Angiotensin-Receptors Blockers but not Angiotensin-Converting Enzyme Inhibitors Delay the Progression of Aortic Stenosis

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Abstract

Background: Recent experimental studies in animal models and explanted valve tissues suggested that activation of renin-angiotensin system (RAS) may play a role in pathogenesis of calcific aortic stenosis (AS). Previous clinical studies provided conflicting results regarding the effect of RAS inhibitors on AS progression. However these studies have included only patients with angiotensin-converting enzyme inhibitors (ACEIs) or have pooled patients with ACEIs and with angiotensin receptor blockers (ARBs). The objective of this study was to examine the effect of ACEIs and ARBs on AS progression.

Method: 340 consecutive patients with AS and preserved LV function (95% were included), were on ACEIs, 16% on ARBs and 54% had no medication targeting RAS. Mean follow-up time was 3.9 ± 2.1 years. Hemodynamic data were available in Whole cohort (n=340), ARBs group (n=56), ACEIs group (n=115) and No RAS medication group (n=169).

Results: The activation of renin-angiotensin system (RAS) exacerbates the production of angiotensin II, which stimulates medial smooth muscle cells proliferation and activation, leading to increased collagen production and calcification. The findings of this study support the hypothesis that ARBs but not ACEIs delay AS progression. These results could be explained by the fact that ARBs provide more complete blockade of inflammatory and fibro-calciﬁc processes contributing to stenosis progression.

Conclusion: The findings of this study open new avenues for the pharmacological treatment of aortic stenosis and provide strong impetus for the elaboration of randomized studies focusing on ARBs in this population.

Doppler-Echocardiographic Data

<table>
<thead>
<tr>
<th>Model</th>
<th>Univariate</th>
<th>Multivariate Model 1</th>
<th>Multivariate Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>coeff.</td>
<td>p value</td>
<td>coeff.</td>
<td>p value</td>
</tr>
<tr>
<td>Peak aortic jet velocity, m/s</td>
<td>2.8 ± 0.3</td>
<td>0.01</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>Peak transvalvular gradient, mmHg</td>
<td>35 ± 21</td>
<td>0.01</td>
<td>31 ± 10</td>
</tr>
<tr>
<td>Mean transvalvular gradient, mmHg</td>
<td>19 ± 7</td>
<td>0.01</td>
<td>17 ± 6</td>
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<tr>
<td>Aortic valve area, cm²</td>
<td>0.86 ± 0.08</td>
<td>0.54</td>
<td>1.20 ± 0.29</td>
</tr>
<tr>
<td>Aortic valve area index, cm²/m²</td>
<td>0.05 ± 0.04</td>
<td>0.01</td>
<td>0.06 ± 0.05</td>
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<tr>
<td>Velvalvular arterial impedance, mmHg.L/m²</td>
<td>3.9 ± 0.9</td>
<td>0.01</td>
<td>3.8 ± 0.9</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>67 ± 7</td>
<td>0.01</td>
<td>65 ± 7</td>
</tr>
</tbody>
</table>

Mean follow-up time: 3.9±2.1 years

Background

- The activation of renin-angiotensin system (RAS) exacerbates the production of angiotensin II, which stimulates medial smooth muscle cells proliferation and activation, leading to increased collagen production and calcification.
- Recent experimental studies in animal models or explanted valve tissues suggested that the local tissue RAS and thereby of inflammatory and fibro-calciﬁc processes contributing to stenosis.
- The use of angiotensin-receptor blockers (ARBs) provides a more complete blockade of RAS compared to angiotensin-converting enzyme inhibitors (ACEIs).

Objective

To examine speciﬁc effect of ACEIs and ARBs on aortic stenosis progression

Methods

- Study population
  - 340 consecutive patients with AS were included
  - Inclusion criteria:
    • Age >18 years
    • Peak aortic jet velocity >2.0 m/s
    • Left ventricular ejection fraction (LVEF) >50%
    • Concomitant use of ACEIs and ARBs
    • Moderate or severe aortic regurgitation
    • Peak aortic jet velocity, m/s
    • Mean transvalvular gradient, mmHg
    • Aortic valve area, cm²
    • Global LV hemodynamic load
  - Exclusion criteria:
    • Moderate or severe aortic regurgitation
    • Mitral valve disease
    • Concomitant use of ACEIs and ARBs
    • Patients were separated into three groups: Patients on ACEIs (n=115)
    • Patients on ARBs (n=56)
    • Patients without RAS medication (No ACEIs or ARBs, n=169)

- Propensity score
  - To eliminate covariate differences that may lead to biased estimates of treatment effect, we adjusted for propensity score representing probability of having RAS inhibitors or ARBs vs. no RAS medication.

- Baseline peak aortic jet velocity, valvulo-arterial impedance and propensity score, treatment with ARBs (p=0.005) but not with ACEIs (p=0.72), was an independent predictor of lower AS progression.

- These results could be explained by the fact that ARBs provide more complete blockade of the local tissue RAS and thereby of the inflammatory and fibro-calciﬁc processes contributing to stenosis progression.

Conclusion

- This study suggests that ARBs but not ACEIs delay the progression of aortic stenosis.
- These results could be explained by the fact that ARBs provide more complete blockade of the local tissue RAS and thereby of the inflammatory and fibro-calciﬁc processes contributing to stenosis progression.

Acknowledgements

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References

1. Andrews et al., JACC, 11:1569-82, 2007
2. Côté et al., Eur J Clin Invest, in press