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ACE inhibitors and ARBs: Managing potassium and renal function

ABSTRACT

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are used primarily to treat hypertension and are also useful for conditions such as heart failure and chronic kidney disease, independent of their effect on blood pressure. This article reviews the indications for ACE inhibitors and ARBs and offers advice for managing their adverse effects, particularly declining renal function and hyperkalemia.

KEY POINTS

ACE inhibitors and ARBs reduce proteinuria by lowering the intraglomerular pressure, reducing hyperfiltration.

These drugs tend to raise the serum potassium level and reduce the glomerular filtration rate (GFR). Monitoring the serum potassium and creatinine levels and the GFR is therefore imperative.

Despite the benefits, concern for adverse effects including hyperkalemia and a rise in serum creatinine has led to reluctance to prescribe these drugs, and they are underused in the patients who may derive the greatest benefit.

A highly active, water- and alcohol-soluble, basic pressor substance is formed when renin and renin-activator interact, for which we suggest the name “angiotenin.”

—Irvine H. Page and O. M. Helmer, 1940.¹

THE RENIN-ANGIOTENSIN-ALDOSTERONE system regulates salt and, in part, water homeostasis, and therefore blood pressure and fluid balance through its actions on the heart, kidneys, and blood vessels.² Drugs that target this system—angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs)—are used primarily to treat hypertension and also to treat chronic kidney disease and heart failure with reduced ejection fraction.

See related editorial, page 608

Controlling blood pressure is important, as hypertension increases the risk of myocardial infarction, cerebrovascular events, and progression of chronic kidney disease, which itself is a risk factor for cardiovascular disease. However, the benefit of these drugs is only partly due to their effect on blood pressure. They also reduce proteinuria, which is a graded risk factor for progression of kidney disease as well as morbidity and death from vascular events.³

Despite the benefits of ACE inhibitors and ARBs, concern about their adverse effects—especially hyperkalemia and a decline in renal function—has led to their underuse in patients likely to derive the greatest benefit.³

■ ACE INHIBITORS AND ARBs

The renin-angiotensin-aldosterone system is activated when hypoperfusion to the glomerular afferent arteriole, reduced sodium delivery to the distal convoluted tubule, or increased

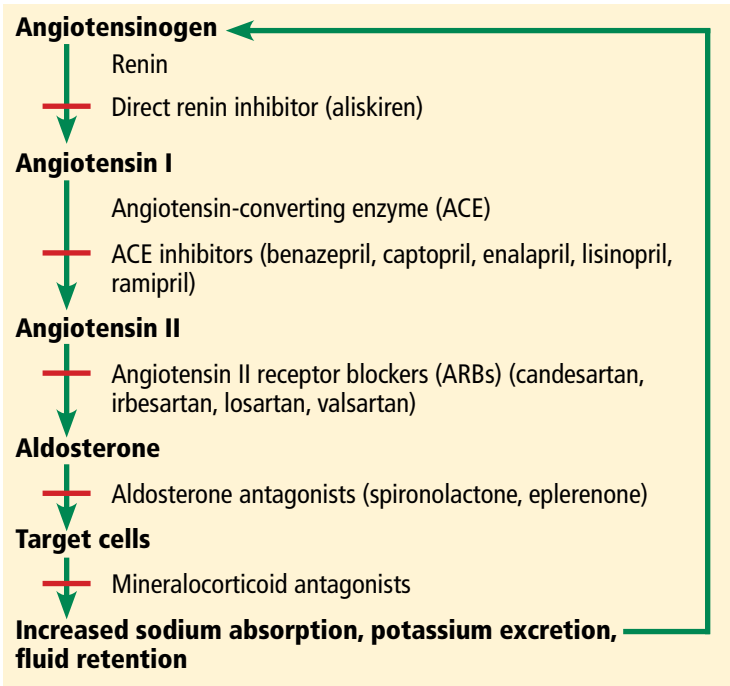


Figure 1. The renin-angiotensin-aldosterone system and drugs that inhibit it.

The benefit of these drugs is only partly due to their effect on blood pressure

sympathetic activity stimulates the renal juxtaglomerular apparatus to produce renin (**Figure 1**). This leads to a cascade of effects culminating in sodium retention and potassium excretion, thus increasing blood pressure.

ACE inhibitors, as their name indicates, inhibit conversion of angiotensin I to angiotensin II by ACE, resulting in vasodilation of the efferent arteriole and a drop in blood pressure. Inhibition of ACE, a kininase, also results in a rise in kinins. One of these, bradykinin, is associated with some of the side effects of this class of drugs such as cough, which affects 5% to 20% of patients.⁴ Elevation of bradykinin is also believed to account for ACE inhibitor-induced angioedema, an uncommon but potentially serious side effect. Kinins are also associated with desirable effects such as lowering blood pressure, increasing insulin sensitivity, and dilating blood vessels.

ARBs were developed as an alternative for patients unable to tolerate the adverse effects of ACE inhibitors. While ACE inhibitors reduce the activity of angiotensin II at both the AT1 and AT2 receptors, ARBs block only the AT1 receptors, thereby inhibiting their vasoconstricting activity on smooth muscle. ARBs

also raise the levels of renin, angiotensin I, and angiotensin II as a result of feedback inhibition. Angiotensin II is associated with release of inflammatory mediators such as tumor necrosis factor alpha, cytokines, and chemokines, the consequences of which are also inhibited by ARBs, further preventing renal fibrosis and scarring from chronic inflammation.³

What is the evidence supporting the use of ACE inhibitors and ARBs?

ACE inhibitors and ARBs, used singly, reduce blood pressure and proteinuria, slow progression of kidney disease, and improve outcomes in patients who have heart failure, diabetes mellitus, or a history of myocardial infarction.^{5–11}

While dual blockade with the combination of an ACE inhibitor and an ARB lowers blood pressure and proteinuria to a greater degree than monotherapy, dual blockade has been associated with higher rates of complications, including hyperkalemia.^{12–17}

RISK FACTORS FOR HYPERKALEMIA

ACE inhibitors and ARBs raise potassium, especially when used in combination. Other risk factors for hyperkalemia include the following—and note that some of them are also indications for ACE inhibitors and ARBs:

Renal insufficiency. The kidneys are responsible for over 90% of potassium removal in healthy individuals,^{18,19} and the lower the GFR, the higher the risk of hyperkalemia.^{3,20,21}

Heart failure

Diabetes mellitus^{6,21–23}

Endogenous potassium load due to hemolysis, rhabdomyolysis, insulin deficiency, lactic acidosis, or gastrointestinal bleeding

Exogenous potassium load due to dietary consumption or blood products

Other medications, eg, sacubitril-valsartan, aldosterone antagonists, mineralocorticoid receptor antagonists, potassium-sparing diuretics, beta-adrenergic antagonists, non-steroidal anti-inflammatory drugs, heparin, cyclosporine, trimethoprim, digoxin

Hypertension

Hypoaldosteronism (including type 4 renal tubular acidosis)

Addison disease

Advanced age

Lower body mass index.

Both hypokalemia and hyperkalemia are associated with a higher risk of death,^{20,21,24} but in patients with heart failure, the survival benefit from ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists outweighs the risk of hyperkalemia.^{25–27} Weir and Rolfe²⁸ concluded that patients with heart failure and chronic kidney disease are at greatest risk of hyperkalemia from renin-angiotensin-aldosterone system inhibition, but the increases in potassium levels are small (about 0.1 to 0.3 mmol/L) and unlikely to be clinically significant.

Hyperkalemia tends to recur. Einhorn et al²⁰ found that nearly half of patients with chronic kidney disease who had an episode of hyperkalemia had 1 or more recurrent episodes within a year.

■ ACE INHIBITORS, ARBs, AND RENAL FUNCTION

Another concern about using ACE inhibitors and ARBs, especially in patients with chronic kidney disease, is that the serum creatinine level tends to rise when starting these drugs,²⁹ although several studies have shown that an acute rise in creatinine may demonstrate that the drug is actually protecting the kidney.^{30,31} Hirsch³² described this phenomenon as “pre-renal success,” proposing that the decline in GFR is hemodynamic, secondary to a fall in intraglomerular pressure as a result of efferent vasodilation, and therefore should not be reversed.

Schmidt et al,^{33,34} in a study in 122,363 patients who began ACE inhibitor or ARB therapy, found that cardiorenal outcomes were worse, with higher rates of end-stage renal disease, myocardial infarction, heart failure, and death, in those in whom creatinine rose by 30% or more since starting treatment. This trend was also seen, to a lesser degree, in those with a smaller increase in creatinine, suggesting that even this group of patients should receive close monitoring.

Whether renin-angiotensin-aldosterone system inhibitors provide a benefit in advanced progressive chronic kidney disease remains unclear.^{35–37} The Angiotensin Converting Enzyme Inhibitor (ACEi)/Angiotensin Receptor Blocker (ARB) Withdrawal in Advanced Renal Disease trial (STOP-ACEi),³⁸

currently under way, will provide valuable data to help close this gap in our knowledge. This open-label randomized controlled trial is testing the hypothesis that stopping ACE inhibitor or ARB treatment, or a combination of both, compared with continuing these treatments, will improve or stabilize renal function in patients with progressive stage 4 or 5 chronic kidney disease.

■ NEED FOR MONITORING

Taken together, the above data suggest close and regular monitoring is required in patients receiving these drugs. However, monitoring tends to be lax.^{34,37,39} A 2017 study of adherence to the guidelines for monitoring serum creatinine and potassium after starting an ACE inhibitor or ARB and subsequent discontinuation found that fewer than 10% of patients had follow-up within the recommended 2 weeks after starting these drugs.³⁴ Most patients with a creatinine rise of 30% or more or a potassium level higher than 6.0 mmol/L continued treatment. There was also no evidence of increased monitoring in those deemed at higher risk of these complications.

■ WHAT DO THE GUIDELINES SUGGEST?

ACE inhibitors and ARBs in chronic kidney disease and hypertension

Target blood pressures vary in guidelines from different organizations.^{4,40–45} The 2017 joint guidelines of the American College of Cardiology and American Heart Association (ACC/AHA)⁴⁰ recommend a target blood pressure of 130/80 mm Hg or less in all patients irrespective of the level of proteinuria and whether they have diabetes mellitus, based on several studies.^{46–48} In the elderly, other factors such as the risk of hypotension and falls must be taken into consideration in establishing the most appropriate blood pressure target.

In general, a renin-angiotensin-aldosterone system inhibitor is recommended if the patient has diabetes, stage 1, 2, or 3 chronic kidney disease, or proteinuria. For example, the guidelines recommend a renin-angiotensin-aldosterone system inhibitor in diabetic patients with albuminuria.

None of the guidelines recommend routine use of combination therapy.

**Cough affects
5% to 20%
of patients
who take
ACE inhibitors**

The kidneys are responsible for > 90% of potassium removal in healthy individuals

ACE inhibitors and ARBs in heart failure

The 2017 ACC/AHA and Heart Failure Society of America (HFSA) guidelines for heart failure⁴⁹ recommend an ACE inhibitor or ARB for patients with stage C (symptomatic) heart failure with reduced ejection fraction, in view of the known cardiovascular morbidity and mortality benefits.

The European Society of Cardiology⁵⁰ recommends ACE inhibitors for patients with symptomatic heart failure with reduced ejection fraction, as well as those with asymptomatic left ventricular systolic dysfunction. In patients with stable coronary artery disease, an ACE inhibitor should be considered even with normal left ventricular function.

ARBs should be used as alternatives in those unable to tolerate ACE inhibitors.

Combination therapy should be avoided due to the increased risk of renal impairment and hyperkalemia but may be considered in patients with heart failure and reduced ejection fraction in whom other treatments are unsuitable. These include patients on beta-blockers who cannot tolerate mineralocorticoid receptor antagonists such as spironolactone. Combination therapy should be done only under strict supervision.⁵⁰

Starting ACE or ARB therapy

Close monitoring of serum potassium is recommended during ACE inhibitor or ARB use. Those at greatest risk of hyperkalemia include elderly patients, those taking other medications associated with hyperkalemia, and diabetic patients, because of their higher risk of renovascular disease.

Caution is advised when starting ACE inhibitor or ARB therapy in these high-risk groups as well as in patients with potassium levels higher than 5.0 mmol/L at baseline, at high risk of prerenal acute kidney injury, with known renal insufficiency, and with previous deterioration in renal function on these medications.^{3,41,51}

Before starting therapy, ensure that patients are volume-replete and measure baseline serum electrolytes and creatinine.^{41,51}

The ACC/AHA and HFSA recommend starting at a low dose and titrating upward slowly. If maximal doses are not tolerated, then a lower dose should be maintained.⁴⁹ The

European Society of Cardiology guidelines⁵² suggest increasing the dose at no less than every 2 weeks unless in an inpatient setting. Blood testing should be done 7 to 14 days after starting therapy, after any titration in dosage, and every 4 months thereafter.⁵³

The guidelines generally agree that a rise in creatinine of up to 30% and a fall in eGFR of up to 25% is acceptable, with the need for regular monitoring, particularly in high-risk groups.^{40–42,51,52}

What if serum potassium or creatinine rises during treatment?

If hyperkalemia arises or renal function declines by a significant amount, one should first address contributing factors. If no improvement is seen, then the dose of the ACE inhibitor or ARB should be reduced by 50% and blood work repeated in 1 to 2 weeks. If the laboratory values do not return to an acceptable level, reducing the dose further or stopping the drug is advised.

Give dietary advice to all patients with chronic kidney disease being considered for a renin-angiotensin-aldosterone system inhibitor or for an increase in dose with a potassium level higher than 4.5 mmol/L. A low-potassium diet should aim for potassium intake of less than 50 or 75 mmol/day and sodium intake of less than 60 mmol/day for hypertensive patients with chronic kidney disease.

Review the patient's medications if the baseline potassium level is higher than 5.0 mmol/L. Consider stopping potassium-sparing agents, digoxin, trimethoprim, and nonsteroidal anti-inflammatory drugs. Also think about starting a non-potassium-sparing diuretic as well as sodium bicarbonate to reduce potassium levels. Blood work should be repeated within 2 weeks after these changes.

Do not start a renin-angiotensin-aldosterone system inhibitor, or do not increase the dose, if the potassium level is elevated until measures have been taken to reduce the degree of hyperkalemia.⁵¹

In renal transplant recipients, renin-angiotensin-aldosterone system inhibitors are often preferred to manage hypertension in those who have proteinuria or cardiovascular disease. However, the risk of hyperkalemia is also greater with concomitant use of immu-

TABLE 1

Our advice for managing patients receiving ACE inhibitors or ARBs**Before starting or changing the dose**

Review medications

Check baseline blood values of potassium, bicarbonate, and creatinine; assess proteinuria

Ensure patient is volume-replete

Do not start or increase the dose of a renin-angiotensin-aldosterone system inhibitor if serum potassium is elevated

Use an ACE inhibitor or ARB cautiously; start with a low dose and titrate upward slowly every 2 weeks if creatinine rises < 30% from baseline and GFR drops < 25%

Reduce dose if maximal doses are not tolerated (see below)

Repeat blood testing 10–14 days after starting or changing the dose

Check potassium and renal function after each dose escalation

If serum potassium is persistently > 5.0 mmol/L

Give dietary advice

Review medications again

Consider a thiazide or loop diuretic to reduce potassium level

Consider adding sodium bicarbonate if serum bicarbonate level is < 22 mmol/L

Remeasure potassium after 10–14 days

If < 5.0 mmol/L, continue

If 5.0–5.5 mmol/L, reduce dose and monitor closely

if > 5.5 mmol/L, consider stopping

If renal function declines, ie, if creatinine rises > 30% from baseline or GFR drops > 25%

after starting an ACE inhibitor or ARB:

Investigate for any other underlying cause, eg, bilateral renal artery stenosis

Repeat blood tests after 10–14 days

If no improvement, reduce dose by 50%

If still no improvement, reduce the dose further or stop the drug

For patients with illness or dehydration

Temporarily stop the ACE inhibitor or ARB, diuretics, and other antihypertensive and nephrotoxic drugs

Avoid medications that may impair renal function

Restart once symptoms resolve and the patient is rehydrated and biochemically stable

Recheck renal function after starting to ensure it remains stable

Ongoing monitoring

Continue to monitor once patient is established and stabilized on treatment with an ACE inhibitor or ARB according to the stage of their chronic kidney disease and heart failure, their medication history, and clinical condition. Monitoring every 3–6 months, as well as when patients have an intercurrent illness, is usually adequate.

ACE = angiotensin-converting enzyme, ARB = angiotensin II receptor blocker

An acute rise in creatinine may show that the drug is actually protecting the kidney

nosuppressive drugs such as tacrolimus and cyclosporine. Management of complications should be approached according to guidelines discussed above.⁵¹

Monitor renal function, potassium. The National Institute for Health and Care Excellence guideline⁵⁴ advocates that baseline renal function testing should be followed by repeat blood testing 1 to 2 weeks after starting renin-angiotensin-aldosterone system inhibitors in patients with ischemic heart disease. The

advice is similar when starting therapy in patients with chronic heart failure, emphasizing the need to monitor after each dose increment and to use clinical judgment when deciding to start treatment. The AHA advises caution in patients with renal insufficiency or a potassium level above 5.0 mmol/L.⁴⁹

Sick day rules. The National Institute for Health and Care Excellence encourages discussing “sick day rules” with patients starting renin-angiotensin-aldosterone system inhibi-

tors. This means patients should be advised to temporarily stop taking nephrotoxic medications, including over-the-counter nonsteroidal anti-inflammatory drugs, in any potential state of illness or dehydration, such as diarrhea and vomiting. There is, however, little evidence that this advice can actually reduce the incidence of acute kidney injury.^{55,56}

Potassium-lowering agents. Evidence is emerging to support the use of potassium-lowering agents to manage hyperkalemia. New compounds such as patiromer and zirconium cyclosilicate bind potassium in the gastrointestinal tract so it is excreted fecally. Meaney

et al⁵⁶ performed a systematic review and meta-analysis of current phase 2 and 3 trials and concluded that these drugs lowered serum potassium levels by up to 0.70 mmol/L. There may be a significant role for these novel agents in diseases such as chronic kidney disease and heart failure, in which hyperkalemia is the limiting factor in the use of renin-angiotensin-aldosterone system inhibitors.⁵⁷

OUR RECOMMENDATIONS

Our advice for managing patients receiving ACE inhibitors or ARBs is summarized in Table 1.

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