



Are Angiotensin Receptor Blockers as safe as Angiotensin Converting Enzyme Inhibitors in Patients with Heart Failure?

A Systematic Review and Meta Analysis of Randomized Controlled Trials

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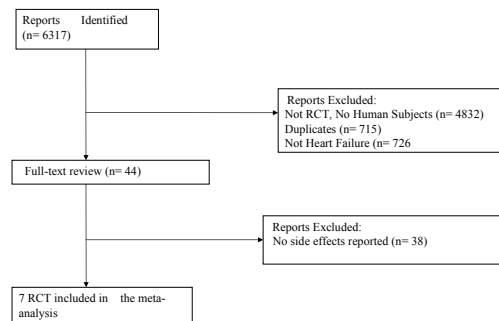


Background

- Angiotensin converting enzyme inhibitors (ACE-I) are standard care in all patients with heart failure without contraindications.
- Concerns related to adverse effects limit the use of ACE-I in some patients. Angiotensin receptor blockers (ARB) directly block the action of angiotensin II at the receptor level and have no effect on bradykinin production, which lead to some of the adverse effects seen with ACE-I (cough, angioedema).
- The most recent heart failure guidelines recommend that ARB may be used as alternatives to ACE-I as first-line therapy for patients with mild to moderate heart failure and reduced left ventricular ejection fraction (class IIA recommendation). However, it is not clear whether a superior safety profile of ARB's justify equal footing with ACE-I.
- ARB and ACE-I have shown similar efficacy in a growing number of randomized trials in heart failure patients. However, the safety and tolerability of ACE-I and ARB has not received as much scrutiny. Most trials were not primarily designed to assess safety and tolerability.
- We therefore, performed a systematic review and meta-analysis of randomized controlled trials to test the hypothesis that ACE-I and ARB have the same tolerability and safety profile in patients with heart failure.

Methods

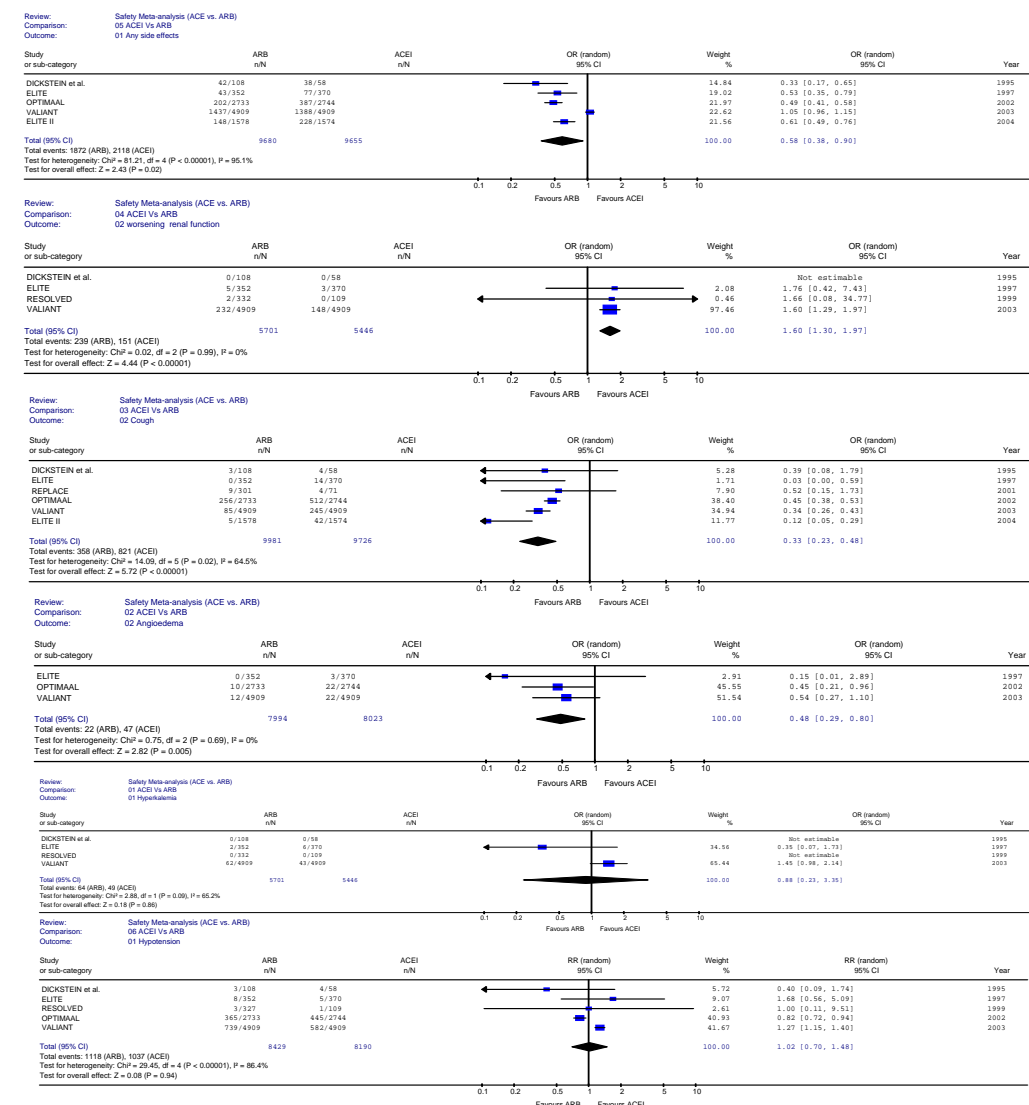
- All randomized, placebo-controlled trials that looked into the use of ACEI and ARB use in CHF patients were identified using a 2-level search strategy
- We searched public domain databases including MEDLINE, the Cochrane database, EMBASE and BIOSIS Previews
- We used the following key words: heart or cardiac failure, angiotensin converting enzyme inhibitors and angiotensin receptor blockers as well as individual medication names
- Relevant studies were identified through a manual search of secondary sources, including references of initially identified articles and proceedings from national cardiology meetings from 2003 through 2006
- We excluded trials that did not have an ACEI or ARB arm, those that did not report safety, tolerability and side effects of the studied drugs
- The search was performed without any language restrictions
- Trials were not excluded based on the number of patients or follow-up duration.
- We characterized the methodological quality of the trials by using a scoring system developed by Jadad and colleagues which is based on the description of randomization, blinding, and withdrawals and can range from 0 to 5, where higher score indicates better methodological quality
- The meta-analysis was performed by computing Odds Ratio (OR) using random-effects model
- Inter- study heterogeneity was quantified by means of I²
- The flow diagram summarize the research strategy :



Baseline Characteristics

	Dickstein et al.	ELITE	RESOLVD	REPLACE	ELITE II	OPTIMAAL	VALIANT
Publication Year	1995	1997	1999	2000	2000	2002	2003
ACEI	Enalapril	Captopril	Enalapril	Enalapril	Captopril	Captopril	Captopril
ARB	Losartan	Losartan	Candesartan	Telmisartan	Losartan	Losartan	valsartan
LV EF	≤35%	<40%	<40%	≤40%	≤40%	<35%	≤40%
Sample Size	166	722	768	378	3152	5477	14703
Follow Up (months)	2	12	10.7	3	19.7	32.4	24.7
Age (year ± SD)	64.4(9.6)	73.5(5.9)	62.9	64(10)	71.4(6.8)	67.4(9.8)	65±11.8
Males (%)	77.3	66	89	89	70	71.2	69
Jaddad score	4	4	2	3	4	5	4
Race% (Caucasian)	–	89.5	–	–	82	98.5	93.2
Diuretics (%)	94.6	74	84.5	100	59	63.8	78

Results



Results (cont'd)

- This meta-analysis included data from seven clinical trials with a total of 20143 patients, 10308 patients were assigned to the ARB arm while 9835 patients were assigned to ACE inhibitor arm.
- The overall incidence of adverse events in the trials included was low with the highest prevalence in VALIANT and OPTIMAAL trials.
- ARB's showed a lower rate of any adverse effect compared to ACE-I (HR 0.58) but the significance was not strong (p=0.02) and there was heterogeneity between trials in this outcome.
- Contrary to this, ARB's had a strong association with risk of worsening renal function (HR 1.6, p<0.00001).
- There was a trend toward hyperkalemia with ARBs but the difference between the two arms was not statistically significant
- Cough was the most reported side effect (in 6 out of 7 trials), and as expected cough and angioedema were more common with ACE-I.
- There was no difference observed in risk of hypotension.
- There was no evidence of publication bias on visual inspection of the funnel plot.

Discussion

- ARB use is associated with less overall adverse events compared with the use of ACE-I in patients with heart failure. However, breaking down these events reveals that ARB's are strongly associated with an increased risk of worsening renal function, but reduced risk of cough or angioedema.
- Side effects related to reduced Angiotensin II formation (hypotension, hyperkalemia and renal failure) are the same or higher with ARB use, whereas effects thought to be related to increased kinins (cough, angioneurotic edema and anaphylactoid reactions) were expectedly lower with ARB's, since ACE is also a Kininase.
- The mechanism of the an increased risk of worsening renal function with ARB use is unclear. HF patients (who are often also prescribed diuretics) may be an especially vulnerable population to this adverse event due to their typical fluctuations in fluid status including occasional hypovolemia. Given the strong association of worsening renal function with outcomes among heart failure patients, this a particular important adverse effect to consider in this population.
- One might predict a parallel increase in incidence of hyperkalemia with the worsening renal function with ARB use. However, no difference was found between the two drugs. The fact that the difference failed to reach statistical significance may be due to the low incidence and/or low reporting of hyperkalemia in the included studies, limiting our power for this endpoint.
- Hypotension, on the other hand was well reported across the trials with a moderate event rate. There appears to be no difference between the two drugs when all the trials were combined.
- When VALIANT was excluded in the sensitivity analysis, a statistically significant increase of hypotension incidence was found with ACE-I compared to ARB with no heterogeneity among the trials.

Conclusions

- The cumulative evidence suggests that although ARB are associated with a lower overall risk of adverse events, they are strongly associated with an increased risk of worsening renal function in heart failure patients.
- The clinical relevance of this finding requires further study, until which ARB should remain 2nd line therapy except for patients that are thought to have ACE-I related cough or angioedema.