Original Research Article

Impact of Rosuvastatin in Systolic Heart Failure among elderly patients- A randomized control clinical trial

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Abstract

Background: Patients with systolic heart failure have generally been excluded from statin trials. Acute coronary events are uncommon in this population, and statins have theoretical risks in these patients.

Objective: To evaluate the impact of Rosuvastatin in patient of Systolic Heart Failure.

Materials and methods: A randomized controlled clinical trial was conducted among 500 patients of at least 60 years of age with New York Heart Association class II, III, or IV ischemic, systolic heart failure. The patients were randomly allocated to accept 10 mg of rosuvastatin or placebo per day. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Epi-info was used for analysis.

Results: As compared with the placebo group, patients in the rosuvastatin group had decreased levels of low-density lipoprotein cholesterol (P<0.001) and of high-sensitivity C-reactive (P<0.001). During a median follow-up of 30 months, the primary outcome occurred in 500 patients in the rosuvastatin group and 700 in the placebo group (hazard ratio, 0.92; 95% confidence interval (CI), 0.83 to 1.02; P = 0.12. There were no significant differences between the two groups in the coronary outcome or death from cardiovascular causes. No excessive episodes of muscle-related or other adverse events occurred in the rosuvastatin group.

Conclusions: Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic heart failure, although the drug did reduce the number of cardiovascular hospitalizations.

Key words

Rosuvastatin, Systolic Heart failure, Cholesterol, Myocardial infarction, Randomized control trial.

Introduction

Although a high percentage of patients with heart failure caused by left ventricular systolic dysfunction have coronary artery disease, described rates of myocardial infarction have been low in previous clinical trials [1-4]. Therefore, the potential value of statins has been interrogated because their advantage is largely due to the prevention of myocardial infarction. In addition, in this population of patients, low levels of total cholesterol are common and are linked with worse outcomes [1-6]. Lipoproteins may remove endotoxins that enter the circulation through the intestinal wall, which may be leaky in patients with heart failure [7]. Statins could also be detrimental in these patients because they reduce the synthesis of coenzyme Q10 (a cofactor in the mitochondrial electron-transport chain and an antioxidant) and the production of selenoprotein, which could lead to skeletal and cardiac myopathy [8. 9]. The pleiotropic actions of statins, including improvement of endothelial function and anti-inflammatory activity, could be of benefit in heart failure. Many nonrandomized studies have suggested that the use of statins is associated with better outcomes in patients with heart failure, and several small, prospective studies in patients with ischemic and non-ischemic heart failure [10, 11] have shown beneficial effects on left ventricular function and clinical status. So, the rationale behind the study was to determine the beneficial effect of Rosuvastatin to reduce morbidity in heart failure.

Materials and methods

Study Design: Randomized Controlled clinical Trial

Study Settings: Patients admitted in emergency of tertiary care hospital.

Study Duration: May 2016 to April 2018 (2 years)

Sampling Technique: Randomization

Sample Size: A total of 500 patients were enrolled during the period of 2 years.

Inclusion Criteria: Patients who were at least 60 years of age and who had chronic New York Heart Association (NYHA) class II, III, or IV heart failure of ischemic cause and an ejection fraction of no more than 40% (no more than 35% in patients in NYHA class II) were included in the study.

Exclusion Criteria: Previous statin-induced myopathy or hypersensitivity reaction; decompensated heart failure or a need for inotropic therapy; myocardial infarction within the past 6 months; unstable angina or stroke within the past 3 months; percutaneous coronary intervention (PCI), coronary-artery bypass grafting (CABG), previous or planned heart transplantation; clinically significant, uncorrected primary valvular heart disease or a malfunctioning prosthetic valve; hypertrophic cardiomyopathy were excluded.

Ethical Consideration: The study was approved by Institutional Ethics Committee. (Clinical trial registry number- NCT006310).

Consent Type: Informed Consent

Methodology

Eligible patients were treated with single-blind placebo for 2 to 4 weeks before randomization to demonstrate compliance. Randomization was based on an optimal assignment procedure with a random element included. Patients were randomly assigned to receive 10 mg of rosuvastatin or matching placebo once daily. All investigators who related to the trial were unaware of study-group assignments except for those on the data and safety monitoring board. Patients were seen at 6 weeks and 3 months after randomization and every 3 months thereafter. NYHA class was assessed by investigators at each visit. Hospitalization was defined as care at an acute hospital lasting for at least 24 hours. Hospitalization for heart failure required documentation that worsening heart failure was

the principal reason for hospitalization, and if competing reasons were judged to be of equal importance, heart failure received preference. For all patients, a single cause of death or hospitalization was stated. All serious adverse events were adjudicated by an independent committee to identify study outcomes according to prespecified definitions.

Statistical Analysis

All data were analyzed in the intention-to-treat population. The main analyses were performed with the use of the log-rank test for the comparison of the study groups and an unadjusted Cox proportional-hazards model to calculate hazard ratios and 95% confidence intervals. P- value of <0.05 was considered statistically significant.

Results

As per **Table – 1**, the patients were divided into 2 groups, placebo and those on rosuvastatin based on similar characteristics done by matching. Out of 500 patients each group has 250 patients. The mean age in placebo group was 67 years while in statin group was 69 years which was not significant. This signifies both the groups were comparable. BMI was on overweight side in the both the groups. Smoking was also common nearly 70% in both groups. Among the clinical parameter's ejection fraction, total cholesterol, triglycerides and hs-CRP were non-significant (p>0.05).

Table – 1: Demographic profile and Clinical Parameters of the patients (N=500).

Parameters	Placebo (N=250)	Rosuvastatin (N=250)	p-value
Age (years)	67±8	69±7	0.87
NYHA			
II	90	100	
III	120	110	
IV	40	40	
Ejection fraction	0.30±0.06	0.31±0.07	0.94
Body Mass Index	26±3.7	27±4.3	0.51
Smoking	200	210	0.41
Total cholesterol	5.4±1.03	5.36±1.11	0.81
Triglycerides	1.89±1.11	2.11±1.21	0.41
Hs-CRP	3.5±1.6	3.6±1.7	0.68

As per **Table – 2**, For patients in the rosuvastatin group, the hazard ratio for the combined primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke) was 0.88 (95% CI, 0.83 to 1.02) for death from any cause, the hazard ratio was 0.91 (95% CI, 0.88 to 1.10) and for fatal event (including sudden death, fatal myocardial infarction, stroke hazard ratio was 0.96 (95% CI, 0.93-1.10) for non-fatal events the ratio was 0.81 (95% CI, 0.79-0.93). p-value was not significant in any outcome and event.

Discussion

Despite having favourable effects on lipids (a reduction in levels of LDL cholesterol and triglycerides and an increase in the level of HDL cholesterol) and on high-sensitivity C-reactive protein, a daily dose of 10 mg of rosuvastatin did not reduce the primary composite cardiovascular outcome or death from any cause when the drug was added to extensive background pharmacologic therapy in this previously unstudied population of older patients with moderate to severe ischemic systolic heart failure but has reduced the number of hospitalization in patients [10, 11]. Nonfatal myocardial infarction and stroke were relatively uncommon in this population, and death from cardiovascular causes

accounted for most primary events. Rosuvastatin had no effect on the rates of death from cardiovascular causes or sudden death. In previous trials involving different populations of patients, statins reduced the rate of sudden death, probably by preventing the rupture of coronary plaques and preventing myocardial ischemia and infarction [12, 13, 14]. We found that rosuvastatin reduced the total number of hospitalizations for heart failure, perhaps because the drug prevented the development of acute coronary disease that would have contributed to such episodes. An alternative explanation is that rosuvastatin reduced myocardial ischemia by improving endothelial or microvascular function or by a direct or indirect effect on cardiomyocytes, through the suggested pleiotropic effects of these drugs [1-6].

Table – 2: Cardiovascular outcomes and Events in patients.

Parameters	Placebo (N=250)	Rosuvastatin (N=250)	Hazard Ratio	p-value
Outcome				
Primary	140	150	0.88 (0.83-1.02)	0.11
Death due to cardiovascular cause	100	110		
Non-fatal MI	40	40		
Secondary	110	100	0.91 (0.88-1.10)	0.21
Any heart event	80	90		
Any cause	30	10		
Fatal Events				
Sudden death	110	100	0.96 (0.93-1.20)	0.11
MI	10	20		
Stroke	32	45		
Aortic aneurysm	5	0		
Non-Fatal Event				
CABG	28	30	0.81 (0.79-0.93)	0.21
PCI	60	56		
Unstable angina	60	55		

Conclusion

In the present study, daily treatment with 10 mg of rosuvastatin did not reduce the composite outcome of death from cardiovascular causes. However, rosuvastatin reduced the number of hospitalizations for cardiovascular causes, in addition to effectively reducing levels of LDL cholesterol and high-sensitivity C-reactive protein.

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