DRUG-RELATED PROBLEMS ASSOCIATED WITH USE OF STATINS IN UKRAINE: A HOSPITAL-BASED STUDY

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Abstract. Statins are one of the most prescribed classes of cardiovascular drugs in the world of evidence for benefit. At the same time, lipid-lowering therapy by statins can be the cause of serious adverse reactions, such as myalgia, rhabdomyolysis, arrhythmias etc. Numerous drug-related problems (DRPs) can increase the potential risk of statin adverse reactions. In this retrospective study we analysed 21 medical records of patients admitted to the hospital with acute coronary syndrome in which were detected totally 479 DRPs. The study identified a high rate of inappropriate prescribing of statins because 4.8% (95% confidence interval: 3.1-7.1) of all DRPs were associated with use of these drugs. It was established that statins-induced DRPs were caused by drug-drug interactions (39.2%), excessive dosage (30.4%) and contraindicated use (30.4%). As a result, we formed 4 types of recommendations for reducing DRPs associated with use of statins in hospitalised patients with acute coronary syndrome.

Key words: statins, rational pharmacotherapy, acute coronary syndrome, drug-related problems (DRPs)

Introduction

Statins are widely used in medicine for reducing serum levels of low-density lipoprotein cholesterol and, consequently, for prevention and pharmacotherapy of cardiovascular diseases [11]. Statins are also known as enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, because they block this main enzyme involved in cholesterol synthesis. Besides, statins possess numerous other effects including: nitric oxide-mediated improvement of endothelial dysfunction and upregulation of endothelin-1 expression, antioxidant effects, anti-inflammatory properties, stabilization of atherosclerotic plaques, anticoagulant effects and inhibition of graft rejection after heart and kidney transplantation [6]. The analysis of 76 randomized trials involving 170.255 participants demonstrated important clinical benefits with statin therapy. Statins reduce cardiovascular disease mortality, fatal myocardial infarction, non-fatal myocardial infarction, revascularization and a composite of fatal and non-fatal strokes [9].

The prescription of statins has been increasing rapidly. For example, the European prescription of statins is increasing an average 31% a year [14]. Recently, the American College of Cardiology and the American Heart Association expanded the indications for use of statins, particularly for prevention of cardiovascular diseases. Thus, this would augment the number of adults who would be eligible for statin therapy by 12.8 million [13].

It has been estimated, lipid-lowering therapy in the hospital with statins improves outcomes, motivation and long-term adherence in patients with acute coronary syndromes [10]. At the same time, statins prescribed to inpatients are associated with high risk of different medication errors which are a serious problem because can lead to harm to the patient [1, 5, 8]. They are omission errors, drug-drug interactions (DDIs) and incorrect dosage [8]. The American Heart Association published the main types of medication errors related to different drug classes, including statins. These medication errors include several patterns, such as (1) prescribing errors (inadvertent use of allergenic medications, drug name confusion errors (for example, lovastatin and drug with similar name lotensin which is angiotensin-converting-enzyme inhibitor)), (2) dispensing errors and (3) omission errors [2].

In Ukraine, incorrect prescribing of drugs are analyzed with reference to what are termed «drug-related problems» (DRPs), which are defined to include potential DDIs, contraindicated use of drugs, incorrect dosage of drugs, co-administration of medicines which belong to the same group etc. According to the definition, DRP is «an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes» [15]. The problem of inappropriate administration of statins has not been quantified in Ukraine. Thus, the primary aim of the study was to measure the incidence of DRPs associated with statins intake in patients with acute coronary syndrome. A secondary aim of the study was to determine the types of DRPs, to analyze causes, and from this, to generate recommendations for reducing DRPs.

Materials and methods

This retrospective study included 21 medical records. The data were collected during the first quarter of 2015 in one hospital in Lviv, Ukraine. The criterion for inclusion medical records in the study was administration of statins for hospitalized patients with acute coronary syndrome. Copies of medical records were acquired through an agreement with the hospital. Ethics approval was obtained from the Human Research Ethics Committee of Danylo Halytsky Lviv National Medical University on April 2015.

The research team developed a checklist to review the medical records. The checklist included medical record number, age and gender of patients, medical history, morbidities and drugs with dosage and frequency regimen. All medical records were carefully reviewed by clinical pharmacist and physicians who had been trained for identification of DRPs. Evaluation of DRPs was done by the Pharmaceutical Care Network Europe (PCNE) DRPs classification v5.01 [15]. Information about appropriate use of all prescribed medications (indications, contraindications, route of drug administration, dosage and frequency regimen) was obtained from patient information leaflets [12]. Information about potential DDIs was obtained from drug-interaction checker [7] and patient information leaflets [12].

The data were analysed by Statistica 10 Trial. Descriptive statistics included frequency distributions. A 95% confidence interval (CI) was calculated for the proportion of DRPs associated with use of statins.

The authors declare that they have no competing interests.

Results

The demographic and clinical characteristics of patients (n=21) included in the study are shown in Table 1.

In 10 medical records (47.6%) atorvastatin was prescribed, in 11 (52.4%) – rosuvastatin despite 7 statin drugs are currently available in Ukraine (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin).

A total number of identified DRPs was 479 (an average of 22.8±8.5 DRPs per patient). The

Table 1. *Distribution of demographic and clinical characteristics among 21 inpatients*

Characteristic	n (%)
Age, years	
Range (min-max)	49-83
Mean ± SD*	65,5±9,0
Gender	
Men	17 (81.0)
Woman	4 (19.0)
Length of stay in hospital, days	
Range (min-max)	3-14
Mean ± SD*	9,3±3,3
Administrated drugs, number	
Range (min-max)	10-22
Mean ± SD*	16,3±3,2

**SD* standard deviation

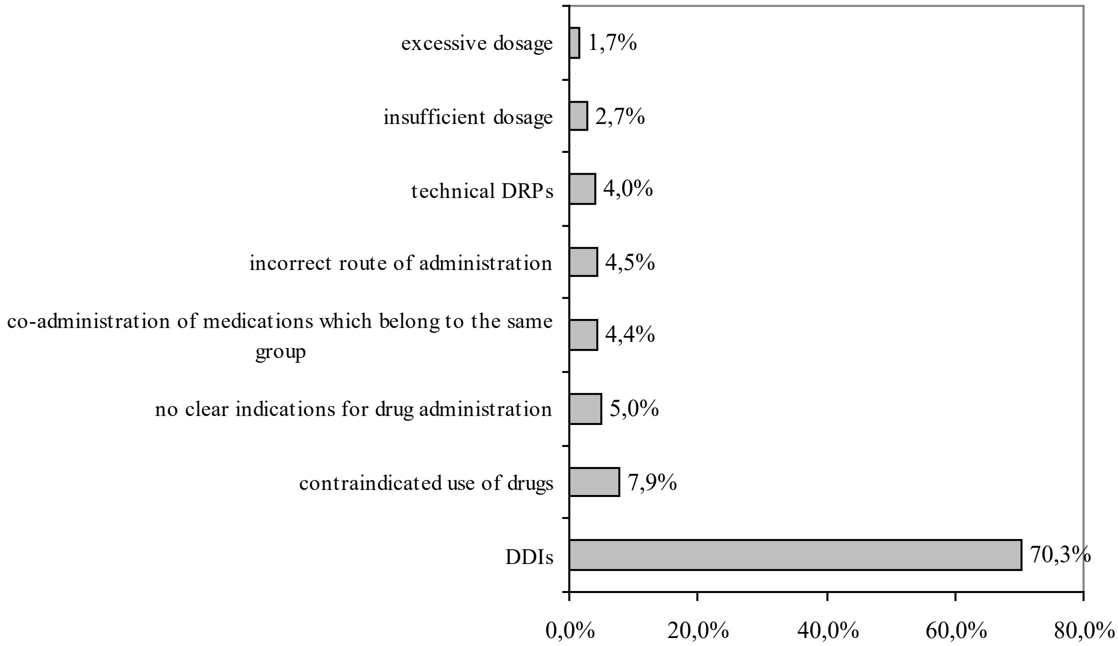

Fig. 1. Distribution of all identified DRPs (n=479) in medical records (n=21)

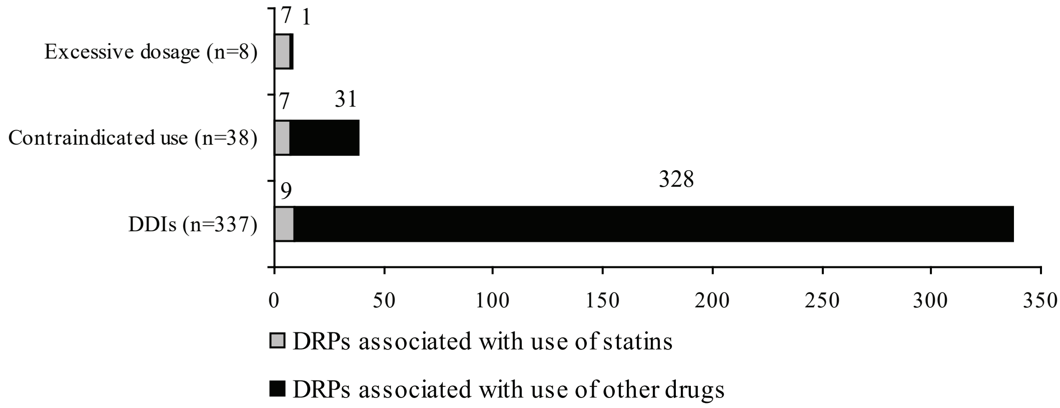

Fig. 2. Distribution of DRPs related to use of statins and other drugs

most prevalent DRPs (70.3%) were potential DDIs, 7.9% – contraindicated use of drugs, 5.0% – no clear indication for drug administration, 4.4% – co-administration of medicines which belong to the same group, 4.0% – incorrect route of drug administration, 2.7% – excessive dosage and 1.7% – insufficient dosage of drugs. Also we detected 4.0% technical DRPs (no dosage regimen, drug form and/or dissolvent) which are the consequence of inadequate completing of medical records (Fig. 1).

It was established that 4.8% (95% CI: 3.1–7.1) of DRPs are associated with use of statins. They include 3 groups of DRPs: 1) DDIs (39.2%); 2) excessive dosage in elderly patients and patients with liver dysfunction (30.4%); 3) cases of contraindicated use (30.4%). The part of these DRPs among a total number of the same DRPs are shown in Fig. 2.

Discussion

Adverse reactions of HMG-CoA reductase inhibitors occur in 19% of patients [14]. The risk factors for statin adverse reactions include numerous conditions: small body frame, Asian ethnicity (Japanese or Chinese), alcohol abuse, hypertension, diabetes mellitus, obesity, high triglycerides, thyroid disorders, hypothyroidism, including unnoticed or asymptomatic hypothyroidism, personal history or family history of hereditary muscle problems, prior muscle problems, hyperkalemia, genetic mutations etc. But the main factors which increase the potential risk of statin adverse reactions are polypharmacy (the concomitant use of multiple drugs which lead to DDIs) and overdose [4]. They are also the most prevalent DPRs in Ukrainian patients with acute coronary syndrome. At the same time, statin monotherapy related to low frequency of adverse events [3, 16].

We established that 39.2% of DPRs associated with use of statins were DDIs. In 3 cases was identified DDI between statin (atorvastatin) and calcium channel blocker (verapamil). This combination is significant because verapamil increases the level and, consequently, effect and toxicity of atorvastatin, so it should be monitor closely [7, 12].

Also we detected 2 cases of co-administration of statins (in one case atorvastatin, in another rosuvastatin) and digoxin. Atorvastatin increases the therapeutic effects of cardiac glycosides [7]. At the same time, digoxin increases toxicity of atorvastatin/rosuvastatin with myopathy and rhabdomyolysis [7, 12].

In 1 medical record we identified concomitant administration of atorvastatin and amiodarone. This antiarrhythmic drug is a weak CYP3A4 inhibitor and increases the level of atorvastatin [4, 7, 12]. Thus, co-administration of HMG-CoA reductase inhibitors and amiodarone associated with possible significant clinical outcomes, primarily muscle lesions [4].

The remaining DDIs, detected in 3 medical records, involved aluminum-containing antacids, agents with documented potential to reduce the gastrointestinal absorption of statins (by on the order of 35%), and thereby reduce their therapeutic effects [12]. Therefore administration of aluminum-containing antacids and statins should be separated by at least 2 hours.

The second group of DRPs associated with use of statins in patients with acute coronary syndrome was excessive dosage. It should be mentioned, that 87.5% (i.e., 7 of 8) of total number DRPs concerning exceeding dosage related to use of statins (particularly rosuvastatin). Only one of these DRPs was entailed by other drug (lansoprazole) prescribed for patient with liver dysfunction with 2-fold excess of daily dose.

We identified 2 causes of statin overdose in analyzed medical records: (1) disregard of pharmacokinetic parameters in patients with liver dysfunction; (2) neglect of age restrictions. In patients with liver dysfunction daily dose of rosuvastatin should be not more than 10 mg because serum level concentration and risk of adverse reactions increase [12]. Despite this, 4 patients received 20 mg of rosuvastatin per day.

Maximum daily dose of rosuvastatin in elderly patients (>70 years) is 5 mg [12]. In 3 medical records of patients aged 71, 72 and 82 years, we detected 4-fold excess of daily dose (i.e., 20 mg of rosuvastatin).

Cases of contraindicated use of statins are a frequent problem in Ukraine. All DRPs (n=7) of this group are the consequence of prescription HMG-CoA reductase inhibitors (atorvastatin and rosuvastatin) for patients with chronic hepatitis in acute phase.

At the same time, we identified no DRPs associated with use of statins from following groups: (1) no clear indication for administration; (2) co-administration of medications which belong to the same group; (3) incorrect route of drug administration; (4) insufficient dosage and (5) technical DRPs.

The American Heart Association released 8 recommendations to promote better quality of pharmacotherapy in hospitalized heart and stroke patients [8]. Some of them, in our opinion, may be relevant to use of statins. For example, (1) in elderly patients heightened surveillance for adverse events must be done; (2) pharmacists and nurses should be integrated within the cardiovascular care teams; (3) promotion of no-fault medication error reporting and interdisciplinary quality improvement review processes is recommended. But these patterns are the part of management process. Considering this fact, we offered recommendations from the present research which may be directly used for reduc-

Table 2. *Recommendations for reducing DRPs associated with use of statins*

Recommendations	Conditions
1. Adjust dose	Elderly patients (>70 years)
	Patients with liver dysfunction
2. Withdraw/ exclude pharmaceutical scheme	Patients with chronic hepatitis in acute phase
3. Separate administration by 2 hours	Co-administration of statins and aluminium- containing antacids
4. Closely monitor drug level	Co-administration of statins and calcium channel blockers (verapamil), cardiac glycosides (digoxin)

ing DRPs related to statins in patients with acute coronary syndrome (Table 2).

Limitations

Finally, this study has several limitations. The main limitation is related to its comparatively modest size sample. However, a high total number of identified DRPs provide valuable results to characterize the occurrence of DRPs associated with statins intake in patients with acute coronary syndrome. Another important limitation of our study is that only the medical records from one hospital in one country were considered. Therefore the findings cannot be statistically generalized. Further investigation is required.

Conclusions

DRPs associated with use of statins for management of patients with acute coronary syndrome are a serious problem. Most of these DRPs are significant and predictable. Thus, efforts to reduce DRPs with statins should particularly focus on averting potential DDIs, ensuring correct dosing regimen, and being alert for co-morbidities that may necessitate dose modification, or may contraindicate statins use.

References

1. F e r n e r RE, Aronson JK. Clarification of terminology in medication errors: definitions and classification. Drug Saf 2006; 29(11): 1011–1022.
2. F r e e d m a n JE, Becker RC, Adams JE, Borzak S, Jesse RL, Newby LK, O'Gara P, Pezzullo JC, Kerber R, Coleman B, Broderick J, Yasuda S, Cannon C. Medication errors in acute cardiac care: An American Heart Association scientific statement from the Council on Clinical Cardiology Subcommittee on Acute Cardiac Care, Council on Cardiopulmonary and Critical Care, Council on Cardiovascular Nursing, and Council on Stroke. Circulation 2002; 106(20): 2623–2629.
3. F r i s h m a n WH, Horn J. Statin-drug interactions: not a class effect. Cardiol Rev 2008; 16(4): 205–212.
4. G o l o m b BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. Am J Cardiovasc Drugs 2008; 8: 373–418.
5. G r o b e r ED, Bohnen JMA. Defining medical error. Can J Surg 2005; 48(1): 39–44.
6. K a p u r NK, Musunuru K. Clinical efficacy and safety of statins in managing cardiovascular risk. Vasc Health Risk Manag 2008; 4(2): 341–353.
7. M e d s c a p e Drug-Interaction Checker. http://reference.medscape.com [Accessed 20 Aug 2015].
8. M i c h a e l s AD, Spinler SA, Leeper B, Ohman EM, Alexander KP, Newby LK, Ay H, Gibler WB. Medication errors in acute cardiovascular and stroke patients: a scientific statement from the American Heart Association. Circulation 2010; 121: 1664–1682.
9. M i l l s EJ, Wu P, Chong G, Ghement I, Singh S, Akl EA, Eyawo O, Guyatt G, Berwanger O, Briel M. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis

of 170,255 patients from 76 randomized trials. QJM 2011; 104(2): 109–124.

10. Paradiso-Hardy FL, Gordon WL, Jackevicius CA, Kertland HR, Pearson GJ, Pickering JL, Poirier L, Semchuk BM, Verret L. The importance of in-hospital statin therapy for patients with acute coronary syndromes. Pharmacotherapy 2003; 23: 506–513.
11. SIGN. Risk estimation and the prevention of cardiovascular disease. A national clinical guideline 2007. http://www.sign.ac.uk [Accessed 20 Dec 2015].
12. State Register of Medicinal Products (Державний реєстр лікарських засобів). http://www.drlz.kiev.ua [Accessed 15 Aug 2015].
13. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63(25PtB): 2889–2934.
14. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, Ward K, Ebrahim S. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; 62 p.
15. The Pharmaceutical Care Network Europe (PCNE) classification for drug related problems (revised 01-05-06 vm) V5.01 (2006). http://www.pcne.org [Accessed 1 Aug 2015].
16. Viktil KK, Blix HS, Moger TA, Reikvam A. Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems. Br J Clin Pharmacol 2007; 63(2): 187–195.

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