Serum Potassium in Dual Renin-Angiotensin-Aldosterone System Blockade

Stephen L. Seliger and Linda F. Fried†*

Clin J Am Soc Nephrol 9: 219–221, 2014. doi: 10.2215/CJN.12411213

Treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) slows the progression of proteinuric diabetic kidney disease (1–3). However, the risk of progression remains high despite these medications. In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan trial and the Irbesartan Diabetic Nephropathy Trial, the treatment-induced decrease in albuminuria correlated with overall benefit in terms of risk of CKD progression, and individuals with residual albuminuria despite ARB treatment were at higher risk for progression (1,3). These observations led to the hypothesis that greater reductions in albuminuria with more intensive renin-angiotensin-aldosterone system (RAAS) blockade would further slow progression of diabetic kidney disease (4). There are a number of approaches to intensifying RAAS blockade, including increasing the dose of monotherapy (*i.e.*, supramaximal doses), combining an ACEI with an ARB, adding aliskiren to an ACEI or an ARB, or adding a mineralocorticoid receptor blocker (MRB) to an ACEI or ARB. Each of these treatments reduces albuminuria (5–8), although there are few studies that directly compare the interventions with regard to efficacy or safety.

One of the main safety concerns with more intensive RAAS blockade is hyperkalemia. Serum potassium levels are maintained through a combination of internal balance (shifts between extracellular and intracellular spaces) and external balance (intake versus excretion). The major determinants of potassium excretion in the normal kidney are distal delivery of sodium, urinary flow rate, and aldosterone activity (9–11). With loss of functioning nephron mass and declining glomerular filtration, remaining functioning nephrons adapt with an increase in fractional excretion of potassium. This helps maintain normal potassium levels until advanced CKD occurs (10). ACEIs, ARBs, or renin inhibitors increase the risk of hyperkalemia by inhibiting aldosterone as well as by decreasing GFR, which can decrease distal delivery of sodium.

Prior studies show that risk factors for hyperkalemia with the use of RAAS blockers are older age, lower eGFR, higher baseline potassium levels, and use of more than one medication that interferes with potassium excretion (12,13). In a recent review of studies of RAAS blockade, Weir and Rolfe found that the incidence of hyperkalemia was <2% in individuals without risk factors for hyperkalemia who received RAAS blockers for hypertension (14). By contrast, the risk of hyperkalemia in patients with CKD or heart failure was 5%–10% in prior studies.

Individuals with diabetic nephropathy are more prone to hyperkalemia at higher levels of GFR due to a greater prevalence of hyporeninemic hypoaldosteronism that impairs renal potassium excretion (15). RAAS blockade further exacerbates this risk and the risk is higher with more intensive blockade. In this issue of *CJASN*, van Buren *et al.* evaluate whether renal potassium excretion (external balance) explains the higher rate of hyperkalemia with combination RAAS blockade in a secondary analysis of a randomized trial (16). The study, the primary results of which were previously reported (17), was a three-arm, randomized, double-blind study comparing placebo, losartan (100 mg), or spironolactone (25 mg) added to maximal lisinopril (80 mg) in individuals with diabetes and residual overt albuminuria despite maximal-dose lisinopril. Median creatinine clearance on 24-hour urine samples was 64.5 ml/min and median 24-hour urine albumin was approximately 1 g.

Compared with placebo, losartan decreased albuminuria by a further 16.8% and spironolactone by 34% at the end of 48 weeks, consistent with prior studies. However, the addition of spironolactone to ACEI therapy also led to significantly greater hyperkalemia. Mean follow-up potassium concentrations were 4.5, 4.7, and 5.0 mEq/L in the placebo, losartan, and spironolactone groups, respectively. In addition to the greater mean potassium with dual-RAAS antagonism, the frequency of clinically significant hyperkalemic events (potassium>6.0 mEq/L) was markedly more common, occurring in 7.4%, 38.5%, and 51.9% in the three groups, respectively. This high rate of hyperkalemia was especially remarkable given the relatively preserved renal filtration function of the participants. Two of the 27 participants in the spironolactone group discontinued the study medication due to recurrent hyperkalemia. Surprisingly, there was no significant difference in the 24-hour urine potassium excretion or fractional excretion of potassium, suggesting that the higher hyperkalemia risk cannot be explained by chronic changes in renal potassium excretion.

One potential explanation for the higher risk of clinically significant hyperkalemia is that combination RAAS more severely affects the kidney's ability to

*Veterans Affairs Maryland Healthcare System and University of Maryland School of Medicine, Baltimore, Maryland; and †Veterans Affairs Pittsburgh Healthcare System and University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Correspondence: Dr. Linda F. Fried, Veterans Affairs Pittsburgh Healthcare System, University Drive C, Mailstop 111F-U, Pittsburgh, PA 15240. Email: Linda.Fried@va.gov

respond to acute increases in potassium intake or to stresses that acutely decrease GFR or distal nephron sodium delivery. This decreased renal "kaliuresis reserve" may not be accurately approximated by 24-hour urine potassium at steady state. Potentially, the effect on this proposed reserve may depend on the degree of RAAS blockade. If the main issue is renal reserve, it may be more difficult to predict which patients with CKD are at higher hyperkalemia risk and would require regular ongoing monitoring of serum potassium levels. More importantly, it implies that we need to develop different approaches to preventing hyperkalemia directed at avoidance of prerenal azotemia and other factors that affect renal perfusion and distal nephron sodium delivery.

A larger question is whether determining the precise mechanisms of increased hyperkalemia with combination RAAS blockade is clinically relevant. Results of recently completed large multicenter clinical trials consistently demonstrated an unfavorable risk/benefit profile of this therapeutic approach for preventing progressive renal disease. In the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial, there was no benefit on renal or cardiovascular outcomes with combination therapy, and there was an increased risk of hyperkalemia and AKI (18,19). However, the study included participants at relatively low risk of ESRD, and the absolute rate of hyperkalemia was modest. In the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints (8) and the Veterans Affairs Nephropathy in Diabetes study (20), the rate of hyperkalemia (potassium≥6.0 mEq/L) was more than two times higher in the combination RAAS blockade group compared with monotherapy. Importantly, both studies were stopped prematurely for safety concerns. The excess risk of adverse events—and lack of benefit on renal progression—occurred despite decreases in albuminuria.

The risk/benefit ratio for preventing progression of proteinuric kidney disease is not clearly answered for MRBs added to maximal ACEI or ARB therapy. Given the different sites of action within the RAAS, one cannot necessarily conclude that such combination therapy would have the same adverse risk/benefit profile as combination ACEI plus ARB therapy. For example, in congestive heart failure, the addition of an MRB to ACEI or ARB treatment reduced all-cause mortality (21), whereas combination ACEI and ARB decreased risk of heart failure admissions without amortality benefit (22). However, caution is needed in the use of such a therapeutic approach in patients with CKD, especially those with impaired GFR, until we have data from long-term randomized trials examining the benefits and risks of MRB added to ACEI or ARB treatment. The risks of widespread MRB therapy were demonstrated after the publication and dissemination of the results of the Randomized Aldactone Evaluation Study (21); compared with the period before release of the study results, the rate of hospital admission for hyperkalemia rose 4-fold, with an associated increase in mortality (23).

The results of the analysis by van Buren *et al*. highlight the importance of careful monitoring of potassium in any CKD patient in whom a mineralocorticoid receptor blocker is to be used in combination with an ACEI or ARB, especially if the patient also has diabetes. van Buren *et al*. also highlight the importance of careful monitoring and treatment of hyperkalemia in clinical trials of combination MRB plus ACEI/ARB therapy in CKD. Until results of such trials show a favorable effect on CKD progression with an acceptable risk profile, prudence may suggest that this combination be avoided in the absence of documented primary hyperaldosteronism.

Disclosures

Merck donated the study medication to the US Department of Veterans Affairs for the Veterans Affairs Nephropathy in Diabetes study.

References

1. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345: 861–869, 2001
2. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; The Collaborative Study Group: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 329: 1456–1462, 1993
3. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde R, Raz I; Collaborative Study Group: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345: 851–860, 2001
4. de Zeeuw D: Albuminuria, not only a cardiovascular/renal risk marker, but also a target for treatment? *Kidney Int Suppl* 66: S2–S6, 2004
5. Tobe SW, Dai MO: Outcomes of antiproteinuric RAAS blockade: High-dose compared with dual therapy. *Curr Hypertens Rep* 11: 345–353, 2009
6. Ponda MP, Hostetter TH: Aldosterone antagonism in chronic kidney disease. *Clin J Am Soc Nephrol* 1: 668–677, 2006
7. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK; AVOID Study Investigators: Aliskiren combined with losartan in type 2 diabetes and nephropathy. *N Engl J Med* 358: 2433–2446, 2008
8. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, Chaturvedi N, Persson F, Desai AS, Nicolaides M, Richard A, Xiang Z, Brunel P, Pfeffer MA; ALTITUDE Investigators: Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 367: 2204–2213, 2012
9. Schrier RW: *Renal and Electrolyte Disorders*, 4th Ed., Boston, Little, Brown and Company, 1992
10. Palmer BF: A physiologic-based approach to the evaluation of a patient with hyperkalemia. *Am J Kidney Dis* 56: 387–393, 2010
11. Palmer BF: Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. *N Engl J Med* 351: 585–592, 2004
12. Khosla N, Kalaitzidis R, Bakris GL: Predictors of hyperkalemia risk following hypertension control with aldosterone blockade. *Am J Nephrol* 30: 418–424, 2009
13. Amir O, Hassan Y, Sarriff A, Awaisu A, Abd Aziz N, Ismail O: Incidence of risk factors for developing hyperkalemia when using ACE inhibitors in cardiovascular diseases. *Pharm World Sci* 31: 387–393, 2009
14. Weir MR, Rolfe M: Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. *Clin J Am Soc Nephrol* 5: 531–548, 2010
15. DeFronzo RA: Hyperkalemia and hyporeninemic hypoaldosteronism. *Kidney Int* 17: 118–134, 1980
16. van Buren PN, Adams-Huet B, Nguyen M, Molina C, Toto RD: Potassium handling with dual renin-angiotensin system inhibition in diabetic nephropathy. *Clin J Am Soc Nephrol* 9: 295–301, 2014
17. Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD: Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol* 20: 2641–2650, 2009
18. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C; ONTARGET Investigators:

Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 358: 1547–1559, 2008
19. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, Wang X, Maggioni A, Budaj A, Chaithiraphan S, Dickstein K, Keltai M, Metsärinne K, Oto A, Parkhomenko A, Piegas LS, Svendsen TL, Teo KK, Yusuf S; ONTARGET investigators: Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): A multicentre, randomised, double-blind, controlled trial. *Lancet* 372: 547–553, 2008
20. Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, Leehey DJ, McCullough PA, O'Connor T, Palevsky PM, Reilly RF, Seliger SL, Warren SR, Watnick S, Peduzzi P, Guarino P; VA NEPHRON-D Investigators: Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med* 369: 1892–1903, 2013
21. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J; Randomized Aldactone Evaluation Study Investigators: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 341: 709–717, 1999
22. Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators: A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 345: 1667–1675, 2001
23. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA: Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 351: 543–551, 2004

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "Potassium Handling with Dual Renin-Angiotensin System Inhibition in Diabetic Nephropathy," on pages 295–301.