The appropriate dose of angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers in patients with dilated cardiomyopathy. The higher, the better?

Junichi Ishida*, Masaaki Konishi and Stephan von Haehling

Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen, Göttingen, Germany

Abstract

Heart failure is a major public issue, and dilated cardiomyopathy (DCM) is one of the common etiologies of heart failure. DCM is generally progressive, and some patients with DCM need heart transplant despite optimal medical and mechanical therapy. Current guidelines recommend inhibitors of renin–angiotensin–aldosterone system, namely angiotensin-converting-enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), and mineralocorticoid receptor antagonist as well as beta-blockers for the medical treatment of heart failure with reduced ejection fraction, including DCM. Furthermore, because they have beneficial effects on the outcome of heart failure in a dose-related fashion, they should be titrated to the target dose. In clinical practice, the underuse and under-dose of these agents matter; however, the efficacy and safety of supramaximal dose of ACE inhibitor or ARB have never been investigated in the patients with DCM. In this issue of ESC Heart Failure, it is demonstrated that benazepril or valsartan at supramaximal dose improved left ventricular function and reduced cardiovascular events compared with each drug at low dose, respectively. In this editorial, the current evidence concerning the use of ACE inhibitor or ARB in patients with HF and future prospective will be discussed.

Heart failure (HF) is still a major public problem with a prevalence of over 23 million people worldwide in spite of consistent efforts of physicians, and dilated cardiomyopathy (DCM) is one of the most common etiologies of this syndrome. DCM is generally a progressive disease, and some patients with DCM need heart transplant despite established medical and mechanical therapy. The current guidelines of the European Society of Cardiology recommend inhibitors of the renin–angiotensin–aldosterone system (RAAS), namely angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) and, particularly in symptomatic patients, mineralocorticoid receptor antagonists. Beta-blockers complement the evidence-based medical treatment of HF with reduced ejection fraction (EF), including DCM. Medications with less established evidence embrace diuretics. Ivabradine can be considered in symptomatic patients whose resting heart rate remains elevated. Beta-blockers, ACE inhibitors, and ARBs, should be titrated to the target dose as they have beneficial effects on the outcomes of HF in a dose-related fashion. It has been based on the results of large-scale randomized trials, and the efficacy and safety of supramaximal dose of ACE inhibitor or ARB have been first investigated in the patients with DCM.

In this issue of ESC Heart Failure, He et al. demonstrate that benazepril or valsartan at supramaximal dose improves left ventricular function and reduces cardiovascular events compared with each drug at low dose, respectively.

Angiotensin-converting-enzyme inhibitor for the treatment of heart failure

In patients with HF, increased RAAS contributes to the pathogenesis, and ACE inhibitors reduce the activity of the RAAS

*Correspondence to: Junichi Ishida MD PhD, Institute of Innovative Clinical Trials, University Medical Centre, Göttingen, Robert-Koch-Str. 40, 3 7075 Göttingen, Göttingen, Germany. Tel: +49 551 39 66380. Fax: +49 551 39 66389. E-mail: juishida-circ@umin.ac.jp

Editorial

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by inhibiting the production of angiotensin II. Two benchmark randomized controlled trials, namely the Cooperative North Scandinavian Enalapril Survival Study\(^7\) and the Studies of Left Ventricular Dysfunction Treatment Trial,\(^8\) demonstrated that ACE inhibitors reduce mortality and improved New York Heart Association class, exercise capacity and cardiac function in patients with HF with reduced EF. Subsequently, the Assessment of Treatment with Lisinopril and Survival study\(^5\) investigated whether ACE inhibitors had favourable effects on the outcome of patients with HF with reduced EF in a dose-dependent manner. In this trial, an ACE inhibitor, lisinopril, at high dose (32.5–35 mg daily) significantly decreased death or hospitalization for any cause by 12% (\(P=0.002\)) compared with that at low dose (2.5–5 mg daily), but not significantly decreased death by 8% (\(P=0.128\)). He et al. show that benazepril at supramaximal dose results in prolonged survival by 41% compared with that at low dose [95% confidence interval (CI) 0.36–0.98, \(P=0.042\)]. Further research should reveal whether ACE inhibitors at supramaximal dose reduce the mortality rate in patients with HF compared with those at high dose.

Common side effects of ACE inhibitors are hyperkalaemia, hypotension, cough, and impaired renal function. According to the severity of these adverse events, it is crucial to manage when to stop up-titrating, reduce dose, or discontinue treatment. Five ACE inhibitors, namely ramipril, enalapril, lisinopril, captopril, andtrandolapril, are listed for the treatment of HF with reduced EF, and the starting dose and the target dose are also described in the current guidelines.\(^3\) However, it remains unclear which ACE inhibitor should be administered or if there are differences between the drugs, because head-to-head comparisons are still missing.

### Angiotensin receptor blocker for the treatment of heart failure

Angiotensin receptor blockers would be expected to exert beneficial effects on the treatment of HF through the stronger inhibition of angiotensin II than ACE inhibitors. The Evaluation of Losartan in the Elderly Study II study\(^9\) showed that losartan was non-inferior to captopril in reducing mortality in elderly patients with HF with reduced EF (hazard ratio 1.13, 95% CI 0.95–1.35, \(P=0.16\)), and the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity-Alternative trial\(^10\) showed that candesartan reduces the risk of cardiovascular death or hospital admission for HF in patients intolerant of ACE inhibitors compared to placebo (hazard ratio 0.70, 95% CI 0.60–0.81, \(P<0.0001\)). Subsequently, the Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan study\(^6\) revealed that losartan at high dose (150 mg daily) reduced death or hospitalization for HF in patients with HF with reduced EF, compared with losartan at low dose (50 mg daily) (hazard ratio 0.90, 95% CI 0.82–0.99; \(P=0.027\)), indicating the dose-related therapeutic effect of ARBs on the outcome of HF as well as ACE inhibitors.

In the Swedish Heart Failure Registry,\(^11\) the use of losartan was associated with significant increase in mortality in patients with HF compared with that of candesartan (hazard ratio 1.43, 95% CI 1.23–1.65, \(P<0.001\)), suggesting the different clinical effects among ARBs. Common side effects of ARBs are well known and include hyperkalaemia, hypotension, and impaired renal function, similar to ACE inhibitors; however, ARBs are believed to be better tolerated than ACE inhibitors. He et al. reports that 29 patients (29%) at supramaximal-dose benazepril withdrew from this study, as did 12 patients (12%) at supramaximal-dose valsartan. Dose-related increase in the development of adverse events in patients receiving both benazepril and valsartan is observed, which is inconsistent with the findings of previous studies using very high-dose ARB.\(^12,13\)

In view of these findings, ARBs are considered second choice in patients with HF with reduced EF who are not tolerated to ACE inhibitors or mineralocorticoid receptor antagonists in the current guidelines.

### Combination therapy with angiotensin-converting-enzyme inhibitor and angiotensin receptor blocker, supramaximal dose of angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker and beyond

Because of the different mechanism of action of ACE inhibitors and ARBs in blocking the RAAS, combination therapy of an ACE inhibitor and an ARB was thought to be attractive for the treatment of HF as well as the monotherapy with an ARB. In the Valsartan Heart Failure Trial,\(^14\) the addition of valsartan to conventional therapy for HF resulted in a significant decrease in cardiovascular events compared to placebo (relative risk 0.87, 97.5% CI 0.77–0.97, \(P=0.009\)); however, a post hoc analysis indicated increased mortality and complications in the subgroup taking an ACE inhibitor, valsartan, and a beta-blocker. Moreover, a recent meta-analysis\(^15\) suggested that combination therapy of an ACE inhibitor with an ARB should not be advocated in patients with HF, because the combination does not seem to reduce mortality or hospitalization and was associated with more adverse events.

As described earlier, an ACE inhibitor, lisinopril, or an ARB, losartan, at high dose produced better clinical outcomes in patients with HF compared with each at low dose but did not decrease mortality significantly.\(^5,6\) On the other
hand, He et al. reports that supramaximal dose of benazepril or valsartan improves not only cardiac function but also survival in patients with DCM compared with the low dose of each medication, which indicates that ACE inhibitors or ARBs at supramaximal-dose might produce better outcomes in patients with EF compared with those at high dose (target dose). These unique findings are derived from a single-centre prospective, randomized, and controlled trial. The sample size is small, but the follow-up period is long enough to detect the statistical difference in the outcomes of HF among the treatment groups. They should be confirmed with double-blind multi-centre randomized controlled studies.

Future perspective

Recently, ivabradine\textsuperscript{17} and LCZ696, a combination of the new nephrilysin inhibitor sacubitril (AHU377) with valsartan,\textsuperscript{18} have attracted attention for the treatment of HF. If the efficacy and safety of supramaximal-dose valsartan were well acknowledged in this field, it would be helpful to investigate the appropriate dose of LCZ696 more precisely.

Conflict of interest

All authors declare that they have no conflict of interest.

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