

PEER REVIEWED

ACEI and ARB Therapy in Chronic Renal Insufficiency

Elevated creatinine at baseline is not a reason for withholding treatment

by Nitish Bangalore, PharmD, BCPS

Few areas of medicine are as well studied as the use of angiotensin-converting enzyme inhibitors (ACEI) for hypertension (HTN), heart failure (HF), acute myocardial infarction (MI), and renal protection in diabetes mellitus (DM). Despite the large evidence base, the existence of numerous clinical guidelines, and the development of quality initiatives by national and state agencies, ACEI and angiotensin receptor blocker (ARB) utilization is less than ideal. Beyond ensuring appropriate care of patients, many sites of care are facing financial pressure to demonstrate maximal use of ACEI in patients that qualify. As a result, these sites have developed specific strategies to maximize compliance with these quality initiatives. Pharmacists and other health care providers are expected to contact prescribers to start ACEI or ARB therapy for patients with a diagnosis or history of HF, HTN, MI, DM, and chronic kidney disease (CKD). In some cases, for example chronic renal insufficiency (CRI), prescribers are hesitant to start ACEI therapy, often citing the risk of elevating serum creatinine (SCr) and hyperkalemia.¹ Some recent evidence shows that despite our best efforts in the hospital setting, following discharge, only a fraction of those patients continue therapy as intended.^{2,3} Though one would expect that certain physician specialists, e.g. cardiologists, would be more likely to use ACEI and ARB therapy in patients that qualify, several studies demonstrate that suboptimal therapy still results.⁴⁻⁶ Reasons for withholding these life-saving and sustaining therapies should be rational and evidence-based. This article will review the indications, contraindications, and evidence to support the use of ACEI

and ARB in appropriate patients with an emphasis on their use in pre-existing kidney disease. With this knowledge and evidence, pharmacists will be able to ensure that ACEI and ARB therapy is initiated in eligible patients despite chronic renal insufficiency, and that such therapy is not stopped unless appropriate discontinuation reasons are documented.

QUALITY INITIATIVES AND FINANCIAL PRESSURES

An extensive evidence base exists for the use of ACEI and ARB for cardiovascular and noncardiac indications. For this reason, ACEI and ARB therapy comprise key quality measures developed by the Centers for Medicare & Medicaid Services (CMS),⁷ Joint Commission for the Accreditation of Healthcare Organizations (JCAHO),⁸ Agency for Healthcare Research and Quality,⁹ and the Wisconsin Hospital Association (WHA).¹⁰ Meeting established benchmarks merely assures that patients are receiving evidence-based therapy. Exceeding benchmarks has tangible financial implications.

Hospitals participating in the CMS Premier Hospital Quality Incentive Demonstration voluntarily submit quality data for specific targeted diagnoses. One example is ACEI prescribed at discharge for patients admitted for MI or HF with left ventricular systolic dysfunction.¹¹ Once the data are compiled, hospitals in the top two deciles in each of the clinical areas will be rewarded with increased reimbursement. Those in the bottom two deciles face decreased reimbursement. Furthermore, once the data is made available, the results are anticipated to be widely publicized. This may impact the choice of hospitals and other health care providers by payers and patients. Hospitals participating in the WHA Quality Ac-

countability Initiative voluntarily submit data on ACEI use in HF. The results for each hospital are currently available to the public.¹² Patients and payers viewing the CMS and WHA data may choose to utilize care only in those institutions that demonstrate the highest compliance rates.

DELETERIOUS EFFECT OF ANGIOTENSIN II

The renin-angiotensin-aldosterone system (RAAS) allows the kidney to autoregulate renal blood flow (RBF) and glomerular filtration rate (GFR).¹³ Angiotensin II (Ang II) is released in response to reduced renal perfusion pressure, e.g., hypovolemia and HF. Ang II causes efferent (post-glomerular) and afferent (pre-glomerular) arteriole vasoconstriction, though the effect on the efferent system is significantly more intense. The result of efferent arteriole vasoconstriction is increased glomerular pressure.¹⁴ This allows GFR to remain steady despite reduced RBF. Ang II also stimulates aldosterone release. Together, Ang II and aldosterone promote salt reabsorption. In normal individuals, once renal perfusion is restored, Ang II and aldosterone levels decrease.

In certain disease states, especially HF, Ang II levels remain persistently elevated. Numerous deleterious effects have been attributed to Ang II.¹⁵ Some of these effects include vascular constriction, inflammation, and remodeling. By stimulating the production or activation of certain inflammatory mediators, enzymes, and hormones, Ang II also promotes thrombosis, myocardial hypertrophy, atherosclerosis and development of CKD.

BENEFICIAL EFFECTS OF ACEI AND ARB

Decreased production of Ang II due to ACEI and antagonism of the angiotensin II type I receptor by ARB would be ex-

pected to halt or reverse the effects previously attributed to Ang II. In addition, ACEI and ARB therapy have been shown to increase vascular compliance,¹⁵ symptoms of CHF, morbidity and mortality in HF, progression to HF following MI,¹⁶ reduced risk of stroke,¹⁷ progression of diabetic nephropathy¹³ and progression of CKD.¹⁸

By preventing the kidney from compensating for decreased renal perfusion via Ang II, ACEI and ARB are nephro-protective.¹³ Reduced Ang II levels cause efferent vasodilation, resulting in decreased glomerular pressure. As glomerular pressure falls, so does GFR. This is reflected by a rise in SCr in patients taking an ACEI. Over time, decreased glomerular pressure reduces the progression of proteinuria and progressive loss of nephrons. It is also possible that ACEI and ARB inhibit direct toxic effects of Ang II on renal glomerular pericytes.

Though many prescribers view the rise in SCr as an adverse effect, this rise aids in monitoring.¹ Such a rise indicates that the ACEI has effectively reduced glomerular pressure. It may also indicate that the patient has been compliant with the medication. In reducing the ability of the kidney to compensate for decreasing renal perfusion, long-term nephron function is preserved. This is analogous to the effects of beta-blockers in HF. Beta-blockers prevent adrenergic compensation of the failing heart with the long-term benefit of reduced mortality.

INCIDENCE OF RENAL DYSFUNCTION AND HYPERKALEMIA DUE TO ACEI AND ARB

In a meta-analysis of ACEI therapy in HF,¹⁹ subjects allocated to ACEI arms withdrew from studies due to renal dysfunction at a rate of 0.9% (59/6191). In the comparator group (placebo or "standard therapy"), withdrawals due to renal dysfunction occurred at a rate of 0.4% (31/5798). The relative risk of withdrawal from a study due to renal dysfunction was 1.84 (95% CI, 1.20-2.81). The relative rate of withdrawal in ACEI arms for any renal reason was 2.03 (95% CI, 1.55-2.67). The authors did not specifically examine exclusion criteria. It may be possible that some of the studies included in the analysis failed to exclude patients

with bilateral renal artery stenosis or other conditions that significantly increase the risk of elevations in SCr. Withdrawal from a study due to hyperkalemia occurred in 0.4% (22/6191) of subjects allocated to ACEI and 0.03% (7/5798) of subjects allocated to the comparator arm. The relative risk of withdrawal due to ACEI-induced hyperkalemia was 7.11 (95% CI, 2.11-23.94).

A meta-analysis of adverse effects due to ARB therapy is not currently available in the peer-reviewed literature. According to the labeling of each approved ARB,²⁰⁻²⁶ there were no statistically significant differences in the incidence of elevated SCr and hyperkalemia between the ARB and placebo. Each of the studies used to develop the adverse effects sections of the

labeling did exclude patients known to be at high risk of elevated SCr due to ACEI, including bilateral renal artery stenosis.

The ELITE study²⁷ measured safety, morbidity, and mortality with the use of losartan vs. captopril in HF patients over the age of 65 years. Subjects were excluded for SCr >2.5 mg/dL. The average SCr in both arms was 1.2 mg/dL. This would suggest that the average subject in the study exhibited mild renal insufficiency at enrollment. Data was collected for 48 weeks. The reason for discontinuation of captopril due to renal dysfunction was 0.8% (3/370) and for losartan was 1.4% (5/352). The rate of discontinuation for hyperkalemia was 1.6% (6/370) for captopril and 0.56% (3/352) for losartan. Differences in discontinuation rate for

TABLE 1. FDA-APPROVED INDICATIONS FOR ACE INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS AVAILABLE IN THE UNITED STATES^{20-26,32-43}

		APPROVED INDICATION				
Drug name	Trade name	HTN	CHF	AMI	Diabetic nephropathy	Other
ACE INHIBITORS						
Benazepril	Lotensin®	●				
Captopril	Capoten®	●	●	●	●	
Enalapril	Vasotec®	●	●	●		
Fosinopril	Monopril®	●	●			
Lisinopril	Prinivil®	●	●	●		
Lisinopril	Zestril®	●	●	●		
Moexipril	Univasc®	●				
Perindopril	Aceon®	●				
Quinapril	Accupril®	●	●			
Ramipril	Altace®	●	●	●		● *
Trandolopril	Mavik®	●				
ANGIOTENSIN RECEPTOR BLOCKERS						
Candesartan	Atacand®	●				
Eprosartan	Teveten®	●				
Irbesartan	Avapro®	●			●	
Losartan	Cozaar®	●			●	● †
Olmесartan	Benicar®	●				
Telmisartan	Micardis®	●				
Valsartan	Diovan®	●	●			

Abbreviations: HTN, hypertension; CHF, congestive heart failure; AMI, acute myocardial infarction.

* Reduction in cardiovascular causes of AMI, stroke, and death⁴²

† Reduction in stroke risk in patients with HTN and left ventricular hypertrophy²³

renal dysfunction and hyperkalemia were not statistically significant.

The Val-HeFT study²⁸ measured the effect of valsartan vs. placebo in addition to optimal therapy for HF. The trial recruited 5010 subjects with nearly equal numbers in both arms. The average SCr in both arms was approximately 1.3 mg/dL. This would indicate that there were large numbers of subjects with mild renal insufficiency at baseline. Approximately 92% of subjects in both arms were on an ACEI during the trial. Therefore the vast majority of subjects in the valsartan arm were on combination ACEI and ARB. In this group, the rate of discontinuation for development of renal insufficiency was

1.1% compared to 0.2% in the placebo arm ($p < 0.001$). In the valsartan arm, SCr increased an average of 0.18 mg/dL and in the placebo arm, 0.1 mg/dL ($p < 0.001$). Potassium rose an average 0.12 mmol/L in the valsartan arm and 0.07 in the placebo arm ($p < 0.001$).

The results of a post hoc analysis of subjects not taking ACEI in the Val-HeFT study were reported.²⁹ A total of 366 subjects were included in this analysis. Average SCr was not significantly different than the general study population (SCr 1.3 vs. 1.28 mg/dL). The subjects in this analysis were on average older, a larger proportion were NYHA Class III and IV, and had higher average serum brain

natriuretic peptide (BNP), norepinephrine, and aldosterone levels, and a larger proportion exhibited an S₃ heart sound at baseline than those taking ACEI. The mean increase in SCr in the valsartan arm was 0.18 ± 0.2 mg/dL and in the placebo arm was 0.1 mg/dL ± 0.2 ($p = 0.009$). The mean increase in serum potassium was not statistically different between arms, though the actual data were not reported. The rates of discontinuation of study drug due to life threatening alteration in laboratory readings, including SCr and potassium, were 0.5% (1/185) and 0.6% (1/181) for valsartan and placebo respectively ($p = 0.988$). Though not direct proof, these results suggest that valsartan slightly increases the risk of elevated SCr but not potassium.

APPENDIX 1. STRENGTH OF EVIDENCE FROM CITED GUIDELINES

K/DOQI¹⁸

Grade	Description
A	Strong evidence demonstrating improved health outcomes
B	Moderately strong evidence demonstrating improved health outcomes
C	Weak evidence or expert opinion that intervention may improve outcomes

ACC/AHA^{16,31}

Class	Description
I	Evidence and/or consensus that treatment is beneficial and effective
II	Conflicting evidence and/or lack of consensus that treatment is beneficial and effective
Ila	Conflicting evidence generally supporting recommendation
Ilb	Poor evidence supporting recommendation
III	Evidence that treatment is not effective or may cause harm

ADA³²

Level	Description
A	Strong evidence from well-designed randomized clinical trials
B	Evidence from well-designed cohort studies
C	Evidence from poorly-designed studies or conflicting evidence favoring support for the recommendation
E	Expert opinion

APPENDIX 2. ACC/AHA DEFINITIONS OF STAGES OF HEART FAILURE¹⁶

Stage	Definition
A	At high risk of development of heart failure (HF) and no cardiac abnormalities; no personal history of symptomatic HF
B	Structural heart disease without symptoms of symptomatic HF
C	Active HF or history of symptomatic HF due to structural heart disease
D	Symptomatic HF at rest despite optimal medical management

INDICATIONS FOR ACEI AND ARB

Each currently available ACEI and ARB is indicated for treatment of hypertension (HTN). Table 1 lists select drugs within these classes approved for HTN and other indications, including HF, following MI, and diabetic nephropathy.

Several nationally and internationally recognized therapeutic guidelines recommend the use of ACEI and ARBs. The JNC 7 guidelines³⁰ recommend ACEI or ARB therapy as second line antihypertensives (lifestyle modification and thiazide diuretics as first line) for patients without compelling indications. These compelling indications include HF, history of or following MI, high risk of coronary disease, DM, CKD, and history of stroke. In any of these cases, ACEI therapy is first line. Compelling indications for ARB therapy are HF, DM, and CKD.

The K/DOQI guidelines on hypertension in CKD¹⁸ recommend with grade A evidence ACEI or ARB therapy as first line in patients with HF, post MI with HF, high risk for coronary artery disease (CAD), history of stroke, DM, and urine protein to creatinine ratio of ≥ 200 mg/g regardless of etiology. The guidelines recommend ACEI and ARB therapy following kidney transplant with grade B evidence. (See Appendix 1 for definition of strength of evidence.)

The ACC/AHA guidelines on the management of MI³¹ list ACEI as a class I recommendation within the first 24 hours following ST segment-elevation MI

or MI with known HF (EF <40%) without hypotension. As class IIa and IIb recommendations, ACEI therapy is indicated for mildly impaired left ventricular function.

The ACC/AHA guidelines on the management of CHF¹⁶ list ACEI as a class I recommendation for HF in stages B-D and for stage A with risk factors. (See Appendix 2 for stage definitions.)

The American Diabetes Association guidelines on management of hypertension in diabetics³² recommend initial anti-hypertensive therapy with an ACEI or ARB as a class E recommendation. As a class A recommendation, ACEI or ARB therapy is indicated for any degree of albuminuria to delay the progression of nephropathy.

CONTRAINDICATIONS AND PRECAUTIONS TO ACEI AND ARB

The product labeling for each ACEI³²⁻⁴³ lists a history of hypersensitivity to ACEI or angioedema as an absolute contraindication. Lisinopril and enalapril^{35,37,38} include history of hereditary or idiopathic angioedema as a contraindication. The product labeling for each ACEI also warns that there is an increased risk of adverse effects in patients with aortic stenosis, hypertrophic cardiomyopathy, renal artery stenosis, severe HF, undergoing major surgery or general anesthesia, and hemodialysis with a high-flux membrane filter.

Schoolwerth, et al.,¹³ outline clinical situations in which patients are at increased risk of development of acute renal failure due to ACEI therapy. These are arterial pressure insufficient to maintain renal perfusion (low cardiac output or low blood pressure), hypovolemia (also excessive diuresis), renal vascular disease (renal artery stenosis, atherosclerosis in smaller renal vessels) and concomitant therapy with nephrotoxins. The clinician must weigh the relative risks and benefits of ACEI therapy in each of these conditions. In some cases, the risk factor may be modifiable. If the risk factor can be eliminated, then the benefit of ACEI therapy would outweigh the risks. For example, a patient may be taking an NSAID for pain. If this were to be replaced by a less nephrotoxic drug, the patient would be at less risk for ACEI-induced renal failure.

Quality measure initiatives such as the CMS Premier Hospital Quality Incentive Demonstration and WHA data collection project require acceptable documentation of an absolute or relative contraindication to the use of ACEI and ARB therapy by a physician, nurse practitioner or physician assistant.

The labeling of each ARB²⁰⁻²⁶ lists history of hypersensitivity to any component of the dosage form as an absolute contraindication. In addition, caution is

advised in patients with severe HF, renal artery stenosis or who are volume- or salt-depleted. The labeling of valsartan²⁶ states that the drug should not be used in combination with an ACEI and a beta blocker.

Table 2 summarizes the above contraindications and other acceptable situations for not using ACEI or ARB therapy. The table incorporates information available in the product labeling, the K/DOQI guidelines on hypertension in

TABLE 2. SUMMARY OF ACCEPTABLE REASONS FOR WITHHOLDING ACE INHIBITOR (ACEI) OR ANGIOTENSIN RECEPTOR BLOCKER (ARB) THERAPY

CLINICAL FINDING	NOTES
History of angioedema or other hypersensitivity to that agent ³²⁻⁴³	<u>Contraindication:</u> per ACEI and ARB labeling; considerable cross-sensitivity between classes
History of hereditary or idiopathic angioedema ^{35,37,38}	<u>Contraindication:</u> specifically mentioned in labeling for lisinopril and enalapril
History of cough with ACEI ³²⁻⁴³	ARB generally considered safe in this circumstance
Bilateral renal artery stenosis ^{20-26,32-43}	Or renal artery stenosis in solitary native or transplanted kidney
Moderate or severe aortic stenosis ^{8,32-43}	Specifically mentioned in labeling of ACEI
Severe heart failure ³²⁻⁴³	Specifically mentioned in labeling of ACEI
Hypertrophic cardiomyopathy ³²⁻⁴³	Specifically mentioned in labeling of ACEI
Major surgery or general anesthesia ³²⁻⁴³	Specifically mentioned in labeling of ACEI
Triple combination for treatment of heart failure with ACEI, ARB, and beta-blocker ²⁶	Specifically mentioned in labeling for valsartan
Hemodialysis with polyacrylonitrile membrane filter ^{13,32-43}	May use ARB as alternative
Volume or salt-depleted ²⁰⁻²⁶	Specifically mentioned in labeling of ARB
Acute renal failure ¹³	May start or restart once acute phase resolved
Untreated hyperkalemia ¹³	May start or restart once corrected
Concomitant therapy with nephrotoxic drug that cannot be discontinued ¹³	Example: cyclosporine
Pregnancy ⁸	JCAHO monograph on HF; FDA Category C (first trimester), Category D (second and third trimesters)
Age <18 years ⁸	JCAHO monograph on HF
Patients discharged to hospice ⁸	JCAHO monograph on HF
Participation in a clinical trial testing alternatives to ACEI as first-line therapy ⁸	JCAHO monograph on HF

CKD,¹⁸ the JCAHO core measures for HF⁸ and risk factors described by Schoolwerth.¹³

ACEI AND ARB THERAPY IN SELECTED PATIENT POPULATIONS WITH BASELINE CKD

Heart failure

Frances, et al.,⁴⁴ conducted a large cohort study examining the effect of ACEI therapy on survival following discharge for MI with depressed ejection fraction. Data was collected by chart review of over 20,000 patients discharged from all non-federal acute care hospitals in the United States in the mid-1990s. Patient data was analyzed separately for SCr above or below 3 mg/dL. Only one-third of patients with baseline SCr greater than 3 mg/dL received an ACEI following discharge compared with 60% of patients with SCr \leq 3 mg/dL received an ACEI following discharge. The mortality hazard ratio for those patients with SCr >3 mg/dL receiving an ACEI was 0.63 (95% CI, 0.48-0.84). For those with SCr \leq 3 mg/dL receiving an ACEI, the mortality hazard ratio was 0.84 (95% CI, 0.77-0.92). The mortality benefit due to aspirin alone was less pronounced. The mortality hazard ratio for patients with SCr >3 mg/dL taking aspirin was 0.96 (95% CI, 0.29-1.18) and for those with SCr \leq 3 mg/dL was 0.90 (95% CI, 0.82-0.98). One troubling result was that concomitant aspirin therapy reversed the mortality benefits of ACEI. In those with SCr >3 mg/dL treated with combined ACEI and aspirin, the mortality hazard ratio was 1.46 (95% CI, 1.01-2.1). For those with SCr \leq 3 mg/dL, the mortality hazard ratio was 1.05 (95% CI, 0.94-1.18). These data suggest that aspirin alone is more beneficial than combined aspirin and ACEI for post-MI patients with SCr \leq 3 mg/dL. ACEI without concomitant use of aspirin is more beneficial than aspirin and combined aspirin/ACEI for post-MI patients with SCr >3 mg/dL.

Shlipak reviewed several drug therapy trials conducted over the past 15 to 20 years in HF patients with existing renal insufficiency.⁴⁵ Only one ACEI trial reviewed included a subgroup analysis of patients with elevated SCr at baseline. The CONSENSUS study⁴⁶ enrolled subjects with New York Heart Association

HF class IV. The studied population included 26 out of 253 subjects with SCr between 2.0 and 2.8 mg/dL. The average SCr was 1.4 mg/dL, or an estimated creatinine clearance (CrCl) of 45 mL/min. At one year, the mortality hazard ratio for all subjects taking enalapril compared to placebo was 0.73. This mortality benefit occurred even for those subjects that experienced more than 30% rise in SCr. The SOLVD,⁴⁷ SAVE,⁴⁸ TRACE,⁴⁹ and AIRE⁵⁰ studies of patients with heart failure excluded subjects with moderate to severe CKD (SCr 2.0, 2.5, 2.3 mg/dL, and not specified, respectively). Nevertheless, each trial included substantial numbers of subjects with mild renal insufficiency (typical average SCr 1.2 mg/dL). These trials demonstrated an all-cause mortality risk reduction of 8 to 27% versus comparator and HF hospitalization risk reduction of 20 to 29%.

Clinical trial data supporting the use of ARB therapy in HF patients with CKD is not yet available. As previously described, the Val-HeFT trial²⁸ studied valsartan vs. placebo in 5010 subjects receiving standard therapy for HF. The average SCr was 1.3 mg/dL. A specific subgroup analysis of patients with CKD has not yet been reported.

Nondiabetic CKD

Mann, et al.,⁵¹ reported a post hoc analysis of renal insufficiency in the HOPE trial. The original trial randomized 9297 subjects with HF to ramipril or placebo for a median followup of 4.5 years. A total of 980 subjects with SCr 1.4 to 2.3 mg/dL were included in this analysis. There were no statistically significant differences in demographic characteristics of these subjects. In the placebo arm, 32.1% of subjects had DM at baseline while 35.8% in the ramipril arm were diabetic. Therefore, the majority of renal insufficiency was nondiabetic in origin. Subjects with mild renal insufficiency in both arms combined were found to have a cardiovascular mortality hazard ratio of 1.90 (95% CI, 1.53-2.36, $P < 0.001$). Those with renal insufficiency treated with ramipril had a cardiovascular mortality hazard ratio of 0.59 (95% CI, 0.39-0.91) while those without renal insufficiency had a hazard ratio of 0.78 (95% CI, 0.66-0.93). Therefore, a greater mortality benefit due

to the ACEI was seen in those with renal insufficiency compared to those with normal renal function.

The REIN trial⁵² examined the benefits of an ACEI for risks and benefits in patients with pre-existing nondiabetic proteinuria. A total of 322 subjects were randomized to ramipril or placebo and followed for up to five years. Participants were allowed to continue all other medications, including other antihypertensives except ACEI and ARBs. Included were subjects with urinary protein excretion \geq 1 gram/24 hours and CrCl 20 to 70 mL/min. Randomization was stratified based on amount of urinary protein excretion. Subjects in the ramipril arm experienced a statistically significant difference in drop in glomerular filtration rate (GFR) than did those in the placebo arm at each level of baseline renal function. For subjects in the lowest tertile of renal function (GFR 10.5 to 32.7 mL/min), those on ramipril experienced a decline in GFR of 0.38 ± 0.06 mL/min while those in the comparator group experienced a decline of 0.49 ± 0.08 mL/min. The most dramatic difference came in incidence of progression to end-stage renal disease (ESRD). In the tertile of patients with the lowest baseline renal function, in the placebo arm, 60% progressed to ESRD. In the ramipril arm, 40% progressed ($p < 0.05$).

Maschio, et al.,⁵³ conducted a trial of 583 subjects with baseline SCr 1.5 to 4 mg/dL due to a variety of etiologies. Diabetic nephropathy comprised a small fraction (21/583) of the study population. Subjects were randomized to benazepril or placebo and were monitored over three years for the primary endpoint of doubling of SCr or progression to hemodialysis. Of those taking benazepril, 10% (31/300) reached the primary endpoint compared to 20% (57/283) taking placebo ($p < 0.001$). No statistically significant differences in hyperkalemia were detected.

Extrapolating on the results of ramipril and benazepril, ACEI appear to exert substantial nephroprotective effects at all levels of nondiabetic CKD.

Diabetic nephropathy

Many ACEI trials have been done examining the nephroprotective effects of

ACEI in pre-existing nephropathy due to type 1 DM. Two recent meta-analyses have been published. Kshirsagar, et al.,⁵⁴ performed a meta-analysis and systematic review of nine ACEI trials of renal protection in diabetic and nondiabetic nephropathy. The total number of subjects randomized to the ACEI arms was 326 while 316 were randomized to the comparator arms. The studies included in the analysis studied progression of microalbuminuric subjects (urine albumin excretion 76-158 mg/24 hr) with primarily normal CrCl (92-187 mL/min) to overt macroalbuminemia. The aggregate relative risk of developing macroalbuminemia was 0.35 (95% CI, 0.24-0.53). The ACE Inhibitors in Diabetic Nephropathy Trialist Group performed a meta-analysis of 12 studies of microalbuminuria in type 1 diabetics.⁵⁵ Followup data for a total of 698 subjects was included in the analysis. The overall odds ratio for progression to overt macroalbuminuria in two years of followup was 0.38 (95% CI, 0.25-0.57, $p < 0.001$) in favor of ACEI therapy. This effect seemed to wane for longer followup, from a high of 75% difference in albumin excretion at one year down to 32% difference at four years. The odds ratio for regression of microalbuminuria to normoalbuminuria was 3.07 (95% CI, 2.15-4.44, $p < 0.001$) in favor of ACEI. These highly convincing data firmly establish ACEI therapy as safe and effective for protection from progression of established nephropathy in type 1 DM.

Insufficient data exists examining the nephroprotective effect of ACEI in pre-existing type 2 diabetic nephropathy. Some recent clinical trials have examined the use of ARB in this condition.

Lewis, et al.,⁵⁶ conducted a study of irbesartan vs. amlodipine vs. placebo in 1715 hypertensive patients with nephropathy due to type 2 DM. Subjects were included for urine protein excretion ≥ 900 mg per 24 hr and SCr between 1 and 3.0 mg/dL (1.2 mg/dL lower limit for women). After 2.6 years median followup, taking irbesartan was associated with a relative risk reduction of doubling SCr was 33% ($p = 0.003$) compared to placebo and 37% ($p < 0.001$) compared to amlodipine. Bakris, et al.,⁵⁶ reviewed the RENAAL study of nephropathy due to type 2 DM. A total of 1513 patients with urine albu-

min excretion ≥ 800 mg/day and SCr 1.3 to 3 mg/dL were followed for a median followup of 3.4 years. Subjects were randomized to losartan or placebo. Other antihypertensive medications were allowed to achieve blood pressure goals. In subjects randomized to losartan, a relative risk reduction in progression to ESRD of 53.5% ($p = 0.003$) and a reduction of 35.5% ($p = 0.02$) for composite outcome of ESRD and death. These results establish the role of ARB therapy in minimizing progression of diabetic nephropathy due to type 2 DM.

RECOMMENDATION

The JNC 7,³⁰ K/DOQI,¹⁸ and ADA guidelines³² on hypertension specify a blood pressure target of $< 130/80$ mm Hg for any patient with evidence of CKD. Drug therapy starting with an ACEI should be strongly considered without regard for baseline renal function. For patients that do not tolerate ACEI, i.e., due to cough, elevation in SCr, hyperkalemia, or angioedema, it would be reasonable to attempt ARB therapy. Should any of the situations as outlined in Table 2 exist in a patient's case that would preclude the use of ACEI and ARB, suitable alternatives should be used to achieve target blood pressure. In particular, the ACC/AHA guidelines on the treatment of HF¹⁶ recommend combination hydralazine and isosorbide dinitrate for HF patients with history of intolerance to an ACEI.

The majority of clinical research in this area has been done using ACEI. Also, some ACEI agents are available as generic products. Therefore, ACEI therapy is preferred over ARB. Evidence is not widely available establishing ACEI therapy as first line for nephroprotection in type 2 DM. Therefore, this specific use appears to be the sole indication for ARB therapy over ACEI.

For all patients, to reduce the risk of adverse effects, an attempt should be made to maintain proper hydration status.¹⁸ To reduce the risk of hyperkalemia, a diuretic should be used in combination. Any medication that may increase the risk of hyperkalemia should be avoided (e.g., potassium-sparing diuretics).

There is scant evidence for choosing specific agents for patients with ESRD.¹³

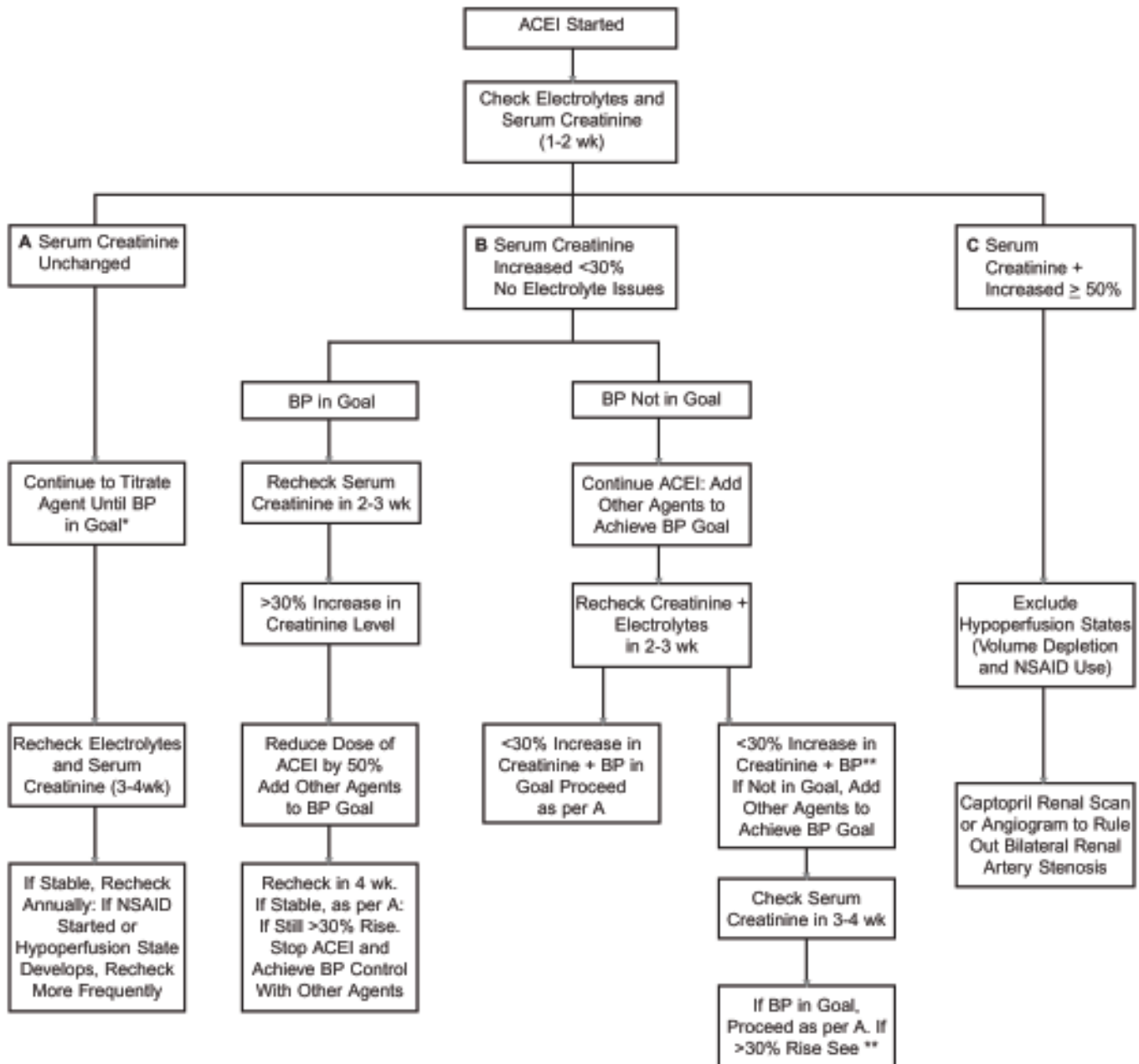
Starting an ACEI with nonrenal clearance mechanisms would prevent accumulation of the drug. Fosinopril and trandolopril are partially cleared by the liver. For patients on hemodialysis, it might be advantageous to select an ACEI that is not dialyzable. This would ensure more consistent drug levels. This is true of fosinopril and quinapril.

The Council on the Kidney in Cardiovascular Disease and Council for High Pressure Research of the American Heart Association¹³ recommends using ACEI therapy for compelling indications without regard for baseline renal function. One week following initiation, electrolytes and SCr should be measured. A significant elevation in SCr is defined as > 0.5 mg/dL for baseline SCr ≤ 2.0 mg/dL (or > 1.0 mg/dL for baseline SCr > 2.0 mg/dL). If a significant elevation in SCr is detected, the ACEI should be immediately withheld and the patient evaluated for renal vascular disease. In most cases, SCr returns to baseline within two to three days. Once ARF has resolved and renal vascular disease ruled out, restarting the ACEI is warranted.

The K/DOQI guidelines¹⁸ recommend regular monitoring of ACEI and ARB therapy. Monitoring parameters include blood pressure, GFR, and serum potassium. In most cases, ACEI and ARB therapy may be continued as long as the decrease in GFR over four months is $< 30\%$ from baseline and potassium remains under 5.5 mEq/L.

Bakris and Weir¹ suggest an alternate algorithm for monitoring and adjusting of ACEI therapy following initiation. (See Figure 1) Serum electrolytes and SCr should be checked one to two weeks after initiation. If SCr does change but the magnitude of this change is an elevation of less than 30% above baseline, the ACEI should be titrated to the patient's blood pressure goal. Agents in other classes may be added in order to achieve goal blood pressure. If the SCr rises more than 30% above baseline, hypoperfusion and concomitant nephrotoxic drug therapy (e.g., NSAID) should be ruled out. At followup, if SCr has not fallen to below 30% above baseline, the ACEI dose should be halved. At any time if SCr increases by more than 50% above baseline, the patient should be evaluated for

FIGURE 1. A SCHEMATIC APPROACH TO A PATIENT WITH RENAL INSUFFICIENCY STARTED ON THERAPY WITH AN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR (ACEI)¹



Asterisk indicates blood pressure (BP) less than 130/85 mm Hg for those with renal insufficiency or diabetes; double asterisks, if serum creatinine level increases more than 30%, reduce ACEI dose by 50% and add other BP-lowering agents; plus sign, if serum creatinine rise is greater than 30% and less than 50% within the first month of therapy, causes for hypoperfusion are eliminated, and nonsteroidal anti-inflammatory drugs (NSAIDs) are not given, treat as if bilateral renal arterial disease is present. Reprinted with permission. Copyrighted © 2000 American Medical Association. All Rights reserved.

renal vascular disease (e.g., bilateral renal artery stenosis).

THE PHARMACIST'S ROLE

In the acute care and outpatient settings, the pharmacist is the drug expert. As such, the pharmacist plays an important role in the strategy adopted by each site

of care for meeting or exceeding benchmarks set by national quality initiatives. In the inpatient setting, pharmacists must work closely with the other members of the health care team to ensure that ACEI or ARB therapy is initiated for every patient admitted with HF and MI. In the outpatient setting, pharmacists must en-

sure that ACEI or ARB therapy is initiated for every acceptable indication, e.g., HF, HTN with compelling indications, such as evidence of proteinuria. Whether inpatient or outpatient, if a reason to withhold ACEI and ARB therapy has been identified, pharmacists must ensure that this reason is documented. This arti-

cle should arm pharmacists with the knowledge and evidence to make a compelling argument to initiate ACEI or ARB therapy when indicated without regard for baseline elevated creatinine and to assess if reasons for withholding ACEI or ARB therapy are evidence-based and rational.

SUMMARY

Evidence supports the use of ACEI and ARB therapy for accepted indications without regard for baseline SCr. Patients treated with ACEI or ARB at all levels of renal function experience reduced morbidity and mortality. There is evidence that patients with pre-existing renal disease have the most to benefit. Though in most cases ACEI are preferred, ARB therapy is recommended for prevention of the progression of nephropathy in type 2 DM. As health care providers and sites of care come under increasing pressure to maximize ACEI therapy for accepted indications, reasons for withholding therapy should be evidence-based and rational. Of those myriad reasons, elevated SCr at baseline is not a valid reason to withhold this lifesaving and life-sustaining treatment modality. ●

Nitish Bangalore is an education/investigational drug specialist for St. Luke's Medical Center in Milwaukee.

REFERENCES

- Bakris GL, Weir MB. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: Is this a cause for concern? *Arch Intern Med* 2000; 160:685-693.
- Stafford RS, Saglam D, Blumenthal D. National patterns of angiotensin-converting enzyme inhibitor use in congestive heart failure. *Arch Int Med* 1997; 157:2460-2464.
- Butler J, Arbogast PG, Daugherty J, et al. Outpatient utilization of angiotensin-converting enzyme inhibitors among heart failure patients after hospital discharge. *J Am Coll Cardiol* 2004; 43: 2036-2043.
- Auerbach AD, Hamel MB, Davis RB, et al. Resource use and survival of patients hospitalized with congestive heart failure: Differences in care by specialty of the attending physician. *Ann Intern Med* 2000; 132:191-200.
- Ayanian JZ, Landrum MB, Guadagnoli E, et al. Specialty of ambulatory care physicians and mortality among elderly patients after myocardial infarction. *N Engl J Med* 2002; 347:1678-1686.
- Jollis JG, Delong ER, Peterson ED, et al. Outcome of acute myocardial infarction according to the specialty of the admitting physician. *N Engl J Med* 1996; 335:1880-1887.
- Centers for Medicare & Medicaid Services. Hospital Quality Initiative. Baltimore, MD: Centers for Medicare & Medicaid Services; [updated 2004 May 7; cited 2004 May 30]. Available at: <http://www.cms.hhs.gov/quality/hospital/>
- Joint Commission on Accreditation of Healthcare Organizations. Specifications manual for national implementation of hospital core measures: HF3 [monograph on the Internet]. Oakbrook Terrace, IL: Joint Commission on Accreditation of Healthcare Organizations; [updated 2004 Apr 26; cited 2004 May 30]. Available from: http://www.jccho.org/pms/core-measures/4d_hf3.pdf
- Agency for Healthcare Research and Quality. Heart failure and left ventricular systolic dysfunction: Effect in female, Black, and diabetic patients, pharmacologic management [monograph on the Internet]. Santa Monica, CA: Southern California-RAND Evidence-based Practice Center; 2003 July [cited 2004 May 30]. Available from: <http://www.ahrq.gov/clinic/epcsums/hrtfailsum.htm>
- Wisconsin Hospital Association. First Set of Measures [monograph on the Internet]. Madison, WI: WHA Quality Steering Committee; 2003 May 5 [cited 2004 May 30]. Available from: <http://www.wha.org/qualityAndPatientSafety/pdf/firstmeasures.pdf>
- Centers for Medicare and Medicaid Services. Baltimore, MD: Premier Hospital Quality Incentive Demonstration: Fact Sheet; 2004 Feb 18; [cited 2004 May 30]. Available from: <http://www.cms.hhs.gov/quality/hospital/PremierFactSheet.pdf>
- Checkpoint. Measure and Hospital Selection Reports. Madison, WI: WHA Quality Steering Committee; [cited 2004 May 30]. Available from: <http://www.wicheckpoint.org/reports/>
- Schoolwerth AC, Sica DA, Ballermann BJ, et al. 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. *Circulation* 2001; 104:1985-1991.
- Palmer BF. Renal dysfunction complicating the treatment of hypertension. *N Engl J Med* 2002; 347:1256-1261.
- McFarlane SI, Kumar A, Sowers JR. Mechanisms by which angiotensin-converting enzyme inhibitors prevent diabetes and cardiovascular disease. *Am J Cardiol* 2003 91:30H-37H.
- Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2001; 38:2101-2113.
- Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomized trials. *Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet* 2000; 356:1955-1964.
- National Kidney Foundation. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis* 2004; 43 (Suppl 1):S1-S290.
- Agusti A, Bonet S, Arnau JM, et al. Adverse effects of ACE inhibitors in patients with chronic heart failure and/or ventricular dysfunction meta-analysis of randomised clinical trials. *Drug Safety* 2003; 26:895-908.
- Candesartan cilexetil (Atacand®) Prescribing Information, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT November 2003.
- Eprosartan mesylate (Teveten®) Prescribing Information, Biovail Pharmaceuticals, Bridgewater, NJ January 2004.
- Irbesartan (Avapro®) Prescribing Information, Bristol-Myers Squibb Sanofi-Synthelabo Partnership, New York, NY September 2002.
- Losartan potassium (Cozaar®) Prescribing Information, Merck and Company, Whitehouse Station, NJ February 2004.
- Olmesartan medoxomil (Benicar®) Prescribing Information, Sankyo Pharma, Parsippany, NJ March 2003.
- Telmisartan (Micardis®) Prescribing Information, Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT November 2003.
- Valsartan (Diovan®) Prescribing Information, Novartis Pharmaceuticals, East Hanover, NJ August 2002.
- Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997; 349:747-752.
- Cohn JN, Tognoni G; Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001; 345:1667-1675.
- Maggioli AP, Anand I, Gottlieb SO, et al; Val-HeFT Investigators. Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. *J Am Coll Cardiol* 2002; 40:1414-1421.
- Chobanian AV, Bakris GL, Black HR; National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *Hypertension*. 2003; 42:1206-1252.
- Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1999; 34:890-911.
- Arauz-Pacheco C, Parrott MA, Raskin P; American Diabetes Association. Hypertension management in adults with diabetes. *Diabetes Care* 2004; 27 Suppl 1:S65-67.
- Benazepril hydrochloride (Lotensin®) Prescribing Information, Novartis Pharmaceuticals, East Hanover, NJ January 2003.
- Captopril (Capoten®) Prescribing Information, Par Pharmaceutical Incorporated, Spring Valley, NY June 2003.
- Enalapril maleate (Vasotec®) Prescribing Information, Par Pharmaceutical Incorporated, Spring Valley, NY March 2003.
- Fosinopril sodium (Monopril®) Prescribing Information, Bristol-Myers Squibb Company, Princeton, NJ May 2003.
- Lisinopril (Prinivil®) Prescribing Information, Merck & Company, Whitehouse Station, NJ April 2003.
- Lisinopril (Zestril®) Prescribing Information, AstraZeneca Pharmaceuticals, Wilmington, DE July 2003.
- Moexipril hydrochloride (Univasc®) Prescribing Information, Schwartz Pharma, Milwaukee, WI February 2003.
- Perindopril erbumine (Aceon®) Prescribing Information, Solvay Pharmaceuticals, Marietta, GA March 2003.
- Quinapril hydrochloride (Accupril®) Prescribing Information, Pfizer Pharmaceuticals, Vega Baja, PR February 2003.
- Ramipril (Altace®) Prescribing Information, Monarch Pharmaceuticals, Bristol, TN February 2003.
- Trandolapril (Mavik®) Prescribing Information, Abbott Laboratories, North Chicago, IL July 2003.
- Frances CD, Noguchi H, Massie BM, et al. Are we inhibited? Renal insufficiency should not preclude the use of ACE inhibitors for patients with myocardial infarction and depressed left ventricular function. *Arch Intern Med* 2000; 160:2645-2650.
- Shlipak MG. Pharmacotherapy for heart failure in patients with renal insufficiency. *Ann Intern Med* 2003; 138:917-924.
- The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; 316:1429-1435.
- The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; 325:293-302.
- Pfeffer MA, Braunwald E, Moye LA, et al; The SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. *N Engl J Med* 1992; 327:669-677.
- Kober L, Torp-Pedersen C, Carlsen JE, et al; Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995; 333:1670-1676.
- The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993; 342:821-828.
- Mann JF, Gerstein HC, Pogue J, et al. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 2001; 134:629-636.
- Ruggenenti P, Perna A, Remuzzi G. ACE inhibitors to prevent end-stage renal disease: When to start and why never to stop: A *post hoc* analysis of the REIN trial results. *J Am Soc Nephrol* 2001; 12:2832-2837.
- Maschio G, Alberti D, Janin G, et al. Effect of the angiotensin-converting enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med* 1996; 334:339-345.
- Kshirsagar AV, Joy MS, Hogan SL, et al. Effect of ACE inhibitors in diabetic and nondiabetic chronic renal disease: A systematic overview of randomized placebo-controlled trials. *Am J Kidney Dis* 2000; 35:695-707.
- The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with Type 1 diabetes mellitus and microalbuminemia receive angiotensin-converting enzyme inhibitors? *Ann Intern Med* 2001; 134:370-379.
- Bakris GL, Weir MR, Shanifar S, et al. Effects of blood pressure on progression of diabetic nephropathy: Results from the RENAAL study. *Arch Intern Med* 2003; 163:1555-1565.