VA Pharmacy Benefits Management Strategic Healthcare Group
-Medical Advisory Panel
Drug Class Review
Angiotensin Converting Enzyme Inhibitors

This review was adapted from the VISN # 12 P & T Review, written by Barbara Staley, Pharm.D., edited by Rick Weideman, Pharm.D., Patricia Barriuso, Pharm.D., Peter Glassman, M.D., Jeff Etchason, M.D., and Bill Korchick, M.D.

OBJECTIVE

1. To review the efficacy, safety, and administration of the currently available angiotensin converting enzyme inhibitors (ACEIs).

Table 1 Agents available in U.S.

GENERIC NAME	TRADE NAME	GENERIC AVAILABLE	MANUFACTURER	PATENT EXPIRATION
Benazepril	Lotensin®	No	Ciba/Norvartis	Aug 2003
Captopril	Capoten®	Yes	BMS & Various	Feb 1996
Enalapril	Vasotec®	No	Merck	Feb 2000
Fosinopril	Monopril®	No	BMS	Dec 2002
Lisinopril	Zestril®/Prinivil®	No	Zeneca/Merck	Dec 2001
Moexipril	Univasc®	No	Schwarz Pharma	Feb 2007
Quinapril	Accupril®	No	Parke-Davis	Aug 2001
Ramipril	Altace®	No	Hoechst- Marion Roussel	Jan 2005
Trandolapril	Mavik®	No	Knoll	not available

2. To define selection criteria when contracting these agents for the Veterans Health Administration

I. INDICATIONS

There are currently five main indications for the use of ACEIs; they include: hypertension (HTN), congestive heart failure (CHF), post myocardial infarction (post MI), left ventricular dysfunction (LVD) and the treatment of diabetic nephropathy (DN). Table 2 summarizes the clinical status of the ACEIs and their indications.

Table 2 FDA Approved Indications

GENERIC NAME	HYPERTENSION	CONGESTIVE HEART FAILURE	POST-MYOCARDIAL INFARCTION	LEFT VENTRICULAR DYSFUNCTION	DIABETIC NEPHROPATHY
Benazepril	Yes	No	No	No	No
Captopril	Yes	Yes	Yes	Yes[a]	Yes
Enalapril	Yes	Yes	No	Yes[b]	No
Fosinopril	Yes	Yes	No	No	No
Lisinopril	Yes	Yes[c]	Yes	No	No
Moexipril	Yes	No	No	No	No
Quinapril	Yes	Yes[c]	No	No	No
Ramipril	Yes	Yes[d]	No	No	No
Trandolapril	Yes	No	No	No	No

[a] symptomatic LVD post MI, [b] asymptomatic LVD, [c] adjunctive therapy , [d] CHF post MI

II. PHARMACOLOGY[1-3]

ACEIs work by suppressing the renin-angiotensin-aldosterone system. Angiotensin converting enzyme (ACE) catalyzes the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor which also stimulates aldosterone secretion from the adrenal cortex. Inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased sodium and fluid retention from aldosterone secretion. Decrease aldosterone secretion may result in a small increase of serum potassium. Due to the structural similarity to kininase II, ACE may play a role in the inactivation of bradykinin, which induces vasodilatation in vascular systems as well as possible bronchial constriction. The role of bradykinin in the therapeutic effects of ACEIs remains to be elucidated. Figure 1 illustrates the relationship of the renin-angiotensin-aldosterone system. [3]

III. PHARMACOKINETICS [1]

Table 3[a]

DRUG	ONSET/ DURATION (hrs)	PROTEIN BINDING	EFFECT OF FOOD ON ABSORPTION	ACTIVE METABOLITE	HALF-LIFE (hrs)[b]	ELIMINATION
Benazepril	1/24	>95%	none	benazeprilat	10 - 11	renal
Captopril	0.25/ dose related	25-30%	reduced	none	< 2	renal
Enalapril	1/24	NA	none	enalaprilat	11	renal
Fosinopril	1/24	≅95%	none	fosinoprilat	12	renal/hepatic
Lisinopril	1/24	NA	none	none	12	renal
Moexipril	1/24	≅50%	reduced	moexiprilat	12	renal/hepatic
Quinapril	1/24	≅97%	reduced [c]	quinaprilat	3	renal/hepatic
Ramipril	1 - 2/24	≅56%	reduced[d]	ramiprilat	13 - 17	renal/hepatic
Trandolapril	1/24	80%	none	trandolaprilat	16	renal/hepatic

[a]Adapted from Hebel SK, ed. Drug Facts and Comparisons, St. Louis: Facts and Comparisons Inc., 1996:164i.
[b] Half-life reflects active metabolite when appropriate; accumulation half-life reported
[c] Rate and extent of absorption decreases moderately (≈ 25-30%) with a meal high in fat; clinical relevance unclear
[d] Rate of absorption reduced, not extent

IV. CLINICAL EFFICACY

A. Treatment of Hypertension [1, 3-12]

All ACEIs are effective antihypertensives. Because ACEIs block the conversion of angiotensin I to angiotensin II, hypotensive effects may be seen due to decreased sodium and fluid retention and increased vasodilation. Although the hypotensive action of each of the ACEIs are similar, the reason to chose one agent over another may be dependent on differing pharmacokinetics properties. Most newer agents have relatively long half-lives and in general can provide 24-hour blood pressure control. However, some patients may require divided doses for adequate control.

B. Treatment of Congestive Heart Failure [13-15]

ACEIs decrease peripheral resistance, reduce afterload (peripheral vascular resistance), preload (pulmonary capillary wedge pressure), pulmonary vascular resistance and heart size, and increase cardiac output and exercise tolerance time in patients with heart failure.[16] Six of the nine ACEIs on the US market have FDA approval for the CHF indication.

A number of clinical trials with ACEI have resulted in beneficial effect for treatment of patients with CHF. The landmark study CONSENSUS [17] demonstrated a 40% reduction in mortality with enalapril in patients with severe heart failure. In subsequent studies, enalapril showed lower mortality at 2 years when compared with combination hydralazine and isosorbide (V-HeFT II), [18] and a decrease in mortality and hospitalization for heart failure in patients with heart failure and low ejection fraction (SOLVD) [19]. Other studies have shown that treatment with benazepril, quinapril, and/or fosinopril [20-23] significantly increases exercise tolerance in patients with heart failure although only quinapril and fosinopril have FDA approval for CHF and only fosinopril has proven benefits with or without concomitant digoxin. On the other hand, FDA approval for some ACEIs (lisinopril [16] and ramipril [24]) have been granted due to well designed post MI studies which showed a reduction in progression to CHF. Although trandolapril [25] does not currently have FDA approval for CHF, it has also been shown to decrease signs and symptoms and/or progression

to CHF post MI. To date, no studies have investigated the use of moexipril in CHF. Refer to Table 4 for a summary of these studies.

Table 4 Summary of Studies: ACEIs in CHF[a]

CLINICAL TRIAL	INCLUSION CRITERIA	RESULTS	DOSE
CONSENSUS I[17] Enalapril Multicentered, RDBPC 253 pts intention-to-treat	EF not available NYHA IV post MI > 60 d	Follow-up range 1 day - 20 months (mean: 6.3 mo) Overall reduction in mortality 40% with enalapril at 6 mo (p=0.002), and a 27% reduction at end of study (p=0.003) Crude Mortality 26% vs 44% in placebo at 6 mo (p=0.003) Reduction in progressive CHF 50% (p<0.0021) Premature termination in favor of enalapril	Enalapril 2.5 - 5 mg bid, ↑ as tolerated Max dose 20 mg bid final mean dose 18.4mg/d
V-HeFT II[18] Enalapril vs. Hydralazine/isosorbide (HYD/ISDN) Multicentered, RDB 804 pts	EF < 45% post MI ≤ 120 d	Follow-up range 6 months - 5.7 years Mortality after 2 yrs significantly ↓ with enalapril (18%) vs combination (25%) (p=0.016); Overall mortality tended to be lower with enalapril (p=0.08) Body O_2 consumption at peak exercise was ↑ only by HYD/ISDN group (p<0.05) & EF ↑ with both regimens	Enalapril 5 mg bid, ↑ as tolerated Max dose 20 mg/d final mean dose 15mg/d
SOLVD-Treatment[19] Enalapril Multicentered, RDBPC 4569 pts intention-to-treat	EF ≤ 35% symptomatic post MI > 28 d	Follow-up range 22 - 55 months (mean: 41.4 months) Mortality risk reduction of 16% with enalapril (p=0.0036) CV death risk reduction 18% (p<0.002) CHF death risk reduction 22% (p<0.0045) Hospitalization due CHF risk reduction 26% (p<0.0001)	Enalapril 2.5 mg bid, ↑ to 10 mg bid as tolerated Dose (pts): 2.5 mg qd (1.8%); 5 mg qd (6.7%); 10 mg qd (9.5%); 10 mg bid (49.3%)
Benazepril[20] Multicentered, RDBPC 172 pts randomized 2:1 treatment vs placebo	EF ≤ 35% NYHA II - IV	Follow-up 3 months; **No Risk Reduction Data** Exercise Duration Mean benazepril: +95 ± 12 sec from baseline vs placebo: +37 ± 18 sec (p=0.007) Symptoms of CHF improved by 1 or more NYHA class benazepril 31% vs placebo 15% (p=0.05)	Benazepril 2 mg; then 5 mg qd, ↑ to 20 mg qd as tolerated; pts were on stable doses of digoxin and diuretics Dose (pts): 2 mg qd (15%); 5 mg qd (18%); 10 mg qd (24%); 20 mg qd (43%)
Quinapril vs. Captopril[21] Multicentered, RDB 146 pts intention-to-treat	NYHA I - III	Follow-up 3 months; **No Risk Reduction Data** Exercise Duration Mean: quinapril: baseline 422.1 sec vs 12 wks 497.2 sec (p<0.05) captopril: baseline 451.7 sec vs 12 wks 519 sec (p<0.05) *Captopril had more homogeneous distribution NYHA I-III vs quinapril group which had more NYHA II (p<0.05) No significant difference in results between groups	Quinapril 10 mg qd x 4 wks, ↑ to 20 mg qd x 8 wks Captopril 25 mg bid x 4 wks, ↑ to 50 mg bid x 8 wks Pts remained on pre-study digoxin and diuretics
Quinapril[22] Multicentered, RDBPC-withdrawal trial 224 pts	EF ≤ 35% NYHA II - III	Follow-up 4 months; **No Risk Reduction Data** After ≥ 10 weeks of single-blind quinapril therapy pts were randomized in double-blind fashion to quinapril or placebo Exercise Duration Mean quinapril +3sec; from baseline vs placebo -16 sec (p=0.015) NYHA functional class (p=0.004) and quality of life were improved & signs and symptoms of CHF were lessened in quinapril therapy Therapeutic Failures quinapril 5 pts vs placebo 18 pts (p<0.001)	Quinapril 5 mg bid x 1 wk, ↑ to 10 mg bid as tolerated pts were on stable doses of digoxin and diuretics Dose (pts) 5 mg bid (19%); 10 mg bid (81%)
Fosinopril[23] Multicentered, RDBPC 241 pts	EF ≤ 35% mean: 25 ± 7% Exclusion with recent MI	Follow-up 6 months; **No Risk Reduction Data** Improvement in Exercise Tolerance fosinopril +28.4 sec vs -13.5 sec placebo (p=0.047) Hospitalized for Worsening CHF fosinopril (5.2%) vs placebo (9.6%) (p=0.226) Withdrawal for Worsening CHF fosinopril 16 vs placebo 40 (p=0.001)	Fosinopril 10 mg qd, ↑ to 20 mg qd as tolerated Digoxin discontinued prior to trial
Lisinopril vs. Captopril[26] Multicentered, RDBPC 387 pts	EF < 45% NYHA II - III	Follow-up 3 months; **No Risk Reduction Data** Exercise Duration lisinopril +47.2 sec; captopril +44.3sec 6 wks (p=0.77) exercise tolerance continued to ↑ for both 12 wks (p=0.68) No significant differences between groups *Compared to baseline, both treatment groups ↑ exercise duration at both 6 and 12 weeks significantly (p=0.0001)	Lisinopril (pts): 5 mg qd (44%) ↑ to 10 mg qd (38%) as tolerated; max 20 mg qd (18%) Captopril (pts): 12.5 mg bid (43%) ↑ to 25 mg bid (34%) as tolerated Max 50 mg bid (23%) Adjunct to digoxin & diuretic therapy

[a] RDBPC = randomized double blind placebo controlled; RDB = randomized double-blind, EF = ejection fraction, NYHA= New York Heart Association class of severity of CHF symptoms; sec = seconds; MI = myocardial infarction

C. Treatment of Left Ventricular Dysfunction and Prevention of Heart Failure after MI [27-30]

Myocardial infarction (MI) may precipitate CHF due to a compensatory mechanism known as remodeling. Although initially beneficial, remodeling (left ventricular dilatation and hypertrophy) has been associated with progressive cardiac dysfunction over time. Several studies have shown that afterload reduction from an ACEI may prevent excessive remodeling and improve survival. Captopril (SAVE [31] & ISIS-4 [32]), lisinopril (GISSI-3 [16]), ramipril (AIRE [24]) and trandolapril (TRACE [25]) significantly decrease total mortality and prevent the progression of heart failure in patients who experienced an acute MI. However, patient populations and time of initial dose differed between studies.

Although no benefit was seen in patients administered early intravenous ACEI (CONSENSUS II [33]), several studies have since demonstrated benefit of early oral administration of an ACEI (GISSI-3 [16] & ISIS-4 [32]). One possible explanation for differing results is the potential of hypotension with intravenous enalaprilat, especially in the elderly, resulting in further myocardial necrosis.[16] A recent smaller single center study, PRACTICAL, [34] used early administration of both oral captopril and enalapril and showed improved LV function and prevented progression of ventricular dilation post MI. [25] Preliminary results from the Chinese Cardiac Study [35] also showed that early use of captopril is safe and prevents about 5 deaths per 1000 patients treated in the first month.

Both SAVE [31] and SOLVD-prevention [36] showed the beneficial effects of ACEI in patients with asymptomatic left ventricular dysfunction. GISSI-3 [16] and ISIS-4 [32] also demonstrated the safe use of nitrates in post MI, but with little effect on mortality. Table 5 summarizes these studies.

Table 5 Summary of Studies: ACEIs in Post-MI and/or Asymptomatic Left Ventricular Dysfunction[a]

CLINICAL TRIAL	INCLUSION CRITERIA	RESULTS	DOSE
SAVE [31] Captopril Multicentered, RDBPC 2231 pts intention-to-treat	EF ≤ 40% asymptomatic post MI 3 - 16 d	Follow-up range 24 - 60 months (mean 42) Average days post MI = 11 Total Mortality risk reduction for captopril 19% (p=0.019) CV Death risk reduction 21% (p=0.014) Progressive CHF risk reduction 37% (p=0.032) Hospitalized for CHF risk reduction 22% (p=0.019) Recurrent MI risk reduction 25% (p=0.015)	Captopril 6.25 - 12.5 mg initially , ↑ to 50 mg tid as tolerated 79% pts received 50mg tid
SOLVD-Prevention [36] Enalapril Multicentered, RDBPC 4228 pts intention-to-treat	EF ≤ 35% asymptomatic post MI > 28 d	Follow-up range 14.6 - 62 months (mean: 37.4 months) Total Mortality risk reduction for enalapril 8% (p=0.30) Development of CHF risk reduction 29% (p<0.001) Died or Hospitalized for New or Worsening CHF 20% (p<0.001)	Enalapril 2.5 mg bid, ↑ to 10 mg bid as tolerated average 16.7 mg/d final 20 mg/d (56% pts)
CONSENSUS II [33] Enalapril Multicentered, RDBPC 6090 pts enrolled 2952 pts followed for 6 months intention-to-treat	post MI within 24 hours	Proposed: 6 months; actual 41 - 180 days Early discontinuation of trial due to concern over possible early adverse hypotensive events in elderly No Risk Reduction Data Death enalapril (10.2%) vs placebo (9.4%) (p=0.26) Death due to CHF enalapril (3.4%) vs placebo (4.3%) (p=0.06) Change of Therapy due to Heart Failure enalapril 27% vs placebo 30% (p≤0.006)	Enalaprilat (IV) 1 mg over 2 hours, 6 hours later, enalapril 2.5 mg bid, ↑ to 20 mg/d as tolerated
GISSI-3 [16] Lisinopril ± transdermal glyceryl trinitrate (GTN) Multicentered Randomized Open label 19,394 pts intention-to-treat	EF at 6 weeks post MI within 24 hours No patient selection	Follow-up 6 months Mortality risk reduction at 6 weeks with lisinopril 11% (p=0.03); Odds Ratio 0.88 (0.79-0.99) 6 week combined endpoint (death, clinical heart failure, EF ≤ 35%, akinesis, dyskinesis score > 45%): Lisinopril 8% reduction (p=0.009); Odds ratio 0.90 (0.84-0.98) 6 month combined endpoint: Lisinopril 6% reduction (p=0.03); Odds ratio 0.92 (0.86-0.99) No difference was found between patients with and without GTN	Pts. received 5mg initially, 5mg at 24 hrs., 10mg at 48 hrs, the 10mg qd for 6 weeks Lisinopril (pts): 2.5 mg (3.2%) to 5 mg (28.3%); ↑ to 10 mg (47.5%) qd as tolerated x 6 weeks Combination of lisinopril + GTN, IV nitroglycerin x 14h, then GTN 10 mg qd patch Transdermal GTN alone No treatment medication
AIRE [24] Ramipril Multicentered, RDBPC 2006 pts intention-to-treat	Clinical evidence and signs and symptoms of CHF (NYHA IV excluded) post MI 2-9 d	Follow-up 6 - 26 months (mean 15); post MI mean 5.4d Overall mortality risk reduction with ramipril 27% Total Mortality ramipril (17%) vs placebo (23%) (p=0.002) Secondary outcomes (death, severe/resistant heart failure, MI or stroke) 19% reduction with ramipril (p=0.008)	Ramipril 1.25 mg or 2.5 mg bid,↑ to 5 mg bid as tolerated
TRACE [25] Trandolapril Multicentered, RDBPC 1749 pts	EF ≤ 35% post MI 3-7 d	Follow-up 24 - 50 months (mean 26); study medication started 3-7 d post MI Relative Risk of Death in trandolapril group vs placebo was 0.78 (95 % CI, 0.67-0.91) Total Mortality 34.7% vs. 42.3% placebo; 22% reduction (p=0.001) Progressive CHF 125 pts vs. 171 placebo 29% reduction (p=0.003) CV Deaths 226 pts vs. 288 placebo; 25% reduction (p=0.001) Sudden Deaths 105 pts vs. 133 placebo; 24% reduction (p=0.03)	Trandolapril 2mg qd ↑ to 4mg qd (forced titration after 4 weeks)
ISIS-4 [32] Captopril Mononitrates Magnesium (Mg^{++}) iv Multicentered RPC 2x2x2 factorial design 58,050 pts intention-to-treat	post MI within 24 hours No patient selection	Follow-up 5 weeks & 1 year Total Mortality deaths at 5 weeks: captopril (7.19%) vs.(7.69%) placebo (2p=0.02) benefit persisted at 1 year mononitrates (7.34%) vs.(7.54%) placebo (2p=0.3) no further changes in survival curves at 1 year vs. 1 month Mg^{++}(7.64%) vs. (7.24%) open control (2p=0.07) no changes in mortality curve at 1 year, no significant survival advantages	Captopril 6.25 mg initially, then 12.5 mg 2 hrs later, then 25 mg 10 - 12hrs later, then 50 mg bid x 28 d Mononitrates (Imdur®) 30 mg initially, then 30 mg 10 - 12 hrs later, then 60 mg qd x 28 d Mg^{++} (IV) 8mmol bolus then 72mmol in 50mL over 24hrs

[a] RDBPC = randomized double blind placebo controlled; EF = ejection fraction, NYHA = New York Heart Association class of severity of CHF symptoms, MI = myocardial infarction

D. Renal Disease / Diabetic Nephropathy [37-39]

There are several proposed mechanisms in which ACEIs are believed to exert their beneficial effects in DN including reduction in systemic arterial blood pressure, reduction in intraglomerular pressure due to efferent vasodilation, and reduction in glomerular hypertrophy . [40] With the exception of a few studies, most studies evaluating ACEI in DN have been small, open label, and of short duration. From the studies available, ACEIs have decreased albumin excretion rates (AER) and slowed decline in renal function in both hypertensive and normotensive insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM) patients. Although to date no studies have shown reduction in mortality, progression to dialysis or transplantation in NIDDM patients The beneficial effects of ACEI may be independent of blood pressure control.

The Collaborative Study Group was one of the first groups to study captopril's renal protective properties in a large randomized multicentered double blind, placebo controlled trial in IDDM patients. [41] Serum creatinine concentration doubled in 25 patients receiving captopril and 43 patients on placebo ($p = 0.007$, relative risk reduction = 48%). The greatest risk reduction was seen in the patients with the highest baseline creatinine. Captopril treatment was associated with a 50% reduction in the risk of combined endpoints of death, dialysis and transplantation which appeared to be independent of blood pressure. Although beneficial effects were seen in the captopril group, baseline urinary protein excretion was higher in the placebo group than in captopril group ($p=0.02$). The authors did not address this in their conclusion.

In two other larger, randomized double blind, placebo controlled studies published, captopril significantly decreased progression to clinical proteinuria in patients with IDDM over placebo. [42,43] In contrast to the placebo group, the AER for captopril treatment group declined in both studies. These studies were important because it demonstrated the beneficial effects of administration of captopril during the early stage of microalbuminuria. Because the patients were normotensive, the beneficial effects of captopril suggest an additional renal specific mechanism rather than systemic blood pressure alone.

Ravid and associates[44] studied the long term renal effects of enalapril in 94 normotensive NIDDM patients with microalbuminuria and normal renal function. At the end of the 5 year follow up, the enalapril group showed little change in proteinuria, whereas proteinuria significantly increased in the placebo group by the end of the study period. A second phase of this study followed patients openly for 2 more years and patients were given the option to receive enalapril or no treatment. [45] For patients who continued enalapril, renal function and AER remained stable. Those patients who chose to discontinue enalapril a gradual but significant rise in serum creatinine and AER was noted. Stabilization of serum creatinine and AER was observed for patients who were initiated on enalapril. Although the authors claim enalapril has beneficial effects of renal function, creatinine clearance was not reported.

A recent randomized, double blind study[46] with 335 patients with mild hypertension, NIDDM and microalbuminuria has shown a significant decrease in UAE with lisinopril vs nifedipine SR at 12 months. Secondary outcome measures included metabolic control, lipid profile, and safety and tolerability. Although lisinopril reduced UAE rate significantly more than nifedipine, both treatments had similar effects on blood pressure and metabolic variables.

Smaller studies have examined the use of other ACEIs in diabetic patients. Two trials compared lisinopril to other classes of antihypertensives (atenolol + furosemide, atenolol alone and diltiazem). [47,48] Lisinopril and diltiazem as single agents reduce albuminuria to a significantly greater extent than the combination of atenolol and furosemide. Similar results were seen with lisinopril versus atenolol alone.

Another study reported beneficial effects of benazepril over placebo in renal diseases of differing etiologies, including DN. [49] Over a three year period, renal survival was significantly better in the benazepril group ($p<0.001$). Although only a small subset of patients had DN (21 pts), the proportion of these patients reaching the primary end point (doubling of serum creatinine or dialysis) was lower in the benazepril group than in the placebo group (1 of 6 vs. 7 of 15).

A recent study evaluated the use of quinapril in hypertensive patients (30 pts), and patients with both HTN and NIDDM (24 pts).[50] Microalbuminuria was defined as a urinary albumin excretion rate (UAE) at or above 15μg/min to 150μg/min. After 8 weeks, quinapril significantly reduced the UAE in both essential and diabetic hypertensive patients ($p<0.05$). UAE decreased from 32.5 ± 5.5 μg/min to 14.7 ± 3.7μg/min in the diabetic-hypertensive group ($p < 0.05$) and 27.5 ± 3.0 μg/min to 11.6 ± 2.7 μg/min ($p < 0.05$) in the hypertensive group.

A summary of the larger randomized double bind, placebo control trials can be found in Table 6.

Table 6. Summary of Studies: ACEIs in Renal disease and Diabetic Nephropathy

CLINICAL TRIAL	INCLUSION CRITERIA	RESULTS
Captopril [41] multicentered, RDBPC 409 pts	Onset IDDM < 30 yrs, age 18 - 49 yrs old, duration of DM ≥ 7 yrs, proteinuria ≥ 500 mg/24 h, $_{S}$Cr ≤ 2.5 mg/dL BP goal ≤ 140/90, no Calcium Channel Blocker (CCB) Captopril dose 25 mg tid	Follow up 3 yrs Captopril treatment 50% risk reduction for combined endpoints(death, dialysis, transplantation) $_{S}$Cr doubled in 25 captopril pts vs. 43 placebo patients (p=0.007) Mean rate of decline in CrCl for captopril pts was 11 ± 21%/yr vs. 17 ± 20%/yr in the placebo group (p=0.03) Pts with baseline $_{S}$Cr ≥ 1.5 mg/dL: rate of decline in CrCl for captopril pts was 23 ± 25%/yr vs. 37 ± 25%/yr (p=0.01)
Captopril [42] multicentered, RDBPC 92 pts intention-to-treat	Onset IDDM < 39 yrs, age 18 - 55 yrs old, duration of DM 4 - 28 yrs, AER 20 - 200µg/min, $_{s}$Cr < 1.7 mg/dL BP < 160/95 for pts ≥ 35 yrs or < 145/90 for pts < 35 yrs, no concomitant use of antihypertensives Captopril dose 50 mg bid	Follow up 2 yrs 12 pts placebo vs. 4 pts captopril progressed to clinical proteinuria (AER > 200µg/min or at least 30% ↑ from baseline) (p=0.05); AER ↑ in placebo 52 (39 - 68) to 76 (47 - 122) µg/min but ↓ from 52 (41 - 65) to 41 (28 - 60) µg/min in captopril group (p<.01) GFR was unchanged in captopril group; GFR tended to ↓ in placebo group (not significant)
Captopril [43] multicentered, RDBPC 143 pts	Onset IDDM < 45 yrs, age 14 - 57 yrs old, duration of DM 4 - 33 yrs AER 20 - 200 µg/min, $_{s}$Cr normal range BP < 140/90 no concomitant use of CCB or β-blockers Captopril dose 50 mg bid	Follow up 2 yrs Captopril treatment 67.8% risk reduction 18.6 % pts placebo vs. 6% pts captopril progressed to clinical proteinuria (AER > 200 µg/min and at least 30% above baseline) (Fisher's exact test p=0.037) AER ↑ annual rate 11.8% (CI -3.3% - 29.1%) in placebo and ↓ by 17.9% (CI-29.6% to -4.3%) in captopril group (p=0.004) CrCl for captopril group ↑ slightly 79 ± 3 to 83 ± 4 mL/min per 1.73m^2 vs placebo ↓ from 81 ± 3 to 72 ± mL/min per 1.73m^2 (p=0.033)
Enalapril [44] multicentered, RDBPC 94 pts	NIDDM, age < 50 yrs old, duration of DM < 10 yrs AER 30 - 300 mg/24 h Normotensive (BP ≤ 140/90) Enalapril dose 10 mg qd	Follow up 5 yrs Risk reduction of 30% (95% CI,15 - 45 p<0.001) 42% pts placebo vs. 12% pts enalapril progressed to clinical proteinuria (AER > 300 mg/24h) AER ↑ in placebo from 123 ± 58 to 134 mg/24 h in the 1st year and ↑ to 310 mg/24 h by the 5th year; AER ↓ from 143 ± 64 to 122 ± 67 mg/24 h with enalapril and then slowly ↑ to 140 ± 134 mg/24 h by the 5th year
Lisinopril[46] multicentered, RDB parallel group 335 pts	Stable NIDDM for > 3 months Males (18-75 yrs old); postmenopausal females (40-75 years old) Microalbuminuria and incipient nephropathy (UAE 20-300 µg/min)	Follow up 1 yr Lisinopril was associated with a fall in median UAE rate of 24.5 µg/min (range -210 to 699µg/min) at 6 months and 17µg/min (range -216 to 397 µg/min) at 12 months Nifedipine SR was associated with a net fall of 8µg/min (range -211 to 529 µg/min) and 2.0 µg/min (range -195 to 933 µg/min) at 6 and 12 months, respectively. Median differences between treatment groups at 6 months was 20 µg/min (CI -30 to -10 µg/min) (p=0.0002) and 20 µg/min (CI -32 to -9 µg/min) (p=0.0006)
Benazepril [49] multicentered, RDBPC 583 pts	CRI defined as $_{s}$Cr 1.5 to 4 mg/dl and a 24-hour estimated CrCl of 30 to 60 ml/min	Follow up 3 yrs glomerulopathies (n = 192), interstitial nephritis (n = 97), nephrosclerosis (n = 97), polycystic kidney disease (n = 64), diabetic nephropathy (n = 21), and miscellaneous/unknown (n = 104) A total of 88 pts (31 in the benazepril group and 57 in placebo group) reached primary end point (86 pts had doubling of base-line $_{s}$Cr and 2 required dialysis (renal survival was significantly better in the benazepril group (p<0.001) Of the pts with diabetic nephropathy 1 of 6 pts in the benazepril group and 7 of 15 in the placebo group reached the primary end point Overall unadjusted reduction in the risk of progressive renal insufficiency was 53% in the benazepril group. After an adjustment for supine diastolic pressure and AER the reduction in risk was 38 and 39% respectively which was significant

V. ADVERSE EFFECTS [1, 51-58]

Table 9[a,b]

SIDE EFFECT	MECHANISM	RISK FACTORS & COMMENTS
Hypotension (especially first dose)	Inhibition of renin angiotensin system	CHF Elderly High dose diuretics Malignant HTN Preexisting renal impairment Renal artery stenosis Renin-dependent HTN Sodium and/or volume depletion
Acute Renal Impairment	Inhibition of angiotensin II synthesis in the kidney	Aortic stenosis Bilateral renal artery stenosis CHF Diuretic therapy DM NSAID therapy Preexisting hypotension Preexisting renal impairment Sodium and/or volume depletion
Hyperkalemia	Reduction of aldosterone secretion	Exogenous potassium Hypoaldosteronism Potassium sparing diuretics Preexisting renal impairment
Dry Cough	Inhibition of breakdown of inflammatory mediator, bradykinin, in the lung; ↑ in local inflammatory mediators	Nonsmokers > smokers Usually occurs within 1st month Women > men
Skin Rash	Inhibition of kininase II ↑ kinin activity in skin and ↑ histamine-mediated inflammatory reactions	Dose related May not be cross reactive but expect with all agents Occurs in 1 - 5% treated for HTN See drug interactions, allopurinol
Dysgeusia	Most commonly with captopril (sulfhydryl group), however also occurs with enalapril (carboxyl)	May be self-limiting and dose related
Hepatotoxicity	Unknown Cross-reactivity could implicate all ACEIs	Rare but serious
Angioedema	Unclear mechanism Immune mediated kinins and/or genetic or environmental factors	History of idiopathic angioedema May be more common in blacks Most occur within 1st week although reports exist
Neutropenia	Unknown Neutropenia may be dose related	Renal, collagen-vascular, or autoimmune disease (concomitant use of immunosuppressants)
Other	Musculoskeletal pain and fatigue	

[a] Birth defects occur with all ACEIs and are contraindicated in pregnancy
[b] CHF = congestive heart failure; HTN = hypertension; DM = diabetes mellitus; NSAID = non-steroidal anti-inflammatory drug

VI. DRUG INTERACTIONS[54,58]

Table 10[a]

ACEI	INTERACTING DRUG	DESCRIPTION
All	Diuretics	Hypotension in the presence of sodium or volume depletion; may need to adjust dose of ACEI
All	*Lithium*	↑ toxicity; suggested mechanism is ACEI induced sodium depletion resulting in ↑ reabsorption
All	*NSAIDs*	NSAIDs ↓ antihypertensive effects due to inhibition of PG synthesis resulting in ↓ GFR, ↓ sodium and water excretion, and vasoconstriction
All	K^+ preparations K^+-sparing diuretics	Concomitant therapy may ↑ K^+ serum levels

[a] **Bold** serious drug interaction; *Italics* = moderate; Regular = minor

VII. DOSING AND ADMINISTRATION[1,59]

Like with many medications, the dose of any ACEI needs to be individualized with special consideration to age, indication, renal function, concomitant medications and/or comorbid diseases such as hepatic dysfunction. Caution should be used when starting any ACEI in the elderly, and in some cases half the usual initial dose should be administered. For patients who have difficulty swallowing tablets, ramipril capsules may be opened and sprinkled on applesause or mixed with orange juice or water. The primary route of elimination for most ACEI is renal. With the exception of fosinopril in which elimination is compensated partially by hepatobiliary elimination, the dose of the ACEI should be adjusted in renal dysfunction. In patients taking diuretics, symptomatic hypotension may occur following initiation of an ACEI. If the diuretic cannot be discontinued prior to initiation, a lower starting dose of an ACEI should be considered. Because African Americans are considered low renin producers, higher doses may be needed to see a therapeutic response in this population. Trandolapril is the only ACEI with FDA approved dosing recommendations in the African American population. Due to age and concomitant use of diuretics, lower initial doses should be considered in CHF patients. Doses then should be titrated to the maximum tolerated dose. Lower initial doses should also be administered for hemodynamically stable post-MI patients. In general, higher doses than usual maintenance range provides little therapeutic advantage (blood pressure control), although few patients may benefit. Proper monitoring within 1-2 weeks should occur after initiating an ACEI.

Table 11[a,b] Dosing

Doses	Benazepril	Captopril[c]	Enalapril	Fosinopril	Lisinopril	Moexipril[c]	Quinapril	Ramipril[e]	Trandolapril
Usual initial dose per indication (Usual target doses[d])	**HTN** 10 mg qd (10-40 mg qd or divided bid) **CHF** 5 mg qd (20mg qd)	**HTN** 25 mg bid or tid (50-150 mg in 2 or 3 divided doses) **CHF** 25 mg tid (25-50mg tid) **Post-MI** 12.5mg tid (25-50 mg tid)	**HTN** 5mg qd (10-40 mg qd or divided bid) **CHF** 5 mg bid (5-10mg bid) **ALVD[f]** 2.5 mg bid (10mg bid)	**HTN** 10 mg qd (20-40mg qd or divided bid) **CHF** 10 mg qd (20 mg qd)	**HTN** 10 mg qd (10-40 mg qd) **CHF** 5mg qd (20 mg qd) **Post-MI** 5 mg initially 5 mg 24 hrs 10 mg 48 hrs (10-20 mg qd)	**HTN** 7.5 mg qd (7.5-15 mg qd or divided bid)	**HTN** 10 or 20 mg qd (20-40 mg qd or divided bid) **CHF** 5 mg bid (10-20 mg bid)	**HTN** 2.5 mg qd (2.5-20 mg qd or divided bid) **CHF** 2.5 mg bid (5 mg bid)	**HTN** [whites] 1mg qd [African American] 2 mg qd (2 - 4mg qd) **Post-MI** 1 mg qd (4 mg qd)
Renal adjustment	yes CrCl <30 ml/min	yes CrCl < 30 ml/min	yes CrCl < 30 ml/min	no	yes CrCl < 30 ml/min	yes CrCl < 40 ml/min	yes CrCl < 30 ml/min	yes CrCl < 40 ml/min	yes CrCl < 30 ml/min

[a] Adapted from Hebel SK ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 1996: 164h-165p.
[b] Adapted from Heart failure: Management of patients with left ventricular systolic dysfunction. Clinical Practice Guideline, No. 11. Rockville, MD. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 94-0613.
[c] One hour before meals - on an empty stomach
[d] Target CHF doses and post MI doses were derived from major trials and AHCPR guidelines; Except for captopril and enalapril, doses for CHF reflect doses used to increase exercise tolerance in CHF patients
[e] Ramipril capsule may be opened and the contents sprinkled on a small amount of applesauce or mixed in orange juice or water
[f] ALVD = asymptomatic left ventricular dysfunction

VIII. CONCLUSIONS[60,61]

Efficacy/Outcomes:

All ACEI are effective hypertensive agents although they may differ in pharmacokinetic properties.

Many clinical studies have documented the beneficial effects of ACEI in both symptomatic and asymptomatic left ventricular dysfunction. When used in patients with CHF, ACEI have been shown to improve survival , decrease progression of CHF, decrease hospitalization due to CHF, and increase exercise tolerance. Studies supporting mortality risk reduction for patients with CHF exist for captopril and enalapril. All patients with symptomatic CHF and decreased ejection fraction should be treated with an ACEI unless otherwise contraindicated.

Treatment with an ACEI post-MI has shown to prevent excessive remodeling and improve survival. These benefits have also been seen in patients with asymptomatic left ventricular dysfunction post-MI. Several studies support early administration (within 24 hours) of oral ACEI, although early oral administration with ACEIs should be used cautiously in patients who are hypotensive. Studies supporting mortality risk reduction for patients post MI or asymptomatic left ventricular dysfunction include captopril, enalapril, lisinopril, ramipril and trandolapril.

Very few large controlled studies exist with ACEI in the use of DN. Most of the larger studies have evaluated the efficacy of both captopril and enalapril. From the studies available, ACEIs have decreased AER and slowed decline in renal function in both hypertensive and normotensive IDDM and NIDDM patients. More studies are needed to evaluate effects of ACEI on end stage renal disease and/or dialysis as study end points.

Safety:

The major side effects appear to be related to the pharmacology of the ACEIs and have a similar incidence among agents. Others are idiosyncratic and cannot be predicted. With the exception of captopril, there does not appear to be any major differences in adverse effects or drug interactions between ACEIs.

Compliance and Cost:

Although most agents can be given once a day for blood pressure control, many are given twice a day when adequate control is not achieved. Most agents are given twice a day for patients with CHF. Many of the ACEIs have one price for all tablet and/or capsule strengths. However, this advantage is lost if bid administration is required.

IX. RECOMMENDATIONS

- Captopril is unique in that it clearly has the shortest duration of effect, which is important in frail patients in need of a slow titration with an ACEI. It has been approved for the most FDA indications and therefore provides the broadest base of experience. Captopril is available as a generic and can be provided at a favorable cost. It, therefore, should be included for formulary addition.

- Many studies and review articles address the beneficial effects of ACEI for numerous indications. Although the results of several smaller studies for various indications in general match the findings of larger studies, agents used in the larger well controlled studies should be heavily considered. In conjunction with FDA approved indications, an emphasis should be placed on those agents which contain mortality data for both CHF and post-MI. Captopril aside, two other long acting ACEIs should be considered for formulary addition based on efficacy, outcomes, safety and price.

- Due to compliance and cost, a true once a day long acting agent is preferred. Although most agents can be used once a day for hypertension, many are given twice a day for better blood pressure coverage. Also, several agents are given twice a day for CHF. Target ranges have been derived from the clinical trials. It is important to achieve target dosing ranges to see maximum benefit in patients with CHF.

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