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RESEARCH ARTICLE
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EFFECT OF ACE INHIBITORS ON RENAL SALT REGULATION

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Abstract

Introduction: ACE inhibitors are currently among the most widely prescribed classes of antihypertensive medications. Their application has expanded to include the long-term care of patients with congestive heart failure (CHF) and both diabetic and nondiabetic nephropathies, in addition to their effectiveness in managing hypertension. The use of ACE inhibitor therapy has been linked to a syndrome known as "functional renal insufficiency" and/or hyperkalemia, despite the fact that it typically improves renal blood flow (RBF), sodium excretion rates in CHF, and the rate at which renal damage progresses in chronic renal disease. Treatment with furosemide and ACE inhibitors together may be used to treat dilutional hyponatremia. The correction of azotemia and an increase in low serum sodium values can occur when ACE inhibitor doses are carefully titrated to prevent severe hypotension. The primary causes of these effects are decreased thirst and ADH release.

Aim of the study: This article discusses the uses of ACE inhibitors and provides guidance on how to manage side effects, and renal salt regulation such as hyperkalemia and deteriorating renal function.

Methodology: The study is a comprehensive research of PUBMED since the year 1990 to 2019.

Conclusion: Angiotensin-converting enzyme (ACE) inhibitors have a wide range of effects on renal hemodynamics, depending on the kidneys' underlying physiologic and pathologic conditions. It's still debatable whether ACE inhibitors should be used to treat renovascular hypertension. ACE inhibition has the potential to impair the angiotensin II-mediated autoregulation of GFR and worsen renal function, particularly in individuals with bilateral renal artery stenosis or stenosis of a single kidney. As long as ACE inhibitor and diuretic dosages are adjusted to prevent systemic hypotension and

sodium and fluid depletion, ACE inhibitors can generally be started cautiously and used safely in CHF patients.
There are no overt adverse effects of ACE inhibitors on the kidneys' ability to handle salt and water. However, the patient's capacity to enhance sodium reabsorption and retain water is compromised during severe dehydration and salt deprivation. As a result, in these circumstances, ACE inhibitors should be stopped or used carefully.

Keywords: ACE inhibitors, Renal salt regulation, renal hemodynamic, congestive heart failure

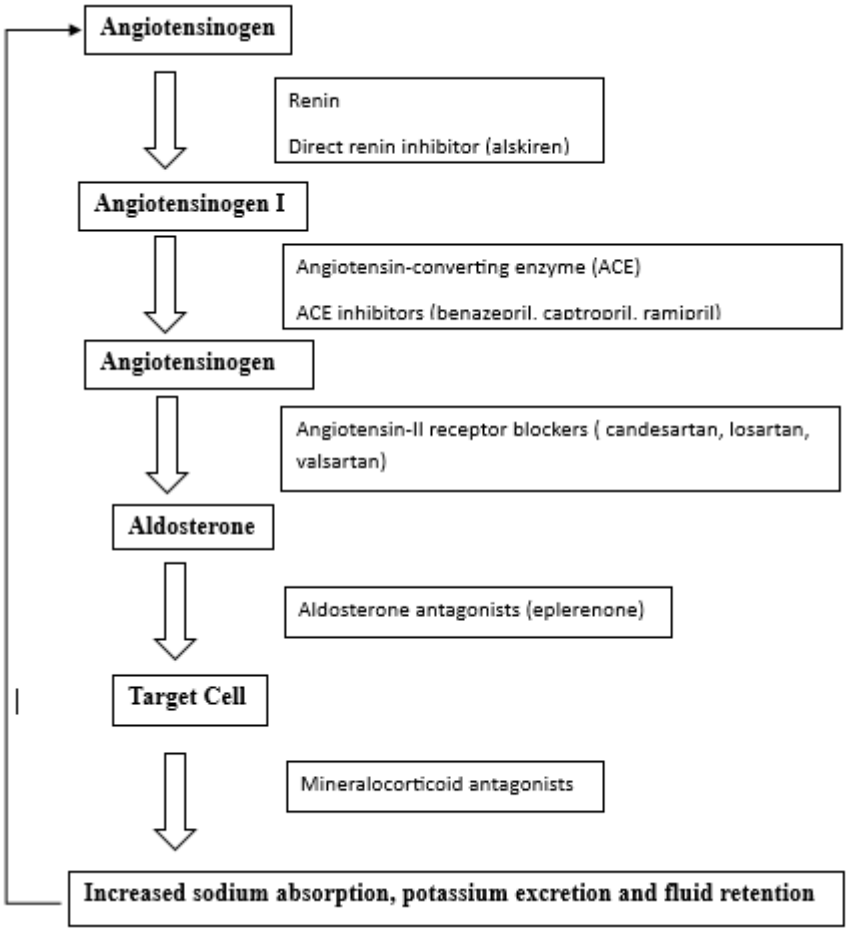
Introduction

In recent years, there has been a rise in awareness regarding the role of the renin-angiotensin system (RAS) in the salt and water manifestation of congestive heart failure (CHF). The knowledge of how angiotensin II (A a) influences perfusion and function has contributed to the use of angiotensin I converting enzyme inhibitors (A-). The renin-angiotensin-aldosterone system controls blood pressure and fluid balance as well as salt and, to some extent, water homeostasis by influencing the heart, kidneys, and blood vessels. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are two medications that target this system and are mainly used to treat hypertension, chronic kidney disease, and heart failure with a reduced ejection fraction.[1]
It is crucial to control blood pressure because high blood pressure raises the risk of myocardial infarction, cerebrovascular accidents, and the advancement of chronic kidney disease, which is a risk factor for cardiovascular disease in and of itself. Nevertheless, these medications' effects on blood pressure account for only a portion of their benefits. They also lessen the risk of kidney disease progression, morbidity, and death from vascular events associated with proteinuria, a graded risk factor. [2]
Even though ACE inhibitors have many advantages, patients who stand to gain the most from them are not using them because of worries about side effects, particularly hyperkalemia and decreased renal function.[2]

Mechanism of ACE inhibitors

When the renal juxtaglomerular apparatus is stimulated to produce renin by hypoperfusion to the glomerular afferent arteriole, reduced sodium delivery to the distal convoluted tubule, or increased sympathetic activity, the renin-angiotensin-aldosterone system is triggered. This sets off a series of events that eventually result in potassium excretion and sodium retention, raising blood pressure.[3]
As the name suggests, ACE inhibitors prevent angiotensin I from being converted to angiotensin II by ACE, which lowers blood pressure and causes the efferent arteriole to vasodilate. Kinins are also increased when the kininase ACE is inhibited. Among these, bradykinin is linked to a few of the adverse effects of this medication class, including cough, which affects 5% to 20% of individuals. Another uncommon but potentially dangerous side effect of ACE inhibitors is angioedema, which is thought to be caused by elevated bradykinin. Additionally linked to positive outcomes include dilating blood vessels, raising insulin sensitivity, and lowering blood pressure are kinins. [3]
As a stand-in for patients who cannot withstand the side effects of ACE inhibitors, ARBs were created. ARBs only block the AT1 receptors, preventing the vasoconstricting action of angiotensin II on smooth muscle, in contrast to ACE inhibitors, which decrease angiotensin II activity at both the AT1 and AT2 receptors. Due to feedback inhibition, ARBs also increase the levels of renin, angiotensin I, and angiotensin II. ARBs further prevent renal fibrosis and scarring from chronic inflammation by inhibiting the release of inflammatory mediators like tumor necrosis factor-alpha, cytokines, and chemokines that are linked to angiotensin II. [2]
ACE inhibitors improve outcomes for patients with heart failure, diabetes mellitus, or a history of myocardial infarction. They also lower blood pressure and proteinuria and slow the progression of kidney disease. Dual blockade, which combines the effects of an ACE inhibitor and an ARB, is more effective than monotherapy in lowering blood pressure and proteinuria; however, it is also associated with a higher risk of complications, such as hyperkalemia.[4,5]

The drugs that inhibit the renin-angiotensin-aldosterone system:[6]



ACE Inhibitors and Renal Function

The serum creatinine level tends to rise when ACE inhibitors are started, which is concerning for patients with chronic kidney disease in particular. However, a number of studies have shown that an acute rise in creatinine may be an indication that the medication is actually protecting the kidney. Hirsch called this phenomenon "prerenal success," arguing that it is not appropriate to reverse the hemodynamic decline in GFR because it is secondary to a decrease in intraglomerular pressure brought on by efferent vasodilation.[7,8]

In a study involving 122,363 patients who started ACE inhibitor therapy, Schmidt et al. discovered that patients whose creatinine increased by 30% or more since beginning treatment had worse cardiorenal outcomes, including increased rates of myocardial infarction, heart failure, and death. Even this patient group should be closely monitored, as this trend was also observed, albeit to a lesser extent, in those whose creatinine increased less.[9]

It is unknown if renin-angiotensin-aldosterone system inhibitors help patients with advanced progressive chronic kidney disease. This knowledge gap will be filled in part by the Angiotensin Converting Enzyme Inhibitor (ACEi)/Angiotensin Receptor Blocker (ARB) Withdrawal in Advanced Renal Disease trial (STOP-ACEi), which is presently underway. In patients with progressive stage 4 or 5 chronic kidney disease, this open-label randomized controlled trial is testing the hypothesis that stopping treatment with ACE inhibitors, ARBs, or both, will improve or stabilise renal function when compared with continuing these treatments.[10,11]

Acute renal failure (ARF) is characterized by a sudden decrease in renal function, typically accompanied by an increase in serum creatinine levels. A useful working definition of ARF is an increase of ≥0.5 mg/dL (44 μmol/L) if the serum creatinine was initially <2.0 mg/dL or ≥1.0 mg/dL if it was above 2.0 mg/dL. However, there is no exact definition for ARF. When ACE inhibitor therapy is started or in patients receiving chronic ACE inhibitor therapy, especially in those with CHF, renal

function may deteriorate abruptly. Even after months or years of uneventful ACE inhibitor therapy, ARF can still develop. Regarding the latter issue, not much has been written up to this point. Furthermore, it can be challenging to interpret changes in renal function as measured by serum creatinine levels in patients with chronic heart failure (CHF) who take ACE inhibitor medication.[11,12]

One or more of the four mechanisms are at play in the majority of patients who experience ARF in this context:[14]

1. Insufficient MAP for adequate renal perfusion
- inadequate cardiac output
- minimal resistance to systemic vascular flow
2. Depletion of Volume (using diuretics)
3. Renal Vascular Diseases
- Renal artery stenosis on both sides
- Single or dominant kidney stenosis
- Afferent arteriolar narrowing caused by cyclosporin A and hypertension
- In smaller renal arteries, diffuse atherosclerosis
4. Vasoconstrictor agents

When mean arterial pressure (MAP) drops to a point where it is either insufficient to maintain renal perfusion or causes a significant reflex activation of the renal sympathetic nervous system, ACE inhibitor therapy will cause ARF. Apart from inducing an abrupt drop in Ang II levels, ACE inhibitor treatment can also cause hypotension through alternative pathways, such as a rise in prostaglandins that promote vasodilation and/or a reduction in total peripheral resistance in a situation where the cardiomyopathy may not significantly alter cardiac output. [15]

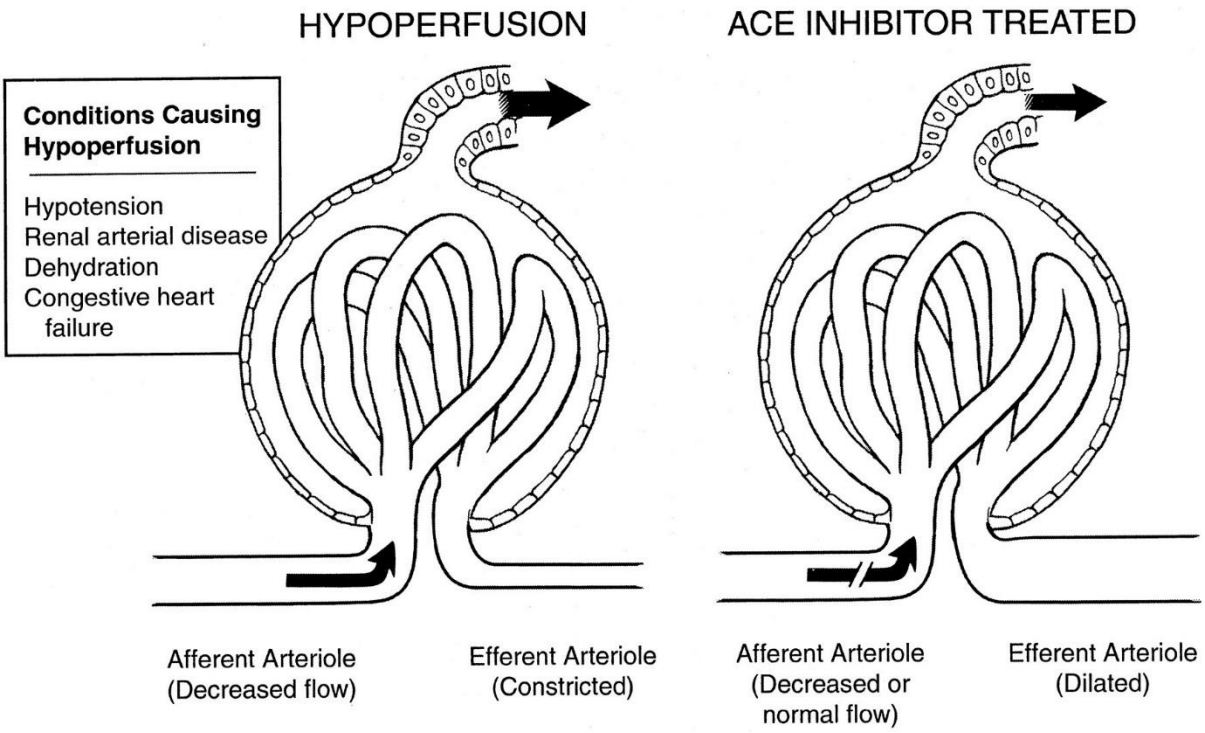


Fig. 1 Diagrammatic representation of the situations in which renal function may deteriorate as a result of ACE inhibitor therapy. Renal hypoperfusion can be caused by a number of conditions, such as CHF, high-grade renal artery stenosis, ECF volume contraction (which is represented in the figure as "dehydration"), systemic hypotension, and the administration of vasoconstrictor drugs, such as NSAIDs or cyclosporine (not shown). [15]

Compared to patients with normal renal function, patients with chronic renal insufficiency of any cause have a higher risk of ACE inhibitor-induced ARF. In fact, patients with a low number of surviving nephrons exhibit adaptive modifications, such as a hyperfiltration response, that preserve GFR. Due to predominant efferent arteriolar vasodilatation and a decrease in glomerular capillary pressure, the reversal of glomerular hyperfiltration is thought to be a significant contributing factor to the positive long-term effect of ACE inhibitor therapy in these patients. Thus, in patients with chronic renal insufficiency, ACE inhibitor therapy reversing hyperfiltration will unavoidably cause an initial decline in GFR and an increase in blood urea nitrogen and serum creatinine. [16]
When chronic ACE inhibitor use is present, ARF typically suggests altered systemic hemodynamics or altered extracellular fluid volume. In relation to the dominant effect of Ang II on the efferent glomerular arteriole, maintenance of GFR becomes dependent upon Ang II during renal hypoperfusion or significant volume depletion. If and when Ang II generation is checked, a number of factors, including sepsis, severe hyperglycemia with osmotic diuresis, diarrhea, and worsening of CHF with a decrease in cardiac output, can tip the renal hemodynamic balance and make it impossible to maintain GFR.[15]

Risk Factors for Hyperkalemia

Potassium is elevated by ACE inhibitors, particularly in combination. The following are additional risk factors for hyperkalemia; take note that some of these are also signs that an ACE inhibitor may be necessary: [17,18]

1. Inadequate renal function In healthy people, the kidneys remove more than 90% of the potassium from the body; the risk of hyperkalemia increases with decreasing GFR.
2. Heart attack
3. Type 1 diabetes
4. Endogenous potassium load brought on by lactic acidosis, hemolysis, rhabdomyolysis, insulin insufficiency, or gastrointestinal bleeding
5. Exogenous potassium load brought on by eating certain foods or using blood products
6. Additional medication, such as beta-adrenergic antagonists, potassium-sparing diuretics, aldosterone antagonists, mineralocorticoid receptor antagonists, sacubitril-valsartan, non-steroidal anti-inflammatory drugs, heparin, cyclosporine, trimethoprim, and digoxin
7. Hypertension
8. Hypoaldosteronism (including type 4 renal tubular acidosis)
9. Addison disease
10. Advanced age
11. Lower body mass index.

While both hypokalemia and hyperkalemia are linked to an increased risk of death, ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists are more beneficial in terms of survival for patients with heart failure than they are in terms of lowering the risk of hyperkalemia. The renin-angiotensin-aldosterone system inhibition that causes hyperkalemia is most likely to affect patients with heart failure and chronic kidney disease, according to Weir and Rolfe However, these patients are unlikely to experience clinically significant hyperkalemia because the increases in potassium levels are small (about 0.1 to 0.3 mmol/L). Hyperkalemia frequently reappears. Nearly half of the patients with chronic kidney disease who experienced an episode of hyperkalemia also experienced one or more recurrent episodes within a year, according to research by Einhorn et al [19,20]

Monitoring and Guidelines for ACE inhibitors

Less than 10% of patients had follow-up within the recommended 2-week period after starting an ACE inhibitor or ARB, according to a 2017 study on adherence to the guidelines for monitoring serum creatinine and potassium after starting these drugs and then discontinuing them. Most patients who experienced a 30% increase in creatinine or a potassium level greater than 6.0 mmol/L persisted in

receiving treatment. Furthermore, no proof of heightened surveillance in individuals identified as being more susceptible to these issues was found.[9]

Kidney diseases and Hypertension:
Guidelines for target blood pressure differ amongst organizations. Based on multiple studies, the 2017 American College of Cardiology and American Heart Association (ACC/AHA) joint guidelines recommend a target blood pressure of 130/80 mm Hg or less in all patients, regardless of their degree of proteinuria or diabetes mellitus. When choosing the best blood pressure target for the elderly, it's important to take into account additional factors like their risk of hypotension and falls.[21]

Heart Failure:
Given the established benefits for cardiovascular morbidity and mortality, patients with stage C (symptomatic) heart failure and a reduced ejection fraction are advised to take an ACE inhibitor or an ARB, according to the 2017 ACC/AHA and Heart Failure Society of America (HFSA) guidelines for heart failure.[22]
Patients with asymptomatic left ventricular systolic dysfunction and those with symptomatic heart failure with reduced ejection fraction are advised to take ACE inhibitors, according to the European Society of Cardiology. Even in patients with normal left ventricular function who have stable coronary artery disease, an ACE inhibitor should be taken into consideration.[23]
When an individual cannot tolerate ACE inhibitors, ARBs should be considered as a backup option.
Combination therapy should be avoided because of the higher risk of hyperkalemia and renal impairment; however, patients who have heart failure and a low ejection fraction and for whom other treatments are not appropriate may want to consider it. Among them are people taking beta-blockers and those who are intolerant to spironolactone or other mineralocorticoid receptor antagonists. It is only appropriate to use combination therapy under close supervision.[18]

Condition when serum potassium or creatinine rises during treatment:
The presence of hyperkalemia or a marked decline in renal function should prompt the identification and treatment of underlying causes. If there is no improvement, the blood work should be repeated in a week or two and the dosage of the ACE inhibitor or ARB should be lowered by 50%. It is advised to stop taking the medication altogether or to further reduce the dosage if the laboratory results do not return to an acceptable level. [18]
All patients with chronic kidney disease who are being evaluated for a renin-angiotensin-aldosterone system inhibitor or a dose increase if their potassium level is greater than 4.5 mmol/L should be given dietary advice. For hypertensive patients with chronic kidney disease, a low-potassium diet should aim for a potassium intake of less than 50 or 75 mmol/day and a sodium intake of less than 60 mmol/day. [18]
If the patient's baseline potassium level is greater than 5.0 mmol/L, review the patient's prescription regimen. Digoxin, trimethoprim, potassium-sparing medications, and nonsteroidal anti-inflammatory drugs should all be stopped. To lower potassium levels, begin taking sodium bicarbonate and a non-potassium-sparing diuretic. Two weeks following these modifications, blood work should be repeated. [18]
If the potassium level is elevated, wait to start a RAAS inhibitor or increase the dosage until steps have been taken to lessen the severity of hyperkalemia.
Renin-angiotensin-aldosterone system inhibitors are frequently chosen by recipients of renal transplants to treat hypertension in patients with proteinuria or cardiovascular disease. Nevertheless, concurrent use of immunosuppressive medications like tacrolimus and cyclosporine increases the risk of hyperkalemia. The above-discussed guidelines should be followed when managing complications.[24]
Monitor potassium and renal function - In patients with ischemic heart disease, the National Institute for Health and Care Excellence guideline54 recommends that repeat blood work be done one to two weeks after beginning renin-angiotensin-aldosterone system inhibitors. This baseline renal function

testing should be followed. When beginning therapy in patients with chronic heart failure, the recommendations are similar, stressing the need for monitoring following each dose increase and the application of clinical judgment in initiating treatment. Patients with renal insufficiency or a potassium level greater than 5.0 mmol/L are advised to use caution, according to the AHA.[18,22]
Agents that lower potassium - There is growing evidence to support the management of hyperkalemia with potassium-lowering medications. Potassium is bound by new substances like patiromer and zirconium cyclosilicate in the digestive system, causing it to be expelled from feces. A systematic review and meta-analysis of ongoing phase 2 and 3 trials was conducted by Meaney et al.56, who came to the conclusion that these medications could reduce serum potassium levels by as much as 0.70 mmol/L. These new medications may play a big part in treating conditions like heart failure and chronic kidney disease, where the use of renin-angiotensin-aldosterone system inhibitors is restricted by hyperkalemia.[25]

Conclusion

ACE inhibitors are used for the treatment of hypertension, which is a major risk factor for heart failure, stroke, coronary disease, and several other cardiovascular disorders. By decreasing the intraglomerular pressure and thereby decreasing hyperfiltration, ACE inhibitors, and ARBs lessen proteinuria. These medications often cause a decrease in the glomerular filtration rate (GFR) and an increase in serum potassium levels. It is therefore essential to monitor the serum potassium and creatinine levels as well as the GFR. Despite the advantages, doctors are reluctant to prescribe these medications due to fear of side effects, such as hyperkalemia and an increase in serum creatinine, which means that the patients who stand to gain the most from them are not getting enough of them.

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