Are Statins Beneficial for Patients With Heart Failure?

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ABSTRACT

There is a tremendous amount of evidence about the beneficial roles of statins, as related to primary and secondary prevention, for patients with ischemic heart disease. Many cardiologists are prescribing these drugs to their patients regardless of the left ventricular systolic function, and especially for patients with old myocardial infarction. After the report on the post-hoc analysis of the Scandinavian Simvastatin Survival Study, there have been many reports about the roles of statins for the patients with heart failure from ischemic or non-ischemic etiologies. But most of these reports were non-randomized, observational, post-hoc subgroup analyses and small prospective short term studies, and the power of the evidence was too weak to set a guideline for statin therapy in patients with heart failure. The conclusions of the previous reports were that two large prospective randomized trials might shed light on choosing to administer statins. Last November, the COntrolled ROsvastatin multiNAtional trial in heart failure (CORONA) study was presented and many cardiologists believed that this study did not resolve the lack of evidence for the current practice of administering statins to heart failure patients with ischemic heart disease, but it proved the safety of administering 10 mg of rosuvastatin. So, we review the potential benefits of statins, beyond the cholesterol lowering effects in patients with heart failure, and we will reexamine the use of statins in patients with heart failure after the CORONA study. (Korean Circ J 2008; 38:185-190)

KEY WORDS: Statins; Heart failure.

Introduction

Heart failure is associated with increased morbidity and mortality despite of the advances in pharmacological and interventional therapy, including angiotensin converting enzyme inhibitor, beta-adrenergic receptor blocker, aldosterone inhibitor and cardiac resynchronization therapy.1-3) The advances of heart failure treatment have come from the improved understanding of the pathophysiology related with the development and progression of heart disease. According to previous reports, the activated sympathetic nervous system, inflammation and endothelial dysfunction are important factors in the continuum of heart failure, regardless of the presence of coronary heart disease.4) HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors (statins) have some effects on above mentioned factors, including plaque stabilization, and many experimental and clinical studies have reported on their promising therapeutic benefits for patients with heart failure.

As determined from the large clinical trials on congestive heart failure, only 1-2% of the patients with congestive heart failure take statins in the case of their heart disease being combined with hypercholesterolemia. From the currently available practice guidelines, statins should be prescribed for established coronary heart disease regardless of cholesterol level. This guideline is from previous reports that enrolled patients who had a high risk of heart disease or established coronary heart disease, including 0-10% of patients with heart failure.5) Yet some patients with ischemic heart disease receive statins from their cardiologists without the patients’ left ventricular systolic or diastolic functions being considered. There is a variety of evidence for the beneficial role of statins in heart failure with various results from the subgroup analysis of the previous studies, the large observational studies and small prospective non-randomized clinical trials.6-10) The COntrolled ROsvastatin multiNAtional trial in heart failure (CORONA)12) is the first prospective large randomized placebo-controlled study that focused on elderly patients with ischemic heart failure. Many doctors read this recently published report with great concern
because they believed the study could resolve the lack of evidence for the current treatment of heart failure patients who are with or without ischemic heart disease. But the weak results compared to the anticipated outcomes created some questions and this caused physicians to be confused in their clinical practices.

It is time to reexamine the previous reports of using statins in patients with heart failure after the CORONA study and physicians must decide whether to change the current treatment of older patients with systolic heart failure. In this article, we review the previous evidence and we discuss the current role of statins in patients with heart failure for preventing cardiovascular events.

Potential Benefits of Statins in Patients With Heart Failure

Anti-atherosclerotic effects

The cumulative damage to the myocardium that’s due to the ischemic events from coronary artery disease is the major cause of morbidity and mortality in patients with ischemic heart failure, and also in the patients with non-ischemic heart failure. From the autopsy data, half of the sudden cardiac deaths in heart failure patients are due to acute coronary events. It is well established that statins decrease the mortality, occurrence and recurrence of myocardial infarction and statins aid revascularization of the coronary arteries in patients with known risk factors or high risk of ischemic heart disease. There is much evidence for the anti-ischemic effects of statins as related with plaque stabilization, which is due to changes of the plaque composition and anti-inflammation, reducing the size of necrosis and the myocardial remodeling, and improving the coronary endothelial function and formation of new vessels.

Anti-inflammation

Many pro-inflammatory cytokines and adhesion molecules are increased in heart failure and these markers are associated with the development and progression of heart failure. The role of statins in inflammation is related to the inhibition of mevalonate synthesis, which causes favorable actions on nitric oxide (NO) synthesis, plasminogen activator inhibitor-1 (PAI-1), and nuclear factor κB. The initial step for inflammation is the activation and increased number of adhesion molecules such as intracellular adhesion molecule 1 (ICAM-1) and vascular cellular adhesion molecule 1 (VCAM-1), and there have been in vitro and in vivo reports on statins reducing these molecules’ effects.

The anti-inflammatory effects of statins are effective regardless of the changes of the cholesterol level. Small sized randomized studies proved the role of various statins on the inflammation in patients with heart failure. From the reports of simvastatin (5 to 10 mg) by Node et al., cerivastatin by Hasegawa et al. (1 mg/kg/d) and Laufs et al. (0.4 mg/kg/d), and atorvastatin (10 mg) by Tousoulis et al., various pro-inflammatory cytokines such as tumor necrotic factor alpha (TNF-α), interleukins (IL) 1 and 6, C-reactive protein (CRP), B-type natriuretic peptide (BNP) and PAI-1 were reduced as early as 4 weeks after administering statins in patients with heart failure.

The beneficial effects of statins could extend to the patients with non-ischemic heart failure. Sola et al. examined the effects of atorvastatin (20 mg/day) on the left ventricular systolic function and the serum markers of inflammation in 108 patients with non-ischemic heart failure and their left ventricular ejection fraction was ≤ 35% for 12 months. Compared with placebo, atorvastatin improved the left ventricular systolic function (0.33 ± 0.05 to 0.37 ± 0.04, p = 0.01) and it reduced the levels of high sensitivity C-reactive protein, interleukin-6 and tumor necrotic factor-alpha receptor II. Even though statins have many beneficial effects for inflammation, the relationship between statins, inflammation and the final clinical benefits should be proven.

Endothelial function

The imbalance between vasodilator NO production and vasoconstrictor endothelin-1 production induces progression of heart failure, regardless of the etiologies. There is a vicious cycle of endothelial function and nitric oxide in heart failure. A decrease in nitric oxide production by endothelial cell induced atherosclerosis and subsequent worsening of the endothelial dysfunction. The data related with the potential mechanisms of endothelial dysfunction in heart failure has revealed that statins might have beneficial roles in restoring endothelial dysfunction.

Statins improve endothelial function, independent of the changes of the cholesterol level, and mainly in a NO dependent manner. Several reports suggest that statins have roles in eNOS (endothelial nitric oxide synthase) mRNA stabilization and protein kinase Akt activation for eNOS activation, and that statins inhibit eNOS inhibitors such as cavelin and oxygen free radicals, and Rho GTPase. Other additional mechanisms for the beneficial roles of statins on endothelial function are decreased oxidative stress, inhibited inflammation and increased extracellular superoxide dismutase activities.

Finally, statins reduce the endothelin-1 (ET-1) level by inhibition of the pre-pro ET-1 mRNA expression and inhibition of isoprenoids such as Rho, Rac and Ras, which are required for the posttranslational modification. Inhibition of Rho activation by statins increases NO production and reduces the ET-1 expression (Table 1).
Thrombosis

From the reports based on autopsy and clinical trials, the patients with chronic heart failure have a high risk of thromboembolism at the rate of 1-3% per year and a high risk of acute coronary syndrome regardless of the etiology. The probable mechanisms of this hypercoagulable status are stasis of blood flow and increased P-selectin, β-thromboglobulin and osteonectin, which are activators of platelets. Statins have roles in reducing thrombogenicity due to decreased P-selectin expression, enhanced NO bioavailability and decreased antithrombin-III, protein C and factor V. But the guideline do not recommend antithrombotics in heart failure patients due to the lack of evidence, except for patients with atrial fibrillation and who have a previous embolic history with uncertain mechanisms.

Neurohormonal activation

The knowledge of neurohormonal activation in the pathophysiology of chronic heart failure has led to great improvements in treatment. The main neurohormonal systems related with the disease severity and mortality are the renin angiotensin aldosterone systems and the sympathetic nervous system. The activity of these systems is expressed via the heart rate variability, the heart rate recovery after exercise and the plasma norepinephrine level. The proposed mechanisms for statins’ beneficial effects on these indices are down regulation of both angiotensin I receptor in smooth muscle cells and the sympathetic activity, and modification of the endothelin-1 receptor. Statins also have a protective role against arrhythmic actions such as atrial fibrillation and ventricular arrhythmia.

The Optimal trials in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) trial proved the additive effects of statin and beta-blocker in 5,477 patients with myocardial infarction and heart failure. The 1-year reduction in mortality by statin was only 26%, that of beta-blocker was only 31%, and a combination of both statin and beta-blocker reduced the mortality by 48%.

Myocardial function, remodeling and apoptosis

Myocardial remodeling is described as hypertrophy and dilatation, and this remodeling is an important pathophysiological process in the development and progression of heart failure, and the resulting left ventricular (LV) dysfunction is a powerful predictor of mortality. There is much evidence about the beneficial effects of various statins on the remodeling and LV dysfunction in patients with acute myocardial infarction and chronic heart failure with ischemic or non-ischemic etiologies. It seems that statins can reduce mortality in all kinds of heart failure, and especially in acute ischemic heart failure like myocardial infarction.

There are some models for heart failure according to different etiologies, such as the left anterior descending coronary artery ligation model for ischemia and the pressure overload model, the vasoconstrictor overexpression model or the tachycardia model for the non-ischemia model. Many postulated mechanisms have been reported from these models (Table 2). Statins could decrease the activity of matrix metalloproteinase (MMPs), which are increased in heart failure and they are related with the progression of heart failure. As described previously, statins have a role for decreasing isoprenoids, Ras, Rho and Rac, and these are involved in inflammation and LV hypertrophy. The role for improving endothelial function via increasing the eNOS expression, inhibiting the renin angiotensin aldosterone system and angiotensin II signaling could be another mechanism of statins’ effects on the remodeling after myocardial infarction. Akt is a protein kinase that’s activated with statin and this is related with increased endothelial cell survival and new vessel formation, and decreased apoptosis and endothelial NO production. Additional reported mechanism is decreased connective tissue growth factor (CTGF) via the inhibition of transforming growth factor β (TGF-β) and mitogen-activated protein kinase (MAPK), and MARK is important in the development of heart failure.

Yamada et al. reported beneficial effects of atorvastatin (10 mg/day) in chronic heart failure patients with a decreased LV end-diastolic dimension and an increased LV ejection fraction as compared to the control group. Node et al. also reported improvement of the
LV function and the New York Heart Association functional class (NYHA) with administering statins. But the Rosuvastain Impact on Ventricular Remodeling Lipids and Cytokines (UNIVERSE) trial reported negative results. Well designed large-scale prospective randomized trials could resolve the complicated results about statins’ role in heart failure, and especially for the aspect of the LV remodeling and function.

Statins in retrospective or observational clinical studies: previous positive reports

The first investigation of the beneficial role of statins in heart failure was reported from a post-hoc analysis study of the 4S (Scandinavian Simvastatin Survival Study) 3 years after the original report. Although the study group excluded the patients with clinical heart failure and it included the hypercholesterolemic patients, Kjekshus et al., who is also the first author of the CORONA study, reported a reduction of mortality in the statin group (20-40 mg of simvastatin) and this occurred for the patients who had newly developed heart failure during 5.4-year follow-up. Besides the mortality benefits, statins also have role in preventing heart failure (8.3% heart failure in the statin group and 10.3% heart failure in the non-statin group, p<0.015).

Go et al. conducted an observational study to evaluate the association of incidental statins usage with the clinical outcomes such as death and hospitalization for patients with heart failure [n=24,590 subjects, 12,648 subjects for the statin group (51.4%)] for 2.4 years. The statin group had a lower death rate [14.5 per 100 person-year versus 25.3 per 100 person-year, respectively, adjusted hazard ratio: 0.76 (95% confidence interval: 0.72-0.80)] and lower hospitalization for heart failure regardless of the presence of coronary artery disease.

From the post-hoc, non-randomized analysis of the CIBIS-II (Second Cardiac Insufficiency Bisoprolol Study), statins had additive roles with bisoprolol in reducing all causes of cardiovascular and sudden death rate compared to the statin or bisoprolol alone groups and the no statin/bisoprolol group.

The preventive role of statin for the development of heart failure was evaluated in the CARE (Cholesterol and Recurrent Event) study. Heart failure occurred less often in the pravastatin treated group than in the control group (10.9% versus 13.8%, respectively, a non-significant 21% relative risk reduction). The beneficial role of statins in preventing cardiovascular events was reported regardless of the severity of the left ventricular function. In the PRAISE (Prospective Randomized Amlodipine Survival Evaluation) trial, the role of statin in severe heart failure patients (EF<30% and NYHA IIIb or IV) was shown with a reduction of mortality for 15 months, and the CARE study group reported that pravastatin had role for secondary prevention in patients with previous myocardial infarction and moderate LV dysfunction (25 ≤ EF ≤ 40%).

There has been only one prospective nonrandomized study for evaluating the roles of statins in 137 patients with diastolic heart failure (a left ventricular ejection fraction ≥50%), and this was performed by Fukuda et al. They reported the mortality benefits of statin (adjusted relative death rate: 0.20, 95% confidence interval: 0.06-0.62, p=0.005) during 21 months of follow-up, which was different from that of other drugs such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-adrenergic receptor blockers and calcium channel blockers.

There were many limitations in these retrospective studies such as they were small prospective studies, various surrogate markers were used with various results, the non-uniform types of statins and doses and the studies were conducted in various clinical settings.

Even though there are many supportive reports for the beneficial effects of statins on the development and progression of heart failure, and for reducing cardiovascular events, the uniform conclusion of these reports was the need for large scale prospective randomized trials to confirm the effects of statin.

Some negative reports

In 2005, Robinson et al. reported a meta-regression analysis study that focused on the pleiotropic effects of statins to improve cardiovascular outcomes. They gathered qualified studies that were done from 1966 to 2004 and they standardized the analysis protocol, which enrolled 81,859 patients. They reported reduced cardiovascular events, including mortality, according to the cholesterol reduction, but there was no differences between the statin and non-statin groups such as diet, bile acid sequestrants and surgery. The results denied the potential pleiotropic effects of statins on the clinical outcomes which have been reported by many previous studies.

Krum et al. performed a double-blind randomized placebo-controlled study on the effect of 40 mg of rosvastatin on the left ventricular remodeling, the pro-inflammatory cytokines and the clinical outcomes for 6 months in patients with systolic heart failure. Despite of the safety and the reduced cholesterol level, rosvastatin did not improve the above mentioned parameters, including the clinical outcomes. As expected from the study design, a 6 month duration is too short to reveal the benefits of statins.

Implications of the CORONA Study

CORONA was designed to confirm the beneficial effects of statin in older patients with systolic heart failure; the study enrolled 5011 patients who were at
least 60 years of age and the possible harmful effects of statins as related to lowering the lipoproteins were assessed. The patients with a low EF (<40%) and clinical heart failure (NTHA II, III, IV) received 10 mg of rosuvastatin for 32.8 months. Many aspects of the clinical outcomes were evaluated with measuring the inflammatory markers. But the results were different from the previous observational, retrospective reports. Rosuvastatin did not reduce deaths from cardiovascular causes, nor did it reduce the nonfatal myocardial infarction, nonfatal stroke, deaths from any causes, any coronary events and deaths from cardiovascular causes, but it reduced number of cardiovascular hospitalizations and it decreased the high sensitivity C-reactive protein level. The study was stopped due to the occurrence of planned primary events after a relatively short follow-up duration. The majority of the previous beneficial effects were achieved with a higher dose of drugs regardless of the types of statins and the etiologies of heart failure. The study population consisted of patients with known cardiovascular disease and their recommended target for LDL-cholesterol was below 70 mg/dL. But the achieved mean LDL-cholesterol level was 76 mg/dL with 10 mg of rosuvastatin being administered for more than two years, which means more than half the patients did not reach the target levels for LDL-cholesterol. Even though the patients of this study were older patients with a mean age of 73-year-old, the dose of drug was not enough to achieve the target LDL-cholesterol level. The clinical significances of the phrase, ‘The lower, the better’, stands as being valid. We should not make mistakes of expanding the results of the above mentioned study to other patients who are younger than that particular study group, and younger patients can tolerate a higher dose of statins for a long duration; who have an early stage of heart failure, which has more potential for an improved outcome with statin’s cholesterol lowering effect and also with its effects that are beyond cholesterol lowering.

From another point of view, for 10 mg of rosuvastatin, which is the usual dose and this lowers the LDL-cholesterol to the target level (86.7%) of the subjects had a LDL-cholesterol level <100 mg/dL, and 48.3% of the subjects had a LDL-cholesterol level <70 mg/dL) in Korean patients with acute coronary syndrome, there were no harmful effects of statins compared to placebo.49 It is important to conduct further studies to determine the effects of statins in patients with heart failure.

Conclusions and Future studies

There were many direct or indirect, theoretical or clinical evidences of the potential benefits of statins in patients with heart failure. But the clinical significances of the previous observational, post-hoc subgroup analyses and the nonrandomized or small studies call into question the true roles of statins. One large randomized multicenter study was performed in advanced, high risk elderly patients (41% patients >75 years) who had heart failure for a relatively short duration. According to the critics of this report, the results lacked evidence for the role of statins for achieving potential benefits in patients with heart failure. But the study proved the safety of 10 mg of rosuvastatin even though this was administered to elderly patients and it leaves room for further studies to investigate other patient groups such as younger patients and patients with non-ischemic heart failure or a preserved left ventricular function with using various doses of statins for a longer duration.

Should we prescribe statins in a 56-year-old man with decreased systolic ventricular function, but no ischemic heart disease and who well tolerated higher doses of other drugs? We still have no answer for this question. We should determine the ideal dose and type of statins and which groups will achieve the maximal benefits and minimal side effects with the administration of statins.

REFERENCES

13) Khush KK, Waters DD. Effects of statin therapy on the develop-
41) Cleland JG, Coletta AP, Nikitin NP, Clark AL. Clinical trials update from the American College of Cardiology: Darbepoetin alfa, ASTEROID, UNIVERSE, paclitaxel, doxorubicin, UNLOAD and ICELAND. Eur J Heart Fail 2006;8:326-9.