Monitoring Adverse Drug Reactions and Incidence of Potential Statin-Drug Interactions

Cardiovascular diseases are the first disease in Albania that caused mortality and morbidity according to the Public Health Institute the Statistical Institute of Albania.[1,2] Hydroxymethylglutaryl-CoA reductase inhibitors (known as statins) are widely used as lipid-lowering drugs. They caused adverse events such as myotoxicity, renal, and hepatic problems which are considerably elevated in combination with other drugs. Drug–drug interactions (DDIs) can result in a change in either drug efficacy or toxicity. The value of therapy is defined by ineffectiveness or increased toxicity. Statins are the therapeutic class of medicines that reduce morbidity and mortality in patients with atherosclerotic cardiovascular disease.[3,4] Adverse events caused by DDI with clinical significance are preventable. DDIs involving statins include individual pharmacokinetics characteristics (e.g., binding affinity, half-life, dose of medications, and timing and sequence of administration duration of therapy) patients' factors (e.g., age, sex, lifestyle, disease implicating metabolism hepatic, renal impairments and cardiac failure), genetic polymorphism, hypersensitivity, etc. Physicians choose a noninteracting alternative, but if none is available, they prescribe in combination by evaluating the benefits and risks of the co-commitment of medications.[5,6]

This is a retrospective study. We enrolled 780 hospitalized patients' files in random ways. We included patients/adults who met the following criteria: statins prescribed and other prescriptions for cardiovascular disease, diabetes mellitus, renal and hepatic disease, etc., Statistical analyses were performed with the SPSS version 22. We have received data from the Biochemistry Laboratory for the value of creatine kinase (CK), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), and international normal ratio where a value upper the limit of normal range was identified after the clinical symptoms that patients have had. Interactions were identified also using free platforms such as Drugs.com and Medscape.[7,8]

Seven hundred and eighty hospitalized patients' files were observed their statins prescription and other drugs. There were five types of statins used: atorvastatin (10 mg, 20 mg, and 80 mg), simvastatin (10 mg, 20 mg, 40 mg, and 80 mg), rosuvastatin (10 mg and 20 mg), fluvastatin (20 mg and 40 mg), and lovastatin (10 mg and 20 mg). The most used statins remain atorvastatin, rosuvastatin followed by simvastatin, lovastatin, and fluvastatin. Treatment with statins was "more aggressive" statins such as atorvastatin and rosuvastatin. Being in the conditions of polymedications, the number of drugs used during the treatment has been high 6 (2-7). We have had in consideration, other risks factors that predispose clinically possible adverse drug events such as gender, age, and hospital duration.[7] The most affected were men in relation to women with a distribution of 77.69% (men) and 22.31% (women). Demographic characteristics of the patients receiving statins are presented below [Table 1].

The total potentially statin-drug interactions were 42, when atorvastatin was the statin most affected for DDI in values 42.8% [Table 2].

There are few studies reporting the incidence of pSDIs.[3,4,8-10] In our study, the statin most prescribed was atorvastatin with dosage of 20 mg [Table 2]. The second one was simvastatin considered the statin most sensitive to pharmacokinetic drug interactions due to its low bioavailability. There is no difference through young and older patients in dosage. As the possibility of interactions increases in older patients,' dosage of statins is lower than normal. Possibility of Statin-Drug Interactions (pSDIs) is increased significantly with other cardiovascular drugs used concurrently with statins which affect the cardiovascular system. The toxicity of statins during concomitant administration with other drugs is modified by different pharmacokinetic or pharmacodynamic mechanisms for example, calcium channels blockers and statins.[3,4,8] The most used calcium channel blockers in

Table 1: Demographic data, statin, and nonstatin drugs prescribed

Patients	Men	Women
Total (*n*=780), *n* (%)	606 (77.69)	174 (22.31)
Age (years), mean	62.6	73.2
Statins (%)		
Atorvastatin	47.00	
Simvastatin	18.00	
Rosuvastatin	14.50	
Fluvastatin	12.00	
Lovastatin	8.50	
Nonstatins drugs prescribed (mean, range)	6 (2-7)	
Primary diagnosis, *n* (%)	780 (100)	
Coronary heart disease (included acute myocardial infarction, unstable angina*		
Others (acute heart failure, ventricular arrhythmia, arterial hypertension, diabetes mellitus type II, dyslipidemia, etc)**	530 (68%)	

*Patients had only one primary diagnosis, **Patients had one/more others diagnosis

Table 2: Possible statin-drug interaction with clinical significance

Statins	Statins (n)	Possible statins drug interactions (%)	DDIs (statin/drug)	Side effects	Cardiologist decision
Atorvastatin 20 mg	18	42.8	Atorvastatin 20 mg/digoxin 0.25 mg (6 patients)	Arrhythmia	Reduce statin dosage to 10 mg
			Atorvastatin 20 mg/fenofibrate 160 mg (3 patients)	Muscle related toxicity (minor)	Stopping atorvastatin
			Atorvastatin 20 mg/omeprazole 20 mg (5 patients)	Muscle related toxicity (minor)	Reduce statin dosage to 10 mg
			Atorvastatin 20 mg/amiodarone 100 mg (4 patients)	Increased level of ALAT and ASAT	Reduce statin dosage to 10 mg
Simvastatin 80 mg	8	19.1	Simvastatin 40 mg/amiodarone) 100 mg (2 patients	Increased level of ALAT and ASAT	Reduce statin dosage to 20 mg
			Simvastatin 80 mg/amlodipine 10 mg (6 patients)	Muscle related toxicity (minor)	Reduce statin dosage to 20 mg
Rosuvastatin 20 mg	11	26.2	Rosuvastatin 20 mg/amlodipine 10 mg (11 patients)	Muscle related toxicity (minor) and ALAT ASAT higher	Reduce statin dosage to 5 mg
Lovastatin 20 mg	5	11.9	Lovastatin 20 mg/diltiazem 60 mg (5 patients	Muscle related toxicity (minor)	The treatments have continued without dosage changes
Total	42	100			

DDI=Drug–drug interactions, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase

our clinic were amlodipine 10 mg. The pair amlodipine/simvastatin increases the plasma concentrations of simvastatin. These combinations increase the possibility of the occurrence of myopathy and rhabdomyolysis.[3,7] By increasing the level of CK, which was identified in biochemistry results. The clinicians have modified the dosage but not interrupt the treatment. Simvastatin 20 mg and atorvastatin 10 mg were used. The combinations atorvastatin/diltiazem have followed the same clinical incidence. The antiarrhythmic (amiodarone)/simvastatin is the most prescribed. Side effects reports show increased level of ALAT and ASAT and myopathy. The patients developed muscle pain and weakness.[3,8-10] Our clinicians do not recommend stopping taking statins. Concomitant use of atorvastatin with digoxin has shown an increase in plasma digoxin concentration to 15%–20% accompanied with arrhythmia, and the statin treatment has stopped.

In conclusion, potential statin-drug interactions in cardiovascular patients are unavoidable and should be clinically managed. Dose limits, adverse events, and biochemical data should be monitored closely and identified early to a safer statins' dosage or another statin.

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Conflicts of interest

There are no conflicts of interest.

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