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COMMENTARY

Eplerenone in chronic renal disease: the EVALUATE trial

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In this issue of *Hypertension Research*, there is a description of the EVALUATE trial, administration of the selective mineralocorticoid receptor antagonist eplerenone in patients with essential hypertension and some measure of renal impairment. The inclusion criteria are wide (age 20–80 years; blood pressure: systolic 130–180 mm Hg, diastolic 80–100 mm Hg; urinary albumin to creatinine (CR) ratio 30–600 mg g^{-1}) and the exclusion criteria are largely appropriate. The trial will be over 1 year, with a run-in period of 16 weeks, plus observation and sampling at baseline, and at 4, 18, 16, 28, 40 and 52 weeks. The trial is sponsored by Pfizer, with Professor Toshiro Fujita chairing the Steering and Coordinating Committees and Professor Akira Yamada the Protocol Committee.

Such a study is long overdue and is very welcome. As the investigators write, 'Japanese people, many of whom have a high salt diet, are expected to benefit in particular from treatment with MR antagonists. However, since most people in the world consume more salt than is ideal, we anticipate that the EVALUATE trial results can be extrapolated to populations worldwide.' There are previous studies, in Japan and elsewhere, that address a similar question, but none with the patient population or primary end point of EVALUATE. The authors cite these studies and the animal experimental studies that support a renoprotective role for MR blockade, initially by spironolactone and more recently by the selective MR antagonist eplerenone.

The particular reason why EVALUATE is welcome is that it squarely addresses a belief that has become a limiting factor in the use of MR antagonists, that of hyperkalemia. There is no question that natriuresis and/or hyperkalemia is an obligate side effect of MR blockade, as was seen at modest doses in RALES ($\bar{X}$=26 mg of spironolactone per day) and EPHESUS ($\bar{X}$=43 mg of eplerenone per day), both of which were trials in heart failure. In essential hypertensives low doses of eplerenone produced minimal changes in plasma [K^+] ($\bar{X}$=<0.1 m eq l^{-1}, 95% confidence limit (CL) 0.0–0.2 m eq l^{-1}), and even when dose-titrated up to 200 mg per day, very modest changes ($\bar{X}$=⩽0.2 m eq l^{-1}, 95% CL 0.1–0.3 m eq l^{-1}) occurred.[1] These minimal effects were seen with eplerenone as monotherapy; as is well recognized, concurrent ACE inhibition and/or angiotensin receptor blockade might be anticipated to exacerbate hyperkalemia.

The studies combining angiotensin-converting enzyme inhibitors (ACEi's) and MR blockade to date have been small, and of relatively short duration, as noted by the authors of the EVALUATE study; even under those conditions, gross hyperkalemia was not a problem. One of these trials was conducted in patients with type 2 diabetes and associated nephropathy, in which 50–100 mg per day eplerenone decreased the urinary albumin to CR ratios, again without levels of hyperkalemia sufficient to cause concern.[2]

The reason why hyperkalemia has assumed ogre status appears to be two-fold. First, in progressive renal disease, hyperkalemia is a common index of deterioration, and is recognized as such. On the other hand, a low-dose of MR blockade, clinically and experimentally, has been clearly shown to reverse progressive renal disease: in this instance hyperkalemia is an obligate side effect of effective therapy, not an index of progressive renal deterioration. This distinction appears lost on many clinicians, and even the regulators, in that the packet inserts for eplerenone recommend it not be used in diabetes, despite the weight of evidence of its beneficial effect and safety. A second reason is the unsupported reasoning that if a small dose of MR antagonist is good, more will be better—on occasion allied with failure to discontinue potassium supplementation, in up to one-third of the heart failure patients given spironolactone in one trial.[3]

The EVALUATE thus represents a further step in the validation of MR blockade in patients with mild-to-moderate renal disease. There are, however, a number of issues to be considered in terms of the study design. The inclusion criteria are very broad, in three dimensions. The age range is 20–80 years, which is surprising. It might be anticipated that, as the prevalence of essential hypertension increases with age, most subjects will be in the top half of the range, possibly in the top third. A case can thus be made that more insight might be gained from a rather restricted age range, either 40–80 or even 50–80 years. Secondly, there is a very wide range of BP that is deemed acceptable for inclusion (systolic 130–180 mm Hg, diastolic 80–100 mm Hg). It should be noted that all such subjects are truly hypertensive, given these BP levels despite antihypertensive medication(s). Finally, the extent of renal damage, as estimated by urinary albumin to CR ratio, spans a 20-fold range (30–600 mg g^{-1} in the waking void specimen). Added to this is the heterogeneity in medication—ACBi, ARB or both, and then other classes potentially added as required to reach the goal BP (<130/80 mm Hg). Therein lies a complicated matrix of variables for the statisticians to make whole cloth of. As the authors state 'if necessary, the data will be adjusted by important background factors, including

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gender, age, BP response to treatment, eGFR urinary L-FABP levels, and urinary Na^+ excretion—not to mention starting BP and urinary albumin/CR, plasma $[K^+]$ and aldosterone levels, etc.

What is also not clearly stated within the paper are the criteria whereby secondary causes of hypertension are excluded—that is, the certainty with which the starting diagnosis can be established. In an unselected group of 340 hypertensives, it could be anticipated that 5–10% might prove to have primary aldosteronism; patients in the 20–30 age range are similarly more likely to have secondary hypertension, with BP remaining elevated despite ACEi/ARB therapy. Subjects with BP levels maintained high (170+ systolic BP, 95+ diastolic BP) despite ACEi/ARB administration may prove to have so-called resistant hypertension, which is particularly sensitive to the addition of MR antagonists, with a relatively high percentage of patients with primary aldosteronism.

Clinical trials in general are assessed on the basis of important but narrow criteria—of efficacy and safety. On this basis, it is overwhelmingly likely that EVALUATE will be a success. It is powered to show a substantial lowering of urinary proteinuria in the eplerenone plus ACEi/ARB arm compared with ACEi/ARB alone. Secondly, the possibility of hyperkalemia prompting withdrawal is remote, despite the very conservative cut-off value (undefined, but presumably a $[K^+]$ of $>5\,\mathrm{m\,eq\,l^{-1}}$, as instanced in the exclusion criteria). Finally, even more remote is the possibility that the trial will reveal hitherto unsuspected adverse effects of eplerenone, given that headache is the most commonly reported adverse effect (in 0.1% of the patients) in post-marketing surveys in Japan. Given that polling 1000 random subjects might produce at least 10 complaining of a headache, it has been jokingly suggested that eplerenone might be as good in preventing headache as it is in terms of end-organ protection.

What clinical trials also represent is a rich depositary of data, optimally able to be mined by both trial participants and other investigators in the area. These data may prompt further *in vivo* and *in vivo* experimental studies, which, when taken with the original findings, in turn may allow radical reconsideration of the underlying basic biology and clinical physiology: several examples of this retrospective process have recently been published,[4,5] in addition to that previously cited.[1] Whether prospecting the data accumulated by the EVALUATE investigators will prove to be rewarding cannot be determined in advance: suffice to say that every encouragement should be given to Pfizer to make all the data generally accessible, and to the investigators to interrogate their findings in detail and in depth. Without this, and given the overwhelming probability that the trial will be successful in terms of efficacy and safety, it will become more of a marketing exercise than scientific inquiry.

In summary, EVALUATE is both timely and welcome. It very sensibly chooses a single (low) dose of eplerenone, runs for a year, and compares the renoprotective effect of ACEi/ARB therapy with and without eplerenone. The investigators exclude diabetics, but not—at least not explicitly—patients with primary aldosteronism. The cohort is likely to be very heterogenous, with a very complex matrix of age, gender, starting BP and starting urinary albumin to CR ratio; on top of this is the addition of other antihypertensive agents, triggered (presumably at the end of the trial) if BP is not 130/80 mm Hg or better. Even though patients with resistant hypertension can show large falls in BP when MR blockade is instituted, it is not likely that most of those with a starting systolic BP of 180 mm Hg on ACEi/ARB will reach the goal of 130 mm Hg: it is therefore not altogether clear why this post-trial intervention has been included. That said, EVALUATE should provide a clear validation for the use of MR blockade in hypertensive chronic kidney disease, and we await both the results and their analysis with keen interest.

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