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Original article

Pre-stroke statin use was associated with lower risk of in-hospital death in non-thrombolysed patients

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ABSTRACT

Background: Prior studies suggested that statins might have a neuroprotective effect in patients with acute ischemic stroke. The aim of this study was the evaluation of the short-term effects of statins following ischemic stroke among non-thrombolysed patients. **Methods:** In this cohort retrospective study we have included 810 ischemic stroke patients (mean age 69.7±11.5, 48.6% females), not-thrombolysed on admission. Based on their prior medication history patients were categorized into pre-stroke statin user and non- statin user patients. The risk of in-hospital mortality was compared between two groups. **Results:** Of the 810 ischemic stroke patients, 146 (18.2%) were using a statin before stroke. Statin therapy before stroke-onset was associated with a lower risk of in-hospital mortality (3.4% vs. 26.9%), $p<0.001$. In the multivariable analysis, statin use was independently associated with a favorable outcome (OR = 0.119, 95% CI = 0.047-0.299, $p < 0.001$). **Conclusion:** Prior statin therapy in patients with acute ischemic stroke non-thrombolysed patients is associated with lower risk of in-hospital death, and this is independent of other risk factors.

KEYWORDS: Stroke, statins, in-hospital death, mortality.

INTRODUCTION

Stroke is one of the leading causes of death and a major cause of morbidity worldwide [1]. Atherosclerosis disease and inflammation play important roles in the pathogenesis of acute ischemic stroke [2, 3]. Statins, the 3-hydroxy 3-methyl-glutaryl coenzyme-A (HMG-CoA) reductase inhibitors, are medications originally used for the control of hypercholesterolemia [4]. However, there is increasing evidence showing that statins have some other pleiotropic effects aside from their cholesterol-lowering properties [5].

Statin therapy has been shown to reduce cardiovascular and cerebrovascular events, including myocardial infarction, stroke, and death [6-8]. Several studies using animal models of ischemic stroke showed that statin therapy might have neuroprotective effects when started before or immediately after induction of focal cerebral ischemia [9]. However, the benefits of pre-stroke statin therapy in patients with acute ischemic stroke remain controversial [10, 11]. Moreover, most of previous studies have included patients treated with tissue plasminogen activator (tPA) on admission.

The aim of our study was to evaluate the effects of prior statin therapy early after stroke (in-hospital mortality rate) in a cohort of ischemic stroke patients who do not underwent thrombolysis on admission.

MATERIALS AND METHODS

The University Clinical Centre of Kosovo (UCCK) is the only tertiary health care centre in Kosovo and most of the stroke patients in Kosovo are admitted and treated to the Neurology Clinic, UCCK. In this study we have retrospectively analyzed data of all of the patients admitted to the hospital from January 1, 2015 to December 31, 2015. Patients with hemorrhagic stroke and those with venous sinus thrombosis were excluded from the study. None of the patients included in this study have received intravenous or intra-arterial thrombolytic therapy.

All patients included in this study have been hospitalized for a period of at least 6 days prior discharge. In total, 1073 patients (mean age 69 12, 51.6% females) with ischemic or hemorrhagic stroke were included in this study. We have previously used the clinical data of this cohort of patients and have already published a paper on another subject, by Hundozi et al. [12].

Patients' clinical data collection

The diagnosis of stroke was based on direct observation by the medical staff, and also by evaluating clinical signs and analysing imaging (computed tomography (CT) and magnetic resonance imaging (MRI)) results. Blood pressure (BP) on admission was considered to be the average of all readings (median = 2) obtained in the emergency department and admission room before the administration of any antihypertensive drugs. All patients underwent a CT scan within 24 h after admission and a second one within 72 h when necessary.

All patients with ischemic stroke were investigated with carotid Doppler and ECG; most also received transthoracic echocardiography. Prognostic risk factors were assessed for each patient, including age, gender, serum glucose, hypertension (defined as the use of antihypertensive agents, a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg), prior stroke, prior/on-going coronary artery disease, atrial fibrillation, diabetes mellitus, hypercholesterolemia (defined as the use of antihyperlipidaemic agents or a serum cholesterol level >220 mg/dl), current smoking (defined as a history of smoking during the preceding 3 months). In addition, information about the patient's medication at stroke onset was determined.

The morning after admission, fasting blood samples were taken to determine complete blood count (CBC), cholesterol concentration, serum glucose level, and liver and kidney function tests. Data for the early after stoke (in-hospital) mortality was recorded and compared between patients with and without prior statin therapy.

Statistical analysis

Categorical variables were expressed as percentages and continuous variables were expressed as the means standard deviations (SD). We used Student's t-test to compare the mean age (continuous variable) between patients in-hospital mortality rate, and for the remaining comparisons, we used the chi-square test with a pre-selected significance level of $p < 0.05$. Logistic regression models were used to determine the relationship between pre-stroke statin use and in-hospital mortality rate. In addition, we have performed several models in order to determine the effects of statins on stroke patients' outcome independently of different clinical and demographic data. All statistical analyses were performed using IBM SPSS Statistics 22.

RESULTS

In this study we have included 810 ischemic stroke patients. Mean age was 69.7±11.5 and 48.6% were females. Patients demographics, clinical data and data for their pre-stroke medications used are presented in table 1. Based on their prior medication history patients were categorized into pre-stroke statin user and non- statin user patients.

Table 1: Patients' clinical and demographic data

Patients data	n (%)
Male	421 (51.4)
Female	389 (48.6)
Age, mean (SD)	69.7 (11.5)
Hypertension	547 (68.3)
Diabetes mellitus	194 (24.3)
Cardiomyopathy	103 (13.0)
Atrial fibrillation	47 (5.9)
Dyslipidemia	101 (12.7)
Any anticoagregation	469 (58.6)
Anticoagulation	51 (6.7)
Statins	146 (18.2)
ACE inhibitors	317 (38.6)
Beta blockers	108 (13.5)
Ca blockers	48 (6.0)
Aangiotension receptor blockers	48 (6.0)

Of the 810 ischemic stroke patients, 146 (18.2%) were using a statin before stroke. Statin therapy before stroke-onset was associated with a lower risk of in-hospital mortality (3.4% vs. 26.9%), p<0.001 (table 2). In the multivariable analysis, using different clinical variables as cofounders, pre-stroke statin use was independently associated with a favorable outcome (OR = 0.119, 95% CI = 0.047-0.299, p < 0.001) (table 3). In addition, older patients (>65 years) were significantly associated with increased risk of in-hospital mortality after ischemic stroke (table 2 and 3).

Table 2: Comparison of in-hospital mortality between different patients' clinical features, and pre-stroke statin use

	In-hospital death		
	Yes	No	
Pre-stroke statin use, n(%)			
Yes	5 (3.4)	141 (96.6)	<0.001
No	176 (26.9)	478 (73.1)	
Gender, n (%)			
Male	96 (23.4)	315 (76.6)	0.611
Female	85 (21.3)	304 (78.1)	
Hypertension, n (%)			
Yes	115 (21.1)	431 (78.9)	0.121
No	66 (26)	118 (74.0)	
Age, n (%)			
<65	37 (13.9)	229 (86.1)	<0.001
>65	144 (27.0	389 (73.0)	
Diabetes mellitus, n (%)			
Yes	37 (19.2)	156 (80.8)	0.2
No	143 (23.6)	463 (76.4)	
Cardiomyopathy, n (%)			
Yes	30 (29.1)	73 (70.9)	0.093
No	115 (21.7)	545 (78.3)	
Atrial fibrillation, n (%)			
Yes	11 (23.4)	36 (76.6)	0.899
No	117 (22.6)	582 (77.4)	
Dyslipidemia, n (%)			
Yes	31 (30.6)	70 (69.4)	0.101
No	116 (17.4)	547 (83.6)	

Table 3: Regression analysis. Univariable and multivariable using different models

	Regression analysis			
	OR	95% CI	Standard error	p-value
Pre-stroke statin use	0.096	(0.019-0.238)	0.45	<0.001
Model 1	0.106	(0.013-0.265)	0.77	<0.001
Model 2	0.108	(0.043-0.268)	0.83	<0.001
Model 3	0.12	(0.048-0.299)	0.84	<0.001
Model 4	0.119	(0.047-0.299)	0.84	<0.001

Gender (female)	0.917	(0.658-1.278)	0.123	0.611
Age (>65)	2.29	(1.541-3.406)	0.098	<0.001
Hypertension	1.316	(0.92-1.86)	0.105	0.122
Diabetes mellitus	1.3	(0.869-1.951)	0.183	0.201
Atrial fibrillation	0.956	(0.476-1.918)	0.345	0.89

Model 1-pre-stroke statin use, age and gender; Model 2-pre-stroke statin use, age, gender, hypertension; Model 3-prestroke statin use, age, gender, hypertension, diabetes mellitus; Model 4- pre-stroke statin use, age, gender, hypertension, diabetes mellitus and atrial fibrillatio

DISCUSSION

There is mounting evidence that statin (3- hydroxy-3-methylglutaryl-coenzyme A inhibitors [HMG-CoA]) therapy may alter vascular atherosclerosis and reduce cardiovascular events, including myocardial infarction and stroke [6, 7], with reports published as early as 1994 (4S trial) [13]. However, the decreased risk of stroke could not be explained by inhibition of cholesterol biosynthesis alone. It was determined that in addition to lipid profile improvement; statins also induce some cholesterol-independent, "pleiotropic", effects that contribute to atherosclerotic plaque stabilization.

Indeed, numerous experimental and clinical studies indicated that some of these effects might involve: restoring endothelial function, decreasing oxidative stress and decreasing vascular inflammation [5]. By improving endothelial cell function or restoration, inhibition of secretion of several matrix matalloproteinases (MMPs) by inflammatory cells, inhibition of proliferation and migration of SMC from media to intima, also decreasing vascular inflammation that consists to stability of atherosclerotic plaques [14].

Statins are among the most effective drugs in reducing the risk of stroke. An early meta-analysis [15] showed a significant reduction of stroke risk in patients receiving statins compared to placebo with an overall risk reduction of 31%. The JUPITER study further demonstrates that rosuvastatin significantly reduces the incidence of major cardiovascular events in apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C- reactive protein levels. Furthermore, the abrupt withdrawal of statin therapy may increase the risk of cardiovascular events and death because of rebound of inflammatory response [16].

Recent studies also show that prior or early use of statins may reduce the severity and improve the outcome of myocardial infarction, ischemic stroke, and intra-cerebral hemorrhage [17-20]. Consistent with previous research, the current study reveals that pre-treatment with statins may be associated with reduced clinical severity and favorable three-month outcome in patients with acute ischemic stroke [18, 19].

Although, pre-stroke treatment showed better outcome compared to placebo in animal models, the effects of pre-stroke statin use on clinical stroke severity and functional outcomes have been inconsistent [21]. In addition, previous studies have evaluated patients that underwent thrombolysis on admission, showing that statin therapy might be associated with slight increase risk of hemorrhage after thrombolysis [22].

According to this, it seems important to evaluate the effects of pre-statin use in stroke patients after excluding patients who received thrombolysis on admission. We suggest that this might explain our study results, showing clear benefit of pre-statin use on stroke outcome, with over 20% absolute risk reduction of in-hospital mortality rate compared to patients who were not receiving statin therapy.

Limitations: This is a retrospective study, which presents limitations. One limitation of our study is the lack of information about the dosage of the statins for most patients included. Another limitation is the lack of the data of the infarct size and also the lack of information for the presence and stability of the carotid atherosclerotic plaques, a well-known factor that might influence stroke recurrences among patients with acute ischemic stroke.

CONCLUSION

Patients that were using statin therapy showed lower in-hospital mortality rate after acute ischemic stroke. These protective effects of statins seem to be independent of the prior co morbidities and patients' clinical data on admission.

Competing interest: The authors declare that they have no competing interests.

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