström T (2003) Landsomfattande konsensus för behandling av höga blodfetter (För landets läkemedelskommittéordförande LOK) (Consensus for treatment of high lipids) (in Swedish). Lund, Sweden
- Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (2006) Evaluation of the effects of statins (with particular consideration of atorvastatin). IQWiG, Cologne
- LaRosa JC, He J, Vupputuri S (1999) Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *J Am Med Assoc* 282(24):2340–2346
- Vrečer M, Turk S, Drinovec J, Mrhar A (2003) Use of statins in primary and secondary prevention of coronary heart disease and ischemic stroke. Meta-analysis of randomized trials. *Int J Clin Pharmacol Ther* 41(12):567–577
- Davis P, Gribben B (1995) Rational prescribing and interpractitioner variation. A multilevel approach. *Int J Technol Assess Health Care* 11(3):428–442
- Davis P, Gribben B, Lay-Yee R, Scott A (2002) How much variation in clinical activity is there between general practitioners? A multi-level analysis of decision-making in primary care. *J Health Serv Res Pol* 7(4):202–208
- Ohlsson H, Lindblad U, Lithman T, Ericsson B, Gerdttham UG, Melander A, Rastam L, Merlo J (2005) Understanding adherence to official guidelines on statin prescribing in primary health care – a multi-level methodological approach. *Eur J Clin Pharmacol* 61(9):657–665
- Ohlsson H, Merlo J (2007) Understanding the effects of a decentralized budget on physicians' compliance with guidelines for statin prescription; a multilevel methodological approach. *BMC Health Serv Res* 7:68 (8 May 2007)
- Carey V, Zeger SL, Diggle P (1993) Modelling multivariate binary data with alternating logistic regression. *Biometrika* 80(3):517–526
- Socialstyrelsen (2008) Läkemedelsregistret. http://www.socialstyrelsen.se/Statistik/statistik_amne/lakemedel/Lakemedelsregistret.htm. Accessed 12 May 2008
- Chaix B, Rosvall M, Merlo J (2007) Assessment of the magnitude of geographical variations and socioeconomic contextual effects on ischaemic heart disease mortality: a multilevel survival analysis of a large Swedish cohort. *J Epidemiol Comm Health* 61(4):349–355
- World Health Organisation (2008) About the ATC/DDD system. <http://www.whocc.no/atcddd/>. Accessed 12 Apr 2008
- Scott A, Shiell A, King M (1996) Is general practitioner decision making associated with patient socio-economic status? *Soc Sci Med* 42(1):35–46
- WorldBank (2008) Country classification. <http://www.worldbank.org/data/countryclass/countryclass.html>. Accessed 15 Jan 2008
- Swedish Association of Local Authorities and Regions (2005) Swedish health care in an international context. SAoLAA, Stockholm
- Bengtsson H (2003) Nuvarnade kommunuppdelning (Classification of municipalities) (in Swedish). Svenska Kommunförbundet <http://www.skf.se/artikel.asp?A=11248&C=445>. Accessed 22 Jan 2008
- Glass H, Rosenthal B (2004) Demographics, practices, and prescribing characteristics of physicians who are early adopters of new drugs. *Pharm Therapeut* 29(11):699–708
- Wamala SP, Mittleman MA, Schenck-Gustafsson K, Orth-Gomer K (1999) Potential explanations for the educational gradient in coronary heart disease: a population-based case-control study of Swedish women. *Am J Public Health* 89(3):315–321
- Jacoby A, Smith M, Eccles M (2003) A qualitative study to explore influences on general practitioners' decisions to prescribe new drugs. *Br J Gen Pract* 53(487):120–125
- Rogers E (1962) Diffusion of innovation. Free Press, New York
- Brookhart MA, Solomon DH, Wang P, Glynn RJ, Avorn J, Schneeweiss S (2006) Explained variation in a model of therapeutic decision making is partitioned across patient, physician, and clinic factors. *J Clin Epidemiol* 59(1):18–25
- Lopez-Valcarcel B, Ortun-Rubio V, Cabeza-Mora A, Lopez-Cabañas A, Diaz-Berenger J, Alamo-Santana F (2002) Evaluation del uso apropiado de medicamentos en atención primaria. Como se puede mejorar? (Evaluation of the appropriate use of medication in primary care. How do we improve it?) (in Spanish). *Aten Primaria* 30:467–471
- Hjerpe P, Fornwall S, Merlo J (2004) Therapeutic traditions and compliance with local therapeutic guidelines on lipid lowering drugs – a multilevel analysis in the Skaraborg Primary Healthcare Database (SPHD). International Society for Pharmacoepidemiology, Bordeaux, France
- Smits HL (1986) Medical practice variations revisited. *Health Aff (Millwood)* 5(3):91–96
- Wennberg JE, Barnes BA, Zubkoff M (1982) Professional uncertainty and the problem of supplier-induced demand. *Soc Sci Med* 16(7):811–824

39. Bobashev GV, Anthony JC (1998) Clusters of marijuana use in the United States. *Am J Epidemiol* 148(12):1168–1174
40. Bobashev GV, Anthony JC (2000) Use of alternating logistic regression in studies of drug-use clustering. *Subst Use Misuse* 35(6–8):1051–1073
41. Chauvin C, Bouvarel I, Beloeil PA, Orand JP, Guillemot D, Sanders P (2005) A pharmaco-epidemiological analysis of factors associated with antimicrobial consumption level in turkey broiler flocks. *Vet Res* 36(2):199–211
42. Delva J, Bobashev G, Gonzalez G, Cedeno M, Anthony JC (2000) Clusters of drug involvement in Panama: results from Panama's 1996 National Youth Survey. *Drug Alcohol Depend* 60(3):251–257
43. Katz J, Carey V, Zeger SL, Sommer A (1993) Estimation of design effects and diarrhea within households and villages. *Am J Epidemiol* 138:994–1006
44. Katz J, Zeger SL, West KJ, Tielsch J, Sommer A (1993) Clustering of xerophthalmia within households and villages. *Int J Epidemiol* 22:709–715
45. Petronis KR, Anthony JC (2003) A different kind of contextual effect: geographical clustering of cocaine incidence in the USA. *J Epidemiol Community Health* 57(11):893–900
46. Preisser JS, Arcury TA, Quandt SA (2003) Detecting patterns of occupational illness clustering with alternating logistic regressions applied to longitudinal data. *Am J Epidemiol* 158(5):495–501