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ORIGINAL RESEARCH

High Degree of Adherence to Statin Therapy Among the Elderly Despite High Frequency of Side Effects

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Abstract: The aims of the present study were to investigate adherence and side effects of statin therapy in elderly patients (≥75 years) after primary statin prescription, to identify possible differences related to whether statin treatment was initiated in primary care or in hospital, and to investigate whether there was any correlation between side effects of statin therapy and statin dose or renal impairment. In two primary health care populations, all patients ≥75 years of age recently initiated on statin therapy were identified through the patient data records ($n = 90$) and asked to complete a questionnaire. Of 68 subjects responding to the questionnaire, 87% reported adherence to the statin therapy and 29% reported side effects. No statistically significant difference was seen for adherence or frequency of side effects depending on whether therapy was initiated in primary care or in hospital. In conclusion, elderly patients appear to exhibit a high degree of adherence to statin treatment despite a high incidence of side effects.

Keywords: statins, elderly, polypharmacy, adherence

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Introduction

Statins are the most important and most well-documented group of lipid-lowering drugs. Statin therapy has been shown to reduce cardiovascular morbidity and mortality in several meta-analysis studies.[1–3] The morbidity of these diseases increases with age, therefore the age at initiation of statin therapy also tends to increase. Reduced mortality by secondary prevention has been demonstrated for coronary heart disease in all age groups, even in individuals more than 80 years of age.[4] However, data on morbidity and mortality by primary prevention is insufficient in elderly people more than 75 years of age. Therapy recommendations and guidelines are based on the individual's estimated total risk of developing cardiovascular disease.[5]

In Sweden, simvastatin is recommended by all regional drug committees as the primary choice statin.[6] Eighty-three percent of all patients treated with statins in Sweden are prescribed simvastatin. Switch of therapy to another statin is mainly on the basis of side effects, or if the intended target value of blood lipids cannot be reached. The other statins marketed in Sweden, representing the remaining 17% of the market share, are atorvastatin, rosuvastatin, pravastatin, and fluvastatin. Of these, atorvastatin is the most common (14%); the other 3 are only used by 3% of those treated with statins.[6]

Statins act by inhibiting the enzyme HMG-CoA reductase (3-hydroxy-3-methylglutaryl-CoA reductase) which regulates cholesterol synthesis. Treatment with statins is generally safe, with few side effects. The most clinically important side effect is myopathy, defined as muscle pain, tenderness or weakness. In clinical trials, a tenfold increase in serum creatine kinase (CK) is also included as a side effect.[5,7,8] Occasionally myopathy can develop into rhabdomyolysis (muscle breakdown), resulting in myoglobinuria (excretion of myoglobin in the urine), and acute renal failure. In very rare cases, a fatal outcome may occur.[9] The risk for myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. In a database derived from clinical trials, myopathy incidences of 0.02%, 0.08%, and 0.53% for simvastatin doses of 20, 40, and 80 mg/day, respectively, have been described. The patients in these trials were carefully monitored, and certain interacting drugs were excluded.[7,8] Other listed side effects of simvastatin were gastrointestinal (constipation, abdominal pain, diarrhea, nausea, and vomiting), neurological (headache, paresthesia, and dizziness), and dermatological (pruritus, rash, and hair loss). All side effects have been classified as rare ($\geq$1/10,000, $<$1/1000).[9]

Renal function, expressed as a glomerular filtration rate (GFR), declines with increasing age. At the age of 75 years, the GFR has declined by 50% on average.[10] It is recommended that in patients with severe renal insufficiency (creatinine clearance $<$30 mL/min), simvastatin doses exceeding 10 mg/day should be considered carefully, and if necessary, implemented cautiously. In the current regional guidelines for lipid-lowering therapy in south eastern Sweden, where the present study was performed, no reservations for impaired renal function are mentioned. The recommendation is to initiate 40 mg simvastatin as the starting and target dose "to all patients for whom treatment indication exists".[11] Furthermore, the importance of target values (varying according to patients' different risks of developing cardiovascular disease, eg, total cholesterol $<$4–5 mmol/L, and low-density lipoprotein (LDL) $<$2–3 mmol/L), as well as strategies to achieve them, are highlighted. However, studies conducted solely on the basis of the proposed target values are lacking. Most existing statin trials have examined fixed doses of statins (placebo versus statins, or low dose versus high dose of statins) and, as a consequence, the current blood lipid target values are based on indirect conclusions on the effect of different statin doses related to morbidity and mortality.[12]

Surveys of drug utilization among the elderly reveal that $>$90% of persons aged 75 years or older use medications regularly. Elderly people living in private homes are prescribed an average of 5 medications, and those living in special housing are prescribed an average of 10 medications.[13,14] This polypharmacy entails a risk for interactions and unwanted side effects.[15] Adherence levels vary, but some studies have shown a 66%–75% adherence to drug treatment for cardiovascular diseases.[16,17] However, considering all aspects of compliance, such as the incorrect use of prescribed drugs at home, the estimated adherence has been reported to be less than 50%.[18]

The dose–response curve for statins reveals that doubling the dose only results in 6% additional decrease in LDL.[19] The benefit of lowering LDL cholesterol with a high dose of simvastatin was recently investigated in a multicenter study involving 12,064

patients with a history of myocardial infarction.[20] One group was randomly assigned to 20 mg and a second group to 80 mg simvastatin. At a mean follow-up of 6.7 years, the results showed that LDL was on average 0.35 mmol/L lower in the high dose group, but no statistically significant difference was seen in terms of primary end points (major cardiovascular events, stroke, and revascularization) between the groups. However, there was an overall difference in adverse events, with 53 (0.9%) patients affected by myopathy in the high dose group and only 2 (0.03%) in the low-dose group.[20]

Side effects may thus constitute a barrier to successful drug treatment. Because statins are an important element in the treatment of cardiovascular disease, it is crucial to create good conditions for patients to adhere to the treatment and to receive the full benefits of statin therapy.

The aims of the present study were:

- to investigate adherence and side effects of statin therapy in elderly patients (≥75 years) after primary statin prescription
- to identify possible differences related to whether statin treatment was initiated in primary care (PC) or in hospital (HC), and
- to investigate whether there was any correlation between the side effects of statin therapy and statin dose or renal impairment.

Materials and Methods

The study population was based on patients listed at 2 primary health care centers in Linköping, Sweden. The population was identified by searching the patient data records in 2 settings (BMS arkiv, Vårdöversikt DRIFT 1.0.0.9 and Cambio COSMIC, 1.1.0.4). All patients ≥75 years who had been initiated on simvastatin or atorvastatin treatment between January 1, 2006 and December 31, 2008 (inclusion criteria) were recruited. Prescribed treatment that, for some reason, was never initialized, was the only exclusion criterion. The subjects were divided into 2 groups: one group for which statins were prescribed in PC and a second group prescribed in HC. The HC group included both outpatient and inpatient care given in hospitals.

A questionnaire on adherence and side effects of statin treatment was sent to all patients in both groups. A written letter with information about the study was sent with the questionnaire. After 4 weeks, a reminder was sent to the patients who had not responded to the first request. Patients who were willing to participate gave written informed consent.

In the present study, adherence was defined as a positive answer to the question on whether the subjects were taking simvastatin or atorvastatin as prescribed by their doctor. For those patients who reported adherence to the treatment, further verification was performed by searching patient data records to see if they had received a renewed prescription during the last 12 months following initial prescription, indicating that the treatment had continued.

Renal function was defined as the estimated GFR and was obtained using the Cockcroft–Gault formula:

$$\text{Men} \geq 20 \text{ years: } \text{GFR} = (1.23 \times (140 - \text{age}) \times \text{weight}) / \text{serum creatinine}$$

$$\text{Women} \geq 20 \text{ years: } \text{GFR} = (1.04 \times (140 - \text{age}) \times \text{weight}) / \text{serum creatinine}$$

Creatinine values were obtained from the laboratory modules in the patient data records. If creatinine levels were not recorded within the last 6 months, subjects were requested by letter to undergo a new creatinine blood test.

Statistical analysis

Data from the questionnaire were analyzed using SPSS Statistics 17.0 software. Pearson's χ^2 test was performed to determine possible differences between primary and hospital care concerning compliance, side effects, statin dose, and renal function. Whether the level of side effects was related to compliance, statin dose, or renal function was also investigated. A significance level of $P < 0.05$ was chosen.

Ethics approval

The study was reviewed and approved by the Regional Ethical Review Board in Linköping, Sweden (No. M204-09).

Results

A total of 90 individuals fulfilling the inclusion criteria were identified. Simvastatin was the drug used primarily for all patients (PC 51, HC 39). Response were received from 70 subjects (PC 37, HC 33), giving

an overall response rate of 78%. Two patients were excluded from the study, because their prescribed treatment was never initialized. Three patients were deceased and 17 did not answer. The demographic characteristics of the 2 groups were similar (Table 1).

Adherence

Fifty-nine of the 68 subjects reported that they had followed the doctor's prescription, which corresponds to 87% adherence. No significant difference was noted between the 2 groups (PC 83%, HC 91%). For further verification of the adherence level, the patients' data records were examined. It was found that 95% of subjects reporting adherence to the statin therapy had received a renewed prescription during the last 12 months. Of the 9 subjects who reported that they did not follow the prescription, 5 declared side effects as the reason. Of these, 2 were received atorvastatin instead with good tolerance. The remaining 4 (PC 3; HC 1) reported that they had initiated lifestyle changes and therefore did not consider themselves to be in need of statin treatment.

Side effects

The occurrence of side effects was reported by 20 patients (29%). No significant difference was found depending on where the treatment was initiated (PC 25%, HC 34%). The proportions of side effects were similar for neurological, dermatological and muscle-related symptoms. In contrast, gastrointestinal side effects were more uncommon. Regarding only muscular symptoms as side effects, the overall rate was 15%.

Adherence related to side effect frequency

Adherence was higher (92%) among the patients who reported no side effects from their medication compared with those with side effects (75%). However, the difference was not statistically significant ($P = 0.065$) (Fig. 1).

Table 1. Characteristics of subjects subdivided according to whether statin treatment was initiated in primary care (PC) or in hospital (HC).

	PC ($n = 36$)	HC ($n = 32$)	Total ($n = 68$)
Male (individuals)	15	15	30
Female (individuals)	21	17	38
Mean body weight (kg)	73	72	73
Mean age (years)	82	82	82
Median age (years)	81	82	81

Statin dose

Simvastatin was prescribed in doses of 10, 20, or 40 mg/day. The distribution of the doses differed significantly between hospital and primary care. In the hospital group, 81% of patients received high dose simvastatin (40 mg); the corresponding proportion in the primary care group was 36% ($P < 0.001$) (Fig. 2). The proportion of reported side effects was similar for the higher dose (40 mg) and the lower dose (≤20 mg) simvastatin (28% and 31%, respectively).

Renal function

Renal impairment, defined as estimated GFR < 60 mL/min, was present in 65% of the subjects. In the upper age interval (ie, higher than the mean age of 82 years), renal impairment was noted in as many as 82% of the subjects. There was no significant difference in renal function between patients in the PC group (61%) and the HC group (69%). Subjects with impaired renal function reported equal frequency of side effects as those with normal renal function (30% and 29%, respectively).

Discussion

In the present study, we examined the adherence and side effects of statin treatment in a population of elderly patients (≥75 years) who initiated the treatment between January 2006 and December 2008), using a questionnaire sent out in January/February 2010.

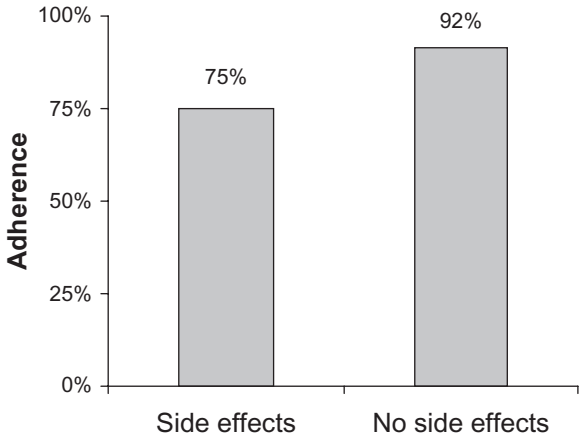

Figure 1. Adherence among subjects who reported the presence of side effects ($n = 20$) compared with those who reported no side effects ($n = 48$) ($P = 0.065$).

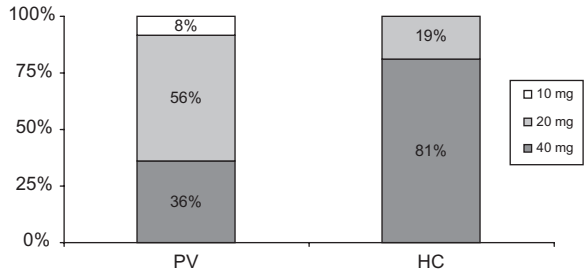

Figure 2. Distribution of simvastatin treatment according to whether it was initiated in primary care (PC) or in hospital (HC).

Thus, the patients were on the treatment for at least a year when the survey was conducted. The study focused on the two statins (simvastatin and atorvastatin) most commonly used in Sweden. In all cases in this study, however, simvastatin was the primary medication at the beginning of treatment and shows excellent adherence to existing guidelines.

A surprisingly high proportion of patients (87%) claimed to be taking their medicine in accordance with how their prescription was intended. Previous studies have suggested a markedly lower adherence to statin treatment (66%–75%), but these studies report the average of all age groups.[16,17] This may suggest that patients ≥75 years in general have a higher adherence to statin treatment than the average population on statin treatment. The high adherence level in this study was confirmed by the fact that 95% of patients who reported adherence to treatment had received a new prescription during the last 12 months. However, adherence is difficult to measure and there is no universal definition of the term. Depending on which aspects of adherence are being studied, the outcome may vary. There are disadvantages to all methods. In the present study, for example, it was not possible to display the frequency of renewal of prescriptions for nonresponders, and it is likely that adherence among this group is lower.

The overall incidence of side effects was high; nearly 3 out of 10 patients reported side effects of treatment. In the larger clinical trials on statins, no specific differences in the frequency of side effects between study samples and control groups have been reported.[7,8] The frequency of myopathy in combination with a tenfold rise in CK levels has been reported to be 0.02%–0.08%.[9] In the present study, measurement of CK was not included, thus it is not possible to fully relate to these numbers. The frequency of muscle-related symptoms without an associated increase in CK was more than twice as high (15%) in the present study compared with previous studies (6%).[7,8] This may indicate that elderly patients are more likely to develop myopathy from statin therapy. However, because there was no control group for comparison (a weakness of the study) conclusions must be drawn with caution. Many elderly patients utilize multiple drugs, and it is difficult for them to decide which drug is causing side effects. However, irrespective of cause, these side effects are still a reality for the patient. Therefore, it is important for health care providers to be observant and receptive of reports on possible adverse drug reactions from the patients, in order to reconsider the medication if necessary.

When comparing patients prescribed statins in PC and HC, no significant difference in adherence or side effect rates could be demonstrated between the 2 groups. In the total patient population in the study, lower adherence was seen in the group of subjects who reported side effects (75%) compared with those who experienced no side effects (92%), but this difference did not reach statistical significance ($P = 0.065$). This may possibly reflect the limited size of the population, which is the main weakness of the study.

The study shows that hospital clinicians prescribe higher doses of simvastatin to a much greater extent than primary health care physicians. This might be explained by the fact that statin treatment initiated in primary care is often done for primary prevention purposes, and that the acceptance of side effects in that situation is lower. In the present study, however, no dose relationship with side effects was observed. The frequency of side effect was similar in the group treated with low-dose simvastatin compared with patients receiving higher doses. Thus, these data would support the recommendation to begin treatment by prescribing 40 mg of simvastatin. However, the population in this study is too small to reliably draw such conclusions. Moreover, it is not determined whether a higher dose of simvastatin results in increased benefits, especially when parts of the results of the extensive SEARCH study (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) are considered. There was no significant reduction in primary end points after treatment with 80 mg simvastatin compared with 20 mg, but the frequency of side effects was much higher.[20]

An established reference interval for renal function in the elderly does not exist, but a GFR ≥ 60 mL/min is a recommendation. Renal insufficiency (GFR < 60 mL/min) was noted in almost two thirds of the patients throughout the study population. There was, however, as expected an age-related skewness in the distribution of renal function impairment, which reached 82% in the upper age range. A large proportion of elderly people with impaired renal function has also been confirmed in previous studies.[10] Health care providers should therefore pay special attention to renal function in the elderly in the prescription of drugs with potential renal effects (eg, nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, etc).

There was no association in this study between renal function and side effects. The frequency of adverse events was similar in the group with renal impairment compared with the group with normal renal function. There might be other parameters that are central to the occurrence of side effects. In the dose recommendation for simvastatin it is stated that a creatinine clearance below 30 mL/min requires dose adjustment. In the present study there was only one patient with renal function below this level.

Conclusion

In conclusion, elderly patients appear to exhibit a high degree of adherence to statin treatment despite a high incidence of side effects. Simvastatin is used in higher doses in hospital clinics compared with primary care, but the incidence of side effects does not seem to be greater at the higher doses. Almost two thirds of the older patients in the study had renal dysfunction but no correlation was found between renal impairment and the frequency of side effects. The material in this study is relatively limited and it is possible that the outcome would have been different in a larger study population. This study would thus need to be replicated in an extended study in order to confirm these findings.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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