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Review

The Use of Renin-Angiotensin System Inhibitors in Patients With Chronic Kidney Disease

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ABSTRACT

Chronic kidney disease (CKD) is a growing public health issue worldwide. It is acknowledged that CKD is associated with increased risk of cardiovascular disease, which is the leading cause of morbidity and mortality in this population. The role of the renin-angiotensin-aldosterone system in the pathophysiology of hypertension, and cardiovascular and kidney diseases is well known and the renin-angiotensin-aldosterone system is a major regulator of blood pressure through its effect on body fluids and electrolyte homeostasis. For 2 decades, renin-angiotensin system inhibitors have been the mainstay of treatment for CKD. Clinical trials have shown that prescription of monotherapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers reduces albuminuria and slows the progression of nephropathy in patients with diabetes. In clinical practice guidelines, renin-angiotensin system inhibitors are recommended as the antihypertensive drug of choice in patients with CKD with or without diabetes. Moreover, renin-angiotensin system inhibitors have been shown to offer cardiovascular protection beyond those resulting after blood pressure control. However, the benefits of renin-angiotensin system inhibitor prescriptions for patients with advanced CKD remain controversial. Patients with advanced CKD or who undergo dialysis are under-represented in clinical trials, and studies in this population are urgently needed.

RÉSUMÉ

L'insuffisance rénale chronique (IRC) est un problème de santé publique croissant dans le monde entier. L'IRC est notoirement associée à un risque accru de maladie cardiovasculaire, principale cause de morbidité et de mortalité au sein de la population touchée. Le rôle du système rénine-angiotensine-aldostérone dans la physiopathologie de l'hypertension et des maladies cardiovasculaires et rénales est bien connu, et ce système constitue un régulateur majeur de la pression artérielle par ses effets sur l'homéostasie hydroélectrolytique. Depuis deux décennies, le traitement de l'IRC repose principalement sur l'administration d'inhibiteurs du système rénine-angiotensine. Les essais cliniques ont montré que les inhibiteurs de l'enzyme de conversion de l'angiotensine et les antagonistes des récepteurs de l'angiotensine prescrits en monothérapie réduisent l'albuminurie et ralentissent la progression de la néphropathie chez les patients diabétiques. Dans les lignes directrices de pratique clinique, les inhibiteurs du système rénine-angiotensine sont recommandés en tant qu'antihypertenseurs de première intention chez les patients atteints d'IRC, qu'ils soient diabétiques ou non. En outre, les inhibiteurs du système rénine-angiotensine offrent une protection cardiovasculaire avérée au-delà de celle que procure la maîtrise de la pression artérielle. Cependant, les avantages de la prescription d'inhibiteurs du système rénine-angiotensine chez les patients atteints d'IRC avancée demeurent controversés. Les patients atteints d'IRC avancée ou sous dialyse sont sous-représentés dans les essais cliniques, et des études au sein de cette population s'imposent de toute urgence.

Chronic kidney disease (CKD) affects millions worldwide and represents a major public health problem. The prevalence of CKD in adult Canadians is approximately 12.9%, which is similar to the prevalence reported in the United States, but higher than European estimates.[1] Patients with CKD have an increased risk of cardiovascular and all-cause mortality[2] as well as progression to kidney failure.

Many therapies aimed to reduce the progression of CKD have been studied. Irrespective of the cause of CKD, treatment has focused on blood pressure control and reduction of protein excretion. The role of the renin-angiotensin-aldosterone system (RAAS) in the pathophysiology of hypertension, and cardiovascular and kidney diseases is well known. The RAAS is a major regulator of blood pressure by its effects on water and electrolyte homeostasis. Furthermore, it exerts its effect on blood pressure by the vasoconstriction action of angiotensin II and its stimulation of the sympathetic nervous systems that leads to increased vascular resistance.[3] In the

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kidneys, the angiotensin II receptor type 1 (AT_1) receptors are the main receptors that mediate the action of angiotensin II, the main effector of the RAAS.[4,5] Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been shown to reduce the progression of kidney disease in several large outcome trials. Blockage of the renin-angiotensin system (RAS) with ACEI/ARBs offer cardiovascular and renal protection beyond those resulting after blood pressure control.[6] They further exert renoprotective and antiproteinuric effects and are considered first-line agents for CKD stage 1-3.[6]

The efficacy and safety of RAS inhibitors (RASIs) remains less certain in patients with advanced CKD (stage 4-5).[7] In this population, ACEIs or ARBs must be used with caution because they can lead to hyperkalemia, acute declines in estimated glomerular filtration rate (eGFR), and these patients are inadequately represented in clinical trials. In this review, we aim to summarize the contemporary evidence for the use of ACEIs/ARBs in patients with CKD.

Proteinuria or Albuminuria

Proteinuria or albuminuria is an important marker of vascular health, and is perhaps the strongest risk factor for progression of CKD to kidney failure. In the United States, data from the **N**ational **H**ealth **a**nd **N**utrition **E**xamination **S**urvey (NHANES) 1999-2004 survey estimated that 8.2% of participants had at least 1 measurement of albuminuria > 30 mg/g,[8] and albuminuria has also been shown to be an independent risk factor for cardiovascular disease and all-cause mortality in patients with CKD.[9,10]

Albuminuria can be classified into glomerular, overflow, or tubular depending on the type of molecules excreted into the urine (Table 1). Progression of kidney disease mediated through albuminuria is thought to occur via multiple pathways. Albuminuria further generates proinflammatory and profibrotic responses that contribute to the chronic tubule-interstitial damage.[11] Regardless the cause, albuminuria has harmful effects on the kidney. In a meta-analysis including 13 cohorts (21,688 individuals), higher albuminuria level was independently associated with mortality and end stage renal disease (ESRD).[12] Additionally, albuminuria had been independently associated with an increased risk of CKD progression, cardiovascular events, and death over 1-3 years.[13] As such, high blood pressure and albuminuria are markers as well as therapeutic goals of renal disease.

The preferred method to detect and monitor albuminuria is spot albumin/creatinine ratio (ACR) because this is a more sensitive and specific measure of kidney damage compared with 24-hour urine collection.[14] Moreover, standardization of ACR measurement is ongoing and shows less variability than measurement of urine protein.[6] Albuminuria was recently incorporated as a key parameter to diagnose and classify CKD in several guidelines. In 2012 the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended that CKD should be classified on the basis of cause, glomerular filtration rate (GFR) category, and albuminuria category.[6] Other guidelines also recommend the ACR test for screening in diabetic and nondiabetic patients.[14,15] Furthermore, a prediction tool (the Kidney Failure Risk Equation) requires age, sex, eGFR, and ACR to predict kidney failure (need for dialysis or kidney transplantation) over the next 2 or 5 years.[16] The Kidney Failure Risk Equation has been validated in several cohort studies,[17] and it is currently in use as a population-level tool in Canada.[18]

A decrease in albuminuria is associated with improvement of long-term outcomes in patients with CKD.[19] RAS inhibition has shown a protective effect against renal failure progression and reduction of proteinuria.[20] Recent studies have further shown that in patients with diabetic and non-DKD, the additional use of dietary sodium restriction and or diuretic prescription can potentiate the reduction of albuminuria and thus enhance the effects of RAS inhibition.[21-23]

Screening for albuminuria is recommended by guidelines for the management of diabetes,[24] and RASIs significantly reduce albumin excretion.

Evidence from randomized trials shows that RAS inhibition with ACEIs or ARBs reduce adverse kidney events in patients with diabetes or hypertension and albuminuria, and KDIGO guidelines favour ACEIs or ARBs over other medications in these individuals (Table 2).[25] Finally, studies have also shown a reduction in cardiovascular end points in patients with diabetes treated with RASIs, further cementing their first-line indication in patients with diabetes.[26,27] As such, albuminuria is an important risk factor for kidney disease progression and cardiovascular mortality and an important effect modifier for RASI in CKD.

RAS Inhibition in DKD

Although diabetes is the leading cause of kidney failure, most patients with CKD from diabetes die of cardiovascular disease before progressing to kidney failure.[28] Several large studies have shown that inhibition of the RAS slows the progression of kidney disease and reduces the risk of mortality and cardiovascular events in patients with diabetic kidney disease (DKD).[29,30]

ACEIs are recommended for patients with type 1 diabetes and microalbuminuria, including normotensive patients.[31] Early studies showed that ACEIs decreased albuminuria in patients

Table 1. Proteinuria classification

Type	Cause
Glomerular	Most common form of proteinuria (up to 90%) Increased glomerular permeability to high molecular-weight proteins (albuminuria)[61]
Tubular	When there is an insufficient tubular reabsorption of low molecular-weight proteins[61]
Overflow	There is an increase of the plasma concentration of low-weight proteins like immunoglobulins[61]

Table 2. Key points: RAS inhibition in albuminuria

Key points
- Screening for albuminuria should be implemented as a key component of the management of diabetes and CKD.
- RAS inhibition significantly reduces albumin excretion.
- In patients with albuminuria, ACEI and ARB are recommended first-line treatments.
- In proteinuric CKD ACEI/ARBs are considered first-line therapy.
- Sodium restriction and diuretic prescription might enhance the response of RAS inhibitors.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; RAS, renin-angiotensin system.

with diabetes mellitus type 1. This effect was independent of the blood pressure-lowering effect of the medications.[32,33] Captopril, an ACEI, showed long-lasting benefits in the prevention of diabetic nephropathy and was associated with the preservation of normal GFR in patients with type 1 diabetes.[34] The Collaborative Study Group (CSG) captopril trial showed the renoprotective effect of captopril in 409 patients with type 1 diabetes mellitus and nephropathy.[33] In this multicentre randomized control trial captopril was associated with a lower rate of doubling of serum creatinine 12.1% vs 21.3% in the placebo group ($P = 0.007$), an effect independent of the mean blood pressure.

Two landmark clinical trials have shown the efficacy of ARBs vs placebo in the type 2 diabetes population: **R**eduction of **E**ndpoints in **N**IDDM With the **A**ngiotensin II **A**ntagonist **L**osartan (RENAAL) trial and the **I**rbesartan **D**iabetic **N**ephropathy **T**rial (IDNT).[29,35] The RENAAL trial evaluated ARB vs placebo in 1513 patients with type 2 diabetes mellitus with nephropathy (urinary albumin:creatinine ratio $>$ 300 mg/g in a first morning void or a 24-hour urine protein $>$ 500 mg). Use of losartan showed a reduced incidence of doubling of serum creatinine by 25% (relative risk [RR], 0.75; $P = 0.02$) and ESRD by 28% (RR, 0.72; $P = 0.002$). In this study there was a reduction in heart failure hospitalization ($P = 0.005$) but there was not a significant difference in cardiovascular morbidity and mortality. In a post hoc analysis of the RENAAL trial, every 50% reduction in albuminuria was associated with a 36% risk reduction for doubling of serum creatinine and 45% for ESRD.[36]

The IDNT trial randomized 1715 patients with DKD and hypertension to irbesartan, amlodipine, or placebo. Irbesartan was associated with 30% and 37% lower risk of doubling the serum creatinine compared with placebo and amlodipine, respectively.[35] Likewise, among those who received losartan, the risk of doubling of the serum creatinine concentration was 25% lower compared with placebo.[29]

The effect of RAS inhibition in patients at high risk of cardiovascular disease was investigated in the **H**eart **O**utcomes **P**revention **E**valuation (HOPE) and **S**urvival **a**nd **V**entricular **E**nlargement (SAVE) trials, among others.[37,38] In the HOPE trial, 9297 patients with high-risk cardiovascular disease or diabetes plus 1 cardiovascular risk factor were randomized to ramipril or placebo. Ramipril was associated with a reduced number of cardiovascular events compared with placebo. In a subgroup analysis in patients with diabetes mellitus (n = 3577) the rate of the combined primary outcome (myocardial infarction, stroke, or cardiovascular death) was significantly lower in the ramipril arm compared with placebo (RR reduction 25% [95% confidence interval (CI), 12-36], $P = 0.0004$).[27] This ramipril effect was maintained when the outcomes were analyzed separately. In the SAVE trial the cardioprotective effect of captopril in patients with an acute myocardial infarction and left ventricular dysfunction was evaluated. Patients in the captopril arm had a reduction on the risk of death of 19% compared with placebo (RR, 0.81; 95% CI, 0.68-0.97; $P = 0.019$).[38] Subgroup analyses of SAVE in patients with diabetes showed similar results when the analysis was performed in this population.[39] Subsequently, several large trials including the **Eu**ropean Trial on **R**eduction **o**f Cardiac Events With **P**erindopril in Stable Coronary **A**rtery Disease (EUROPA),[40] **P**revention of **E**vents With **A**ngiotensin **C**onverting **E**nzyme Inhibition (PEACE) trial,[41] and **T**elmisartan **R**andomised **A**ssessmen**t** **S**tudy in A**C**E **I**ntolerant Subjects With Cardiovascular **D**isease (TRANSCEND)[42] all confirmed the efficacy of RASIs for prevention of cardiovascular events in high-risk populations.

The benefits of RAS inhibition in DKD progression in patients with albuminuria is also supported by meta-analyses of clinical trials. In a patient-level meta-analysis of individuals with type 1 diabetes and microalbuminuria, ACEIs were associated with lower risks of progression to higher levels of albuminuria ($>$ 300 mg/d), and were also associated with potential regression to normoalbuminuria. These findings were independent of blood pressure and supported the use of RASIs in patients with diabetes and early stages of CKD, who might still be normotensive.

More recently, Palmer et al.,[43] in a network meta-analysis of 157 trials assessed the efficacy of blood pressure-lowering agents in reducing kidney failure and mortality in patients with diabetes and kidney disease. The investigators reported that RASIs were the only agents associated with a lower risk of progression to kidney failure, but all antihypertensive agents were equivalent for the outcomes of all-cause mortality. Finally, in another meta-analysis (63 trials; 36,917 participants) in which combination therapies for patients with diabetes were evaluated showed that combinations of RASIs and calcium channel blockers (CCBs) might be optimal in this population.[44]

Initiation of RASIs in patients with or at risk for CKD has being associated with an initial and transient elevation in serum creatinine and hyperkalemia.[45] However, with long-term use there is often a stabilization of the creatinine levels, and a transition to a slower rate (slope) of decline of eGFR. Although larger decreases in serum creatinine levels have been associated with a higher risk of cardiorenal outcomes,[46] it is unclear whether this is simply an association or a causative effect of RASIs. As such, current guidelines continue to recommend a threshold of 30% increase in creatinine for stopping treatment.[45]

Studies that have compared the effects of ACEIs vs ARBs in patients with DKD have shown that they are similar when it comes to short-term[47] and long-term[48] renoprotection in DKD. Moreover, in a network meta-analysis the effects of ACEIs and ARBs on cardiovascular and renal outcomes in patients with diabetes mellitus were evaluated. ARBs were not superior to ACEIs in terms of all-cause and cardiovascular mortality, kidney failure, or doubling of serum creatinine level.[49] In summary, the evidence firmly shows that inhibition of the RAS system with ACEIs or ARBs slows the progression of DKD placing these drugs as required standard of care for these individuals (Table 3).

RASIs in Non-DKD

Evidence of RAS blockade in the treatment of non-DKD compared with DKD is more limited (Table 4). Studies have shown that adequate treatment of hypertension is key for slowing kidney disease progression in non-DKD. In the **A**ntihypertensive and **L**ipid-**L**owering Treatment to Prevent **H**eart **A**ttack **T**rial (ALLHAT), the incidence of major cardiovascular outcomes in high-risk hypertensive patients treated with a CCB, an ACEI, or an α-blocker, were each compared with diuretic treatment as first-line therapy. A long-term assessment of renal and cardiovascular outcomes stratified according to baseline eGFR was perfomed.[50] In this trial,

Table 3. Key points: RAS inhibition in DKD

Key points
• RAS inhibition reduces the risk of mortality and cardiovascular event in DKD.
• Guidelines recommend RAS inhibition with an ACEI or ARB.
• Studies have shown that ARBs are as effective as ACEIs in patients with DKD.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DKD, diabetic kidney disease; RAS, renin-angiotensin system.

no significant difference was observed between the lisinopril and chlorthalidone arms for cardiovascular outcomes (11.4% vs 11.5%; RR, 0.99; $P = 0.81$) or all-cause mortality (17.2% vs 17.3%; RR, 1.00; $P = 0.90$). However, blood pressure reduction in the ACEI arm was lower than with the diuretic, so we need to be cautious with the data interpretation. Moreover, there was a lack of a high-risk CKD population with albuminuria.

Two important trials have supported the benefits on kidney outcomes of use of ACEIs in patients with non-DKD: the **R**amipril **E**fficacy **i**n **N**ephropathy (REIN) and **A**frican **A**merican **S**tudy of **K**idney Disease and Hypertension (AASK) trials (Table 5).[51,52] In the REIN trial 352 patients with chronic nondiabetic nephropathies were randomized to ramipril or placebo. Patients randomized to ramipril had a slower decline in GFR compared with patients randomized to placebo. This effect was independent of the blood pressure level. Similarly, the AASK trial also showed a superior renoprotective effect of ACEIs compared with other antihypertensive medications like β-blockers or CCBs. The AASK trial had an early termination of the amlodipine arm because of faster decline in mean GFR in the amlodipine group compared with ramipril and metoprolol groups.[53]

A pooled analysis of 11 randomized trials (including the REIN study) showed that ACEIs were superior in slowing progression of non-DKD. A risk-based analysis using these patient-level data to evaluate the risk of progression of non-DKD showed heterogeneity in the benefit from RASI use according to level of albuminuria.[54] In all patients with non-DKD, treatment with ACEIs was more effective than regimens without angiotensin-converting enzyme inhibition in terms of slowing the progression of kidney disease; however, the degree of benefit was directly correlated with the level of albuminuria. Although current guidelines make no distinction between diabetic and non-DKD, literature supports the prescription of RASIs in nondiabetic CKD, particularly in patients with albuminuria.

Table 4. Key points: RAS inhibition in nondiabetic kidney disease

Key points
• Dual inhibition has not shown additional renoprotection or decrease in mortality compared with monotherapy.
• Dual inhibition has been associated with increased risk of adverse events.
• Dual RAS blockade with ACEIs or ARBs is not recommended in CKD.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; RAS, renin-angiotensin system.

Dual RAS Inhibition

It is plausible that dual inhibition of the RAS with an ACEI and ARB can achieve a more complete inhibition of the RAS and thus confer greater cardiovascular and renal protection. However, clinical trials that evaluated monotherapy vs dual RAS inhibition have shown increased risk of adverse events such as hyperkalemia and acute kidney injury (AKI), and absence of any additional benefit on CKD progression.

The **On**going **T**elmisartan **A**lone and in Combination With **R**amipril **G**lobal **E**ndpoint **T**rial (ONTARGET) was the largest trial of dual RAAS inhibition.[55] In this trial, 25,620 patients with cardiovascular disease or diabetes mellitus were randomized to telmisartan and ramipril vs ramipril alone. Dual therapy was not superior to ramipril alone in the study (median follow-up, 56 months) and there was no improvement in major renal outcomes in dual therapy compared with ramipril alone. Moreover, dual therapy was associated with higher rates of adverse events like hypotension, diarrhea, hyperkalemia (11.3% vs 7.8%), and AKI (1.4% vs 0.8%) and there was no increase in benefit compared with monotherapy. ONTARGET moreover provided evidence that ARBs have efficacy similar to ACEIs in the prevention of clinical outcomes in patients with high cardiovascular risk.

In the **V**eterans **A**ffairs **Nephro**pathy i**n** **D**iabetes (VA NEPHRON-D) trial[56] losartan with lisinopril was compared with losartan alone in patients with type 2 diabetes mellitus and DKD (n = 1448). This trial was stopped early after a median follow-up of 2.2 years when it showed an increased rate of hyperkalemia (9.9% vs 4.4%) and AKI (18% vs 11%) with combination therapy compared with monotherapy. There was no significant reduction in mortality or cardiovascular events.

Aliskiren is a renin inhibitor that has been shown to reduce albuminuria in DKD.[57] The **Al**iskiren **T**rial **i**n **T**ype 2 Diabetes **U**sing Car**di**orenal **E**ndpoints (ALTITUDE) trial randomized patients to aliskiren or placebo in DKD patients receiving ACEI or ARBs. In patients with DKD dual therapy of aliskiren and ACEI or ARB did not improve cardiovascular or renal outcomes. Moreover, its association led to increased adverse events. This study was stopped early because of safety concerns.

As such, dual therapy with ARBs/ACEIs fails to provide additional benefit in renoprotection or mortality and is associated with increased risk of adverse events. Therefore, dual RAAS blockade is not recommended in patients with CKD.[58]

Controversies in RAAS Inhibition: Late Stage CKD

The use of RASIs in patients with CKD or advanced CKD (eGFR < 20 mL/min/1.73 m^2 or those receiving dialysis or transplantation) remains controversial. In CKD (stage G5) the risk of cardiovascular mortality is 8.1-fold greater than in the general population without kidney disease.[6] However, adverse events associated with RASIs including hyperkalemia, metabolic acidosis, worsening anemia, and an acute decrease in GFR all limit the use of RASIs.

In a recent observational study, Ahmed et al. reported that in patients with advanced CKD, stopping RASIs was associated with improvement in kidney function (increase of $> 25\%$ in 61.5% of the cases).[59] In a systematic review and meta-analysis CCBs and RASIs were compared in patients

Table 5. Effect of RAAS inhibitor therapy on kidney function

Reference	Intervention	Study population	Study duration, years	Baseline mean creatinine (mg/dL) or eGFR (mL/min/1.73 m^2) vs placebo	Doubling of serum creatinine, RR (95% CI)	Progression to ESRD, RR (95% CI)
IDNT[35] N = 1715	Irbesartan vs amlodipine vs placebo	Patients with type 2 DM and nephropathy	3	1.67 ± 0.53 vs 1.69 ± 0.57	Adjusted RR Irbesartan vs placebo: RR, 0.81 (95% CI, 0.67-0.99) ($P = 0.03$) Irbesartan vs amlodipine: 0.76 (0.63-0.92) ($P = 0.005$)	Irbesartan vs amlodipine: RR 0.77 (95% CI, 0.57-1.03) $P = 0.07$
RENAAL trial[29] N = 1513	Losartan vs placebo	Patients with type 2 DM and nephropathy	3	1.9 ± 0.5 vs 1.9 ± 0.5	21.6% vs 26.0% (RR, 0.75; $P = 0.006$) Risk of ESRD: 19.6% vs 25.5% (RR, 0.72; $P = 0.002$)	RR, 0.72 (95% CI, 0.58-0.89) $P = 0.002$
CSG[33] N = 409	Captopril vs Placebo	Patients with type 1 DM and nephropathy	4	1.3 ± 0.4 vs 1.3 ± 0.4	RR 0.52; 95% CI 0.31-0.84; $P = 0.007$	
ALLHAT subgroup analysis[50] N = 31,350	Lisinopril vs amlodipine vs chlorothiazide	Patients age 55 or older with hypertension and 1 cardiovascular risk factor	4.9	eGFR (mL/min/1.73 m^2): Lisinopril: 50.1 ± 8.6 Chlorothiazide: 50.1 ± 8.7		Lisinopril vs chlorothiazide: RR, 0.91 (95% CI, 0.73-1.31) $P = 0.41$
REIN trial[51] N = 352	Ramipril vs placebo	Nondiabetic CKD patients	3	Mean SCr: 2.4 mg/dL	Mean rate of decline of GFR in ramipril group decreased from 0.44 to 0.10 mL/min/1.73 m^2 Placebo group: 0.81-0.14 mL/min/1.73 m^2	
AASK trial[53] N = 1089	Ramipril vs amlodipine vs metoprolol	African American population with hypertensive nephrosclerosis	3.8	GFR 46 (range, 20-65) mL/min/1.73 m^2	Chronic phase: mean decline in GFR: 36% slower in the ramipril group ($P = 0.002$).	End point (GFR, ESRD, or death) risk reduction for the ramipril vs amlodipine groups was 38% (95% CI, 13%-56%) $P = 0.005$
ONTARGET trial[55] N = 25,620	Telmisartan, ramipril, or both	Adult patients (≥ 55 years with DM or vascular disease)	4.6	SCr 93 μmol/L	There were no significant differences in the rates of kidney outcomes	Combination therapy vs ramipril: RR, 1.37 (95% CI, 0.94-1.98)
VA NEPHRON-D trial[56] N = 1148	Losartan vs losartan and lisinopril	Veterans with type 2 DM, eGFR of 30-89.9 mL/min/1.73 m^2	2.2	SCr 1.5 ± 0.5 mg/dL	First occurrence of change in eGFR, ESRD, and death: 21.0% vs 18.2% HR, 0.88; 0.70-1.12; $P = 0.30$	

AASK, African American Study of Kidney Disease and Hypertension; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CI, confidence interval; CKD, chronic kidney disease; CSG, Collaborative Study Group; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; GFR, glomerular filtration rate; HR, hazard ratio; IDNT, Irbesartan Diabetic Nephropathy Trial; ONTARGET, Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial; RAAS, renin-angiotensin-aldosterone system; REIN, Ramipril Efficacy in Nephropathy; RENAAL, Reduction of end points in NIDDM with the angiotensin II antagonist losartan; RR, relative risk; SCr, serum creatinine; VA NEPHRON-D, **V**eterans **A**ffairs **Nephro**pathy i**n** **D**iabetes.

Table 6. Key points: RAS inhibition in advanced CKD

Key points
• Use of RAS inhibition in advanced CKD remains controversial.
• Clinical guidelines recommend treatment individualization in patients with advanced CKD.
• Clinical trials on the safety and efficacy of RAS inhibition in patients with advanced CKD are needed.

CKD, chronic kidney disease; RAS, renin-angiotensin system.

with CKD 3-5.[60] The analysis showed no significant differences between the CCB and ACEI groups with regard to mortality, as well as cardiovascular mortality. Furthermore, an analysis of randomized controlled trials showed no significant difference in dialysis events in comparisons of CCBs and ACEIs (RR, 1.12; 95% CI, 0.95-1.21) as well as no significant differences in the eGFRs between CCBs and ACEIs. As such, clinical practice guidelines recommend treatment individualization in this population according to different patient characteristics such as age, albuminuria suppression with RAS inhibition, and rate of kidney function decline (Table 6).

The Multi-centre Randomised Controlled Trial of Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker Withdrawal in Advanced Renal Disease (STOP-ACEi) STOP-ACEI study, a 3-year trial, is evaluating the effects of ACEI/ARB use in patients with advanced CKD. It aims to determine whether discontinuation of ACEIs/ARBs in these patients can help to stabilize or improve kidney function, compared with continued use. The results of this trial might provide additional clarity for making decisions about ACEI/ARB treatment in patients with advanced CKD.[7]

Conclusion

Treatment of CKD with RASIs has been the main recommendation of guidelines in the past 20 years. It has been credited with the decrease of albuminuria and slowing of kidney disease progression. Currently, 7 ARBs and 10 ACEIs are available in Canada plus several combined preparations of ARB and CCB or diuretics. There are several trials supporting the use of RAAS inhibitors in diabetic and nondiabetic CKD, and there is insufficient evidence and potential harm in using an ACEI with an ARB.

The continuation of RASIs in patients with CKD stage 4-5 remains controversial. Adverse events in this population like hyperkalemia and possible reduction in eGFR leads very often to the decision to discontinue RASIs in this population. Studies addressing the safety of continuation of RASIs in patients with late stage kidney disease and those receiving dialysis are lacking.

Disclosures

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