EDITORIAL

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Appropriate candidates for statin use in heart failure

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See Article on Page 754-763

Heart failure (HF) is a clinical syndrome resulting from structural and functional impairments of the heart associated with various cardiovascular diseases and is characterized by impaired cardiac performance, neurohormone imbalance, endothelial dysfunction, and inflammation [1]. Current guidelines for treating congestive heart failure (CHF) focus on improving cardiac performance and correcting the neurohormone changes [2,3] Recently, significant advances have been made in the treatment of HF with renin-angiotensin-aldosterone system blockers, β-blockers, devices, diuretics, and digitalis [2,3]. There has been a 40% reduction in the age-standardized death rate due to HF over the past two decades and a concomitant increase in the age of death from HF [4]. Despite advances in therapy, however, the 5-year mortality of HF is still approximately 50%, which is worse than that of many cancers [5]. Therefore, further strategies are needed to improve these poor outcomes.

Cardiac tissue inflammation plays a major role in the initiation and progression of HF [6]. Endothelial dysfunction is common in patients with CHF and is thought to be related to the clinical complications of CHF [7]. Endothelial dysfunction in CHF patients is often associated with increased inflammatory cytokines, reactive oxygen species, endothelial cell apoptosis, decreased endothelial nitric oxide synthase expression, reduced blood flow, and shear stress [8]. Following the initial insult of a cardiac event, increased production of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin (IL) 6, IL-1, and IL-18, compromises the cardiac tissue via the increased inflammatory response and through direct effects that alter cardiomyocyte structure and function. Cardiac myocyte hypertrophy, contractile dysfunction, cardiac myocyte apoptosis, and extracellular matrix remodeling are the major mechanisms by which CHF develops and progresses [9]. Although many of the deleterious effects of inflammatory mediators are potentially reversible once the inflammation subsides, HF remains a progressive process despite optimal therapy [10]. Consequently, anti-inflammatory strategies can be rationalized in patients with HF.

Some of these anti-inflammatory strategies include use of anti-TNF-α therapy with monoclonal antibodies [11] or soluble TNF receptor fusion proteins [12], β-adrenergic agonists [13], adenosine [14], phosphodiesterase inhibitors [15], amiodarone [16], ouabain [17], and estrogen [18]. In clinical trials, however, the use of either a soluble TNF receptor or an anti-TNF antibody did not benefit patients with HF [11,12], which contrasts with the results of experimental studies. The clinical benefits of other anti-

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cytokines in CHF are also not reassuring and patients with severe HF should not be treated with anticytokines [10].

The 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, commonly known as statins, have lipid-lowering, and pleiotropic effects, which include anti-inflammatory and plaque-stabilizing actions. Statins are used routinely in patients with coronary artery disease for secondary prevention [19]. In patients with HF, statins might directly improve the microvascular circulation and endothelial function by stimulating angiogenesis and modulating the synthesis and activity of endothelial nitric oxide synthase and endothelin-1 [20]. They also have anti-inflammatory and antioxidant effects and reduce the levels of inflammatory biomarkers and cytokines, irrespective of cholesterol levels [21]. In animal models, statins reduced angiotensin II receptor expression and matrix metalloproteinase secretion [22], resulting in cardiac remodeling [23]. All of these effects can play a critical role in HF progression and prognosis. Statins appear to have many pleiotropic effects believed to influence the pathophysiology of HF progression. However, the results of large randomized clinical trials conflict with other clinical studies [24]. Small prospective trials have suggested that statin treatment in patients with HF has a positive impact that is pleiotropic and independent of any underlying atherosclerotic disease [25]. Moreover, observational studies and post hoc analyses of randomized trials suggest that statin therapy more strongly influences the prognosis of patients with HF [26]. Based on these promising findings, large randomized trials of rosuvastatin were performed: the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio-Heart Failure (GISSI-HF) trial [27] and the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) [28]. The CORONA study was a large, randomized, placebo-controlled trial of rosuvastatin 10 mg versus a placebo in patients with chronic systolic HF of ischemic etiology [28]. The study enrolled 5,011 patients older than 60 years with New York Heart Association (NYHA) class II symptoms and an ejection fraction of less than 35%, or NYHA class III to IV symptoms and an ejection fraction of less than 40% with an average 3 years of follow-up. Rosuvastatin did not have survival benefits, but did reduce the number of HF hospitalizations in older patients with ischemic systolic HF. The GISSI-HF trial was a multicenter, randomized, double-blind study that assessed the effect of N-3 polyunsaturated fatty acids and rosuvastatin 10 mg versus placebo on cardiovascular morbidity and mortality of patients with chronic symptomatic HF [27]. This study enrolled 4,574 HF patients and had broad criteria requiring NYHA class II to IV symptoms of any etiology. There were no exclusions based on ejection fraction or baseline cholesterol levels. Like the CORONA study, the GISSI-HF trial also did not show any significant effect of rosuvastatin on the clinical outcomes of patients with CHF of both ischemic and nonischemic etiologies after 3 years of follow-up. The results of these trials were contrary to what was expected, in that rosuvastatin did not reduce the number of deaths in patients with HF [27,28].

However, several issues should have been considered regarding the assessment of statin benefits in patients with ischemic HF. The first issue is related to the target disease status and the benefit of statin therapy being dependent on heart failure severity. Although many trials have demonstrated that statins reduce cardiovascular morbidity and mortality in patients with ischemic heart disease, this does not seem to hold true in patients with ischemic HF, as the CORONA trial showed [28]. According to the results of the JUPITER, CORONA, and AURORA trials, it is critical to start statin treatment as early as possible in the cardiovascular continuum [29]. Initiation of statin therapy when a patient is already at end-stage disease is most likely too late. Although it is vital to control all cardiovascular risk factors along the continuum, the beneficial effects of therapy differ depending on the stage at which treatment is started. Therefore, if statins are prescribed at earlier stages, the improvement in cardiovascular prognosis will be markedly greater than if therapy was initiated during later stages [30]. In the CORONA trial, the lowest N-terminal pro-B-type natriuretic peptide tertile (< 868 pg/mL) did benefit from rosuvastatin, showing a significant improvement in the primary end point [31]. It has been suggested that in milder HF, statins can modify coronary events, whereas in severe HF, statin use does not improve the progressive loss of pump function [32]. Another issue is related to the dose and characteristics of statins. Specifically, trials have shown increasingly beneficial results with higher doses [33]. Notably, both

the CORONA and GISSI-HF trials, which had negative results, were conducted using low-dose rosuvastatin (10 mg). Different dose-dependent effects of atorvastatin treatment on the arterial wall properties and on indices of left ventricular remodeling have also been reported in ischemic HF [34]. Short-term treatment with atorvastatin 40 mg has beneficial effects on the arterial wall properties and improves the indices of left ventricle remodeling in HF patients, while no significant changes in these parameters occur after treatment with atorvastatin 10 mg/day. Therefore, high-dose statins are recommended for the treatment of HF.

Regarding the pharmacodynamic properties of statins, hydrophilic statins such as rosuvastatin rely on active transport into hepatocytes to exert their effect and have poor penetration into extrahepatic tissues. Consequently, they have a lower risk of adverse effects, but also have very low uptake by cardiac muscle. However, lipophilic statins including simvastatin tend to achieve higher levels of exposure in nonhepatic tissues and have very high cardiac muscle uptake [35]. A recent study of a real-life cohort followed for a maximum of 9.1 years showed that lipophilic statins were independently and significantly associated with a lower mortality risk, including patients with nonischemic HF etiology, which contrasts the results of large randomized trials with hydrophilic statins [24]. Another possible issue is the presence of comorbidities with HF. The results of the CORONA trial might have been influenced by the enrollment of elderly patients, since this age group might have comorbidities that could attenuate the potential benefits of treatment [36]. Furthermore, the drug could interact with the complex medical therapy typical in older patients with HF.

In this issue of *The Korean Journal of Internal Medicine*, Lee et al. [37] report the effects of intense versus mild lipid-lowering programs with statins by analyzing 69 ischemic CHF patients receiving pravastatin 10 mg or pitavastatin 4 mg daily. They found that in CHF patients with ischemic origin, both very-low-dose/low potency pravastatin and high-dose/high-potency pitavastatin had beneficial effects on cardiac remodeling and systolic function. According to the demographic characteristics, patients receiving low-dose pravastatin were younger and had lower levels of serum B-type natriuretic peptide than those receiving high-dose pitavastatin. These are intrinsic group-specific caveats that must be considered when assessing the beneficial effects of statins in patients with ischemic HF. Despite achieving higher low density lipoprotein cholesterol and lower high density lipoprotein cholesterol levels with low-dose pravastatin treatment, the patients in this group exhibited significant improvement only in exercise capacity. These results suggest the importance of patient characteristics when evaluating the effects of statin therapy in ischemic HF, which is consistent with the CORONA trial [31]. The authors also suggest that lowering cholesterol too aggressively might not be beneficial to CHF patients. They explained the lack of improvement in functional capacity and the possible side effect of fatigue, likely due to the different doses and lipophilicity of statins, and other possible toxic effects of statins, which include those described by the endotoxin lipoprotein, coenzyme Q10 (ubiquinone), and selenoprotein hypotheses. Despite these concerns, statin trials, systematic reviews, and meta-analyses of statin treatment in HF have revealed no detrimental effects and actually suggest favorable effects in HF populations [38]. In addition, some evidence from recent nonrandomized studies complements the findings of the small randomized trials, but suggests that lipophilic statins provide better outcomes than hydrophilic statins in patients with HF [24].

While large randomized trials of statins in HF reported negative results, statins are still expected to have beneficial effects in certain groups of patients with HF because their robust beneficial effects and minimal harmful effects are well documented in atherosclerotic disease, which has an underlying pathophysiology identical to that of HF. To conclude, the effect of statin therapy in ischemic HF suggests that the age of the study population, severity of HF, drug dosage, and pharmacokinetic character of statins must be considered more meticulously when designing clinical trials.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Dahl CP, Gullestad L, Fevang B, et al. Increased expression of LIGHT/TNFSF14 and its receptors in experimental and clinical heart failure. Eur J Heart Fail 2008;10:352-359.
2. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787-1847.
3. Writing Committee Members, Yancy CW, Jessup M, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:e240-e327.
4. Laribi S, Aouba A, Nikolaou M, et al. Trends in death attributed to heart failure over the past two decades in Europe. Eur J Heart Fail 2012;14:234-239.
5. Braunwald E. Heart failure. JACC Heart Fail 2013;1:1-20.
6. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990;323:236-241.
7. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation 1998;98:2709-2715.
8. Tousoulis D, Charakida M, Stefanadis C. Inflammation and endothelial dysfunction as therapeutic targets in patients with heart failure. Int J Cardiol 2005;100:347-353.
9. Hedayat M, Mahmoudi MJ, Rose NR, Rezaei N. Proinflammatory cytokines in heart failure: double-edged swords. Heart Fail Rev 2010;15:543-562.
10. El-Menyar AA. Cytokines and myocardial dysfunction: state of the art. J Card Fail 2008;14:61-74.
11. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT; Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation 2003;107:3133-3140.
12. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594-1602.
13. Yoshimura T, Kurita C, Nagao T, et al. Inhibition of tumor necrosis factor-alpha and interleukin-1-beta production by beta-adrenoceptor agonists from lipopolysaccharide-stimulated human peripheral blood mononuclear cells. Pharmacology 1997;54:144-152.
14. Feldman AM, Wagner DR, McNamara DM. AMPD1 gene mutation in congestive heart failure: new insights into the pathobiology of disease progression. Circulation 1999;99:1397-1399.
15. Matsumori A, Shioi T, Yamada T, Matsui S, Sasayama S. Vesnarinone, a new inotropic agent, inhibits cytokine production by stimulated human blood from patients with heart failure. Circulation 1994;89:955-958.
16. Matsumori A, Ono K, Nishio R, Nose Y, Sasayama S. Amiodarone inhibits production of tumor necrosis factor-alpha by human mononuclear cells: a possible mechanism for its effect in heart failure. Circulation 1997;96:1386-1389.
17. Matsumori A, Ono K, Nishio R, et al. Modulation of cytokine production and protection against lethal endotoxemia by the cardiac glycoside ouabain. Circulation 1997;96:1501-1506.
18. Ammann P, Rizzoli R, Bonjour JP, et al. Transgenic mice expressing soluble tumor necrosis factor-receptor are protected against bone loss caused by estrogen deficiency. J Clin Invest 1997;99:1699-1703.
19. Cholesterol Treatment Trialists' (CTT) Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-1681.
20. Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998;97:1129-1135.
21. Tousoulis D, Antoniades C, Bosinakou E, et al. Effects of atorvastatin on reactive hyperemia and inflammatory process in patients with congestive heart failure. Atherosclerosis 2005;178:359-363.
22. Bellosta S, Via D, Canavesi M, et al. HMG-CoA reductase inhibitors reduce MMP-9 secretion by macrophages. Arterioscler Thromb Vasc Biol 1998;18:1671-1678.
23. Oi S, Haneda T, Osaki J, et al. Lovastatin prevents angiotensin II-induced cardiac hypertrophy in cultured neo-

natal rat heart cells. Eur J Pharmacol 1999;376:139-148.
24. Gastelurrutia P, Lupon J, de Antonio M, et al. Statins in heart failure: the paradox between large randomized clinical trials and real life. Mayo Clin Proc 2012;87:555-560.
25. Sola S, Mir MQ, Lerakis S, Tandon N, Khan BV. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. J Am Coll Cardiol 2006;47:332-337.
26. Mozaffarian D, Nye R, Levy WC. Statin therapy is associated with lower mortality among patients with severe heart failure. Am J Cardiol 2004;93:1124-1129.
27. Gissi-HF Investigators, Tavazzi L, Maggioni AP, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231-1239.
28. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248-2261.
29. Barrios V, Escobar C. Rosuvastatin and cardiovascular continuum when time is important. J Am Coll Cardiol 2010;55:1645-1646.
30. Barrios V, Escobar C. Rosuvastatin along the cardiovascular continuum: from JUPITER to AURORA. Expert Rev Cardiovasc Ther 2009;7:1317-1327.
31. Cleland JG, McMurray JJ, Kjekshus J, et al. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure). J Am Coll Cardiol 2009;54:1850-1859.
32. Athyros VG, Karagiannis A, Mikhailidis DP. Statins and heart failure. J Am Coll Cardiol 2010;55:1644-1645.
33. Khush KK, Waters DD, Bittner V, et al. Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study. Circulation 2007;115:576-583.
34. Tousoulis D, Oikonomou E, Siasos G, et al. Dose-dependent effects of short term atorvastatin treatment on arterial wall properties and on indices of left ventricular remodeling in ischemic heart failure. Atherosclerosis 2013;227:367-372.
35. Nezasa K, Higaki K, Matsumura T, et al. Liver-specific distribution of rosuvastatin in rats: comparison with pravastatin and simvastatin. Drug Metab Dispos 2002;30:1158-1163.
36. Bonsu KO, Kadirvelu A, Reidpath DD. Statins in heart failure: do we need another trial? Vasc Health Risk Manag 2013;9:303-319.
37. Lee HY, Cho HJ, Kim HY, et al. Effects of intensive versus mild lipid lowering by statins in patients with ischemic congestive heart failure: South Korean Pitavastatin Heart Failure (SAPHIRE) study. Korean J Intern Med 2014;29:754-763.
38. Ramasubbu K, Estep J, White DL, Deswal A, Mann DL. Experimental and clinical basis for the use of statins in patients with ischemic and nonischemic cardiomyopathy. J Am Coll Cardiol 2008;51:415-426.

http://dx.doi.org/10.3904/kjim.2014.29.6.730