Aldosterone blockade in patients with heart failure and a reduced left ventricular ejection fraction

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This editorial refers to 'Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials' by J.A. Ezekowitz and F.A. McAlister on page 469

Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-adrenergic receptor blockers (BBs), and aldosterone blockers (ABs) have been shown to be effective in reducing cardiovascular mortality and the need for hospitalizations for heart failure (HF) in patients with chronic HF and a reduced left ventricular ejection fraction (HFREF) and in patients with HFREF post-myocardial infarction (MI). The use of ACEIs, ARBs, and BBs in appropriate patients in clinical practice has, however, been far greater than for ABs.1 There are probably a number of reasons for this apparent gap in the application of ABs to clinical practice despite their class 1 indication for patients with severe chronic HFREF.2

The recent meta-analysis by Ezekowitz and McAlister3 of 19 randomized trials comprising 10,807 patients with either chronic HFREF or HF post-MI randomized to an AB (spironolactone, eplerenone, or canrenone) or placebo focuses attention on the role of ABs in patients with HFREF and shows a 20% reduction in all-cause mortality [95% confidence interval (CI) 0.74–0.87] in patients randomized to an AB. Although the RALES and EPHESUS trials supplied the overwhelming majority of the evidence supporting the effectiveness of AB in these patient populations, the results of the remaining relatively smaller trials are consistent with the results of the larger trials. These beneficial results were associated with an absolute 2.9% increase in hyperkalaemia in EPHESUS, whereas in those with an eGFR <60 mL/min/1.73 m², in whom the risk of hyperkalaemia is increased, serum potassium should be monitored closely over the long term.

The mechanisms responsible for the beneficial effects of ABs in patients with HFREF continue to evolve but include: an increase in antioxidant reserves and a decrease in oxygen free radical formation; an increase in the availability of nitric oxide and an improvement in endothelial function; a decrease in vascular and myocardial fibrosis, hypertrophy, and remodelling; a decrease in sympathetic nervous system activation; a decrease in myocardial calcium channel expression; a decrease in myocardial apoptosis; as well as an increase in sodium excretion with a concomitant decrease in plasma volume.

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in adverse effects including symptomatic hypotension, hyperkalaemia, and renal dysfunction.\(^6\)\(^5\) One explanation for the apparent better efficacy of ABs when added to an ACEI and/or an ARB than an ARB is the finding in EPHESUS that the AB eplerenone did not have any significant effect on blood pressure when added to an ACEI and/or a BB,\(^6\) whereas adding an ARB often results in symptomatic hypotension and its consequences. This is important since a recent study using ambulatory blood pressure monitoring in patients with HFREF has found a relatively high incidence of unrecognized hypotensive episodes, especially during the night, when neurohumeral blocking agents including a BB or ARB are added to an ACEI, and has suggested that these episodes were associated with an adverse effect on cardiovascular outcomes.\(^7\) It has also been suggested that the effects of angiotensin II and mineralocorticoid receptor activation in the heart are additive and that it may be necessary to combine an AB with an ACEI or ARB to obtain maximal benefits.\(^8\)

While one would like to see further large-scale trials of ABs in patients with severe chronic HFREF or HF post-MI, it is unlikely they will be available, in large part since the currently available ABs are generic or soon to be generic. We will, however, as pointed out by Ezekowitz and McAlister,\(^3\) have further evidence in patients with NYHA Class II HFREF (EMPHASIS-HF)\(^9\) and in patients with HF and a preserved left ventricular ejection fraction (HFPEF) (TOPCAT).\(^10\) The latter trial is of particular importance in view of the failure of I-Preserve to show a benefit of irbesartan in patients with HFREF.\(^11\)

While ABs have great promise across the entire spectrum of HF, their greatest potential may lie in preventing the development of HF. An increase in serum aldosterone levels post-MI has been shown to predict an increase in mortality independent of the presence of HF,\(^12\) suggesting that ABs might be important in reducing mortality before HF develops as well as preventing the development of HF. In patients with HFREF post-MI in EPESUS, those with a prior history of hypertension had a significantly greater reduction in mortality than those without a prior history,\(^13\) suggesting an upregulation of the mineralocorticoid receptor in patients with hypertension. In patients with essential hypertension, ABs have been shown to be of benefit in reducing blood pressure, reducing myocardial hypertrophy, and reducing urinary albuminuria, and are particularly effective in patients with resistant hypertension.\(^14\)\(^15\) Thus, it can be postulated that ABs may be of value in preventing the development of HF and its consequences in patients with essential hypertension, post-MI, and in other high risk groups such as those with diabetes mellitus. This hypothesis will, however, require evaluation as to the safety as well as the efficacy of this strategy in large-scale randomized trials. Until further information is available, the meta-analysis by Ezekowitz and McAlister\(^3\) focuses our attention on the role of ABs in HFREF and their potential to reduce cardiovascular mortality further in these high risk patients.

**Conflict of interest:** B.P. has served as a consultant for Pfizer, Novartis, Merck, Takeda, and AstraZeneca.

**References**