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Survey of the instruction method about adverse reactions of HMG-CoA Reductase Inhibitor (Statin) and the patients intelligibility:

As cause search of non-compliance

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Summary

Concern about rhabdomyolysis, an adverse reaction to 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitors (statins), is considered to be a cause of poor compliance among patients taking them. In this study, patients undergoing statin treatment received information on rhabdomyolysis from pharmacists and physicians. We then investigated the causes of their concerns and how well the patients understood the information given to them. A questionnaire survey was conducted by interviewing outpatients who were prescribed statins from November and December 2006. Eighty-eight percent of the patients gave the response of "I received a written explanation on the medication", while 32% and 51% of patients responded that the adverse reactions to statins were explained orally by a doctor and a pharmacist, respectively. With regard to the contents of the oral explanation, there were many descriptions of the initial symptoms of rhabdomyolysis, but there was little information on how to cope when adverse reactions occur. Only 47% of patients indicated that they remembered the information on the adverse reactions to statins. With regard to the method used to explain about statins, many patients received a written explanation, while fewer patients received an oral explanation from the attending physician or pharmacist. Moreover, it was suggested that the method of coping when adverse reactions appear was insufficiently explained to those patients who received an oral explanation. It is necessary to match the method of coping with the adverse reactions and the initial symptom of the adverse reactions clearly and to improve patients' understanding of potential adverse reactions.

Keywords: statin, rhabdomyolysis, patients' compliance, pharmacist, providing information

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Introduction

Among the hyperlipidemia drugs presently used in Japan, there are six types of HMG-CoA reductase inhibitors (statins), namely, pravastatin, rosuvastatin, simvastatin, fluvastatin, atorvastatin, and pitavastatin. These statins have been reported to lower serum cholesterol levels significantly by 20~30% by inhibiting HMG-CoA reductase, and are useful in the primary and secondary prevention of coronary artery diseases¹⁾²⁾. However, treatment of hyperlipidemia is a long-term process, and there is often a decrease in compliance, which is a concern. Long-term use of statins for 2 to 5 years has been reported to have a compliance rate of about 50%~80%³⁾⁴⁾. This decreased compliance is one factor contributing to the decrease in treatment efficacy. It is very important to maintain compliance over long periods⁵⁾.

Factors that have been reported to cause a decrease in compliance are “inadequate supply of information to patients from medical personnel”, “low awareness of subjective symptoms and diseases”, “increased number of drug types and frequency of administration”, “inadequate understanding of how to use the prescription drugs and the effects of the drugs”, “experience of adverse reactions due to the drugs”, and “anxiety concerning adverse reactions”, among others⁶⁾⁷⁾.

Experience of drug-related adverse reactions and anxiety concerning adverse reactions are the two major factors contributing to the decrease in compliance. Statins have potent cholesterol-lowering effects but, on the other hand, they are associated with rhabdomyolysis, which is a serious adverse reaction. Rhabdomyolysis is a phenomenon whereby lysis of skeletal muscle tissue results in the release of breakdown products of the damaged muscle cells into the bloodstream. This may trigger renal failure. The subjective symptoms are weakness of the limbs, muscle pain, and reddish-brown urine. Test findings are increased blood and urinary myoglobin levels, and sharp increases in creatine phosphokinase (CPK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH), among others. The frequency of lethal rhabdomyolysis is 0.02~0.005%, and thus it is a rare occurrence. However, as it can occur, the symptoms need to be watched closely⁸⁾⁹⁾.

Pharmacists are obliged to provide patients and their families with information on early symptoms of adverse reactions, interactions, and interventions for the safe administration of medications that they prepare. The supply of information on adverse reactions alleviates the anxiety toward such adverse reactions, and leads to the opportunity to deal with the problem of adverse reactions more appropriately. This has been reported to prevent a decrease in compliance due to anxiety about adverse reactions¹⁰⁾¹¹⁾.

Since rhabdomyolysis became associated with statins, the Ministry of Health, Labor and Welfare of Japan has instructed drug manufacturers and medical institutions to provide patients who use statins with information on rhabdomyolysis. As such, patients who use statins are periodically supplied with information on it. However, despite this periodic supply of information, there are still some patients with low compliance due to anxiety about rhabdomyolysis.

One factor contributing to the decrease in compliance of statin drugs is anxiety about adverse reactions. The results of a questionnaire survey that we conducted for pharmacists working in pharmacy outlets demonstrated the inadequacy of information on adverse reactions supplied to patients taking medications and patients' poor understanding of rhabdomyolysis, which are likely causes of decreased patient compliance¹²⁾. Thus, this study examined the type of information on rhabdomyolysis that pharmacists and physicians supply to patients who are on statin drugs, and the extent to which the patients understand the information received. In addition, patients' anxiety towards adverse reactions was examined.

Methods

Study period

From November to December, 2006.

Study Sample

Patients undergoing statin treatment who made only outpatient visits to the Endocrinology and Metabolism Department of Nippon Medical School Hospital were the candidate subjects. After completing the outpatient examinations, the patients received an explanation of the objective and composition of this survey. The patients who

consented to participate in the survey were entered into the study. An interview-based questionnaire survey was then performed.

Approval to conduct this survey was obtained from the ethics committee of Nippon Medical School Hospital.

Details of the questionnaire survey (Table 1)

- Method of explaining adverse reactions related to statin drugs, content of the explanation, and level of patient understanding.
- Status of compliance with statin drugs.
- Status of anxiety towards the statin drug currently being administered.

Statistical analysis

Associations between categorical variables were assessed by Fisher's exact test. $P < 0.05$ was regarded as significant. For analysis, we employed JMP 7 (SAS Institute Inc., Japan).

Results

Basic subject information

Sixty patients participated in the study; their mean age (Q. 1) was 62.6 ± 11.2 years (mean \pm SD) and there were 18 (31%) males and 42 (69%) females. Their history of statin use (Q. 3) was less than 3 months for 8 (3%) patients, 3 months to less than 6 months for 4 (7%) patients, 6 months to less than 1 year for 1 (2%) patient, 1 year to less than 2 years for 6 (10%) patients, and greater than 2 years for 41 (68%) patients. This showed that most patients had been taking statin medication for a long period. Of all the patients (Q. 2), 50 (84%) obtained the medication from a pharmacy outlet, 8 (13%) at a pharmacy in front of a hospital, and 2 (3%) at a neighborhood pharmacy.

Supply of information on rhabdomyolysis

(1) Level of understanding about adverse reactions related to statin drugs

Of the 60 patients, 28 (47%) responded that they remember information on the adverse reactions to statin drugs (Q. 4). More patients who had taken statin for two years or more did not remember information about adverse reactions from statin administration compared with patients taking statin for less than two years (Table 2).

(2) Method of explaining and content of the explanation on adverse reactions to statin drugs

With regard to how patients were given information on the adverse reactions to statin drugs (Q. 5), 53 (88%) of the patients responded that they had received an explanatory leaflet about adverse reactions. This indicates that most of the patients received an explanatory pamphlet on drugs. In addition, 19 (32%) and 32 (51%) of the patients received an oral explanation from their attending physician (Q. 6) and pharmacist (Q. 7), respectively. With regard to the content of the oral explanation given by the attending physician (Q. 6), the responses of the patients were: "it was about symptoms of rhabdomyolysis" by 14 (69%) patients, "the fact that nausea and urticaria may occur" by 1 (8%) patient, "consult a doctor when symptoms such as adverse reactions occur" by 8 (39%) patients, "discontinue taking the medication if adverse reactions appear" by 1 (8%) patient, "I received an explanation but I have forgotten the details" by 4 (23%) patients, and other responses by 3 (15%) patients (Fig. 1a). With regard to the content of the oral explanation given by a pharmacist (Q. 7), the patients responded as follows: "it was about symptoms of rhabdomyolysis" for 17 (55%) patients, "the fact that nausea and urticaria may occur" by 2 (6%) patients, "I was instructed to consult a doctor when symptoms such as adverse reactions occur" by 8 (26%) patients, "discontinue taking the medication if adverse reactions appear" by 3 (10%) patients, and "I received an explanation but I have forgotten the details" by 11 (35%) patients (Fig. 1b). In addition, there were also patients who did not remember the details even though they received an oral explanation. More patients who had received an oral explanation of the adverse reactions to statin from their attending physician or pharmacist remembered these adverse reactions (Table 3a,b).

When asked about the significance of taking statin drugs (Q. 14), the patients responded as follows: "it is to prevent complications due to hyperlipidemia" by 16 (27%) patients, "it is to lower cholesterol" by 23 (38%) patients, "I simply administer the drug as prescribed by the doctor without considering anything in particular" by 17 (28%) patients, and "there is no need to take medications" by 4 (7%) patients.

Patient compliance with statin drugs

(1) Forgot to administer the drug

Of the 60 patients, 23 (38%) forgot to administer the statin medication (Q. 8). The frequency of forgetting to administer the medication was about 1-2 times a month for 14 (61%) patients, about 1-2 times a week for 8 (35%) patients, and about 3-4 times a week for 1 (4%) patient. Ninety percent of these patients who forgot to administer the medication still attained administration rates of 80 percent or more for one month, which showed that this was a group of patients with comparatively good compliance.

(2) Self-adjustment of statin drugs

Of the 60 patients surveyed, only 4 (7%) had adjusted administration of the statin drug on the basis of their own judgment (Q. 9). This also showed that the group of patients in this survey had good compliance. The reasons for giving the response of "I adjust the administration of the medication on the basis of my own judgment" were: "I adjust the dose according to the level of cholesterol" by 2 patients, "I adjust the administration because I do not have enough of the medication" by 1 patient, and "I periodically forget to administer the medication" by 1 patient.

Anxiety concerning adverse reactions to the statin drugs

(1) Status of anxiety

Of the 60 patients who personally administered statin drugs, 24 (40%) gave the response "I am worried about adverse reactions" (Q. 11). The patients who did not remember information on adverse reactions to statin did not worry about adverse reactions (Table 4).

(2) Reasons for the anxiety

The reasons for being anxious about adverse reactions (Q. 13) were: "I have experienced adverse reactions when taking medications" by 6 patients, which was the most common reason, followed by "I heard about adverse reactions from the pharmacist" by 3 patients, "I received an explanation about adverse reactions from my doctor" by 3 patients, "I read the package insert of the drug" by 2 patients, "I got information on adverse reactions from the TV, books, and the internet" by 2 patients, and

"I heard about adverse reactions from my family and acquaintances" by 1 patient. Other responses were "Because I have been taking the medication for a long time" by 3 patients, "I have some kind of anxiety" by 2 patients, "I do not know much about adverse reactions" by 1 patient, and "there are too many drugs to take" by 1 patient (Fig. 2a).

(3) Interventions by patients

The interventions patients took to cope with their anxiety towards adverse reactions to the drug (Q. 12) that they were administering were: "I consult with my attending physician" by 12 (50%) patients, "I do not consult with anybody, I just follow the prescription of my attending physician" by 8 (33%) patients, "I consult with a pharmacist" by 7 (29%) patients, "I find out about adverse reactions on my own" by 4 (17%) patients, and "I change the dose of the drug" by 2 (8%) patients (Fig. 2b).

Discussion

Supply of information on adverse reactions and its understanding

In this survey, 28 (47%) of the patients responded that they did not remember the adverse reactions to statin drugs. This proportion is larger than that in other studies¹⁴. However, the proportions of patients who received an oral explanation on the drug from a physician or pharmacist were 32% and 51%, respectively, which is only about half of the patients; this is a concern. This survey investigated whether there are differences in the content of information on adverse reactions that physicians and pharmacists give to patients. However, there was no notable difference in the content of the explanations given. The oral explanation received by most patients was on the early symptoms of rhabdomyolysis. Few patients received an explanation on how to respond when an adverse reaction occurs. In a previous study on awareness of the risks of medications in patients, it was demonstrated that patients felt that their compliance with drug treatment will improve if they are given preventive measures and cautions regarding prescription drugs in advance¹⁵. Thus, the information on adverse reactions that physicians and pharmacists provide should not only be about the early symptoms of rhabdomyolysis but also include a thorough explanation on how to cope

when an adverse reaction occurs.

There is a report that, when the form of information supplied on adverse reactions is both oral and written, patients' level of understanding of adverse reactions is increased¹³. However, in this study, of the patients who received an oral explanation from a physician or pharmacist, many forgot the details of the explanation (Fig. 1a, b). Furthermore, even though close to 90% of the patients responded that they had received a written explanation on the drug taken, their level of understanding of adverse reactions was low. This suggested that it is not easy to deepen patients' understanding of adverse reactions. Thus, when supplying patients with medications, pharmacists need to confirm their level of understanding about the initial symptoms of adverse reactions and about possible adverse reactions themselves thoroughly. This will stabilize patients mentally and thus alleviate fear about adverse reactions.

Compliance of hyperlipidemia drugs

In this study, 40% of the patients tended to forget administering the statin drug. However, of the $\geq 90\%$ of the patients with this tendency, $\geq 80\%$ took the prescribed medication. Furthermore, 4 (7%) of the patients discontinued treatment or altered the dose using their own judgment. These findings showed that the patients in this study had good compliance. This may be due to the fact that the patients in this study were receiving outpatient medical care at a university hospital and so were more conscious of their illness and positive towards the treatment received. In addition, 65% of the patients administered the treatment after understanding the significance of treatment with statin drugs. As such, many of the patients understood the necessity of statin drug treatment.

Nevertheless, one cannot say that the information on adverse reactions given to the patients undergoing treatment with statin drugs in this study was adequate. However, none of the patients discontinued treatment or altered the dose owing to excessive concern about adverse reactions. As observed from the results of the questionnaire survey that targeted one pharmacist¹², the information on adverse reactions supplied by pharmacists is inadequate and explanations that can give rise to misunderstanding are likely to

cause decreased compliance of patients. Therefore, adequate information needs to be supplied and carefully explained to patients.

Patient anxiety about adverse reactions

One of the main reasons for the decreased compliance is patients' anxiety about adverse reactions to medications. Even among these patients, 40% responded that they are anxious about the adverse reactions to the drugs that they are being treated with. The common response among patients regarding the reason for this anxiety about adverse reactions was experience of adverse reactions in the past. According to a report by the American Association of Retired Persons, of the elderly Americans who are receiving treatment with prescription drugs, 40% have experienced adverse reactions¹⁵. At the first sign of symptoms of a drug-related adverse reaction, if patients know that they should promptly contact a pharmacist or physician, and the pharmacist or physician can take account of adverse reactions quickly and constantly inquire about the progress of treatment, there is a high possibility that patients will no longer be anxious about the problem of these adverse reactions. In this study, 30% of patients continued treatment without consulting anybody about adverse reactions even though they had anxiety regarding them (Fig. 2b). When pharmacists give information on adverse reactions to patients, they need to tell the patients that they can contact them whenever a problem occurs or if they have a concern. By so doing, unpleasant adverse reactions that are the cause of non-compliance will be discovered early.

Conclusion

The problems that became evident from this study were that patients receive biased explanations on the early symptoms of rhabdomyolysis associated with the statin drugs, and the information given to them on how to cope when an adverse reaction occurs was inadequate. Patients themselves are the first to notice adverse reactions and therefore they need to be aware of the meaning of such changes. Pharmacists need to instruct patients to make contact with a pharmacist or physician quickly when they first notice adverse reactions, and the pharmacist or physician should be able to intervene

promptly when an adverse reaction occurs and follow up on the progress of the patient. Moreover, pharmacists need to establish a close relationship with patients to find out what they are thinking and their level of awareness before providing them with the necessary and precise information, and not to cause non-compliance with patients in the future.

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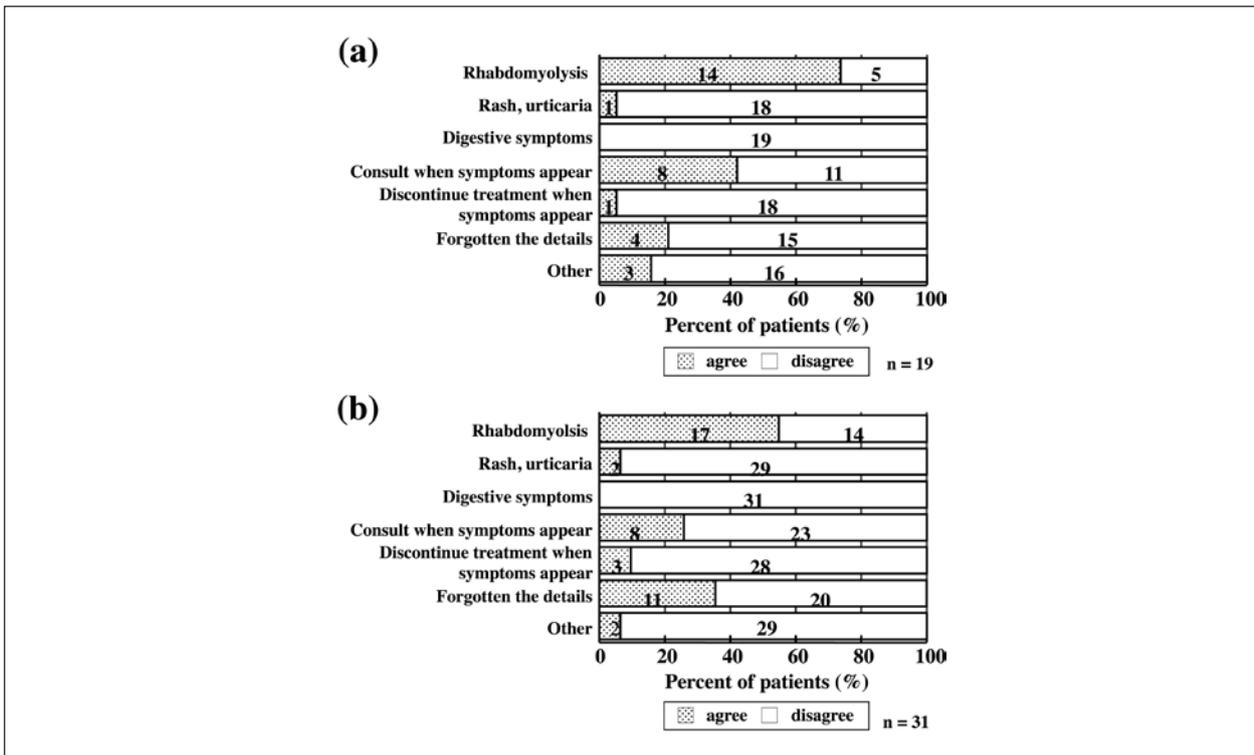


Figure 1 Percentage of the patients who received an oral explanation or not or forgot and content of the oral explanation (Q. 6 and 7). Values indicate the patient load.

- a) Content of the oral explanation given by the attending physician
- b) Content of the oral explanation given by the attending pharmacist

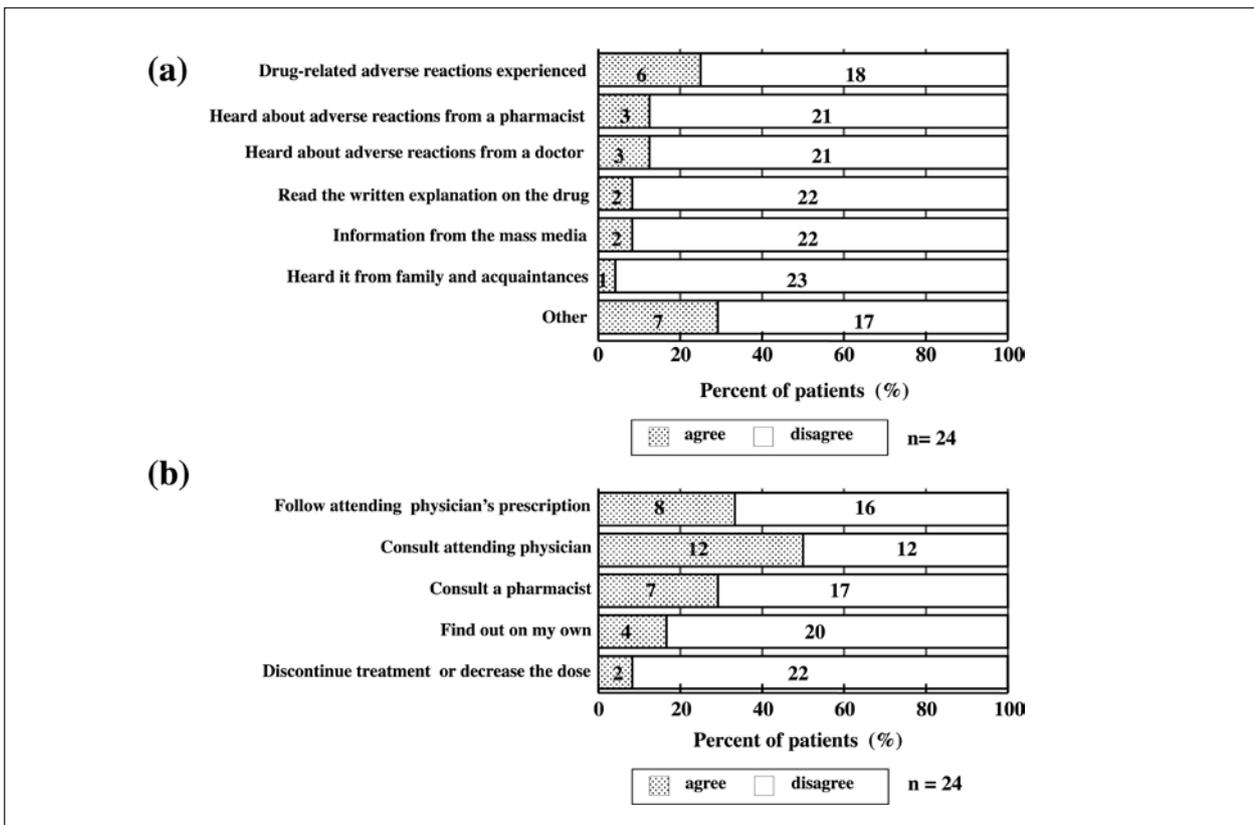


Figure 2 Anxiety about adverse reactions to statin drugs. Values indicate the patient load.

- a) Trigger of the anxiety about adverse reactions (Q. 13)
- b) How patients cope with anxiety about adverse reactions (Q. 12)

Table 1 Questionnaire survey on the administration of hyperlipidemia medications

1. What is your age and gender?
 () years male female
2. Where do you obtain your medication from?
 In the hospital A pharmacy close to the hospital A neighborhood pharmacy
3. When did you start taking hyperlipidemia medications?
 Less than 3 months 3 to 6 months 6 months to 1 year
 1 to 2 years At least 2 years
4. Do you remember what adverse reactions are associated with hyperlipidemia medications?
 Yes No
5. Have you received an explanatory pamphlet on hyperlipidemia medications?
 Yes No
6. Have you received an explanation on the adverse reactions of hyperlipidemia medications from your attending physician?
 Yes No I cannot remember
- * For patients who have received an explanation. Place a check mark against all answers that apply to the content of the explanation received.
 Symptoms such as muscle pain, numbness/foot cramps, reddening of urine (rhabdomyolysis) may occur
 Symptoms such as constipation, diarrhea and nausea occur
 Rash and urticaria may occur
 When you have concerns about adverse reactions, consult your attending physician or a pharmacist
 If adverse reaction-like symptoms appear discontinue treatment immediately.
 Other ()
7. Have you received an explanation on the adverse reactions of hyperlipidemia medications from a pharmacist?
 Yes No I cannot remember
- * For patients who have received an explanation. Place a check mark against all answers that apply to the content of the explanation received?
 Symptoms such as muscle pain, numbness/foot cramps, reddening of urine (rhabdomyolysis) may occur
 Symptoms such as constipation, diarrhea and nausea occur
 Rash and urticaria may occur
 When you have concerns about adverse reactions, consult your attending physician or a pharmacist
 If adverse reaction-like symptoms appear discontinue treatment immediately.
 Other ()
8. Have you ever forgotten to take your hyperlipidemia medication?
 Yes No
- * For patients that have forgotten to take their medication. Place a check mark against the frequency that applies.
 About 3 to 4 times a week About 1 to 2 times a week About 1 to 2 times a month
 Other ()
9. Have you adjusted (decreased the dose or suspended treatment) the dose of the hyperlipidemia medication? (Not applicable if instructed by a physician)
 Yes No
10. For patients that answered "yes" to 9. Why did you adjust the dose of the hyperlipidemia medication?
 What is the reason? (Place a check mark on all answers that apply)
 I was worried about side effects
 As disease has no subjective symptoms, I did not think it necessary
 Daily administration was not convenient
 I thought the drug is not effective.
 Other ()
11. Nothing in particular, I just follow the drug-related adverse reactions (not only hyperlipidemia medications).
 Yes No
12. For patients that answered "yes" to 11. How do you cope when you get worried about adverse reactions? (Place a check mark on all answers that apply)
 Nothing in particular, I just following the instructions of the prescription given by my attending physician
 I consult my attending physician
 I consult a pharmacist
 I find out about adverse reactions on my own.
 I will consider discontinuing taking the drug or reduce the dose
 Other ()
13. For patients that answered "yes" to 11. What triggered your concern about adverse reactions?
 (Place a check mark on all answers that apply)
 adverse reactions have appeared while taking the medication
 I became worried after hearing about adverse reactions from the pharmacist
 I became worried after hearing about adverse reactions from the physician
 I became worried after reading the explanation on adverse reactions in the explanatory pamphlet of the drug
 I became worried after learning about adverse reactions from the TV, newspaper, internet etc.
 I became worried after hearing about adverse reactions from family, acquaintances etc.
 I do not remember
 Other ()
14. What is your opinion on the significance of taking hyperlipidemia medication to treat hyperlipidemia?
 (Select one applicable answer)
 Hyperlipidemia is the cause of various complications such as arteriosclerosis and myocardial infarction, and so medications must be taken.
 Hyperlipidemia has no subjective symptoms and so it may not be necessary to take medications.
 I do not have any opinion in particular, I just take my medications according to the doctor's prescription
 Other ()

Table 2 Association analysis of the level of understanding about adverse reactions related to statin drugs with the history of statin use

	History of statin use		P value
	≥ 2 years	< 2 years	
Not remember information on adverse reactions to statin	28	4	0.0008
Remember information on adverse reactions to statin	13	15	

Table 3 Association analysis of the receipt of an explanation of the adverse reactions and remembering the adverse reactions

(a)	Not remember information on adverse reactions to statin	Remember information on adverse reactions to statin	P value
Not received oral explanation from physician	29	12	< .0001
Received oral explanation from physician	3	16	

(b)	Not remember information on adverse reactions to statin	Remember information on adverse reactions to statin	P value
Not received oral explanation from pharmacist	20	9	0.0227
Received oral explanation from pharmacist	9	19	

Table 4 Association analysis of worrying about adverse reactions and remembering about information of adverse reactions

	Not remember information on adverse reactions to statin	Remember information on adverse reactions to statin	P value
Worried about adverse reactions	9	15	0.0404
Not worried about adverse reactions	23	13	