HEART REVIEW

Angiotensin blockade or aldosterone blockade as the third neuroendocrine-blocking drug in mild but symptomatic heart failure patients

A D Struthers

Heart 2006;92:1728–1731. doi: 10.1136/hrt.2005.068668

Recent clinical trials have explored whether angiotensin receptor blockers (ARBs) or aldosterone blockade should be added to standard angiotensin-converting enzyme (ACE) inhibitor/ β blocker treatment in heart failure. Both strategies are of some value but it is unclear which strategy should be used first in patients with mild but symptomatic heart failure. The arguments for and against each strategy are discussed. The strongest argument for aldosterone blockade is the consistency in the results of the RALES (Randomized Aldactone Evaluation Study) and EPHEUS (Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study) studies, but what is lacking is a trial of aldosterone blockade in patients with mild, symptomatic heart failure as such. The strongest argument for ARBs is that the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) Added trial result was positive in the precise patient population of interest (mild, symptomatic heart failure). The strength of this argument is diminished by the somewhat different results in Val-HeFT (Valsartan Heart Failure Trial). A third possibility is to use neither an ARB nor an aldosterone blocker and arguments can be marshalled for this position also. Clinicians should now assess these various arguments to select what they believe would be best for their patients.

present the strengths and weaknesses of the evidence for and against each of these therapeutic manoeuvres, which I hope will help the reader to decide between the two. Table 1 summarises these arguments.

In this discussion, ACE inhibitor-intolerant people are excluded, as the evidence is clear that ARBs should be used in this situation as part of a double neuroendocrine-blocking strategy. The CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) Alternative trial is therefore not relevant to the question of which is the best third drug to use.

The main clinical trials that we have to guide us in making a decision between these two strategies are RALES (Randomized Aldactone Evaluation Study) and EPHEUS (Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study) for aldosterone blockade.^{3–4} The trials that guide us for angiotensin receptor blockade are Val-HeFT (Valsartan Heart Failure Trial), CHARM and VALIANT (Valsartan in Acute Myocardial Infarction Trial).^{5–7} In the RALES trial, spironolactone was given to patients with severe heart failure, where it reduced total mortality by a highly significant 30% including an impressive reduction in sudden cardiac death. In the EPHEUS trial, eplerenone was given to patients with post-myocardial infarction (MI) and left ventricular dysfunction, where it reduced total mortality by a highly significant 15%. Sudden cardiac death was also impressively reduced (21%). Table 2 summarises these results.

With regard to ARBs, the first trial was Val-HeFT. Total mortality was not altered at all but the combined end point of total mortality or heart failure hospitalisation was significantly reduced. This was followed by the CHARM

It is well established in all grades of chronic heart failure that an angiotensin-converting enzyme (ACE) inhibitor and a β blocker are efficacious. Much evidence has shown, however, that the renin-angiotensin-aldosterone system is not fully suppressed by our current use of ACE inhibitors in heart failure.^{1,2} Because of that, trials have been undertaken to see whether blocking the residual angiotensin or the residual aldosterone in addition to standard ACE inhibitor treatment is beneficial. Results have been positive with each of these treatment strategies, but an angiotensin receptor blocker (ARB) and an aldosterone receptor blocker have not been compared head to head in this situation. Hence, it is hard to know whether the third neuroendocrine-blocking drug to be used in mild but symptomatic chronic heart failure should be an ARB or an aldosterone receptor blocker. Here I

Correspondence to:
Professor Allan D Struthers,
Division of Medicine &
Therapeutics, Ninewells
Hospital, Dundee DD1
9SY, UK; a.d.struthers@
dundee.ac.uk

Accepted
16 November 2005
Published Online First
9 December 2005

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BEST, Beta-blocker Evaluation of Survival Trial; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; CONSENSUS II, Cooperative New Scandinavian Enalapril Survival Study II; EPHEUS, Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study; MI, myocardial infarction; LIFE, Losartan Intervention For Endpoint reduction in hypertension; MOSES, Morbidity and mortality after Stroke: Eprosartan compared with nitrendipine in Secondary prevention; RALES, Randomized Aldactone Evaluation Study; Val-HeFT, Valsartan Heart Failure Trial; VALIANT, Valsartan in Acute Myocardial Infarction Trial; VALUE, Valsartan Antihypertensive Long-term Use Evaluation

Table 1 Summary of the case for and against aldosterone versus angiotensin receptor blockade**The case for aldosterone blockade**

- Consistency between RALES and EPHESUS trial results
- Positive effect on total mortality
- Cheapness of spironolactone

The case against aldosterone blockade

- Lack of specific trial in mild to moderate heart failure
- Side effects
- Lack of regulatory licence to use in mild to moderate heart failure

The case for angiotensin blockade

- Correct patient population considered in CHARM Added

The case against angiotensin blockade

- Inconsistent results between Val-HeFT and CHARM Added
- Lack of positive effect documented on total mortality
- Adverse effect of triple neuroendocrine blockade in Val-HeFT

CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; EPHESUS, Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study; RALES, Randomized Aldactone Evaluation Study; Val-HeFT, Valsartan Heart Failure Trial.

Added trial, where the combined end point of cardiovascular death or heart failure hospitalisation was significantly (15%) reduced, although the study was not powered for total mortality itself. Thereafter, the VALIANT trial with a post-MI population showed that valsartan had no added benefit in addition to an ACE inhibitor, although the dose of valsartan used as a third drug was low. Clearly, these five trials do not give a clear-cut picture and therefore I will discuss the case for and against aldosterone blockade, and then the case for and against using an ARB.

THE CASE FOR ALDOSTERONE RECEPTOR BLOCKADE

The strongest argument here is that the two trials, which both used aldosterone receptor blockade, are consistent in that total mortality was significantly reduced in both. There are no contrary studies. This consistency of trial result is really important because, even for well-established treatments such as ACE inhibitors and β blockers, at least one trial result has been contrary—for example, CONSENSUS II (Cooperative New Scandinavian Enalapril Survival Study II) and BEST (Beta-blocker Evaluation of Survival Trial).⁸

Another argument in favour of aldosterone receptor-blocking drugs is that total mortality is the best end point to have in a trial because it is an unequivocal end point. Only the aldosterone receptor-blocking drugs have significantly altered total mortality.

Another argument in favour of aldosterone receptor blockade is cost, although this is obviously complex. Spironolactone is a generic drug, which is extremely cheap and is certainly much cheaper than the currently available ARBs. This is not a clear-cut argument, however, because the EPHESUS trial was done with a non-generic aldosterone receptor-blocking drug called eplerenone. A whole other issue is therefore whether spironolactone or eplerenone should be given to these patients. Clearly, cost would be a differentiating feature only if the aldosterone receptor-blocking drug chosen to be used were spironolactone.

THE CASE AGAINST ALDOSTERONE RECEPTOR-BLOCKING DRUGS

The main argument against aldosterone receptor-blocking drugs is that they have not been investigated in patients with mild but symptomatic congestive heart failure. The RALES trial recruited patients with severe heart failure with left ventricular ejection fraction of 25%; 71% were in New York Heart Association class III with the rest in class IV. Arguing that we know only in chronic heart failure that aldosterone receptor-blocking drugs are effective in fairly severe heart

Table 2 Summary of trial results

Trial	Results	Number of participants
Angiotensin receptor blockers added to ACE inhibitors		
Val-HeFT	Neutral	5010
CHARM Added	Positive	2548
VALIANT	Neutral	14703
Aldosterone blockade added to ACE inhibitors		
RALES	Positive	1663
EPHESUS	Positive	6642

ACE, angiotensin-converting enzyme; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; EPHESUS, Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study; RALES, Randomized Aldactone Evaluation Study; Val-HeFT, Valsartan Heart Failure Trial; VALIANT, Valsartan in Acute Myocardial Infarction Trial.

failure is therefore legitimate. The EPHESUS trial recruited patients within 3–14 days of an acute MI and therefore some doubt must exist as to whether the EPHESUS benefit would occur if the aldosterone blocker were begun after this acute MI period. On the other hand, left ventricular ejection fraction in RALES and Val-HeFT differs by only 2% and in RALES and CHARM Added by only 3% (table 3). Clearly extrapolating left ventricular ejection fraction between different trials is fraught with danger but it does illustrate the point that, although the severity of the disease differed between RALES, Val-HeFT and CHARM, the differences were not huge.

How convincing these arguments are depends on how closely the strict inclusion criteria for each study are applied in day-to-day clinical practice. The principles of evidence-based medicine do suggest we apply such criteria fairly closely, in which case a reasonably strong argument against aldosterone receptor-blocking drugs is that no clinical trial has tested them in patients with mild symptomatic heart failure. The enthusiast for aldosterone receptor-blocking drugs could counter that argument a bit by pointing out that, in the subgroup analysis of the RALES trials, spironolactone was actually more beneficial in patients with a left ventricular ejection fraction higher than 26% than in those with a left ventricular ejection fraction less than 26%. The enthusiast for aldosterone blockade could also argue that aldosterone blockade was studied at the beginning of heart failure in the post-MI period in EPHESUS and at the end of heart failure in RALES and, as it was positive at both extremes, it would probably be positive in the middle—that is, in patients with mild to moderate congestive heart failure (table 4). This only partially counters the argument, however, that there is no actual clinical trial of aldosterone

Table 3 Overview of severity of left ventricular dysfunction and trial results

Study	LVEF* (%)	Result
RALES	25 (7)%	Positive for ALDO B
Val-HeFT	27 (7)%	Neutral for ARB
CHARM Added	28 (7.5)%	Positive for ARB
EPHESUS	33 (6)%	Positive for ALDO B

*Mean (SD).

ALDO B, aldosterone receptor blocker; ARB, angiotensin receptor blocker; CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; EPHESUS, Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study; LVEF, left ventricular ejection fraction; RALES, Randomized Aldactone Evaluation Study; Val-HeFT, Valsartan Heart Failure Trial.

Table 4 Results of clinical trials of ARB and ALDO B in the spectrum of heart failure

Treatment	Post-MI	Mild to moderate CHF	Severe CHF
ALDO B	Positive results	Unstudied	Positive results
ARB	Neutral results	Inconsistent results	Unstudied

ALDO B, aldosterone receptor blocker; ARB, angiotensin receptor blocker; CHF, congestive heart failure; MI, myocardial infarction.

receptor-blocking drugs in patients with mild symptomatic heart failure, which is distant in time from their acute MI.

A related argument against aldosterone receptor-blocking drugs is that the results of EPHEUS, which is a post-MI patient trial, cannot be extrapolated to patients with chronic heart failure because clinical trials of these two different scenarios have very different rates of each end point. Indeed, in the meta-analysis of ACE inhibitors by Flather *et al.*,⁸ the event rates are different in post-MI trials and heart failure trials.⁸ For example, MI is about 4% more common in post-MI trials than in heart failure trials, whereas heart failure rehospitalisation is about 5% higher in heart failure trials than in post-MI trials. The time sequence for these events is also different, as events cluster in the first six months in post-MI trials but less so in heart failure trials. The argument is therefore that the results of a post-MI heart failure trial cannot be extrapolated to chronic heart failure and vice versa. There is validity in this argument. On the other hand, all treatments that work in one of these conditions have so far always turned out to work also in the other condition—for example, ACE inhibitors, β blockers, aldosterone blockers and implantable cardioverter-defibrillators. Nevertheless, it is a fair argument against aldosterone receptor-blocking drugs that results from post-MI heart failure trials should only be extrapolated with caution to the treatment of patients with chronic heart failure, who are distant from their index MI.

A further argument against aldosterone receptor-blocking drugs is that their incidence of adverse effects on potassium and renal function is fairly high when they are used in routine clinical practice.⁹ Clearly, the side effect burden of a treatment is an important consideration. An argument against this, however, is that detailed examination of the CHARM Added trial shows a 1.59% excess in serious hyperkalaemia for the active drug over the placebo drug. This compares with a 1.62% excess of serious hyperkalaemia with the active drug over the placebo drug in EPHEUS. The incidence of serious hyperkalaemia in the clinical trials is therefore similar with an ARB and an aldosterone receptor drug in addition to an ACE inhibitor (table 5). Such comparisons are of course very approximate, as hyperkalaemia was not measured or recorded in the same way in the different trials.

Once people start using ARBs in real clinical practice, the incidence of hyperkalaemia may well be as high as has been documented for spironolactone in real live patients.⁹ No such

Table 5 Incidence of serious hyperkalaemia in excess of treatment with placebo

	Placebo	Active drug	Excess
RALES	1.19%	1.70%	0.51%
EPHEUS	3.82%	5.44%	1.62%
CHARM Added	1.09%	2.68%	1.59%

CHARM, Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity; EPHEUS, Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study; RALES, Randomized Aldactone Evaluation Study.

data yet exist, however, either to confirm or to deny this possibility. The biochemical side effects of aldosterone blockade are a concern, whereas we do not yet know how much of a concern they might be for ARBs in the real world. Even less do we know what the side effect level would be in the real world if we used both an ARB and spironolactone, along with an ACE inhibitor. Hence, triple renin-angiotensin-aldosterone system blockade cannot be recommended, except possibly for highly selected patients who are intensively monitored.

Another argument against using aldosterone blockade in mild to moderate heart failure is that there is only guideline justification for using spironolactone in severe heart failure. This is based on the RALES trial and therefore the guidelines say that spironolactone should be used only in severe heart failure. There is no licence or regulatory approval to use spironolactone outside this precise indication. If a doctor were to prescribe spironolactone to a patient with mild heart failure and the patient developed hyperkalaemia or renal dysfunction and came to harm from this, the doctor would therefore have less legal protection and could be criticised. Doctors do not risk legal criticism only when they prescribe spironolactone for severe heart failure or eplerenone to patients in the immediate post-MI period, or when they prescribe candesartan for moderate chronic heart failure. If doctors were to extrapolate from these strict criteria, they may be opening themselves to legal criticism if their patients experienced side effects.

A further argument against aldosterone blockade arises because β blockers were seldom used in the RALES trial. This is another valid argument, although it can be countered to some extent by the finding in a subgroup analysis of RALES that spironolactone was still highly significantly effective at reducing mortality in the 10% of RALES patients who were already taking β blockers. In fact, spironolactone appeared even more effective in those RALES patients already taking β blockers.

THE CASE FOR ARBS

The main case for using an ARB comes from the CHARM Added trial, because of which there is regulatory approval to use candesartan in milder versions of heart failure. In fact, only candesartan can be recommended in this situation because Val-HeFT did not fully agree with the CHARM Added trial, as a result of which there is no regulatory approval to use valsartan in addition to an ACE inhibitor in heart failure.

A second powerful argument is that the recent European Society of Cardiology guidelines on heart failure endorse the use of candesartan in this situation.

These are two powerful arguments in favour of ARBs in less than severe heart failure.

THE CASE AGAINST ARBS

The only "positive" ARB trial (out of three trials) is the CHARM Added trial, which used candesartan. The totality of the evidence therefore shows that the case for using ARBs is far from watertight. To emphasise this point, a meta-analysis has been published by Dimopoulos *et al.*,¹⁰ which was restricted to patients already taking β blockers. The effect of angiotensin receptor blockade on total mortality gave an odds ratio of 1.08 (95% confidence interval 0.9 to 1.29).

There is, however, a counterargument to this viewpoint because a pattern is emerging that supports the idea that the CHARM Added trial should be seen on its own and not be assessed alongside the valsartan trials. This is because of a developing idea that valsartan may be an underperforming ARB compared with other ARBs. For example, in the different clinical situation of essential hypertension, losartan was significantly better than atenolol in the LIFE (Losartan

Intervention For Endpoint reduction in hypertension) study despite blood pressure control being the same.¹¹ In the recent MOSES (Morbidity and mortality after Stroke: Eprosartan compared with nitrendipine in Secondary prevention) study¹² (presented at the European Society of Cardiology annual meeting, Munich, 2004), eprosartan outperformed nitrendipine in stroke reduction despite similar blood pressures. Clearly, therefore, the LIFE trial and the MOSES trial are suggesting that ARBs can outperform other hypertension drugs. Yet, in the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial, valsartan did not outperform amlodipine.¹³ There is therefore a discrepancy between the performance of valsartan against hypertension in the VALUE trial and that of other ARBs in other trials (LIFE and MOSES) for stroke reduction beyond blood pressure control. This apparent underperformance of valsartan in VALUE as compared with LIFE and MOSES raises the possibility that valsartan is less good than other ARBs at reducing cardiovascular events. There is no clear reason why valsartan should be an underperforming ARB but, if this speculative possibility is true, then it may of course also explain why Val-HeFT and CHARM results were not entirely consistent. This argument could justify treating heart failure with candesartan in the belief that the cause of the discrepancy between CHARM Added and Val-HeFT could be that valsartan underperforms other ARBs. This idea is of course entirely speculative and is based on trial results in another disease (hypertension), which may be extrapolating too far. In addition, valsartan appeared to produce, if anything, a greater mortality reduction in ACE inhibitor-intolerant patients in Val-HeFT than candesartan did in CHARM Alternative, which goes against the idea that valsartan is an underperforming ARB.^{14 15}

The second argument against ARBs is, in the Val-HeFT trial, a worryingly adverse effect of using valsartan in patients who were already taking an ACE inhibitor and a β blocker. Probably the problem in this subgroup was the unfortunate play of chance but the adverse effect on mortality was significant in this subgroup by itself. It is difficult to totally ignore this finding. Reassurance that this was probably pure bad luck comes from the lack of such an adverse effect of ARBs when they were added to ACE inhibitors and β blockers in both CHARM and VALIANT.

CONCLUSIONS

It is possible to marshal strong arguments on either side of this debate. It is up to individual doctors and to those who write guidelines to assess the respective merits of each drug for each of their patients. The strongest argument for aldosterone blockade is the consistency found in the two trials with this strategy. This cannot be said for ARBs because the trial results are inconsistent, although explanations for this inconsistency do exist. On the other hand, only candesartan has been used in a positive trial with the correct patient population with mild to moderate symptomatic chronic heart failure. Many will see this argument as having an advantage over the consistency seen with aldosterone blockade. A third position is, of course, that the evidence is not compelling enough to treat mild to moderate heart failure

with either aldosterone or angiotensin blockade for two reasons: aldosterone blockade has not been studied in this precise clinical situation and ARBs have produced inconsistent results when they have been studied in this precise situation. This option would also be cheaper, require less monitoring and have a lower risk of hyperkalaemia and renal dysfunction. Although this third option is not unreasonable, its downside is that the patient retains increased symptoms and increased risk that could arguably be alleviated to some extent by a third drug. Unfortunately, no new trial results will guide us on this issue in the foreseeable future and practising clinicians will need to decide between these three options on the basis of the various arguments presented.

Research funding from the British Heart Foundation and the Chief Scientist Office.

Competing interests: The author has received honoraria for speaking from Pfizer (aldosterone blockers) and from Takeda, Astra Zeneca and Novartis (angiotensin receptor blockers), and has a small amount of stock in Astra Zeneca.

REFERENCES

- 1 Farquharson C, Struthers AD. Gradual reactivation over time of vascular tissue angiotensin I to angiotensin II conversion during chronic lisinopril therapy in chronic heart failure. *J Am Coll Cardiol* 2002;**39**:767–75.
- 2 MacFadyen RJ, Lee AFC, Morton JJ, et al. How often are angiotensin II and aldosterone concentrations raised during chronic ACE inhibitor treatment in cardiac failure? *Heart* 1999;**82**:57–61.
- 3 Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;**341**:709–18.
- 4 Pitt B, Remme W, Zannad F, et al. Eplerenone a selective aldosterone blocker in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–21.
- 5 Cohn JN, Tognoni G. A randomised trial of the angiotensin receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;**345**:1667–75.
- 6 McMurray JJV, Ostergren J, Svedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left ventricular systolic function taking angiotensin converting inhibitors: the CHARM Added trial. *Lancet* 2003;**362**:767–71.
- 7 Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril or both in myocardial infarction complicated by heart failure, left ventricular dysfunction or both. *N Engl J Med* 2003;**349**:1893–906.
- 8 Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction, a systemic overview of data from individual patients. *Lancet* 2000;**355**:1575–81.
- 9 Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalaemia after publication of the randomised aldactone evaluation study. *N Engl J Med* 2004;**51**:543–51.
- 10 Dimopoulos K, Salukhe TV, Coats AJS, et al. Meta-analyses of mortality and morbidity effects of an angiotensin receptor blocker in patients with chronic heart failure already receiving an ACE inhibitor (alone or with a beta-blocker). *Int J Cardiol* 2004;**93**:105–11.
- 11 Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002;**359**:995–1003.
- 12 Schrader J, Luders S, Kulschewski A, et al. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomised controlled study (MOSES). *Stroke* 2005;**36**:1218–26.
- 13 Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004;**363**:2002–31.
- 14 Maggioni AP, Anand I, Gottlieb SO, et al. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin converting enzyme inhibitors. *J Am Coll Cardiol* 2002;**40**:1414–21.
- 15 Granger CB, McMurray JJV, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet* 2003;**362**:772–6.