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Renal Considerations in Angiotensin Converting Enzyme Inhibitor Therapy

A Statement for Healthcare Professionals From the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association

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Angiotensin converting enzyme (ACE) inhibitors are now one of the most frequently used classes of antihypertensive drugs. Beyond their utility in the management of hypertension, their use has been extended to the long-term management of patients with congestive heart failure (CHF), as well as diabetic and nondiabetic nephropathies. Although ACE inhibitor therapy usually improves renal blood flow (RBF) and sodium excretion rates in CHF and reduces the rate of progressive renal injury in chronic renal disease, its use can also be associated with a syndrome of "functional renal insufficiency" and/or hyperkalemia. This form of acute renal failure (ARF) most commonly develops shortly after initiation of ACE inhibitor therapy but can be observed after months or years of therapy, even in the absence of prior ill effects. ARF is most likely to occur when renal perfusion pressure cannot be sustained because of substantial decreases in mean arterial pressure (MAP) or when glomerular filtration rate (GFR) is highly angiotensin II (Ang II) dependent. Conditions that predict an adverse hemodynamic effect of ACE inhibitors in patients with CHF are preexisting hypotension and low cardiac filling pressures. The GFR is especially dependent on Ang II during extracellular fluid (ECF) volume depletion, high-grade bilateral renal artery stenosis, or stenosis of a dominant or single kidney, as in a renal transplant recipient. Understanding the pathophysiological mechanisms and the common risk factors for ACE inhibitor-induced functional ARF is critical, because preventive strategies for ARF exist, and if effectively used, they may permit use of these compounds in a less restricted fashion.

Renal and Systemic Effects of Ang II During Volume Depletion and CHF

Under normal physiological conditions, renal autoregulation adjusts renal vascular resistance, so that RBF and GFR remain constant over a wide range of MAPs.¹ The intrinsic renal autoregulation mechanism is adjusted by Ang II and the sympathetic nervous system. When renal perfusion pressure falls (as in hypovolemia or CHF), the sympathetic nervous system is activated and renin is secreted from juxtaglomerular cells of afferent arterioles, with consequent Ang II production. At the level of the renal glomerulus, Ang II can be expected to cause vasoconstriction of postglomerular efferent to a much greater degree than preglomerular afferent arterioles. This imbalance of effect on the efferent arteriolar circulation restores glomerular capillary pressure and thereby maintains glomerular filtration despite reduced perfusion pressure. Under these circumstances, filtration fraction (GFR/renal plasma flow) increases, which favors proximal tubular Na⁺ reabsorption.

Ang II also independently promotes proximal tubule Na⁺ reabsorption and, through its effect on aldosterone synthesis, collecting duct Na⁺ reabsorption.² In the presence of excess Ang II, as in CHF, urinary Na⁺ excretion can be expected to fall dramatically, although other factors, such as low blood pressure, make important contributions to the antinatriuretic state that is characteristic of CHF. Ang II is also a proven dipsogen (that is, an agent that induces thirst) in experimental animals because of an effect on central thirst centers. An increase in water intake may be explained in part by the physiologically inappropriate thirst drive in CHF.³ In volume-depleted normal individuals, these mechanisms preserve ECF volume by curbing additional losses, and taken together, they

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maintain GFR. In patients with CHF, the same pathophysiological mechanisms prevail, although in this instance ECF volume is expanded. The renal actions of Ang II in patients with CHF preserve GFR in the face of a reduced cardiac output and, in parallel, cause avid renal salt retention. These factors, together with the central dipsogenic effect of Ang II and ongoing secretion of arginine vasopressin, frequently result in hyponatremia. This is an ominous prognostic sign in the CHF patient.⁴

Benefits of Long-Term ACE Inhibitor Use

In patients with both symptomatic and asymptomatic myocardial dysfunction, long-term administration of ACE inhibitors reduces symptoms from CHF, as well as long-term morbidity and mortality.⁵ This beneficial effect of ACE inhibitors has been recognized for some time. For example, as early as 1984, Levine et al⁶ reported symptomatic relief, increased exercise time, and improved cardiac function in 9 patients with severe CHF treated with enalapril for 4 weeks. Furthermore, in a randomized, placebo-controlled trial of 2231 patients with left ventricular dysfunction (but no overt CHF) due to myocardial infarction, Pfeffer et al⁷ reported a 19% reduction in mortality in patients treated with captopril compared with those in the placebo-treated group. They also observed a highly significant reduction in the development of overt CHF in the patients who received the ACE inhibitor. Lewis et al⁸ found that long-term captopril administration markedly reduced the rate of progression to end-stage renal failure in patients with nephropathy due to type I diabetes mellitus. More recently, ACE inhibitors have been shown to reduce the rate of progression in nondiabetic chronic renal insufficiency if the level of proteinuria exceeds 1 to 3 g/d.^{9–12} Finally, ACE inhibitors have proved beneficial in treating a range of patients at high risk for cardiovascular events, presumably in relation to an established ability of this drug class to favorably modify structure and function of the vasculature.^{13,14} Thus, long-term ACE inhibitor therapy has highly beneficial effects in a large number of patients. The beneficial effects in CHF and in chronic nephropathies are related in part to hemodynamic actions of the ACE inhibitors, but they are also probably a consequence of the inhibition of direct Ang II effects on cardiac myocytes, renal glomerular pericytes, and the vascular endothelium.

Cardiac, Renal, and Systemic Hemodynamic Effects of ACE Inhibitor Therapy

A number of studies have been performed to assess the systemic and regional hemodynamic effects of ACE inhibitors in the setting of CHF.^{15,16} Acutely, a uniform reduction in MAP pressure is observed after ACE inhibitor administration owing to a reduction in systemic vascular resistance. Right atrial, pulmonary artery, and capillary wedge pressures all fall in response to ACE inhibitor therapy.¹⁷ Total renal vascular resistance decreases, and an increase in RBF is observed in most patients. Nevertheless, the GFR usually remains unchanged or falls slightly.^{17,18} This discrepancy between RBF and GFR is due to the relatively greater effect of the ACE inhibitor in dilating postglomerular efferent than afferent arterioles, with a resultant reduction in glomerular capillary

hydrostatic pressure and GFR.^{1,19} Indeed, a slight but not progressive rise in serum creatinine concentration (usually <10% to 20%; see below) can be anticipated and reflects the beneficial effects of ACE inhibitors on renal hemodynamics. Beneficial renal effects of ACE inhibitor therapy in patients with CHF also result from an increase in urinary Na⁺ excretion. This effect is due to altered glomerular and peritubular hemodynamics, reduced proximal tubule Na⁺ reabsorption, and reduced aldosterone-dependent collecting duct Na⁺ reabsorption.^{15,20} An improvement in hyponatremia may also be observed, presumably because the dipsogenic and arginine vasopressin-releasing action of Ang II is lessened in conjunction with improved renal handling of water.²¹ These beneficial effects of ACE inhibitor therapy are seen as long as MAP does not fall below 60 to 65 mm Hg, significant renal arterial disease is not present, diuretic-induced volume depletion is not excessive, and cardiac output is adequate.

ARF Due to ACE Inhibitor Therapy

ARF is defined as an abrupt reduction in renal function, usually heralded by a rise in serum creatinine concentration. Although no precise increase in serum creatinine defines ARF, an increase of ≥ 0.5 mg/dL (44 μ mol/L) if the serum creatinine was initially <2.0 mg/dL or ≥ 1.0 mg/dL if the serum creatinine was above 2.0 mg/dL can be used as a useful working definition. It should also be appreciated that situations exist in which a rise in creatinine occurs without a change in GFR, such as with inhibition of proximal tubule creatinine secretion by competing pharmaceutical agents or circulating substances that interfere with creatinine in laboratory assays. However, these situations rarely result in a rise in serum creatinine ≥ 0.5 mg/dL.

Renal function can deteriorate acutely when ACE inhibitor therapy is initiated^{22–25} or in patients receiving chronic ACE inhibitor therapy, particularly in patients with CHF. ARF can occur even if ACE inhibitor therapy has been uneventful for months or years. To date, little has been written about this latter problem. In addition, interpretation of change in renal function, as assessed by serum creatinine values, can prove difficult in the CHF patient who is chronically medicated with ACE inhibitors. The frequency with which renal function changes in CHF patients treated chronically with ACE inhibitors has been evaluated and reported in several studies.^{26–30} For example, in the 6090 patients in the CONSENSUS II trial (Cooperative North Scandinavian Enalapril Survival Study II), there was a 2.4% incidence of an increase in serum creatinine ≥ 0.5 mg/dL.²⁸ Furthermore, in the Studies of Left Ventricular Dysfunction (SOLVD), there were 3379 patients randomly assigned to enalapril with a median follow-up of 974 days and 3379 patients randomly assigned to placebo with a mean follow-up of 967 days. Decreased renal function was defined as a rise in serum creatinine of ≥ 0.5 mg/dL (44 μ mol/L) from baseline. Sixteen percent of patients randomly assigned to enalapril had a decrease in renal function compared with 12% in the placebo controls, indicating a 4% (16% minus 12%) greater likelihood of decreased renal function. By multivariate analysis, in both the placebo and enalapril groups, older age, diuretic therapy, and diabetes were associated with decreased renal

TABLE 1. Causes of ARF on Initiation of ACE Inhibitor Therapy

MAP insufficient for adequate renal perfusion
Poor cardiac output
Low systemic vascular resistance
Volume depletion (diuretic use)
Presence of renal vascular disease
Bilateral renal artery stenosis
Stenosis of dominant or single kidney
Afferent arteriolar narrowing (hypertension, cyclosporin A)
Diffuse atherosclerosis in smaller renal vessels
Vasoconstrictor agents (NSAIDs, cyclosporine)

function, whereas β -blocker therapy and a higher ejection fraction were renoprotective.^{26,27}

In most patients who experience ARF in this setting, 1 or more of 4 mechanisms are involved (Table 1; Figure).^{22,31,32} First and foremost, if MAP falls to levels that cannot adequately sustain renal perfusion or that provoke substantial reflex activation of renal sympathetic nerves, ARF will ensue with ACE inhibitor therapy.³³ In addition to triggering a sudden decline in Ang II levels, ACE inhibitor therapy may result in hypotension by other potential mechanisms, including an increase in vasodilatory prostaglandins and/or a decline in total peripheral resistance in a setting in which there may be little change in cardiac output because of the cardiomyopathy.¹⁹ The incidence of ACE inhibitor-related hypotension is generally more conspicuous with long-acting agents or in situations in which the pharmacological half-life of an ACE inhibitor is unduly prolonged, as occurs when the degree of renal insufficiency is underestimated and an ACE inhibitor cleared by renal mechanisms is administered.^{17,34–36} Ribstein and Mimran³⁷ reported ARF in 2 of 16 patients treated with captopril for severe CHF. The patients who experienced a decrease in MAP to 55 mm Hg or below had the highest probability of developing ARF.

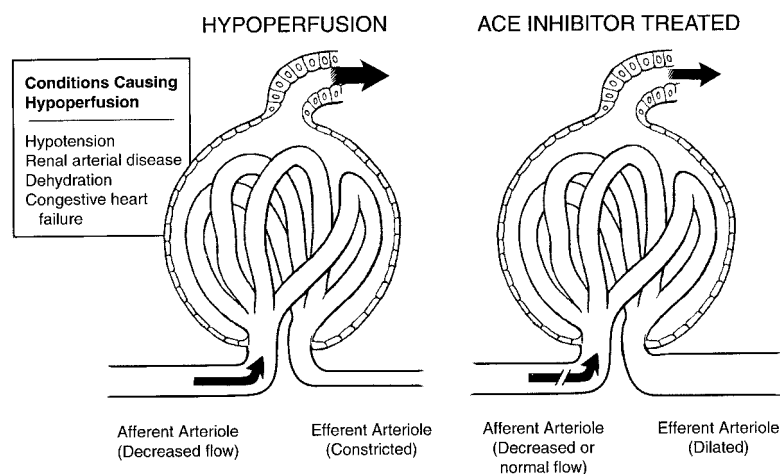
Second, ACE inhibitors commonly lead to ARF in patients who are volume depleted from diuretic therapy.^{25,26,31,38,39} Mandal et al³⁸ reported that 33% of patients with CHF undergoing diuretic therapy developed ARF when ACE inhibitors were administered, compared with only 2.4% of

patients who were not taking diuretics. Packer et al³⁴ showed that among patients with CHF treated with ACE inhibitors, those whose serum creatinine levels rose had received higher doses of diuretics, had lost more weight, and had lower left ventricular and right atrial pressures than those whose creatinine levels remained stable or decreased. Moreover, serum creatinine levels returned to pretreatment levels in the former group of patients when salt intake was liberalized and diuretic doses were reduced.

Third, ACE inhibitors may induce ARF in patients with high-grade bilateral renal artery stenosis or stenosis of a dominant or a single kidney, as in renal transplant recipients; in patients with atherosclerotic disease in smaller preglomerular vessels; or in patients with afferent arteriolar narrowing due to hypertension or chronic cyclosporine use.^{31,32,40}

Fourth, ACE inhibitors may precipitate ARF in patients who are taking agents that have vasoconstrictor effects, most commonly nonsteroidal anti-inflammatory agents (NSAIDs) or cyclosporine.^{41,42} In this regard, the cyclooxygenase-2-specific inhibitors have not been specifically studied in the presence of ACE inhibitor therapy, although preliminary evidence exists to indicate that cyclooxygenase-2-specific inhibitors have an effect similar to that of traditional NSAIDs on GFR.^{43,44}

Finally, the risk of ACE inhibitor-induced ARF is higher in patients with chronic renal insufficiency of any cause than in patients with normal renal function. Indeed, patients with few surviving nephrons have adaptive changes that maintain the GFR, including a hyperfiltration response. An important component of the beneficial long-term effect of ACE inhibitor therapy in such patients is believed to be due to reversal of glomerular hyperfiltration as a result of predominant efferent arteriolar vasodilatation and a decline in glomerular capillary pressure. Therefore, reversal of hyperfiltration by ACE inhibitor therapy for patients with chronic renal insufficiency will inevitably lead to an initial fall in GFR and rises in blood urea nitrogen and serum creatinine. Indeed, this is an indication that the drugs are exerting their desired actions to help preserve renal function. A corollary to these observations is that there is no serum creatinine level per se for which use of ACE inhibitor therapy is contraindicated. Thus, a 10% to 20% increase in serum creatinine can be anticipated in such



Schematic illustration of settings wherein ACE inhibitor therapy may result in worsening renal function. Conditions causing renal hypoperfusion include systemic hypotension, high-grade renal artery stenosis, ECF volume contraction (simplified as "dehydration" in the Figure), administration of vasoconstrictor agents (eg, NSAIDs or cyclosporine, not shown), and CHF. These conditions typically increase renin secretion or Ang II production. Ang II constricts the efferent arteriole to a greater extent than the afferent arteriole, such that glomerular hydrostatic pressure and GFR can be maintained despite hypoperfusion. When these conditions occur in ACE inhibitor-treated patients, Ang II formation and effect are diminished, and GFR may decrease. GFR is usually maintained or improved in patients with CHF unless one of the other conditions is also present.

patients as therapy with ACE inhibitors is initiated, and this is not in itself an indication to discontinue treatment. However, unless 1 of the above 4 situations exists, the decrease in GFR in patients with chronic renal disease is usually <20% and is transient, followed by a stabilization or even a decline of serum creatinine levels due to the renoprotective effects of long-term ACE inhibitor administration.^{45,46}

ARF in the setting of chronic ACE inhibitor use usually indicates that there has been a change in systemic hemodynamics or in ECF volume. As was noted above, during renal hypoperfusion or significant volume depletion, maintenance of GFR becomes dependent on Ang II in relation to the prevailing effect of Ang II on the efferent glomerular arteriole. Worsening of CHF with a reduction in cardiac output, overly aggressive diuresis, intercurrent volume depletion due to diarrhea or severe hyperglycemia with osmotic diuresis, and sepsis all can tip the renal hemodynamic balance so that GFR can no longer be maintained if and when Ang II generation is checked. ACE inhibitor therapy also predisposes to radiocontrast-induced ARF,⁴⁷ and NSAID and cyclosporine administration during an ARF episode will either potentiate or independently initiate an ARF episode. ARF in association with ACE inhibitor therapy typically reverses with discontinuation of the ACE inhibitor or volume repletion, although occasionally, recovery is delayed or does not occur.^{48,49}

Management of ARF During ACE Inhibitor Therapy

If monitoring is sufficiently judicious, those patients prone to ARF with ACE inhibitors can be identified early, without having to withhold ACE inhibitor therapy out of fear of the possibility of renal functional deterioration after their use.⁵⁰ Serum creatinine and electrolyte levels should be evaluated before and again 1 week after therapy with ACE inhibitors is begun in the CHF patient. There is little merit in checking serum creatinine levels sooner than several days unless oliguria or a significant decrease in blood pressure has been sustained or is anticipated. This is particularly the case in the hyponatremic patient with CHF, in whom the renin-angiotensin axis is typically excessively activated. It is reasonable to establish in advance what a tolerable upper limit should be, above which both discontinuation of the medication and possible diagnostic studies for reversible vascular disease should be undertaken. For example, a rise in serum creatinine >0.5 mg/dL if the initial serum creatinine is <2.0 mg/dL (or a rise >1.0 mg/dL if the baseline creatinine exceeds 2.0 mg/dL), particularly if the level progressively increases thereafter, should prompt consideration for stopping the medication while additional renal evaluation is undertaken. The relationship between serum creatinine and creatinine clearance is that of a rectangular hyperbola. Thus, in the steady state, a doubling of serum creatinine, as occurs when serum creatinine increases from 0.5 to 1.0 mg/dL, represents a 50% decrease in creatinine clearance. Such a change must be explained and corrected, if possible, before ACE inhibitor therapy proceeds further. Renal artery stenosis and microvascular renal disease are not uncommon in the CHF patient.

Identification and correction of such lesions can be followed by greater tolerance of an ACE inhibitor.

ARF complicating ACE inhibitor therapy is almost always reversible.^{42,43} The reversible nature of ACE inhibitor-associated ARF is explained by the fact that loss of GFR is due to an inadequate glomerular capillary pressure, which is restored as soon as sufficient Ang II is produced. If recognized before any tubular damage has occurred, renal function improves within 2 to 3 days after cessation of ACE inhibitor use. Under these circumstances, Ang II receptor antagonists (AT₁ receptor blockers) should not be substituted, because they exert similar effects on renal hemodynamics. Nevertheless, oliguria or anuria is not uncommon in this setting, and hyperkalemia frequently complicates ACE inhibitor-associated ARF. Although there have been few studies on the subject, ARF is thought to occur most commonly in clinical settings when either frank hypotension has occurred or when GFR has become more Ang II dependent owing to the superimposition of ECF volume depletion. Repletion of ECF volume and discontinuation of diuretic therapy in these situations is the most efficacious approach to resolution of the ARF episode. It is not known whether temporary withdrawal of the ACE inhibitor therapy in this circumstance speeds the rate of renal functional recovery, but this is recommended by many clinicians. In addition, withdrawal of interacting drugs, supportive management of fluid and electrolytes, and temporary dialysis where indicated are the mainstays of therapy. It is not known whether the use of dialysis to remove dialyzable ACE inhibitors also influences the time course of the ARF episode.⁵¹ In addition, underlying causes of volume depletion and reduced renal perfusion must be reversed as far as is possible. Unless renal vascular disease or chronic renal insufficiency is the cause of acute ACE inhibitor-associated ARF, therapy can usually be reinstated once systemic hemodynamics and renal function have been restored. If a patient with previous myocardial infarction or CHF has been thoroughly evaluated and treated and renal dysfunction persists, the clinician must weigh the risk of a decrease in creatinine clearance on ACE inhibitor therapy with the proven mortality benefit of this therapy.

Where chronic renal insufficiency is present, and especially where renal function is variable (as with unstable CHF), several options are available in selecting an ACE inhibitor. One is to select a drug that is eliminated in part by hepatic clearance rather than by renal excretion and is therefore less likely to accumulate in the presence of renal dysfunction. Alternatively, one can select a drug eliminated solely by renal clearance, in which case drug accumulation may occur. At this time, the significance or potential consequences of such accumulation in patients with renal insufficiency are not known. Likewise, when a patient needs hemodialysis, it is important to select an ACE inhibitor that is not significantly dialyzed, so that therapy can be stable and sustained (Table 2).⁵¹ ACE inhibitors are not contraindicated in patients with end-stage renal disease. In fact, they are used frequently in dialysis patients. In this setting, they should not be administered to patients who are treated with polyacrylonitrile dialysis membranes because of the risk of anaphylactoid dialyzer reactions with this combination.⁵¹ The polyac-

TABLE 2. Elimination Characteristics of ACE Inhibitors in Hemodialysis

Drug	Dialyzable*	Route of Elimination
Captopril	Yes	Kidney
Enalapril	Yes	Kidney
Lisinopril	Yes	Kidney
Perindopril	Yes	Kidney
Ramipril	Yes	Kidney
Fosinopril	No	Kidney/liver
Quinapril	No	Kidney
Benazepril	NA	Kidney
Moexipril	NA	Kidney
Trandolapril	NA	Kidney/liver

*"Yes" indicates drug is removed during dialysis; NA, data not available.

Postdialysis drug supplementation or administration within 4 hours after dialysis is considered when the drug is removed by dialysis or blood pressure levels warrant treatment.

Modified from Sica et al.⁵¹

rylonitrile dialysis membrane should not be used for patients taking ACE inhibitors. Alternately, an AT₁ receptor antagonist can be substituted for ACE inhibitor therapy and polyacrylonitrile membrane use continued.

A number of unanswered questions exist regarding ACE inhibitor-related functional renal insufficiency. For example, it is known that the DD genotype for ACE is associated with elevated serum and tissue ACE levels. However, whether this phenotype affects the propensity for renal failure after ACE inhibition is unclear. In addition, there is no available information that would support the use of angiotensin-receptor antagonists in place of ACE inhibitors in the CHF patient prone to deterioration in renal function with these drugs. In the only broad-based trial of ACE inhibitors versus angiotensin-receptor antagonists in CHF, there was no difference in the frequency with which renal function changed over a 48-week period of study-drug administration.⁵² It is not known whether the timing of ACE inhibitor administration influences the development of renal failure. Diuretic action, especially that of loop diuretics, is critically dependent on a threshold MAP. This is particularly the case in the CHF patient. Timing of administration of an ACE inhibitor so that its peak blood pressure-lowering effect does not coincide with diuretic administration may allow for more predictable diuresis.⁵³ Clinically, this variable may be important in maintaining an optimal state of salt-and-water balance and lessening the risk of ACE inhibitor-related renal dysfunction in the CHF patient. Finally, it is unclear as to the extent to which aspirin therapy makes the CHF patient more susceptible to ACE inhibitor-associated renal failure.^{54,55}

Hyperkalemia

Hyperkalemia is relatively common in ACE inhibitor-treated patients with CHF or uremia. Fortunately, increases in plasma potassium are generally fairly modest (≤ 1 mEq/L), and severe hyperkalemia with ACE inhibitors is uncommon.⁵⁶ In the SOLVD trials, only 6.4% of the 1285 patients given enalapril developed serum potassium levels >5.5 mEq/L.⁴⁶

The most relevant factor for predicting hyperkalemia is a baseline serum creatinine level of 1.6 mg/dL (144 μ mol) or greater.⁵⁶ Mechanistically, by lowering plasma aldosterone levels and thereby reducing urinary potassium excretion, ACE inhibitor therapy may lead to hyperkalemia.⁵⁷ Patients undergoing treatment with ACE inhibitors typically have diuretics coadministered, which further lessens the risk of severe hyperkalemia. In this regard, ACE inhibitors usually offset the hypokalemia that might otherwise accompany diuretic therapy.

ACE inhibitor-related hyperkalemia is more common when other risk factors for the development of hyperkalemia are present. Thus, disruption of internal homeostasis may occur in patients with diabetes and hyperglycemia, in individuals receiving β -blockers, or in individuals receiving potassium supplements, heparin,⁵⁸ or potassium-sparing diuretics⁵⁹ who are particularly prone to the development of hyperkalemia. In such patients, the routine use of potassium supplements or potassium-sparing agents should be discouraged, even if digoxin or loop diuretics are being administered, until the pattern of potassium handling has been established.

Risks During Cardiac Surgery

Several reports have warned of episodes of profound hypotension during anesthesia in patients treated chronically with ACE inhibitors.^{60,61} Recent studies have yielded conflicting results. Some have shown no significant difference in severe hypotension in ACE inhibitor-treated patients.⁶²⁻⁶⁴ Other studies have found that ACE inhibitor use is associated with a greater reduction in blood pressure during cardiac bypass surgery and a resultant requirement for more vasopressor support.⁶⁵⁻⁶⁷ ACE inhibitor use may be an independent predictor of post-cardiac bypass vasodilatory shock,⁶⁸ although this is not found uniformly.⁶² The suggestion has been made that withholding ACE inhibitor therapy for 24 to 48 hours before surgery reduces the incidence of severe hypotension,⁶¹ but this suggestion is not supported by others.⁶⁹ A single study⁷⁰ found a greater blood pressure reduction in patients treated chronically with Ang II receptor antagonists than in those treated with other antihypertensive agents, including ACE inhibitors.

Hypotension is an independent risk factor for the development of postoperative ARF in patients undergoing cardiac surgery.⁷¹ However, chronic ACE inhibitor therapy does not appear to alter renal hemodynamics and function independently during cardiac surgery.⁷²

Summary

The use of ACE inhibitors in patients with CHF, hypertension, and chronic nephropathies is often a double-edged sword. As long as renal perfusion pressure is adequate and volume depletion is not severe, ACE inhibitors can improve renal hemodynamics so that an improvement in renal salt excretion can be achieved. However, because Ang II is necessary for maintenance of GFR during states of significant volume depletion, these agents also can cause GFR to decrease rapidly, with consequent oliguric or anuric renal failure. ACE inhibitors can generally be safely restarted after resolution of an ARF episode, particularly if the underlying

TABLE 3. Principles of ACE Inhibitor Therapy: Renal Considerations

1. ACE inhibitors improve RBF and stabilize GFR in most patients with CHF.
2. ACE inhibitor therapy is indicated in patients with diabetic nephropathy and in patients with nondiabetic nephropathies when protein excretion exceeds 1 g/d.
3. A rise in serum creatinine may occur after initiation of therapy in patients with CHF. This rise usually occurs promptly, is less than 10% to 20%, is not progressive, and is a consequence of the renal hemodynamic changes brought about by ACE inhibitor therapy. Serum creatinine often stabilizes and may decline thereafter.
4. Although there is no serum creatinine level per se that contraindicates ACE inhibitor therapy, greater increases in serum creatinine occur more frequently when ACE inhibitors are used in patients with underlying chronic renal insufficiency.
5. The occurrence of ARF should prompt a search for systemic hypotension (MAP < 65 mm Hg), ECF volume depletion, or nephrotoxin administration. An attempt should be made to correct or remove these factors. Consideration should also be given to high-grade bilateral renal artery stenosis or stenosis in a single kidney.
6. ACE inhibitors should be discontinued temporarily while precipitating factors for ARF are corrected; Ang II receptor blockers are not an appropriate substitute under these conditions. Once ARF has resolved with correction of the precipitating factors, ACE inhibitor therapy can be reinstated.
7. Hyperkalemia is a potential complication of ACE inhibitor therapy, particularly in patients with diabetes or chronic renal failure. Monitoring of serum potassium early after initiation of therapy, appropriate reduction in dietary potassium intake, and avoidance of agents that can aggravate hyperkalemia (eg, potassium-sparing diuretics and NSAIDs) are recommended.

conditions having predisposed to the episode can be rectified. The principles of ACE inhibitor therapy are summarized in Table 3.

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