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Extended Research Article

Benefits of aldosterone receptor antagonism in chronic kidney disease: the BARACK-D RCT

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Scientific summary

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Scientific summary

Background

Chronic kidney disease (CKD) is a major cause of increased mortality and morbidity through increased vascular events and progression to end-stage renal failure (ESRF). These increased events result in CKD having high cost to healthcare systems, with the dialysis required in ESRF benchmarked as at the maximum acceptable cost-effectiveness threshold for an intervention by most healthcare systems. However, the most important component of CKD in terms of mortality and morbidity is cardiovascular disease (CVD).

While the cardiovascular risk of end-stage CKD is extreme, in public health terms the burden resides in early-stage (CKD stages 1–3) disease, which is more prevalent, affecting around 40% of those over 70 years. When added to conventional risk factors, renal markers substantially improve risk stratification and CKD is therefore an important and under-recognised risk factor for CVD in the general population. Although the risks of myocardial infarction and other manifestations of coronary artery disease are increased in CKD, the pattern of CVD is atypical, with a much greater incidence of heart failure and sudden cardiac death than in the general CVD population.

Few therapies have proved effective in modifying the increased CVD risk or the rate of renal decline in CKD. There are accumulating data that aldosterone receptor antagonists (ARAs) may offer cardio-protection and delay renal impairment in patients with the cardiovascular (CV) phenotype in CKD. The use of ARA in CKD has therefore been increasingly advocated and even termed the 'renal aspirin'. Prior to the initiation of benefits of aldosterone receptor antagonism in chronic kidney disease (BARACK-D), no large study of ARAs with renal or CVD outcomes was underway. This trial evaluates the benefits of an ARA, spironolactone, in patients with stage 3b CKD.

Objectives

The primary objective was to determine the effect of aldosterone receptor antagonism with spironolactone on mortality and cardiovascular outcomes in people with CKD stage 3b. Secondary objectives included determining the effect on renal function and blood pressure control, cost-effectiveness and the safety of this treatment approach.

End points

Primary end point

The primary outcome was the time from randomisation to the first occurring of all-cause mortality, hospitalisation for heart disease (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, failed sudden death), stroke, heart failure, transient ischaemic attack or peripheral arterial disease, or first onset of any of these conditions in the primary care record if not listed at baseline.

Secondary end points

Secondary outcome measures included

- Individual components of the primary outcome, including all-cause mortality, heart disease (coronary heart disease, arrhythmia, atrial fibrillation, sudden death, failed sudden death), stroke, heart failure peripheral artery disease or transient ischaemic attack.
- Measures of cardiovascular haemodynamics, including changes in blood pressure and prevalence of hypotension.
- The effect on left ventricular (LV) function, determined by changes in B-type natriuretic peptide.
- A decline in renal function, measured by changes in estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio.
- Safety measures, including incidence of hyperkalaemia.
- Cost-effectiveness, including changes in health status measured on EuroQol-5 Dimensions, five-level version.

Study design and methodology

The BARACK-D was a prospective, randomised, open, blinded endpoint (PROBE) trial. 1985 eligible patients, from a minimum of 120 practices, with previously recorded blood test results suggesting CKD stage 3b, were invited to take part in the study and randomised to either spironolactone 25 mg once daily in addition to standard care or standard care alone. Blood pressure in both groups was titrated (monitored and adjusted accordingly) by the clinicians against NICE guideline standards and checks of electrolytes undertaken.

Study recruitment was initially much slower than planned because of excessive delays to negotiating appropriate service support costs, and initial concern by practices to engage with the study on the grounds that they would need to subsidise their time. Also, there was refusal to fund the (minimal) excess treatment costs from some clinical commissioning groups (CCGs). While various measures were put in place and recruitment did improve, in March 2018 the decision was taken with the Health Technology Assessment to close the study to recruitment as of July 2018, and to follow up those enrolled for 3 years (as per protocol) then close the trial.

In addition to these delays, the number of patients recruited per practice recruitment was lower than expected. Mail-out numbers were less than anticipated, and the response rate to those mail-outs was also low.

Results

One thousand four hundred and thirty-four participants were randomised of the 3022 we planned. One thousand three hundred and seventy-two (96%) were included in the analysis. Of the participants, 113/677 (16.7%) in the spironolactone arm and 111/695 (16.0%) in the standard care arm had a primary combined vascular event. We found no evidence of differences between the intervention and control groups in terms of effectiveness with the primary outcome [hazard ratio 1.05, 95% confidence interval (0.81 to 1.37); $p = 0.70$], nor with the secondary clinical outcomes, including progression in renal decline. These findings were consistent whether analysing the total treatment periods or a 3-year follow-up period as was originally planned. Adverse events were experienced more often, and participants were more likely to discontinue treatment in the intervention group. Two-thirds of participants randomised to spironolactone discontinued taking treatment within six months, with the most frequenst reasons being a decrease in the estimated glomerular filtration rate that met pre-specified stop criteria ($n = 239$, 35.4%), treatment side-effects ($n = 128$, 18.9%) and hyperkalaemia ($n = 54$, 8.0%). The addition of low-dose spironolactone was unlikely to be cost-effective

Conclusions

The BARACK-D trial found no evidence of benefit with the addition of low-dose spironolactone at 25 mg daily in patients with CKD 3b on the high rates of cardiovascular events seen in the trial follow-up, either for the combined primary or for individual components. There was also no benefit observed in rates of renal function decline over the trial with much higher initial creatinine rise and eGFR decline, and to a higher percentage rate, in the first few weeks of spironolactone treatment. These higher rates of negative renal change reduced in scale over the study but did not equalise between arms. The addition of 25 mg of spironolactone therefore provided no reno- or cardio-protection but was associated with more adverse events.

Trial registration

Current Controlled Trials ISRCTN44522369.

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