Review

Spironolactone Use in Heart Failure Patients With End-Stage Renal Disease on Hemodialysis: Is It Safe?

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ABSTRACT

Background: Spironolactone is used in the treatment of cardiovascular disease, but is contraindicated in renal dysfunction due to the risk of hyperkalemia. It is not known if patients with end-stage renal disease (ESRD) on hemodialysis are at the same risk for hyperkalemia. The objective of this study was to systematically review the evidence evaluating the incidence of hyperkalemia with spironolactone use in ESRD patients on hemodialysis.

Hypothesis: Spironolactone use in ESRD patients on hemodialysis may not lead to greater incidence of hyperkalemia.

Methods: We searched the MEDLINE, Embase, CINAHL, Cochrane, and PubMed databases up to January 2010 for English-language, human-subject clinical trials that evaluated the rate of hyperkalemia with spironolactone use in ESRD patients on hemodialysis. Search terms included were "spironolactone," "eplerenone," "aldosterone antagonist," "heart failure," "kidney failure," "hemodialysis," "dialysis," and "renal replacement therapy."

Results: Six prospective trials demonstrated that spironolactone use was safe in ESRD patients on hemodialysis. The incidence of hyperkalemia with spironolactone treatment in these studies was similar to control groups. The studies involved a small population of compliant subjects who were at low risk for hyperkalemia.

Conclusions: Small pilot studies demonstrated that spironolactone treatment in ESRD patients on hemodialysis did not result in higher hyperkalemia rates. Larger studies are needed to confirm these preliminary results before spironolactone is routinely considered in hemodialysis patients.

Introduction

Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD).[1] Ischemic heart failure (HF), diabetes, hypertension, and atherosclerosis are strongly associated with the development of ESRD, and a significant number of patients with ESRD have reduced left ventricular function.[2,3] Contemporary treatment of HF includes multiple pharmacotherapeutic strategies to reduce mortality and slow the progression of HF.

The renin-angiotensin-aldosterone system (RAAS) has been identified as a maladaptive, neurohormonal pathway in HF and has been the focus of several treatment approaches. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been well established as standard therapy in HF by inhibiting the RAAS.[4–9] Aldosterone is also an important contributor in the pathophysiology of both kidney and heart disease.[10,11] Aldosterone mediates sodium retention, cardiac remodeling, myocardial fibrosis, and baroreceptor dysfunction and is involved with inflammatory and fibrotic processes in the kidney.[12–15] Landmark trials have demonstrated that the use of aldosterone antagonists for HF provided significant mortality reduction.[16,17] Aldosterone antagonist use is a Class IB recommendation in New York Heart Association Class III-IV HF patients in addition to standard, background therapy.[18,19]

However, hyperkalemia is a serious adverse effect of aldosterone antagonist use. The more prominent use of aldosterone antagonists as part of contemporary HF management has recently been associated with higher rates of hyperkalemia necessitating hospitalization and has prompted concern.[20] Current HF guidelines caution against the use of aldosterone antagonists in patients with an elevated serum creatinine (>2.5 mg/dL) due to the fear of hyperkalemia.[18,19]

The dilemma arises in patients who have HF and would derive the greatest benefit from aldosterone antagonist therapy, but likely have concomitant renal disease, thus are at the highest risk for hyperkalemia. One-third to one-half of patients with HF have some degree of impaired renal function, and ESRD is among the strongest predictors of cardiovascular death.[21] Up to 70% of patients in ESRD and requiring hemodialysis have concomitant

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HF.[22] Renal failure requiring hemodialysis promotes a hyperaldosteronic state, which can contribute extensively to the progression of heart disease.[23] Serious hyperkalemia (defined as serum potassium [K+] >6.0 mEq/L) occurs in 10% of patients with ESRD, and 3%–5% of deaths in this population are attributed to it.[24] Thus, the use of aldosterone antagonists in patients with significant kidney disease have been contraindicated due to the fear of life-threatening hyperkalemia in a patient population already at risk of hyperkalemia.[25–28]

However, hyperkalemia may be less of a prominent issue in ESRD patients on hemodialysis because serum K+ concentrations are regulated by hemodialysis treatments, rather than by renal tubular function. The safety of aldosterone antagonist use in patients with HF and ESRD requiring hemodialysis is not clear, as these types of patients were excluded from major clinical trials. Therefore, we conducted a search of the literature for any studies investigating the rate of hyperkalemia with aldosterone antagonist therapy in patients with ESRD on hemodialysis.

Methods

The MEDLINE (1966–January 2010), PubMed (1949–January 2010), Embase (1980–January 2010), CINAHL (1980–January 2010), and Cochrane (up to January 2010) databases were searched for English-language, human-subject clinical trials that evaluated the safety of aldosterone antagonist use in ESRD patients on hemodialysis. The search terms used were "spironolactone," "eplerenone," "aldosterone antagonist," "kidney failure," "kidney disease," "hemodialysis," "dialysis," and "renal replacement therapy." The primary outcome identified from the studies was incidence of hyperkalemia. Studies were included for review if there was a control and treatment arm, the incidence of hyperkalemia was reported, and subjects were on chronic hemodialysis. Case reports, case series, single-group cohort studies, commentaries, review articles, abstracts, and patients on peritoneal and continuous dialysis were excluded from this review.

Results

Eight studies were retrieved.[26–33] Two were excluded, as they studied patients on peritoneal dialysis.[26,27] Six studies that examined the safety of spironolactone in patients on hemodialysis are reviewed (Table 1).[8–33]

Hussain et al performed a single-center prospective cohort study in 15 adult patients receiving intermittent hemodialysis.[28] The inclusion criteria were expected survival of >6 months, adequate dialysis clearances (monthly urea reduction ratios >65%), and average K+ concentration <5.5 mEq/L (without exceeding 6 mEq/L during the preceding 4 months). The exclusion criteria were serum K+ >5.5 mEq/L over the previous 4 months or any single serum K+ concentration >6.0 mEq/L, urea reduction ratios <65%, or a history of noncompliance with medications or hemodialysis treatments. Patients who were enrolled received 25 mg of spironolactone daily for 28 days. Serum K+ was measured before each hemodialysis session, and all other background medications were continued without any changes. Six of the 15 patients were on background ACEI or ARB therapy. The primary outcome of this single-cohort study was the incidence of hyperkalemia (defined as serum K+ >6.0 mEq/L) during the study period. Thirteen patients completed the study successfully without any serum K+ value exceeding 6 mEq/L; of these, 4 patients had a serum K+ between 5.5 and 6.0 mEq/L. One patient was withdrawn from the study at day 20 after developing significant hyperkalemia (7.6 mEq/L), and another patient was withdrawn at day 25 after missing a hemodialysis session. Two patients needed their hemodialysis solution content adjusted to account for a rise in serum K+. There was no statistical difference between mean K+ concentrations at baseline compared with concentrations at completion of the study (4.6 mEq/L at baseline vs 4.9 mEq/L at study completion; $P = 0.14$).

Saudan et al conducted a prospective study in 35 chronic hemodialysis patients.[29] If patients consented to the study, they were assigned to the spironolactone treatment arm. Those who declined participation in the study served as the control group. All patients were receiving hemodialysis 3 times a week. Twenty-one patients served as controls, and 14 patients who consented to the study were given spironolactone 12.5 mg 3 times a week for 2 weeks, followed by 25 mg 3 times a week for another 2 weeks, and then a 2-week washout phase. Serum K+ was drawn before each hemodialysis treatment in both study groups. Eight of the 14 patients in the spironolactone group and 11 of the 21 patients in the control group were on background ACEI or ARB therapy. Mean baseline serum K+ in the spironolactone group was similar to the control group (5.0 ± 0.4 mEq/L vs 4.8 ± 0.8 mEq/L, respectively). The mean serum K+ in the spironolactone group did not differ from the control group throughout the study period (4.9 mEq/L in the control group vs 4.9 mEq/L in spironolactone group; *P* value not reported).

Michea et al studied the effects of spironolactone in 9 hemodialysis patients in a prospective, single-center cohort study.[30] Patients who were receiving hemodialysis 3 times a week during the past 18 months were enrolled and served as their own control. Patients were excluded if they were taking an ACEI, ARB, or any K+ ion binding resins; experiencing symptomatic HF; had uncontrolled hypertension or chronic liver disease; or had a serum K+ >6 mEq/L. Patients received spironolactone 50 mg 3 times weekly for 2 weeks, followed by a 2-week washout period, and then received placebo 3 times weekly for another 2 weeks. Serum K+ concentrations were drawn before each

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Table 1. Studies of Hyperkalemia Rates With Spironolactone Use in ESRD Patients on Hemodialysis

Study	Design	Groups	Results
Hussain et al[28]	Prospective single-cohort study of patients on IHD (n = 15); duration 28 d; patient characteristics: ACEI/ARB therapy, 40%; HF, NR	Spironolactone 25 mg daily	Mean K+ concentration (mEq/L): baseline, 4.6 ± 0.6; study completion, 4.9 ± 0.9; $P = 0.14$
Saudan et al[29]	Prospective, nonrandomized, nonblinded study of patients on IHD (n = 35); duration 4 wk; patient characteristics: ACEI/ARB therapy, 54%; HF, NR	Control vs spironolactone, 12.5 mg 3×/wk for 2 wk, then 25 mg 3×/wk for 2 wk	Mean K+ concentration (mEq/L) during study period: control, 4.9 ± 0.7; spironolactone, 4.9 ± 0.3; P = NR
Michea et al[30]	Prospective single-cohort study of patients on IHD (n = 9); duration 4 wk; patient characteristics: ACEI therapy, 0%; HF, NR	Spironolactone, 50 mg 3×/wk for 2 wk followed by placebo for 2 wk	Mean K+ concentration (mEq/L) during study period: spironolactone, 4.56 ± 0.18; placebo, 4.67 ± 0.11; P = NS
Gross et al[31]	Prospective, randomized, double-blind, placebo crossover study of patients on IHD (n = 8); duration 4 wk; patient characteristics: ACEI therapy, 0%; HF, NR	Placebo vs spironolactone, 50 mg 2×/d	Mean K+ concentration (mEq/L) during study period: placebo, 4.7 ± 0.5; spironolactone, 5.0 ± 0.8; $P > 0.05$
Taheri et al[32]	Randomized, double-blind, placebo-controlled trial of HF patients on IHD (n = 16); duration 6 mo; patient characteristics: ACEI/ARB therapy, 100%; HF, 100%	Placebo vs spironolactone, 25 mg 3×/wk	Mean K+ concentration (mEq/L) at baseline: spironolactone, 3.86; placebo, 4.66; $P = 0.001$. Mean K+ concentration (mEq/L) at end of study period: spironolactone, 4.88; placebo, 4.74; P = NR
Matsumoto et al[33]	Prospective single-cohort study of patients on IHD (n = 61); duration 8 mo; patient characteristics: ACEI/ARB therapy, 58%; HF, NR	Baseline × 2 mo, followed by 6 mo of spironolactone 25 mg/d	Mean K+ concentration (mEq/L): at baseline, 4.96; spironolactone period, 5.18; $P < 0.05$

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ESRD, end-stage renal disease; HF, heart failure; IHD, intermittent hemodialysis; K+, serum potassium; NR, not reported; NS, not significant.

hemodialysis session during each of the 2 study periods. The mean serum K+ concentrations during the spironolactone and placebo treatment period were similar (4.67 mEq/L in placebo group vs 4.56 mEq/L in spironolactone group; P not significant).

A recent randomized, double-blind, placebo-controlled crossover study in 8 hemodialysis patients was published.[31] Patients enrolled into the study were receiving hemodialysis 3 times a week, had an entry serum K+ <6 mEq/L, and were not receiving any background ACEI or ARB. Patients were excluded if they were experiencing hypotension or severe hypertension, or if they were noncompliant. Patients were randomized to either spironolactone 50 mg or placebo orally twice daily for 2 weeks, followed by a 3-week washout period, after which patients crossed over in their study arms for an additional 2 weeks. Patients served as their own controls, and no change to dialysate solutions was permitted during the entire study. The mean prehemodialysis K+ concentration was not statistically different between the spironolactone and placebo study periods. No patient experienced serious hyperkalemia during the study.

Taheri et al conducted a randomized, double-blind, placebo-controlled trial with spironolactone use specifically in HF patients on hemodialysis.[32] Sixteen patients with HF (ejection fraction <45%) and on chronic hemodialysis were randomized to placebo or spironolactone 25 mg 3 times a week for 6 months. Patients who entered the trial were required to already be on ACEI or ARB treatment and have a serum K+ <5.5 mEq/L. The mean ejection fraction increased significantly more in the spironolactone group by the end of the study compared with the placebo group (6.2% ± 1.64% vs 0.83% ± 4.9%, respectively; $P = 0.046$). The serum K+ concentration of the placebo group was higher than the spironolactone group at the start of the study (4.66 mEq/L vs 3.86 mEq/L, respectively; $P = 0.001$). However, at the end of the study there was no difference in the serum K+ concentration between the placebo and spironolactone group (4.74 mEq/L vs 4.88 mEq/L; P not reported). The incidence of hyperkalemia was not significantly increased in either group.

Matsumoto et al examined the safety of spironolactone use in a cohort study with 61 oligoanuric patients on hemodialysis.[33] These patients were prospectively

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followed during a 2-month baseline period, followed by a 6-month treatment period. Spironolactone 25 mg daily was administered to the patients during the 6-month treatment period. The 50 patients who completed the study did not show a K+ concentration of >6.8 mEq/L or require additional ion exchange resin therapy during the treatment period. Eleven patients discontinued treatment due to reasons unrelated to hyperkalemia. The mean serum K+ concentration at the end of the treatment period was statistically higher than compared with baseline, but was only marginally significant (4.96 ± 0.72 vs 5.18 ± 0.72 mEq/L, respectively; $P < 0.05$).

Discussion

Patients with ESRD requiring hemodialysis are at increased cardiovascular risk for several reasons. ESRD patients have a high incidence of cardiovascular comorbidities, such as diabetes, HF, and hypertension. This alone accounts for a significantly higher mortality and morbidity in the ESRD patient population.[34] As well, dialytic treatment and the complications of hemodialysis are additional factors that accelerate cardiovascular morbidity.[11] Studies have shown that elevated levels of aldosterone are related to renal deterioration. Aldosterone causes renal vasculature fibrosis and progression of renal disease.[11] Thus, advanced cardiac disease due to elevated aldosterone levels and RAAS activity is more prominent in ESRD patients on dialysis. Blockade of aldosterone may attenuate renal damage and progression of cardiovascular disease.

The safety of aldosterone antagonists in patients with ESRD on hemodialysis is still unclear. Although the studies reviewed suggest that patients with ESRD on hemodialysis treated with spironolactone do not experience greater rates of clinically significant hyperkalemia, several factors must be considered.

It has been suggested in the literature that patients with ESRD on hemodialysis are able to tolerate higher levels of hyperkalemia without clinical manifestations compared with the general population.[24,35,36] This tolerance to hyperkalemia is thought to be due to an adaptive response to gradual increases in serum K+. Acute changes in serum K+ can lead to cardiac instability, but gradual increases in serum K+ are reported to be better tolerated. As well, patients on hemodialysis have other metabolic derangements, such as hypercalcemia, which can help stabilize cardiac excitability in the setting of hyperkalemia. It has been reported that hemodialysis patients with hyperkalemia (>5.5 mEq/L) may not manifest electrocardiographic changes due to the adaptive changes mentioned above.[37] However, serum K+ >5.5 mEq/L in hemodialysis patients is associated with increasing mortality.[35] African American patients may better tolerate hyperkalemia due to lower dietary K+ intake, racial differences in urinary K+ excretion and lower renin activity, and because they are more prone to unprovoked hypokalemia.[38] Thus, this adaptive tolerance for hyperkalemia could explain why studies have shown that spironolactone use in patients on hemodialysis did not result in increased rates of clinically significant hyperkalemia.

The methodology of the reviewed studies warrants further discussion. All the studies performed enrolled a limited number of patients, and many studies did not have a prospective, parallel control arm as a comparator. The studies by Michea, Gross and Matsumoto specifically studied anuric or oligoanuric ESRD patients on hemodialysis, whereas details regarding residual renal function were not reported in the other studies.[30,31,33] As well, dietary K+ intake, dialysate solution content, and spironolactone dose differed between studies. All these uncontrolled factors have not been adequately assessed in the available small studies.

All the studies enrolled chronic, compliant ESRD patients on hemodialysis and specifically recruited patients whose serum K+ was historically stable. As well, given the nature of being enrolled into a study, close electrolyte monitoring and hemodialysis adjustments may be a factor in the low rates of hyperkalemia seen in the spironolactone group. The use of an ACEI or ARB was not prevalent in the majority of the studies reviewed (approximately 50% of the patients were on background ACEI or ARB therapy), and other studies excluded patients on ACEI or ARB therapy altogether. The low usage of ACEI or ARB therapy may have been a contributing factor to the low incidence of significant hyperkalemia in the studies. The studies required patients to be compliant with hemodialysis treatments and laboratory monitoring, thus selected a highly compliant patient population. As well, the duration of spironolactone treatment in the studies was relatively short, in some cases lasting only 4 weeks.

The incidence of HF or even cardiovascular disease was not reported in detail in most of the reviewed studies. Most of the studies only investigated the rate of hyperkalemia with spironolactone use in a generalized group of hemodialysis patients. Only 1 study specifically studied spironolactone use in hemodialysis patients with HF.[32] Further studies are required to confirm these benefits and safety.

Conclusion

Spironolactone has been suggested to be safe in ESRD patients on hemodialysis for short-term therapy and if close monitoring of electrolytes is performed. Extrapolation of these preliminary results to a general population of hemodialysis patients with HF is premature and should not be considered routinely at present.

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References

1. Levin A. Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. *Semin Dial.* 2003;16:101–105.
2. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Part 7—Stratification of risk for progression of kidney disease and development of cardiovascular disease. *Am J Kidney Dis.* 2002;39:S170–S212.
3. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Part 4—Definition and classification of stages of chronic kidney disease. *Am J Kidney Dis.* 2002;39:S46–S75.
4. Schmieder RE, Hilgers KF, Schlaich MP, et al. Renin-angiotensin and cardiovascular risk. *Lancet.* 2007;369:1208–1219.
5. McMurray JJ, Pfeffer MA. Heart failure. *Lancet.* 2005;365: 1877–1889.
6. Yan AT, Yan RT, Liu PP. Narrative review: pharmacotherapy for chronic heart failure: evidence from recent clinical trials. *Ann Intern Med.* 2005;142:132–145.
7. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet.* 2003;362:772–776.
8. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet.* 2003;362: 767–771.
9. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med.* 2001;345:1667–1675.
10. Epstein M. Aldosterone as a determinant of cardiovascular and renal dysfunction. *J R Soc Med.* 2001;94:378–383.
11. Brewster, EC, 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. Plow EF, D'Souza SE. A role for intercellular adhesion molecule-1 in restenosis. *Circulation.* 1997;95:1355–1356.
13. Brilla CG, Matsubara LS, Weber KT. Anti-aldosterone treatment and the prevention of myocardial fibrosis in primary and secondary hyperaldosteronism. *J Mol Cell Cardiol.* 1993;25:563–575.
14. Rocha R, Funder JW. The pathophysiology of aldosterone in the cardiovascular system. *Ann N Y Acad Sci.* 2002;970:89–100.
15. Wang W. Chronic administration of aldosterone depresses baroreceptor reflex function in the dog. *Hypertension.* 1994;24:571–575.
16. Pitt B, Zannad F, Remme WJ, et al; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med.* 1999;341:709–717.
17. Pitt B, Remme W, Zannad F, et al; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction [published correction appears in *N Engl J Med*. 2003;348:2271]. *N Engl J Med.* 2003;348:1309–1321.
18. 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–e479.
19. Arnold JM, Liu P, Demers C, et al. Canadian Cardiovascular Society Consensus conference recommendations on heart failure 2006: diagnosis and management. *Can J Cardiol.* 2006;22: 23–25.
20. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. *N Engl J Med.* 2004;351:543–551.
21. Ritz E, Ditkow R, Adamzcak M, et al. Congestive heart failure due to systolic dysfunction: the Cinderella of cardiovascular management in dialysis patients. *Semin Dial.* 2002;3:135–140.
22. Silverberg D, Wexler D, Blum B, et al. The association between congestive heart failure and chronic renal disease. *Curr Opin Nephrol Hypertens.* 2004;2:163–170.
23. Epstein M. Aldosterone receptor blockade and the role of eplerenone: evolving perspectives. *Nephrol Dial Transplant.* 2003;18:1984–1992.
24. Ahmed J, Weisberg LS. Hyperkalemia in dialysis patients. *Semin Dial.* 2001;14:348–356.
25. Ramadan FH, Masoodi N, El-Solh AA. Clinical factors associated with hyperkalemia in patients with congestive heart failure. *J Clin Pharm Ther.* 2005;30:233–239.
26. Hausmann MJ, Liel-Cohen N. Aldactone therapy in a peritoneal dialysis patient with decreased left ventricular function. *Nephrol Dial Transplant.* 2002;17:2035–2036.
27. Azar R, Hogede L, Carru V. Aldactone therapy in a peritoneal dialysis patient. *Nephrol Dial Transplant.* 2003;18:1232–1233.
28. Hussain S, Dreyfus DE, Marcus RJ, et al. Is spironolactone safe for dialysis patients? *Nephrol Dial Transplant.* 2003;18: 2364–2368.
29. Saudan P, Mach F, Perneger T, et al. Safety of low-dose spironolactone administration in chronic haemodialysis patients. *Nephrol Dial Transplant*. 2003;18:2359–2363.
30. Michea L, Vukusich A, Gonzalez M, et al. Effect of spironolactone on K(+) homeostasis and ENaC expression in lymphocytes from chronic hemodialysis patients. *Kidney Int.* 2004;66: 1647–1653.
31. Gross E, Rothstein M, Dombek S, et al. Effect of spironolactone on blood pressure and the renin-angiotensin-aldosterone system in oligo-anuric hemodialysis patients. *Am J Kidney Dis.* 2005;46:94–101.
32. Taheri S, Mortazavi M, Shahidi S, et al. Spironolactone in chronic hemodialysis patients improves cardiac function. *Saudi J Kidney Dis Transpl.* 2009;20:392–397.
33. Matsumoto Y, Kageyama S, Yakushigawa T, et al. Long-term low-dose spironolactone therapy is safe in oligoanuric hemodialysis patients. *Cardiology.* 2009;114:32–38.
34. Locatelli F, Carcelli D, Conte F, et al. Cardiovascular disease in chronic renal failure: the challenge continues. *Nephrol Dial Transplant.* 2000;15(suppl 5): S69–S80.
35. Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med.* 2009;169:1156–1162.
36. Salem MM, Rosa RM, Batlle DC. Extrarenal potassium tolerance in chronic renal failure: important implications for the treatment of acute hyperkalemia. *Am J Kidney Dis.* 1991;18:421–440.
37. Aslam S, Friedman EA, Ifudu O. Electrocardiography is unreliable in detecting potentially lethal hyperkalemia in haemodialysis patients. *Nephrol Dial Transplant.* 2002;17:1639–1642.
38. Andrew ME, Jones DW, Wofford MR, et al. Ethnicity and unprovoked hypokalemia in the atherosclerosis risk in communities study. *Am J Hypertens.* 2002;15:594–599.

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