Time trends in lipid lowering drug use in The Netherlands. Has the backlog of candidates for treatment been eliminated?

Aukje K. Mantel-Teeuwisse,[1] Olaf H. Klungel,[1] W. M. Monique Verschuren,[2] Arijan J. Porsius[1] & Anthonius de Boer[1]

[1]*Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht and* [2]*Department for Chronic Diseases Epidemiology, National Institute of Public Health and the Environment, Bilthoven, The Netherlands*

Aims To assess time trends in lipid lowering drug use in The Netherlands.

Methods Data were obtained from the PHARMO-database, comprising pharmacy records of approximately 300 000 people in The Netherlands. In the period from 1991–98, we estimated prevalence of lipid lowering drug use on the first Wednesday of October. A patient was defined as incident user if (s)he filled a prescription for lipid lowering medication after a 360 days lipid lowering drug free interval. Both prevalence and incidence estimates were weighted for the sex and age distribution of the general Dutch population.

Results From 1991 to 1998, the prevalence of lipid lowering drug use increased from 0.5% (95% confidence interval (CI): 0.5, 0.6) to 2.3% (95% CI: 2.2, 2.4) in women and from 0.6% (95% CI: 0.6, 0.6) to 2.9% (95% CI: 2.8, 3.0) in men. Prevalence increased with increasing age and was highest in the age category 60–69 years (in 1998: 9.9% (95% CI: 9.4, 10.4) in women and 11.6% (95% CI: 11.0, 12.1) in men). In 1992, the estimated incidence of lipid lowering drug use was 251(95% CI: 226, 277)/100 000 person years in women and 251(95% CI: 225, 276)/100 000 person years in men. The largest incidence estimates were observed in 1996 (685(95% CI: 644, 726)/100 000 person years in women and 881(95% CI: 834, 928)/100 000 person years in men). After 1996, incidence stabilized in 1997 and decreased in 1998 to 599(561, 637)/100 000 person years in women and 731(688, 773)/100 000 person years in men. Most of the patients (approximately 95%) were treated with one lipid lowering agent. Statins were used by over 90% of patients from 1996 onwards. In 1998, 35% of the patients started with a statin that was not a first choice drug (mainly atorvastatin).

Conclusions In the period from 1991–98, prevalence of lipid lowering drug use significantly increased in The Netherlands. However, incidence stabilized and decreased after 1996 which may be explained by the fact that the number of patients eligible for treatment was reached. The question remains whether lipid lowering medication was targeted to the appropriate patients.

Keywords: drug utilization, incidence, lipid lowering drugs, pharmacy records, prevalence

Introduction

The association between high cholesterol levels and cardiovascular disease has been well established [1–3]. In the eighties, several national guidelines were issued to identify and treat patients who would benefit most from reducing their cholesterol [4–6]. However, the use of lipid lowering drugs remained controversial, because of the possible increase of non-cardiac mortality in patients treated with

Correspondence: Dr A. K. Mantel-Teeuwisse, Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, P.O. Box 80082, 3508 TB Utrecht, The Netherlands. Tel.: +31 30 2536976; Fax: +31 30 2539166; E-mail: A.K.Mantel-Teeuwisse@pharm.uu.nl

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the older types of lipid lowering drugs [7, 8]. With the introduction of HMG-CoA reductase inhibitors (statins) a new class of lipid lowering drugs became available, which proved to be safe and effective in reducing fatal and non-fatal cardiovascular events in both primary [9, 10] and secondary prevention [11–13]. Hence, new and revised national and international guidelines were issued [14–16]. As a result of these developments in the treatment of hypercholesterolaemia the worldwide sale and consumption of lipid lowering drugs increased and changed over time [17–20].

Drug utilization research can provide useful information to health care providers and policy makers. It offers the prospect of improving the quality of pharmacotherapy [21] and gaining insight in volume and cost developments of drug use [22]. However, in most drug utilization studies the number of prescriptions, the number of defined or prescribed daily doses or costs are not measured on an individual patient level. Furthermore, these measures usually reflect current consumption of drugs and the majority of all filled prescriptions will be repeated dispensings of the same drug to the same patient. New insights (e.g. Publications of trial results and guidelines) and choices made in daily medical practice, however, will be better reflected by the start of medication as is measured by incidence rates. To our best knowledge only one study [23] assessed incidence rates of lipid lowering drug use. Between 1995 and 1996, the authors observed a small increase in incidence in Funen (Denmark) and an unexpected decrease in Bologna (Italy).

The aim of this study was to evaluate time trends in lipid lowering drug use in a population-based sample in a longer time frame (1991–98) during which new insights in the treatment of hypercholesterolaemia were established.

Methods

Prescription data

We used data from the PHARMO database, a record linkage system containing drug-dispensing records from community pharmacies and linked hospital discharge records of approximately 300 000 subjects. This database covers a well defined population of residents of six medium-sized cities in the Netherlands. Clustering of all pharmacies within each city results in drug-dispensing histories that contain more than 95% of all prescriptions dispensed to a particular patient. Records of non-residents of one of the PHARMO cities are excluded [24]. Medication histories were complete as of January 1, 1991 until December 31, 1998.

All prescription drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification system [25]. ATC-codes B04 and C10 were used to select prescriptions of lipid lowering agents. These include HMG-CoA reductase inhibitors (simvastatin, pravastatin, fluvastatin, atorvastatin and cerivastatin), bile acid sequestrants (cholestyramine, colestipol), fibrates (clofibrate, bezafibrate, ciprofibrate, gemfibrozil) and derivatives of nicotinic acid (nicotinylalcohol and acipimox). Prescriptions for nicotinylalcohol 25 mg were not selected, because treatment of peripheral vascular disease is the only indication for nicotinylalcohol in this low dose. We also excluded prescriptions for xantinol nicotinate (ATC-code C04AD02) because the main indication for this agent in The Netherlands is peripheral vascular disease.

The data registered on prescriptions include date of birth and sex of the patient, drug name, dispensing date and amount of units dispensed of the drug and prescribed daily dose. Records were excluded when sex, date of birth or product name were missing, the amount of units dispensed was less than 1 or when a record was used for administrative purposes only. When information regarding the prescribed dose was not available, it was obtained from previous prescriptions of the same patient (0.7% of all records). If this information was not available, the average prescribed dose for that trade product in the database was used (0.2% of all records).

Prevalence estimation

All prevalences were estimated on the first Wednesday of October of each year. This day was chosen to exclude potential influence of weekends and holidays on the filling of prescriptions. A patient was defined as prevalent user if the first Wednesday of October fell between the dispensing date and the theoretical end date of the prescription. The theoretical end date equals the dispensing date plus the legend duration of drug use, the latter being calculated by dividing the number of units dispensed by the prescribed daily dose. The legend duration of drug use was arbitrarily multiplied by 1.1 in order to control for irregular drug use and early drug collection from the pharmacy [26].

Incidence estimation

A patient was defined as incident user in a particular year if he or she filled a prescription for lipid lowering medication during that year after a 360 days lipid lowering drug free interval. The duration of this prescription had to be at least 14 days (In The Netherlands this is the recommended duration of a first prescription for a drug meant to be used chronically) or, if the duration was less than 14 days, had to be followed by a second prescription for a lipid lowering agent.

Analysis

In order to estimate population-based prevalences we obtained the total number of inhabitants of the six PHARMO cities from Statistics Netherlands. Prevalence and incidence rates were weighted for the sex and age distribution of the general Dutch population.

Prevalence rates, incidence rates and their 95% confidence intervals were calculated according to Greenland and Rothman [27], using a binomial distribution for calculation of a 95% confidence interval of prevalence and a Poisson distribution for calculation of a 95% confidence interval of incidence.

Results

The number of persons who were registered in the PHARMO database increased from 314 036 on 1 January 1991 to 331 068 on 1 January 1999. The proportion of men in the PHARMO population (49.5%) was similar to the proportion of men in the general Dutch population (49.4%). However, the PHARMO population is somewhat younger.

We retrieved all 197 143 prescriptions with ATC-codes C10 and B04. After exclusion of records with missing data ($n=381$ for sex, $n=745$ for date of birth, $n=429$ for product name), records for which the amount of units dispensed was less than 1 ($n=69$) or records for administrative purposes only ($n=11$), 195 508 records remained for analysis. These records comprised 13 643 patients.

In women lipid-lowering drug use increased from 0.5% in 1991 to 2.3% in 1998 (344% increase) and in men from 0.6% to 2.9% (385% increase) (Table 1). The largest increase was observed between 1995 and 1996. Prevalence of drug use varied between age categories (Figure 1a and b). In both men and women, prevalence was lowest among those less than 20 years of age. Prevalence increased with age and was highest among those aged 60–69 years. Subsequently, prevalence decreased in the elderly (≥70 years). This pattern was observed in all calendar years and was similar for men and women, although prevalences were generally lower in women. Incidence estimates showed that the number of starters increased about threefold from 251 per 100 000 person years in men and 251 per 100 000 person years in women in 1992 to 881 and 685 per 100 000 person years in 1996, for men and women, respectively (Table 1). Again, the largest increase was observed between 1995 and 1996. In women, overall incidence stabilized after 1996 and decreased in 1998. Different age categories show different patterns (Figure 2a). However, in all age categories except among those aged 30–39 years incidence was lower in 1998 than in 1996. In men, incidence decreased after 1996 in all age categories except among those aged 30–39 years, 40–49 years and

Table 1 Prevalence and incidence (and their 95% confidence intervals) of cholesterol lowering drug use in The Netherlands from 1991 to 1998.

	Women	*Men*	*Total*
Prevalence (%)⋆			
1991	0.5 (0.5, 0.6)	0.6 (0.6, 0.6)	0.6 (0.5, 0.6)
1992	0.6 (0.6, 0.7)	0.7 (0.7, 0.7)	0.7 (0.6, 0.7)
1993	0.7 (0.7, 0.8)	0.8 (0.8, 0.8)	0.8 (0.7, 0.8)
1994	0.8 (0.8, 0.9)	1.0 (0.9, 1.0)	0.9 (0.9, 1.0)
1995	1.1 (1.0, 1.1)	1.3 (1.2, 1.4)	1.2 (1.1, 1.2)
1996	1.5 (1.5, 1.6)	1.9 (1.8, 2.0)	1.7 (1.7, 1.8)
1997	2.0 (1.9, 2.0)	2.5 (2.4, 2.5)	2.2 (2.2, 2.2)
1998	2.3 (2.2, 2.4)	2.9 (2.8, 3.0)	2.6 (2.6, 2.7)
Incidence (per 100 000 person years)⋆			
1991	NA	NA	NA
1992	251 (226, 277)	251 (225, 276)	251 (233, 269)
1993	254 (228, 279)	270 (244, 296)	262 (244, 280)
1994	300 (273, 328)	379 (348, 410)	339 (319, 360)
1995	413 (381, 445)	534 (498, 571)	473 (449, 497)
1996	685 (644, 726)	881 (834, 928)	782 (751, 813)
1997	687 (646, 728)	836 (790, 882)	760 (730, 791)
1998	599 (561, 637)	731 (688, 773)	664 (636, 693)

⋆weighted by the age and sex distribution of the general Dutch population; NA indicates not applicable.

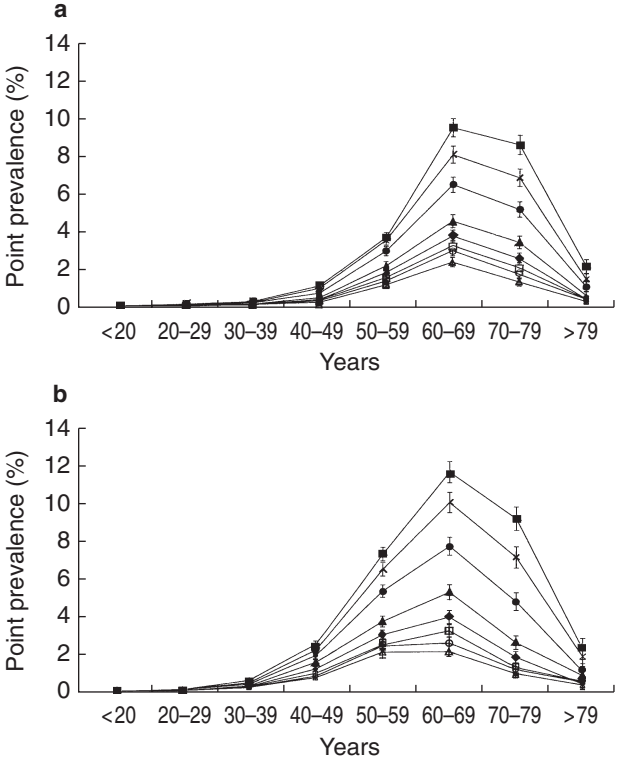

Figure 1 Prevalence estimates of lipid lowering drug use and their 95% confidence intervals across different age categories during the time period 1991–1998 (△ 1991; ○ 1992; □ 1993; ◆ 1994; ▲ 1995; ● 1996; ★ 1997; ■ 1998) in women (a) and in men (b).

over 79 years (Figure 2b). For these age categories, incidence increased slightly until 1997 and subsequently decreased. Restriction of the analyses to statins alone showed the same patterns of stabilization and decrease of incidence estimates after 1996 (data not shown).

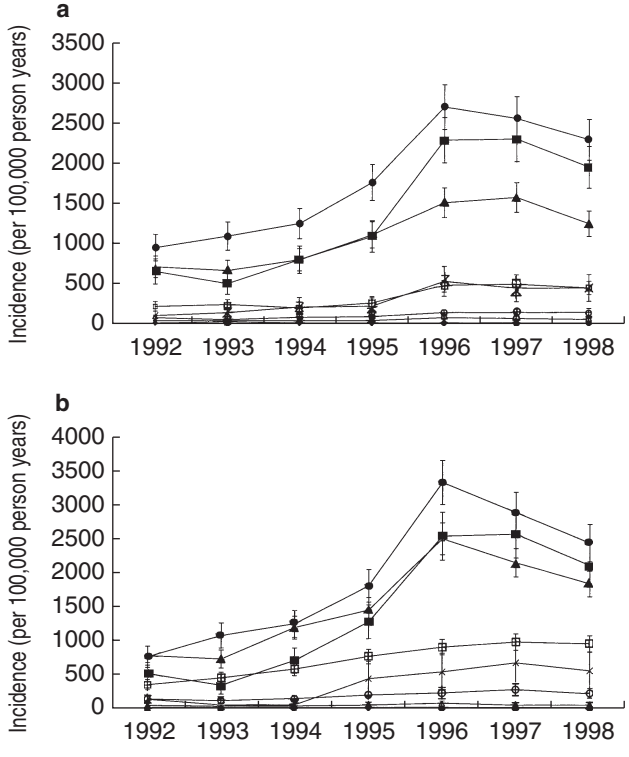

Figure 2 Incidence estimates of lipid lowering drug use and their 95% confidence intervals across different age categories (◆ <20 years; △ 20–29 years; ○ 30–39 years; □ 40–49 years; ▲ 50–59 years; ● 60–69 years; ■ 70–79 years; ★ >79 years) during the time period 1992–98 in women (a) and in men (b).

During the study period, the proportion of patients treated with one agent ranged from 94.6% to 97.5%, the proportion treated with two agents ranged from 2.5% to 5.2% and the proportion treated with three agents ranged from 0% to 0.2%. The proportion of patients treated with more than one agent increased from 1991 (2.5%) to 1996 (5.4%) and decreased again in subsequent years (3.5% in 1998). The percentage of patients who used more than one agent was larger in men (3.5–7.3%) than in women (1.4–3.1%). Incident users mainly started with monotherapy. Occasionally, patients started with two agents at the same time (<1%).

Between 1991 and 1998, the use of statins and fibrates has increased while the use of bile acid sequestrants has decreased. The proportions of patients using a specific class of lipid lowering drugs or starting with a specific class are listed in Table 2. From 1996 onwards, over 90% of all prevalent users of lipid lowering medication received at least a statin. Until 1997, the proportion of patients starting with a statin was smaller than the proportion of patients using a statin. The opposite was true for bile acid sequestrants and partly true for fibrates and derivatives of nicotinic acid. This indicates that a large part of the patients starting with one of these agents either discontinued lipid lowering medication or switched to another class of lipid lowering drugs.

Simvastatin is the most frequently consumed statin. However, the proportion of simvastatin prescriptions among all statin prescriptions fell from 92.9% in 1991 to 62.1% in 1998. In this year, pravastatin, atorvastatin and fluvastatin were used by, respectively, 15.0%, 13.4% and 9.0% of all statin users whereas the use of cerivastatin was limited (0.4%). A similar pattern was observed in new users, although the proportion starting with simvastatin

Table 2 Proportions of patients using a specific class of lipid lowering drugs or starting with a specific class of lipid lowering drugs among those treated with lipid lowering drugs.

				Calendar year				
Drug class	*1991*	*1992*	*1993*	*1994*	*1995*	*1996*	*1997*	*1998*
Prevalence	(n=1648)	(n=2009)	(n=2314)	(n=2795)	(n=3608)	(n=5294)	(n=6850)	(n=8182)
Statins	83.4★	86.6	87.8	87.2	87.6	90.6	92.6	92.6
Bile acid sequestrants	11.5	8.0	5.9	4.8	3.5	2.4	1.8	1.3
Fibrates	6.3	6.8	7.7	9.2	9.8	10.2	9.0	5.9
Nicotinic acid derivatives	1.4	2.1	2.9	3.5	4.1	2.3	1.7	1.2
Incidence		(n=752)	(n=796)	(n=1038)	(n=1457)	(n=2418)	(n=2373)	(n=2095)
Statins	NA	78.5	75.6	72.6	79.2	87.6	90.7	93.5
Bile acid sequestrants	NA	10.5	7.5	5.6	4.9	2.4	2.8	3.6
Fibrates	NA	6.7	10.0	15.2	12.4	10.1	6.2	2.9
Nicotinic acid derivatives	NA	5.0	7.3	6.9	3.7	0.5	0.4	0.4

NA = not applicable.

★percentages are weighted by the age and sex distribution of the general Dutch population; the sum of all percentages per year may exceed 100% due to use of more than 1 lipid lowering agent per individual.

was lower (42.3%) and the proportions starting with pravastatin and atorvastatin were higher (22.5% and 22.1%, respectively).

Discussion

This study indicates that use of lipid lowering medication increased about fivefold from 1991 to 1998 in The Netherlands. However, incidence of lipid lowering drug use increased until 1996 and subsequently stabilized (1997) and decreased (1998) in both men and women.

According to the Dutch cholesterol guidelines, the number of patients eligible for pharmacological treatment of hypercholesterolaemia in The Netherlands ranges from 300 000 to 530 000 [16]. We estimated that these numbers have been achieved in 1997 and 1998 (an estimated number of 345 000 and 410 000 patients, respectively, were being treated pharmacologically). The backlog of candidates for treatment may have been eliminated and this could explain the observed stabilization and decrease in incidence after 1996. The question remains when a steady state in incidence will be reached.

An important strength of this study is that we used incidence measures in addition to prevalence measures to study trends in prescribing patterns. Although a physician may have a preference for certain lipid lowering agents or treatment strategies (s)he may still prescribe less-preferred drugs because of unwillingness to change medication in a patient who is satisfied with his treatment. Incidence measures, representing new episodes of drug use, give more insight into the treatment preferences of physicians during the study period. Therefore, incidence measures are preferred when studying the effects of publications and the release of guidelines on prescribing patterns.

The validity of our data is not affected by reimbursement restrictions, because all lipid lowering drugs are reimbursed to everyone without co-payment. Furthermore, data were derived from a large, population based database comprising virtually complete medication histories on a patient level [24]. Pharmacy records are considered more complete than medical records [28] and their use bypasses the potential recall bias that may arise in interview data [29]. A limitation of our study was the lack of additional medical information. Therefore we can not be certain that the selected prescriptions were actually prescribed for the indication of hyperlipidaemia. However, statins, fibrates, acipimox and nicotinylalcohol in high dosages are only approved for this indication. Bile acid sequestrants are indicated for hyperlipidaemia as well as cholestatic diarrhoea and itching due to obstruction of the bile duct. Since these two indications are rare, this will probably not substantially have influenced our estimates.

The consumption of lipid lowering drugs in our study was generally higher than the consumption in the Nordic countries [23, 30, 31], similar to the use in countries like Australia [31], England [32] and Spain [33], but lower than the use in Italy [31]. The overall incidence estimates of lipid lowering drug use in our study were higher than in Denmark, but smaller than in Italy. However, we observed a more pronounced increase in incidence rates between 1995 and 1996.

We may relate our results to the publication of some important trial results. The 4S study [11] was published in November 1994 after which we saw an increase in the prescribing of lipid lowering drugs. The incidence of statin use was largest in 1996 which could be due to the late effect of the publication of the 4S study combined with the effect of the publication of the results of the WOSCOPS study [9] in November 1995. Jackevicius *et al.* observed a 3.6-fold increase in the monthly rate of statin use in patients after acute myocardial infarction after the publication of the Scandinavian Simvastatin Survival Study (4S) compared with before the publication of 4S [34].

Publication of important trials, the discussion of their results in (Dutch) medical literature and probably postgraduate meetings seem to have had a large effect on the prescribing of lipid lowering drugs. It is however, not possible to separate these effects from the influence of marketing by the pharmaceutical industry. The prescribing of lipid lowering drugs already changed before the revised Dutch guidelines on the management of hypercholesterolaemia were released. This is in accordance with previous findings of how general practitioners have accessed evidence about statin drug use [35].

The highest prevalence and incidence rates were observed in those aged 60–69 years. This was not surprising, since the risk of coronary heart disease is high in this age group. In the elderly (over 70 years of age), we observed incidence rates that were similar to or even higher than the rates in those aged 50–59 years. Similar age patterns were previously also observed by others [19, 23, 31]. These findings are remarkable, because in the Dutch guidelines on the management of hypercholesterolemia the initiation of lipid lowering treatment was not recommended in men over 70 years of age and women over 75 years of age [16].

According to these guidelines simvastatin and pravastatin are the agents of first choice [16] because their effects on cardiovascular morbidity and mortality have been well established [9, 11–13]. The observed widespread use of atorvastatin probably reflects the strong marketing of this product after it was launched on the Dutch market in 1997, and is not based on evidence derived from randomized clinical trials.

We do not know whether lipid lowering medication was targeted to the most appropriate patients. An accurate assessment of treatment eligibility requires detailed information on cardiovascular risk factors. There is,

however, considerable evidence that adherence to guidelines is poor in other countries [32, 36, 37] and preliminary results show that the same is true for The Netherlands [38]. In addition to undertreatment, overtreatment might have occurred [39]. Therefore, physicians should now focus on treating the right patients instead of treating more patients.

In conclusion, we found an approximately fivefold increase in the use of lipid lowering drugs during the time period 1991–98 in The Netherlands. Incidence increased as well, but only up to 1996 and thereafter decreased in both men and women. Other remarkable findings were the relatively extensive use of lipid lowering medication among the elderly compared with other age categories and the widespread use of atorvastatin which is not a first choice agent. Whether lipid lowering drugs are targeted to the appropriate patients remains to be determined.

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