Factors related to the effectiveness of hypercholesterolemia treatment following hospitalization for coronary artery disease

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KEY WORDS

cardiovascular risk,
cholesterol, coronary
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secondary prevention

ABSTRACT

INTRODUCTION Patients with established coronary artery disease (CAD) are at high risk of recurrent cardiovascular events.

OBJECTIVES The aim of the study was to identify factors related to control of hypercholesterolemia in patients after hospitalization for CAD.

PATIENTS AND METHODS The study included consecutive patients from 5 hospitals with cardiology departments serving one city in southern Poland. Patients were hospitalized for an acute coronary syndrome or for a myocardial revascularization procedure. Interviews and examinations were conducted 6 to 18 months after hospitalization.

RESULTS Overall, 83.6% of the patients were taking statins; 2.1%, fibrates; and 0.5%, ezetimibe. A statin at a high dose (≥ 40 mg of atorvastatin or ≥ 20 mg of rosuvastatin) was taken by 36.1% of the participants. Younger age and index hospitalization in a teaching hospital were significantly associated with a higher probability of taking a statin. Overall, 28.1% of the patients had good control of hypercholesterolemia (low-density lipoprotein [LDL] cholesterol levels < 1.8 mmol/l), whereas 71.9%, 38.6%, 24.4%, and 10.3% had LDL cholesterol levels of 1.8 mmol/l or higher, 2.5 mmol/l or higher, 3.0 mmol/l or higher, and 4.0 mmol/l or higher, respectively. Younger age, high blood pressure, and high fasting glucose levels were related to a higher probability of having LDL cholesterol levels of 1.8 mmol/l or higher, while younger age, shorter period of education, professional inactivity, lack of cardiac rehabilitation, and high blood pressure were related to the probability of LDL cholesterol levels of 4.0 mmol/l or higher.

CONCLUSIONS The frequency of statin use is affected by age and health care-related factors, while control of hypercholesterolemia after hospitalization due to CAD is dependent mainly on patient-related and clinical factors.

INTRODUCTION Patients with established coronary artery disease (CAD) are at high risk of recurrent cardiovascular events. Despite advances in pharmacological and invasive treatment methods, a number of risk factors remain independent predictors of cardiovascular mortality

in patients with CAD.^{1,2} One of the most important risk factors is hypercholesterolemia, while the use of statins is related to improved prognosis. The European guidelines recommend lowering low-density lipoprotein (LDL) cholesterol levels below 1.8 mmol/l in all coronary patients.^{3,4}

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Despite the overwhelming evidence of the benefits of lowering cholesterol levels, especially when using statins, a majority of patients with CAD still have LDL cholesterol levels above the treatment target.⁵⁻¹⁰ Moreover, although high-dose statins should be prescribed to survivors of acute coronary syndromes, most patients take lower doses.¹¹

Furthermore, several factors influencing the quality of secondary prevention in everyday practice have been identified.^{6,12} Nevertheless, identifying the remaining barriers to effective risk factor control is essential to maximize the benefit of preventive interventions. A number of intervention methods aimed at improving secondary prevention in patients with CAD have been proposed to date.¹³⁻¹⁹ However, in order to achieve the maximum benefit from these interventions, their intensity and complexity should be adjusted according to specific populations or even according to specific patients.²⁰ Therefore, the aim of our study was to identify factors related to control of LDL cholesterol levels in patients after hospitalization due to CAD.

PATIENTS AND METHODS The study population and the methods used have been described in earlier reports.^{5,6} A brief description is given below.

Five hospitals serving one city and surrounding districts in southern Poland participated in the survey. The total population in this area is around 1 200 000 inhabitants. In each cardiac department, medical records were reviewed and consecutive patients who had been hospitalized for acute myocardial infarction, unstable angina, percutaneous coronary intervention or were scheduled for coronary artery bypass grafting were retrospectively identified, excluding those who had died during their in-hospital stays. Participants were invited to take part in a follow-up examination 6 to 18 months after discharge. The interviews were started in July 2011 and finished in May 2013. About 64% of the participants included in the present analysis agreed to have their data and blood samples transferred to the EUROASPIRE IV survey.⁷

Data on demographic characteristics, personal history of CAD, smoking status, blood pressure, fasting glucose levels, plasma lipid levels, and prescribed medications were obtained using a standardized data collection form. Patients had their height and weight measured in a standing position without shoes and heavy outer garments, using standard scales with a vertical ruler. The body mass index (BMI) was calculated according to the following formula: BMI = weight [kg]/(height [m])². Blood pressure was measured twice on the right arm in a sitting position after at least 5-minute rest. For plasma lipid and glucose measurements, a fasting venous blood sample was taken between 7:30 AM and 8:30 AM.

For the purposes of the present analysis, we divided the study group according to LDL cholesterol levels (<1.8 mmol/l vs 1.8–3.9 mmol/l vs ≥4.0 mmol/l).

Statistical analysis Categorical variables were reported as percentages and continuous variables as means ± SD. The Pearson χ^2 test was applied to all categorical variables. Normally distributed continuous variables were compared using the *t* test or analysis of variance. Variables without normal distribution were evaluated using the Mann–Whitney test or the Kruskal–Wallis analysis of variance, as appropriate. The multivariate analyses were performed using the logistic regression analysis as implemented in the STATISTICA 8.0 software (StatSoft Inc., Tulsa, Oklahoma, United States). A 2-tailed *P* value of less than 0.05 was regarded as indicating statistical significance.

RESULTS Based on the review of hospital records, 1061 patients were invited to a follow-up interview and examination 6 to 18 months after discharge. Data on 562 patients were included in the present analysis (445 patients did not take part in the interview and 54 did not agree to blood collection). A possible selection bias in the formation of the study population was examined by comparing age, sex, risk factors, and the prescription rate of drugs on discharge between the study population and the 499 patients that could not be included in the analysis. The comparison did not reveal any significant differences with respect to the above factors except for age at the time of hospitalization (63.6 ± 8.8 years in analyzed patients vs 64.9 ± 10.3 years in nonanalyzed patients; *P* < 0.05) and a prescription rate of angiotensin-converting enzyme inhibitors/sartans on discharge (88.0% in analyzed patients vs 83.8% in nonanalyzed patients; *P* < 0.05). We also compared the attendance rates of the index event groups, which showed a slight but significant bias (*P* < 0.05) characterized by a somewhat higher attendance rate in the percutaneous coronary intervention group. The mean time between discharge and the follow-up interview was 1.1 ± 0.2 years.

The characteristics of the analyzed groups are presented in **TABLE 1**. Patients with high LDL cholesterol levels were younger, less well educated, more likely to be smokers, more likely to have high blood pressure, and were more frequently obese. Overall, 83.6% of the patients were taking statins; 2.1%, fibrates; and 0.5%, ezetimibe (**TABLE 2**). Among all study participants, 55.5% were taking atorvastatin; 17.4%, simvastatin; and 10.7%, rosuvastatin. A statin at a high dose (≥40 mg of atorvastatin or ≥20 mg of rosuvastatin) was taken by 36.1% of the patients. When 80 mg of simvastatin was also taken into account, the proportion increased to 36.7%.

The variables independently related to statin use are presented in **TABLE 3**. The same factors were significantly related to the use of a lipid-lowering drug (data not shown). The only significant variable related to the use of fibrates was the duration of education (odds ratio [OR], 1.19; 95% confidence interval [CI], 1.02–1.38).

TABLE 1 Characteristics of the study group

Parameter		LDL cholesterol, mmol/l			P value	Total (n = 562)
		<1.8 (n = 158)	1.8–3.9 (n = 346)	≥4.0 (n = 58)		
age, y, mean ± SD		66.3 ± 8.8	64.5 ± 9.0	62.7 ± 8.2	0.01	64.8 ± 8.9
sex, %	men	69.0	63.3	58.6	0.29	64.4
	women	31.0	36.7	41.4		35.6
duration of education, y, mean ± SD		11.9 ± 3.4	12.0 ± 3.3	10.9 ± 2.6	<0.01	11.9 ± 3.3
professionally active, %		17.8	24.8	8.6	0.01	21.1
index event, %	myocardial infarction	39.2	37.0	19.0	0.02	32.6
	unstable angina	31.0	30.1	51.7		35.8
	PCI	22.8	22.5	24.1		22.8
	CABG	7.0	10.4	5.2		8.9
index hospitalization, %	teaching hospital	56.3	65.3	51.7	0.04	61.4
	other hospital	43.7	34.7	48.3		38.6
cardiac rehabilitation after index hospitalization, %	yes	32.1	31.6	14.0	0.02	29.9
	no	67.9	68.4	86.0		70.1
diabetes diagnosed during index hospitalization, %		37.3	27.7	24.1	0.05	30.1
hypertension diagnosed during index hospitalization, %		81.0	82.7	82.8	0.90	82.2
practice setting, %	hospital outpatient clinic/ cardiologist	81.4	78.2	77.6	0.57	79.0
	general practitioner	6.4	10.5	5.2		8.8
	private cardiac practice	10.3	9.6	15.5		10.4
	no regular health check-up	1.9	1.7	1.7		1.8
smoking, %		12.3	20.2	31.0	<0.01	19.2
blood pressure ≥140/90 mmHg, %		36.2	40.2	61.8	<0.01	41.3
fasting glucose ≥7.0 mmol/l, %		21.5	13.0	17.5	0.05	15.9
body mass index ≥30 kg/m ² , %		34.4	32.0	41.1	0.03	36.3
lipids, mmol/l, mean ±SD	total cholesterol	3.50 ± 0.71	4.61 ± 0.78	7.07 ± 1.12	<0.001	4.55 ± 1.27
	LDL cholesterol	1.46 ± 0.27	2.56 ± 0.57	4.84 ± 0.68	<0.001	2.48 ± 1.07
	HDL cholesterol	1.35 ± 0.49	1.35 ± 0.40	1.35 ± 0.30	0.34	1.35 ± 0.42
	triglycerides	1.50 ± 1.28	1.53 ± 0.81	2.09 ± 1.97	<0.001	1.58 ± 1.14

Abbreviations: CABG, coronary artery bypass grafting; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention

TABLE 2 Treatment of study participants

Parameter	LDL cholesterol, mmol/l			P value	Total
	<1.8	1.8–3.9	≥4.0		
antiplatelets, %	93.7	91.3	81.0	0.02	90.9
β-blockers, %	84.2	81.5	70.7	0.08	81.1
ACEIs/sartans, %	78.5	78.6	63.8	0.04	77.0
calcium antagonists, %	26.6	23.4	27.6	0.65	24.7
diuretics, %	48.1	39.0	48.3	0.10	42.5
antismoking drugs ^a , %	8.3	5.9	9.1	0.48	6.9
lipid-lowering drugs, %	90.5	84.7	60.3	<0.001	83.8
statins, %	90.5	84.4	60.3	<0.001	83.6
fibrates, %	3.2	1.7	1.7	0.57	2.1
ezetimibe, %	1.3	0.0	1.7	0.08	0.5

^a ever in the period from discharge to the follow-up interview

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; others, see [TABLE 1](#)

TABLE 3 Variables independently related to the probability of statin use

Variable	Odds ratio (95% confidence interval)
age, per 10 years	1.30 (1.00–1.68)
index hospitalization in a teaching hospital; yes – 1, no – 0	2.37 (1.48–3.79)
general practitioner; yes – 1, no – 0	0.35 (0.18–0.69)

Overall, 28.1% of the patients had target LDL cholesterol levels (<1.8 mmol/l), whereas 71.9%, 38.6%, 24.4%, and 10.3% of the patients had LDL cholesterol levels of 1.8 mmol/l or higher, 2.5 mmol/l or higher, 3.0 mmol/l or higher, and 4.0 mmol/l or higher, respectively. Among participants aged 65 years or younger, 24.7% had LDL cholesterol levels below 1.8 mmol/l, whereas among those older than 65 years, the proportion was 31.5% ($P = 0.07$). The corresponding proportions were as follows: 30.1% among men vs 24.5% among women ($P = 0.16$), and 29.7% among patients with at least a secondary school education vs 26.6% in less educated participants ($P = 0.42$). Similarly, 23.7% of professionally active participants had LDL cholesterol levels below 1.8 mmol/l, in comparison with 29.3% of those who were professionally inactive ($P = 0.23$). The corresponding proportions were 30.9% among patients with myocardial infarction as an index diagnosis; 26.8% in those with unstable angina, 28.1% in those with percutaneous coronary intervention, and 22.0% in those with coronary artery bypass grafting ($P = 0.61$).

When we limited the analysis to patients taking a statin, 69.6%, 32.3%, 18.3%, and 7.4% had LDL cholesterol levels of 1.8 mmol/l or higher, 2.5 mmol/l or higher, 3.0 mmol/l or higher, and 4.0 mmol/l or higher, respectively. When we limited the analysis to patients taking a high-dose statin, 62.9%, 29.5%, 19.7%, and 8.9% had LDL cholesterol levels of 1.8 mmol/l or higher, 2.5 mmol/l or higher, 3.0 mmol/l or higher, and 4.0 mmol/l or higher, respectively.

The factors related to the lack of adequate control of cholesterol levels are presented in **TABLE 4** (univariate analysis) and in **TABLE 5** (multivariate analysis). When we excluded other risk factors (smoking, hypertension, high fasting glucose levels) from the multivariate model, the only variable significantly related to the probability of having uncontrolled LDL cholesterol (≥ 1.8 mmol/l) was age. Similarly, when we did not include other risk factors into the multivariate model, the following variables were independently related to the probability of having very high LDL cholesterol levels (≥ 4.0 mmol/l): age (OR, 0.47; 95% CI, 0.33–0.68), duration of education (OR, 0.87; 95% CI, 0.79–0.97), professional activity (OR, 0.22; 95% CI, 0.08–0.64), unstable angina as an index event (OR, 2.53; 95% CI, 1.41–4.54), and participation in cardiac rehabilitation following the index hospitalization (OR, 0.36; 95% CI, 0.16–0.80).

DISCUSSION The principal finding of this study is that despite overwhelming evidence that

lipid-lowering therapy improves clinical outcomes in patients with CAD, 71.9% of study participants had LDL cholesterol levels above the recommended target. The majority of these patients probably did not receive proper evaluation and treatment for dyslipidemia following hospitalization due to CAD. In general, our results showed a considerable potential for a further reduction in cardiovascular risk following hospitalization for CAD through improvement in the management of hypercholesterolemia.

In the previous report, we used data from patients hospitalized due to CAD between 1996 and 1999 to analyze factors related to the use of lipid-lowering drugs 6 to 18 months after hospitalization due to CAD, and we showed that hospitalization in a teaching hospital almost doubled the likelihood of taking a lipid-lowering drug following hospitalization.²⁰ Our present results suggest that this association has not changed since the end of the 20th century despite a number of educational activities organized for physicians and despite profound changes in the Polish society induced by the collapse of the communist system in 1989 and by entering the European Union in 2004. The Poland's health care system has been in transition for the last 20 years, both in terms of institutional changes and regulations regarding drug registration, prescription, and reimbursement. Importantly, the relative position of primary care physicians and specialists has evolved. In this respect, it is worth noting that the relationship between the use of lipid-lowering drugs and practice setting has not changed significantly.²⁰

No correlation was observed between a patient's level of education and the probability of having LDL cholesterol levels below 1.8 mmol/l or below 2.5 mmol/l following hospitalization due to CAD among participants of the EUROASPIRE IV survey.²¹ Our results are concordant with those reported by Bruthans et al,²¹ as duration of education was not related to the probability of appropriate control of cholesterol levels in our study group. However, we were able to show the independent relationship between duration of education and the probability of having very high LDL cholesterol levels (≥ 4.0 mmol/l).

Professional inactivity was the most important factor related to very high LDL cholesterol levels. This might be due to financial barriers but other factors (eg, a number of comorbidities as well as psychological factors) might be also responsible for this finding. Indeed, patients with high LDL cholesterol levels were not only taking lipid-lowering drugs less frequently compared with patients with lower LDL cholesterol levels,

TABLE 4 Variables related to the probability of having high low-density lipoprotein (LDL) cholesterol level (univariate analysis)

Variable		Odds ratio (95% confidence intervals)	
		LDL cholesterol ≥ 1.8 mmol/l	LDL cholesterol ≥ 4.0 mmol/l
age, per 10 years		0.76 (0.61–0.94)	0.75 (0.56–1.02)
sex; men – 1, women – 0		0.75 (0.51–1.12)	0.76 (0.44–1.32)
duration of education, per 1 year		1.00 (0.95–1.06)	0.90 (0.82–0.98)
professional activity; yes – 1, no – 0		1.33 (0.83–2.14)	0.32 (0.13–0.83)
index event	myocardial infarction; yes – 1, no – 0	0.81 (0.56–1.19)	0.39 (0.20–0.77)
	unstable angina; yes – 1, no – 0	1.10 (0.74–1.64)	2.46 (1.42–4.26)
	PCI; yes – 1, no – 0	1.00 (0.88–1.13)	1.09 (0.58–2.06)
	CABG; yes – 1, no – 0	1.43 (0.71–2.87)	0.53 (0.16–1.77)
index hospitalization in a teaching hospital; yes – 1, no – 0		1.34 (0.92–1.95)	0.64 (0.37–1.11)
cardiac rehabilitation following index hospitalization; yes – 1, no – 0		0.87 (0.58–1.30)	0.35 (0.16–1.76)
practice setting	hospital outpatient clinic/cardiologist; yes – 1, no – 0	0.81 (0.51–1.30)	0.91 (0.47–1.76)
	general practitioner; yes – 1, no – 0	1.57 (0.76–3.23)	0.54 (0.16–1.79)
	private cardiology practice; yes – 1, no – 0	1.02 (0.56–1.87)	1.69 (0.78–3.66)
	no regular health check-up; yes – 1, no – 0	0.90 (0.23–3.56)	0.96 (0.11–7.98)
smoking; yes – 1, no – 0		1.92 (1.14–3.25)	2.07 (1.13–3.78)
blood pressure $\geq 140/90$ mmHg; yes – 1, no – 0		1.34 (0.91–1.99)	2.53 (1.42–4.50)
fasting glucose ≥ 7.0 mmol/l; yes – 1, no – 0		0.58 (0.36–0.93)	1.14 (0.55–2.36)
body mass index ≥ 30 kg/m ² ; yes – 1, no – 0		0.95 (0.64–1.41)	1.45 (0.83–2.53)

TABLE 5 Variables independently related to the probability of having high low-density lipoprotein (LDL) cholesterol levels (multivariate analysis)

Variable		Odds ratio (95% confidence intervals)	
		LDL cholesterol ≥ 1.8 mmol/l	LDL cholesterol ≥ 4.0 mmol/l
all patients			
age, per 10 years		0.77 (0.62–0.97)	0.46 (0.31–0.66)
sex; men – 1, women – 0		0.64 (0.43–0.97)	–
duration of education, per 1 year		–	0.89 (0.80–0.99)
professionally active; yes – 1, no – 0		–	0.21 (0.07–0.63)
unstable angina as an index event; yes – 1, no – 0		–	2.62 (1.45–4.74)
cardiac rehabilitation following the index hospitalization; yes – 1, no – 0		–	0.37 (0.17–0.83)
smoking; yes – 1, no – 0		1.80 (1.04–3.12)	–
blood pressure $\geq 140/90$ mmHg; yes – 1, no – 0		1.56 (1.04–2.33)	2.50 (1.38–4.56)
fasting glucose ≥ 7.0 mmol/l; yes – 1, no – 0		0.57 (0.34–0.93)	–
patients taking statins			
age, per 10 years		–	0.39 (0.24–0.64)
professionally active; yes – 1, no – 0		–	0.04 (0.00–0.29)
cardiac rehabilitation following index hospitalization; yes – 1, no – 0		–	0.25 (0.08–0.76)
smoking; yes – 1, no – 0		1.83 (1.04–3.23)	–
blood pressure $\geq 140/90$ mmHg; yes – 1, no – 0		1.54 (1.01–2.36)	3.30 (1.52–7.18)
fasting glucose ≥ 7.0 mmol/l; yes – 1, no – 0		0.55 (0.32–0.94)	–

but they were also taking antiplatelet drugs and angiotensin-converting enzyme inhibitors/sartans less frequently. In addition, control of hypercholesterolemia was related to high blood pressure and smoking. The participation in a cardiac rehabilitation program was not related to the

probability of having target LDL cholesterol levels. On the other hand, it was independently related to very high LDL cholesterol levels.

The long time interval since the last coronary event is usually considered as related to non-optimal secondary medical prevention. Indeed,

Meurice et al²² showed that after 5 years since the last coronary event, the nonoptimal secondary medical prevention was significantly more frequent. As we assessed secondary prevention about 1 year since the index hospitalization, we could not address this phenomenon.

Study limitations The present study has several limitations. Firstly, it is possible that some unrecognized factors might have influenced the approach to the management of hypercholesterolemia. Secondly, we were not able to assess the impact of the appropriate hypercholesterolemia management on mortality or morbidity. Thirdly, we could not analyze the influence of lifestyle on the LDL cholesterol level. However, statins were shown to be more potent in decreasing cholesterol levels compared with lifestyle changes in high-risk patients.²³ Nevertheless, both drugs and lifestyle interventions should be used simultaneously in patients with CAD. Fourthly, our study participants were not representative of the entire population of patients with CAD. Participants were limited to those who had experienced an acute CAD event or a revascularization procedure. Therefore, our results should not be directly applied to other subjects. However, an important strength of our analysis is that our results are not just based on abstracted medical record data but on face-to-face interviews and examinations using the same protocol and standardized methods and instruments, including central laboratory analyses of lipids and glucose. Therefore, this analysis provides reliable information on the effectiveness of hypercholesterolemia management following hospitalization due to CAD.

Conclusions Age and health system-related factors are related to the use of statins, whereas mainly patient-related factors are related to control of hypercholesterolemia following hospitalization due to CAD.

Contribution statement PJ conceived the idea for the study. PJ, KK-J, and AP contributed to the design of the research. PJ, DC, KK-J, and AP were involved in data collection. PJ analyzed the data. All authors edited and approved the final version of the manuscript.

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Czynniki związane z kontrolą hipercholesterolemii u osób po hospitalizacji z powodu choroby niedokrwiennej serca

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SŁOWA KLUCZOWE

cholesterol, choroba wieńcowa, ryzyko sercowo-naczyniowe, wtórna prewencja

STRESZCZENIE

WPROWADZENIE U pacjentów ze zdiagnozowaną chorobą niedokrwinną serca (ChNS) ryzyko występowania kolejnych zdarzeń sercowo-naczyniowych jest duże.

CELE Celem badania była ocena czynników związanych z kontrolą hipercholesterolemii u osób po hospitalizacji z powodu ChNS.

PACJENCI I METODY Do badania włączano kolejnych pacjentów z 5 szpitali z oddziałami kardiologicznymi jednego z miast w południowej Polsce. Pacjenci byli hospitalizowani z powodu ostrego zespołu wieńcowego lub w celu rewaskularyzacji mięśnia sercowego. Rekrutację do badania oraz wywiad przeprowadzono 6–18 miesięcy po hospitalizacji.

WYNIKI Ogółem 83,6% pacjentów zażywało statyny, 2,1% – fibraty, a 0,5% – ezetymib. Statynę w dużej dawce (≥ 40 mg atorwastatyny lub ≥ 20 mg rozuwastatyny) stosowało 36,1% uczestników badania. Wiek i hospitalizacja w szpitalu akademickim były istotnie związane z większym prawdopodobieństwem stosowania statyny. Ogółem 28,1% pacjentów miało dobrze kontrolowaną hipercholesterolemię (cholesterol LDL $< 1,8$ mmol/l), natomiast u 71,9, 38,6, 24,4 oraz 10,3% stężenie cholesterolu wynosiło odpowiednio $\geq 1,8$, $\geq 2,5$, $\geq 3,0$ oraz $\geq 4,0$ mmol/l. Młodszy wiek, wysokie ciśnienie tętnicze i wysokie stężenie glukozy na czczo wiązały się z częstotnością występowania stężenia cholesterolu LDL $\geq 1,8$ mmol/l, natomiast młodszy wiek, krótki czas trwania edukacji, brak aktywności zawodowej, brak udziału w rehabilitacji kardiologicznej oraz wysokie ciśnienie tętnicze wiązały się z częstotnością występowania stężenia cholesterolu LDL $\geq 4,0$ mmol/l.

WNIOSKI Na częstość stosowania statyn wpływają wiek i czynniki związane z organizacją systemu opieki zdrowotnej, natomiast kontrolę hipercholesterolemii po hospitalizacji z powodu ChNS warunkują przede wszystkim czynniki demograficzne i kliniczne.

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