Eplerenone: is it time to add this drug to current heart failure therapy?

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Aldosterone blocking agents, or more correctly mineralocorticoid receptor antagonists (MRAs), have been shown to be effective in reducing mortality and hospitalizations for heart failure (HF) in patients with chronic HF with a reduced left-ventricular ejection fraction (REF), and in patients with HFREF early postmyocardial infarction (postMI) [Pitt *et al.* 1999, 2003; Zannad *et al.* 2011].

In the *Randomized Aldactone Evaluation Study* (RALES) [Pitt *et al.* 1999], spironolactone at a dose of 25–50 mg/day on top of standard therapy was administered to patients with a history of New York Heart Association (NYHA) class IV HFREF, but who were in either NYHA class III or IV at the time of randomization. The trial was stopped prematurely due to a significant 30% reduction in all-cause mortality and a 35% reduction in the need for hospitalization for HF. These results have been the basis of a class 1 indication for the use of an MRA in patients with chronic severe HFREF in both the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines [Hunt *et al.* 2009; Dickstein *et al.* 2008]. Many clinicians however questioned the applicability of these results to current clinical practice since only 10% of patients were on a β -adrenergic blocking agent at the time of randomization; at the time the study was initiated the role of β -blockers in patients with chronic severe HFREF was uncertain. It should however be pointed out that the point estimate for a reduction in mortality by spironolactone in the small subgroup of patients receiving a β -blocker was as great as or greater than in those patients not on a β -blocker.

The RALES trial was followed by the *Eplerenone Heart Failure Efficacy and Survival Study*

(EPHESUS) [Pitt *et al.* 2003] in which patients with HFREF between 3 and 14 days postMI were randomized to the more selective MRA, eplerenone, at a dose of 25–50 mg/day or placebo on top of standard therapy. Patients randomized to eplerenone were found to have a significant reduction in total mortality as well as the combined endpoint of cardiovascular mortality and hospitalization for HF. Of interest was the finding that there was a significant reduction in total mortality 30 days postrandomization (the mean time of randomization postMI was 7 days) [Pitt *et al.* 2005]. This reduction in total mortality early postMI was found to be due mainly to a reduction in sudden cardiac death. In contrast to the patients in the RALES trial, approximately 85% of patients in EPHESUS were on a β -blocker and over 90% on an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocking agent (ARB). An analysis of those patients on ‘optimum’ medical therapy in EPHESUS, i.e. patients who had received aspirin, undergone coronary reperfusion, were on a statin, an ACEI or ARB, a β -blocker, and a diuretic, revealed that eplerenone resulted in a significant reduction in mortality in addition to all of our current medical therapies for patients with HFREF. The results of EPHESUS have led to a class 1 indication for the use of a MRA in patients with HFREF early postMI in both the AHA/ACC and ESC guidelines.

The beneficial results of MRA administration to patients with chronic severe HFREF and to patients with HFREF early postMI are supported by a meta-analysis of all randomized trials of an aldosterone blocking agent in patients with chronic HFREF and HFREF postMI [Ezekowitz and McAllister, 2009]. Since publication of this meta-analysis in 2009, the results of the

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Eplerenone in Mild Patients Hospitalization and Survival study in Heart Failure (EMPHASIS-HF) trial have been published [Zannad *et al.* 2011]. In EMPHASIS-HF, patients with HFREF (a left-ventricular ejection fraction of <30%, or if between 30% and 35% if the QRS complex was >130 ms) who had been hospitalized for a cardiovascular reason within the 6 months prior to randomization (and patients who had elevated plasma concentrations of the brain natriuretic peptides BNP or NT-pro BNP who had not been hospitalized), and who were in NYHA class II at the time of randomization were given eplerenone at a dose of 25–50 mg/day or placebo. The trial was stopped prematurely since the patients randomized to eplerenone had a significant reduction in the primary endpoint of cardiovascular mortality and hospitalization for HF as well as a significant reduction in total mortality and total hospitalizations. The baseline medications in patients entered into the EMPHASIS-HF trial reflected contemporary therapy and included >93% on an ACEI or ARB and >87% on a β -blocker. Of interest was the finding that this significant reduction in total mortality and total hospitalizations in patients randomized to eplerenone was accomplished with only a 0.6% nonsignificant increase in the incidence of serious hyperkalemia (serum potassium ≥ 6.0 meq/l), a 0.1% nonsignificant increased incidence of hospitalization for hyperkalemia, and a 0.1% nonsignificant increase in the incidence of hospitalization for worsening renal failure.

It should be emphasized that despite an increased incidence of hyperkalemia in RALES, EPHEUS, and EMPHASIS-HF in patients randomized to an aldosterone blocking agent, there has not been a single death attributed to hyperkalemia but, as pointed out above, a significant reduction in total mortality on top of standard medical therapy has been observed. The recommendation regarding the use of an MRA in patients with mild–moderate HFREF as a result of EMPHASIS-HF in future AHA/ACC and ESC guidelines will likely reflect the patient characteristics in the trial and its results.

Which patients with HF should receive an MRA?

Clearly, patients with chronic severe HFREF (NYHA class III–IV) and patients with HFREF early postMI should receive an MRA in addition to standard therapy including an ACEI or ARB

and a β -blocker if there is no contraindication to their use such as a serum potassium >5.0 meq/l or an estimated glomerular filtration rate (eGFR) <30/ml/min/1.73 m². (Patients, especially those with chronic kidney disease (CKD), who are unwilling or unlikely to undergo serial monitoring of serum potassium, should not receive a MRA.)

Final recommendations regarding the use of an MRA in patients with mild–moderate HFREF (NYHA class II) should await AHA/ACC and ESC guidelines. It would however be reasonable based upon the results of EMPHASIS-HF to use an MRA in patients with NYHA class II who have had a cardiovascular hospitalization within the past 6 months and/or who have elevated plasma BNP or NT-proBNP levels. Patients in NYHA class II HFREF who show evidence of progressive symptoms despite standard therapy with an ACEI or ARB and a β -blocker would also likely be candidates for a MRA.

Which patients with HF should not receive an MRA?

In patients with NYHA class II HFREF who are stable on an ACEI or ARB and a β -blocker and who have normal BNP or NT-proBNP plasma levels, there is no compelling evidence for the use of an MRA. However, as mentioned above, if patients have had a recent cardiovascular hospitalization an MRA should be considered.

In patients with HF and a preserved left ventricular ejection (HFPEF) there is also no evidence on cardiovascular outcomes to support the use of an MRA at this time. These patients are often elderly and may have concomitant diabetes mellitus and/or CKD such that the risk/benefits of an MRA might not be as favorable as in patients with HFREF. The role of an MRA in patients with HFPEF is currently under investigation in the National Heart Blood and Lung Institute (NHLBI) TOPCAT trial (*Trial of Aldosterone Antagonists Therapy in Adults with Preserved Ejection Fraction Congestive Heart Failure*) [Clinical Trials.gov identifier: NCT00094302] and the results are expected sometime in 2013.

In patients admitted to hospital with an episode of acute decompensated HF who have not previously been on an MRA, there is no evidence for initiating an MRA during the acute phase of HF after hospitalization. These patients often have unstable blood pressure and/or renal dysfunction

during the early days posthospitalization and therefore the risk:benefit of an MRA under these circumstances is uncertain. However, once the patient is stable, has evidence of HFREF, and no contraindications to the use of an MRA (such as a serum potassium >5.0 meq/l and/or an eGFR <30 ml/min/1.73 m²), it should be initiated.

Which MRA should be used in a patient with HFREF?

Both the MRAs, spironolactone and eplerenone, have been shown to be effective in reducing mortality in patients with HFREF. Current guidelines in general do not distinguish between the use of these two agents but many clinicians have chosen to use spironolactone in patients with HF due to their long familiarity with its use and the fact that it is now a generic medicine and relatively inexpensive.

Spironolactone however has a known side effect profile including breast pain and gynecomastia in males and menstrual irregularities in premenstrual females due to its relative nonspecificity for the mineralocorticoid receptor and its effects on androgen and progesterone receptors.

Eplerenone, due to its relatively higher specificity for the mineralocorticoid receptor, is devoid of these side effects and therefore better tolerated, at least in males. While the relatively low price of spironolactone has favored its use in comparison to eplerenone it should be pointed out that eplerenone is now generic, at least in the USA, and its price can be expected to fall, although not to the level of spironolactone since its synthesis is more expensive.

There is however another important consideration in the choice of an MRA in patients with HFREF. Spironolactone has been found to increase hemoglobin A1c (HbA1c) levels in patients with diabetes mellitus [Davies *et al.* 2004]. While spironolactone has been shown to improve endothelial dysfunction in patients with HFREF treated with an ACEI [Farquharson and Struthers, 2000], in patients with diabetes mellitus it may worsen endothelial dysfunction associated with an increase in HbA1c levels [Davies *et al.* 2004]. In a recent direct comparative study of spironolactone and eplerenone in patients with diabetes mellitus [Yamaji *et al.* 2010] spironolactone was found to increase HbA1c levels, decrease adiponectin levels, and increase serum cortisol

levels while eplerenone did not. Thus, it would appear that in patients with diabetes mellitus, and likely those with visceral obesity and the metabolic syndrome at risk for the development of diabetes mellitus, that eplerenone would be the MRA of choice.

There is another consideration regarding the choice between spironolactone and eplerenone. While as mentioned above many clinicians have chosen to use spironolactone at a dose of 25–50 mg/day in patients with HFREF early postinfarction and may consider the use of spironolactone in patients with mild–moderate HFREF (using spironolactone doses similar to those used for eplerenone in the EMPHASIS-HF trial), it should be emphasized that the risk:benefit ratio seen in EPHEUS and EMPHASIS-HF with eplerenone 25–50 mg/day may not be the same as with spironolactone 25–50 mg/day. Spironolactone, although less specific for the mineralocorticoid receptor, is more tightly bound than eplerenone and has a longer half life (it produces an active canrenone metabolite) and therefore 25–50 mg of spironolactone in a patient with mild–moderate HFREF would likely result in a higher incidence of hyperkalemia and renal dysfunction with a less favorable risk:benefit ratio than eplerenone 25–50 mg as used in EMPHASIS-HF. Therefore, despite the attraction of the inexpensive option of using spironolactone, it is safer to use eplerenone, at least in patients postMI as well as those in mild HFREF in order to secure the clinical benefits based on the evidence from the EPHEUS and EMPHASIS-HF trials.

How should patients with HFREF treated with a MRA be followed?

Patients with HFREF and normal renal function (eGFR >60 ml/min/1.73 m²) should have a measurement of serum potassium and serum creatinine prior to initiation of an MRA. As mentioned above, patients with a serum potassium >5.0 meq/l and or an eGFR <30 ml/min/1.73 m² should not receive an MRA. After instituting therapy with an MRA these measurements should be repeated within 1–4 weeks. If the serum potassium and creatinine remain within normal limits these measurements can be repeated during routine follow-up visits, preferably every 4 months. At any time a change in electrolyte status is suspected, for example after an episode of diarrhea or vomiting and or when a drug affecting potassium secretion is administered such as a

nonsteroidal anti-inflammatory drug (NSAID), potassium supplement, and/or the addition of multiple renin–angiotensin inhibitor/blockers such as an ARB or direct renin inhibitor, the sequence of monitoring outlined above should be repeated. In patients with CKD and/or diabetes mellitus it would be prudent to continue monitoring serum potassium monthly, at least for the first several months and thereafter every 3–6 months.

At any time serum potassium increases >5.0 meq/l on a nonhemolyzed blood sample, the dose of the MRA should be reduced by half and if at any time serum potassium is >5.5 meq/l, the aldosterone blocking agent should be withheld until serum potassium is <5.0 meq/l. If at any time serum potassium is >6.0 meq/l and/or there are ECG changes suggestive of hyperkalemia, the MRA should be withheld and a careful review of the patient's medications should be undertaken to eliminate any agent such as an NSAID that might contribute to an increase in serum potassium. If the serum potassium remains >6.0 meq/l and/or there are persistent ECG changes suggestive of hyperkalemia despite withdrawal of the MRA, consideration should be given to institute appropriate therapy for hyperkalemia.

While monitoring of serum potassium and renal function is essential in a patient with HFREF receiving an MRA, it should be emphasized that in the large-scale randomized trials of MRAs [Pitt *et al.* 1999, 2003; Zannad *et al.* 2011] where the monitoring strategy detailed above was used there has not been a single death attributed to hyperkalemia. However, in clinical practice where clinicians have ignored the inclusion and exclusion criteria used in the large-scale randomized trials, have used doses of MRAs >25 – 50 mg/day, and or have failed to serially monitor serum potassium and to adjust the dose of the MRA accordingly, there have been several reports of renal failure requiring dialysis and death. Thus, if one wishes to obtain the benefits of an MRA on total mortality as seen in the large-scale randomized trials it is essential to follow the recommendations outlined above.

Conclusion

There is increasing evidence that in patients with chronic HFREF and in patients with HFREF early postMI that an MRA provides a benefit on mortality and morbidity above and beyond that provided by standard therapy including an ACEI or ARB and a β -blocker. While both

spironolactone and eplerenone have been shown to reduce mortality and hospitalizations for HF in patients with HFREF, eplerenone would appear to be the agent of choice in a patient with diabetes mellitus and likely in those with visceral obesity and the metabolic syndrome at risk for diabetes mellitus. In patients with severe HFREF without evidence of diabetes mellitus, spironolactone at a dose of 25–50 mg/day would be the MRA of choice because of its relatively low price and proven efficacy. Male patients with evidence of breast pain or gynecomastia on spironolactone should however be switched to eplerenone.

In patients with HFREF early postMI and in patients with mild–moderate HFREF, similar to those included in EPHESUS and EMPHASIS-HF trials, eplerenone at a dose of 25–50 mg/day, due to its favorable risk:benefit ratio and proven efficacy, would appear to be the MRA of choice. It should however be emphasized that to achieve the benefits and favorable risk:benefit ratio seen in RALES, EPHESUS, an EMPHASIS-HF, it is necessary to carefully adhere to the inclusion and exclusion criteria in these trials, to serially monitor serum potassium and creatinine, and to adjust the dose of the MRA accordingly as well as to follow the recommendations in guidelines such as those from the Heart Failure Society of America [Lindenfeld *et al.* 2010].

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Conflict of interest statement

Both Dr Pitt and Dr Zannad are consultants to Pfizer.

References

- Davies, J.I., Band, M., Morris, A., Struthers, A.D. (2004) Spironolactone impairs endothelial function and heart rate variability in patients with Type 2 diabetes. *Diabetologia* 47: 1687–1694.
- Dickstein, K., Cohen-Solal, A., Filippatos, G., McMurray, J.J., Ponikowski, P., Poole-Wilson, P.A. *et al.* (2008) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur J Heart Fail* 10: 933–989.
- Ezekowitz, J.A. and McAllister, F.A. (2009) Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. *Eur Heart J* 30: 469–477.

- Farquharson, C.A. and Struthers, A.D. (2000) Spironolactone increases nitric oxide bioactivity, improves endothelial vasodilator dysfunction, and suppresses vascular angiotensin I/angiotensin II conversion in patients with chronic heart failure. *Circulation* 101: 594–597.
- Hunt, S.A., Abraham, W.T., Chin, M.H., Feldman, A.M., Francis, G.S., Ganiats, T.G., *et al.* (2009) Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults. *J Am Coll Cardiol* 53: e1–e90.
- Lindenfeld, J., Albert, N.M., Boehmer, J.P., Collins, S.P., Ezekowitz, J.A., Givertz, M.M., *et al.* (2010) Executive Summary: HFSA 2010 Comprehensive Heart failure Practice Guideline. *J Card Fail* 16: 475–539.
- Pitt, B., Remme, W.J., Zannad, F., Neaton, J., Martinez, F., Roniker, B., *et al.* (2003) Eplerenone, a selective aldosterone blocker in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 348: 1309–1321.
- Pitt, B., White, H., Nicolau, J., Martinez, F., Gheorghide, M., Aschermann, M., *et al.* (2005) Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 46: 425–431.
- Pitt, B., Zannad, F., Remme, W.J., Cody, R., Castaigne, A., Perez, A., *et al.* (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 341: 709–717.
- Yamaji, M., Tsutamoto, T., Kawahara, C., Nishiyama, K., Yamamoto, T., Fujii, M., *et al.* (2010) Effect of eplerenone versus spironolactone on cortisol and hemoglobin A_{1c} levels in patients with chronic heart failure. *Am Heart J* 160: 915–921.
- Zannad, F., McMurray, J.J., Krum, H., van Veldhuisen, D.J., Swedberg, K., Shi, H., *et al.* (2011) Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 364: 11–21.

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