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VIEWPOINT

Patiromer use in patients with heart failure: lessons and clinical considerations from the DIAMOND trial

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The benefits of renin–angiotensin–aldosterone system inhibitors (RAASi), including mineralocorticoid receptor antagonists (MRAs), for clinically relevant mortality and morbidity outcomes are strong, consistent across trials and over time, and irrefutable for patients with heart failure and reduced ejection fraction (HFrEF).[1–3] However, concerns related to the risk of hyperkalaemia limit their use, especially for MRAs.[4] Guidelines recommend discontinuing RAASi when potassium levels exceed 6.0 mmol/L and to lower the dose between 5.5–6.0 mmol/L.[5,6] However, data from routine practice repeatedly demonstrate that discontinuing RAASi is common at lesser potassium elevations of between 5.0 and 5.5 mmol/L as well, and when stopped, they are infrequently re-started due to risk or fear of hyperkalaemia.[7,8]

The DIAMOND (Patiromer for the Management of Hyperkalemia in Participants Receiving RAASi Medications for the Treatment of Heart Failure) trial showed that long-term therapy with patiromer lead to a favourable impact on serum potassium control, 37% relative risk reduction in time to hyperkalaemia event, a 34% reduction in total hyperkalaemia events, and a 38% reduction in time to MRA dose reduction, in patients with HFrEF and current or history of hyperkalaemia.[9] The trial also showed that hyperkalaemia events after initiation of MRA in patients with a history of hyperkalaemia are less common than previously thought.

The DIAMOND trial was originally designed to study the impact of patiromer enabled RAASi optimization on clinical outcomes, but with slower recruitment and event rates, the aims of the study were altered. Below are a few research and clinically relevant considerations from the trial (*Figure 1*).

Change in the scope of a clinical trial

The DIAMOND trial was designed with an ambition to study both patients with current (treatment cohort) as well as those with a history of hyperkalaemia (prevention cohort) related alteration in RAASi therapy with an aim to follow the patients' long term to assess for clinical outcomes with patiromer enabled RAASi therapy. Due to COVID-19 related changes in trial conduct and hospitalization patterns globally, both for logistics and patient safety reasons, the decision was made that the original design was not feasible. While the easier path is to abandon the trial mid-way, this would have meant that the enrolled patients' sacrifice would have been wasted. Hence, the executive committee and the sponsor redesigned the aim, the statistical analysis plan, and power calculations to yield maximal benefit from the volunteering of the patients already enrolled. This scenario is not uncommon that for various reasons many trials are not conducted to completion of the original intent. A serious consideration should be given to continue with the original intent or at the least to maximize the yield from the experiences by reconsidering the aims and power of the trial rather than abandoning it. We believe that the DIAMOND trial is an example where this was positively achieved.

Logistic and design considerations in clinical trials

Designing the trial ideally should focus on how to best study the intervention. Many logistics and feasibility considerations nevertheless are necessary to consider as well, and at time, they play a key role in the outcome of the trial. The DIAMOND trial, despite focusing on hyperkalaemia or an at-risk population, enrolled a relatively low-risk population. If it had continued as an event-driven trial, at the observed event rate, the trial would have continued for an impractically long time. A substantial increased sample size would have also resulted in similar long-time frame since the enrolment rate was slower than expected as well. One could conceive of enrolling a higher risk population. However, this entails a concern for the generalizability of the results as well as slowing the

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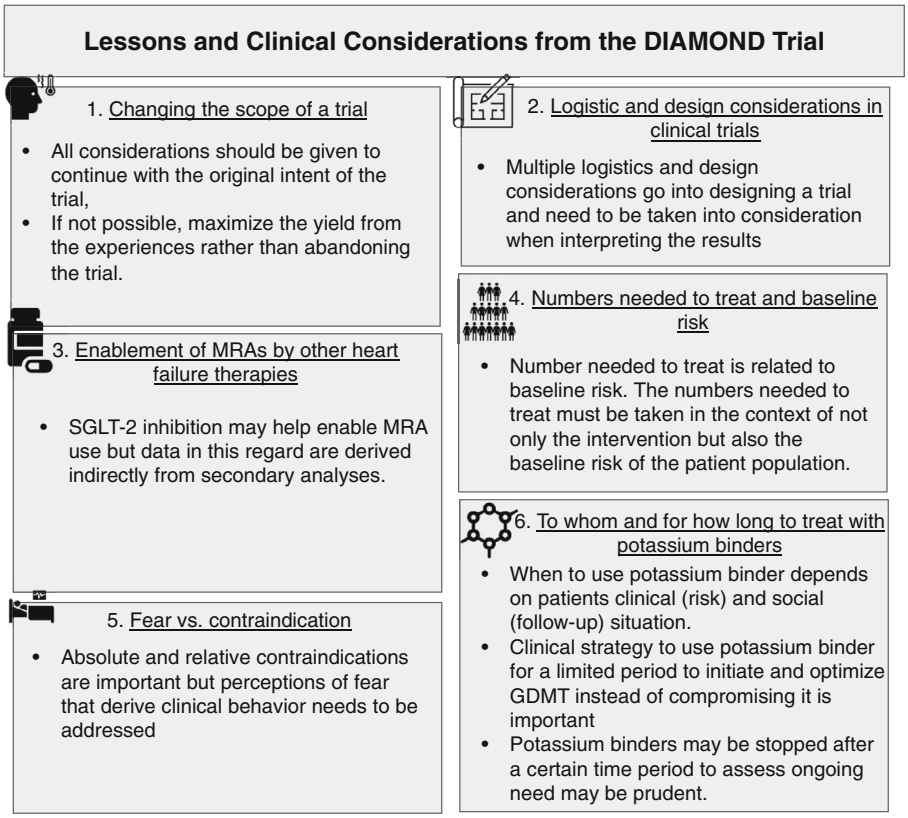

Figure 1 Lessons from the DIAMOND trial. GDMT, guideline-directed medical therapy; MRA, mineralocorticoid receptor antagonist; SGLT-2, sodium–glucose cotransporter 2.

enrolment rate since eligible patients already needed to have hyperkalaemia or history thereof, use of sub-optimal RAASi, elevation in natriuretic peptides, a lower limit of estimated glomerular filtration rate (eGFR), abnormal ejection fraction, and hospitalization in the past. Further increasing the minimum required natriuretic peptide levels at baseline would have further slowed the enrolment, straining logistics and costs. Decreasing the eGFR to <30 ml/min/1.73 m^2 would have led to mixing of population with indication and contraindication to MRA therapy. In short, clinically relevant questions are sometimes difficult to study in a trial setting, necessitating compromises in trial design and the need for clinical interpretation of the results based on the protocol considerations.

The choice of target doses of the intervention in the DIAMOND trial was based on what was believed to be the best evidence for spironolactone and eplerenone.[2,3] In the RALES (Randomized Aldactone Evaluation Study) trial, patients were started on spironolactone 25 mg/day with an option to down-titrate to 25 mg every other day if there was an increase in serum potassium, or to up-titrate to 50 mg/day after 8 weeks, if there were signs of worsening heart failure without hyperkaalemia. While the average dose of spironolactone was 26 mg/day, 50 mg/day dose was thought to be more effective based on the finding of a lower atrial natriuretic hormone levels in the RALES dose-finding study. EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) used a starting dose of 25 mg/day with the option to up-titrate to 50 mg/day. While many patients did not achieve this dose, this dosing strategy was chosen in line with the pivotal trials and a judgment based on higher doses not being assessed in earlier trials precisely due to risk of hyperkalaemia despite better surrogate improvement at higher doses. Thus, while not guideline-recommended, using best judgement based on totality of evidence may be an option when designing trials.

Enablement of mineralocorticoid receptor antagonists by other drugs

It was suggested that sacubitril/valsartan may lower hyperkalaemia risk and facilitate MRA therapy. Secondary analysis of the PARADIGM-HF (Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure) trial showed that among patients taking an MRA at baseline, the overall rates of hyperkalaemia were similar between the sacubitril/valsartan and enalapril groups (17.0% vs. 18.7%), but severe hyperkalaemia was less common in patients assigned to sacubitril/valsartan (4.5% vs. 6.1%).[10] In contrast however, the PIONEER-HF (Comparison of Sacubitril–Valsartan versus

Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial showed that the risk of hyperkalaemia was more in the sacubitril/valsartan arm compared to enalapril (12.5% vs. 9.2%).[11] Thus whether sacubitril/valsartan truly reduces the risk of hyperkalaemia remains debated. Data from the EMPEROR trial programme showed that empagliflozin was associated with an 18% decrease in investigator-reported hyperkalaemia or initiation of potassium binders.[12] Similarly, the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial showed that dapagliflozin reduced the risk of hyperkalaemia by 14% and severe hyperkalaemia by 50% compared with placebo.[13] Indeed, the effect of sodium–glucose cotransporter 2 (SGLT-2) inhibition in reducing serum potassium levels is consistent, but is derived from secondary analysis.

Numbers needed to treat and clinical implication

In has been suggested that considering the results of RALES and EMPHASIS-HF, >400 patients would need to be treated with patiromer to avoid one preventable cardiovascular death or heart failure hospitalization.[2,3,14] It is important to note that the number needed to treat is inversely related to baseline risk. The overall patient population in the DIAMOND trial was a lower risk population; 54% of patients had New York Heart Association (NYHA) functional class II symptoms, mean left ventricular ejection fraction (LVEF) of 33.5%, and 60% of the patients did not have hyperkalaemia at screening, with a baseline serum potassium level of 4.6 mmol/L. In contrast, both RALES and EMPHASIS-HF enrolled a higher risk population. In RALES, 0.5% patients had NYHA class II symptoms and the average LVEF was 25.2%; the average LVEF in EMPHASIS-HF was 26%. Thus, the numbers needed to treat must be taken in the context of not only the intervention but also the risk of the patients enrolled. In the DIAMOND trial, patiromer was able to decrease serum potassium level significantly more in patients with lower eGFR (i.e. <45 ml/min/1.73 m^3 vs. ≥45 ml/min/1.73 m^3). Thus, the number needed to treat proposed may not be applicable in patients with higher risk and more advanced chronic kidney disease.

Fear of hyperkalaemia

In both the RALES and EMPHASIS-HF trials, the risk of severe hyperkalaemia was low (~2%). However, this low incidence may in part be due to eligibility criteria and the close laboratory monitoring.[15,16] Such restrictions and follow-up may not be seen in practice. Bozhurt *et al.*[17] showed that after the publication of the RALES trial, about a third of the patients who received new prescription for spironolactone had renal insufficiency or were receiving prescriptions for potassium supplements. Such differences between trials and practice may have important implications. A population-based analysis of 1.3 million adults showed that the publication of RALES was associated with an abrupt increase in the rates of prescription of spironolactone that was related with considerable increases in the rates of hospital admission for hyperkalaemia and in-hospital deaths.[18] The DIAMOND trial showed that the vast majority of patients with a history of hyperkalaemia may be optimized on RAASi therapy without recurrent hyperkalaemia with patiromer, thus providing evidence that discontinuation of life-saving therapies is not necessary. Clinical use of these therapies may vary according to patient multimorbidity risk profile as well as the social situation and ability for close follow-up. The risk of hyperkalaemia should not be over- or underestimated, and individualized. It is not optimal to conclude that the fear of hyperkalaemia is nothing more than 'just' a fear and that patients and clinicians should 'get over it'. Further education as well as providing enabling aids to the clinicians may yield better use of guideline-directed medical therapies than discarding clinician concerns.

To whom and for how long to give potassium binder therapy

Once MRA or RAASi therapy is initiated in a HFrEF patient despite a history of hyperkalaemia or current hyperkalaemia, which was possible with patiromer use in the run-in phase of the trial, the subsequent risk of developing hyperkalaemia was low in patients randomized to placebo (~20% of patients randomized to placebo had a hyperkalaemia event during a median duration of follow-up of 27 weeks). It may seem that a clinical strategy to use patiromer for a limited period of time to initiate and optimize the guideline-recommended foundational treatments may lead to success in 85% of cases. However, subsequently stopping patiromer once treatment optimization is completed, at least in those patients without high-risk features, may be a prudent consideration. Alternatively, a second try under careful watch is also feasible in patients who have had an episode of hyperkalaemia. In either case, barring accessibility issues, hyperkalaemia should not be a reason for compromising live-saving therapies now that we have effective and well tolerated novel potassium binders.

Clinical implications

The DIAMOND trial showed that patiromer decreases serum potassium levels and lowers the risk of MRA dose reduction as well as time to and overall hyperkalaemia events in patients with HFrEF and history of or current hyperkalaemia. The trial was not designed to specify a serum potassium threshold when patiromer should be given. A patient's clinical status, social situation, and a clinician's judgement should dictate when to start therapy with patiromer. However, barring access issues, the DIAMOND trial suggests that once the decision to compromise RAASi due to hyperkalaemia has been made, patiromer supported enablement may prevent a treatment reduction or discontinuation of live-saving therapy. The recent FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) trials have extended MRA benefit to patients with chronic kidney disease and type 2 diabetes.[19,20] Although the new non-steroidal MRAs have a significantly lower risk of hyperkalaemia, the risk persists compared to placebo. With the evidence from non-steroidal MRAs, the eligible

population for this therapy will increase. While the relative risk will be lower with non-steroidal MRAs, the absolute incidence of hyperkalaemia will likely increase with increasing use of MRAs in varying patient populations, underscoring the importance of the DIAMOND trial results.

Conflict of interest: J.B. is a consultant to Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Berlin Cures, Boehringer Ingelheim, Bristol-Myers Squib, CVRx, G3 Pharmaceutical, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, SC Pharma, V-Wave Limited, and Vifor. T.J.S. has nothing to disclose. S.D.A. has received grants from Vifor; personal fees from Vifor, Bayer, Boehringer Ingelheim, Novartis, Servier, Impulse Dynamics, Cardiac Dimensions, and Thermo Fisher Scientific; grants and personal fees from Abbott Vascular, outside the submitted work.

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