

Therapeutic dimensions of ACE inhibitors- A review of literature and clinical trials

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Abstract: In the 1970s, pharmacological therapy interrupting the renin-angiotensin system was considered beneficial for patients with high-renin hypertension. This gave rise to the development of ACE inhibitors. Surprisingly, the ACE inhibitors proved to be effective not only in patients with high renin hypertension, but also in many patients with normal levels of plasma renin activity. At present ACE inhibitors have a significant position in a wide range of chronic illnesses such as atherosclerosis, hypertension, myocardial infarction, diabetic complications, stroke etc. They are combined safely with drugs like angiotensin receptor blockers, calcium channel blockers and thiazides with varying degree of benefits. Though they are safe drugs, patients need monitoring for renal insufficiency, hypotension, hyperkalemia etc. The safety of these drugs in paediatrics patients is not established. It is better to avoid these drugs during pregnancy.

Keywords: ACE inhibitors, Atherosclerosis, Diabetic complications, Hypertension, Myocardial infarction

Cardiovascular problems pose a major threat to mankind. Family history, hypertension, cigarette smoking and raised serum cholesterol are known to be the major risk factors. Diabetes mellitus is also evolving as a major risk factor for cardiac related morbidity and mortality.¹ Several approaches including pharmacotherapy, physical exercise and dietary modifications are being followed so as to minimize the risk. Low fat diet, large quantities of fruits, vegetables and antioxidants are also considered to be beneficial.² In the 1970s, pharmacological therapy interrupting the Renin-Angiotensin System (RAS) was considered beneficial for patients with high-renin hypertension. This gave rise to the development of drugs that are known to inhibit the Angiotensin Converting Enzyme (ACE); ACE inhibitors. Surprisingly the ACE inhibitors proved to be effective not only in patients with high renin hypertension, but also in many patients with normal levels of plasma renin activity.³ The recent research gives a lot of insights on ACE inhibitors and widens the horizon of use of these agents. Today, ACE inhibitors have gained wide attention because of their wide spread use in several conditions and are becoming indispensable for primary care physicians, cardiologists and general practitioners. In this article, the authors try to explain the therapeutic dimensions of these agents based on the existing literature.

Angiotensin converting enzyme system: Renin is an enzyme that acts on angiotensinogen to catalyze the formation of the decapeptide angiotensin I. This decapeptide is then cleaved by ACE to yield the

octapeptide angiotensin II. Angiotensin II is known to have several effects that are considered to be clinically significant, the major ones being altered peripheral resistance, altered renal function and altered cardiovascular structure. These effects form the basis for majority of therapeutic uses ACE inhibitors. The expression of RAS is found to be important for development of normal kidney morphology too.⁴

Classification: ACE inhibitors can be classified as Sulfhydryl containing ACE inhibitors structurally related to captopril (eg, Fentiapril, Pivalopril, zefenopril, alacepril); Dicarboxyl-containing ACE inhibitors structurally related to enalapril (eg, lisinopril, benazepril, quinapril, moexipril, ramipril, spirapril, perindopril, spirapril, pentopril, cilazapril); phosphorous containing ACE inhibitors structurally related to fosinopril. Many of these ACE inhibitors are ester containing prodrugs that are 100-1000 times less potent than the active metabolites, but have a much better oral bioavailability than the active molecules.³

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Pharmacokinetic profile of ACE inhibitors: These agents are available as oral as well as parenteral forms. Majority of them are prodrugs, which get

activated in the body after administration. Table 1 lists the pharmacokinetic properties of a few ACE inhibitors.

Table 1: Pharmacokinetic profile of ACE inhibitors ^{5, 6, 7, 8}

Agent	Oral absorption	Protein binding	Biotransformation	Half-life	Onset of action	Time of Peak plasma level	Elimination
Captopril	75%	25-30%	Hepatic	Less than 3 hrs	15-60 min	30-90min	Renal
Lisinopril *	25%			12hrs	1 hr	7 hr	Renal
Enalapril *	60%	50-60%	Hepatic	1.3 hrs	1 hr	1 hr	Renal, faecal
Ramipril *	50-60%	73%	Hepatic	5.1hrs	Within 1-2 hr	Within 1 hr	Renal, Faecal
Benazapril	37%	95.3%	Hepatic	0.6 hrs	Within 1 hr	0.5-1 hr	Predominantly renal. Non renal(biliary)-11-12%
Fosinopril	36%	97-98%	Hepatic	-	Within 1 hr	3-4 hrs	Renal, Faecal
Perindopril	65-75%	60%	Hepatic	Approximately 0.8-1hrs	Within 1-2 hr	1 hrs	Renal, Faecal
Moexipril	13%	50%	Hepatic	1.3 hrs	1 hr	1.5 hrs	Renal, Faecal
Quinapril	60%	10-20%	Hepatic,	Approximately 1-2 hrs	Within 1 hr	Within 1 hr	Renal, Faecal
Trandolapril	10%	80%	Hepatic	6hrs	2 hrs	1 hr	Renal, Faecal

* = Available in Nepal

PPL= Peak plasma level

Indications of ACE inhibitors: ACE inhibitors are used in a wide variety of disorders. They have a significant position in a wide range of chronic illnesses. Clinicians should be aware of these viable drugs and should tailor the regimen with patient considerations in mind.

Atherosclerosis: The cause of spontaneous atherosclerosis is unclear, although it is thought that in the presence of hypercholesterolemia, a non denuding form of injury occurs to the endothelial lining of coronary artery and other vessels. Clinical evidence for the potential anti-atherosclerotic effect of ACE inhibition comes mainly from the Studies of Left Ventricular Dysfunction (SOLVD) and Survival and Ventricular Enlargement (SAVE) trials, where long term (6 months to 2+ years) observation showed an overall 23% reduction in ischemic events such as myocardial infarction, development of unstable angina, and need for revascularization procedures.⁹ However, in a study by McMohan M *et al*, ramipril failed to show convincing evidence of any ability to reverse mean carotid far wall thickness or change carotid plaque scores when given to elderly, normotensive patients with histories of acute MI, angina, ischemia stroke or TIA, or peripheral vascular disease.¹⁰

The Heart Outcomes Prevention Evaluation (HOPE) study involving 9541 subjects who received ramipril or placebo, and vitamin E (from natural sources) or placebo showed primary cardiovascular events (myocardial infarction, stroke, and death from cardiovascular causes) occurred in 16.2% of patients who received vitamin E and 15.5% of those who received placebo. There were no significant differences due to vitamin E treatment for any of the specific cardiovascular events. However, ramipril significantly reduced the risk of major cardiovascular events as well as the secondary outcome of revascularization.^{11,12}

Essential hypertension: The Joint National Committee (JNC) VII guidelines have placed ACE inhibitors as one of the first line drugs for hypertension. Patients belonging to stage-I hypertension (systolic BP 140-159 or diastolic BP 90-99 mm of Hg) may be offered ACE inhibitors.² The Antihypertensive and Lipid Lowering Therapy in Heart Attack Trial (ALLHAT) trial also supports the use of ACE inhibitors as initial therapy alone or in combination with thiazide diuretics¹³ with overall response of 50% to 70% in mild to moderate disease. Cilazapril, enalapril, fosinopril, lisinopril, perindopril, trandolapril were all confirmed by 24-hour blood pressure monitoring as effective once

daily dosage regimens. Captopril, quinapril monotherapy may not be effective once daily, especially in moderate- to-severe disease; twice daily dosing or combination with thiazide diuretics may provide full 24-hour coverage.¹⁴ It was found that black patients experience a lower magnitude of response in blood pressure reduction from baseline (6% to 8%) when compared to non-blacks (10% to 14%) with ACE inhibitors.

Reno vascular hypertension: ACE inhibitors, particularly captopril, can be recommended as an alternative to surgical corrective procedures in patients with strong contraindications to surgery or renal artery angioplasty. Bilateral stenosis or stenosis of a solitary kidney, which obviously represents greatest risk for azotemia and renal failure, and must be carefully monitored.¹⁵

Resistant hypertension: It is the condition associated with the failure to achieve a blood pressure of 150/90 mm Hg despite the use of a rational triple-drug regimen in optimal doses. In resistant hypertension, ramipril 5 to 10 milligrams (mg) daily as a single oral dose was effective when combined with other drugs in treating 10 patients with severe hypertension in an open trial.¹⁶

Congestive cardiac failure (CCF): The goals of drug therapy in CCF are to relieve symptoms, delay progression of the disease, reduce hospitalization and mortality and improve quality of life. Use of an ACE inhibitor is recommended in all patients with heart failure due to Left Ventricular (LV) systolic failure (unless contraindicated or intolerant), patients with LV systolic dysfunction without symptoms of heart failure, to reduce mortality following acute myocardial infarction, especially in patients with prior myocardial injury, to prevent/delay development of LV dilation and overt heart failure in patients with LV dysfunction (recent or remote).¹⁷

ACE inhibitors should be initiated in all patients with mild, moderate, or severe heart failure due to left ventricular systolic dysfunction (ejection fractions less than 35% to 40%), with or without a diuretic, a beta-blocker, or digitalis.^{18,19,20} ACE inhibitors are indicated in all symptomatic patients without contraindications who can tolerate them, with probable lifetime duration of therapy.¹⁹ Patients not responding or those developing intolerable side effects should be switched to regimens including directly acting vasodilators plus nitrates.^{19,20}

ACE inhibitors are known to improve survival in CHF patients. These agents may also prevent or delay

development of left ventricular dilatation and overt heart failure in patients with both asymptomatic and symptomatic left ventricular dysfunction.^{21,22,23,24,25} Symptomatic improvement (dyspnea, exercise tolerance) may occur within 48 hours, although more commonly clinical response is delayed and may not be apparent for 1 to 2 months. Even if symptomatic improvement does not occur, long-term ACE inhibitor treatment should be continued to reduce the risk of death and hospitalization.¹⁸ Meta-analysis of 5 trials of ramipril in CHF showed that ramipril improves exercise tolerance and New York Heart Association functional class.²⁶

Myocardial infarction: Beneficial results from ACE inhibitor therapy added early on to conventional treatment of acute MI are clearly established, and confirmed by analysis of 4 trials (Consensus-II; GISSI-3; ISIS-4; CCS-1) involving over 49,000 patients exposed to ACE inhibitors early (0 to 36 hours) and generally treated for 4 to 6 weeks compared to 49,000 control patients not exposed to ACE inhibitors.²⁷

Overall, treatment with ACE inhibitors following acute MI is estimated to prevent about 5 to 16 deaths per 1000 patients when considering either overall or subgroup (anterior infarct) analysis,^{28,29,30,31} a risk reduction of approximately 20%.

The Healing and Early Afterload Reducing Therapy (HEART) Trial randomized 352 patients to standard therapy only (placebo control), low dose ramipril, or full-dose ramipril for days 1 through 14 (early phase) following the initial event. During the late phase (day 15 through 90), all placebo control and full-dose patients were maintained on full-dose ramipril while the low-dose patients continued on 0.625-mg ramipril for the duration. Echocardiographic monitoring during the early phase showed that those patients with the lowest LVEF had the greatest benefit and recovery during ramipril use.³²

Diabetic complications: Diabetic Nephropathy is a clinical syndrome that is characterized by staged-progression of increasing Urinary Albumin Excretion (UAE). Established diabetic nephropathy is characterized by persistent proteinuria (300 mg or more per 24 hours), progressive decline in Glomerular Filtration Rate (GFR) at a rate of 10 ml each year in untreated patients, elevated blood urea nitrogen (BUN), elevated serum creatinine, and increased arterial blood pressure. Untreated diabetics (either type 1 or type 2 DM) will progress over an average period of 30 years from normal renal

function and normal urinalysis to end-stage renal disease End Stage Renal Disease (ESRD).³³

In patients with chronic nephropathy characterized by proteinuria greater than 3 grams/24 hours, ramipril effectively reduced both the rate of urinary protein loss as well as the expected rate of loss of Glomerular Filtration Rate (GFR), and halved the combined risk of doubling of serum creatinine or progression to End Stage Renal Disease (ESRD) compared to placebo.³⁴

The SOLVD reported that enalapril may retard or prevent progression to diabetes among patients with chronic heart failure, and patients who were borderline diabetic at baseline benefited the most from enalapril therapy. The authors calculated that it would be necessary to treat 6 patients with left ventricular dysfunction for 2.9 years to prevent 1 new case of diabetes.³⁵

However, the recent Cochrane review concluded that inhibition of ACE can arrest or reduce the albumin excretion rate in microalbuminuric normotensive diabetics, as well as reduce or prevent an increase in blood pressure. But, given the drop in blood pressure in patients on ACE inhibitors, it is not certain that the reduction of albumin excretion rate is due to a separate renal effect. A direct link with postponement of end-stage renal failure has not been demonstrated. There appear to be no substantial side effects.³⁶

Stroke: In a sub-study of the HOPE trial, prolonged use of ramipril was found to reduce the risk of stroke in patients at high risk for cardiovascular events because of history of vascular disease (coronary artery disease, stroke, peripheral vascular disease) or diabetes, and at least one other risk factor (hypertension, elevated total cholesterol, low HDL-cholesterol levels, smoking, micro-albuminuria).³⁷

Erythrocytosis : ACE inhibitors, including captopril 25 milligrams once daily, enalapril 5 milligrams once daily, and lisinopril 2.5 milligrams daily, are effective in sufficiently lowering both haemoglobin and haematocrit to eliminate the need for or reduce the frequency of phlebotomy in patients experiencing post renal transplant erythrocytosis.^{38,39}

An average haematocrit reduction of 7% (from baseline 54%) was noted in nearly 90% of the enalapril patients compared to 60% of the captopril patients, and eliminating the need for phlebotomy. An additional 25% of the captopril patients had a partial response (about 3% reduction), which reduced the frequency of phlebotomy. About 10% of patients failed to respond to either treatment.³⁸

The mechanism of beneficial effect remains to be established. However, response was maintained in one patient when losartan, an angiotensin-II receptor blocking agent, was substituted for lisinopril-induced hypotension.³⁸

Migraine headache: Surprisingly, ACE inhibitors are found beneficial in prophylaxis in migraine in spite of their vasodilatory action. In a brief report, both enalapril and lisinopril 10 to 25 milligrams daily provided moderate to marked benefit in 16 of 17 patients with chronic migraine headache. Duration of benefit was up to 3 years in some patients ACE inhibitor modulation of cerebral blood flow auto regulation or vasomotor tone were postulated as mechanisms.⁴⁰

Other indications: In a controlled study in 17 patients, enalapril 20 milligrams daily was reported effective in reducing the frequency of Raynaud's attacks in patients with Raynaud's phenomenon, especially in patients with primary Raynaud's.⁴¹

Limited studies have been conducted using ACE inhibitors in the treatment of rheumatoid arthritis. Sulfhydryl-containing ACE inhibitors such as captopril have also been investigated as second line drugs in the treatment of rheumatoid arthritis and may provide some incremental benefit.^{42,43}

Combining ACE Inhibitors with Angiotensin Receptor Blockers (ARBs): Upon combining ACE inhibitors with ARBs there is additional advantage of decrease of side effects (dry cough) and more complete blockage of RAS. Based on the double-blind, multi-centre Val-HeFT study (Valsartan Heart Failure Trial; n=5010). Valsartan was generally well tolerated, although significantly more valsartan-treated subjects discontinued than did controls.⁴⁴

Adding candesartan to ACE inhibitor therapy produced significant reductions in blood pressure and urinary protein excretion among normotensive patients with chronic renal disease and proteinuria, based on an open-label, controlled, cross-over trial.⁴⁵

Combining ACE Inhibitors with CCBs: Combining ACE inhibitors with CCBs provides an additional advantage of additive/synergistic antihypertensive effect. This combination is approved in JNCVI and VII as initial therapy and is available in a Fixed Dose Combination (FDC). FDCs generally are not recommended for initial therapy in stage 1 whereas; the JNC VII guidelines recommend fixed dose combination in stage 2 and hypertension with

coexistent disease (diabetes and renal disease) or risk factors. For the treatment of hypertension, the recommended dosage of amlodipine/benazepril is 2.5 to 5/10 to 20 milligrams (mg) once daily. Patients receiving amlodipine and benazepril in separate formulations may be switched to the combination therapy, containing the same component doses. It is also effective in reducing the excretion of urinary albumin in type 2 DM patients with hypertension.^{2,46}

Combining ACE Inhibitors with thiazides: A fixed combination of captopril and hydrochlorothiazide is available for the treatment of hypertension. Addition of small dose of diuretic to ACE inhibitor enhances the hypotensive effects. The usual dose for initial therapy of hypertension is one fixed-dose tablet of captopril 25 mg/hydrochlorothiazide 15 mg once daily. Other ACE inhibitors may offer efficacy/safety advantages over captopril. Other combinations are lisinopril/hydrochlorothiazide 10/12.5 milligrams (mg) or 20/12.5 mg once daily and enalapril / hydrochlorothiazide containing 5/12.5 milligrams (mg) and 10/25 mg. The fixed combination is usually given once daily, although two divided doses may be indicated in some patients. Usual daily doses of enalapril and hydrochlorothiazide are 10 to 40 mg and 12.5 to 50 mg, respectively.⁴⁶ However the use of this combination is associated with profound hypotension.

Precautions and contraindications: Though ACE inhibitors are relatively safer drugs, certain precautions should be considered in special conditions. Some of the precautions and contraindications of ACE inhibitors are discussed below:

Renal insufficiency: ACE inhibitors can cause a irreversible reduction in blood flow, in clinical settings such as bilateral renal stenosis, severe CHF, volume depletion, hyponatremia, high dosage of diuretics, combined treatment with NSAIDs, and DM. The current practice of avoiding ACE inhibitors in severe renal insufficiency, to prevent further renal impairment and hyperkalemia seem no longer justified. Base line creatinine levels up to 3.0mg.dl (27 μ moles per L) are generally considered safe. An increase in 20 percent in the serum creatinine level is common and is not a cause for discontinuing the medication.⁴⁷ Deterioration in renal function, including increasing blood concentrations of urea and creatinine, and reversible acute renal failure have been reported on ACE inhibitor therapy. This occurs mainly in patient with the existing renal or renovascular dysfunction or heart failure and may be

aggravated by hypovolaemia. Proteinuria progressing to nephrotic syndrome has been reported.

Hypotension: Pronounced first dose hypotension may occur at the start of therapy with ACE inhibitors, particularly in patients with heart failure and sodium or volume depleted patients. Any underlying cause should be corrected, starting with a low dose and titrating slowly. Hypotension is not a reason to discontinue ACE inhibitors. Patients should be rechallenged at one half the previous dosages. If they are taking a diuretic, the dosage should be reduced or held for 3 days before reattempting therapy.⁴⁷

Cough: Persistent and nonproductive cough reported with all ACE inhibitors, resolves after drug discontinuance. The incidence of ACE inhibitor-induced cough has been estimated to range from 0.7% to 48% in a review of literature from the 1980's.⁴⁸ Later post marketing surveys reported an incidence rate of between 0% to 12%, while specifically designed prospective studies of cough reported an incidence between 7% to 15% within the general population.^{49,50,51,52} A Nigerian study showed incidence of 27% with a 3:1 female-preponderance.⁵³

The mechanism of cough is due to accumulation in the lungs of bradykinin and substance-P. This occurs because ACE is a substrate for many endogenous substances like the aforementioned ones, which tend to accumulate when ACE is inhibited.³ Various therapies have been explored for management of ACE inhibitor induced cough, but the most reliable method is to stop the ACE inhibitor therapy and initiate ARBS. In conditions where stopping therapy is not an option, other beneficial options are iron supplementation, inhalation local anaesthetic, cromolyn sodium inhalation, sulindac and diclofenac. Antitussives are found to be not effective.

Hyperkalemia: Hyperkalemia can develop, especially in those with renal impairment or DM and those receiving drugs that can increase serum potassium concentration (e.g. Potassium- sparing diuretics, potassium supplements, potassium containing salt substances).⁴⁷

Others: Other adverse drug reactions (ADRs) of ACE inhibitors include angioedema, chest pain, palpitations, tachycardia, stomatitis, abdominal pain, pancreatitis, hepatocellular injury or Cholestatic jaundice, alopecia, muscle cramps, paraesthesias, mood and sleep disturbances, and impotence.⁶

Drug interactions: Since the patients on ACE inhibitors require adjuvant therapy, drug interactions

play an important role. Table 2 lists some of the clinically significant drug interactions of ACE

inhibitors.

Table 2. Clinically significant drug interactions of ACE inhibitors^{5, 6, 7, 46}

S.No	Interacting drugs	Outcomes	Onset	Probable mechanism	Management
1	Allopurinol	May result in Stevens Johnson Syndrome	Delayed	Unknown	Monitor for hypersensitivity
2	Thiazides	First dose hypotension	Rapid	Diminished response to pressor amines	-
3	NSAIDs	May result in decrease antihypertensive and natriuretic effects	Delayed	Inhibition of prostaglandin synthesis	Monitor BP, hyperkalemia and acute renal failure
4	Potassium	Concurrent use of potassium and ramipril may result in hyperkalemia.	Delayed	lowered aldosterone levels	Monitor serum potassium for renal dysfunction and elderly patient.
5	Loop diuretics	Postural hypotension (first dose).	Moderate	Vasodilatation and relative intravascular volume depletion	Monitor for hypotension, fluid status, and body weight regularly for up to two weeks after dose adjustments.
6	Lithium	May result in lithium toxicity (weakness, tremor, excessive thirst, confusion) and/or nephrotoxicity.	Delayed	Unknown	Monitor serum lithium levels and follow for any evidence of lithium toxicity if ramipril is added to therapy; lower lithium doses may be required
7	Amiloride	Enhanced hypotensive effect/hyperkalemia	Delayed	Increased potassium retention secondary to lowered aldosterone levels	Monitor serum potassium level
8	COX 2 selective inhibitors	May result in decreased antihypertensive and natriuretic effects.	Minor	Interference with production of vasodilator and natriuretic prostaglandins	Caution especially in patients predisposed to or with preexisting nephropathy. Monitor blood pressure and cardiovascular function for a reduction in the efficacy of the ACE inhibitor. Also monitor patient for hyperkalemia or acute renal failure.
9	Digoxin	Increase in serum-digoxin concentrations	-	Deterioration of renal function	-
10	General anaesthetics	Marked hypotension may occur during general anaesthesia in patients receiving ACE inhibitors	-	-	-

Paediatric considerations: Safety and efficacy of ACE inhibitors is not established in children. No appropriate studies on the relationship of age to the effects of ACE inhibitors have been done. However, the use of ACE inhibitors in a limited number of neonates and infants has identified some potential paediatrics-specific problems. In neonates and infants there is risk of oliguria and neurologic abnormalities, possibly as a result of decreased renal and cerebral blood flow secondary to marked and prolonged reductions in blood pressure caused by ACE inhibitors, a lower initial dose and close monitoring are recommended.⁷

Safety in pregnancy: Women of childbearing age should be warned to notify their physicians immediately if they become pregnant during ACE inhibitor therapy. ACE inhibitors are not considered teratogenic if they are discontinued during the first trimester, but they are considered teratogenic in second and third trimesters.⁴⁷ There is evidence from animal studies that administration of ACE inhibitors during pregnancy is associated with foetal toxicity and can increase in still births. ACE inhibitors can cause severe disturbances of foetal and neonatal RF, pulmonary hypoplasia, and long-lasting neonatal anuria. All the ACE inhibitors are categorized by United States Food and Drug Administration's (FDA) pregnancy category C during the first trimester and pregnancy category D during the second and third trimesters.⁵⁴

Advice to the patients: The patients should be asked regarding the pregnancy status and should be advised to inform the doctor if they become or are willing to become pregnant. Patients should be also be informed regarding the first dose hypotension, dry cough, angioedema and other important side effects due to these drugs. In case if the patient misses a dose of drug he/she should be asked to take the dose as soon as possible. However if it is almost time for the next dose, then the dose should be skipped and the patient should go for the regular dose schedule from then on. The dose should never be doubled.⁵⁵

Conclusion: The clinical applications of ACE inhibitors are widening with newer dimensions in cardiovascular and related morbidities. The role of these agents in non cardiac indications is also strengthening. However the precautions and contraindications should be kept in mind while choosing the agents. The head on comparison between these drugs are lacking and warrants further research. Potential and preventable drug interactions and adverse drug reactions should not be neglected while selecting these drugs. It is also a noticeable

factor that majority of data available on ACE inhibitors are from white population.

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