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EDITORIAL COMMENT

A promise unfulfilled: the use of mineralocorticoid receptor antagonists in patients with heart failure and a reduced left ventricular ejection fraction

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This article refers to 'Temporal trends in initiation of mineralocorticoid receptor antagonists and risk of subsequent withdrawal in patients with heart failure: a nationwide study in Denmark from 2003–2017' by D. Zahir *et al.*, published in this issue on pages 539–547.

The steroidal mineralocorticoid receptor antagonists (MRAs) reduce mortality and hospitalizations for heart failure (HHF) in patients with heart failure and a reduced ejection fraction (HFrEF). Their incorporation into US and European guidelines as a class I indication for HFrEF held the promise for a substantial reduction in cardiovascular mortality, HHFs, and consequentially health care costs. It is therefore discouraging to observe that despite a class I indication in guidelines, over several years their use remains suboptimal in comparison to the other major guideline-recommended therapies for HFrEF.

In this issue of the Journal, Zahir *et al.*[1] report upon the temporal trends in initiation and subsequent withdrawal of an MRA from a nationwide study of 51 512 patients with HFrEF in Denmark from 2003 to 2017. They found that only 40% of patients initiated an MRA within 6 months of their heart failure (HF) diagnosis. Furthermore, the use of an MRA did not increase significantly over the past decade. In those in whom an MRA was initiated, 49% of patients discontinued them and only 40% of these patients restarted them. The suboptimal use of MRAs in patients with HFrEF in Denmark[1] is unfortunately not unique. The US Get With the Guidelines Heart Failure Registry (GWTG-HF)[2] also found that the use of MRAs in patients with HFrEF was suboptimal, even in patients with normal renal function in whom the risk of inducing hyperkalaemia (HK) is minimal. In view of the widespread underutilization of MRAs and their poor persistence in patients with HFrEF[1,2] despite evidence of their benefit and repeated recommendations in guidelines, it is highly unlikely that further reemphasis and dissemination of guidelines will remedy the situation. Consequently, we propose that the time has come to implement bold disruptive steps that will change the future trajectory of MRA use in HFrEF.

The failure to initiate and to remain on an MRA once initiated is in part due to the fear of inducing HK and/or exacerbating renal dysfunction and therefore the need to serially monitor serum potassium (K^+) and renal function. In many part of the world, the majority of patients with HF are cared for by family physicians or internists, who are often overwhelmed and do not have either the time or economic incentives to monitor serum K^+ or renal function and to discontinue or adjust the dose of the MRA if required. Consequently the path of least resistance is not to administer an MRA. Regretfully, negative consequences are incurred since while avoiding the necessity and costs of monitoring K^+ and renal function, the failure to initiate and to persist on an MRA in a patient with HFrEF is associated with an unacceptable increase in cardiovascular mortality.[3] In the Danish[1] and GWTG-HF[2] studies the major reason for discontinuing an MRA once initiated however was not an increase in K^+ but rather a decrease in renal function.

Constructive proposals to increase the use of mineralocorticoid receptor antagonists in patients with HFrEF

Introduction of an MRA in hospital or soon after an episode of heart failure hospitalization

There is increasing evidence that after haemodynamic stabilization and the use of intravenous diuretic therapy that guideline-recommended HF therapies can be safely initiated

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prior to hospital discharge or shortly afterwards.[3,4] The hospital team caring for HF patients has the best opportunity to initiate guideline-recommended therapy for HF. In contrast, after discharge there is often a gap of several weeks before the patient is seen in follow-up and often a change in the physician responsible for the care of the patient. The Danish[1] and GWTG-HF[2] registries suggest that MRAs are not being initiated prior to hospital discharge or soon thereafter in most medical centres. If they are not initiated in hospital it is likely that they will not be initiated at follow-up.

The use of a non-steroidal MRA

Recent evidence suggests that the use of the non-steroidal MRA finerenone, recently approved by the US Food and Drug Administration for patients with diabetic nephropathy, prevents the progression of renal disease and reduce cardiovascular outcomes, mainly HHF, in patients with diabetic nephropathy with approximately a 1% discontinuation rate due to HK.[5,6] In contrast to spironolactone, finerenone has a shorter half-life, a different mode of binding to the mineralocorticoid receptor and a more favourable distribution between the heart and kidney.[7] While it has recently been suggested[8] that the incidence of HK incurred with finerenone in the "real world" will be similar to the incidence of HK associated with spironolactone noted by Juurlink *et al.*,[9] there is evidence from a head-to-head comparison in patients with HFrEF that finerenone 5–10 mg/day, at a similar reduction in N-terminal pro-B-type natriuretic peptide, is associated with a lower incidence of HK than spironolactone 25–50 mg/day.[10] What is often unappreciated, but plainly clear, is that the incidence of HK noted by Juurlink *et al.*[9] promoted by spironolactone was confounded by the absence of both preselection of patients or mitigation strategies. In contrast, adherence by clinicians to recent guidelines and the selection of a non-steroidal MRA should diminish this risk .

While fewer episodes of HK are likely with the non-steroidal than the steroidal MRAs, when HK is encountered or anticipated, such as in patients with an estimated glomerular filtration rate <45 ml/min/1.73 m^2, the new potassium binders such as patiromer or sodium zirconium cyclosilicate, both of which have enabled sustained normokalaemia for at least a year in patients on an MRA,[11] can be administered. While the cost of the novel potassium binders has been invoked to limit their use, a recent propensity matched study of patients with a K^+ >5.0 mmol/L either receiving or not receiving patiromer found that the use of patiromer was associated with a reduction in both hospitalizations and emergency room encounters associated with a significant reduction in costs.[12]

The combination of an MRA and a sodium–glucose cotransporter 2 inhibitor

There is evidence from a preclinical model of hypertension-induced cardiorenal disease that a low-dose combination of finerenone and the sodium–glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin is additive in reducing mortality.[13] It can therefore be postulated that in the future the use and persistence of MRAs in patients with HFrEF might be enhanced by the concomitant use of a SGLT2i.

New incentives for prescribing MRAs in HFrEF

Barriers for implementing and sustaining MRA use should be identified and overcome. These barriers include an incomplete knowledge of current guidelines and the reluctance of many family physicians and internists to undertake the burden and costs of serial monitoring serum K^+ and renal function. Consequently, there is an urgent need to adopt new quality measures and economic incentives to enhance the use and persistence of MRAs. An example of the role of incentives is the successful introduction and adoption of pay-for-performance indicators; screening for urinary albuminuria in the United Kingdom resulted in a increase in screening to >80%.[14] When the QOF indicator incentivizing the recording of urine albumin:creatinine ratio was discontinued from April 2014, the percentage of people receiving this care process has since decreased considerably.[15]

Conclusion

In summary, we propose a series of next steps that hold the promise of closing the gap between the promise of guideline-directed MRA therapying patients with HFrEF and their suboptimal utilization. Initiation of an MRA in hospital prior to discharge after an episode of HHF; use of a non-steroidal MRA, such as finerenone, alone or in conjunction with a SGLT2i; the addition a potassium binder, if necessary; as well as new quality metrics and economic incentives to implement guideline recommendations for MRA use collectively hold the promise that the reduction in cardiovascular outcomes originally suggested by the approval of MRAs for HFrEF will eventually be realized. It will however be necessary to perform further adequately powered prospective randomized and comparative studies evaluating the efficacy and safety of these strategies before the full potential of MRAs to reduce cardiovascular mortality, HHF and therefore health care costs can be realized. While the search for new drugs, devices and strategies to further reduce cardiovascular outcomes in patients with HFrEF is important, efforts to increase the initiation and persistence of existing therapies, such as MRAs, are as or more important and more cost effective. It is therefore imperative that the proposals outlined above be evaluated in rigorous prospective studies and, if successful, rapidly implemented.

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