Potassium Homeostasis and Renin-Angiotensin-Aldosterone System Inhibitors

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Inhibition of the renin-angiotensin-aldosterone system (RAAS) is a key strategy in treating hypertension and cardiovascular and renal diseases. However, RAAS inhibitors (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, and direct renin inhibitors) increase the risk of hyperkalemia (serum potassium >5.5 mmol/L). This review evaluates the effects on serum potassium levels of RAAS inhibitors. Using PubMed, we searched for clinical trials published up to December 2008 assessing the effects on serum potassium levels of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, and direct renin inhibitors, alone and in combination, in patients with hypertension, heart failure (HF), or chronic kidney disease (CKD); 39 studies were identified. In patients with hypertension without risk factors for hyperkalemia, the incidence of hyperkalemia with RAAS inhibitor monotherapy is low (≤2%), whereas rates are higher with dual RAAS inhibition (≈5%). The incidence of hyperkalemia is also increased in patients with HF or CKD (5% to 10%). However, increases in serum potassium levels are small (≈0.1 to 0.3 mmol/L), and rates of study discontinuation due to hyperkalemia are low, even in high-risk patient groups (1% to 5%). Patients with HF or CKD are at greater risk of hyperkalemia with RAAS inhibitors than those without these conditions. However, the absolute changes in serum potassium are generally small and unlikely to be clinically significant. Moreover, these patients are likely to derive benefit from RAAS inhibition. Rather than denying them an effective treatment, electrolyte levels should be closely monitored in these patients.

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The renin-angiotensin-aldosterone system (RAAS) plays key roles in the regulation of blood volume, BP, and cardiovascular function. Therapeutic manipulation of the RAAS is an important treatment strategy for hypertension, chronic kidney disease (CKD), heart failure (HF), and diabetes. It is generally accepted, however, that RAAS inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone receptor antagonists (ARAs), and direct renin inhibitors (DRIs), are associated with an increased risk of hyperkalemia, particularly when administered in combination (1,2). ACEIs, ARBs, and DRIs increase serum potassium levels by interfering with angiotensin II-mediated stimulation of aldosterone secretion from the adrenal gland and by decreasing renal blood flow and GFR in special patient populations. ARAs increase the risk of hyperkalemia by blocking interaction of aldosterone with its receptor, reducing renal potassium excretion.

ACEIs, ARBs, ARAs, and DRIs may have different effects on potassium levels, reflecting the differences in their actions on potassium homeostasis. This raises the question of what effect different combinations of these agents might have on serum potassium levels—a subject of topical interest given that the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) raised concerns over renal safety and the risk of hyperkalemia with combination therapy using two RAAS inhibitors (*i.e.*, dual RAAS inhibition) (3). Patients with diabetes, HF, or CKD are at an increased risk of hyperkalemia compared with those without these conditions (4). Furthermore, a number of medications are known to cause hyperkalemia, including nonsteroidal anti-inflammatory drugs (NSAIDs) (5), β-blockers (2), heparin (6), and calcineurin inhibitors (7).

In addition to increased serum potassium levels, signs of hyperkalemia include characteristic electrocardiographic changes, which can vary depending on how severe and acute the potassium changes are. Serum potassium ≥6.0 mmol/L is generally considered to be clinically significant and is estimated to complicate 1.4% of hospital admissions (8). However, both the magnitude and rapidity of serum potassium increases are important factors in determining their clinical significance.

This review aims to provide a critical overview of the incidence of hyperkalemia during treatment with ACEIs, ARBs, ARAs, and DRIs alone and in combination. Data for patients with CKD or HF will also be evaluated, because these groups are at particular risk of hyperkalemia but may derive the most benefit from RAAS inhibition.

Materials and Methods

Data Sources and Searches

We conducted a comprehensive search of the PubMed database for clinical trials that reported the effects on serum potassium levels of

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treatment with ACEIs, ARBs, ARAs, and DRIs, alone or in combination with each other, in patients with hypertension, HF, or CKD.

The PubMed database was searched using terms to identify drug treatments as follows: ([angiotensin-converting enzyme inhibitor] OR [ACE inhibitor] OR ACEI), ([angiotensin II receptor antagonist] OR [angiotensin receptor antagonist] OR [angiotensin II receptor blocker] OR [angiotensin receptor blocker] OR ARB), ([aldosterone receptor antagonist] OR [aldosterone blocker] OR [aldosterone antagonist] OR [aldosterone receptor blocker] OR ARA OR eplerenone OR spironolactone), OR ([renin inhibitor] OR [direct renin inhibitor] OR DRI).

Clinical trials with an active treatment period of ≥4 weeks were included. The search was limited to English-language articles published up to December 2008. References identified by this initial search were transferred to a central database for further analysis.

Subsearches of the identified articles were performed to identify major surrogate marker and outcomes studies using the following terms to identify disease status: (hypertension OR [blood pressure]), (nephropathy OR albuminuria OR proteinuria OR [renal impairment]), OR ([heart failure]). The phrase (patient OR subject) was also included in the search terms.

Recent large-scale reviews, meta-analyses, and pooled analyses of clinical trials were also included. Clinical trials assessed in the systematic reviews identified by this analysis (9,10) were not evaluated individually.

Data Extraction

Identified articles were searched by hand to select papers reporting data for mean or median serum potassium concentrations, rates of occurrence of serum potassium >5.5 or ≥6.0 mmol/L, incidences of hyperkalemia as an adverse event, or study discontinuations due to hyperkalemia. Papers presenting the incidence of hyperkalemia without providing a definition (*e.g.*, serum potassium threshold) were excluded.

Results

Hyperkalemia Risk with RAAS Inhibitor Monotherapy

Hypertension. Studies of RAAS inhibitor monotherapy in patients with uncomplicated hypertension suggest that the risk of hyperkalemia is low in these patients (≤2%; Table 1). Moreover, absolute increases in serum potassium levels are typically small (≈0.1 mmol/L) and are unlikely to be of clinical significance.

In a study by Fogari *et al.* (11) of the effects of ACEI monotherapy in 118 patients with mild-to-moderate hypertension, treatment with the ACEI lisinopril 20 mg/d was associated with a small but statistically significant increase in serum potassium of 0.2 mmol/L from baseline. Similarly, in a case-controlled study in 1818 outpatients receiving ACEI monotherapy, the incidence of serum potassium >5.5 mmol/L was 2%; the incidence of serum potassium ≥6.0 mol/L was also low (Table 1) (12). The study authors concluded that, "In the absence of renal insufficiency, azotemia or congestive heart failure, hyperkalemia is unusual."

The risk of hyperkalemia with ARB monotherapy was assessed by Goldberg *et al.* (13) in a pooled analysis of 16 randomized, double-blind, clinical trials in 2085 patients with hypertension; rates of serum potassium >5.5 mmol/L were 1.5% in those receiving the ARB losartan and 1.3% in patients treated with an ACEI. In a separate pooled analysis of seven randomized, double-blind trials in 3095 patients with mild-to-moderate hypertension, rates of hyperkalemia with the ARB olmesartan (2.5 to 80 mg/d) were similar to those with placebo (Table 1) (14). Finally, in a randomized, double-blind, multifactorial study in 818 patients with hypertension, monotherapy with the ARB telmisartan (20 to 160 mg/d) was associated with small increases in serum potassium of up to 0.131 mmol/L from baseline (Table 1) (15).

ARA monotherapy has also been associated with small increases in serum potassium in patients with hypertension. In a study by Levy *et al.* (16), serum potassium levels increased by ≤0.2 mmol/L from baseline after treatment with the ARA eplerenone at doses of up to 200 mg/d (Table 1). In a separate study by White *et al.* (17), a small but statistically significant increase in serum potassium of 0.2 mmol/L was reported with eplerenone 200 mg/d, although only one patient had serum potassium >5.5 mmol/L.

The effects of DRI monotherapy in patients with hypertension were assessed in a pooled analysis of seven randomized, double-blind studies in a total of 7045 patients treated with the DRI aliskiren. The incidence of serum potassium >5.5 mmol/L with aliskiren 150 mg/d (0.7%) and 300 mg/d (1.0%) was similar to that with placebo (0.6%) (18). In a study by Oparil *et al.* (19) in patients with hypertension, rates of hyperkalemia with aliskiren or the ARB valsartan were low and similar to those with placebo (Table 1). In a separate study by Uresin *et al.* (20) in patients with hypertension and diabetes, rates of serum potassium >5.5 mmol/L were 2.2% with aliskiren (300 mg/d) and 2.6% with ramipril (10 mg/d). Few patients experienced serum potassium ≥6.0 mmol/L with either monotherapy (Table 1).

Heart Failure. Our evaluation of clinical trials of single-site RAAS inhibition in patients with HF suggests that there is an increased risk of hyperkalemia in these patients compared with those without HF. However, the incidence of clinically significant hyperkalemia (serum potassium ≥6.0 mmol/L) is low (<2%; Table 2), and there is little evidence to suggest that the increases in serum potassium are associated with worse outcomes.

ACEI or ARB monotherapy is associated with small increases in serum potassium levels in patients with HF (Table 2). The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) in patients with severe congestive HF showed that the incidence of serum potassium >5.5 mmol/L was more frequent with the ACEI enalapril (5 to 20 mg twice daily; 7.1%) than with placebo (4.0%) (21). In the Evaluation of Losartan in the Elderly (ELITE) study in patients aged ≥65 years with HF, approximately 20% of patients experienced serum potassium elevations ≥0.5 mmol/L, although discontinuations due to hyperkalemia were low with an ACEI or an ARB alone (Table 2) (22).

In the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Alternative trial in patients with symptomatic HF not receiving an ACEI, discontinuations due to hyperkalemia were higher with candesartan (4 to 32 mg) than with placebo (1.9% *versus* 0.3%; $P = 0.0005$) (23). Rates of serum potassium ≥6.0 mmol/L were also higher

with candesartan than with placebo (Table 2). Moreover, in a *post hoc* analysis of data from the CHARM program, single-site RAAS inhibition with candesartan was associated with a higher incidence of "clinically important" hyperkalemia (fatal hyperkalemia, or hyperkalemia requiring dose reduction, study discontinuation, or hospitalization) than was placebo (4.0% *versus* 1.5%; odds ratio: 2.7; 95% confidence interval (95% CI): 1.5 to 5.0) (24).

The effects of ARA and DRI monotherapy on serum potassium levels in patients with HF have not been reported; data for dual RAAS inhibition with ARAs and DRI-based combinations are discussed later in this review.

Chronic Kidney Disease. The incidence of serum potassium elevations with single RAAS inhibition in patients with CKD has been assessed in a number of clinical trials (Table 3). The data show that although patients with CKD are at an increased risk of serum potassium elevations, the observed absolute increases are typically small (<0.3 mmol/L) and generally are not associated with clinically relevant adverse effects or study discontinuations (1% to 2%).

Monotherapy with an ACEI or an ARB is associated with an increased risk of hyperkalemia in patients with CKD. A long-term study by Hou *et al.* (25) in patients with nondiabetic CKD (proteinuria >300 mg/d) showed that in those with baseline serum creatinine 3.1 to 5.0 mg/dl, serum potassium levels at follow-up were significantly higher for those receiving the ACEI benazepril than for those on placebo ($P = 0.001$). However, the rate of serum potassium ≥6.0 mmol/L with benazepril was similar to that with placebo (5.4% *versus* 4.5%). It should be noted that mean estimated GFR (eGFR) in this group was 25.8 to 26.3 ml/min per 1.73 m^2 (*i.e.*, stage 4 CKD), and these patients were therefore at particularly high risk of hyperkalemia. In the subgroup of the patients with baseline serum creatinine 1.5 to 3.0 mg/dl, rates of serum potassium ≥6.0 mmol/L were low (Table 3).

Monotherapy with lisinopril (10 mg/d) or valsartan (80 mg/d) caused small increases from baseline in serum potassium (≤0.12 mmol/L) in a 10-week, randomized, double-blind, crossover study by Bakris *et al.* (26) in patients with CKD (renal insufficiency with creatinine clearance 30 to 80 ml/min). Larger increases in serum potassium were observed in the subgroup of patients with eGFR ≤60 ml/min per 1.73 m^2 (Table 3). An analysis by Takaichi *et al.* (2) of data from more than 9000 patients with diabetes or CKD (serum creatinine <5 mg/dl) in clinical practice showed significantly higher serum potassium levels in patients receiving ACEI (4.59 mmol/L) or ARB (4.58 mmol/L) treatment than in patients not receiving a RAAS agent (4.45 mmol/L; both $P < 0.001$). In the Irbesartan Diabetic Nephropathy Trial (IDNT) in 1715 patients with diabetes-associated CKD (with proteinuria ≥900 mg/d), rates of discontinuation due to hyperkalemia were significantly higher with the ARB irbesartan (300 mg/d) than with the calcium channel blocker amlodipine (10 mg/d) or placebo (Table 3; $P = 0.01$ for both comparisons) (27).

ARA monotherapy is also associated with serum potassium increases in patients with CKD (Table 3). In a study by Matsumoto *et al.* (28) in patients with diabetes-associated CKD (urinary albumin-creatinine ratio (UACR) > 30 mg/g), the ARA spironolactone (50 mg/d), but not amlodipine (2.5 mg/d), was associated with a small but statistically significant increase in serum potassium of 0.4 mmol/L from baseline; however, no patient exhibited serum potassium >5.5 mmol/L (Table 3).

Hyperkalemia Risk with Dual RAAS Inhibition

Hypertension. The risk of serum potassium elevations with dual RAAS inhibition in patients with hypertension but without risk factors for hyperkalemia has been assessed in a number of clinical trials. The data suggest that the incidence of serum potassium >5.5 mmol/L is greater than that with a single RAAS inhibitor (Table 1). However, there is little evidence that the changes are associated with adverse effects in these patients.

The risk of hyperkalemia with ACEI/ARB combination therapy was evaluated in ONTARGET in more than 25,000 patients with controlled BP but at high cardiovascular risk (29). Dual RAAS inhibition with telmisartan (80 mg/d) and the ACEI ramipril (10 mg/d) was associated with a higher incidence of serum potassium >5.5 mmol/L compared with telmisartan or ramipril monotherapy (5.6% *versus* 3.4% and 3.3%, respectively, $P < 0.001$ *versus* ramipril; Table 1). In the A Multicenter Trial using Atacand and Zestril *versus* Zestril to Evaluate the Effects on Lowering Blood Pressure (AMAZE), the ACEI/ARB combination lisinopril/candesartan (20/32 mg/d) was associated with more discontinuations due to hyperkalemia than was lisinopril (40 mg/d) alone (0.7% *versus* 0%; Table 1). However, the number of patients experiencing "hyperkalemia events" (discontinuation or adverse event of hyperkalemia or serum potassium ≥6.0 mmol/L) was similar for combination therapy and lisinopril monotherapy (30).

Adding an ARA to ACEI or ARB therapy is also associated with elevations in serum potassium compared with a single RAAS inhibitor in patients with hypertension. The study by Krum *et al.* (31) assessing dual RAAS inhibition with eplerenone (50 to 100 mg/d) plus an ACEI or ARB in 341 patients with hypertension showed that the increase in serum potassium with eplerenone/ACEI was not significantly different from that with placebo/ACEI (Table 1). However, eplerenone/ARB combination therapy was associated with a small but statistically significant increase in serum potassium (0.20 mmol/L) compared with placebo/ARB (0.05 mmol/L; $P < 0.05$).

Dual RAAS inhibition with a DRI in combination with an ACEI or ARB was assessed in the short-term studies by Uresin *et al.* (20) and Oparil *et al.* (19), respectively (Table 1). In patients with hypertension and diabetes, the incidence of serum potassium >5.5 mmol/L was higher with aliskiren/ramipril (300/10 mg/d) than with ramipril or aliskiren alone (5.5% *versus* 2.6% and 2.2%, respectively), although rates of serum potassium ≥6.0 mmol/L were similar in the combination therapy and monotherapy groups (Table 1) (20). For DRI/ARB combination therapy, aliskiren/valsartan (300/320 mg/d) was associated with a higher incidence of serum potassium >5.5 mmol/L (4%) than monotherapy with aliskiren or valsartan (both 2%) or

Table 1. Effect of single and dual RAAS inhibition on serum potassium levels in clinical trials in patients with hypertension

Study (Reference Citation)	Type of RAAS Inhibition	Duration, wk[a]	No. of Patients	Treatment Dose, mg/d[a]	Incidence of Potassium >5.5 mmol/L, %	Incidence of Potassium ≥6.0 mmol/L, %	Discontinuation Due to Hyperkalemia, %	Mean Change in Serum Potassium [Baseline], mmol/L	Concomitant Medications, %
Single RAAS inhibition									
Fogari *et al.* (11)	ACEI	8	118	LIS 20	NR	NR	NR	LIS, +0.21 ($P < 0.001$ *versus* baseline) [4.37]	NR
				AML 10				AML, +0.01 [4.39]	
				ATL 100				ATL, −0.02 [4.45]	
				HCT 25				HCT, −0.28 ($P < 0.001$ *versus* baseline) [4.41]	
Reardon *et al.* (12)	ACEI	52	1818	ACEI (89% received LIS)	2.0	0.17	0.8	NR	Loop diuretic, 30[b] Thiazide diuretic, 10 BB, 19 NSAID, 13 Potassium supplement, 13
Goldberg *et al.* (13)	ARB	8 to 12	2085	LOS (Comparators included ACEI)	LOS, 1.5 ACEI, 1.3	NR	LOS, none	NR	NR
Püchler *et al.* (14)	ARB	6 to 52	3095	OLM 2.5, 5, 10, 20, 40, 80	OLM (2.5), 0.4	NR	NR	NR	NR
				PBO	OLM (5), 0.2 OLM (10), 0.2 All other OLM doses, 0 PBO, 0				

McGill *et al.* (15)	ARB	8	818	TEL 20, 40, 80, 160 HCT 6.25, 12, 25 TEL/HCT (all combinations) PBO	NR	NR	NR	TEL (20), +0.005 TEL (40), +0.123 TEL (80), +0.131 TEL (160), +0.057 TEL/HCT, −0.232 to +0.160 HCT, −0.025 to −0.232 PBO, +0.072	NR
Levy *et al.* (16)	ARA	12	397	EPL 50 to 200[c]	NR	NR	NR	EPL (50), +0.04/ +0.09[d] EPL (100), +0.13/ +0.20[d] EPL (200), +0.19/ +0.20[d] [Baseline, 4.27]	NR
White *et al.* (17)	ARA	12	400	EPL 25, 50, 100, 200 PBO	EPL (200), 1.1 Other EPL doses, 0 PBO, 0	All EPL, 0 PBO, 1.1	NR	EPL (200), +0.2 ($P < 0.001$ *versus* PBO) All 4 groups of EPL had <5% increase from baseline	NR
Weir *et al.* (18)	DRI	6 to 8	7045[e]	ALI 75, 150, 300, 600 PBO	ALI (75), 0.7 ALI (150), 0.7 ALI (300), 1.0 ALI (600), 0 PBO, 0.6	NR	NR	NR	NR

Table 1. (Continued)

Study (Reference Citation)	Type of RAAS Inhibition	Duration, wk[a]	No. of Patients	Treatment Dose, mg/d[a]	Incidence of Potassium >5.5 mmol/L, %	Incidence of Potassium ≥6.0 mmol/L, %	Discontinuation Due to Hyperkalemia, %	Mean Change in Serum Potassium [Baseline], mmol/L	Concomitant Medications, %
Single and dual RAAS inhibition									
Oparil *et al.* (19)	DRI/ARB	8[f]	1797	ALI/VAL 150/160 to 300/320	ALI/VAL, 4	ALI/VAL, 0.5	NR	NR	NR
	DRI			ALI 150–300	ALI, 2	ALI, 1			
	ARB			VAL 160–320	VAL, 2	VAL, 1			
				PBO	PBO, 3	PBO, 1			
Uresin *et al.* (20)	DRI/ACEI	8[f]	837	ALI/RAM 150/5 to 300/10	ALI/RAM, 5.5	ALI/RAM, 1.5	NR	NR	NR
	DRI			ALI 150 to 300	ALI, 2.2	ALI, 1.1			
	ACEI			RAM 5 to 10	RAM, 2.6	RAM, 1.1			
ONTARGET (29)	ARB/ACEI	56 mo (median follow-up)	25,620	TEL/RAM 80/10[g]	TEL/RAM, 5.6 ($P < 0.001$ *versus* RAM)	NR	NR	NR	Diuretic, 33 BB, 57 ASA, 76
	ARB		TEL80	TEL, 3.4					
	ACEI		RAM 10[g]	RAM, 3.3					
AMAZE (30)	ARB/ACEI	8[h]	1096	CAN/LIS 16/20 to 32/20	NR	CAN/LIS, 1.6[i]	CAN/LIS, 0.7	NR	NR
	ACEI			LIS 40		LIS, 2.0[i]	LIS, 0		
Krum *et al.* (31)	ARA/ACEI	8	341	EPL 50 to 100	EPL/ACEI, 1.2	NR	None	EPL/ACEI, +0.14 [4.32]	NR
	ACEI			PBO	PBO/ACEI, 0			PBO/ACEI, +0.06 [4.36]	
	ARA/ARB			EPL 50 to 100	EPL/ARB, 0			EPL/ARB, +0.20 ($P < 0.05$ *versus* PBO/ARB) [4.31]	
	ARB			PBO	PBO/ARB, 0			PBO/ARB, +0.05 [4.29]	

ACEI, angiotensin-converting enzyme inhibitor; ALI, aliskiren; AML, amlodipine; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; ATL, atenolol; BB, β-blocker; CAN, candesartan; DRI, direct renin inhibitor; EPL, eplerenone; HCT, hydrochlorothiazide; LIS, lisinopril; LOS, losartan; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; OLM, olmesartan; PBO, placebo; RAAS, renin-angiotensin-aldosterone system; RAM, ramipril; TEL, telmisartan; VAL, valsartan.

[a]Unless otherwise stated.

[b]Concomitant medications for the 194 case study patients with potassium ≥5.1 mmol/L at screening.

[c]Up-titration for BP control at week 4 (50 to 100 mg) and week 8 (100 to 200 mg).

[d]Data shown for responders/nonresponders (DBP <90/≥90 mmHg).

[e]Safety data analyzed for 3097 patients.

[f]4 weeks at the initial dose, then 4 weeks at double the initial dose.

[g]RAM 5 mg for the first 2 weeks.

[h]CAN 16 mg for 2 weeks, then CAN 32 mg for 6 weeks.

[i]Potassium ≥6.0 mmol/L or adverse event of hyperkalemia or discontinuation due to hyperkalemia.

placebo (3%). However, the incidence of serum potassium ≥6.0 mmol/L was similar among the treatment groups (Table 1).

Heart Failure and Myocardial Infarction. Studies of dual RAAS inhibition in patients with HF point toward an increased risk of hyperkalemia in these patients compared with those without HF (Table 2). However, the absolute increases are small (0.1 to 0.3 mmol/L), and rates of discontinuation due to hyperkalemia are typically <1%. Thus, these changes are unlikely to be of clinical significance.

The effects of ACEI/ARB combination therapy on hyperkalemia in patients with HF were assessed in a meta-analysis of data from the Valsartan Heart Failure Trial (Val-HeFT), CHARM-Added, Valsartan in Acute Myocardial Infarction Trial (VALIANT), and Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study. The analysis showed a statistically significant increased risk of serum potassium >5.5 mmol/L with ACEI/ARB combination therapy compared with control treatment in patients with chronic HF (3.5% *versus* 0.7%; risk ratio: 4.87; 95% CI: 2.39 to 9.94) (32). Although the meta-analysis did not assess the clinical relevance of the serum potassium elevations, combination therapy was associated with a significantly greater incidence of discontinuation due to adverse events (combination: 15.0%; control: 11.0%; risk ratio: 1.38; 95% CI: 1.22 to 1.55).

In the CHARM-Added trial, the number of discontinuations due to hyperkalemia was significantly higher with addition of candesartan to ACEI therapy than with add-on placebo ($P < 0.0001$; Table 2) (33). Moreover, a *post hoc* analysis of the CHARM program data showed that adding candesartan to ACEI therapy increased the combined incidence of fatal hyperkalemia and hyperkalemia requiring dose reduction, study discontinuation, or hospitalization from 2.9% to 8.4% ($P < 0.0001$) (24). Importantly, however, the addition of candesartan to ACEI therapy reduced cardiovascular death and HF hospitalizations in the subgroups of patients at high risk of hyperkalemia, such as those with CKD (serum creatinine >2.0 mg/dl) (24).

In the individual RESOLVD and Val-HeFT studies, serum potassium levels increased from baseline with combination therapy but decreased with either monotherapy (RESOLVD) or add-on placebo (Val-HeFT; Table 2) (34). In VALIANT, the rates of discontinuation due to hyperkalemia were similar with the combination of valsartan and the ACEI captopril, and either agent alone (0.2% *versus* 0.1%) (35). Finally, in the Vasodilator Heart Failure Trial (V-HeFT) in patients with symptomatic, stable, chronic HF (36), serum potassium levels increased by 0.2 mmol/L with the addition of valsartan (80 mg or 160 mg twice daily) to existing ACEI therapy, compared with a decrease of 0.2 mmol/L with add-on placebo.

The addition of an ARA to an ACEI or ARB also increases the risk of serum potassium elevation in patients with HF. In the Randomized Aldactone Evaluation Study (RALES) (37) and Eplerenone Post-acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) (38), addition of an ARA to standard therapy (including an ACEI or ARB) was associated with a small but statistically significant increase in serum potassium levels of 0.3 mmol/L ($P < 0.001$). The incidence of serum potassium ≥6.0 mmol/L was greater with the addition of ARA than with add-on placebo in both studies, although this only achieved statistical significance in EPHESUS ($P = 0.002$; Table 2).

In a *post hoc* analysis of EPHESUS, eplerenone was associated with a 4.4% and a 1.6% absolute increase in the risk of serum potassium >5.5 mmol/L and ≥6.0 mmol/L, respectively, compared with placebo (39). However, fewer than 1% of patients discontinued add-on ARA therapy because of hyperkalemia, despite the use of background therapy including β-blockers, ACEIs, and/or ARBs (Table 2). Importantly, no relationship was found between change in serum potassium level and the benefit of eplerenone with regard to all-cause mortality. The analysis identified eGFR <60 ml/min per 1.73 m^2, baseline serum potassium >4.3 mmol/L, diabetes, and use of antiarrhythmic drugs, but not add-on eplerenone treatment, as independent predictors for hyperkalemia (39). After the publication of RALES, the number of prescriptions for spironolactone rose, as did the incidence of hyperkalemia-associated morbidity and mortality (40). This may reflect the increased use of ARAs in clinical practice in the elderly and in patients with more severe CKD than those enrolled in RALES.

Dual RAAS inhibitor therapy with a DRI added to standard therapy including an ACEI or ARB was assessed in 302 patients with HF in the Aliskiren Observation of Heart Failure Treatment (ALOFT) study (Table 2) (41). Addition of aliskiren (150 mg/d) was not associated with a significantly increased incidence of serum potassium >5.5 mmol/L compared with add-on placebo (both 8.3%). Rates of serum potassium ≥6.0 mmol/L were slightly lower in the aliskiren group than in the placebo group (Table 2). Moreover, ALOFT evaluated the incidence of hyperkalemia (defined as serum potassium >5.5 mmol/L, or Medical Dictionary for Regulatory Activities adverse event term for hyperkalemia) as a prespecified safety endpoint; the rate of hyperkalemia with the addition of aliskiren was similar to that with placebo (6.4% *versus* 4.8%; $P = 0.499$)

Chronic Kidney Disease. The effects of dual RAAS inhibition on serum potassium levels in patients with CKD have been assessed in several clinical trials and reviewed in two meta-analyses. Hyperkalemia is known to be a risk with dual RAAS inhibition in patients with CKD (Table 3). However, analysis of the data reveals that the magnitude of the serum potassium increases is modest (typically ≤0.5 mmol/L), and the rates of hyperkalemia requiring discontinuation of dual RAAS inhibition are generally low (<5%).

Moderate-dose ACEI/ARB combination therapy is associated with small increases in serum potassium levels in patients with CKD, according to the data from two meta-analyses (Table 3). In the meta-analysis by Jennings *et al.* (42) of 10 clinical trials in 315 patients with CKD (diabetic nephropathy), serum potassium increased by 0.2 mmol/L with combination therapy compared with ACEI monotherapy ($P < 0.01$). Similar increases in serum potassium were also observed in the meta-analysis by MacKinnon *et al.* (9) of 14 crossover studies in 373 patients with CKD (proteinuria >300 mg/d; Table 3). In the Candesartan and Lisinopril Microalbuminuria (CALM) trial in 199 patients with

Table 2. Effect of single and dual RAAS inhibition on serum potassium levels in clinical trials in patients with heart failure

Study (Reference Citation)	Type of RAAS Inhibition	Duration, wk[a]	No. of Patients	Treatment Dose, mg/d[a]	Incidence of Potassium >5.5 mmol/L, %	Incidence of Potassium ≥6.0 mmol/L, %	Discontinuation Due to Hyperkalemia, %	Mean Change in Serum Potassium [Baseline], mmol/L[a]	Concomitant Medications, %
Single RAAS inhibition									
CONSENSUS (21)	ACEI	188 d (mean follow-up)	253	ENL 5 to 20 b.i.d.[b] PBO (added to standard therapy)	ENL, 7.1 PBO, 4.0	NR	NR	NR	Diuretic: Furosemide, 98 SPI, 53 Other, 12 BB, 3
ELITE (22)	ARB	48	722	LOS 12.5 to 50[c]	NR	NR	LOS, 0.6	Persistent ≥0.5 mmol/L increase from baseline LOS, 18.8%	Diuretic, 74 BB, 16 ASA, 48 Potassium, 25
	ACEI			CAP 6.25 to 50 t.i.d.[c]			CAP, 1.6	CAP, 22.7% [Overall baseline, 4.3 mmol/L]	
CHARM-Alternative (23)	ARB	33.7 mo (median follow-up)	2028	CAN 4 to 32[d] PBO (added to standard therapy, no ACEI)	NR	CAN, 3.0 PBO, 1.3	CAN, 1.9 PBO, 0.3 $P = 0.0005$	NR	Diuretic, 85 BB, 55 SPI, 24 ASA, 58
Single and dual RAAS inhibition									
CHARM-Added (33)	ARB/ACEI ACEI	41 mo (median follow-up)	2548	CAN 4 to 32[d] PBO (added to standard therapy including ACEI)	NR	CAN, 3 PBO, 1	CAN, 3.4 PBO, 0.7 $P < 0.0001$	NR	Diuretic, 90 SPI, 17 BB, 55 ASA, 51
RESOLVD (59)	ARB/ACEI	43	768	CAN/ENL 4 or 8 o.d./ 10 b.i.d.	NR	NR	NR	CAN/ENL, +0.11 ($P <$ 0.05 *versus* ENL) [4.42]	Diuretic, 84 BB, 15 ASA, 53
	ARB			CAN 4, 8, 16				CAN, −0.23 (P < 0.05 *versus* ENL) [4.48]	
	ACEI			ENL 10 b.i.d.				ENL, −0.01 [4.40]	

Val-HeFT (34)	ARB/ACEI	23 mo (mean follow-up)	5010	VAL 40 to 160 b.i.d.[e]	NR	NR	NR	VAL, +0.12	ACEI, 93 Diuretic, 86
	ACEI			PBO (added to standard therapy, including ACEI)				PBO, −0.07 ($P < 0.001$)	BB, 35
VALIANT (35)	ARB/ACEI	24.7 mo (median follow-up)	14,703	VAL/CAP 80 b.i.d./ 50 t.i.d.[f]	NR	NR	VAL/CAP, 0.2	NR	Potassium-sparing diuretic, 9
	ARB			VAL 160 b.i.d.[f]			VAL, 0.1		Other diuretic, 50
	ACEI			CAP 50 t.i.d.[f] (added to standard therapy)			CAP, 0.1		BB, 70 ASA, 91
V-HeFT (36)	ARB/ACEI	4	83	VAL 80 b.i.d. VAL 160 b.i.d.	NR	NR	NR	VAL (80 or 160 mg b.i.d.), +0.2 [4.2]	Diuretic, 93
	ACEI			PBO (added to ACEI)				PBO, −0.2 [4.2]	
RALES (37)	ARA/ACEI	24 mo (mean follow-up)	1663	SPI 25 to 50[g]	NR	SPI, 2	NR	SPI, +0.3[h]	ACEI, 95
	ACEI			PBO (added to standard therapy including ACEI)		PBO, 1		PBO, 0.0[h] ($P < 0.001$)	Loop diuretic, 100 BB, 11 ASA, 37 Potassium supplement, 28

Table 2. (Continued)

Study (Reference Citation)	Type of RAAS Inhibition	Duration, wk[a]	No. of Patients	Treatment Dose, mg/d[a]	Incidence of Potassium >5.5 mmol/L, %	Incidence of Potassium ≥6.0 mmol/L, %	Discontinuation Due to Hyperkalemia, %	Mean Change in Serum Potassium [Baseline], mmol/L[a]	Concomitant Medications, %
EPHESUS (38,39)	ARA/ACEI or ARB	16 mo (mean follow-up)	6642	EPL 25 to 50[i]	EPL, 15.6	EPL, 5.4	EPL, 0.7	EPL, +0.3 [4.3]	ACEI or ARB, 87
	ACEI or ARB			PBO (added to standard therapy including ACEI or ARB)	PBO, 11.2 ($P < 0.001$)	PBO, 3.8 ($P = 0.002$)	PBO, 0.3 ($P \geq 0.05$)	PBO, +0.2 [4.3] ($P < 0.001$ *versus* PBO)	Diuretic, 60 BB, 75 ASA, 88
ALOFT (41)	DRI/ACEI or ARB	12	302	ALI 150	ALI, 8.3	ALI, 1.9	NR	ALI, −0.04 [4.48]	ACEI, 84 ARB, 15
	ACEI or ARB			PBO (added to standard therapy including ACEI or ARB)	PBO, 8.3	PBO, 4.2		PBO, +0.04 [4.441]	ARA, 33 BB, 94

ACEI, angiotensin-converting enzyme inhibitor; ALI, aliskiren; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BB, β-blocker; b.i.d., twice daily; CAN, candesartan; CAP, captopril; DRI, direct renin inhibitor; ENL, enalapril; EPL, eplerenone; LOS, losartan; o.d., once daily; NR, not reported; PBO, placebo; SPI, spironolactone; t.i.d., three times daily; VAL, valsartan.

[a]Unless otherwise stated.

[b]Up-titration to maximum dose 20 mg b.i.d., according to tolerability and clinical response.

[c]Dose doubled every 7 days, as tolerated.

[d]Dose doubled, as tolerated, at a minimum of every 2 weeks to a target dose of 32 mg.

[e]Dose doubled every 2 weeks to target dose of 160 mg b.i.d.

[f]Up-titration from VAL/CAP 20/6.25, VAL 20, or CAP 6.25 mg/d to target dose.

[g]Up-titration to 50 mg allowed after 8 weeks, depending on disease progression.

[h]Median change from baseline.

[i]Up-titration to 50 mg after 4 weeks.

hypertension, non-insulin-dependent diabetes and CKD (microalbuminuria; UACR 2.5 to 25 mg/mmol), treatment with candesartan/lisinopril (16/20 mg/d) increased serum potassium concentrations by 0.3 mmol/L from baseline (43).

The risk of hyperkalemia with an ARA added to an ACEI or ARB was investigated by Bomback *et al.* (10) in a systematic review of 15 studies involving patients with proteinuric CKD (albuminuria ≥30 mg/d). In all, 5.5% of patients receiving an ARA added to ACEI and/or ARB treatment experienced serum potassium >5.5 mmol/L. Small-scale studies in patients with CKD (diabetic nephropathy with UACR >20 mg/min (44) or proteinuria 1.0 to 3.0 g/g (45), or idiopathic chronic glomerulonephritis (46)) have also demonstrated that addition of an ARA to ACEI and/or ARB treatment increases serum potassium levels and the risk of hyperkalemia (Table 3) (44–46). In the two randomized, controlled trials in patients with diabetic nephropathy, serum potassium increased by up to 0.8 mmol/L after add-on spironolactone therapy for up to 52 weeks (Table 3) (44,46).

The risk of hyperkalemia with the combination of a DRI and an ARB was assessed in the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial in 599 patients with hypertension, type 2 diabetes, and CKD (diabetic nephropathy with UACR >300 mg/g) (47). The incidence of serum potassium >5.5 mmol/L was higher with aliskiren/losartan combination therapy than with losartan alone (13.7% *versus* 10.8%), although discontinuations due to hyperkalemia (Table 3) and rates of hyperkalemia reported as an adverse event (aliskiren, 5.0%; placebo, 5.7%) were similar between the two treatment groups.

Hyperkalemia Risk with Triple RAAS Inhibition. A handful of small studies have assessed the effects of triple RAAS inhibition with combinations of ACEIs, ARBs, or ARAs in patients with CKD (Table 3) (48–50). Although there are insufficient data to draw firm conclusions, the studies suggest that triple RAAS inhibition is associated with an increased risk of hyperkalemia compared with the use of two RAAS agents. In a long-term study by Tylicki and colleagues in patients with nondiabetic CKD (proteinuria >300 mg/d), combination therapy with spironolactone (25 mg), telmisartan (80 mg), and the ACEI cilazapril (5 mg) was associated with a statistically significant increase in serum potassium levels compared with the combination of telmisartan and cilazapril (0.31 *versus* 0.16 mmol/L; $P = 0.02$; Table 3) (50). In a separate study in patients with nondiabetic CKD (proteinuria >500 mg/d), spironolactone/losartan/enalapril (25/50/5 mg) combination therapy increased serum potassium by 0.15 mmol/L from baseline, whereas losartan/enalapril therapy slightly reduced serum potassium (−0.06 mmol/L; Table 3) (49). Finally, in the study by Chrysostomou *et al.* (48) in patients with CKD (proteinuria >1500 mg/d), increases in serum potassium with triple RAAS inhibition (spironolactone 25 mg, ramipril 5 mg, and irbesartan 150 mg) were similar to those with dual RAAS inhibition (Table 3).

Discussion

Physicians now have many options for dual RAAS inhibition, and various combinations of agents have been evaluated for the treatment of hypertension, HF, and CKD. Clinical trials show that the risk of serum potassium >5.5 mmol/L with RAAS inhibitor monotherapy is low (≤2%) in patients without predisposing factors for the condition. Coadministration of RAAS inhibitors is associated with a higher incidence of serum potassium >5.5 mmol/L (≈5%). Rates of hyperkalemia are also increased in patients with risk factors such as HF or CKD (5% to 10%). However, absolute increases in serum potassium are generally small (<0.3 mmol/L), and the clinical relevance of most of these increases is doubtful.

Renal excretion is the main route of potassium elimination; hence, hyperkalemia is common in patients with chronic renal failure (GFR less than ≈10 to 15 ml/min per 1.73 m^2). Extrarenal mechanisms of potassium elimination can partially compensate for reduced renal excretion in these patients, with the gastrointestinal route becoming increasingly important as renal function declines (51). Up to half of patients with congestive HF are estimated to have renal insufficiency, and so are at increased risk of hyperkalemia (52). Moreover, as patients with CKD and/or HF are likely to be treated with at least one RAAS inhibitor, the likelihood of hyperkalemia will be increased further. In patients with diabetes, insulin deficiency limits potassium movement from plasma to the cells, thus increasing the risk of serum potassium elevation (53). Risk is also increased as a result of hyporeninemic hypoaldosteronism, in which impaired renin release decreases aldosterone levels, and in patients with renal tubular acidosis (53).

It should be acknowledged that the rates of hyperkalemia observed in clinical trials of RAAS inhibitors may not represent the risk in clinical practice. By necessity, patients in clinical trials are carefully selected and closely monitored. Indeed, many studies exclude patients with high baseline serum potassium concentrations or severely impaired renal function—subgroups expected *a priori* to be at an increased risk of hyperkalemia (54). Moreover, screening of electrolyte levels in clinical trials is more rigorous than in clinical practice (55,56), and thus occurrences of hyperkalemia are more likely to be reported and appropriately managed with changes to the patient's regimen or diet. However, regular monitoring of serum electrolyte levels in clinical practice should be sufficient to detect any changes in potassium.

Clinical trials typically assess the risk of hyperkalemia as rates of serum potassium above a predefined threshold (>5.5 or ≥6.0 mmol/L). However, blood samples are highly susceptible to confounding effects, such as lysis of erythrocytes, which releases intracellular potassium, leading to an overestimation of serum potassium levels (57,58). Indeed, many of the increases observed in trials appear to be artifactual and are not seen again when the measurement is repeated using a new sample. Unfortunately, more clinically meaningful measures of the risk of serum potassium elevation, such as discontinuations due to hyperkalemia or serum potassium increases >1.0 mmol/L from baseline, are rarely assessed.

Table 3. Effect of single, dual, and triple RAAS inhibition on serum potassium levels in clinical trials in patients with chronic kidney disease

Study (Reference Citation)	Type of RAAS Inhibition	Duration, wk[a]	No. of Patients	Mean eGFR, ml/min per 1.73 m^2[a]	Treatment Dose, mg/d[a]	Incidence of Potassium >5.5 mmol/L, %	Incidence of Potassium ≥6.0 mmol/L, %	Discontinuation Due to Hyperkalemia, %	Mean Change in Serum Potassium [Baseline], mmol/L[a]	Concomitant Medications, %
Single RAAS inhibition										
Hou *et al.* (25)	ACEI	3.4 yr (mean follow-up)	328	Creatinine 3.1 to 5.0 mg/dl: eGFR, 25.8 to 26.3 Creatinine 1.5 to 3.0 mg/dl: eGFR, 37.1	Creatinine 3.1 to 5.0 mg/dl: BEN 10 b.i.d.; PBO Creatinine 1.5 to 3.0 mg/dl: BEN 10 b.i.d.	NR	Creatinine 3.0 to 5.1 mg/dl: BEN, 5.4; PBO, 4.5 Creatinine 1.5 to 3.0 mg/dl: BEN, 1.9	Creatinine 3.0 to 5.1 mg/dl: BEN, 1.8; PBO, 0.9 Creatinine 1.5 to 3.0 mg/dl: BEN, 0	NR	Diuretic, 82 BB, 49
Bakris *et al.* (26)	ACEI ARB	10[b]	35	65	LIS 10 VAL 80	NR	NR	NR	Overall: LIS, +0.12 [4.47] VAL, 0.0 [4.42] *eGFR* ≤60[c]: LIS, +0.28 ($P = 0.047$ *versus* baseline) [4.6] VAL, +0.12 [4.5]	NR
Takaichi *et al.* (2)	ACEI	Retrospective case study	9117	NR	ACEI	NR	NR	NR	Mean values: ACEI, 4.59 No ACEI, 4.45 ($P < 0.001$)	NR
	ARB				ARB				ARB, 4.58 No ARB, 4.45 ($P < 0.001$)	
IDNT (27)	ARB	2.6 yr (mean follow-up)	1715	NR	IRB 75 to 300[d] AML 2.5 to 10[d] PBO[d]	NR	NR	IRB, 1.9 AML, 0.5 ($P = 0.01$ *versus* IRB) PBO, 0.4 ($P = 0.01$ *versus* IRB)	NR	NR

Matsumoto *et al.* (28)	ARA	12	33	NR	SPI 50	SPI, 0	NR	NR	SPI, +0.4 ($P = 0.003$ *versus* baseline) [4.1]	NR
					AML, 2.5	AML, NR			AML, value NR but no significant change	
Single and dual RAAS inhibition										
Jennings *et al.* (42)	ACEI/ARB ACEI	8 to 12	315	NR	ACEI/ARB ACEI	NR	NR	NR	ACEI/ARB, +0.2 *versus* ACEI (95% CI: 0.08 to 0.32) ($P < 0.01$)	NR
MacKinnon *et al.* (9)	ACEI/ARB ACEI	4 to 16	373	NR	ACEI/ARB ACEI	NR	NR	NR	ACEI/ARB, +0.11 *versus* ACEI (95% CI: 0.05, 0.17) ($P < 0.05$)	NR
CALM (43)	ARB/ACEI ACEI ARB	24[e]	199	NR	CAN/LIS 16/20 CAN 16 LIS 20	NR	NR	NR	CAN/LIS, +0.30	NR
van den Meiracker *et al.* (44)	ARA/ACEI or ARB	52	59	64 to 87	SPI 50[f]	NR	SPI, 17.2[g]	NR	SPI, +0.5 ($P = 0.02$ *versus* PBO) [4.1]	NR
	ACEI or ARB				PBO (added to ACEI or ARB)		PBO, 3.3[g]		PBO, +0.2 [4.2]	
Bianchi *et al.* (46)	ARA + ACEI and/or ARB	52	165	62.3	SPI 25 + ACEI and/or ARB	NR	NR	SPI, 4.8	SPI, +0.8 ($P < 0.001$ *versus* baseline; $P < 0.001$ *versus* no SPI) [4.2]	Diuretic, 70
	ACEI and/or ARB				ACEI and/or ARB			No SPI, 2.4	No SPI, +0.1 [4.2]	

Table 3. (Continued)

Study (Reference Citation)	Type of RAAS Inhibition	Duration, wk[a]	No. of Patients	Mean eGFR, ml/min per 1.73 m^2[a]	Treatment Dose, mg/d[a]	Incidence of Potassium >5.5 mmol/L, %	Incidence of Potassium ≥6.0 mmol/L, %	Discontinuation Due to Hyperkalemia, %	Mean Change in Serum Potassium [Baseline], mmol/L[a]	Concomitant Medications, %
Epstein *et al.* (45)	ARA/ACEI	12	268	Median eGFR, 73 to 75	EPL/ENL 100/20	100/20, 3.7[h]	100/20, 6.1	100/20, 8.1	NR	NR
					EPL/ENL 50/20	50/20, 2.2[h]	50/20, 2.2	50/20, 4.4		
	ACEI				ENL 20	ENL, 1.1[h]	ENL, 3.4	ENL, 2.2		
Bomback *et al.* (10)	ARA + ACEI and/or ARB	4 to 52	436	NR	ARA + ACEI and/or ARB	ARA + ACEI and/or ARB, 5.5	NR	NR	NR	NR
AVOID (47)	DRI/ARB	26[i]	599	66.8 to 68.5	ALI/LOS 150/100 to 300/100	ALI/LOS, 13.7	ALI/LOS, 4.7	ALI/LOS, 1.0	ALI/LOS, +0.06 [4.5]	Thiazide diuretic, 34
	ARB				LOS 100 (plus optimal therapy)	LOS, 10.8	LOS, 1.7	LOS, 0.7	LOS, −0.02 [4.5]	Loop diuretic, 32 BB, 38
Dual and triple RAAS inhibition										
Tylicki *et al.* (50)	ARA/ARB/ ACEI	16[j]	18	107.8	SPI/TEL/CIL 25/80/5	SPI/TEL/CIL, 11.1	NR	NR	SPI/TEL/CIL, +0.31 (P = 0.02 *versus* baseline)	NR
	ACEI/ARB				TEL/CIL 80/5	TEL/CIL, 0			TEL/CIL, +0.16 [Overall, 4.50]	
Furumatsu *et al.* (49)	ARA/ARB/ ACEI	52	32	NR	SPI/LOS/ ENL 25/50/5	NR	NR	NR	SPI/LOS/ ENL, +0.15 [4.28]	NR
	ACEI/ARB				LOS/ENL 50/5				LOS/ENL, −0.06 [4.28]	

Chrysostomou *et al.* (48)	ARA/ARB/ ACEI	26	41	NR	SPI/RAM/ IRB 25/5/ 150	NR	SPI/RAM/ IRB, 18.2	NR	SPI/RAM/ IRB, +0.1 [4.8]	NR
	ARA/ACEI				SPI/RAM 25/5		SPI/RAM, 10.0		SPI/RAM, +0.4 [4.5]	
	ARB/ACEI				IRB/RAM 150/5		IRB/RAM, 0		IRB/RAM, +0.2 [4.5]	
	ACEI				RAM 5		RAM, 0		RAM, 0 [4.4]	

ACEI, angiotensin-converting enzyme inhibitors; ALI, aliskiren; AML, amlodipine; ARA, aldosterone receptor antagonist; ARB, angiotensin receptor blocker; AVOID, Aliskiren in the Evaluation of Proteinuria in Diabetes; BB, β-blocker; BEN, benazepril; CAN, candesartan; CI, confidence interval; CIL, cilazapril; DRI, direct renin inhibitor; eGFR, estimated glomerular filtration rate; ENL, enalapril; EPL, eplerenone; IDNT, Irbesartan Diabetic Nephropathy Trial; IRB, irbesartan; LIS, lisinopril; LOS, losartan; NR, not reported; PBO, placebo; RAM, ramipril; SPI, spironolactone; TEL; telmisartan; VAL, valsartan.

[a]Unless otherwise stated.

[b]Cross-over study: 4 weeks on each active treatment, separated by a 2-week washout.

[c]Subgroup of patients with estimated GFR ≤60 ml/min per 1.73 m^2 at baseline.

[d]Other antihypertensive agents (except ACEIs, ARBs, and calcium channel blockers) allowed for blood pressure control.

[e]12-week CAN or LIS monotherapy, then 12-week monotherapy or CAN/LIS combination.

[f]Dose reduction to 25 mg for patients with serum potassium >5.5 mmol/L.

[g]Patients discontinued, as per protocol.

[h]On 2 consecutive occasions.

[i]ALI 150 mg for 13 weeks, then ALI 300 mg for a further 13 weeks.

[j]Cross-over study: 8 weeks on each active treatment, with no washout between treatments.

Several studies, such as Val-HeFT, CHARM-Added, RALES, and CALM, have demonstrated the potential benefits of ARB/ACEI or ARA/ACEI combinations. Importantly, *post hoc* analyses of the CHARM-Added and EPHESUS studies have shown that the benefits of dual RAAS inhibition for cardiovascular morbidity and mortality over a single RAAS inhibitor are maintained in the subgroups of patients at the highest risk of developing hyperkalemia, such as those with CKD (24,39,54). More recently, the AVOID and ALOFT studies have shown potentially promising effects on markers of renal function and HF progression when a DRI is added to standard therapy including an ACEI or ARB (41,47). However, some studies (*e.g.*, VALIANT, ONTARGET) (29,35) suggest that combination therapy is associated with a poorer tolerability profile than monotherapy, highlighting the need for further evaluation to determine the best approach for dual RAAS inhibition. Continued assessment in clinical practice may well reveal slight, but potentially important, variations in efficacy and tolerability between combinations involving different types of RAAS inhibitor.

The ONTARGET renal subanalysis has raised broad concerns over the renal safety and lack of efficacy in reducing cardiovascular endpoints of ARB/ACEI combination therapy. However, the study was not powered to evaluate renal outcomes; indeed, of the nearly 3500 individual composite endpoint events, only 600 were specifically renal, and death from any cause was the key driver of the result. Hence, inappropriate extrapolation of the ONTARGET findings should be avoided. A properly conducted, prospective trial in patients with CKD is needed to assess the effects of dual RAAS inhibition on disease progression. Thus, on balance, the key message from ONTARGET should be that although there is an increased risk of serum potassium elevations with dual RAAS inhibition, the absolute incidence remains low, and patients with risk factors predisposing to hyperkalemia should have serum electrolytes monitored when receiving RAAS inhibitor combinations. Approaches to the monitoring, detection, and management of serum potassium elevations in patients with hypertension, HF, or CKD are summarized in the Clinical Perspectives section.

Clinical Perspectives: Hyperkalemia

Hypertension. If hyperkalemia occurs in patients with hypertension and normal kidney function, it is usually related to excess ingestion or impaired excretion of potassium, or to hemolysis of the blood specimen. If a repeat sample confirms that serum potassium is elevated, a reduction in dietary potassium and avoidance of NSAIDs is usually sufficient to control the serum level. It is unusual to have to withdraw therapy with one or more inhibitors of RAAS in people with normal kidney function. Monitoring serum levels of potassium every 6 months should be sufficient to detect any changes.

Heart Failure. In patients with HF, particularly those with reduced GFR, the risk of hyperkalemia is substantial. Dietary advice and avoiding NSAIDs is the first step. Dose adjustment of the RAAS inhibitor, particularly if the drug is excreted renally, and the use of loop diuretics should be considered as the

primary approach for reducing potassium levels. Rarely, patients may require potassium-binding resins. The use of fludrocortisone and sodium bicarbonate is much more problematic and may cause volume overload. Some patients may require serum potassium monitoring every few weeks as changes are made to the medication regimen. If patients with HF receiving dual RAAS inhibition have recurrent hyperkalemia that does not respond to these measures, then one RAAS inhibitor should be discontinued.

Chronic Kidney Disease. In patients with advanced CKD (particularly with GFR less than 30 ml/min per 1.73 m^2) or type IV renal tubular acidosis (more common in diabetes), the risk of clinically significant changes in serum potassium is more common. These patients will require closer monitoring (1 to 2 weeks after medication changes), dietary advice, and strict avoidance of NSAIDs. In addition, adjustment of the RAAS inhibitor dose, careful use of loop diuretics, and addition of sodium bicarbonate may be helpful, especially if the patient is slightly acidotic. This will facilitate greater exchange of sodium for potassium in the distal nephron. Rarely, fludrocortisone or chronic use of potassium-binding resins is required. However, there is a theoretical concern that fludrocortisone may hasten progression of kidney disease, and chronic use of resins is not well tolerated. If patients with kidney disease who are receiving dual RAAS blocker therapy have recurrent hyperkalemia, one RAAS inhibitor should be discontinued.

Conclusion

Patients with conditions that reduce potassium excretion, such as CKD, diabetes, or HF, are at greater risk of serum potassium elevation; however, these are the very patients likely to derive greatest benefit from RAAS inhibitors. Rather than denying patients effective treatment, it seems prudent to monitor on-treatment potassium levels in patients at high risk of hyperkalemia, make sure that they are not taking NSAIDs or using potassium-containing salt substitutes, and also make sure that they are educated about the potassium content of different foods. Some patients may also require the judicious use of kaliuretic diuretics. Patients with diabetes or renal failure are already closely monitored, and regular assessment of potassium can form part of this monitoring. The results of this analysis indicate that the types of patient described here can be successfully treated with RAAS inhibitors. However, these findings cannot be broadly extrapolated to the general population. Appropriate selection of patients and the applicability of these results should be carefully assessed for each patient before treatment.

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