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COMBINED METHOD FOR ASSESSMENT OF MEDICATION ADHERENCE – A PILOT STUDY OF OUTPATIENTS TREATED WITH STATINS

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Abstract: Medication adherence is multifactorial and has a direct influence on the efficacy of statins to prevent cardiovascular disease events. The aim of this study was to pilot the combined method for assessment of medication adherence of patients receiving statin therapy for a longer period of time compared with those who initiated treatment. Patient self-assessment questionnaire, pill count adherence (PCA), medicines possession ratio (MPR), and total cholesterol levels test were used. The study group (long term users) included 15 outpatients (statin use >1 year). The reference group consisted of 17 patients who initiated treatment. All patients participated in the study for 6 months. During the study period, the mean PCA and MPR were higher in the long term users' group than in the other group. Total cholesterol level decreased 33% in the long term users' group and 82% in the new users' group. Thus, the majority of patients were at least partially adherent to statin treatment. However, regular monitoring of patients using statins by a general practitioner or pharmacist is crucial to reach consistent high adherence to therapy, especially for those patients who started their treatment. Based on the pilot study, it could be recommended to use a combined assessment of medication adherence towards statins. However, further studies with larger patient groups and with respective measures "between fills" would be needed.

Keywords: statins, Estonia, outpatients, medication adherence

Statins or HMG-CoA reductase inhibitors are cholesterol-lowering medicines that reduce the incidence and mortality of cardiovascular disease (CVD) (1-3). Statins are likely to be cost-effective in the primary prevention of CVD events (4). Long-term use of statins is essential to prevent CVD (2). Statin therapy produces significant reductions in major vascular events irrespective of age

Medication adherence or compliance indicates the patient's consent to the prescribed treatment and describes the extent to which the treatment regimen is followed (5, 6). This process consists of three phases: the initiation, the implementation, and the discontinuation of drug treatment (5). The initiation of therapy is a crucial point in medication adherence and non-initiation may affect up to 20% of patients (7). In the implementation phase, it is important to follow does the patient's actual dose of medicine corresponds to the prescribed dosing regimen. The

persistence represents the time between initiation and discontinuation of medicine use (6, 8).

In the management of chronic ambulatory pharmacotherapy, it is challenging to achieve and maintain a high level of medication adherence what is more often reached when the patient is aware of his or her illness and understands the need to use the medicine. Non-adherence to medicines is common in the treatment of asymptomatic diseases, and statins used in hyperlipidemia are one of these medicines (1, 8, 9). About half of patients stop taking statins during the first year of treatment, and the proportion of patients who discontinue treatment increases over time. Discontinuation of treatment is often connected to adverse drug reactions (10, 11). Based on age, adherence follows a U-shaped curve: younger (< 50 years) and older (≥ 70 years) show lower medication adherence than patients aged 50-69 years (10). Therefore, it is very important that the

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healthcare provider is prepared to deal with potential problems and assess the benefit-risk balance of statin therapy (12).

Medication adherence is assessed with direct and indirect methods. Direct methods include, for example, the analysis of statin use as statin itself or its metabolites in the biological fluids (e.g., blood or urine). The most well-known indirect methods are the patient’s self-assessment of the use of medicines, the use of various electronic devices and apps supporting the consumption of medicines, and various prescription or pharmacy claims data indicating patients’ ability to refill prescriptions. The ideal method of assessing medication adherence should be inexpensive, user-friendly, easy to implement, reliable, flexible, and practical. Unfortunately, the described method has not been developed yet and it is, therefore, advisable to combine the existing methods (13, 14).

The aim of this study was to pilot the combined method for assessment of medication adherence of patients who have received statin therapy for a longer period of time compared with those who initiated treatment.

EXPERIMENTAL

The pilot study was carried out in Tartu University Family Medicine Center in 2017 where the study participants were recruited by general practitioners. The study group included 15 male and female outpatients who had received statin therapy (atorvastatin, simvastatin, rosuvastatin) for more than one year (long-term users). Outpatients who just started treatment with statins (new users) were studied in 2014-15 from another study (15). The new users’ group consisted of 29 patients. After age adjustment to long term users’ group patients who were older than the new users’ group, the number of patients in the long-term users’ group remained 17. None of the patients discontinued statin therapy during the study and those patients who were withdrawn from the study continued statin use according to the prescribed schedule.

To assess medication adherence with statins, a combined research method, developed in Estonia, was used: a patient self-assessment questionnaire on the use of medicines in general and on the use of statins; pill count adherence (PCA), prescription

Table 1. Formulas used for calculating statin treatment adherence (16).

Pill count adherence (PCA) %	$= \frac{\text{quantity dispensed} - \text{quantity remaining}}{\text{prescribed daily number of tablets} - \text{number of days between dispensing date and interview}} \times 100$
Medicines possession ratio (MPR) %	$= \frac{\text{sum of days supply in interval}}{\text{actual number of days in interval between first and last fill}} \times 100$

Table 2. Demographics of patients starting statin therapy and those taking statins for a longer period and description of statins used.

Parameter	Long term users (n = 15)		New users (n = 17)	
	n	%	n	%
Female patients	9	60	12	71
Male patients	6	40	5	29
Age (years, mean ± SD)	70 ± 11.6	-	61 ± 9.6	-
Polypharmacy	9	60	1	6
Mean use of statins	8 years	-	Start of treatment	-
Statins				
Atorvastatin	1	7	10	59
Rosuvastatin	2	13	4	23
Simvastatin	12	80	3	18

refill (calculated as medicines possession ratio – MPR) and total plasma cholesterol (15). Authorization no. 263 / T-10 from the University of Tartu Ethics Committee of Human Research was received for this study.

Each patient participated in the study for 6 months including meeting with researcher three times: at months 1, 3, and 6. A two-part questionnaire was used to assess factors influencing medication adherence. The first part of the questionnaire covered general questions about the use of medicines and demographics of the respondents and was completed by patients at month 1. The second part of the questionnaire addressed specific questions about statin use and was completed by patients at months 3 and 6. The questionnaires are available from the authors by request.

Analysis of PCA was performed at months 3 and 6 in the long-term users' group and at months 1, 3 and 6 in the new users' group. PCA is a measure describing how well a patient follows the prescription schedule. In addition, electronic prescription claims data were used to calculate MPR describing the patient's ability to pick-up refills, but not the actual use of medicines. To calculate the MPR, the patient had to have made at least two statin purchases during the previous year of the study (long term users) and during the six months' study period (new users). At the end of the study, in the sixth month, the extracts from the digital prescription database on pharmacy claims data were analyzed. The formulas for the calculation of PCA and MPR are given in Table 1.

Medication adherence of the patient was considered low if only 0-19% of the prescribed statin was used, the patient was partly adherent if 20-79% of the statin was used and with high medication adherence if 80-100% of medicine was used.

In addition, the total cholesterol was calculated in both groups at months 1 and 6 of the study to assess the effect of statin use on plasma cholesterol levels and thereby determine patients' adherence to statin treatment. The target value for total cholesterol in patients was 5.0.

RESULTS

Table 2 shows the demographics of both groups and the distribution of different statins prescribed to the patients. The proportion of male patients in the long term users' group was higher than in the new users' group, and the mean age of the patients in the first-mentioned group exceeded the mean age of the new users by 9 years. The age

difference could be explained by the fact that patients who started statin treatment were generally younger than those who had already been taking the medicine for years. The median duration of statin consumption in the long-term users' group was eight years and they were using different statins than in the new users' group. This can also be explained by them starting treatment earlier than the new users, the selection of statins available in Estonia has changed over the years.

General perception on the use of medicines and factors influencing medication adherence

The majority of the patients in both patient groups (92% long term users and 77% new users) agreed that medicines bring benefits rather than harm. However, there was a difference of opinion that people who use medicines regularly should stop taking them from time to time. More than half of the patients in the long term users' group (69%), but less than a quarter of the patients in the new users' group (18%) disagreed with this statement.

The long term users reported only minor problems in using the tablets. Less than a quarter of patients (23%) sometimes forgot to take their tablets on time, and a few patients had difficulty getting tablets from a jar or swallowing the tablets (both 8%). However, almost half of the patients (46%) were worried or disturbed about potential adverse drug reactions. The new users had more problems with regular use of the medicines (35%); mixing the tablets or difficulty with swallowing the tablets (both 6%).

Both groups had different opinions towards the need for statin therapy. In the first month, about half of the patients in the long-term users' group (46%) and a quarter in the new users' group (24%) agreed that their health was currently dependent on a statin. While the proportion of long term users remained the same during the study, the respondents in the new users' group became more skeptical about the need for statins (13%).

It was easy to remember the dose of the statin in both patient groups. Some patients in the long term users' group (15%) and in the new users' group (20%) sometimes had difficulty paying for their medicines. However, it was pointed out that the problem for the long term users was not the cost of a statin, but the total cost of all prescription medicines for pensioners. In the new users' group, the reasons for payment difficulties remained unclear. There were no problems with the refill of prescriptions in both groups.

In addition to the prescribed statins, more than half of the patients in the long term users' group

consumed four or more medicines: antihypertensives, other CVD medicines, and those to treat joint pain and inflammation. Almost half of the patients were also taking antidiabetic medicines. In the new users' group, about half used antihypertensives and less than half used prescription medicines for headaches or joint pain. An analysis based on the drug-drug interaction database Inxbase (17) showed no interactions between other medicines and statins that could have increased adverse drug reactions of statins, and therefore this factor was excluded from the assessment of the adverse drug reactions of statins.

In the long-term users' group, only a few patients complained about adverse drug reactions (e.g. allergies, itchy skin, stomach complaints, muscle or joint pain, and specific taste in the mouth) that could not be directly linked with the use of statins. In the new users' group, more than half of the patients at month 3 reported dry mouth, muscle cramps and numbness in the hands and feet, sleeping disorders and tiredness, but similarly to the long-term users the causes of described problems remained unclear.

Assessment of medication adherence

PCA analysis

PCA analysis provided more relevant data for new users than for long-term users' as the formula used for calculation did not include information about the additional supply of medicines patients had at home (Table 3).

Over the six months, the mean medication adherence based on pill count was 140% in the long-term users' group and 61% in the new users' group (Table 4). Existing data, however, demonstrated that at the initiation stage 59% of the patients in the new users' group and 55% in the long-term users' group were highly adherent (80-100%) to statin use. However, 11% of patients in the new users' group were non-adherent (0-19%) at the beginning of treatment. Moreover, while in the long-time users' group the medication adherence level remained unchanged during the study, it decreased significantly in the new users' group where only 19% of the patients were highly adherent to statin therapy at month 6.

Figure 1. Evaluation of total plasma cholesterol levels at baseline and after 6 months among long term and new users of statins (mmol/L ± SD).

Table 3. Example of calculation of pill count adherence (PCA).

Pill count	quantity dispensed (60 tablets) – quantity remaining (47 tablets)		× 100
adherence =			
(PCA) %	prescribed daily number of tablets (1 tablet) (× number of days between dispensing date and interview (07.09.2017 - 25.08.2017 = 14 days)		

Table 4. Comparison of the mean results for pill count adherence (PCA), medicines possession ratio (MPR) and six-month total cholesterol levels in patients starting statin and taking statins for a longer period.

Long term users N = 15	CPA %	MPR %	Total cholesterol 0-month (mmol/L)	Total cholesterol 6 months (mmol/L)	Change in cholesterol level (mmol/L)
01ML368P	213	68	7.5	6.8	-0.7
02ET435P	N/A	0	5.8	6.2	0.4
03EG459P	17	38	10.1	6.5	-3.6
04JV348P	68	82	4.2	4.7	0.5
05OV354P	N/A	85	4.1	W	W
06OL567P	556	78	4.5	4.5	0
07LK452P	62	71	6.2	6.5	0.3
08TS346P	104	95	5.1	4.4	-0.7
09GU347P	162	63	4.1	4.4	0.3
10MT444P	W	39	5.7	W	W
11HT432P	130	90	5.4	5.2	-0.2
12JS341P	54	97	5.5	4.5	-1
13NK435P	146	94	5.1	5.5	0.4
14JS430P	107	105	4.2	3.6	-0.6
15JL446P	66	74	7	4.5	-2.5
New users N = 17	PCA %	MPR %	Total cholesterol 0-month (mmol/L)	Total cholesterol 6- months (mmol/L)	Change in cholesterol level (mmol/L)
01ÜA469E	93	90	8.8	5.1	-3.7
03MS458E	84	84	7.2	4.9	-2.3
09AR346E	63	69	8	6.3	-1.7
10SU474E	62	62	8.3	6.9	-1.4
11MP467K	20	0	6.7	6.7	0
12RM347E	86	84	6.6	6.2	-0.4
13RI457K	80	84	8.3	6.6	-1.7
14TZ460K	N/A	0	7.3	W	W
16IV464K	N/A	0	7.7	7.6	-0.1
18MK460E	29	31	7.6	W	W
19IR468K	80	64	6.7	3.9	-2.8
22VT346E	52	41	6.7	6	-0.7
23HM478E	89	81	8.2	4.5	-3.7
24ED459E	82	87	7.5	6.3	-1.2
25AS351E	52	49	8.4	7.6	-0.8
27RR471E	88	97	7.6	4.6	-3
29VK362E	75	86	9.3	7.9	-1.4

*W Withdrawn from the study; *N/A Patient did not take statin to the PCA analysis.

MPR analysis

The mean MPR values during the study were 72% in the long term users' group and 59% in the new users' group (Table 4). Of the long-term users 57% and among new users 52% were highly

acquired to purchase statins at the beginning of the study. MPR was higher in male patients in the long term users' group and in female patients in the new users' group. Similarly, to the PCA results, the number of patients with high adherence was stable in

long time users group throughout the study but decreased rapidly by month 6 in the new users' group (22%).

Total plasma cholesterol analysis

Plasma total cholesterol was similar at baseline and month 6 in the long term users' group. In the new users' group, the respective values were different. At the end of the study, total cholesterol decreased more in the new user' group than in the long-term users' group (Fig. 1). At the end of the study, there were 7 (47%) patients with a total cholesterol target in the long-term users' group and 5 (29%) in the new users' group, but almost for all patients, the cholesterol levels lowered in the latter group. There could be seen a clear trend between results of CPA and MPR and change in the total cholesterol levels (Table 4).

In both groups, patients' adherence improved with age. However, there were few patients over 65 years of age in both groups, and the results cannot be extrapolated to a larger number of patients. Patients with better self-assessed health had lower medication adherence. The results did not show a clear correlation between the number of medicines used and medication adherence in either group. A similar adherence to treatment was found for those taking 2-3 or 6-7 prescription medicines.

DISCUSSION AND CONCLUSION

This study compared medication adherence to statins of two patients' groups (regular users and patients who initiated therapy) with the combined method (questionnaire-based self-assessment; PCA, MPR, and total plasma cholesterol test). The new users' group was studied in 2014. It is not likely that the general knowledge of patients on adherence has changed in a couple of years between the two studies as there have been no campaigns or any other interventions targeting this subject nationally.

Differences in the use of statins were identified in the two patient groups, with more frequent use of simvastatin in the long term users' group which may be related to the fact that atorvastatin and rosuvastatin were still new active ingredients without reimbursement and were with higher co-payment for the patient than simvastatin when the patients in the long time users' group were prescribed statins (18). Despite the fact that this study did not identify significant effects of medicines price on medication use, this problem may have existed in the past. As the patients in the long-term users' group did not appear to have any problems with simvastatin (e.g.

adverse drug reactions), there was no reason to replace the medicine with atorvastatin or rosuvastatin.

The survey identified patients' perception about the use of medicines in general and problems with the use of statins, which may affect medication adherence. It is necessary to combine this method with other analytical methods, as self-assessed feedback on the use of medicines may not reflect the real situation as described in other studies. This study also showed that, although the majority of patients did not think they had problems with dosing and regular use of the medicines, their medication adherence was medium to low when calculated from other methods of analysis, indicating some irregularity in the use of statins.

The responses from both groups also revealed a variety of drug-related issues that could lead to decreased medication adherence. While the main concern of the patients in the long term users' group was the potential problems with long-term use of statins (e.g. potential adverse drug reactions), it was more difficult for the new users' group to follow the regular use of the medicines and they were uncertain about the effect of statins. Problems with medication adherence of new users may have been due to the fact that continuous use of the medicine was not yet the norm. This may pose a risk to the continued use of medicines, as previous international studies found that about 20% of the patients did not start statin therapy and more than half of first-time statin users discontinue treatment within the first year (7, 10). Long term users reported being disturbed by the risk of muscle-related problems connected to statin use as described in journals and patient leaflets. It is a common problem described earlier in other studies (10, 11).

Based on the PCA and MPR analysis the medicines acquisition and adherence to the treatment prescribed was higher in the long term users' group than in the new users' group. For example, the mean MPR was 72% in the long term users' group and 59% in the new users' group. In both groups, the patients with high MPR had corresponding high PCA results demonstrating that patients who purchase medicines regularly also use them regularly. Calculation of PCA was complicated in both study groups because patients did not bring all available statin tablets to appointments and therefore it was not always possible to assess patients' actual treatment adherence. Besides, long-term users' had an additional supply of statins at home before the new refill and even if all statin was taken to PCA analysis, it did not correspond to the medicine patient

should have according to the treatment schedule. The extra supply of statins could be a result of medicine dispensed for six months at a time or from originals with a larger amount of tablets purchased at community pharmacies than were prescribed by a physician (e.g. 100 tablets instead of 60).

Despite some problems in calculating adherence, it can be seen that approximately half of the patients in both groups followed their treatment. Similarly, a large-scale meta-analysis of statins found that 53% of patients were adherent to statin treatment. However, at the end of the study, there were no patients in both groups who were not taking their prescribed statins.

Total cholesterol results in both groups confirmed that with continuous regular use of statins results close to the target value could be achieved. However, three patients in the long term users' group still had high total cholesterol levels despite long-term treatment. This may be due to the low medication adherence, which increased during the study when patients were told about the need to use statins and resulted in a decrease in total cholesterol levels, even 3.6 units per patient. Pharmacists can be a great help to doctors, as it is very important to talk to the patient to find out about their medication problems (19). As seen from the study even with patients who have taken their medicines for several years already, discussing their medicines and adherence can result in positive outcomes in plasma cholesterol levels, thus underlining the importance of patient counseling.

Based on the results of the pilot study it is recommended to combine descriptive and analytical methods: the survey, PCA, MPR, and the analysis of total cholesterol to assess medication adherence to statins in different patient groups (long-term users and those initiated therapy). However, in the future studies with larger patient groups and with respective measures "between fills" would be needed. In the pilot study, total plasma cholesterol levels decreased by 33% of the long term users and 82% of the new users. This indicates that most patients at least partially followed the statin treatment schedule. Patients need counseling about the use of their medicines and the problems that may arise, both when starting treatment and when taking the medicine for a long time.

Limitations of the study

The combined medication adherence assessment method used in this study can be successfully implemented in patients starting statin therapy. In patients with long-term use of statins, further studies

with a larger group of patients should be performed. In order to find out why patients' medication adherence is decreasing, the survey could be turned into oral communication. An oral interview would provide more information to the patient and allow for better contact with the patient. In addition to the analysis of total cholesterol, HDL and LDL cholesterol could also be measured, as these indicators provide more information about the patient's condition.

In the future for calculation of PCA and MRP, the formulas including calculation of additional supply of medicines should be used and a longer refill period could be selected for analysis.

Conflict of interest

No conflicts of interest have been declared.

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