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Impact of Different Types of Statins on Clinical Outcomes in Patients Hospitalized for Ischemic Heart Failure

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ABSTRACT

Introduction: The effect of statins on risk of heart failure (HF) hospitalization and lethal outcome remains dubious. **Aim:** To investigate whether statin therapy improves clinical outcomes in patients hospitalized for ischemic heart failure (HF), to compare the efficacy of lipophilic and hydrophilic statins and to investigate which statin subtype provides better survival and other outcome benefits. **Material and Methods:** Total amount of 155 patients in the study were admitted to the Clinic for Cardiology, Rheumatology and Vascular diseases in Clinical Center University of Sarajevo in the period from January 2014- December 2017. Inclusion criteria was HF caused by ischemic coronary artery disease upon admission. For each patient the following data were obtained: gender, age, comorbidities and medications on discharge. New York Heart Association (NYHA) class for heart failure was determined by physician evaluation and left ventricle ejection fraction (LVEF) was determined by echocardiography. The patients were followed for a period of two years. Outcome points were: rehospitalization, in-hospital death, mortality after 6 months, 1 year and 2 years. All-cause mortality included cardiovascular events or worsening heart failure. **Results:** Overall, 58.9% of HF patients received statin therapy, with 33.9% patients receiving atorvastatin and 25.0% rosuvastatin therapy. The most frequent rehospitalization was in patients without statin therapy (66.7%), followed by patients on rosuvastatin (64.1%), and atorvastatin (13.2%), with statistically significant difference $p = 0.001$ between the groups. Mortality after 6 months, 1 year and 2 years was the most frequent in patients without statin therapy with a statistically significant difference ($p = 0.001$). Progression of HF accounted for 31.7% of mortality in patients without statin therapy, 12.8% in patients on rosuvastatin therapy and 3.8% in patients on atorvastatin therapy ($p = 0.004$). **Conclusion:** Lipophilic statin therapy is associated with substantially better long-term outcomes in patients with HF.

Keywords: heart failure, treatment, statins.

1. INTRODUCTION

Heart failure (HF) is one of the major clinical priorities worldwide (1). Due to the aging of population, there is a higher incidence of HF requiring hospitalization. Statins are well studied and known therapy that lowers cardiovascular morbidity. Statin therapy has been shown to reduce the risk of HF (2). Statins are hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors and lipid-lowering drugs that are prescribed for various types of dyslipidemia. They also have beneficial effects in ischemic heart disease (3). Apart from the lowering of lipids, statins have shown additional effects such as the improvement of endothelial function, reduction of the inflammation and stabilization of coronary

artery thrombus plaque (4). Some cholesterol-independent effects of statins are mediated by inhibition of isoprenoids, which are lipid attachments for intracellular signalling molecules such as small Rho guanine triphosphate binding proteins, which explains their antioxidative effects (5). Pleiotropic effects also include vasodilation and decreased platelet aggregation, neurohormonal activation, and reversal of myocardial remodeling (6).

There are several possible mechanisms by which statin therapy may produce a benefit. Although the antiatherosclerotic effects of statins are well studied, several studies have demonstrated that statins reduce

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myocardial necrosis and preserve myocardial viability and ventricular function (7).

Statins are divided into hydrophilic and lipophilic groups based on their tissue selectivity. Presence or absence of polar parts of molecules on the statin structures influences their solubility and localisation which causes different metabolic effects (8). Lipophilic statins (atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin and pitavastatin) enter into cells by passive diffusion and are distributed in different tissues, in contrast to hydrophilic statins (rosuvastatin, pravastatin) which show greater hepatoselectivity (9).

Large randomized studies, namely the Controlled Rosuvastatin Multinational Study in Heart

Failure (CORONA) study and Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca (GISSI-HF)–evaluated whether statin therapy improves clinical outcomes in patients with HF, did not show significant outcome benefits in primary end points compared with placebo (10, 11). The CORONA study, however, showed significant reductions in hospitalizations and improved prognosis in patients with low N-terminal pro-B type natriuretic peptide levels on rosuvastatin therapy (10). Although some studies have suggested that statin therapy is associated with improved prognosis in patients with HF of both ischemic and non ischemic etiology, the role of statins in HF still remains unclear.

2. AIM

The aim of this study was to investigate whether statin therapy improves clinical outcomes in patients hospitalized for ischemic heart failure (HF), to compare the efficacy of lipophilic and hydrophilic statins and to investigate which statin subtype provides better survival and other outcome benefits.

3. MATERIAL AND METHODS

Study design and data collection

Hundred and fifty five (155) patients included in the study were admitted to the Clinic for cardiology, rheumatology and vascular diseases in Clinical Center University of Sarajevo in the period from January 2014–December 2017. Inclusion criteria was heart failure caused by ischemic coronary artery disease upon admission.

For each patient the following data were obtained: gender, age, history of myocardial infarction, previous PTCA or CABG, smoking status, comorbidities (arterial hypertension, diabetes mellitus, atrial fibrillation, previous stroke, chronic obstructive pulmonary disease, dyslipidemia, renal failure). New York Heart Association (NYHA) class for heart failure was determined by physician evaluation and left ventricle ejection fraction (LVEF) was determined by echocardiography. Medication used on discharge was also taken: beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), diuretic, digoxin, acetylsalicylic acid, dual antiplatelet therapy (DAPT), nitrates, oral anticoagulant (OAC), statin therapy (no statin, lipophilic statin- atorvastatin/simvastatin, or hydrophilic statin-rosuvastatin/pravastatin). The patients were followed for

a period of two years after the hospital admission for HF. The primary outcome was all-cause mortality. We examined also the effects of statins on cardiovascular mortality or worsening HF, and rehospitalization as secondary outcomes. Data for the study were abstracted from clinical records of HF patients from the Clinic of cardiology, rheumatology and vascular diseases. The institutional review board was waived as there was no need for informed consent for the administrative data.

Statistical analyses were performed, data were tabulated for continuous variables as means and standard deviation, and for categorical variables as absolute and relative frequencies. Statistical significance was $p \leq 0.05$.

4. RESULTS

One hundred and fifty five patients admitted with HF were included in the study. The mean age of the patients was 65.7 ± 6.4 years and the majority were male (63.2%). Comorbidities were quite common. All of the patients had a history of CAD. A large proportion of patients had a history of arterial hypertension (63.9%), atrial fibrillation (45.2%) and diabetes (29.0%). On admission, NYHA class I was present in 12.3 % of patients, while class II, class III and class IV was present in 30.3 %, 40.0 %, and 17.4 % patients respectively. Echocardiography was performed in all admitted patients. Of these, 50.9% had LVEF 30-39%, 42.6 % had ejection fractions 20-29% and 6.5% had ejection fraction <20% (Table 1).

Characteristic		Total, n (%)
Gender	Female	57 (36.8%)
	Male	98 (63.2%)
NYHA	NYHA I	19 (12.3%)
	NYHA II	47 (30.3%)
	NYHA III	62 (40%)
	NYHA IV	27 (17.4%)
LVEF	LVEF 30-39%	79 (51.0%)
	LVEF 20-29%	66 (42.6%)
	LVEF <20%	10 (6.5%)
Smoker	Yes	36 (23.2%)
Arterial hypertension	Yes	99 (63.9%)
Diabetes mellitus type 2	Yes	45 (29%)
Atrial fibrillation	Yes	70 (45.2%)
Coronary artery disease	Yes	155 (100%)
Status post myocardial infarction	Yes	101 (65.2%)
PTCA	Yes	58 (37.4%)
CABG	Yes	33 (21.2%)
Stroke	Yes	34 (21.9%)
COPB	Yes	39 (25.2%)
Renal failure	Yes	31 (20.0%)
Dyslipidemia	Yes	66 (42.6%)

Table 1. Patient baseline characteristics and comorbidities

Medication used during the hospitalization and recommended on discharge was as follows: beta-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), diuretic digoxin, acetylsalicylic acid, dual antiplatelet therapy (DAPT), nitrates, oral anticoagulant (OAC), statin therapy (no statin, lipophilic statin- atorvastatin/simvastatin, or hydrophilic

statin- rosuvastatin/pravastatin). Table 2. shows prescribed therapy for the patients admitted for HF.

Therapy		Total, n (%)
Beta blocker	Yes	116 (75.2%)
Angiotensin-converting enzyme inhibitors	Yes	130 (83.9%)
Diuretic	Yes	141 (91.0%)
Digoxin	Yes	67 (57.1%)
Acetylsalicylic acid	Yes	150 (96.8%)
Dual anti platelet therapy	Yes	77 (49.7%)
Nitrates	Yes	102 (65.8%)
Oral anticoagulant therapy	Yes	61 (39.4%)
Statin therapy	No statin	64 (41.0%)
	Atorvastatin	53 (33.9%)
	Rosuvastatin	39 (25.0%)

Table 2. Prescribed therapy for the admitted patients with HF.

Overall, 92 (58.9%) of HF patients without contraindications for statins received a statin therapy, with 53 (33.9%) patients receiving atorvastatin and 39 (25.0%) rosuvastatin therapy. The most frequent rehospitalization was observed in patients without statin therapy (66.7%), followed by patients on rosuvastatin (64.1%), and atorvastatin (13.2%), with statistically significant difference $p=0.001$ between the groups. Regarding the choice of therapy, significant difference was found in patients with atorvastatin, in the sense that atorvastatin therapy significantly reduced the number of rehospitalization ($p < 0.001$).

Mortality after 6 months was the most frequent in patients without statin therapy (15.4%), followed by patients on rosuvastatin (1.92%) and 0.6% on atorvastatin. Mortality after 6 months was the most frequent in patients without statin therapy (16.6%), followed by patients on rosuvastatin (3.2%) and 1.3% on atorvastatin.

Mortality after two years was 24.4% for patients without statin therapy, followed by rosuvastatin (6.4%) and 2.6% for atorvastatin. A statistically significant difference was found between patients without statin therapy and those on rosuvastatin and atorvastatin therapy ($p=0.001$). Stroke was the most frequent in patients without statin therapy (20.7%), followed by rosuvastatin (12.8%) and 5.6% atorvastatin ($p=0.001$). Progression of HF accounted for 31.7% of mortality in patients with out statin therapy, 12.8% in patients on rosuvastatin therapy and 3.8% in patients on atorvastatin therapy ($p=0.004$). These findings are summarized in Table 3.

5. DISCUSSION

Although treatments such as angiotensin-converting enzyme inhibitors, beta-adrenergic antagonists and implantable cardioverter-defibrillators have significantly improved outcomes for patients suffering from HF, mor-

tality remains high at around 50% after 5 years from initial diagnosis (12).

In our study, total mortality for patients with HF after two years was 33.3%. Out of those, 2-year mortality was 24.4% for patients without statin therapy, followed by rosuvastatin (6.4%) and 2.6% for atorvastatin. Progression of HF accounted for 31.7% of mortality in patients without statin therapy, 12.8% in patients on rosuvastatin therapy and 3.8% in patients on atorvastatin therapy. In a study by Alehagen et al, use of statins was associated with reduced all-cause mortality, cardiovascular mortality, HF hospitalization, and the combined outcome of all-cause mortality and cardiovascular hospitalization (13).

In a large meta- analysis by Preiss et al, statin use showed a significant reduction in non-fatal MI and a significant but modest reduction in HF hospitalizations (14). Additional observational studies in HF suggest risk reduction for all-cause mortality associated with statin use (15).

In our study, NYHA class III was present in 40.0% of admitted patients, and NYHA class IV in 17.4% patients,

		No statin	Atorvastatin	Rosuvastatin	Total	X ²	P
Rehospitalisation	No	21 (33.3%)	46 (86.8%)	14 (35.9%)	81 (52.3%)	42.065	0.001
	Yes	42 (66.7%)	7 (13.2%)	25 (64.1%)	74 (47.7%)		
Mortality period	6months	24 (15.4%)	1 (0.6%)	3 (1.92%)	28 (17.9%)	12.256	0.001
	1year	26 (16.6%)	2 (1.3%)	5 (3.2%)	33 (21.2%)		
	2years	38 (24.4%)	4 (2.6%)	10 (6.4%)	52 (33.3%)		
Mortality total	No	26 (16.6%)	49 (31.4%)	29 (18.5%)	104 (66.7%)	26.926	0.001
	Yes	38 (24.4%)	4 (2.6%)	10 (6.4%)	52 (33.3%)		
CV	No	45 (70.3%)	50 (94.3%)	34 (87.2%)	129 (82.7%)	14.976	0.001
	Yes	19 (29.7%)	3 (5.6%)	5 (12.8%)	27 (17.3%)		
HF	No	43 (68.3%)	20 (96.2%)	34 (87.2%)	128 (82.6%)	8.226	0.004
	Yes	20 (31.7%)	2 (3.8%)	5 (12.8%)	27 (17.4%)		

Table 3. Outcomes for patients with HF with regard to statin therapy

which means that almost 60% of patients in our study had severe HF. Statin therapy was associated with a 48% lower risk of death in the Mozaffarian et al study, which included patients with severe HF of ischemic and non ischemic origins (16). In our study, the mean age of the patients was 65.7 years. Statin therapy is associated with better long-term mortality in older patients with HF (17).

Both the American Heart Association and the European Society of Cardiology guidelines on treatment of ischemic heart disease state that statin treatment is recommended and they do not make exceptions for or qualify recommendations based on HF with reduced ejection fraction (18, 19). A closer examination of the previous trials in the meta-analyses suggests that the researchers did not compare effects of statin types used in the individual studies but treated them as if they were a uniform class of drugs.

Still there are some trials offering different results. For example, a study by Sakamoto et al found that hydrophilic pravastatin is superior to lipophilic statins in preventing new Q-wave appearance and reducing cardiovascular events in normocholesterolemic patients (20). However, in a study of patients with coronary artery disease, no

significant difference in the incidence of all-cause events was observed with the two types of statins (21). Lipophilic atorvastatin was found to be superior to hydrophilic rosuvastatin in improving cardiac sympathetic nerve activity and reducing plasma NT-proBNP levels in HF patients (22). Lipophilic statin treatment was associated with reduced mortality outcomes compared with no statin treatment in the study by Bonsu et al. Among the statins, rosuvastatin is the most potent regarding lipid-lowering effects (23). Lipophilic statins have very high uptake in myocardial tissue, whereas hydrophilic statins have very low uptake (24). Lipophilic statins improve cardiac function and reduce inflammation and show significant reductions in HF hospitalizations, all-cause and cardiovascular mortality compared with hydrophilic statin (rosuvastatin) treatment (25, 26).

A study by Liu et al found a significant effect of lipophilic statins on major outcomes in patients with HF (27). Results of our study are consistent with a large body of evidence supporting these agents in patients with HF, regardless of the presence or absence of atherosclerosis or cholesterol levels. In the end, we might be closer to the conclusion that lipophilic but not hydrophilic statins may benefit patients with HF (28).

We have included NYHA classification of patients upon admission, whereas many previous studies did not report baseline status of heart failure in studied patients. Our study raises important questions and sheds light on the use of different types of statins and associations with outcomes.

6. CONCLUSION

Our data demonstrate that lipophilic statin therapy is associated with better long-term survival in patients with HF. Rates of rehospitalization, and mortality rates after 6 months, 1 year and 2 years were significantly lower in patients receiving atorvastatin compared to rosuvastatin or no-statin treatment. Given the high mortality rates associated with HF, lipophilic statin therapy in these patients could have important public health implications.

- **Authors' contributions:** Conception and design: FZ, AG, AD; Acquisition, analysis and interpretation of data: FZ, AG, AI; Drafting the article AR; Revising it critically for intellectual content: FZ, AR, AD. Approved final version of the manuscript: FZ, MV.
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