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EDITORIAL

Potassium binders for patients with heart failure? The real enlightenment of the DIAMOND trial

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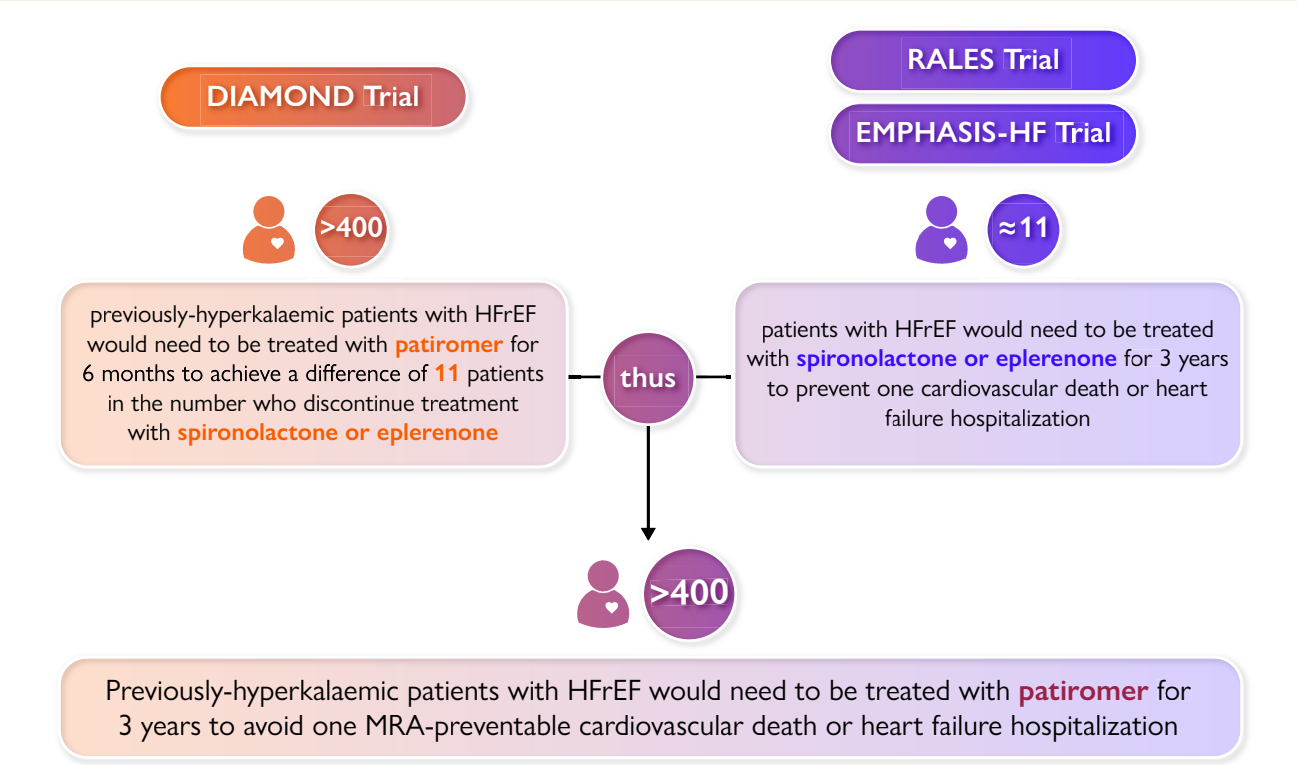
This editorial refers to 'Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial', by J. Butler *et al.*, https://doi.org/10.1093/eurheartj/ehac401.

Graphical Abstract



Estimation of Number-Needed-to-Treat with Patiromer for 3 years to Prevent One Cardiovascular Death or Hospitalization for Heart failure in Patients with Heart Failure and a Reduced Ejection Fraction. Estimates of number-needed-to-treat for the RALES and EMPHASIS-HF trials are derived from calculations published by Ferreira et al.[13] Estimates for the DIAMOND trial are derived from results presented by Butler et al.[11] Abbreviations: MRA = mineralocorticoid receptor antagonist. HFrEF = heart failure and a reduced ejection fraction.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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Mineralocorticoid receptor antagonists (MRAs)—spironolactone and eplerenone—produce remarkable benefits in patients with heart failure and a reduced ejection fraction (HFrEF). MRAs decrease all-cause mortality by 25–30%,[1,2] in part by reducing sudden death, an effect not possessed by conventional renin–angiotensin system inhibitors.[1–3] In addition, MRAs reduce hospitalizations for heart failure by 35–45%.[1,2] These benefits were demonstrated in two large-scale trials.

The RALES and EMPHASIS-HF trials

The RALES trial studied patients with severe HFrEF not generally receiving beta-blockers, who were randomized to spironolactone 25 mg/day or placebo for a mean of 24 months.[1] In a pilot trial, doses from 12.5 mg/day to 75 mg/day had produced meaningful decreases in natriuretic peptides, with minimal incremental effect but more hyperkalaemia at doses >25 mg/day.[4] Accordingly, 25 mg/day was designated as the target dose for spironolactone in RALES,[4] and it is the target dose in clinical practice.[5,6] In RALES, 50 mg/day could be prescribed if, after 8 weeks, patients experienced progression of heart failure without hyperkalaemia. However, up-titration did not occur in most patients; the mean dose was 26 mg/day. At this dose, spironolactone reduced all-cause mortality by 30% and hospitalizations for heart failure by 35%.[1] A serum potassium concentration ≥5.5 mmol/L was seen in 5.5% of the placebo group, in 13.5% taking 25 mg/day, and in 41% taking 50 mg daily.[7] Serious hyperkalaemia was observed in 1–2% of patients.[1]

The EMPHASIS-HF trial enrolled patients with mild HFrEF treated with beta-blockers, who received eplerenone 25 mg/day or placebo for 4 weeks, followed by 50 mg/day for a mean of 21 months, if they had preserved renal function. The doses were halved in those with chronic kidney disease. There is a 2:1 to 4:1 ratio between pharmacodynamically equivalent doses of eplerenone and spironolactone.[8] Eplerenone reduced all-cause mortality by 24% and hospitalizations for heart failure by 42%.[2] A serum potassium concentration >5.5 mmol/L was reported in 7.2% and 11.8% of the placebo and eplerenone groups, respectively. A serum potassium >6.0 mmol/L was noted in ~2%.

The terror of hyperkalaemia and the advent of new potassium binders

The results of these two trials established MRAs as foundational drugs for HFrEF. Yet, in clinical practice, only ~15–30% of patients with heart failure receive an MRA,[5,6] because of fears that serious hyperkalaemia is common and life-threatening. Juurlink *et al.* reported an excess of hyperkalaemia-associated hospitalizations and deaths following the publication of the RALES trial.[9] This risk was attributed to the use of inappropriately high doses of spironolactone, the lack of serum potassium monitoring, and the use of potassium supplements in many patients.[10] Trevisan *et al.*[11] confirmed the risk of serious hyperkalaemia with spironolactone >25 mg/day and reported that, at the first sign of hyperkalaemia, practitioners generally stopped spironolactone permanently—instead of reducing the dose, as was done in RALES and EMPHASIS-HF.

Potassium binders have been used to reduce the gastrointestinal absorption of potassium for decades, and agents with enhanced tolerability (e.g. patiromer) have been developed. Patiromer reduces the risk of hyperkalaemia in chronic kidney disease[12] and, in the PEARL-HF trial,[13] patients with HFrEF (enriched for the risk of hyperkalaemia) were randomized to patiromer or placebo to determine if treatment might enhance the tolerability of spironolactone 50 mg/day. After 4 weeks, patiromer-treated patients were more likely to be receiving 50 mg/day (91% vs. 74%), but the between-group difference was not striking. Nevertheless, the use of patiromer might allow more HFrEF patients to receive the highest doses of MRAs. If very high MRA doses are superior to lower doses in preventing major heart failure outcomes, patiromer might facilitate MRA-mediated decreases in death and heart failure hospitalizations in patients with prior hyperkalaemia.

Aspirations and findings of the DIAMOND trial

The DIAMOND trial (published in this issue of the *European Heart Journal*[14]) was designed to test this hypothesis. Patients with HFrEF and a serum potassium concentration >5.0 mmol/L or who had had a reduction in the dose or discontinuation of a renin–angiotensin system inhibitor or MRA because of hyperkalaemia within 12 months entered a run-in period, during which they received (i) spironolactone 50 mg/day or eplerenone 50 mg/day while taking other renin–angiotensin system inhibitors at ≥50% of target dose; and (ii) patiromer (8.4–25.2 g/day). The doses of eplerenone and spironolactone did not follow the expected 2:1 to 4:1 ratio. If patients had a serum potassium ≥4.0 and ≤5.0 mmol/L at the end of the run-in period, they were randomized to continue patiromer or be switched to placebo (double-blind) and be followed for the trial's duration. If hyperkalaemia was subsequently observed, investigators were asked (whenever possible) to reduce the dose of (while maintaining treatment with) the MRA, as was done in the RALES and EMPHASIS-HF trials. The original primary endpoint was cardiovascular death or hospitalization for heart failure, with a plan to treat 2388 patients for ~2.5 years. When faced with slow event accrual, the investigators heroically salvaged the trial by refocusing it on changes in serum potassium concentration in 878 patients who had been followed for a median of 27 weeks.

What did the DIAMOND trial find? Serum potassium concentration was lower in the patiromer group than in the placebo group; a serum potassium >5.5 mmol was reported in 19.4% of the placebo group and 13.9% of the patiromer group.[14] These treatment differences were expected. Yet, amazingly, ~80% of historically hyperkalaemic patients did not report a serum potassium concentration >5.5 mmol/L during double-blind follow-up—even in the absence of patiromer—even though most were being treated with very high doses of spironolactone (and other potassium-retaining drugs) at randomization.

In DIAMOND, patiromer had a modest effect on increasing the proportion of patients receiving >25 mg/day of spironolactone (as

in PEARL-HF[13]). Yet, as shown in table S4 of the paper,[14] the drug did not enhance dosing of renin–angiotensin system inhibitors. Furthermore, the proportion of patients taking comparable HFrEF doses of an MRA—spironolactone 25 mg/day or eplerenone 50 mg/day—was nearly identical in the treatment groups (119 on patiromer and 121 on placebo). In light of these findings, would the incremental use of very high doses of MRAs in the patiromer group have yielded a reduction in morbidity and mortality if the DIAMOND trial followed its original plan?

Higher doses of MRAs do not improve outcomes more than lower doses

The answer to this question depends on whether the DIAMOND-specified target doses of MRAs are truly needed to produce optimal decreases in mortality and mortality in HFrEF. In RALES, mortality was reduced using a mean of 26 mg/day of spironolactone, with no survival difference between 25 and 50 mg/day.[1,8] Similarly, when tested in the post-infarction setting, eplerenone reduced cardiovascular death and hospitalization for heart failure when patients were taking only 25 mg/day, with a magnitude of benefit similar to that seen with 50 mg/day.[15] Finally, in EMPHASIS-HF, patients randomized to 25 or 50 mg/day of eplerenone had a similar reduction in the combined risk of cardiovascular death or hospitalization for heart failure.[16] Therefore, the totality of evidence suggests that the shape of the dose–response relationships for both spironolactone and eplerenone for the reduction of major heart failure events is flat between 25 and 50 mg/day. If true, the use of patiromer to facilitate the prescribing of spironolactone 50 mg/day (as opposed to lower doses) might not be expected to yield benefits on heart failure outcomes.

Given these observations, the most important finding in the DIAMOND trial is that MRAs were discontinued altogether in 31 placebo patients (7.1%) and 20 patiromer patients (4.6%).[14] The investigators treated >400 previously hyperkalaemic patients with patiromer for 6 months to achieve this 11 patient difference—and this difference closely approximates the number of patients who would need to be treated with an MRA to prevent one major heart failure event, assuming the 11 patient difference in MRA utilization were sustained for 3 years (*Graphical Abstract*).[17] Given the expense of patiromer, one can wonder if treating >400 previously hyperkalaemic patients with HFrEF with a potassium binder for 3 years to avoid one major event represents a cost-effective strategy, as patients must bear the concurrent financial burden of foundational drugs that have a far more favourable number needed to treat ratios. A prior cost–benefit analysis of patiromer in HFrEF[18] assumed that MRAs would be fully discontinued in 60% of previously hyperkalaemic patients not treated with the potassium binder, based on a trial in chronic kidney disease.[12] However, guidance about the management of hyperkalaemia in DIAMOND properly emphasized MRA dose reduction rather than discontinuation, as have other heart failure trials (RALES and EMPHASIS-HF). As a result, >80% of patients not taking patiromer in DIAMOND were still receiving clinically effective doses of MRAs at the trial's end (see table S4 in Butler *et al.*).[14]

The real enlightenment of the DIAMOND trial

By salvaging the DIAMOND trial, the investigators delivered real enlightenment. Specifically, the vast majority (~80%) of patients with HFrEF and a history of hyperkalaemia will not experience recurrent hyperkalaemia in the absence of patiromer, even when challenged with doses of MRAs that are probably higher than those needed to reduce mortality. Importantly, the proportion of patients who tolerate MRAs without hyperkalaemia and without potassium binders will only increase in the future, since two foundational drugs—sacubitril/valsartan and sodium–glucose cotransporter 2 inhibitors—mitigate the risk of hyperkalaemia while having direct benefits on heart failure outcomes.[19,20] These immensely reassuring findings mean that, if we truly seek to improve outcomes in clinical practice, we must assuage physicians' exaggerated fears about the dangers of hyperkalaemia, since trial-based MRA dosing strategies currently represent an exceptionally cost-effective and well-tolerated (but regrettably scorned) way to slow the progression of HFrEF.

Conflict of interest: M.P. reports receiving fees from Abbvie, Altimmune, Amarin, Amgen, Ardelyx, AstraZeneca, Boehringer Ingelheim, Caladrius, Casana, CSL Behring, Cytokinetics, Imara, Lilly, Moderna, Novartis, Reata, Relypsa, and Salamandra.

Data availability

No new data were generated or analysed in support of this research.

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Corrigendum

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Corrigendum to: Empagliflozin and serum potassium in heart failure: an analysis from EMPEROR-Pooled

This is a corrigendum to: João Pedro Ferreira, Faiez Zannad, Javed Butler, Gerasimos Filipattos, Ivana Ritter, Elke Schüler, Bettina J Kraus, Stuart J. Pocock, Stefan D. Anker, Milton Packer, Empagliflozin and serum potassium in heart failure: an analysis from EMPEROR-Pooled, *European Heart Journal,* 2022; ehac306, https://doi.org/10.1093/eurheartj/ehac306.

In the originally published version of this manuscript, affiliations for several authors were erroneous. The affiliations were given as follows:

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The affiliations have now been updated.