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Original Research Article

Influence of Lipophilic Statins Treatment in Heart Failure

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Abstract

Background: Studies on statins have not shown any appreciable improvements in heart failure outcomes (HF). Studies might not, however, necessarily be generalizable. Comparing the incidence of heart failure (HF) among initiators of hydrophilic and lipophilic statins was the goal.

Methods: We discovered new initiators of hydrophilic or lipophilic statins data gathered from our hospital situated at Bhubaneshwar. Following a one-year waiting period following the start of statin therapy, follow-up for the primary endpoint of incident HF started. 1 inpatient or 2 outpatient diagnosis codes for HF and the usage of loop diuretics were considered the outcome. Confounding was taken into consideration using propensity scores (PS). To produce dose-adjusted effect estimates, hazard ratios (HR) for incident HF were first estimated separately for low- and high-intensity statin users.

Results: All 204 individuals who were eligible to start taking statins did so (hydrophilic and lipophilic statins). The average age was 58 years, and 23% had diabetes mellitus and 40% had hypertension. There were 120 patients in the high-intensity statin group and 84 patients in the low-intensity statin group following PS matching. There were 89 cases of incident HF (95 percent confidence interval [CI] 4.4-4.6) after a median follow-up of 25 days. For hydrophilic versus lipophilic statins, the unadjusted HR for the risk of HF was 0.77 (95% CI 0.76-0.79), and the pooled adjusted HR for incident HF after PS matching was 0.94 (95% CI 0.90-0.98). For hydrophilic versus lipophilic statins, the HR for incident HF was 1.06 (95 percent CI 1.00–1.12) for the low-intensity statin group and 0.82 (95 percent CI 0.78–0.87) for the high-intensity statin group. When comparing rosuvastatin and atorvastatin, as well as those who were younger and older than 65 years old, a similar tendency persisted in subgroup analyses.

Conclusion: When compared to lipophilic statins in this observational cohort analysis, hydrophilic statins were associated with a moderate risk reduction in incident HF. It is advised that future studies replicate similar findings in various populations.

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Introduction

Heart failure (HF) has elevated to a top clinical and public health concern on a global scale. Increased oxidative stress [1-3] and inflammation brought on by the activation of cell adhesion molecules, endothelial cells, cardiac myocytes, and cardiac autoantibodies made by activated macrophages [1-6] are two characteristics of HF. The development of HF is directly linked to ventricular remodelling, which

takes the form of ventricular dilatation and myocyte hypertrophy. In order to reduce the chance of an incidence of HF, it is crucial to address preventative and risk factors.

Statins continue to be essential for avoiding HF because they are known to lower cardiovascular events. Statins are medications that lower blood cholesterol and are used all over the world to stop cardiovascular illnesses [7, 8, 9]. Regardless of a patient's cholesterol level, statins play a significant role in the primary and secondary prevention of coronary artery disease [10]. Additionally, there is solid evidence in favour of statins' ability to prevent new cases of heart failure (HF). Because of several pleiotropic (i.e., non-cholesterol-lowering) effects, there have been some discussions in more recent times about the possible benefits of statins for the treatment of established heart failure (HF) [11].

Clinical investigations with small sample numbers have shown the beneficial effects of atorvastatin (lipophilic), including improvements in heart function and all-cause mortality in individuals with HF [12]. The Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA) and Gruppo Italiano per lo Studio della Sopravvivenza nell' Insufficienza cardiaca (GISSI-HF), two sizable randomised controlled trials (RCT) on patients with HF, found no difference in the primary outcome when compared to placebo treatment [13]. Following CORONA and GISSI-HF, other investigations showed that statin medication improved clinical outcomes in HF [14]. Although these studies lacked randomization, they did raise the possibility that lipophilic statins would be more effective than hydrophilic statins in the treatment of HF. In indirect comparison meta-analyses of RCTs, lipophilic statin medication was found to significantly reduce hospitalizations for worsening HF, all-cause mortality, and cardiovascular mortality in contrast to hydrophilic statin treatment.

However, no prior investigation has compared the impact of lipophilic and hydrophilic statin medication on the likelihood of developing HF. It is noteworthy that both studies analysed outcomes in individuals who had already been diagnosed with HF. In order to examine the risk of incident HF between hydrophilic and lipophilic statins, we created a sizable cohort study using health care data.

Methods

Study Population

A longitudinal cohort of newly diagnosed HF patients of age ≥18 who were hospitalised between three years was used for the study. The modified Framingham criteria and echocardiographic data were used to determine the presence of HF. Patients who were hospitalised for heart failure as their primary reason for admission or who had the condition discovered while they were there were eligible for the trial. The index admission was the first admission for HF. From the index admission's date of release to the time of all-cause, cardiovascular, or worsening heart failure mortality; loss to follow-up; or the study's conclusion, the follow-up period was in effect.

Covariates

During the 180-day pre-index period, covariates were assessed. Hyperlipidemia, Hypertension, PVD, CVD, atrial fibrillation, conduction disorders, cerebrovascular disease, dementia, warfarin, liver disease, diabetes, bipolar disorder, COPD, depression, obesity, HIV, anemia, were included as covariates.

Statistical Analysis:

R statistical software version 3.2.4 was utilised for data analysis (R Foundation for Statistical Computing, Vienna, Austria). For categorical and continuous variables, respectively, we looked at bivariate

relationships between predictor variables and results using the v2 and t-tests. To investigate the impact of statin medication on HF mortality outcomes, two distinct methodologies were applied. First, a time-dependent Cox model was created, and then, using inverse probability weights, a marginal structural Cox model was built. Multiple imputation was used to address missing data for variables based on the pattern for all available observations. The level of significance for each analysis was set at 0.05, and all reported P values are two-sided.

Results

All 204 individuals who were eligible to start taking statins did so (hydrophilic and lipophilic statins). There were 84 (46.1%) patients in the low-intensity statin group and 120 (53.9%) patients in the high-intensity statin group after the propensity scores within the dose strata were matched. Table 1 displays the patient characteristics of the PS-matched cohorts by statin lipophilicity and intensity. Patients averaged 58 years old, and 40% of them were diagnosed with hypertension. About 23% of patients had a history of diabetes, and the majority of patients had hyperlipidemia.

	High dose statins		Low dose statins	
	lipophilic	hydrophilic	lipophilic	hydrophilic
Age, years (mean ± SD)	57.0±10.9	57.0±11.0	58.6±11.9	58.5±11.6
Men	54	66	42	42
Cardiac conditions and risk factors				
Hyperlipidemia	8	13	7	5
Hypertension	8	11	8	4
PVD	12	13	9	8
CVDa	9	10	6	4
Atrial fibrillation	5	7	8	3
Conduction disorders	7	9	5	6
Cerebrovascular disease	8	9	4	7
Dementia	19	14	9	6
Warfarin	19	17	9	9
Liver disease	17	11	5	14
Diabetes	12	6	3	11
Bipolar disorder	10	9	4	9
COPD	4	7	7	15
Depression	23	4	16	8
Obesity	22	23	10	11
HIV	21	2	12	5
Anemia	14	9	19	13
Calcium-channel blockers	12	5	4	1
Renal dysfunction	13	27	6	15
ARBs	9	8	4	4
Novel oral anticoagulants	7	16	3	8
β-Blockers	10	16	6	9
ACE inhibitors	9	19	6	13
Antiplatelet medication	11	5	7	2
Other hyperlipidemias	8	12	6	4
Malnutrition	7	14	2	8
Health care utilization				

Emergency department visits	6	11	5	2
Non-CV hospitalizations	21	43	9	5
CV hospitalizations	18	27	13	14

Incidence rates for HF were 3.8 (95% confidence interval [CI] 3.7-4.0) for hydrophilic statin exposure and 4.6 (95% CI 4.5-4.8) for lipophilic statin exposure in the PS-matched cohorts of high-intensity groups. The incidence rates for the low-intensity hydrophilic and lipophilic statin-exposed groups in the PS-matched cohort were 5.0 (95% CI 4.8-5.2) and 4.7 (95% CI 4.5-4.9), respectively. After combining estimates from PS-matched low and high intensity cohorts, the incidence rates for HF (per 1,000 person years) dependent on statin lipophilicity can be seen. For hydrophilic versus lipophilic statins, the unadjusted HR for risk of HF was 0.79 (95 percent CI 0.77-0.82). The PS-matched HR for the incidence of incident HF for the low-dose statin group was 1.06 (95% CI 1.00-1.12) and for the high-dose statin group was 0.82 (95% CI 0.78-0.87). In comparison to lipophilic statins, the pooled HR for incident HF was 0.94 (95 percent CI 0.90-0.98).

Discussion

Patients on hydrophilic statins had a slightly lower risk of incident HF than those taking lipophilic statins, according to our research. This result was primarily caused by a significant reduction in the incidence of HF among individuals who had previously started using high-dose hydrophilic statins. The estimates held true across a variety of sensitivity analyses in which we changed the follow-up strategy and duration of the baseline period in the highdose statin group. They also held true for subgroup analyses in older patients and women [15, 16]. At 3 years of follow-up, the HR, however, was not significant in the ITT analysis; nonetheless, it was significant at 5 years of follow-up. Given that clinical HF takes time to emerge, this is not surprising.

Since most occurrences of HF are caused by CAD and statins lessen the risk and development of CAD, it makes sense that they may reduce the risk of developing HF [20]. Because of their varied solubilities and pleiotropic effects, lipophilic and hydrophilic statins may function in distinct ways. While hydrophilic statins are primarily liver-specific and need active protein transport, lipophilic statins are dispersed throughout the body and passively diffuse into cells [17]. Additionally, we discovered that hydrophilic statins decreased the incidence of HF in people ≥65. Multiple organic processes are impacted by ageing, which can lead to increased oxidative stress, the buildup of dense bodies (lipofusin) in liver cells, a decrease in the number of mitrochondrial cells, and malfunction of these cells [18, 19, 20]. While some research suggests that individuals with HF on lipophilic statins have a lower incidence of adverse events such CV events, hospitalisation, and biomarker elevation (like BNP), other research has indicated the opposite.

According to some data, lipophilic statins may have an impact on the mineralocorticoid pathway, which may result in HF and hypertension. According to a recent study, taking statins lowered aldosterone output in the blood and 24-h urine by roughly 30%. In cells exposed to lipophilic (but not hydrophilic) statins, aldosterone secretion after stimulation with potassium and angiotensin II was reduced, but corticosteroid secretion remained unaltered [21-25]. However, statins may also lower blood pressure via reducing oxidative stress, renin-angiotensin-aldosterone system-dependent inflammation, or the expression of angiotensin II receptors [26, 27]. These

outcomes could be unique to hydrophilic statins.

In mice with hypertension or myocardial infarction, statins have also been demonstrated to lessen cardiac remodelling [28, 29]. The effects of cytokines and glucose homeostasis may also make hydrophilic statins less likely to cause heart failure. In order to increase adiponectin and lower HbA1c, for example, rosuvastatin was found to be superior to the lipophilic statin simvastatin [30, 31]. It indicates that the relationship between statin lipophilicity and HF risk is complicated, and additional research is required to clarify these pathways. The negative effects of statins may also be influenced by their lipophilicity. For instance, muscle cells are more thoroughly penetrated by lipophilic statins than by hydrophilic statins. As a result, they might be more prone to harm myoblasts and cause rhabdomyolysis. [32]

Conclusion

When compared to lipophilic statins, treatment with hydrophilic statins was linked to a slightly lower risk of incident HF. Only those starting high-intensity hydrophilic statins, primarily rosuvastatin, had a lower risk. To corroborate these findings, studies that replicate similar results in different populations are advised.

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