**Costarring Statins With ARBs**

– Going to Be a Smash Hit? –

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**B**ased on the accumulating evidence, some major pharmacological strategies for improving the morbidity and mortality of patients with chronic heart failure (HF) have been recently proposed. To date, according to numerous previous clinical studies, renin–angiotensin system (RAS) inhibition and β-adrenergic blockade are the most assured and reliable options.\(^1\) so they are the first-line in the current therapeutic guidelines for chronic HF\(^2\) and most patients are strongly recommended to take as high doses of these medicines as they can tolerate.\(^3\) However, despite the continuous intensive research that has proposed various kinds of mechanistic insights as putative candidates, we do not have any other efficacious pharmacological strategies in daily clinical practice that might be as potent and sufficient to parallel those 2 standard options for coping with HF,\(^4\) which has been a huge problem over the past 2 decades.

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Recently, hydroxymethyl glutaryl coenzyme-A reductase inhibitors (statins), which primarily modify the endogenous cholesterol profile, have emerged as a hopeful candidate for a novel therapeutic option for treating HF,\(^5,6\) pending investigation of the mechanisms underlying their clinical benefits.

In this issue of the Journal, Maejima et al\(^7\) intriguingly report from the results of their randomized study involving 32 patients (the HF-costar trial) that the additional use of simvastatin exerted enhanced benefits, such as further improvement of NYHA classification and significant reduction in plasma B-type natriuretic peptide (BNP) levels, together with a trend toward increased recovery of the echocardiographic ejection fraction, in patients with mild to moderate chronic HF treated with losartan, which alone also brought recovery in part.

Their most noteworthy finding is that the improvements in patient status were independent of any hemodynamic or inflammatory change, except a mild reduction in the plasma cholesterol level, by simvastatin. In their study, the final blood pressure of 122/73 in the losartan group, which remained unchanged throughout the study, strongly supports the pleiotropic benefits of RAS inhibition, apart from blood pressure reduction, as implicated by many previous experimental studies.\(^8\) Actually, the administered dose of losartan in this study was designed to be 25–50 mg/day, which is indeed the standard therapeutic regimen in this patient population. However, we are approved to prescribe the higher dose of 100 mg/day in the same population in daily clinical practice. Moreover, the benefits of RAS inhibition in previous clinical trials were often accompanied by significant blood pressure reduction,\(^9\) and some recent studies reported that higher doses of RAS-inhibiting agents provided a better outcome when safe and tolerable\(^5\) in patients with cardiovascular diseases. Therefore, it is arguable whether the present dose of losartan was optimal for maximal therapeutic potential, not underpowered.

Likewise, we cannot directly distinguish the combined effects of losartan with simvastatin from the effects of simvastatin alone because of the absence of the wing of “treated alone” in this study. Some recent small clinical trials\(^6,8\) demonstrated substantial improvement in cardiac status evaluated by NYHA classification, echocardiographic cardiac function and plasma BNP level, the same parameters used in this study, to a similar extent by additional treatment with simvastatin in patients with chronic HF. Despite the limitation of the number of patients, a direct comparison would have provided more details regarding separate and synergistic effects.

As to the mechanistic insights, Node et al\(^9\) proposed elimination of inflammatory reactions, represented by reduced plasma levels of TNF-α or IL-6, as the potential benefits of simvastatin therapy; however, in this study the plasma hsCRP levels remained unchanged. Because this study is missing a direct evaluation of TNF-α or IL-6, we cannot tell whether hsCRP is directly linked with those 2 cytokines, which might imply unknown “co-starring” beneficial mechanisms other than CRP-related inflammatory cascades. For example, if TNF-α was selectively affected by additional treatment with statins in this study, it might lead to activation of p38MAPK and JNK, which potently modulate the pathophysiology of HF,\(^10\) but that seems somewhat different from the cardioprotective mechanisms induced by RAS-inhibitory agents.\(^8\)

Furthermore, it might also be the case that nitric oxide-dependent mechanisms and anti-oxidant effects, which are also supposed to be pleiotropic cardioprotective cascades induced by both RAS-inhibitory agents and statins,\(^1\) played a role in this situation. However, it remains controversial whether these cardioprotective cascades might be prevailing similarly in the clinical setting, and whether these are common or distinct among RAS-inhibitory agents and statins. Therefore, the opinions expressed in this article are not necessarily those of the editors or of the Japanese Circulation Society.

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further evaluation of the same population is awaited.

In addition, the drug-selective property of statins for downstream modulation and cardioprotection might differ in terms of magnitude,\(^1\) which might also be the case with RAS inhibitors. Further investigations using various class-wide alternatives to identify their class-sensitive as well as drug-specific benefits in patients with HF, and to seek the best combination of the specific drugs, are awaited.

Meanwhile, another remarkable finding is that having only 16 patients in each wing was sufficient to reach statistical significance. Although the present study,\(^1\) as well as previous studies,\(^5,6\) show a remarkable reduction in plasma BNP levels and a substantial recovery of cardiac function in such small study populations, they are hardly reflected in the large clinical trials, which have been mostly negative for drastic changes in plasma BNP level or overall primary outcomes.\(^12\) One reason for the discrepancy is that the patients’ characteristics and group composition would be different from those in the practical large cohorts, as was pointed out in the report from the J-CARE-GENERAL study.\(^13\) Another possible reason is that the major determinants of primary outcome would be significantly biased to cerebrovascular events, arrhythmic events or cancers, which do not correlate with plasma BNP level or overall primary outcomes.

We hope that direct interventions on each potential target will uncover the beneficial mechanisms for preventing HF in the real world in the near future.

**References**


