COMMENTARIES

Impact of Hyperkalemia and Worsening Renal Function on the Use of Renin Angiotensin Aldosterone System Inhibitors in Chronic Heart Failure With Reduced Ejection Fraction

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Patients with heart failure (HF) and reduced ejection fraction (HFREF) are at increased risk of death and hospitalizations for HF. Numerous registries have reported a large and persistent gap between real-life practice in the use of life-saving evidence-based therapies, such as renin angiotensin system inhibitors, beta blockers, mineralocorticoid receptor antagonists (MRAs), and recommended practices in international guidelines. The fears of inducing hyperkalemia and/or worsening renal function are the main triggers of this underuse.

The problem: Epidemiology and lack of use of effective therapeutics

The mineralocorticoid receptor antagonists (MRAs), spironolactone and eplerenone, have been shown to reduce cardiovascular death and hospitalizations for heart failure (HF) as well as total mortality and total hospitalizations in patients with chronic HF and heart failure and reduced ejection fraction (HFREF). On this basis, they have received a class I indication in major European and United States guidelines.[1] In contrast with other class I recommendations for patients with chronic HFREF, such as beta adrenergic receptor antagonists and angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), the use of MRAs remain suboptimal both in Europe and the United States.[1] In large part, this underuse of MRAs in guideline-eligible patients with chronic HFREF seems to be due to a fear of inducing serious hyperkalemia and/or worsening renal function. Although spironolactone was associated with a 30% reduction in cardiovascular mortality as well as a significant reduction in hospitalizations for HF in patients with severe chronic HFREF (Randomized Aldactone Evaluation Study (RALES)), a report by Juurlink *et al.*[2] in the *New England Journal of Medicine* from Canada, soon after the publication of the results of the RALES study, pointed out that the use of spironolactone in patients with chronic HFREF was associated with an increase in hospitalization for hyperkalemia. However, a critical review of the study shows that many patients in this study used a dose higher than the dose of spironolactone recommended in the RALES study (12.5–50 mg/day); had worse renal function than patients included in the RALES study; and, most importantly, in contrast with patients in RALES, many patients from Canada had a baseline serum potassium ($K+$) >5.0 mmol/l and/or did not undergo serial monitoring of $K+$ and renal function. Furthermore, Juurlink's findings were not replicated in a longitudinal analysis of the UK National Health Service in Scotland. In this study, an increase in mild hyperkalemia was reported after the publication of RALES, but it did not translate into increased hospitalizations or death due to hyperkalemia. The authors attributed the finding to more rigorous monitoring practices.[3] Given the risk of sudden cardiac death associated with the development of hyperkalemia ($K+$ >5.0 mmol/l),[4] as well as the increased costs associated with the need for hospitalization of patients with hyperkalemia, it is understandable that clinicians trained to "do no harm" have tended to avoid initiating MRA in guideline-eligible patients with chronic HFREF. However, although the fear of inducing hyperkalemia is reasonable in patients at increased risk for its development, such as those with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m^2 and/or a $K+$ >4.8 mmol/l, MRAs are also avoided in patients with chronic HFREF at a relatively low risk for developing serious hyperkalemia ($K+$ ≥6.0 mmol/l), thereby denying these patients proven life and cost-saving therapy. In a consecutive series of 500 patients hospitalized with a diagnosis of acute decompensated HF, only 21% of eligible patients for

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doi:10.1002/cpt.746

an MRA on admission received them. Of interest was the finding that preadmission and newly started MRAs were discontinued in 36% of patients during the period of hospitalization, with worsening renal function being the most common identifiable reason. After a medium follow-up of 57 days, an additional 6% of patients discontinued their MRAs.[5]

Management of patients when hyperkalemia and/or worsening renal function interferes with successful use of MRA added to a background of renin angiotensin system blockade

Recent data have, however, cast some doubt as to the risks associated with an increase in K+ to >5.0–5.5 mmol/l as well as the risks associated with worsening renal function. Although the risk of serious hyperkalemia (K+ ≥6.0 mmol/l) is well documented, recent data from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) have suggested that the development of mild-moderate hyperkalemia (>5.0–5.5 mmol/l) may not be significantly associated with an increased risk of death with an MRA[6] and that the development of hypokalemia (K+ <4.0–3.5 mmol/l) may be a far greater risk for death in patients with chronic HFREF.[7] Importantly in this trial, as per protocol, the patients' serum potassium were monitored after 1 week, 1 month, and every 4 months thereafter. Patients with an elevation of serum potassium ≥5.5 mmol/l could decrease the dosage of the study drug or discontinue it in case of hyperkalemia ≥6 mmol/l. The study drug could, however, be reintroduced if the serum potassium measured within 72 h was <5.0 mmol/l. Serum creatinine was monitored at baseline, month 5, and then every 8 months. If there was an unplanned interruption in the administration of study drug/eplerenone for any period of time, the subject may resume the study drug/eplerenone as directed by the investigator. The dosage resumed was at the discretion of the investigator, which was not to exceed 50 mg once daily for subjects with an eGFR ≥50 mL/min/1.73m^2 and 25 mg once daily with an eGFR between 30 and 49 mL/min/1.73m^2. The dynamic management of eplerenone[6] may have contributed to maintenance of the study drug throughout the trial as well as to its efficacy and safety. Such an algorithm may provide guidance for the daily management of MRA in clinical practice. Of note, the European Society of Cardiology guidelines for HF management[8] includes tables with practical guidance on the use of ACEI/ARB or MRA in patients with HFREF (see their web tables 7.4 and 7.6).

Although there is evidence that mild to moderate hyperkalemia can be associated with an increased risk of death, the risk associated with any given level of K+ depends upon the rate of change in K+, intracellular potassium and magnesium levels, serum calcium level, and pH. The approach to and the treatment of patients with chronic hyperkalemia is undergoing change. Until recently, patients with chronic hyperkalemia have been recommend to be on a low potassium diet; to eliminate potassium supplements and drugs that compromise renal function, such as nonsteroidal anti-inflammatory drugs; to initiate treatment with a nonpotassium sparing diuretic, if indicated, or if already on a diuretic to increase the dose; as well as to reduce the dose or discontinue renin-angiotensin-aldosterone system inhibitors (RAAS-I), especially MRA. However, reducing the dose of the RAAS-I or discontinuing it could place the patient with HFREF at increased risk for death. In this situation, one might consider the use of a potassium-lowering agent while continuing an RAAS-I.[9] Interestingly, the recent availability in the United States of the well tolerated and effective potassium-lowering agent patiromer, which exchanges potassium for calcium, allows a reduction of K+ to normokalemic values and may open new therapeutic avenues for patients with hyperkalemic HFREF on an optimal RAAS-I regimen.[9]

A recently published meta-analysis of randomized placebo-controlled trials of RAAS-Is in chronic HF shows that, in HFREF, worsening renal function induced by RAAS-I therapy was associated with a less increased relative risk of mortality (relative risk = 1.19 (1.08–1.31); $P < 0.001$), compared with worsening renal function induced by placebo (relative risk = 1.48 (1.35–1.62); $P < 0.001$; P for interaction 0.005).[10] The reason for an increase in serum creatinine after initiation of an RAAS-I, especially an MRA, is well understood and is associated with a decrease in vascular tone. There is no evidence that this decrease in renal vascular tone is detrimental and associated with adverse renal structural changes because RAAS-I withdrawal is associated with a return in serum creatinine toward normal. On the contrary, evidence suggests that RAAS-I, including MRAs, have a beneficial effect on renal function and structure. They reduce mesangial and glomerular fibrosis, apoptosis, podocyte loss, and have been shown to have a beneficial effect on cardiovascular and renal outcomes, at least for ACE-I and ARB. Thus, the accumulating evidence would suggest that patients with chronic HFREF who are initiated on an RAAS-I be allowed to continue therapy if they develop worsening renal function (i.e., an increase in serum creatinine >30%). However, if the worsening renal function is associated with serious hyperkalemia (K+ >6.0 mmol/l) and/or new electrocardiogram changes suggestive of hyperkalemia, or symptoms associated with the development of renal failure, that the RAAS-I be temporarily discontinued and appropriate therapy for hyperkalemia (i.e., a potassium binder), if indicated, be initiated. This may be followed by a re-initiation of RAAS-I after down-titration. This strategy would allow a greater percentage of patients with chronic HFREF to remain on RAAS-I, especially MRAs, thereby potentially preventing cardiovascular death, hospitalizations for HF, and increased healthcare costs. Further prospective adequately powered randomized clinical trials as well as further analysis of "real life" observational databases or registries will be essential to inform clinical guidelines and practice. In the interim, clinicians will need to weigh the risks and benefits of discontinuing RAAS-I, especially MRAs, in patients with chronic HFREF who develop mild to moderate hyperkalemia and/or worsening renal function on an individual basis. Although it may be easier to withdraw an RAAS-I than to continue it, in these circumstances, the accumulating evidence suggests that in many instances the decision to continue the use of an RAAS-I will in the long run result in a favorable

effect on renal structure, function, and cardiovascular outcomes.

CONFLICT OF INTEREST

B.P. receives personal fees (consulting) from Bayer, KBP Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Merck, Takeda, Relypsa, Sanofi, SC Pharmaceuticals, Sarfez Pharmaceuticals, and Tricida; has stock options from KBP Pharmaceuticals, SC Pharmaceuticals, Sarfez Pharmaceuticals, Relypsa, and Tricida; and has a patent pending for site-specific delivery of eplerenone to the myocardium. P.R. receives personal fees (consulting) from Bayer, Novartis, Relypsa, AstraZeneca, Stealth Peptides, Fresenius, Vifor Fresenius Medical Care Renal Pharma, and CTMA; receives lecture fees from CVRx; and is the cofounder of CardioRenal.

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A Call for a Consortium for Optimal Management of Drug–Drug Interactions in Patient Care

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During clinical development of medicines, manufacturers are obliged to assess the risk of drug–drug interactions (DDIs) with their new drug. There is no doubt that product labels of drugs that are nowadays introduced to the market contain much more information on DDIs than in the past. Indeed, the drug label is often the first source for DDIs available to physicians and pharmacists. But how informative are the data presented in the drug labels?

THE IMPORTANCE OF DRUG–DRUG INTERACTIONS

There is increased awareness of the importance of DDIs, as they may be associated with clinical toxicity or treatment failure. This is fueled by a better understanding of mechanisms of DDIs, particularly when drug transporters are involved. Also, the recognition that increased medication use in our aging patient population leads to polypharmacy, which is associated with an elevated risk of DDIs. Regulatory authorities such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have issued guidelines to support manufacturers in evaluating DDIs of not yet licensed drugs.[1,2] A snapshot of that information will be channeled to the description of a drug's DDI potential in the product label.

Here we briefly describe the process of prelicensure DDI evaluation. Second, we address four issues relating to DDI information in the product label from an academic/clinical point of view. These issues have been discussed by other stakeholders.[3] We illustrate this by commenting on two recently FDA and EMA-approved drug labels of direct acting antivirals (DAAs) for the treatment of chronic hepatitis C virus (HCV) infection, i.e., grazoprevir/elbasvir (Zepatier) and sofosbuvir/velpatasvir (Epclusa). These examples were chosen as they 1) reflect the current state of DDI reporting; 2) belong to a group of drugs with a high risk of DDIs[4]; and 3) are used in the treatment of chronic HCV patients who are known to use multiple concomitant medications.[5]

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doi:10.1002/cpt.648