Is there any difference between angiotensin converting enzyme inhibitors and angiotensin receptor blockers for heart failure?

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Abstract

Angiotensin receptor blockers are usually considered as equivalent to angiotensin converting enzyme inhibitors for patients with heart failure and low-ejection fraction. Some guidelines even recommend the former as first line treatment given their better adverse effects profile. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified four systematic reviews including eight pertinent randomized controlled trials. We combined the evidence using meta-analysis and generated a summary of findings following the GRADE approach. We concluded angiotensin receptor blockers and angiotensin converting enzyme inhibitors probably have a similar effect on mortality, and they might be equivalent in reducing hospitalization risk too. Treatment withdrawal due to adverse effects is probably lower with angiotensin receptor blockers than with angiotensin converting enzyme inhibitors.

Problem

Angiotensin converting enzyme inhibitors decrease morbidity and mortality in patients with heart failure and systolic dysfunction. It is generally accepted angiotensin receptor blockers have similar benefits, but recommendations vary in the different guidelines, ranging from using them as first-line treatment to reserve them to patients intolerant to angiotensin converting enzyme inhibitors.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.
Key messages

- Angiotensin receptor blockers and angiotensin converting enzyme inhibitors probably have a similar effect on mortality, and they might be equivalent in reducing hospitalization risk too.
- Treatment withdrawals due to adverse effects are probably lower with angiotensin receptor blockers than with angiotensin converting enzyme inhibitors.
- The conclusions of this summary are in agreement with the systematic reviews identified and the main guidelines.

About the body of evidence for this question

<table>
<thead>
<tr>
<th>What is the evidence. See evidence matrix in Epistemonikos later</th>
<th>We found four systematic reviews [1],[2],[3],[4] including eight randomized controlled trials [5],[6],[7],[8],[9],[10],[11],[12].</th>
</tr>
</thead>
<tbody>
<tr>
<td>What types of patients were included</td>
<td>The average age between studies ranged from 56 to 74 years. All studies included patients with heart failure of any etiology, and the most common cause was ischemic. No study included NYHA functional class I patients. All studies restricted inclusion to low ejection fraction patients; two studies required ejection fraction lower than 45% [8],[9], five &lt; 40% [5],[6],[7],[10],[11] and one &lt; 35% [12].</td>
</tr>
<tr>
<td>What types of interventions were included</td>
<td>The angiotensin converting enzyme inhibitors used in the studies was enalapril in five [5],[6],[8],[9],[12], captopril in two [7],[11] and lisinopril in one [10]. The Angiotensin receptor blocker used as comparator was losartan in four studies [7],[9],[11],[12], valsartan in two [8],[10], telmisartan in one [6] and candesartan in one [5].</td>
</tr>
<tr>
<td>What types of outcomes were measured</td>
<td>All-cause mortality or cardiovascular death, all-cause hospitalization, treatment withdrawal, quality of life, exercise tolerance, neurohumoral biomarkers and echocardiographic parameters.</td>
</tr>
</tbody>
</table>

Summary of findings

The information on the effects of carvedilol is based on eight randomized controlled trials including 5201 patients. All studies reported mortality and three reported all-cause hospitalization, [5],[7],[11].

- Angiotensin receptor blockers and angiotensin converting enzyme inhibitors probably have a similar effect on mortality. The certainty of the evidence is moderate.
- Angiotensin receptor blockers and angiotensin converting enzyme inhibitors might be equivalent in reducing hospitalization. The certainty of the evidence is low.
- Treatment withdrawal due to adverse effects is probably lower with angiotensin receptor blockers than with angiotensin converting enzyme inhibitors. The certainty of the evidence is moderate.
# ACEi versus ARB for heart failure

<table>
<thead>
<tr>
<th>Patients</th>
<th>Heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Angiotensin converting enzyme inhibitors (ACEi)</td>
</tr>
<tr>
<td>Comparison</td>
<td>Angiotensin receptor blockers (ARB)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Absolute effect*</th>
<th>Relative effect (95% CI)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WITH ACEi</strong></td>
<td><strong>WITH ARB</strong></td>
<td><strong>RR 1.05</strong></td>
<td>Moderate</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>Difference: patients per 1000</td>
<td>(0.91 to 1.22)</td>
<td>0.95 less to 2.8 more</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>Difference: patients per 1000</td>
<td>(0.92 to 1.08)</td>
<td>0.95 less to 50 more</td>
</tr>
<tr>
<td></td>
<td>(Margin of error: 15 to 50 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment withdrawal due to adverse effects</td>
<td>Difference: patients per 1000</td>
<td>(0.52 to 0.76)</td>
<td>0.95 less to 72 less</td>
</tr>
<tr>
<td></td>
<td>(Margin of error: 36 to 71 less)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**About the certainty of the evidence (GRADE)**

- **High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different is low.

- **Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different is moderate.

- **Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different is high.

- **Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different is very high.

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RR: Risk ratio.  
Margin of error = 95% confidence interval (CI).  
GRADE: evidence grades of the GRADE Working Group (see later in this article).

The risk **WITH ACEi** is based on the risk in the control group of the trials. The risk **WITH ARB** (and its margin of error) is calculated from relative effect (and its margin of error).

1 The studies have a moderate risk of bias, mainly because of lack of clarity in reporting of randomization and allocation concealment.  
2 The studies are inconsistent. Some have shown a decrease in hospitalizations and others have shown no difference (I² = 70%).

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Other considerations for decision-making

To whom this evidence does and does not apply

- The studies included patients with low ejection fraction heart failure of any etiology.
- Even though studies included only patients with NYHA class 2 or superior, it is reasonable to extrapolate the evidence to patients with functional class 1 if the decision is to use one of the drugs evaluated in this summary.

About the outcomes included in this summary

- The outcomes presented are those considered critical for decision-making according to the authors of this summary, and they agree with those used in the main guidelines [13],[14],[15],[16].

Balance between benefits and risks, and certainty of the evidence

- Considering there are no differences in terms of benefits, the balance is in favor of angiotensin receptor blockers, given their lower rate of adverse effects.

Resource considerations

- Even though angiotensin converting enzyme inhibitors are cheaper than angiotensin receptor blockers, the latter still have a relatively low cost. Given their favorable adverse effects profile, and then better adherence, they might have a favorable cost-benefit balance. However, in settings where the costs of angiotensin receptor blockers are higher the balance can be different.

Differences between this summary and other sources

- The conclusion presented in this summary is in agreement with the individual systematic reviews identified [1],[2],[3],[4].
- The conclusion of this summary agree in general terms with the main guidelines, which provide slightly different recommendations among them. Some recommend angiotensin receptor blockers over angiotensin converting enzyme inhibitors [13],[14], and others [15],[16] mention there is no evidence confirming the superiority of one class, so they only recommend angiotensin receptor blockers in patients intolerant to angiotensin converting enzyme inhibitors.

Could this evidence change in the future?

- The probability of this evidence changing with future studies is low, because of the certainty of the evidence.
- We did not identify additional ongoing studies, so it is unlikely that new information pertinent to this question appears in the future.
How we conducted this summary
Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.

Follow the link to access the interactive version [Angiotensin-receptor blockers versus angiotensin converting enzyme inhibitors for heart failure](http://dx.doi.org/10.5867/medwave.2014.06.5997).

Notes
The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in Medwave or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here [http://dx.doi.org/10.5867/medwave.2014.06.5997](http://dx.doi.org/10.5867/medwave.2014.06.5997).

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database ([www.epistemonikos.org](http://www.epistemonikos.org)).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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