ORIGINAL

# LCZ696, an Angiotensin Receptor-Neprilysin Inhibitor, Attenuates Vascular Inflammation and Atherosclerosis in Apolipoprotein E-deficient Mice

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**Abstract : Objective : Sacubitril/valsartan (LCZ696), an angiotensin receptor neprilysin inhibitor (ARNI), simultaneously inhibits neprilysin and the renin-angiotensin-aldosterone system, but its effects on diet-induced vascular inflammation and atherosclerosis are unclear. Methods : LCZ696 (100 mg/kg/day), valsartan (50 mg/kg/day) or hydralazine (10 mg/kg/day) was orally administered to apolipoprotein E-deficient (*ApoE*$^{-/-}$) mice for 20 weeks. En-face Sudan IV staining of the aortic arch, quantitative reverse transcription polymerase chain reaction (RT-PCR) of abdominal aorta. Results : There were no differences in metabolic parameters between the groups. Valsartan or LCZ696 significantly reduced the progression of atherosclerotic lesions compared to the hydralazine group, as determined by Enface Sudan IV staining of the aortic arch ($p<0.05$). In the abdominal aorta, valsartan or LCZ696 treatment reduced mRNA expression of inflammatory molecules. However, no significant difference was observed between the valsartan group and the LCZ696 group regarding these atherosclerotic changes and vascular inflammation. Conclusion : LCZ696 reduced the progression of diet-induced atherosclerotic plaques and vascular inflammation compared with hydralazine in *ApoE*$^{-/-}$ mice, but showed no difference compared with the valsartan group. J. Med. Invest. 73 : 116-120, February, 2026**

***Keywords*** **:** *atherogenesis, natriuretic peptide, neprilysin, sacubitril/valsartan, vascular inflammation*

## INTRODUCTION

It is widely accepted that atherosclerosis is a chronic inflammatory disease. (1, 2) Many cellular and molecular pathways contribute to the vascular inflammation. (3, 4) The Renin–Angiotensin–Aldosterone System (RAAS) is also involved in the generation and progression of the atherosclerosis. (5-7) Apart from this, neprilysin is an endopeptidase which cleaves various bioactive peptides (e.g. natriuretic peptide, angiotensin I and II), suggesting a broad role in cardiovascular, renal, endocrine, and neurologic functions. (8)

Currently, sacubitril/valsartan (LCZ696) is clinically used as an angiotensin receptor-neprilysin inhibitor (ARNI), simultaneously inhibits neprilysin and the renin-angiotensin-aldosterone system. (9) Several clinical researches to date has shown that LCZ696 not only has antihypertensive effects, (10, 11) but also has nephroprotective effects such as suppressing chronic inflammation and fibrosis in kidney tissue. (12-14) Furthermore, accumulating evidence from pre-clinical researches suggests that LCZ696 has antioxidative and anti-inflammatory effects in many cell types or animal models of cardiovascular disease. (15-18) However, little is known about the effect of LCZ696 on vascular inflammation and atherosclerosis. At least at the level of clinical research, even in large-scale meta-analyses, no clear anti-atherosclerotic effect of LCZ696 has been demonstrated. (19) At the animal study level, there are a very small number of reports suggesting LCZ696 has greater anti-atherosclerotic and anti-inflammatory effects than Valsartan. However, it is important to note that these studies used non-spontaneous atherosclerosis models involving vascular injury from external stimuli or high-dose angiotensin administration. (20, 21)

Therefore, we compared the effects of LCZ696, valsartan, and a non-RAAS inhibitor (hydralazine) on spontaneously occurring vascular inflammation and atherosclerosis induced by long-term high-fat diet feeding in apolipoprotein E-deficient (*ApoE*$^{-/-}$) mice. Our findings indicate that while LCZ696 and valsartan exhibit anti-inflammatory and anti-atherosclerotic effects compared to the non-RAAS inhibitor (hydralazine), no difference was observed between LCZ696 and valsartan. Although these results differ from those of conventional animal model studies, our results provide new evidence consistent with clinical research findings.

## METHODS

### *Animals and Drug Administration*

Male *ApoE*$^{-/-}$ mice (C57BL/6J background), originally purchased from Jackson Laboratory, were used in this study. We administered a normal chow or Western-type diet for 8 or 20 weeks from 8 weeks of age. Mice were randomly divided into sacubitril/valsartan (100 mg/kg/day), valsartan (50 mg/kg/day) or hydralazine (10 mg/kg/day) groups and treated by oral gavage once daily for 20 weeks. LCZ696 (sacubitril/valsartan) and valsartan were supplied by Novartis Pharma AG (Basel, Switzerland). The mice were housed in a room in which lighting was controlled (12 h on/12 h off), and room temperature was kept at 25°C. All experimental procedures conformed to the guidelines for animal experimentation of Tokushima University. The Animal Care and Use Committee of Tokushima University reviewed and approved the protocol under #T2020-127.

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*Blood Pressure and Plasma Lipid Level Measurement*

The blood pressure of each mouse was measured using a tail-cuff system (BP-98A, Softron) in conscious animals. The average value of 3 measurements was used for comparison. At the time of sacrifice, blood was collected from the heart into K2-EDTA-containing tubes. After centrifuge, plasma was stored at -80°C until required. Plasma lipid levels (total cholesterol, high density lipoprotein cholesterol, and triglyceride) were measured at the Sanritsu Zelkova examination center (Japan).

*Preparation of Aortas and Atherosclerotic Lesion Analysis*

Atherosclerotic lesion analysis was performed as described previously (22). Mice were sacrificed by administration of an overdose of pentobarbital and perfused with 0.9% sodium chloride solution at a constant pressure via the left ventricle. Both the heart and whole aorta were immediately removed. The thoracic aorta was excised, opened longitudinally, and fixed with 10% neutral buffered formalin. To quantify atherosclerotic lesions in the aortic arch, en face Sudan IV staining was performed. The percentage of the Sudan IV–positive area was measured

*Reverse transcription, real-time polymerase chain reaction*

Total RNA was extracted from tissues and cells using illustra RNAspin RNA Isolation Kit (GE Healthcare). Reverse transcription was performed using a QuantiTect Reverse Transcription kit (Qiagen) from 1 μg of the extracted total RNA. Quantitative real-time PCR (qPCR) was performed on Mx3000P (Agilent Technologies) using gene-specific primers (Table 1) and Power SYBR Green PCR Master Mix (Applied Biosystems). Data of mice are expressed in arbitrary units that were normalized by β-actin.

*Statistical analysis*

All numerical values are expressed as means ± standard error of the mean (SEM). An unpaired Student's t-test analyzed the parameter comparisons between the two groups. Differences between multiple groups were performed by one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. Comparison of dose-response curves was performed by two-factor repeated measures ANOVA, followed by Dunnett's post hoc test for comparison between groups, and P-value <0.05 was considered significant.

## RESULTS

*Effect of LCZ696 on the Metabolic Parameters in ApoE$^{-/-}$ Mice*

After 20 weeks of administration, there were no significant differences in body weight, blood pressure. plasma glucose level, and plasma lipid levels among the hydralazine, valsartan, and LCZ696 groups (Table 2).

Table 1. Primer sequences

| | forward primer sequence | reverse primer sequence |
|---|---|---|
| **For mice** | | |
| F4/80 | 5'- TGCATCTAGCAATGGACAGC -3' | 5'- GCCTTCTGGATCCATTTGAA -3' |
| ICAM-1 | 5'- TTCACACTGAATGCCAGCTC -3' | 5'- GTCTGCTGAGACCCCTCTTG -3' |
| VCAM-1 | 5'- CCCGTCATTGAGGATATTGG -3' | 5'- GGTCATTGTCACAGCACCAC -3' |
| IL-1β | 5'- GCCCATCCTCTGTGACTCAT -3' | 5'- AGGCCACAGGTATTTTGTCG -3' |
| TNF-α | 5'- ACCCTCACACTCAGATCATCTTC -3' | 5'- TGGTGGTTTGCTACGACGT -3' |
| MCP-1 | 5'- CCACTCACCTGCTGCTACTCAT -3' | 5'- TGGTGATCCTCTTGTAGCTCTCC -3' |
| β-actin | 5'-CCTGAGCGCAAGTACTCTGTGT-3' | 5'-GCTGATCCACATCTGCTGGAA-3' |

ICAM-1 ; intercellular adhesion molecule-1, VCAM-1 ; vascular cell adhesion molecule-1, IL-1β ; interleukin-1β, TNF-α ; tumor necrosis factor-α, MCP-1 ; monocyte chemoattractant protein-1

Table 2. Effect of Each Drug on Metabolic Parameters

| | Hydralazine | Valsartan | LCZ696 | p-value |
|---|---|---|---|---|
| Body weight, g | 39.4 ± 1.5 | 37.1 ± 1.9 | 34.7 ± 1.7 | 0.12 |
| Heart rate/min | 716.8 ± 12.6 | 760.2 ± 9.5 | 746.9 ± 10.3 | 0.11 |
| Systolic BP, mmHg | 86.1 ± 3.4 | 90.1 ± 4.4 | 76.0 ± 4.9 | 0.08 |
| Diastolic BP, mmHg | 50.8 ± 2.6 | 56.6 ± 4.1 | 48.3 ± 3.7 | 0.28 |
| Blood glucose, mg/dl | 138.6 ± 7.3 | 144.0 ± 6.8 | 131.9 ± 4.7 | 0.41 |
| Triglyceride, mg/dl | 95.6 ± 11.1 | 119.9 ± 8.6 | 110.5 ± 14.0 | 0.43 |
| Total cholesterol, mg/dl | 1149.2 ± 94 | 1355.9 ± 61.7 | 1243.9 ± 77 | 0.15 |
| HDL-C, mg/dl | 18.8 ± 2.1 | 22.9 ± 1.7 | 23.1 ± 2.8 | 0.38 |

There were no significant differences in blood pressure and body weight, plasma glucose level, lipid levels between the groups. n = 13-15, per group. BP ; blood pressure. HDL-C ; high-density lipoprotein cholesterol. All values are mean ± SEM.

*LCZ696 Attenuated Plaque Progression in ApoE$^{-/-}$ Mice*

After 20 weeks of Western-type diet feeding, en face Sudan IV staining of the aortic arch revealed significantly reduced atherosclerotic lesions in valsartan-treated mice (24.0 ± 1.8%) and LCZ696-treated mice (23.6 ± 3.0%) compared to the hydralazine control group (33.1 ± 3.3%) ($p<0.05$), but no significant difference was observed between the valsartan and LCZ696 groups (Figure 1). These results demonstrated that valsartan or LCZ696 administration in *ApoE*$^{-/-}$ mice attenuated plaque progression without altering metabolic parameters compared to the hydralazine group, although no difference was observed between valsartan and LCZ696.

*LCZ696 reduced the expression of inflammatory mediators in the aorta*

We also examined the effects of LCZ696 on the expression of inflammatory molecules in atherosclerotic aorta using qPCR. Gene-specific primers are highlighted in Table 1. The expression of the macrophage marker F4/80 was statistically significantly lower in the valsartan or LCZ696 groups than in the hydralazine-treated mice. Furthermore, valsartan or LCZ696 administration significantly reduced mRNA expression of inflammatory mediators such as VCAM-1, IL-1β, and TNFα. No difference in F4/80 or inflammatory cytokine expression was observed between the valsartan and LCZ696 groups (Figure 2). These results indicate that valsartan or LCZ696 administration

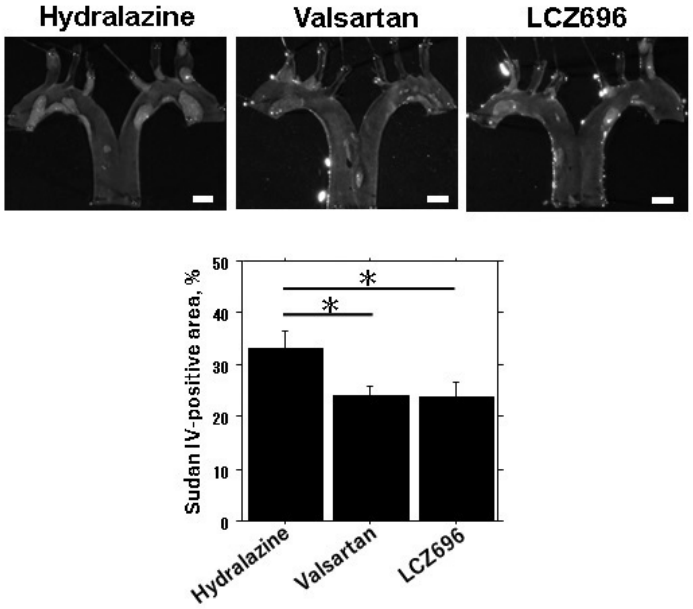


Figure 1. Effect of LCZ696 on atherosclerotic lesion formation in *ApoE*$^{-/-}$ mice.
En face Sudan IV staining of the aortic arch revealed that compared to hydralazine, valsartan (33.1 ± 3.3% vs. 24.0 ± 1.8%, $p<0.05$) and LCZ696 (33.1 ± 3.3% vs. 23.6 ± 3.0%, $p<0.05$) significantly reduced atherosclerotic lesions in *ApoE*$^{-/-}$ mice. No statistically significant difference was observed between the valsartan and LCZ696 groups. n = 13-15 (per group) Scale bar : 1 mm. *$p<0.05$. All values are mean ± SEM.

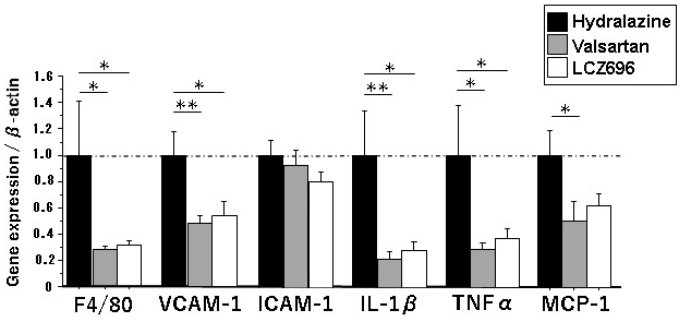


Figure 2. Effect of LCZ696 on vascular inflammation in *ApoE*$^{-/-}$ mice.
Quantitative real-time polymerase chain reaction (qPCR) analyses using abdominal aorta revealed that administration of valsartan or LCZ696 statistically significantly reduced the expression of F4/80, a macrophage marker, compared to the hydralazine-treated group. Furthermore, valsartan or LCZ696 also significantly reduced the expression of inflammatory molecules such as VCAM-1 and IL-1β compared to the hydralazine-treated group in atherosclerotic aortas (n = 13–15). No statistically significant differences were observed between the valsartan group and the LCZ696 group regarding these markers. ICAM-1 ; intercellular adhesion molecule-1, VCAM-1 ; vascular cell adhesion molecule-1, IL-1β ; interleukin-1β, TNF-α ; tumor necrosis factor-α, MCP-1 ; monocyte chemoattractant protein-1. *$p<0.05$, **$p<0.01$. All values are mean ± SEM.

in *ApoE*$^{-/-}$ mice reduces macrophage accumulation and chronic vascular inflammation compared to hydralazine, a non-RAAS inhibitor. However, no difference in macrophage accumulation or vascular inflammation was observed between the valsartan and LCZ696 groups.

## DISCUSSION

Accumulating evidence shows that LCZ696 treatment improves not only hypertension (10, 11) but also the pathogenesis of chronic inflammatory diseases, including renal fibrosis (12-14), glucose intolerance (23-25), and cardiac fibrosis and hypertrophy (26, 27), although little is known about the effect of LCX696 treatment on the development of atherosclerosis. In this study, in order to access anti-arteriosclerotic effect independent of differences in antihypertensive effect, we determine a drug dose of each group that would achieve the same level of antihypertensive effect between LCZ696, valsartan, and hydralazine-treated group. As a result, in this study, there were no significant differences in metabolic parameters including blood pressure between the groups. Our results demonstrated that compared to hydralazine, a non-RAAS inhibitor, valsartan and sacubitril/valsartan (LCZ696) suppressed plaque progression and reduced mRNA expression of multiple inflammatory molecules in the aorta of *ApoE*$^{-/-}$ mice. However, no difference was detected in the anti-atherosclerotic or anti-inflammatory effects between valsartan and LCZ696 in these *ApoE*$^{-/-}$ mice. These findings are consistent with the results of recent large-scale meta-analyses of clinical studies.

Previously, Zhang *et al*. reported that LCZ696 administration to *ApoE*$^{-/-}$ mice with carotid artery external compression injury reduced the carotid arterial plaque volume and vascular inflammation (20). Furthermore, AlSiraj *et al*. reported that LCZ696 administration to *LDLr*$^{-/-}$ mice receiving sustained angiotensin II administration suppressed atherosclerotic plaque formation in the aortic arch compared to valsartan. (21) These studies and our research exhibit numerous model differences, including the genetic background of the mice used, the age at which drug intervention began, the duration of drug administration, and the vessels evaluated. A particularly important difference is that the model mice in previous reports were artificially induced atherosclerosis models developed over a relatively short period through physical injury outside the vessel or high-concentration angiotensin II administration. Our study differs significantly from these previous studies in that we selected and validated a more physiological, naturally occurring atherosclerosis model achieved by long-term high-fat diet feeding in *ApoE*$^{-/-}$ mice to verify consistency with clinical research results. In the more physiological and naturally occurring atherosclerosis model we employed, no difference in anti-vascular inflammatory or anti-atherosclerotic effects was observed between valsartan and LCZ696. This result suggests that the RAAS-inhibitory effects of valsartan, which constitute the anti-inflammatory and anti-atherosclerotic actions of LCZ696 compared to hydralazine, are the primary mechanism.

In conclusion, our data demonstrated that sacubitril/valsartan (LCZ696) administration suppresses atheroma formation and vascular inflammation in ApoE-deficient mice compared to hydralazine, a non-RAAS inhibitor, but its effect was no different from that of valsartan alone. Our findings provide basic evidence consistent with recent clinical research showing that LCZ696 does not demonstrate superior anti-atherosclerotic effects compared to conventional RAAS inhibitors.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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## AUTHOR CONTRIBUTIONS STATEMENT

Conception and design of study, D.F. and M.S.; acquisition of data, J.M. and O.B.; analysis and/or interpretation of data, T.H.; drafting the manuscript, T.H.; revising the manuscript critically for important intellectual content, D.F. and M.S. All authors have read and agreed to the published version of the manuscript.

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