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

What is the evidence. See evidence matrix in Epistemonikos later	We found four systematic reviews [1],[2],[3],[4]including eight randomized controlled trials [5],[6],[7],[8],[9],[10],[11],[12].
What types of patients were included	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 < 40% [5],[6],[7],[10],[11] and one < 35% [12].
What types of interventions were included	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].
What types of outcomes were measured	All-cause mortality or cardiovascular death, all-cause hospitalization, treatment withdrawal, quality of life, exercise tolerance, neurohumoral biomarkers and echocardiographic parameters.

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

Patients	Heart failure
Intervention	Angiotensin converting enzyme inhibitors (ACEi)
Comparison	Angiotensin receptor blockers (ARB)

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH ACEi	**WITH ARB**		
	Difference: patients per 1000			
All-cause Mortality	128 per 1000	134 per 1000	RR 1.05 (0.91 to 1.22)	⊕⊕⊕○[1] Moderate
	Difference: 6 patients more per 1000 (Margin of error: 11 less to 28 more)			
All-cause hospitalization	383 per 1000	383 per 1000	RR 1.00 (0.92 to 1.08)	⊕⊕○○[1,2] Low
	Difference: 0 patients per 1000 (Margin of error: 15 less to 50 more)			
Treatment withdrawal due to adverse effects	149 per 1000	94 per 1000	RR 0.63 (0.52 to 0.76)	⊕⊕⊕○[1] Moderate
	Difference: 55 patients less per 1000 (Margin of error: 36 to 71 less)			

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 (I^2= 70%).

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.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

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.
- Event 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 recommmend 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 inforamation 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.
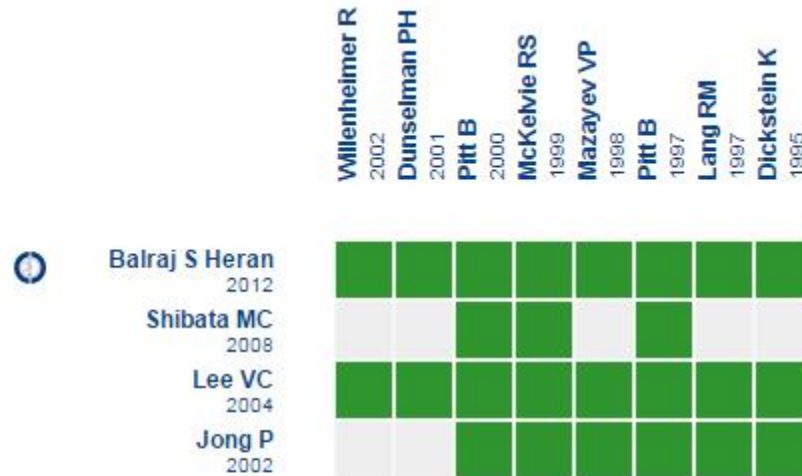
Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version** Angiotensin-receptor blockers versus angiotensin converting enzyme inhibitors for heart failure

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.

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).

These summaries follow a rigorous process of internal peer review.

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

References

1. Lee VC, Rhew DC, Dylan M, Badamgarav E, Braunstein GD, Weingarten SR. Meta-analysis: angiotensin-receptor blockers in chronic heart failure and high-risk acute myocardial infarction. Ann Intern Med. 2004 Nov 2;141(9):693-704. Erratum in: Ann Intern Med. 2005 Mar 1;42(5):391. | PubMed |
2. Jong P, Demers C, McKelvie RS, Liu PP. Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2002 Feb 6;39(3):463-70. |PubMed |
3. Shibata MC, Tsuyuki RT, Wiebe N. The effects of angiotensin-receptor blockers on mortality and

morbidity in heart failure: a systematic review. Int J Clin Pract. 2008 Sep;62(9):1397-402. | CrossRef | PubMed |

4. Heran BS, Musini VM, Bassett K, Taylor RS, Wright JM. Angiotensin receptor blockers for heart failure. Cochrane Database Syst Rev. 2012 Apr 18;4:CD003040. | CrossRef | PubMed |

5. McKelvie RS, Yusuf S, Pericak D, Avezum A, Burns RJ, Probstfield J, et al. Comparison of candesartan, enalapril, and their combination in congestive heart failure: randomized evaluation of strategies for left ventricular dysfunction (RESOLVD) pilot study. The RESOLVD Pilot Study Investigators. Circulation. 1999 Sep 7;100(10):1056-64. | PubMed |

6. Dunselman PH; Replacement of Angiotensin Converting Enzyme Inhibition (REPLACE) Investigators. Effects of the replacement of the angiotensin converting enzyme inhibitor enalapril by the angiotensin II receptor blocker telmisartan in patients with congestive heart failure. The replacement of angiotensin converting enzyme inhibition (REPLACE) investigators. Int J Cardiol. 2001 Feb;77(2-3):131-8; discussion 139-40. | PubMed |

7. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet. 1997 Mar 15;349(9054):747-52. | PubMed |

8. Willenheimer R, Helmers C, Pantev E, Rydberg E, Löfdahl P, Gordon A. Safety and efficacy of valsartan versus enalapril in heart failure patients. Int J Cardiol. 2002 Oct;85(2-3):261-70. |PubMed |

9. Lang RM, Elkayam U, Yellen LG, Krauss D, McKelvie RS, Vaughan DE, et al. Comparative effects of losartan and enalapril on exercise capacity and clinical status in patients with heart failure. The Losartan Pilot Exercise Study Investigators. J Am Coll Cardiol. 1997 Oct;30(4):983-91. | PubMed |

10. Mazayev VP, Fomina IG, Kazakov EN, Sulimov VA, Zvereva TV, Lyusov VA, et al. Valsartan in heart failure patients previously untreated with an ACE inhibitor. Int J Cardiol. 1998 Aug;65(3):239-46. | PubMed |

11. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000 May 6;355(9215):1582-7. | PubMed |

12. Dickstein K, Chang P, Willenheimer R, Haunsø S, Remes J, Hall C, et al. Comparison of the effects of losartan and enalapril on clinical status and exercise performance in patients with moderate or severe chronic heart failure. J Am Coll Cardiol. 1995 Aug;26(2):438-45. |PubMed |

13. Arnold JM, Liu P, Demers C, Dorian P, Giannetti N, Haddad H, et al. Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management. Can J Cardiol. 2006 Jan;22(1):23-45. | PubMed |

14. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. J Card Fail. 2010 Jun;16(6):e1-194. |CrossRef | PubMed |

15. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012 Jul;33(14):1787-847. | CrossRef | PubMed |

16. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2013 Oct 15;128(16):e240-327. | CrossRef | PubMed |

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