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

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ABSTRACT
Recent clinical trials have explored whether ARB or aldosterone blockade should be added to standard ACEI/β Blocker therapy in heart failure. Both strategies are of some value but it is unclear which strategy should be used first in mild but symptomatic heart failure patients. Here I discuss the arguments for and against each strategy. The strongest argument for aldosterone blockade is the consistency in the results of the RALES and EPHESUS studies but what is lacking is a trial of aldosterone blockade in mild, symptomatic heart failure patients as such. The strongest argument for ARBs is that the CHARM Added trial produced a positive result in the precise patient population of interest (mild, symptomatic heart failure) but the strength of this argument is diminished by the fact that ValHeFT produced a somewhat different result. A third possibility is to use neither an ARB nor an aldosterone blocker and arguments can be marshalled for this position also. Each clinician should now weigh up these various arguments to select what they feel would be best for their patients.
It is well established in all grades of chronic heart failure that an angiotensin converting enzyme inhibitor and a beta-blocker are efficacious. However, numerous pieces of evidence have shown that the renin angiotensin aldosterone system is not fully suppressed by our current use of ACE inhibitors in heart failure.\(^1\,^2\) It is because of that, that trials have been undertaken in an effort to see whether blocking the residual angiotensin or the residual aldosterone on top of standard ACE inhibitor treatment is beneficial or not. Positive results have been found with each of these therapeutic strategies, but there has been no head to head comparison of an angiotensin receptor blockade against an aldosterone receptor blockade in this situation, and 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 angiotensin receptor blocker or an aldosterone receptor blocker. Here the strengths and weaknesses of the evidence for and against each of these therapeutic manoeuvres are presented, which hopefully will help the reader to decide between the two. These arguments are summarised in Table 1.

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

<table>
<thead>
<tr>
<th>The Case for Aldosterone Blockade</th>
<th>The Case against Aldosterone Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency between RALES &amp; EPHESUS trial results</td>
<td>No specific trial in mild/moderate heart failure</td>
</tr>
<tr>
<td>Positive effect on total mortality</td>
<td>Side effects</td>
</tr>
<tr>
<td>Cheapness of spironolactone</td>
<td>No regulatory licence to use in mild/moderate heart failure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>The Case for Angiotensin Blockade</th>
<th>The Case against Angiotensin Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARM Added addresses the correct patient population</td>
<td>Inconsistent results between ValHeFT &amp; CHARM Added</td>
</tr>
<tr>
<td></td>
<td>No positive effect documented on total mortality</td>
</tr>
<tr>
<td></td>
<td>Adverse effect of triple neuroendocrine blockade in ValHeFT.</td>
</tr>
</tbody>
</table>

In this discussion, ACE inhibitor intolerant people are excluded since the evidence is clear that angiotensin blockers should be used in this situation as part of a double neuroendocrine blocking strategy. Therefore, the CHARM Alternative trial is not relevant to the question of which is the best third drug to use.

The main clinical trials which we have to guide us in making a decision between these two strategies are the RALES trial and the EPHESUS trial for aldosterone blockade.\(^3\,^4\) The trials which guide us for angiotensin receptor blockade are ValHeFT, CHARM and VALIANT.\(^5\,^7\) 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 EPHESUS trial, eplerenone was given to patients with post myocardial infarction and left ventricular dysfunction where it reduced total mortality by a highly significant 15%. Again, there was an impressive reduction (21%) in sudden cardiac death. These results are summarised in Table 2.
Table 2: Summary of Trial Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect on Total Mortality</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARBs added to ACEIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ValHeFT</td>
<td>Neutral results</td>
<td>5010</td>
</tr>
<tr>
<td>CHARM Added</td>
<td>Positive results</td>
<td>2548</td>
</tr>
<tr>
<td>VALIANT</td>
<td>Neutral results</td>
<td>14703</td>
</tr>
<tr>
<td>ALDO BLOCKADE added to ACEIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RALES</td>
<td>Positive results</td>
<td>1663</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>Positive results</td>
<td>6642</td>
</tr>
</tbody>
</table>

With regard to angiotensin receptor blocking drugs, the first trial was ValHeFT. Total mortality was not altered at all but a significant reduction was seen in the combined endpoint of total mortality or heart failure hospitalisation. This was followed by the CHARM Added trial where a significant (15%) reduction was seen in the combined endpoint of cardiovascular death or heart failure hospitalisation although the study was not powered for total mortality itself. Thereafter, the VALIANT trial in post myocardial infarction patients showed that valsartan had no added benefit on top of an ACE inhibitor although the dose of valsartan used as a third drug was low in VALIANT. Clearly, these five trials don't give a clear-cut picture and therefore I will now discuss the case for and against aldosterone blockade, and then the case for and against using an angiotensin receptor blocker.

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 therapies like ACE inhibitors and β Blockers, there has often been at least one contrary trial result, eg the CONSENSUS II study and the BEST study.8

Another argument in favour of aldosterone receptor blocking drugs is that total mortality is the best endpoint to have in a trial because it is an unequivocal endpoint. 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 angiotensin receptor blocking drugs. However, this is not a clear-cut argument because the EPHESUS trial was done with a non-generic aldosterone receptor blocking drug called eplerenone and therefore a whole other issue is whether one should use spironolactone or eplerenone in these patients and clearly cost would only be a differentiating feature if the aldosterone receptor blocking drug chosen to be used was spironolactone.

The case against Aldosterone Receptor Blocking Drugs

The main argument here is that aldosterone receptor blocking drugs have not been investigated in mild but symptomatic CHF patients. The RALES trial recruited patients with severe heart failure where their current left ventricular ejection fraction was 25% and 71% were in NYHA class III with the rest in NYHA class IV. Therefore, it is a legitimate argument to say that we only know in chronic heart failure that aldosterone receptor blocking drugs are effective in fairly severe heart failure. The EPHESUS trial recruited patients within 3-14 days of an acute myocardial infarction and therefore some doubt must exist as to whether the EPHESUS benefit would occur if the aldosterone blocker was begun after this
acute myocardial infarction period. On the other hand, there is only a 2% difference in LVEF between RALES and ValHeFT and only a 3% difference between RALES and CHARM Added (Table 3). Clearly extrapolating LVEF values between different trials is fraught with danger but it does illustrate the point that although the severity of the disease was different between RALES, ValHeFT and CHARM, the differences were not huge.

Table 3: Overview of severity of LV dysfunction and trial results

<table>
<thead>
<tr>
<th>Study</th>
<th>LVEF %</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES</td>
<td>25 ± 7%</td>
<td>Positive for ALDO B</td>
</tr>
<tr>
<td>ValHeFT</td>
<td>27 ± 7%</td>
<td>Neutral for ARB</td>
</tr>
<tr>
<td>CHARM Added</td>
<td>28 ± 7.5%</td>
<td>Positive for ARB</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>33 ± 6%</td>
<td>Positive for ALDO B</td>
</tr>
</tbody>
</table>

ARB = Angiotensin Receptor Blocker  
ALDO B = Aldosterone Receptor Blocker

How convincing the reader finds these arguments depends on how closely the reader wishes to apply the strict inclusion criteria for each study in applying a study to their day to day clinical practice. The principles of evidence based medicine do suggest we apply such criteria fairly closely in which case it is a reasonably strong argument against aldosterone receptor blocking drugs that they have no clinical trial 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 sub-group analysis of the RALES trials, patients with a left ventricular ejection fraction higher than 26% actually got more of a benefit from spironolactone than did those patients with a left ventricular ejection fraction less than 26%. The enthusiast for aldosterone blockade could also argue that aldosterone blockade has been studied at the beginning of heart failure in the post MI period in EPHESUS and at the end of heart failure in RALES and since it was positive at both extremes, it is likely that it would be positive in the middle, i.e. in patients with mild to moderate CHF (Table 4).

Table 4: Spectrum of Heart Failure

<table>
<thead>
<tr>
<th>Aldo Blockade</th>
<th>Post MI</th>
<th>Mild/moderate CHF</th>
<th>Severe CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB</td>
<td>Positive Results</td>
<td>Unstudied</td>
<td>Positive Results</td>
</tr>
<tr>
<td></td>
<td>Neutral Results</td>
<td>Inconsistent results</td>
<td>Unstudied</td>
</tr>
</tbody>
</table>

However, this only partially counters the argument that there is no actual clinical trial of aldosterone receptor blocking drugs in patients with mild symptomatic heart failure, which is distant in time from their acute myocardial infarction.

A related argument against aldosterone receptor blocking drugs is that one cannot extrapolate the results of EPHESUS, which is a post-myocardial infarction patient trial to patients with chronic heart failure because clinical trials of these two different scenarios have very different rates of each endpoint. Indeed, if one examines the event rates in the meta analysis of ACE inhibitors performed by Flather et al (2000), the event rates are different in post-MI trials from heart failure trials. For example, myocardial infarction is about 4% more common in post-MI trials than in heart failure trials whereas heart failure re-hospitalisation is about 5% higher in heart failure trials than in post-MI trials. The time sequence for these events is also different since events cluster in the first six months in post-MI trials whereas this is less the case for heart failure trials. Therefore the argument is that one cannot extrapolate what one finds in a post-myocardial infarction heart failure trial 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, e.g. ACE inhibitors, beta blockers, aldosterone blockers and ICDs. Nevertheless, it is a fair argument against aldosterone receptor blocking drugs that one should be cautious about extrapolating results from post-myocardial infarction heart failure trials to chronic heart failure patients who are distant from their index myocardial infarction.

A further argument against aldosterone receptor blocking drugs is that they produce a fairly high incidence of adverse effects on potassium and renal function when they are used in routine clinical practice. Clearly the side effect burden of a therapy is an important consideration. However, an argument against this is that if the CHARM added trial is examined in detail, there was 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 where the active drug versus the placebo drug in EPHESUS and therefore the incidence of serious hyperkalaemia in the clinical trials is similar between using an angiotensin receptor blocking drug or an aldosterone receptor drug on top of an ACE inhibitor (Table 5). Such comparisons are of course very approximate since the way hyperkalaemia was measured or recorded varied between the different trials.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Active</th>
<th>Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>RALES</td>
<td>1.19</td>
<td>1.70</td>
<td>0.51</td>
</tr>
<tr>
<td>EPHESUS</td>
<td>3.82</td>
<td>5.44</td>
<td>1.62</td>
</tr>
<tr>
<td>CHARM Added</td>
<td>1.09</td>
<td>2.68</td>
<td>1.59</td>
</tr>
</tbody>
</table>

It may well be that once people start using angiotensin receptor blocking drugs in real clinical practice, the incidence of hyperkalaemia may be as high as has been documented for spironolactone in real life patients. However, no such data yet exist to either confirm or deny this possibility. It would have to be said that 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 angiotensin receptor blocking drugs in the real world. Even less do we know what the side effect level will be in the real world if we used both an ARB and spironolactone, along with an ACE inhibitor and hence triple RAAs blockade cannot be recommended, except possibly in highly selected patients undergoing intensive monitoring.

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 and this is based on the RALES trial and therefore guidelines say that spironolactone should only be used in severe heart failure. There is no licence or regulatory approval to use spironolactone outside this precise indication and therefore if a prescribing doctor was to use spironolactone in mild heart failure and the patient developed hyperkalaemia, or renal dysfunction, and came to harm from this, then the doctor would have less legal protection and could be criticised. The only situations where the doctor does not risk legal criticism are when he/she is using spironolactone in severe heart failure or eplerenone in the immediate post-myocardial infarction patients or if he/she uses candesartan in moderate chronic heart failure. If the doctor were to extrapolate from these strict criteria, he/she may be laying themselves open to legal criticism if side effects occurred.

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

The case for Angiotensin Receptor Blocking Drugs
The main case for using an angiotensin receptor blocking drug comes from the CHARM added trial because of which there is regulatory approval to use candesartan in milder versions of heart failure. In fact it is only candesartan which can be recommended in this situation because the ValHeFT results did not fully agree with CHARM added in its results, as a result of which there is no regulatory approval to use valsartan on top of 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 angiotensin receptor blocking drugs in less than severe heart failure.

The case against Angiotensin Receptor Blocking Drugs (ARBs)
The only “positive” ARB trial (out of three trials) is the CHARM added trial where candesartan was used. Therefore, if one was to examine the totality of the evidence, the case for using ARBs is far from watertight. To emphasise this point, a meta-analysis has been published by Dimopoulos et al.\textsuperscript{10} In the meta-analysis which was restricted to patients already on beta blockers, the effect of angiotensin receptor blockade on total mortality gave an odds ratio of 1.08 (confidence interval 0.9 to 1.29).

There is however a counterargument to this viewpoint because a pattern is emerging which 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 in comparison to other ARBs. For example, in the different clinical situation of essential hypertension, losartan was significantly better than atenolol in the LIFE study despite BP control being the same.\textsuperscript{11} In the recent MOSES study (presented at ESC, Munich 2004), eprosartan outperformed nitrendipine in stroke reduction despite similar BPs. Clearly, therefore, the LIFE trial and the MOSES trial are pointing in the direction that ARBs can outperform other anti-hypertensive drugs. Yet, in the VALUE trial Valsartan did not outperform amlopidine.\textsuperscript{12} There is therefore a discrepancy between how Valsartan performed in hypertension in the VALUE trial and how other ARBs performed in other trials (LIFE and MOSES) in terms of stroke reduction beyond BP control. This apparent underperformance of Valsartan in VALUE as compared to LIFE and MOSES raises the possibility that Valsartan is less good at reducing cardiovascular events than other angiotensin receptor blocking drugs. 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 ValHeFT and CHARM results were not entirely consistent. This would be an argument which could justify our following the results of CHARM added and using candesartan in heart failure in the belief that the discrepancy between CHARM added and ValHeFT could be because Valsartan underperforms other angiotensin receptor blocking drugs. This idea is of course entirely speculative and it is based on trial results in another disease (hypertension) which may be an extrapolation too far. In addition, valsartan appeared to produce, if anything, a greater
mortality reduction in ACEI intolerant patients in ValHeFT than candesartan did in CHARM Alternative which rather goes against the idea that valsartan is an underperforming ARB.\textsuperscript{13,14}

The second argument against ARBs is that in the ValHeFT trial, there was a worryingly adverse effect of using Valsartan in patients who were already on an ACE inhibitor and a beta blocker. Probably the problem in this sub-group was the unfortunate play of chance but the adverse effect on mortality was significant in this sub-group by itself and it is difficult to totally ignore this finding. Reassurance that this was probably pure bad luck comes from the fact that no such adverse effect of ARB therapy was seen when ARBs were added to ACE inhibitors and beta blockers in both CHARM and VALIANT.

CONCLUSIONS

It is possible to marshal strong arguments on either side of this debate and it is up to individuals and to those who write guidelines to weigh up respective merits of the case for each drug in each of their patients. To summarise, the strongest argument for aldosterone blockade is the consistency found in the two trials with this strategy. This cannot be said for ARBs where the available trials are inconsistent although explanations do exist which might explain this inconsistency. On the other hand, it is only with candesartan that a positive trial has been undertaken in the correct patient population of mild to moderate symptomatic chronic heart failure patients and this argument will be seen by many as the one with the edge over the consistency seen with aldosterone blockade. A third position is, of course, that the evidence is not compelling enough to use either aldosterone or angiotensin blockade in mild to moderate heart failure because aldosterone blockade has not been studied in this precise clinical situation and because ARBs have produced inconsistent results when they have been studied in this precise situation. This option would also be cheaper and require less monitoring and produce less 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 based on the various arguments discussed above.
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I have received honoraria for speaking from Pfizer (aldo blockers) and from Takeda, Astra Zeneca and Novartis (ARBs). I have a small amount of stock in Astra Zeneca (£2,000 odd).

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