Cardioprotective Effect of LCZ696 (sacubitril/valsartan) After Experimental Acute Myocardial Infarction

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While the long-term benefits of LCZ696 on cardiac function and prognosis have been reported, it remains to be elucidated whether it can also ameliorate cardiac dysfunction on short-term.

The aim of the present study was to evaluate the effects of LCZ696 on cardiac remodeling at acute phase of experimental MI in mice.
Survival and Cardiac Rupture Rate Post-MI

**Survival Rate (%):**
- **Vehicle n=77**
- **Enalapril 4mg/kg n=79**
  - P=0.792, vs Vehicle
- **LCZ696 20mg/kg n=75**
  - P=0.005, vs Vehicle
  - P=0.013, vs Enalapril

**Cardiac Rupture Free Survival (%):**
- **Vehicle n=77**
- **Enalapril 4mg/kg n=79**
  - P=0.674, vs Vehicle
- **LCZ696 20mg/kg n=75**
  - P=0.008, vs Vehicle
  - P=0.028, vs Enalapril

**Cardiac Rupture (Number of animals):**
- **Vehicle**
- **Enalapril 4mg/kg**
- **LCZ696 20mg/kg**
Gene Expression 3 Days Post-MI

- **TNFα/18S**: P=0.410
- **IL-1β/18S**: P=0.803
- **IL-6/18S**: P=0.631
- **TGFβ-1/18S**: P=0.796
- **Col 1α1/18S**: P=0.652
- **MMP-2/18S**: P=0.480
- **MMP-9/18S**: P=0.803
- **TIMP-1/18S**: P=0.476
- **ANP/18S**: P=0.476
- **BNP/18S**: P=0.358

*Significant differences between groups.*
Gelatinolytic Activity 3 Days Post-MI

- **Vehicle**
- **Enalapril**
- **LCZ696**

- Total MMP-9 (pg/mg protein): P<0.001
- Gelatinolytic activity (Arbitrary unit): P=0.723
- Active MMP-9 (pg/mg protein): P=0.003

*Note: Significance levels are indicated by stars.*
Plasma Aldosterone and cGMP Levels

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<th>Plasma Aldosterone (pg/mL)</th>
<th>P=0.018</th>
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<tr>
<td>P=0.014</td>
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<tr>
<td>P=0.482</td>
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<td>P=0.454</td>
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<tr>
<th>Plasma cGMP (pmol/mL)</th>
<th>P&lt;0.001</th>
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<td>P=0.033</td>
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<td>P=0.073</td>
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<td>P&lt;0.001</td>
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<th>Aldosterone/cGMP ratio</th>
<th>P&lt;0.001</th>
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<td>P=1.000</td>
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<td>P=0.002</td>
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Summary

1. LCZ696 significantly reduced death caused by cardiac rupture within 1 week after MI compared with vehicle and enalapril groups.

2. Echocardiography revealed that %FS was significantly improved in LCZ696 but not in enalapril, compared with that in vehicle group at 14 and 28 days after MI.

3. At 3 days after MI, expression of IL-1β, MMP-9 mRNA and MMP-9 activity in infarcted myocardium were significantly decreased in LCZ696 group compared with other two groups, and IL-6 mRNA were significantly decreased in LCZ696 compared with enalapril.

4. At 3 days after MI, plasma cGMP levels were significantly higher, and plasma aldosterone levels were significantly lower in the LCZ696 group than the other groups.
Schematic Diagram in Mechanism of Protective Effects of LCZ696 on Post-MI Cardiac Rupture
Conclusions

- LCZ696 modulated both RAAS and natriuretic peptides systems on acute phase of MI, and prevented the survival rate after MI via the suppression of inflammatory cytokines and MMP-9 activity.
- LCZ696 might be a novel medical treatment for improving the cardiac remodeling after acute phase of MI.