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Suboptimal choices and dosing of statins at start of therapy

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Aim
To assess dosing and determinants of the choice of statins among starters of statins.

Methods
Data were obtained from the PHARMO database comprising pharmacy and linked hospital discharge records of approximately 300 000 subjects in the Netherlands. All new users of statins in 1998 were selected. Patient characteristics and drug regimens were compared between starters of different statins. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using polytomous logistic regression modelling, using the start of simvastatin therapy as reference category.

Results
In 1998, 1738 patients started using simvastatin (41.1%), pravastatin (23.1%), fluvastatin (11.9%), atorvastatin (22.8%) or cerivastatin (1.0%). Compared with starters with simvastatin [mean dose 1.02 ± 0.39 defined daily doses (DDDs)], starters with pravastatin (1.27 ± 0.56 DDDs) and atorvastatin (1.43 ± 0.59 DDDs) received higher doses ($P < 0.001$), whereas users of fluvastatin (0.78 ± 0.37 DDDs) and cerivastatin (0.81 ± 0.30 DDDs) received lower doses ($P < 0.001$). Patients already using CYP3A4 inhibitors more frequently received fluvastatin (OR = 1.80; 95% CI 1.11, 2.94), metabolized by non-CYP3A4 pathways, and atorvastatin (OR = 1.62; 95% CI 1.06, 2.47), which is metabolized by CYP3A4, than simvastatin. Statin doses were not adjusted when prescribed to patients using CYP3A4 inhibitors.

Conclusions
Many patients starting statin therapy did not receive a statin of first choice. The coadministration of potentially interacting drugs may have led to a change in statin choice, but not in dosage lowering. These findings suggest that the quality of statin therapy could be improved.

Introduction

In the 1990s, several landmark trials showed that HMG-CoA reductase inhibitors (statins) are safe and effective in reducing cardiovascular events and total mortality in both primary and secondary prevention [1, 2]. The statins used in these trials were simvastatin, pravastatin and lovastatin. These first two statins were also the first statins entering the Dutch market in 1988 and 1990, whereas lovastatin has not been available in the Netherlands. Fluvastatin was released on the Dutch market in 1995, and two additional statins, atorvastatin and cerivastatin, were launched in 1997. Evidence of the efficacy

of these lipid-lowering drugs was limited to relatively short-term trials evaluating their effects on serum lipid levels [3–6]. Therefore, in the revised Dutch guidelines on the management of hypercholesterolaemia (1998), simvastatin and pravastatin are advocated as the lipid-lowering drugs of first choice [7]. The European [8] and NCEP [9] guidelines recommend statins in general as lipid-lowering drugs of first choice, but do not state a preferred drug.

Besides evidence for cardiovascular risk reduction, other factors such as expected effects on serum lipid levels, interactions and contraindications could also play a role when choosing a specific statin and dosage at start of lipid-lowering therapy. The aim of the present study was to assess the dosing and determinants of the choice of a statin among starters of statins.

Methods

Pharmacy and hospital discharge data

Data were obtained from the PHARMO record linkage system including drug dispensing records from community pharmacies and linked hospital discharge records of approximately 300 000 residents of six medium-sized cities throughout the Netherlands. Patients tend to visit the same pharmacy for the filling of their prescriptions, and clustering of pharmacies within the PHARMO areas results in drug dispensing histories that contain more than 95% of all prescriptions dispensed to a particular patient [10]. The computerized drug dispensing histories contain data concerning the dispensed drug, prescriber, dispensing date, amount dispensed, prescribed dosage regimen, reimbursed costs, and the estimated duration of use. Drug names are coded according to the Anatomical Therapeutic Chemical (ATC) classification [11]. Hospital discharge data were available from 1 January 1985 and all diagnoses are coded according to the International Classification of Disease (ICD-9-CM).

Study population and study design

All users of statins in the period 1 January 1998 through 31 December 1998 (i.e. the first year after the marketing of both atorvastatin and cerivastatin in the Netherlands) were extracted from the PHARMO database. These include users of simvastatin, pravastatin, fluvastatin, atorvastatin and cerivastatin. A patient was defined as a new user (incident user) of a particular statin if he did not receive any lipid-lowering drug before the first dispensing of the statin in the PHARMO database in 1998. To be able to assess incident use of statins, patients with a medication history of less than 365 days prior to the start of statin therapy were excluded from the analyses.

Table 1
Defined daily doses for different statins [11]

Statin	Defined daily dose (mg)
Atorvastatin	10
Cerivastatin	0.2
Fluvastatin	40
Pravastatin	20
Simvastatin	15

For each new start of statin therapy, several characteristics were determined at the index date. Patient characteristics included age and gender. Drug characteristics of interest were type of statin, prescriber and dosage. To compare dosing of different statins we expressed the prescribed daily dose as the number of defined daily doses (DDDs; Table 1). This unit corresponds to the average daily dose of a drug for its main indication in adults, and is recommended by the World Health Organization for drug utilization studies [11].

Previous use of antihypertensive drugs (ATC codes C02, C03, C07, C08, and C09) was assessed in the year prior to the index date. A patient was considered to have a history of cardiovascular disease if he had been hospitalized for an ischaemic coronary event (ICD-9-CM codes 410–414, 5361/2/3 or 8837) or cerebrovascular event (ICD-9-CM codes 430–438) since 1 January 1985 and prior to the start of statin therapy. In addition, the filling of at least one prescription for a nitrate in the year preceding the index, and the concomitant use of a loop diuretic and an ACE inhibitor or angiotensin-II receptor blocker were used as markers for a history of cardiovascular disease. The presence of diabetes mellitus was based on the use of insulin or oral antidiabetics or any diabetes-related hospitalization (ICD-9-CM codes 250, 251, 357.2, 362.0, 366.4, 648.0, 648.8, 790.2 and 962.3).

The concomitant use of interacting medication was established at the index date. A pharmacodynamic interaction leading to an increased risk of myopathy and rhabdomyolysis has been described for the statin–fibrate combination, but fibrates, especially gemfibrozil, may also affect statin concentrations through the glucuronidation pathway [12]. Drugs including cyclosporin, azole antifungals, macrolide antibiotics, protease inhibitors, nefazodon, verapamil and diltiazem, and mibefradil (available until June 1998) may interact with statins by affecting the cytochrome P-450 (CYP) 3A4 system [13], and other pharmacokinetic pathways, as is

the case for cyclosporin [14]. Because amiodarone is often also included in this list, we included it in our analysis, although to our best knowledge it is not a CYP3A4 inhibitor. Inhibition of CYP3A4 may lead to increased serum levels of statins that are biotransformed by this system, such as simvastatin, atorvastatin and cerivastatin [15], which may also lead to an increased risk of adverse effects, such as myopathy and rhabdomyolysis.

Analyses

The distribution of patient characteristics was calculated for each individual statin. An ANOVA/Student's *t*-test was used to compare mean ages and mean prescribed daily doses (expressed in DDDs), and a χ^2 test was used to compare frequency distributions between the different statin groups. Incident users of simvastatin, the first available statin in the Netherlands, served as a reference group. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated as measures of relative risk using polytomous logistic regression modelling. In the multivariable analysis, estimates were adjusted for age, gender, prescriber, a history of antihypertensive drug use, a history of cardiovascular disease, diabetes mellitus, and concomitant use of any other interacting drug.

Results

In 1998, a total of 1738 patients in our population started statin therapy. Of these, 715 patients (41.1%) started with simvastatin, 402 (23.1%) with pravastatin, 206 (11.9%) with fluvastatin, 397 (22.8%) with atorvastatin and 18 (1.0%) with cerivastatin.

Characteristics of the study population are listed in Table 2. Mean age was approximately 60 years for all users of statins. Compared with simvastatin, atorvastatin (OR 0.57; 95% CI 0.41, 0.79) was less often prescribed to elderly patients (Table 3, $P < 0.05$ for trend with age). Over half of the patients using simvastatin, pravastatin, fluvastatin, and atorvastatin were men, while cerivastatin was more frequently used by females. However, this was not significant compared with simvastatin. Compared with simvastatin, atorvastatin was even less frequently prescribed to women (OR 0.67; 95% CI 0.51, 0.87). General practitioners predominantly prescribed simvastatin, whereas other statins were more frequently prescribed by a cardiologist than simvastatin (ORs between 3.29 and 4.82). Only 1117 subjects (64.3%) started with one of the first-line agents (simvastatin or pravastatin).

Large differences in dosing existed between statins. The prescribed daily dose was about 1 DDD per day in patients starting with simvastatin. Patients using pravas-

Table 2
Characteristics of the study population

Characteristic	Simvastatin *N* = 715	Pravastatin *N* = 402	Fluvastatin *N* = 206	Atorvastatin *N* = 397	Cerivastatin *N* = 18	*P*-value
Age, years (mean ± SD)	59.3 ± 11.2	60.1 ± 11.0	58.8 ± 13.2	57.3 ± 10.8	59.2 ± 9.7	0.011
Gender (male, female)	353 (49.4%) 362 (50.6%)	230 (57.2%) 172 (42.8%)	113 (54.9%) 93 (45.1%)	255 (64.2%) 142 (35.8%)	7 (38.9%) 11 (61.1%)	<0.001
Prescriber (GP, cardiologist, other specialist, unknown)	420 (65.2%) 118 (18.3%) 106 (16.5%) 71	144 (37.3%) 191 (49.5%) 51 (13.2%) 16	84 (41.0%) 100 (48.8%) 21 (10.2%) 1	161 (40.6%) 147 (37.0%) 63 (15.9%) 26	9 (50.0%) 5 (27.8%) 4 (22.2%) 0	<0.001
Dosage in DDD equivalents (mean ± SD)	1.02 ± 0.39	1.27 ± 0.56	0.78 ± 0.37	1.43 ± 0.59	0.81 ± 0.30	<0.001
History of anti-hypertensive drug use	418 (58.5%)	279 (69.4%)	142 (68.9%)	248 (62.5%)	9 (50.0%)	0.001
History of cardiovascular disease	260 (36.4%)	220 (54.7%)	98 (47.6%)	174 (43.8%)	6 (33.3%)	<0.001
Diabetes mellitus	123 (17.2%)	77 (19.2%)	32 (15.5%)	78 (19.6%)	4 (22.2%)	0.65
Co-use of a CYP3A4 inhibitor	60 (8.4%)	52 (12.9%)	37 (18.0%)	56 (14.1%)	1 (5.6%)	0.001

SD, Standard deviation; DDD, defined daily dose.

Table 3
Odds ratios (OR) and their 95% confidence intervals (CI) of determinants in the choice of pravastatin, fluvastatin, atorvastatin or cerivastatin *vs.* simvastatin

Determinant	Pravastatin OR[a] (95% CI)	Fluvastatin OR[a] (95% CI)	Atorvastatin OR[a] (95% CI)	Cerivastatin OR[a] (95% CI)
I. Age (per year)< 55 years,	Ref. 0.78 (0.56, 1.09)	Ref. 0.74 (0.49, 1.11)	Ref. 0.86 (0.63, 1.17)	Ref. 1.07 (0.33, 3.45)
55–64 years, ≥65 years	0.82 (0.59, 1.13)	**0.68 (0.45, 1.02)**	**0.57 (0.41, 0.79)**	0.91 (0.26, 3.12)
Gender (male, female)	Ref. 0.97 (0.74, 1.27)	Ref. 1.07 (0.77, 1.50)	Ref. **0.67 (0.51, 0.87)**	Ref. 1.74 (0.64, 4.74)
II. Prescriber (GP, cardiologist	Ref. **4.48 (3.12, 6.43)**	Ref. **4.82 (3.08, 7.54)**	Ref. **3.73 (2.58, 5.39)**	Ref. 3.29 (0.82, 13.20)
other specialist)	1.25 (0.84, 1.86)	0.96 (0.56, 1.64)	1.45 (0.99, 2.11)	1.83 (0.52, 6.44)
History of antihypertensive drug use	0.99 (0.72, 1.35)	1.12 (0.75, 1.66)	0.96 (0.71, 1.30)	0.61 (0.20, 1.81)
History of cardiovascular disease	1.17 (0.84, 1.63)	0.79 (0.52, 1.20)	0.79 (0.57, 1.10)	0.86 (0.24, 3.06)
Diabetes mellitus	**1.41 (1.01, 1.98)**	1.19 (0.76, 1.86)	**1.41 (1.01, 1.97)**	1.45 (0.44, 4.75)
Co-use of a CYP3A4 inhibitor	1.10 (0.72, 1.69)	**1.80 (1.11, 2.94)**	**1.62 (1.06, 2.47)**	0.65 (0.08, 5.34)

Ref, Rreference. [a]*Estimates are adjusted for all listed factors.*

tatin or atorvastatin received significantly higher doses than users of simvastatin ($P < 0.001$). Atorvastatin was also higher dosed compared with pravastatin ($P < 0.001$). In contrast, patients using fluvastatin and cerivastatin received on average dosages of less than 1 DDD, which was considerably less than the dosing of simvastatin ($P < 0.001$ for both fluvastatin and cerivastatin compared with simvastatin). There were no differences in dosing between fluvastatin and cerivastatin ($P = 0.81$).

Approximately half of the patients receiving pravastatin, fluvastatin or atorvastatin had a history of cardiovascular disease, resulting in statistically significant crude ORs ranging from 1.4 to 2.0 compared with simvastatin. After adjustment for all factors, a history of cardiovascular disease was no longer independently associated with their use and the point estimate even suggested an inverse association. Patients with diabetes mellitus more often received pravastatin or atorvastatin than simvastatin. Concomitant start with a statin and a fibrate was rare. Only one patient (0.06%) started with the combination of atorvastatin and a fibrate.

Concomitant use of any drug that could interact through the CYP3A4 system, mainly verapamil and diltiazem, ranged from 5.6% for cerivastatin to 18.0% for fluvastatin. We observed selective prescribing of fluvastatin and atorvastatin to patients using any drug that is also metabolized by CYP3A4. Fluvastatin is not metabolized by CYP3A4, but atorvastatin is primarily metabolized by CYP3A4. There was a tendency of higher dosing when the statin was concomitantly used with CYP3A4 inhibitors in patients using any statin. However, this was significant only in patients using fluvastatin (mean DDD 0.76 ± 0.37 *vs.* 0.91 ± 0.35, $P = 0.026$).

Discussion

The results of this population-based study show that several differences in characteristics of patients and drug regimens exist between subjects who started using different statins in 1998. Compared with simvastatin, pravastatin or atorvastatin users were more likely to receive higher doses, whereas users of fluvastatin and cerivastatin received considerably lower doses. Selective prescribing of fluvastatin, a statin mainly metabolized by non-CYP3A4 pathways, to patients using CYP3A4 inhibitors could be observed. However, we also observed selective prescribing of atorvastatin, which is metabolized by CYP3A4. We did not observe a lower dosing of simvastatin, atorvastatin or cerivastatin when prescribed to patients using CYP3A4 inhibitors. These findings leave ample room for improving the quality of statin therapy.

Both simvastatin and pravastatin are promoted as the statins of first choice in the Dutch guidelines, because their efficacy in the reduction of coronary heart disease and total mortality has been well established [1, 2]. However, the cost of all statins is reimbursed to every patient without any restrictions. In this study, approximately one-third of all patients (35.7%) started with a

statin that was not a first-choice agent, mainly atorvastatin (22.8%). In trials using intermediate endpoints such as reduction in serum cholesterol levels, atorvastatin showed the largest reductions in serum total and LDL-cholesterol that can be achieved with any available statin [16]. Some physicians may have assumed that larger reductions in serum total cholesterol would also lead to larger reductions in ischaemic heart disease (IHD) events and stroke. Law *et al.* showed that a LDL-cholesterol reduction of 1.0 mmol l^{-1} reduces the risk of IHD events by up to 36% and stroke by 10% [17]. Such a reduction can also be achieved by using simvastatin 40 mg [16, 17]. However, it is not known whether reductions larger than 1.8 mmol l^{-1} (the maximum average reduction achieved in clinical trials until now) will result in even larger relative reductions of the risk of IHD and stroke. Furthermore, statins have additional effects independent of cholesterol lowering such as improvement of endothelial function, inhibition of platelet aggregation, plaque stabilization, and blood pressure reduction [16]. These effects may differ between statins, and may therefore lead to different reductions in cardiovascular disease risk.

Because the largest reductions in serum cholesterol levels may be obtained with high doses of atorvastatin, atorvastatin may have selectively been prescribed to patients with more severe hyperlipidaemia. Unfortunately, our database does not include serum lipid levels, so we were unable to study this determinant. The dosing of statins may possibly serve as a marker for severity of hypercholesterolaemia. We observed that patients using atorvastatin indeed received the highest doses, as expressed in DDDs per day. Users of fluvastatin and cerivastatin received lower doses compared with the dosing of simvastatin. This could suggest that fluvastatin and cerivastatin were selectively prescribed to those with less severe hypercholesterolaemia. The use of DDDs may have some limitations. The WHO recommendations for specific DDDs for statins have been questioned in the past [18], and a more recent study showed that 1 DDD of atorvastatin (10 mg) may more closely equal higher DDDs of the other statins [17]. This corresponds to our assumption that atorvastatin was selectively prescribed to patients with more severe hypercholesterolaemia.

Simvastatin, atorvastatin and cerivastatin are biotransformed by CYP3A4, though the latter is also metabolized by CYP2C8 [15]. These statins are subject to drug interactions when concomitantly prescribed with inhibitors of CYP3A4. Although simvastatin is especially susceptible to CYP3A4 inhibition [19], serum concentrations of atorvastatin and, to a lesser extent, cerivastatin may also rise [20]. Consequently, patients are at increased risk of adverse drug effects, especially myopathy and rhabdomyolysis [21]. In order to improve quality of pharmacotherapy in the individual patient, the risk of myopathy due to the combined use of a statin metabolized by the CYP3A4 pathway and one of these interacting drugs should be limited. This can be achieved by either choosing a statin that is primarily metabolized through a different pathway, or by reducing the dose of the statin. Fluvastatin is metabolized by CYP2C9, which does not lead to important drug–drug interactions resulting in an increased risk of myopathy or rhabdomyolysis [15]. Pravastatin is hardly metabolized by the CYP P-450 system, but is mainly cleared by the kidneys. Both fluvastatin and pravastatin can therefore serve as a safe alternative in patients also using CYP3A4 inhibitors. In the present study, patients using interacting co-medication were more frequently prescribed fluvastatin and atorvastatin. Since atorvastatin was just released, the number of case reports of interactions may have been low, although a rise in levels of atorvastatin when used in combination with CYP3A4 inhibitors could be expected based on its metabolism.

We did not observe a lower dosing of statins metabolized by CYP3A4, when prescribed to patients using CYP3A4 inhibitors. Such dose lowering could be of utmost importance for simvastatin, because several interaction studies described a strong impact of CYP3A4 inhibitors on its pharmacokinetic parameters [19, 22]. Without a simvastatin dose reduction CYP3A4 inhibition might result in serum simvastatin concentrations that are normally associated with supratherapeutic doses. Potentially hazardous drug–drug interactions may not have received adequate consideration in 1998. This may have improved over recent years due to extensive attention paid to statin-associated myopathy and rhabdomyolysis in the medical literature. However, a more recent study showed that even after the withdrawal of cerivastatin [23], adherence to safety instructions at start of statin therapy was limited [24]. The number of creatinine kinase measurements at start of statin therapy was low (13%) and did not increase in the second half of 2001.

Several nonpharmacological factors may have influenced the drug prescribing, which may explain the observed results, e.g. non-adherence to current guidelines and differences in prescribing habits between GPs and specialists. Physicians may perceive a variety of barriers keeping them from adherence to guidelines. These barriers may relate to knowledge (lack of familiarity or awareness), attitudes (lack of agreement with

specific guidelines or guidelines in general, lack of outcome expectancy, self-efficacy or motivation) and behaviour (external barriers including patient factors, guideline factors and organizational factors) [25]. Knowledge of these perceived impediments might contribute to the design of effective interventions and to the improvement of implementation of guidelines. It is unlikely that variation in prescribing habits between GPs and specialists originates from differences in the involvement with the development of the Dutch guidelines on the management of hypercholesterolaemia. All specialities were involved in the development of these guidelines. Although GPs adopted their own guidelines 1 year after the release of the national guidelines [26], they were fully based on the national guidelines and only small differences, e.g. in the frequency of ordering lipid tests, could be observed. However, the dissemination of these guidelines within different groups of doctors may account for the observed diversity in prescribing behaviour.

When prescribing drug therapy, most physicians choose from a limited set of drugs with which they are familiar. This set is largely influenced by the pharmaceutical industry. Meeting with pharmaceutical representatives, attending sponsored continuing medical education programmes, and accepting funding for attending symposia are associated with increased prescription rates of the sponsor's drugs [27]. Changing the set of preferred or prescribing behaviour is a complex process, which needs a multifactorial and active approach. Educational outreach visits appear to be the most promising approach to changing physician behaviour, in particular prescribing [28].

In conclusion, we showed that many patients starting statin therapy did not receive a statin of first choice. In some cases, newer statins were selectively prescribed to more complex patients. The coadministration of potentially interacting drugs, however, did not lead to a well-considered statin choice or dosage lowering. Dosing of statins seemed suboptimal in patients using fluvastatin and cerivastatin. These findings allow potential improvement of the quality of statin therapy.

Competing interests: None declared.

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