Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Chronic Renal Disease: Safety Issues

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Reducing the actions of the renin–angiotensin–aldosterone system with angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs) slows nephropathy progression in patients with or without diabetes. These drug classes have proven therapeutic benefits, particularly in patients with renal insufficiency (ie, serum creatinine level 133-265 μmol/L [1.5-3.0 mg/dL]). This class of drugs could also provide renoprotective effects that are nonblood pressure-dependent when used as part of combination antihypertensive therapy in patients with more advanced renal disease. Although many studies demonstrate the use of ACE inhibitors and ARBs to delay the decline in renal function and reduce proteinuria, many physicians fail to use these drug classes in patients with renal insufficiency for fear that either serum creatinine or potassium levels will rise. Thus, because of these issues, patients are deprived of known strategies that delay progression of renal disease. A strong association exists between acute increases in serum creatinine of up to 30% to 35% after initiating ACE inhibitor therapy and long-term preservation of renal function. This association is predominantly present in people with a baseline serum creatinine of up to 3 mg/dL and usually stablizes within 2 to 3 months of therapy given blood pressure is reduced to goal. Moreover, the appropriate use of diuretics mitigates against profound increases in serum potassium. Thus, withdrawal of an ACE inhibitor in such patients should occur only when the rise in creatinine exceeds this threshold over a shorter period of time or hyperkalemia develops, ie, serum potassium level of 5.6 mmol/L or greater.

THE SEVENTH REPORT of the Joint National Committee (JNC 7) recommends that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) be used in concert with diuretics as first-line therapy to reduce blood pressure in patients with hypertension and renal dysfunction. Many studies have demonstrated ACE inhibitors and ARBs delay the decline in renal function in diabetic and nondiabetic renal disease, decrease proteinuria, and have demonstrated a renoprotective effect independent of blood pressure.[1-6] However, data from the Third National Health and Nutrition Examination Survey III (NHANES III) demonstrate that only half of the 53% of hypertensive patients treated actually achieve the blood pressure goal of less than 140/90 mm Hg.[1] In the more recent NHANES IV report, the control levels for those 18 to 74 years have increased to 34%, which is an improvement but still far below that seen in clinical trials in which control rates are 65% to 85%.

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The failure to achieve these blood pressure goals are multifactorial and could be, in part, the result of physicians failing to dose ACE inhibitors or ARBs appropriately or use them with diuretics, as well as the fear of increases in creatinine or potassium, and angioedema. The complication of increased serum creatinine after initiating an ACE inhibitor or ARB consequently leads to physician reticence to stay the course with a given therapy. This action subsequently results in failure to maintain adequate blood pressure goals with a class of drugs shown to reduce progression of renal disease to a greater extent than others. Thus, because of the increased creatinine, patients are deprived of known strategies that are known to delay progression of renal disease.

Other side effects that occur are primarily related, either directly or indirectly, to genesis of angiotensin II and/or kinins and their interaction with other proteins. These include hypotension, acute renal failure, and problems during pregnancy.[7] Additionally, known complications of ACE inhibitors such as cough, angioneurotic edema, and anaphylactoid reactions are related in part to interactions between kinins and other proteins.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS ON RENAL FUNCTION

Normal Renal Function and Angiotensin II

In patients with essential hypertension and normal renal function (creatinine $<$ 133 μmol/L),

renal perfusion pressure is elevated and therefore maintenance of the glomerular filtration rate (GFR) is not as dependent on angiotensin II. In the setting of hypertension, the kidney is initially able to maintain both blood flow and glomerular filtration through autoregulation.[8] Autoregulation of GFR with the initial decrease in renal artery pressure is primarily mediated by tubuloglomerular feedback (TGF) from the macula densa and the stretch receptor.[9] The mechanism by which autoregulation is mediated is not completely understood. It is hypothesized that the myogenic stretch receptors in the wall of the afferent arteriole are stretched when there is an elevation in renal perfusion pressure. This increases calcium entry into the cell and subsequently promotes arteriolar constriction. This effect will decrease the intraglomerular hydraulic pressure and return both GFR and macula densa flow toward normal.[8,10-12] The net effect is that the GFR and renal blood flow do not begin to fall until these autoregulatory changes in arteriolar resistance are maximized. As a result, an ACE inhibitor generally induces little change in GFR in patients who have normal renal function.[13]

Chronic Renal Insufficiency and Angiotensin II

Declines in renal function are postulated to occur through changes in renal hemodynamics initiated by the loss of nephrons.[6] Rodent models of renal insufficiency show that when renal mass is reduced, the remaining nephrons, remnant "functional" nephrons, undergo sudden hypertrophy, with a concomitant lowering of arteriolar resistance and an increase in glomerular plasma flow.[14,15] The increase in glomerular plasma flow is mediated by vasodilation of the afferent arteriole greater than efferent arteriolar tone. This leads to increases in glomerular capillary hydraulic pressure[16] and increases the amount of filtrate formed by each nephron. The mechanisms by which glomerular hypertension and hypertrophy induce glomerular injury are incompletely understood, because multiple factors could be involved.[14,17]

Angiotensin II constricts both the afferent and efferent arterioles, but preferentially increases efferent resistance. The net effect of the more prominent increase in efferent tone is that the intraglomerular pressure is stable or increased, thereby tending to maintain or even raise GFR. In addition to these arteriolar actions, angiotensin II constricts the mesangial cells an effect that tends to lower the GFR by decreasing the surface area available for filtration. These changes increase the filtration capacity of the remaining nephrons, thus minimizing the functional consequences of nephron loss. Thus, the remnant nephrons function at a relatively higher baseline pressure to maintain stable renal function. However, these adaptive changes are ultimately detrimental.

Benefits of Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers in Chronic Renal Insufficiency

Therapies such as ACE inhibitors and ARBs that attenuate these aforementioned adaptive changes by the nephron could further cause an initial decline in the GFR but minimize structural damage. ACE inhibitors and ARBs, by reducing intraglomerular capillary pressure more effectively than other antihypertensive drugs, consistently protected rats with reduced renal mass[18,19] or diabetes mellitus[16-18] from progressive renal injury.

The effect of ACE inhibitors and ARBs on renal function in the hypertensive patient is related both to the glomerular actions of angiotensin II and to the mechanism of autoregulation of the GFR.[20] In the Angiotensin-Converting Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) trial, patients were randomized to receive antihypertensive therapy that contained either placebo or an ACE inhibitor to achieve blood pressure control.[21] The authors comment on the increased serum creatinine concentration during the first 2 months in the group of patients treated with an ACE inhibitor. Thereafter, it was lower in the ACE inhibitor group compared with placebo during the continuation of the study. A possible mechanism is that blockade of the renin–angiotensin system and decreased blood pressure could lead to a transient, hemodynamically mediated reduction in GFR. This reduction in GFR resulted in improved renal function in the ACE inhibitor-treated group compared with placebo. This increase in creatinine was especially pronounced in participants with a serum creatinine level greater than 177 μmol/L ($>$2.0 mg/dL). However, these participants also had a 66% risk reduction in renal disease progression. This was in contrast to those with a baseline serum creatinine level below 177 μmol/L ($<$2 mg/dL) who had a 38% risk reduction.[22] Likewise in the Ramipril Efficacy in Nephropathy (REIN) trial, participants who had serum creatinine values above 177

μmol/L (>2.0 mg/dL) and more than 3.0 g/day of proteinuria had a 62% risk reduction in renal disease progression.[23] Post-hoc analyses of data from the Modification of Dietary Protein in Renal Disease Trial (MDRD)[24] also supports the concept that those with the baseline lowest GFR had the largest initial reduction in renal function in the presence of an ACE inhibitor. These same participants, however, garnered the greatest overall risk reduction for progression to dialysis.

Regardless of the trial examined, those with the greatest degree of renal insufficiency garner the greatest protection from agents that block the renin–angiotensin–aldosterone system (RAAS) with regard to progression of kidney disease. This is further evidenced by data from participants with type 1 diabetes from the Captopril trial.[5] In this trial patients, whose serum creatinine values were greater than 177 μmol/L (2.0 mg/dL) derived the greatest benefit from ACE inhibition. ACE inhibitor use in this trial resulted in a 74% risk reduction in doubling of serum creatinine and a 75% risk reduction in the incidence of death, dialysis, or transplantation compared with the placebo group. Conversely, patients with a serum creatinine value of less than 88.4 μmol/L (1.0 mg/dL), and similar degrees of blood pressure reduction with the ACE inhibitor, experienced only a 4% risk reduction in doubling of serum creatinine or incidence of death, dialysis, or transplantation.

Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Risk–Benefit Ratio

Patients with proteinuric kidney diseases are, in general, at much higher risk for progression to end-stage kidney disease as well as development of a cardiovascular event. Several randomized clinical trials demonstrate that ACE inhibitors and ARBs not only slow the progression of renal disease in both diabetic and nondiabetic subjects, but are especially beneficial in the subgroup groups with the highest level of proteinuria and lowest level of GFR. This is likely the result of both the reduction in blood pressure and blood pressure-independent effects. The data, however, are limited to persons with serum creatinine values up to 265 μmol/L (3.0 mg/dL) and age 65. This includes studies of patients who have lost more than 75% of their renal function. Thus, no definitive statement can be made about renal outcomes with ACE inhibitors in patients with stage 4 nephropathy, ie, GFR <30 mL/min.

Although theoretically ACE inhibitor can raise the GFR, presumably as a result of reversal of angiotensin II-induced mesangial contraction, in someone with reduced renal function and increased angiotensin II activity, this is generally not observed clinically.[13] Moreover,[25] patients with stage 3 or 4 nephropathy are particularly vulnerable to the effects of ACE inhibitors or ARBs on GFR and other hormonal systems affected by the kidney, eg, erythropoietin and conversion of vitamin D to its active form. Those with GFR values below 30 mL/min will have worsening of anemia and possibly a small reduction in serum calcium with use of these agents.

In addition, in a person with preexisting renal insufficiency, aggressive blood pressure control itself, in the absence of ACE inhibition, could lead to a rise in serum creatinine level as was noted in a subanalysis of the MDRD trial. This blood pressure dependence of renal function results from a loss of renal reserve and autoregulatory ability. Consequently, the nephron fails to maintain the adequate perfusion pressure to sustain GFR in the remnant nephrons.[26,27] Inhibition of the RAS by either an ARB or ACE inhibitor leads to a reversible reduction in intraglomerular pressure in most nephrons.[28] In the case of preexisting renal insufficiency, however, fewer functional nephrons, "remnant nephrons," are present and thus function at a relatively higher baseline pressure to maintain stable renal function.[26] Under these circumstances, if RAAS activity is reduced, the resultant reduction in intraglomerular pressure is proportionally greater in these remnant nephrons. Thus, the fewer the functional nephrons (higher serum creatinine level), the greater the likelihood that GFR will decrease when RAAS activity is reduced. This reduction in renal function might not be reflected as a fall in GFR, however, unless blood pressure falls substantially, ie, at least to levels well below 140/90 mm Hg.[29-31] The change in GFR under these circumstances depends on the amount of autoregulatory ability preserved by the kidney. If autoregulation is not present, then the GFR will change in direct relation to the level of blood pressure.[31,32] The degree of blood pressure reduction necessary to see this effect is variable and depends on a preexistent level of renal function.

Blockade of the RAAS system in patients with normal levels of kidney function have little to no effect on the change in serum creatinine value, although GFR could be slightly reduced. The increase in serum creatinine level can occur within the first 2 weeks after starting therapy. The rise in creatinine concentration generally begins a few days after the institution of therapy, when angiotensin II levels are rapidly reduced in the case of ACE inhibitors or their action blocked by ARBs. This increase in creatinine should stabilize within 4 to 8 weeks. Thus, renal function should be checked within a week after the initiation of an ACE inhibitor or ARB is begun. If the serum creatinine level remains stable within the first month of therapy and blood pressure goal achieved, it is unlikely that there will be any further change in serum creatinine level. However, if the serum creatinine level continues to increase more than 30% to 35% 6 to 8 weeks after therapy, the patient should be evaluated for hypoperfusion states such as volume depletion (initiation or increasing the dose of diuretics or volume depletion from nondiuretic-induced causes such as gastroenteritis), bilateral renal artery stenosis or nonsteroidal antiinflammatory drug use. In the Renoprotective Effect of the Angiotensin-Receptor Antagonist Irbesartan in Patients with Nephropathy Due to Type 2 Diabetes (IDNT) and Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy (RENAAL) trials of ARBs, only four people had a greater than 50% rise in creatinine and were evaluated for renal artery stenosis.[5,33] Three of the four were in the placebo group and no one had documented disease. Thus, elevations in serum phosphorus (as a result of worsening renal function) or potassium levels above 5.6 mmol/L should prompt a reduction in ACE inhibitor or ARB dose, or change to one with a dual mode of excretion (eg, trandolapril or fosinopril), or its discontinuance.[34]

HYPERKALEMIA

The overall incidence of hyperkalemia in patients with normal renal function ranges from 0.1% to 6%, but in patients with stage 3 or greater nephropathy, the incidence increases from 5% to 50%.[35-37] The ability to maintain potassium excretion at near-normal levels is generally maintained in patients with renal disease as long as both aldosterone secretion and distal flow are maintained. Almost all of the filtered potassium is reabsorbed in the proximal tubule and loop of Henle. The major determinant of urinary potassium excretion is the principal cell of the cortical-collecting tubule. The latter step is primarily affected by three factors: (1) the plasma potassium concentration, which can directly stimulate aldosterone release; 2) aldosterone, which is the major hormonal stimulus to distal tubule urinary potassium excretion[38,39]; and 3) the distal delivery of sodium and water. Sodium and water act by maintaining a favorable electrochemical gradient for potassium secretion: sodium reabsorption makes the lumen relatively electronegative with respect to the cell, whereas water delivery minimizes the degree to which potassium secretion will raise the tubular fluid potassium concentration.[55] In addition, dietary intake can also contribute to the hyperkalemia in patients with a reduced ability to excrete potassium as a result of renal insufficiency. Dietary foods high in potassium include a diet high in fruit, especially dried fruit, and vegetable intake or use of a salt substitute.

Several factors contribute to the development of hyperkalemia in the presence of ACE inhibitor use. Treatment with ACE inhibitors or ARBs reduces aldosterone secretion, thereby impairing the efficiency of urinary potassium excretion. ACE inhibitors generally raise the plasma potassium concentration by less than 0.5 meq/L in patients with relatively normal renal function.[40] Reductions in aldosterone production (ACE inhibition) as well as concomitant use of nonsteroidal antiinflammatory agents and/or reduced potassium clearance secondary to reduced GFR are also common contributory factors. It should be noted that greater degrees of hyperkalemia could be seen in patients with renal insufficiency, concurrent use of a drug promoting potassium retention such as a potassium-sparing diuretic or a nonsteroidal antiinflammatory drug, or among the elderly.[35,41]

Several clinical trials that used ACE inhibitors or ARBs for blood pressure control in patients with diabetic or nondiabetic renal disease (serum creatinine levels, 133-265 μmol/L [1.5-3.0 mg/dL]) were examined for the complication of hyperkalemia (Table 1). Taken together these studies demonstrate a very low risk ($<$3%) of hyperkalemia with drugs that block the RAAS when used in patients with moderate to severe renal impairment. Furthermore, the average increase in serum potas-

Table 1. Incidence of Hyperkalemia

Hyperkalemia in Clinical Trials: Impact of ACE inhibitor or ARB Therapy in Patients With Moderate to Severe Renal Impairment (133-265 μmol/L or 1.5-3.0 mg/dL):

	Hyperkalemia			
Study (ref. no.)	ACE or ARB (no.)	Percent	Other (no.)	Percent
AIPRI[22]	5/300	1.7	3/283	1
REIN[23]	1/78	1.3	1/88	1.1
Captopril Trial[4]	3/207	1.4	0/202	0
IDNT[5]	11/579	1.9	3/567;2/569	0.5;0.4
REENAL[41]	8/751	1.1	4/762	0.5
AASK[2]	3/436	0.7	1/441	0.2

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

sium levels was 0.4 to 0.6 mmol/L and were self-limited not requiring discontinuation of the therapy.[5,22]

Predictors of Hyperkalemia

In a case-controlled study, the prevalence and risk factors for hyperkalemia in outpatients who were taking ACE inhibitors were described.[35] Only 194 (11%) of 1818 patients reviewed developed hyperkalemia after receiving a prescription for an ACE inhibitor. Thirty-seven of the 194 patients had potassium levels of 5.6 mmol/L or greater and only three (1.5%) of the 194 had potassium levels of 6 mmol/L or greater. The authors determined that the independent factors *predicting* hyperkalemia were increased creatinine level greater than 1.6 mg/dL, use of a long-acting ACE inhibitor, congestive heart failure, and an increase in serum urea nitrogen level greater that 18 mg/dL. The use of a loop or thiazide diuretic was associated with a decreased risk of hyperkalemia. Once modest hyperkalemia has been identified during the use of ACE inhibitors or ARBs, important predictors of *severe* hyperkalemia (greater that 6.0 mmol/L) are older than 70 years and serum urea nitrogen level higher then 25 mg/dL.

Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers and Hyperkalemia

In patients with moderate chronic renal insufficiency, serum potassium is maintained within the normal range, despite reduced nephron mass, by an increase in potassium excretion by the remaining distal nephrons. The increased potassium excretion is in response to an increase in aldosterone production. Plasma aldosterone level has been documented to increase; as renal function becomes progressively impaired, ACE inhibitors, by blocking angiotensin II formation, can reduce aldosterone production and therefore result in hyperkalemia.[42] However, the use of very low doses of ACE inhibitors could lessen the incidence of hyperkalemia but still provide the renoprotective benefits. In 13 patients with proteinuria and mild renal insufficiency, the incidence of hyperkalemia and the antiproteinuric and antihypertensive effects were evaluated during treatment with low- (1.25 mg/day) and high-dose (10 mg/day) ramipril and placebo.[43] Low-dose ramipril did not alter potassium levels, whereas the higher dose resulted in an increase in the plasma potassium (4.5-4.8 mEq/L, $P < 0.05$). They concluded that low-dose ramipril can reduce proteinuria to the same extent as the higher dose without significantly lowering blood pressure or increasing plasma potassium.

Direct comparisons between the ability of an ACE inhibitor or ARB to increase serum potassium levels was examined in the VAL-K study.[44] In this crossover study involving patients with either normal kidneys or those with chronic renal disease (GFR less than 60 mL/min/1.73 m^2), the ARB in direct comparison with the ACE inhibitor did not significantly increase serum potassium levels. The ACE inhibitor-treated group had a significant increase in serum potassium when compared with an ARB (0.28 mEq/L vs 0.12 meq/L) above the mean baseline level of 4.6 mEq/L. This lower incidence of hyperkalemia with ARBs was observed in another smaller randomized study.[45] The average increase in serum potassium, at the highest dose of an ARB, ranged from 0.05 to 0.3 mmol/L;

the average increase when given an ACE inhibitor was approximately double the ARBs values.[40]

Recent studies have shown that using the combination of an ACE inhibitor and ARB lowers proteinuria to a greater degree than either alone when both are used at high doses. In the combination treatment used in nondiabetic renal disease in the COOPERATE trail, hyperkalemia occurred at a slightly higher rate in the ACE inhibitor group (9.3%) versus the combination group (8.0%) when compared with the ARB group (4.5%). In most cases, however, it was successfully treated with dietary education or a potassium binder.[46]

SIDE EFFECTS

Angiotensin-Converting Enzyme Induce Cough

Cough occurs in 5% to 20% of patients treated with ACE inhibitors. The cough is described as a dry cough that usually begins within 1 to 2 weeks of instituting therapy, but can be delayed up to 6 months.[47] The ACE inhibitor-induced cough is more troublesome and annoying but does not result in pulmonary dysfunction or abnormal pulmonary function tests. Asthmatic patients are not at increased risk.[47] Congestive heart failure patients could have the cough attributed to pulmonary congestion rather than to an adverse reaction to the ACE inhibitor. There is a considerable preponderance of ACE inhibitor cough in women than men. Whether there is an increased incidence of cough in patients with renal insufficiency is not known.

Treatment consists of lowering the dose or discontinuing the ACE inhibitor. Resolution of the cough typically resolves within 1 to 4 days of discontinuing the ACE inhibitor, but can rarely take up to 4 weeks.[48] Although the mechanism of ACE inhibitor-induced cough is not known, involvement of kinins, substance P. prostaglandins, or thromboxanes could be important. Cough does not appear to be a problem with angiotensin II receptor blockers, which have little effect on other hormonal mediators, particularly ACE inhibitor accumulation of bradykinin. It generally recurs with the introduction of the same or a different ACE inhibitor. Therefore, in patients who have had a good antihypertensive response to the ACE inhibitor can be switched to an angiotensin II receptor antagonist. The frequency of cough in patients taking losartan, valsartan, or telmisartan was found to be significantly lower than that observed in patients on lisinopril and comparable with that seen in those on a diuretic or placebo.[49,50]

Angioneurotic Edema and Anaphylactoid Reactions

Angioneurotic edema occurs in 0.1% to 0.7% of patients receiving ACE inhibitors.[47] Angioedema can appear within hours or at most 1 week, but can occur as late as 1 year or more after the onset of therapy.[51] The edema typically is characterized by a well-demarcated swelling of the mouth, tongue, pharynx, and eyelids, and occasionally laryngeal obstruction. Patients should discontinue the drug and call the physician if they develop facial edema or a sore throat independent of an upper respiratory infection. All ACE inhibitors can induce angioneurotic edema, although it is unclear if they do so with same frequency. Angioedema is not related to ACE inhibitor-induced cough, which is much more common among users of ACE inhibitors.

Patients with a history of idiopathic angioedema could be at increased risk for developing angioedema when using an ACE inhibitor. There is a strong association between blacks and an increased risk of angioedema in the presence of ACE inhibitor use. This increase in risk appeared to be unrelated to the dose of ACE inhibitor used or concurrent use of cardiovascular drugs among blacks. Moreover, angioedema appears to be more severe in black users of ACE inhibitors.[52] The incidence of angioedema appears to be lower with ARBs; however, the use of ARBs is not as extensive as compared with ACE inhibitors. Some cases of angioedema have also been reported with ARBs.[49,53] Moreover, those who develop angioedema on an ACE inhibitor have, in a minority of cases, also had it recur with an ARB. Therefore, ARBs are not necessarily a safe alternative for patients with a history of ACE inhibitor-associated angioedema and thus should be used with caution.[54] However, because angioedema can occur with many other substances, a direct causal link is unproven.

Contraindication in Pregnancy

Both ACE inhibitors and angiotensin receptor antagonists are contraindicated during pregnancy, because they are associated with an increased incidence of fetal complications.

CONCLUSIONS

The available clinical evidence suggests that the use of drugs that block the RAAS are appropriate for patients with renal insufficiency. Moreover, ACE inhibitors are specifically indicated for use in patients with renal insufficiency by the JNC 7 as well as all other guideline committees.[1] They have proven therapeutic benefits, particularly in patients with renal insufficiency (ie, serum creatinine level 133-265 μmol/L [1.5-3.0 mg/dL]). The ACE inhibitors and ARBs provide renoprotective effects when used as part of a combination antihypertensive therapy regimen, an effect most prominent in patients with more advanced renal disease. A small rise in serum creatinine level is outweighed by improved long-term renal survival. Once marked elevations in serum creatinine are present and renal reserve is lost (serum creatinine level 265-309 μmol/L [3.0-3.5 mg/dL]) in persons aged $>$60 years and with normal body habitus), the unique benefits of ACE inhibitors might not exceed that of achieving the recommended level of blood pressure reduction alone.

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