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EDITORIAL COMMENT

Spironolactone: diuretic or disease-modifying drug in heart failure with preserved ejection fraction?

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This article refers to 'Diuretic and renal effects of spironolactone and heart failure hospitalizations: a TOPCAT Americas analysis' by A.P. Kalogeropoulos *et al.*, published in this issue on pages 1600–1610.

With monthly costs of approximately US$12 in the USA and €5 in Europe, spironolactone is by a landslide the most cost-effective drug in the management of heart failure (HF) with reduced ejection fraction (HFrEF). In the Randomized Aldactone Evaluation Study (RALES), the treatment of 10 patients with HFrEF in New York Heart Association functional class III or IV saved one life after 2 years,[1] a number that still looks favourable in comparison with any other HF drug. The story is more nuanced in HF with preserved ejection fraction (HFpEF), but given the high number of treatment strategies that have failed over the past 15 years, the results of spironolactone in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial remain among the best we have to offer our patients. In the TOPCAT trial, spironolactone use was associated with a non-significant 10% lower relative risk for all-cause mortality after 3.3 years, and a borderline significant 17% relative risk reduction for HF readmission was observed.[2] However, the primary endpoint of the trial, which combined both individual endpoints together with aborted cardiac arrest, was not statistically significant. Post hoc analyses of the TOPCAT trial identified significant regional differences in patient profiles, event rates and compliance with the study medication, demonstrating that the trial would have been positive if it had been limited to the subpopulation recruited in America or with objective evidence for HFpEF under the form of elevated natriuretic peptide levels.

These somewhat ambiguous results make it even more important to understand *how* spironolactone exerts its beneficial effects in HF. Spironolactone is a prodrug that is rapidly metabolized in its major active metabolites with a long half-life ($t_{1/2}$): 7α-thiomethylspironolactone ($t_{1/2}$ = 13.8 h) and canrenone ($t_{1/2}$ = 16.5 h). Both potently antagonize the mineralocorticoid receptor through reversible competition with its endogenous agonist aldosterone in many organs, including the kidneys, colon, heart, blood vessels, central nervous system, brown adipose tissue and sweat glands. This explains the high potential for pleiotropic effects with spironolactone that are still incompletely understood (*Figure 1*). Aldosterone promotes inflammation, endothelial dysfunction, hypertrophy and fibrosis in the heart, blood vessels, kidneys and many other organs.[3] In the kidneys, mineralocorticoid receptor activation increases the expression of Na^+/K^+ ATPases on the basolateral membrane of tubular cells and epithelial sodium channels at the luminal side in the distal nephron. Furthermore, potassium conductance in the collecting ducts is promoted by aldosterone, leading towards more sodium reabsorption and increased potassium loss. By blocking these effects, spironolactone works as a sodium-losing and potassium-sparing agent. The effect on urine output or *diuresis* is more complex. Water transport in the distal tubules and collecting ducts ultimately determines urine output and primarily depends on the permeability characteristics of those tubular segments and the tonicity gradient towards the medullar interstitium. This explains the diuretic synergy of spironolactone with loop diuretics that potently reduce the medullar tonicity. In contrast, spironolactone on its own (especially at lower dosing) has a less prominent impact on medullar tonicity. Therefore, it might promote natriuresis even without meaningful impact on diuresis.

The natriuretic properties of spironolactone are dose-dependent and increase to a dose of 600 mg, yet this evidence is mainly extrapolated from patients with cirrhosis.[4] In HF, short-term improvements in clinical congestion signs are observed only with doses of ≥50 mg.[5] Therefore, the benefits of spironolactone in HFrEF, observed with a 25 mg dose in the RALES, have largely been attributed to non-diuretic effects. Moreover, in the Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial, which

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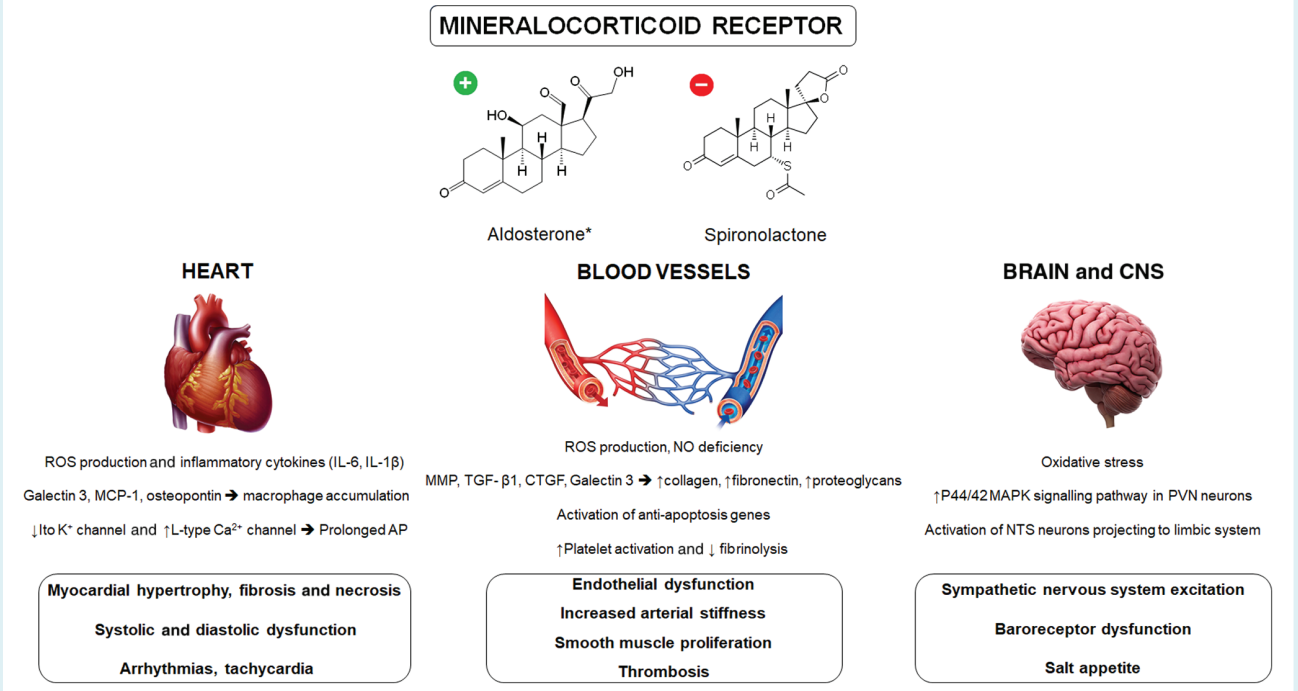

Figure 1 Pleiotropic effects of spironolactone in heart failure. *Some of these effects are actually mediated by cortisol rather than aldosterone in physiological circumstances as a result of the additional high affinity of the mineralocorticoid receptor for glucocorticoids. Tissue-specific expression of 11β-hydroxysteroid dehydrogenase type 2, which inactivates cortisol into cortisone, determines the physiological agonist of the mineralocorticoid receptor. For example, 11β-hydroxysteroid dehydrogenase type 2 expression is relatively low in the heart. Hence, mineralocorticoid receptor antagonism through spironolactone in the heart works primarily through inhibition of cortisol rather than aldosterone. AP, action potential; CNS, central nervous system; CTGF, connective tissue growth factor; IL-1β, interleukin-1β; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; MAPK, mitogen-activated protein kinase; MMP, matrix metallopeptidases; NO, nitric oxide; NTS, nucleus tractus solitarius; PVN, paraventricular nucleus; ROS, reactive oxygen species; TGF-β1, transforming growth factor-β1.

included patients with acute HF (roughly 25% HFpEF), 100 mg vs. 0–25 mg spironolactone was not associated with a meaningful rise in urine output, decrease in natriuretic peptide levels, or improvement of congestion symptoms after 96 h, and a nominally 0.5 kg greater weight loss was not statistically significant.[6] However, this follow-up time may have been too short to evaluate the full diuretic potential of spironolactone as the prodrug needs to be converted to its active metabolites and their actions through transcription regulation via the mineralocorticoid receptor may take some time to kick in, with up to 1 month needed for a peak response.[7] Additionally, even with low-dose spironolactone, there may be a meaningful impact on natriuresis that is not readily appreciated by crude parameters such as net fluid balance or weight loss.[8]

The average spironolactone dose in the TOPCAT trial was 25 mg, roughly similar to that in RALES, although the protocol allowed dose titration up to 45 mg when tolerance was good.[2] Elderly patients (≥75 years) and those with chronic kidney disease or potassium levels >4.5 mmol/L ended up receiving a lower dose, yet without heterogeneity of the spironolactone effect among these subgroups.[9] This also argues against mediation through diuresis in the HFpEF population of the TOPCAT trial. Furthermore, post hoc analysis did not show any significant interaction between spironolactone use and calculated plasma volume for any endpoint.[10,11] In this issue of the journal, Kalogeropoulos *et al.*[12] provide important further insights into the effects of spironolactone on subsequent diuretic use, electrolytes and serum creatinine, as well as their relationship with the risk for HF readmission.

In brief, spironolactone had a marginal (<1%) and short-term (first 8 months) effect on weight loss in the American population of the TOPCAT trial, with superimposed curves after 1 year. Serum creatinine and potassium levels increased by 0.08 mg/dL and 0.21 mmol/L, respectively, and sodium levels dropped by 1.2 mmol/L in spironolactone- vs. placebo-treated patients. These findings were relatively stable over time and statistically significant. Interestingly, in the spironolactone vs. placebo group, use of thiazide-like diuretics and dosing of loop diuretics were lower, with gradual and continued separation over time. The same was true for renin–angiotensin system (RAS) blockers, which were more frequently withdrawn in the spironolactone group. In time-updated models, higher loop diuretic dose, increase in serum creatinine and abnormal sodium levels were associated with a significantly increased risk for HF readmission. However, the beneficial impact of spironolactone was independent and persisted after adjustments for these trends.

There are several lessons to be learned from these results. First, the combination of a lower risk for HF readmission despite less intensive use of diuretics reinforces the concept that congestion was better controlled with spironolactone. Whether this was attributable to a direct diuretic effect of spironolactone, a potentiation of other diuretics, or improvement of underlying HFpEF through non-diuretic effects is difficult to discern. The gradual and continued separation of diuretic intensity between spironolactone and placebo users over time may fit better with the latter option and would be more in line with the dose used in the TOPCAT trial, yet this is somewhat speculative. In contrast, significant electrolyte changes with lower sodium and higher potassium levels indicate potent mineralocorticoid receptor antagonism in the kidneys, assuming there were no differences in major dietary modifications between treatment arms. It is thus likely that spironolactone caused a significant increase in natriuresis, especially if one considers the less intensive use of thiazide-like and loop diuretics. Interestingly, a small prospective cohort study using serial urine spot samples found that deficient natriuretic capacity of the kidneys may precede a hospital admission for acute HF.[13]

Treatment with RAS blockers was more frequently withdrawn in the spironolactone arm (4.2% difference vs. placebo) and also spironolactone itself was stopped in about one-third of patients in the main TOPCAT trial.[2,12] Worsening serum creatinine levels (0.18 mg/dL higher upon visits when RAS blockers were stopped) may have played a role in this decision, whereas elevations in potassium levels at the same time were minimal and unlikely to influence clinical decision making, albeit that they were statistically significant ($\Delta = 0.06$ mmol/L). Most importantly, it is reassuring to see that major elevations of serum creatinine or clinically relevant hyperkalaemia were rare despite prevalent concomitant use of RAS blockers with spironolactone. Nonetheless, only 25% of the American TOPCAT population had an estimated glomerular filtration rate of <50 mL/min/1.73 m^2 at baseline and there was close follow-up inside the context of a randomized clinical trial; hence these numbers are likely to be higher in real-world clinical practice. Current data demonstrate that a small rise in serum creatinine with spironolactone is expected and by itself should not be a reason to withhold the drug, as its beneficial effects are independent of this anticipated increase.

A reduced risk for HF readmission in patients with HFpEF has also been reported with RAS blocker treatment.[14,15] As the TOPCAT trial illustrates, these agents are very frequently used in HFpEF despite less robust evidence for their use in comparison with that in HFrEF. The study by Kalogeropoulos *et al.*[12] now suggests that in the context of a choice between a RAS blocker and spironolactone, the latter may just have the edge in HFpEF. Indeed, the reduction in HF readmission with spironolactone was independent of and persisted despite a higher withdrawal rate of RAS blockers, and had a stronger effect size.[12] This is likely to be most relevant for patients with more pronounced chronic kidney disease, who had similar benefits with spironolactone in the TOPCAT trial compared with their counterparts with normal renal function.[16] Interestingly, post hoc analysis from the Prospective Comparison of Angiotensin Receptor-Neprilysin inhibitor with angiotensin receptor blockers Global Outcomes in Heart Failure with Preserved Ejection Fraction (PARAGON-HF) trial showed a significant reduction in all-cause mortality or HF readmissions with sacubitril–valsartan in patients treated with a mineralocorticoid receptor antagonist (hazard ratio 0.73, 95% confidence interval 0.56–0.95) despite non-significant results in the overall trial and no evidence for a reduction in cardiovascular death.[17] It is tempting to speculate that the two medications may have caused a synergistic effect on natriuresis. This should be further investigated.

In conclusion, is spironolactone a diuretic or a disease-modifying drug in HFpEF? We still cannot know for sure. However, based on the elegant analysis of Kalogeropoulos and colleagues,[12] we should be confident in prescribing it for patients with a TOPCAT America profile, prioritizing it over RAS blockers and potentially combining it with sacubitril–valsartan. A small rise in serum creatinine, without signs of clinical deterioration, should never deter from that incentive![18]

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