Heart Failure and Chronic Kidney Disease: Should We Use Spironolactone?

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Heart Failure and Chronic Kidney Disease: Should We Use Spironolactone?

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Abstract: Half of all deaths in patients with chronic kidney disease (CKD) arise from cardiovascular causes. Congestive heart failure (CHF) is specifically more frequent with CKD. Cardiovascular therapies with proven benefit are often withheld from patients with renal disease for fear of adverse events. The renin-angiotensin-aldosterone system (RAAS) has been implicated as an important maladaptive neurohormonal pathway in heart failure. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been shown to suppress it ineffectively. Current guidelines support the use of spironolactone for more comprehensive suppression of the RAAS in heart failure patients. Most supporting trials have however excluded patients with renal dysfunction resulting in a dearth of data to support use of spironolactone in CKD patients with CHF. Several small studies that prospectively interrogated the benefits of augmented RAAS blockade with spironolactone in CKD patients have shown improvement in predictors of cardiovascular mortality. More recently, improved mortality outcomes were demonstrated with the use of spironolactone in hemodialysis patients. Although reduction in glomerular filtration rate and hyperkalemia are potential adverse effects with its use, the available evidence suggests that it is uncommon and serious consequences can be avoided with close monitoring. Studies investigating the optimal spironolactone dosage in such a setting recommend starting with a low dose and careful uptitration. This review attempts to provide a comprehensive insight into the issues associated with the use of spironolactone in the setting of concomitant CHF and CKD.

Key Indexing Terms: Spironolactone; Aldosterone antagonism; Renal failure; Chronic Kidney Disease; Heart failure. **[Am J Med Sci 2015;350(2):147–151.]**

BACKGROUND

Chronic kidney disease (CKD) patients are at great risk of cardiovascular mortality. Half of all CKD patients will die of cardiovascular causes, at rates that are 20 to 40 times that of the general population.[1] Congestive heart failure (CHF) is significantly more frequent in CKD patients.[2] CKD patients with left ventricle (LV) hypertrophy, a precursor of CHF had a median survival of 38 months.[3] The mineralocorticoid hormone aldosterone acting through nonepithelial targets (myocardium, vascular muscles and endothelium[4]) causes increased LV mass index, myocardial and vascular fibrosis and impaired arterial compliance.[5–9] These are important precursors of cardiac failure and also of renal failure.[10,11] The renin-angiotensin-aldosterone system (RAAS) antagonism is therefore an important target of CHF pharmacotherapy.[5,6,12] Angiotensin-converting enzyme inhibitors (ACEi) improve CHF mortality significantly.[13] Angiotensin receptor blockers (ARBs) are used in patients intolerant of ACE inhibitors. Inhibition of RAAS with ACE inhibitors or ARBs is however transient[14,15] and incomplete.[16] A phenomenon of "aldosterone escape" has been described in 40% to 50% of patients on ACEi/ARBs.[17,18] Non-RAAS mechanisms[19] and local production of aldosterone by tissue RAAS[20] are implicated in this maladaptation. Left ventricle hypertrophy fails to regress and a continued decline in glomerular filtration rates (GFRs) ensues in these patients.[21] Spironolactone, a mineralocorticoid/aldosterone antagonist (MRA), inhibits downstream effects of RAAS by disrupting mineralocorticoid receptor signaling. When added to background medical therapy (consisting of ACEi and β-blockers) in patients with advanced CHF in the Randomized Aldosterone Evaluation Study (RALES) trial, spironolactone decreased cardiovascular mortality and CHF hospitalizations each by ~30%.[22] Similarly, encouraging results were reported in the Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)[23] and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure)[24] studies that used eplerenone, a more selective MRA. MRAs are associated with a risk of hyperkalemia and acute renal failure. CHF patients with impaired renal function (serum creatinine (SCr) ≥2.5 mg/dL in RALES and EPHESUS, GFR <30 mL·min^{-1}·1.73 m^{-2} in EMPHASIS) were therefore excluded in these trials. Unfortunately, this underrepresentation of renal disease in cardiovascular trials is not uncommon.[25] Coronary angiography[26] and ACEi use in renally insufficient patients had met with similar skepticism and paranoia. Use of aldosterone antagonists for CHF therapy in patients with renal impairment (SCr >2.5 mg/dL in men or >2.0 mg/dL in women, GFR <30 mL·min^{-1}·1.73 m^{-2}) is discouraged by current heart failure guidelines (class III, level B).[27] This "renalism" may have led us to withhold potentially life saving therapy. This review attempts to assimilate the current data available on the issue of utilization of spironolactone in CHF therapy for patients with CKD.

Widespread benefits with minimal side effects from use of spironolactone in CKD patients have been repeatedly demonstrated. Predialysis systolic blood pressures were reduced in an average of 11 mm Hg in hemodialysis (HD) patients without increased hyperkalemia.[28] This effect was independent of diuresis. Spironolactone improved LV function (systolic and diastolic) and reduced N-terminal probrain natriuretic peptide (NT-proBNP) levels in patients with early CKD.[29] Regression of LV hypertrophy favorably affects cardiovascular and all-cause mortality in end-stage renal disease.[30] Spironolactone decreased LV mass and LV mass index independent of baseline LV mass in patients with CKD stages 2 to 3. These patients were being treated with maximally tolerated doses of ACEi and/or

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ARBs and had been on them for at least 6 months.[31] Proteinuria is an important predictor of adverse renal and cardiovascular outcomes.[32] A reduction in proteinuria by half resulted in an 18% reduction in cardiovascular risk and a 27% reduction in heart failure risk in patients with diabetic nephropathy.[33] Reductions in proteinuria ranging from 15% to 54% were reported in 15 reports that studied the addition of spironolactone to chronic therapy with ACEi and/or ARBs.[34] A serum potassium ≥5.5 mmol/L was identified in 5.5% of 436 patients. Reductions in GFR were observed in only 3 studies and were clinically insignificant. Proteinuria could therefore be reduced with relatively few adverse effects. Significant increases in aortic distensibility were seen with the use of spironolactone in early CKD.[35] Spironolactone also improved heart rate variability and forearm blood flow reserve in HD patients.[36] These markers of endothelial dysfunction are independent predictors of cardiac mortality in such patients. Carotid intima-medial thickness is a well-documented predictor of future cardiovascular events.[37] Treatment with spironolactone (50 mg 3 times each week) resulted in decreases or even reversal of carotid intima-medial thickness over a 2-year period.[36] In an analysis of the RALES trial data, individuals with reduced baseline GFR (GFR <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) exhibited comparable clinical benefit to those with a higher baseline GFR. Reductions in all-cause mortality and in the combined end point of death or hospital admissions for CHF were similar; the absolute risk reduction was in fact greater.[38] More recently, Matsumoto et al[39] have demonstrated a significant mortality benefit from spironolactone in a randomized trial of 309 oligoanuric patients on HD. In their 3-year follow-up, a 25-mg daily dose of spironolactone significantly reduced the primary outcome (a composite of death from cardiovascular and cerebrovascular causes and hospitalizations), and there was also a significant reduction in all-cause mortality (secondary outcome) in the treatment group. Ninety-eight patients in the treatment arm who had no events of interest did not experience an increase in average K^+ levels. Notably, serious hyperkalemia necessitating discontinuation of therapy was reported only in 3 treated patients despite no restrictions on dietary intake of K^+ in the treatment arm. This trial is pivotal for being the 1st moderate-sized randomized trial to investigate and demonstrate mortality benefit from the utilization of spironolactone in CKD patients on HD.

ALDOSTERONE AND POTASSIUM REGULATION IN OLIGOANURIC PATIENTS

In healthy subjects, potassium (K^+) excretion primarily depends on renal (about 90%) and to a lesser extent (about 10%) on colonic excretion.[40] In patients with chronic renal failure, low sodium to potassium ratios in the saliva[41] and stool[42] and an accompanying enhanced fecal K^+ excretion (2–3-fold higher)[43,44] suggest a role for aldosterone-mediated K^+ homeostasis in patients with decreased GFR. The role of aldosterone in K^+ handling in dialysis patients is however controversial,[45] with trials failing to show an unequivocal K^+ lowering effect of fludrocortisone.[46,47] Plasma aldosterone levels in anuric patients were noted to be low despite elevated K^+ levels in studies of anephric subjects.[48] At the same time, in HD patients with K^+ <5 and low aldosterone levels, spironolactone resulted in rising K^+ levels without significant changes in aldosterone levels suggesting an aldosterone-mediated excretion despite the attendant low levels. In HD patients, K^+ levels are regulated by dialysis and spironolactone has not been shown to reduce dialyzer clearance of K^+ at pharmacological doses.[49] Data suggest that tolerance to an acute K^+ load in healthy patients is not dependent on aldosterone.[50] However, aldosterone blockade with spironolactone resulted in a higher rate of rise in plasma K^+ after an acute load than in controls who did not receive it. It was therefore proposed that aldosterone seems to play an important role in the extrarenal modulation of an acute K^+ load in anephric patients.[48] It will not be advisable to generalize these findings as the study included only 7 patients and used spironolactone at a daily dose of 300 mg.

WHAT IS THE RISK OF HYPERKALEMIA IN CKD PATIENTS?

One in 10 of CKD patients on HD are reported to develop serious hyperkalemia, and 3% to 5% of mortality in these patients is related to hyperkalemia.[45] MRAs especially when combined with ACEi could increase this risk several folds in HD patients. In the RALES[22] study, serious hyperkalemia (K^+ >6 mmol/L) was infrequent and was not significantly more common in spironolactone-treated patients despite the accompanying ACEi/ARB therapy. Hyperkalemia warranting spironolactone discontinuation occurred in only 3 patients. Although the trial excluded patients with SCr >2.5 mg/dL, a number of patients in the treatment group would have had reduced GFRs of varying degrees. Thus, spironolactone was inadvertently given to patients with less serious renal dysfunction albeit in controlled circumstances. Clinical experience in the "real world" has been unequivocal. Hyperkalemia-related hospital admissions and associated mortality were reported to have doubled after publication of the RALES trial.[51] A scrutiny revealed that a large proportion of the population that was prescribed spironolactone did not meet guidelines for such therapy; and that some continued to be prescribed K^+ supplements. In a 2nd study that also reported a similar increase in the utilization of spironolactone, an increase in outpatient rates of hyperkalemia ($K \geq 6$ mEq/L) was not found.[52] Spironolactone was safely used without statistically significant rises in mean K^+ levels in HD patients in studies designed to specifically examine this scenario.[28,53–57] However, the following deficiencies pertaining to these studies must be taken into account. The sample sizes were small, and the study durations were short and included patients with demonstrated compliance with dialysis and historically stable K^+ levels. Furthermore, it is expected that close laboratory monitoring and changes to dialysate compositions (as permissible by the study protocols) were practiced. The frequency of concurrent ACEi/ARB therapy and prevalence of CHF in these studies were variable and usually low and discourages against accepting these results with enthusiasm. Large-scale randomized trials would be needed to gather promising data.

Consistent data are available from several, albeit small, studies about factors that predispose to hyperkalemia in the setting of spironolactone use for CHF. Increasing age[22,52,58] and the attendant decline in renal function[22,52,58,59] were independently associated with spironolactone-associated hyperkalemia. As many as 75% of patients who developed hyperkalemia in one study were more than 65 years old.[52] A creatinine clearance of <40 mL/min, which is higher than the historical threshold of 30 mL/min, is a risk factor. The risk of hyperkalemia was more accurately predicted when the degree of renal dysfunction was assessed using creatinine clearance (derived using the Cockcroft-Gault formula) rather than SCr (<221 μmol/L as used in the RALES). A higher (New York Heart Association) NYHA symptom class and heart failure exacerbations were each associated with more hyperkalemic episodes.[22] This effect of worsening heart failure was probably secondary to an accompanying worsening renal function (WRF)—the cardiorenal

syndrome. Diabetes mellitus was reported as an independent inciting comorbidity on a consistent basis[51,58–60] resulting perhaps from a lack of insulin-driven intracellular transport of an acute K^+ load.[49] Higher doses of spironolactone expectedly led to higher rates of hyperkalemia.[50,57] Forty-four percent of patients who experienced hyperkalemia in 1 study were on a high daily dose (>50 mg/d).[52] The risk for hyperkalemia was magnified several times in patients using both ACEi and spironolactone versus ACEi alone.[6] The need to monitor serum K^+ concentrations closely in any patient with renal insufficiency taking spironolactone cannot be overemphasized. A major gap between the close follow-up in a well-conducted study and in clinical practice by busy physicians is a major risk to the development of hyperkalemia. K^+ levels should be checked periodically when initiating therapy and rechecked during any acute illness. Clinicians cannot afford to neglect the presence of predisposing factors such as diabetes and the concomitant use of medications, such as ACEi/ARBs, β-blockers, nonsteroidal anti-inflammatory drugs and K^+ supplements, especially in the older patient who often has several of these risk factors.

WHAT IS THE RISK OF ACUTE RENAL DYSFUNCTION IN CKD PATIENTS?

A study in which 115 patients with nondiabetic early stage CKD (GFR 30–89 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) received 25 mg spironolactone daily showed that an early reduction in GFR can be anticipated with spironolactone akin to the use of ACEi and ARBs.[61] The clinical importance of this observation is uncertain. Subanalysis of the Survival And Ventricular Enlargement (SAVE)[62] and Studies of Left Ventricular Enlargement (SOLVD)[63] trials data that used ACEi treatment in patients with asymptomatic LV dysfunction and symptomatic CHF respectively showed that WRF (defined as increase in SCr >0.3 mg/dL) was neither significantly more common in patients treated with ACEi therapy nor associated with increased mortality when it occurred in these patients. Vardeny et al[38] investigated the prognostic significance of WRF (defined as a 30% reduction in GFR) in the RALES trial population. Patients in the placebo arm with WRF experienced higher mortality and more rehospitalizations; however, patients receiving spironolactone did not. A net benefit still remained in the spironolactone arm after accounting for hyperkalemia, which was higher in patients with reduced baseline renal dysfunction and in those with WRF. This reduction in GFR associated with inhibition of RAAS might not reflect actual kidney injury and maybe secondary to changes in renal blood flow after reductions in blood pressure. An absence of progressive renal function decline after an initial worsening has been demonstrated and supports this notion.[61] Spironolactone exerts a powerful natriuretic effect when used in combination with ACEi.[56] Excessive diuresis that might account for renal dysfunction in nonoliguric CKD patients taking spironolactone is less likely in oliguric patients. Age, lower LV ejection fraction and higher NYHA functional class are predictors of azotemia with spironolactone use.[64] Changes in body weight should raise concern and dosing of other diuretics may need adjustment to avoid precipitating renal failure.[64] It might be advisable to monitor renal function with greater frequency in the 1st month. Later, monitoring is probably not needed any more frequently than is required for patients on ACEi s/ARBs.

WHAT IS THE RENAL DOSE OF SPIRONOLACTONE?

Optimal dosing and frequency for spironolactone use in CKD patients remains to be established. The doses of concomitant ACEi/ARB medications and other similar therapy capable of causing hyperkalemia and/or renal dysfunction have to be taken into account, and therefore, a strict "one for all" dosage cannot be proposed. A 12.5 to 25 mg daily dose was effective in aldosterone blockade and serious hyperkalemia occurred most frequently with 50 mg daily or more in patients with no renal dysfuntion.[22] Higher dosages of spironolactone (up to 24% with 75 mg a day) result in a higher risk of hyperkalemia.[22] In HD patients, 25 mg of spironolactone dosed every other day could be considered the renal dosing equivalent of the average daily dose used in the RALES study.[54] A study of plasma canrenone levels (a major metabolite of spironolactone) in HD patients receiving this dose has confirmed this equivalence.[65] A titration schedule of 25 mg on alternate days for a month with an increase to daily treatment if potassium remains ≤5 mmol/L can be used.[66] With greater acceptance of its usage in clinical practice, spironolactone at a "baby" dose of 12.5 mg daily could become the CKD equivalent of aspirin.[67]

CONCLUSIONS

In summary, data from research with surrogate end points suggest that spironolactone-mediated inhibition of the RAAS provides beneficial results at structural and physiological levels in heart failure patients with CKD patients. There is now data available from a moderate-sized randomized trial to support a mortality benefit from spironolactone use in CKD patients. These benefits were obtained with acceptable incidences of adverse events, such as hyperkalemia and acute renal failure. In most cases, these were not significantly higher than in patients without CKD. However, achieving a favorable risk-benefit ratio demands careful monitoring during initiation of therapy with spironolactone and particularly during periods of acute illness. Patient selection is also of paramount importance. Certain characteristics were consistently associated with adverse events and knowledge of these may aid patient selection. With most side effects being dose dependent, a dosing regimen governed by residual renal function will need to be devised. Despite encouraging results, the lack of data from large randomized studies has relegated the use of spironolactone in CHF patients with concomitant CKD to being mostly experimental in current practice.

REFERENCES

1. **Foley RN, Parfrey PS, Sarnak MJ.** Epidemiology of cardiovascular disease in chronic renal disease. J Am Soc Nephrol 1998;9(12 suppl): S16–23.
2. **Foley RN, Murray AM, Li S, et al.** Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol 2005;16:489–95.
3. **Parfrey PS, Harnett JD, Foley RN.** Heart failure and ischemic heart disease in chronic uremia. Curr Opin Nephrol Hypertens 1995;4:105–10.
4. **Struthers AD, MacDonald TM.** Review of aldosterone and angiotensin II induced target organ damage and prevention. Cardiovasc Res 2004;61:663–70.
5. **Barr CS, Lang CC, Hanson J, et al.** Effects of adding spironolactone to an angiotensin-converting enzyme inhibitor in chronic congestive heart failure secondary to coronary artery disease. Am J Cardiol 1995;76:1259–65.
6. **MacFadyen RJ, Barr CS, Struthers AD.** Aldosterone blockade reduces vascular collagen turnover, improves heart rate variability and

reduces early morning rise in heart rate in heart failure patients. Cardiovasc Res 1997;35:30–4.

7. **Wang W.** Chronic administration of aldosterone depresses baroreceptor reflex function in the dog. Hypertension 1994;24:571–5.
8. **Duprez DA, De Buyzere ML, Rietzschel ER, et al.** Inverse relationship between aldosterone and large artery compliance in chronically treated heart failure patients. Eur Heart J 1998;19:1371–6.
9. **Rocha R, Chander PN, Khanna K, et al.** Mineralocorticoid blockade reduces vascular injury in stroke-prone hypertensive rats. Hypertension 1998;31:451–8.
10. **Epstein M.** Aldosterone as a determinant of cardiovascular and renal dysfunction. J R Soc Med 2001;94:378–83.
11. **Brewster UC, Setaro JF, Perazella MA.** The renin-angiotensin-aldosterone system: cardiorenal effects and implications for renal and cardiovascular disease states. Am J Med Sci 2003;326:15–24.
12. **Swedberg K, Eneroth P, Kjekshus J, et al.** Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation 1990;82:1730–6.
13. **Yan AT, Yan RT, Liu PP.** Narrative review: pharmacotherapy for chronic heart failure: evidence from recent clinical trials. Ann Intern Med 2005;142:132–45.
14. **Borghi C, Boschi S, Ambrosioni E, et al.** Evidence of a partial escape of renin-angiotensin-aldosterone blockade in patients with acute myocardial infarction treated with ACE inhibitors. J Clin Pharmacol 1993; 33:40–5.
15. **Staessen J, Lijnen P, Fagard R, et al.** Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. J Endocrinol 1981;91:457–65.
16. **Brown NJ.** Aldosterone and vascular inflammation. Hypertension 2008;51:161–7.
17. **Struthers AD.** Aldosterone escape during angiotensin-converting enzyme inhibitor therapy in chronic heart failure. J Card Fail 1996;2:47–54.
18. **Lakkis J, Lu WX, Weir MR.** RAAS escape: a real clinical entity that may be important in the progression of cardiovascular and renal disease. Curr Hypertens Rep 2003;5:408–17.
19. **Hollenberg NK.** Aldosterone in the development and progression of renal injury. Kidney Int 2004;66:1–9.
20. **Delcayre C, Silvestre JS, Garnier A, et al.** Cardiac aldosterone production and ventricular remodeling. Kidney Int 2000;57:1346–51.
21. **Bomback AS, Toto R.** Dual blockade of the renin-angiotensin-aldosterone system: beyond the ACE inhibitor and angiotensin-II receptor blocker combination. Am J Hypertens 2009;22:1032–40.
22. **Pitt B, Zannad F, Remme WJ, et al.** The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341(10):709–17.
23. **Rossignol P, Cleland JG, Bhandari S, et al.** Determinants and consequences of renal function variations with aldosterone blocker therapy in heart failure patients after myocardial infarction: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study. Circulation 2012;125:271–9.
24. **Zannad F, McMurray JJ, Krum H, et al.** Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11–21.
25. **Coca SG, Krumholz HM, Garg AX, et al.** Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. JAMA 2006;296:1377–84.
26. **Chertow GM, Normand SL, McNeil BJ.** "Renalism": inappropriately low rates of coronary angiography in elderly individuals with renal insufficiency. J Am Soc Nephrol 2004;15:2462–8.
27. **Hunt SA, Abraham WT, Chin MH, et al.** 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2009;119:e391–479.
28. **Gross E, Rothstein M, Dombek S, et al.** Effect of spironolactone on blood pressure and the renin-angiotensin-aldosterone system in oligoanuric hemodialysis patients. Am J Kidney Dis 2005;46:94–101.
29. **Edwards NC, Ferro CJ, Kirkwood H, et al.** Effect of spironolactone on left ventricular systolic and diastolic function in patients with early stage chronic kidney disease. Am J Cardiol 2010;106:1505–11.
30. **London GM, Pannier B, Guerin AP, et al.** Alterations of left ventricular hypertrophy in and survival of patients receiving hemodialysis: follow-up of an interventional study. J Am Soc Nephrol 2001;12: 2759–67.
31. **Edwards NC, Steeds RP, Stewart PM, et al.** Effect of spironolactone on left ventricular mass and aortic stiffness in early-stage chronic kidney disease: a randomized controlled trial. J Am Coll Cardiol 2009;54:505–12.
32. **Asselbergs FW, Diercks GF, Hillege HL, et al.** Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators. Circulation 2004;110:2809–16.
33. **de Zeeuw D, Remuzzi G, Parving HH, et al.** Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation 2004;110:921–7.
34. **Bomback AS, Kshirsagar AV, Amamoo MA, et al.** Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. Am J Kidney Dis 2008;51:199–211.
35. **Macdonald JE, Kennedy N, Struthers AD.** Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. Heart 2004;90:765–70.
36. **Vukusich A, Kunstmann S, Varela C, et al.** A randomized, double blind, placebo-controlled trial of spironolactone on carotid-intima media thickness in non diabetic hemodialysis patients. Clin J Am Soc Nephrol 2010;5:1380–7.
37. **Lorenz MW, Markus HS, Bots ML, et al.** Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007;115:459–67.
38. **Vardeny O, Wu DH, Desai A, et al.** Influence of baseline and worsening renal function on efficacy of spironolactone in patients with severe heart failure: insights from RALES (Randomized Aldactone Evaluation Study). J Am Coll Cardiol 2012;60:2082–9.
39. **Matsumoto Y, Mori Y, Kageyama S, et al.** Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. J Am Coll Cardiol 2014;63:528–36.
40. **Putcha N, Allon M.** Management of hyperkalemia in dialysis patients. Semin Dial 2007;20:431–9.
41. **Goll RD, Mookerjee BK.** Correlation of biochemical parameters in serum and saliva in chronic azotemic patients and patients on chronic hemodialysis. J Dial 1978;2:399–44.
42. **Wilson DR, Ing TS, Metcalfe-Gibson A, et al.** The chemical composition of faeces in uraemia, as revealed by in-vivo faecal dialysis. Clin Sci 1968;35:197–209.
43. **Hayes CP Jr, McLeod ME, Robinson RR.** An extrarenal mechanism for the maintenance of potassium balance in severe chronic renal failure. Trans Assoc Am Phys 1967;80:207–16.
44. **Bastl C, Hayslett JP, Binder HJ.** Increased large intestinal secretion of potassium in renal insufficiency. Kidney Int 1977;12:9–16.

45. **Ahmed J, Weisberg LS.** Hyperkalemia in dialysis patients. Semin Dial 2001;14:348–56.

46. **Kaisar MO, Wiggins KJ, Sturtevant JM, et al.** A randomized controlled trial of fludrocortisone for the treatment of hyperkalemia in hemodialysis patients. Am J Kidney Dis 2006;47:809–14.

47. **Furuya R, Kumagai H, Sakao T, et al.** Potassium-lowering effect of mineralocorticoid therapy in patients undergoing hemodialysis. Nephron 2002;92:76–581.

48. **Sugarman A, Brown RS.** The role of aldosterone in potassium tolerance: studies in anephric humans. Kidney Int 1988;34:397–403.

49. **Vlassopoulos D, Sonikian M, Dardioti V, et al.** Insulin and mineralocorticoids influence on extrarenal potassium metabolism in chronic hemodialysis patients. Ren Fail 2001;23:833–42.

50. **Nicolis GL, Kahn T, Sanchez A, et al.** Glucose induced hyperkalemia in diabetic subjects. Arch Intern Med 1981;141:49–53.

51. **Juurlink DN, Mamdani MM, Lee DS, et al.** Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543–51.

52. **Wei L, Struthers AD, Fahey T, et al.** Spironolactone use and renal toxicity: population based longitudinal analysis. BMJ 2010;340:c1768.

53. **Michea L, Vukusich A, González M, et al.** Effect of spironolactone on K(+) homeostasis and ENaC expression in lymphocytes from chronic hemodialysis patients. Kidney Int 2004;66:1647–53.

54. **Saudan P, Mach F, Perneger T, et al.** Safety of low-dose spironolactone administration in chronic haemodialysis patients. Nephrol Dial Transplant 2003;18:2359–63.

55. **Hussain S, Dreyfus DE, Marcus RJ, et al.** Is Spironolactone safe for dialysis patients? Nephrol Dial Transpl 2003;18:2364–8.

56. **Taheri S, Mortazavi M, Shahidi S, et al.** Spironolactone in chronic hemodialysis patients improves cardiac function. Saudi J Kidney Dis Transpl 2009;20:392–7.

57. **Matsumoto Y, Kageyama S, Yakushigawa T, et al.** Long-term low-dose spironolactone therapy is safe in oligoanuric hemodialysis patients. Cardiology 2009;114:32–8.

58. **Wrenger E, Müller R, Moesenthin M, et al.** Interaction of spironolactone with ACE inhibitors or angiotensin receptor blockers: analysis of 44 cases. BMJ 2003;327:147–9.

59. **Ramadan FH, Masoodi N, El-Solh AA.** Clinical factors associated with hyperkalemia in patients with congestive heart failure. J Clin Pharm Ther 2005;30:233–9.

60. **Cruz CS, Cruz AA, Marcílio de Souza CA.** Hyperkalaemia in congestive heart failure patients using ACE inhibitors and Spironolactone. Nephrol Dial Transplant 2003;18:1814–9.

61. **Edwards NC, Steeds RP, Chue CD, et al.** The safety and tolerability of spironolactone in patients with mild to moderate chronic kidney disease. Br J Clin Pharmacol 2012;73:447–54.

62. **Blankstein R, Bakris GL.** Changes in kidney function following heart failure treatment: focus on renin-angiotensin system blockade. Heart Fail Clin 2008;4:425–38.

63. **Jose P, Skali H, Anavekar N, et al.** Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. J Am Soc Nephrol 2006;17:2886–91.

64. **Svensson M, Gustafsson F, Galatius S, et al.** Hyperkalaemia and impaired renal function in patients taking spironolactone for congestive heart failure: retrospective study. BMJ 2003;327:1141–2.

65. **Flevari P, Kalogeropoulou S, Drakou A, et al.** Spironolactone improves endothelial and cardiac autonomic function in non heart failure hemodialysis patients. J Hypertens 2013;31:1239–44.

66. **Pitt B.** Pharmacotherapy: cardiovascular effects of aldosterone blockade in CKD. Nat Rev Cardiol 2009;6:679–80.

67. **Bomback AS, Kshirsagar AV, Klemmer PJ.** Renal aspirin: will all patients with chronic kidney disease one day take spironolactone? Nat Clin Pract Nephrol 2009;5:74–5.