Pharmacology and Therapeutics Committee
Submitted: October 31, 2001

A.H.F.S 24:04

ANGIOTENSIN-CONVERTING ENZYME INHIBITOR (ACE INHIBITOR) CLASS REVIEW

Indications:

Table 1

HPB Approved Indications[1]

	Hypertension	Heart Failure	Post AMI
[a]**Benazepril** (Lotensin™; Novartis)	✓[b]		
[c]**Captopril** (Capoten™; BMS; generics)	✓[d]	✓[e]	✓
Cilazapril (Inhibace™; HLR)	✓	✓	
Enalapril (Vasotec™; Merck Frosst)	✓	✓	
Fosinopril (Monopril™; BMS)	✓[b]	✓[e]	
Lisinopril (Prinvil™, Merck Frosst; Zestril™, AstraZeneca; generics)	✓[d]	✓[e]	✓[f]
Perindopril (Coversyl™; Servier)	✓[b]		
Quinapril (Accupril™; Parke-Davis)	✓[e]	✓[e]	
Ramipril (Altace™; HMR)	✓		✓
Trandolapril (Mavik™; Knoll)	✓		✓

a) data for use in diabetic nephropathy exists, but is not an approved indication
b) mild to moderate essential hypertension
c) also used in treatment of diabetic nephropathy in patients with type IDM and retinopathy
d) essential or renovascular hypertension
e) adjunctive therapy with a diuretic
f) within 24 hours of myocardial infarction

Pharmacokinetics:

A summary of pharmacokinetic properties is outlined in Table 2. Subtle pharmacokinetic differences exist between the various ACE inhibitors. Differences in absorption, or bioavailablity, exist among agents, but they have little clinical significance.[2] Captopril is the only ACE inhibitors that are affected by food and as such should be given on an empty stomach. All ACE inhibitors,

with the exceptions of captopril and lisinopril, are pro-drugs and need to be converted by liver metabolism.

In respect to onset of action, oral captopril and intravenous enalaprilat have the fastest initial onset of action. The peak onset of action is reached in about an hour with captopril and 30 minutes with enalaprilat.

The trough-peak ratios are used in determining once daily dosing. Ratios above 50% can be suitable for once daily dosing, however higher ratios are preferable. Perindopril has the highest ratio between 75-100%, while ramipril and trandolapril have rations between 50-63% and 50-100% respectively. Enalapril is on the border of once daily dosing with a trough-peak ratio of 40-79%.

All ACE inhibitors need to be adjusted in renal failure with the exception of fosinopril. Fosinopril is eliminated by both the renal and hepatic routes, making it the only ACE inhibitor that does not need to be adjusted in renal or hepatic failure. Benazepril, cilazapril and fosinopril do not need adjustment during dialysis while all other ACE inhibitors are removed during dialysis.

Table 2:

Summary Of Pharmacokinetic Properties Of ACE Inhibitors[1,3,4,5]

			Onset of Action[a]				Half Life[a]		
	Prodrug	**Active Metabolite**	**Initial (h)**	**Peak (h)**	**Duration of Action (h)[a]**	**Trough-Peak Ratios[2,3] (%)**	**Parent (h)**	**Metab-olite (h)**	**Effect if Taken with Food**
Benazepril	Yes	benazeprilat	-	2-6	24	40	0.6	22	ø
Captopril	No	NA	15-30 min	1-1.5	8-12	25	2	NA	↓ absorption by 15-50%. Take on an empty stomach
Cilazapril	Yes	cilazaprilat	1-2[b]	2-5[c]	24	-	1.3	30-50	ø
Enalapril	Yes	enalaprilat	1-4[d]	8-18[e]	24[f]	40-79	1.3	11	ø
Fosinopril	Yes	fosinoprilat	1	2-7	24	64	minutes	12	ø
Lisinopril	No	NA	1	6	24	30-70	12	NA	ø
Perindopril	Yes	perindoprilat	1.5	3-7	24	75-100	1	5-10	↓ absorption by 35%. Take on an empty stomach
Quinapril	Yes	quinaprilat	1	2-4	12-24	<10-40	0.8	2-25	ø
Ramipril	Yes	ramiprilat	1-2	3-6	24	50-63	1-5	13-17	ø
Trandolapril	Yes	trandolaprilat	-	-	24	50-100	0.6-1.3	16-24	ø

- = unknown or no data available; NA = not applicable

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a) for PO route of administration and for hypertension only, unless otherwise stated
b) 3-5 hours in CHF
c) 6 hours in CHF
d) IV administration = 30 minutes
e) IV administration = 0.5-4 hours
f) IV administration = 8-12 hours after single dose only

Table 2 (cont.)

Comparative Angiotensin Converting Enzyme Inhibitors Pharmacokinetics (cont.) [1,3, 4,5]

	Bioavail-ability (%)[g]	Metabolism	Excretion[g] % un-changed	Excretion[g] % renal	Excretion[g] % hepatic	Protein Binding Parent (%)	Protein Binding Metab-olite (%)	Adjustment in Renal Failure	Adjustment in Liver Failure	Adjustment in HD/PD
Benazepril	37	Liver	20	33	12	96	90	Yes	No	No
Captopril	70-75	Liver (50%)	30-40	95	-	25-30	NA	Yes	No	Yes[h]
Cilazapril	50-75	Liver	80-90	53	-	-	-	Yes	Yes	No
Enalapril	60	Liver (70%)	43	61	33	-	50-60	Yes	Yes/No[i]	Yes[h]
Fosinopril	30-36	Liver	9-16	44	46	89-96	-	No[j]	No	No
Lisinopril	25	Liver (7%)	80-90	29	69	minimal	minimal	Yes	No	Yes[h]
Perindopril	75	Liver (90%)	<10	75	25	10-20	60	Yes	No	Yes[h]
Quinapril	50	Liver (extensive)	30	55	33	-	97	Yes	Yes/No[i]	Yes[h]
Ramipril	60	Liver (extensive)	10-21	40-60	40	73	56	Yes	No	Yes[h]
Trandolapril	10	Liver (extensive)	-	33	66	80	94	Yes	Yes	-

HD = hemodialysis; PD = peritoneal dialysis
- = unknown or no data available; NA = not applicable
g) for PO route of administration and for hypertension only, unless otherwise stated
h) supplement 25% of dose post HD; no adjustment necessary for PD
i) questionable depending on severity of liver dysfunction. Monitor BP (expect ↓ efficacy of drug with ↑ liver dysfunction)
j) only in severe renal dysfunction should the dose be reduced by 25%

CLINICAL EFFICACY

Hypertension:

All currently available ACE inhibitors are indicated for hypertension (Table 1). Enalaprilat and captopril are the only ACE inhibitors that have been investigated for efficacy in hypertensive crisis.[2] All ACE inhibitors have studies published in the treatment of hypertension and the major studies for use of ACE inhibitors in the treatment of hypertension, and especially in diabetics are outlined in Table 3.

The last report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI), published in 1997, recommends that when drug therapy is required to achieve good blood pressure control, diuretics or β-blockers be used as first-line agents for uncomplicated hypertension[6]. ACE inhibitors are recommended as first-line therapy in patients with type I diabetes mellitus with proteinuria, patients with heart failure, and patients who have had a myocardial infarction.[4,6]

Since the publication of JNC-VI, many other studies have included ACE inhibitors as first-line therapy for treating hypertension. As a result the Canadian Guidelines for the Treatment of Hypertension will be changed to include low dose thiazide-like diuretics; beta blockers (only if age

<60 years); ACE inhibitors; and long-acting dihydropyridine calcium antagonists as first-line agents.[7]

The Captopril Prevention Project (CAPPP) was a prospective intervention trial that compared cardiovascular morbidity and mortality in uncomplicated hypertensive patients receiving an ACE inhibitor or conventional therapy which included diuretics and/or β-blocker (Table 3). The results showed that there was no difference in the efficacy of the two groups in preventing cardiovascular morbidity and mortality, showing that ACE inhibitors are just as effective as conventional first-line therapy.

The United Kingdom Prospective Diabetes Study Group trial (UKPDS 39) was designed to evaluate the effects of tight blood pressure control with either a β-blocker (atenolol) or an ACE inhibitor (captopril) on macrovascular and microvascular complications on type 2 diabetes (Table 3). Results indicated that captopril and atenolol were equally effective at lowering blood pressure and reducing the risk of macrovascular endpoints. Also, tight blood pressure control (<150/<85) was associated with a relative risk reduction of complications than patients who did not vigorously control their blood pressure (<180/<105). The authors concluded that there is no difference between β-blockers and ACE inhibitors in reducing blood pressure in hypertensive type 2 diabetics.

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial was designed to compare enalapril and nisoldipine in type 2 diabetes, in normotensive and hypertensive groups, in the prevention or slowing of nephropathy, neuropathy, retinopathy, and cardiovascular events (Table 3). Sixty-seven months into the study, the Data and Safety Monitoring Committee (DSMC) observed a significant difference in cardiovascular event rates between the hypertensive cohorts: Patients receiving enalapril had fewer cardiovascular events than those receiving nisoldipine. The DSMC opened the randomization code for this cohort and recommended that all patients randomized to nisoldipine be switched to enalapril. The authors' concluded that ACE inhibitors may be the optimal initial antihypertensive medication in patients with diabetes.

The Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) was an open-label, single-center study that evaluated hypertensive type 2 diabetes with respect to diabetes control and cardiovascular events (Table 3). Both fosinopril and amlodipine had no significant differences in controlling blood pressure and had no effect on diabetic control in terms of hypo/hyperglycemia. However, fosinopril resulted in a significantly lower risk of major vascular events. The combined incidence of myocardial infarction, stroke, and hospitalized angina was significantly lower in the fosinopril group than the amlodipine group (7.6% vs 19.1%, p=0.03). The results of this study should be taken cautiously because of its open-label, single-center study design and because patients who received both study drugs had the lowest incidence of major cardiovascular events (3.7%).

The Ramipril Efficacy in Nephropathy (REIN) study tested the effectiveness of ramipril in limiting the progression of renal disease in non-diabetic nephropathies. Ramipril was compared to placebo plus conventional antihypertensive therapy targeted at achieving diastolic blood pressure less than 90 mm Hg (Table 3). There were two stratums in this study base on decline in renal function which was determined by urinary protein excretion. Stratum 1 was moderate renal dysfunction with 24 hour urinary protein excretion between 1-3 g/24 h and stratum 2 was severe renal dysfunction with urinary protein excretion > 3g/24h. The mean rate of GFR decline per month was significantly lower for patients receiving ramipirl in both stratums. The patients in stratum 2 had significantly less GFR decline than those on conventional therapy (0.39 mL/min vs 0.89 mL/min, p= 0.001), and

for this reason stratum 2 was discontinued, the randomization code opened and patients were to have the most effective therapy provided. Ramipril decreased end-stage renal failure by 56% over conventional therapy (p=0.01) for patients in stratum 1.

The Heart Outcomes Prevention Evaluation Study Investigators (HOPE) evaluated the effects of ramipril on cardiovascular outcomes in high risk patients with evidence of vascular disease or diabetes plus one other risk factor but no evidence of heart failure or low ejection fraction. Patients either received ramipril or placebo (Table 3). Results showed that there was a favourable outcome with use of ramipril when compared to placebo in terms of the primary endpoints of MI, stroke or death from cardiovascular disease (14% vs 17.8%, p<0.001). This and other treatment effects outlined in the study were independent of blood pressure reduction.

The MICRO-HOPE sub-study included 3577 people who had diabetes and who were included in the HOPE trial. Patients included had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction, and who were not taking any ACE inhibitors (Table 3). Results of this sub-population from the HOPE trial also showed favourable outcomes with ramipril use. Total mortality and overt nephropathy was significantly decreased by 24%.

Table 3: Summary of selected trials involving ACE inhibitors in the treatment of hypertension

CAPPP: Effect of ACE inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomized trial[8]	
# of Patients	10985 — Published: Lancet 1999
Study Design	Open label, randomized prospective trial with blinded endpoint evaluation.
Patient Population	Treated or untreated primary hypertension (diastolic > 100 mm Hg).
Study Length	6 years
Treatment	Captopril (50-100 mg/day) vs. Conventional therapy (diuretics and/or β-blockers).
Endpoints	Fatal and non-fatal MI, stroke and other cardiovascular deaths.
Findings	● Cardiovascular mortality was lower with captopril (76 vs. 95 events, p=0.092) ● Rate of fatal and non-fatal MI was similar (162 vs 161) ● Fatal and non –fatal stroke more common with captopril (189 vs 148, p=0.044)
Authors' Interpretation	Captopril and conventional treatment did not differ in efficacy in preventing cardiovascular morbidity and mortality. The difference in stroke risk is probably due to the lower levels of blood pressure obtained initially in previously treated patients randomized to conventional therapy.

UKPDS 39: Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes[9]	
# of Patients	1148 — Published: BMJ 1998
Study Design	Randomized prospective controlled trial
Patient Population	hypertensive patients with type 2 diabetes (mean blood pressure = 160/94 mm Hg).
Study Length	8.4 years
Treatment	Two groups: tight blood pressure control and less tight control. ● Tight blood pressure control: Captopril (25-50 mg bid) vs. atenalol (50-100 mg od) ± other adjunctive antihypertensives if needed (e.g., diuretics, calcium channel blockers, etc.) to achieve a target blood pressure of <150/<85 mm Hg. ● Less tight control: any antihypertensive medications other than ACE inhibitors or β-blockers (usually nifedepine was used) to achieve a target blood pressure of <180/<105.

Continued

Endpoints	Any diabetes related end point, deaths related to diabetes and all cause mortality.
Findings	● Captopril and atenolol were equally effective in reducing blood pressure to a mean of 144/83 mm Hg and 143/81 mm Hg respectively, with a similar proportion of patients requiring three or more antihypertensive treatments. ● captopril and atenolol were equally effective in reducing the risk of macrovascular end points. ● Tight blood pressure control was associated with reduction in the risk of diabetes related mortality and morbidity in hypertensive patients with type 2 diabetes.
Authors' Conclusion	Blood pressure lowering with captopril or atenolol was similarly effective in reducing the incidence of diabetic complications. This study provided no evidence that either drug has any specific beneficial or deleterious effect, suggesting that blood pressure reduction in itself may be more important than the treatment used.

ABCD: Antihpertensive therapy in type 2 diabetes: Implications of the Appropriate Blood pressure Control in Diabetes (ABCD) trial[10]

		Published:
# of Patients	950	Am J Cardiol 1998
Study Design	Blinded, randomized prospective trial	
Patient Population	Normotensive patients (DBP 80-89 mm Hg) n= 480 and Hypertensive patients (DBP >89 mm Hg) n =470	
Study Length	5½ years; after which randomization code was opened for all hypertensive patients (see Findings).	
Treatment	Two groups: ● Normotensive: nisoldipine vs enalapril vs placebo ● Hypertensive: nislodipine vs. enalapril ± open-label antihypertensives (metoprolol and hydrochlorothiazide)	
Endpoints	Prevention or slowing of nephropathy, neuropathy, retinopathy, and cardiovascular events	
Findings	● The incidence of fatal and non-fatal MI was significantly lower among those receiving enalapril compared to those receiving nisoldipine in the hypertensive group (5 vs 25 p=0.001). This trend was also seen in the normotensive group. ● These results were significant and after 67 months the Data Safety Monitoring Committee opened the hypertensive randomization code and recommended that all patients randomized to nisoldipine be switched to enalapril. ● The findings in the ABCD trial were based on secondary endpoints without a control group (due to ethical considerations). Therefore, whether the difference seen in the present study was secondary to the beneficial effects of enalapril vs. deleterious effect of nisoldipine, or this combination of the two is unknown.	
Authors' Conclusion	Results from the ABCD trial, showing a differential effect of nisoldipine versus enalapril on cardiovascular event rates, indicate that ACE inhibitors may be the optimal initial antihypertensive medication in patients with diabetes.	

FACET: Outcome results of the fosinopril vs. amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM[11,12]

		Published:
# of Patients	380	Diabetes Care 1998 Am J Cardiol 1998
Study Design	Open-label, randomized prospective trial	
Patient Population	NIDDM patients with hypertension (SBP >140 mm Hg or DBP >90 mm Hg)	
Study Length	3 years	
Treatment	● Fosinopril 20mg/day or amlodipine 10mg/day to achieve adequate blood pressure ● adequate blood pressure = if SBP/DBP < 160/110 at baseline than target blood pressure goal was SBP <140 mm Hg and DBP <90 mm Hg; otherwise a decrease of 20 mm Hg of SBP and DBP was the goal ● adjunctive therapy if needed was added and consisted of the treatment arm of the other study drug (e.g., fosinopril + amlodipine)	
Endpoints	All cause mortality, fatal or non-fatal stroke, fatal or non-fatal AMI, hospitalized angina, CABG, PTCA, and other cardiovascular events or procedures	

Continued

Findings	● Both treatments were effective in lowering blood pressure. ● The patients receiving fosinopril had a significantly lower risk of the combined outcome of AMI, stroke, or hospitalized angina than those receiving amlodipine (7.6 % vs 19.1% p=0.03). ● The patients who received both study drugs had the lowest incidence of major cardiovascular events (3.7%)
Authors' Conclusion	Fosinopril and amlodipine had similar effects on biochemical measures, but the patients randomized to fosinopril had a significantly lower risk of major vascular events, compared with the patients randomized to amlodipine.

REIN: Randomized placebo controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy[13,14]

		Published:
# of Patients	352	Lancet 1997 Lancet 1999
Study Design	Randomized, prospective, double blind, placebo controlled trial	
Patient Population	Two stratums based on baseline proteinuria: ● Stratum 1: 1-3 g/24 h ● Stratum 2: ≥3g/24 h) Patients were either hypertensive or normotensive and were all non-diabetic.	
Study Length	Mean follow up: 16 months. Stratum 2 randomization code was opened early because of the favourable effect of ramipril on rate of GFR decline.	
Treatment	Ramipril or placebo plus conventional antihypertensive therapy targeted at achieving diastolic blood pressure under 90 mm Hg	
Endpoints	Rate of GFR decline and time to doubling of baseline serum creatinine or end-stage renal failure.	
Findings	The mean rate of GFR decline per month was significantly lower in the patients in the ramipril group than in the placebo group for both stratums: ● Stratum 1: 0.53 vs 0.88 ml/min, p=0.03 ● Stratum 2: 0.39 vs 0.89 ml/min, p=0.001 ⇒ these results were significant and as a result this stratum was discontinued and the randomization code was opened early. For patients in stratum 1, ramipril decreased the risk of end-stage renal failure by 56% (p=0.01) compared with conventional therapy.	
Authors' Interpretation	In chronic nephropathies with proteinuria of 3 g or more per 24 h, ramipril safely reduces proteinuria and the rate of GFR decline to an extent that seems to exceed the reduction expected for the degree of blood-pressure lowering.	

The HOPE Investigators: Effects af an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in the high risk patients[15]

		Publsished:
# of Patients	9297	N Engl J Med 2000
Study Design	Randomized, prospective, double blind, placebo controlled trial	
Patient Population	55 years old and over, with no evidence of heart failure or low ejection fraction, and with a history of CAD, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol, elevated LDL, cigarette smoking or documented microalbuminuria).	
Study Length	5 years	
Treatment	Ramipril 10 mg/d or placebo	
Endpoints	MI, stroke, or death from cardiovascular disease	
Findings	14% of ramipril patients reached the primary endpoints (above) as compared to 17.8% of patients on placebo (p<0.001)	
Authors' Interpretation	Ramipril significantly reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure.	

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MICRO-HOPE: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy[39]		
# of Patients	3577	Published: Lancet 2000
Study Design	Multi-centred; prospective; randomized; placebo-controlled trial	
Patient Population	3577 people with diabetes who were included in the HOPE trial, who had a previous cardiovascular event or at least one other cardiovascular risk factor, no clinical proteinuria, heart failure, or low ejection fraction, and who were not taking ACE inhibitors	
Study Length	4.5 years	
Treatment	Ramipril 10 mg/day (n=1808) or placebo (n=1769)	
End Points	Primary: MI, stroke or cardiovascular death Secondary: total mortality, admission to hospital for CHF or unstable angina, cardiovascular revascularization or development of overt nephropathy	
Findings	Primary end point: 15.3% ramipril vs 19.8% placebo (25% RRR (95%CI 12-36), p=0.0004) Total mortality: 10.8% ramipril vs 14% placebo; 24% (8-37), p=0.004 Overt nephropathy: 6.5% ramipril vs 8.4% placebo; 24% (3-40), p=0.027 Dialysis: 0.5% ramipril vs 0.5% placebo; -20% (-205-53), p=0.7	
Authors' Conclusion	Ramipril was beneficial for cardiovascular events and overt nephropathy in people with diabetes. The cardiovascular benefits was greater than that attributable to the decrease in blood pressure. This treatment represents a vasculoprotective and renoprotective effect for people with diabetes.	

Heart Failure:

The mainstay of treatment and management of heart failure is through pharmacological intervention. There is an abundance of clinical trials and data that address the use of particular classes and agents, used alone and together, and used in symptomatic and asymptomatic patients. Currently diuretics, ACE inhibitors, and β-blockers, with or without digoxin are the main classes of agents used in the treatment and or management of heart failure.[16,17,18]

ACE inhibitors have beneficial effects in the treatment and prevention of heart failure. They have been proven to alleviate symptoms, prevent ventricular remodeling, favourably affect neurohormonal changes and, in effect, improve prognosis in patients in all clinical stages of heart failure (NYHA classes I-IV).[19] They have been shown to reduce mortality from either symptomatic or asymptomatic left ventricular dysfunction.[16]

Most data regarding the effect of ACE inhibitor use in heart failure comes from trials involving enalapril. Major trials that provided clear evidence that enalapril reduces mortality in patients with CHF (Table 4) include the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), the Studies of Left Ventricular Dysfunction (SOLVD) and the Vasodilator-Heart Failure Trial II (V-HeFT II)[20]. These trials were conducted in the late eighties and early nineties with SOLVD and V-HeFT II being published in 1991. More recently the Assessment of Treatment with Lisinopril and Survival (ATLAS) addressed the concern of optimal dosing of lisinopril in heart failure (Table 4). Smaller trials exist with other ACE inhibitors in heart failure, but the enalapril studies continue to be the driving force for use of ACE inhibitors in this disease. Currently, focus of ACE inhibitor trials are aimed at preventing heart failure after myocardial infarction.

The CONSENSUS trial is the only trial that evaluated the use of ACE inhibitors for effect on mortality in patients with NYHA class IV. This placebo controlled trial showed that enalapril at an average dose of 18 mg/day significantly reduced mortality with a relative risk reduction of 40% at six months and 31% at one year (Table 4). Mortality was reduced primarily through slowing the progression of heart failure. Two year follow-up showed that enalapril had a marked carryover effect on mortality lasting an additional 15 months.[16]

The SOLVD treatment trial studied patients with mild to moderate heart failure (NYHA classes II and III). Patients with chronic heart failure and an ejection fraction of ≤ 35% were randomly assigned enalapril at an average dose of 16.6 mg/day or placebo. Patients were followed for an average of 41 months. Enalapril resulted in a significant relative risk reduction of 16% in all cause mortality (Table 4). The major significant differences was death due to progressive heart failure and, mortality or hospitalization due to heart failure, with a relative risk reduction of 22% and 26% respectively.

The V-HeFT II trial compared enalapril with the combination of hydralazine and isosorbide dinitrate with patients who had NYHA classes II and III heart failure, and who were stabilized on digoxin and diuretics (Table 4). This was a continuation of the Veterans Administration Heart Failure Trial (V–HeFT I) which recruited patients similar to those in V-HeFT II and compared hydralazine and isosorbide dinitrate to placebo. After two years of follow-up in V-HeFT II, enalapril resulted in significantly less mortality than hydralazine plus isosorbide dinitrate, 18% and 25% respectively. These results are consistent with the V-HeFT I trial where the combination of hydralazine and isosorbide dinitrate decreased two-year mortality by 24% over placebo.[21] If the results of these two trials can be combined, then enalapril reduced two-year mortality by approximately 47% when compared with placebo.[16]

The optimal dosage of ACE inhibitors was studied in two trials, NETWORK and ATLAS.[22,23] The NETWORK trial was a randomized, double-blind, placebo controlled trial that evaluated the dose-response effects of enalapril on 1532 patients at 2.5 mg bid, 5 mg bid and 10 mg bid primarily to patients with NYHA class II heart failure (65%). Patients were followed for 6 months. The primary combined end-point of death, hospitalization from heart failure, and worsening heart failure occurred in 12.3%, 12.9% and 14.7% (p=NS) of patients receiving 2.5, 5 and 10 mg bid dosing respectively.[24] Mortality of these groups was 4.2%, 3.3% and 2.9% (p=NS) respectively. The authors concluded that increasing enalapril dose from 2.5 mg bid to 10 mg bid did not result in better clinical outcomes in patients with heart failure.[25]

Contrary to the NETWORK trial, ATLAS showed that high dose lisinopril was associated with better outcomes. ATLAS recruited patients with CHF (NYHA classes II-IV) with an ejection fraction ≤30%. Patients were stabilized on 12.5 or 15 mg/day of lisinopril before being randomized to a low dose group (2.5 or 5 mg/day) or high dose group (32.5 or 35 mg/day) and were followed for an average of 46 months. The primary end-point of all cause mortality decrease by 8% with high dose lisinopril (p=NS). Hospitalization was reduced by 24% (p=0.003) and the combined end-point of reduced hospitalization or all cause mortality decreased by 12% (p=0.002) with high dose lisinopril (Table 4).

Other ACE inhibitors have been studied in heart failure, but these trials have been much smaller. A 1995 meta-analysis of 32 clinical trials of ACE inhibitor identified 3381 patients who received enalapril, 1227 received ramipril, 875 received quinapril, 697 received captopril, 546 received

lisinopril and 379 received benazepril, perindopril, or cilazapril. Analysis showed no significant heterogeneity in mortality among the ACE inhibitors.[20]

Table 4: Selected trials of ACE inhibitors in heart failure

CONSENSUS: Effects of enalapril on mortality in severe congestive heart failure[26]		
# of Patients	253	Published: N Engl J Med 1987
Study Design	Randomized, prospective, double-blind, placebo-controlled trial	
Patient Population	Severe congestive heart failure (NYHA class IV)	
Study Length	1 year	
Treatment	Enalapril 10-40 mg/day (average dose 18 mg/day) or placebo + conventional therapy	
Endpoints	Mortality and cause of death	
Findings	● Mortality at six months: 44% placebo, 26% enalapril; 40% relative risk reduction, p=0.002 ● Mortality at one year: 52% placebo, 36% enalapril; 31% relative risk reduction, p=0.001 ● Total mortality: 54% placebo, 39% enalapril; 27% relative risk reduction, p=0.003	
Authors' Conclusion	The addition of enalapril to conventional therapy in patients with severe congestive heart failure can reduce mortality and improve symptoms. The beneficial effect on mortality is due to a reduction in death from the progression of hearth failure	

SOLVD: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure[27]		
# of Patients	2569	Published: N Engl J Med 1991
Study Design	Randomized, prospective, double-blind, placebo-controlled trial	
Patient Population	Congestive heart failure with ejection fractions ≤ 0.35 (90% were in NYHA classes II and III)	
Study Length	22-55 months (average follow-up 41.4 months)	
Treatment	Enalapril 2.5-20 mg/day (average dose 16.6 mg/day) or placebo + conventional therapy (not including prior ACE inhibitor use)	
Endpoints	All cause mortality	
Findings	● Mortality: 39.7% placebo, 35.2% enalapril; 16% relative risk reduction, p=0.0036 ● Cardiovascular mortality: 35.9% placebo, 31.1% enalapril; 18% relative risk reduction, p<0.002 ● Mortality due to heart failure: 19.5% placebo, 16.3% enalapril; 22% relative risk reduction, p<0.0045 ● Mortality or hospitalization due to heart failure: 57.3% placebo, 47.7% enalapril, 26% rrr, p<0.0001	
Authors' Conclusion	The addition of enalapril to conventional therapy significantly reduced mortality and hospitalizations for heart failure in patients with chronic congestive heart failure and low ejection fractions.	

V-HeFT II: A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure[18]		
# of Patients	804	Published: N Engl J Med 1991
Study Design	Randomized, prospective, double blind trial	
Patient Population	Men aged 18-75 receiving digoxin and diuretic therapy for heart failure (NYHA classes II and III) with a maximum ejection fraction of ≤ 0.45.	
Study Length	6 months-5.7 years, average 2.5 years	

Continued

Treatment	enalapril 20 mg/day or hydralazine 300 mg/day + isosorbide dinitrate 160 mg/day
Endpoints	All cause mortality
Findings	Two year mortality: 25% hydralazine arm, 18% enalapril; 28% relative risk reduction, p=0.016
Authors' Conclusion	The similar two-year mortalitity in the hydralazine-isosorbide dinitrate arms in our previous Vasodilator-Heart Failure Trial (26%) and in the present trial (25%), as compared with that in the placebo arm in the previous trial (34%), and the further survival benefit with enalapril in the present trial (18%) strengthen the conclusion that vasodilator therapy should be included in the standard treatment for heart failure. The different effects of the two regimens (enalapril and hydralazine-isosorbide dinitrate) on mortality and physiologic end points suggest that the profile of effects might be enhanced if the regimens were used in combination.

ATLAS: Toleration of high doses of angiotensin-converting enzyme inhibitors in patients with chronic heart failure: results from the ATLAS trail[22,28]

# of Patients	3164	Published: Circulation 1999
Study Design	Randomized, prospective, double-blind trial	
Patient Population	CHF (NYHA classes II-IV) with an ejection fraction ≤0.3 and on diuretic therapy for a minimum of 2 months	
Study Length	median follow-up 46 months	
Treatment	Two groups prior to randomization: ACE inhibitor naïve patients and previous ACE inhibitor treated patients: ● ACE inhibitor naïve: titration of lisinopril from 2.5 mg/day to 12.5 or 15 mg/d ● Prior ACE inhibitor use: lisniopril 12.5 or 15 mg/d Two groups post randomization: Low dose group and high dose group: ● Low dose group (n=1596): lisinopril 2.5 or 5 mg/d ● High dose group (n=1568): lisinoptil 32.5 or 35 mg/d	
Endpoints	All cause mortality	
Findings[25]	Comparing low dose to high dose lisinopril, the higher dose resulted in a reduction of: ● hospitalizations or all cause mortality by 12% (p=0.002) ● number of hospitalizations by 24% (p=0.003) ● all cause mortality by 8% (p=NS) ● cardiovascular mortality by 10% (p=NS)	
Authors' Conclusion[25]	High dose ACE inhibitors with lisinopril was more effective than lower dose for treating congestive heart failure. High dose ACE inhibitor was associate with better outcomes.	

Acute Myocardial Infarction:

ACE inhibitors have become established as one of the cornerstones of medical treatment after an acute myocardial infarction.[29] The rationale behind using ACE inhibitors post-MI is based on the fact that the renin-angiotensin system is activated in the very early phase of AMI and carries deleterious consequences.[30] Currently there are four ACE inhibitors that are approved by the HPB for use post-MI and include captopril, lisinopril, ramipril and trandolapril (Table 1).

Several landmark clinical trials (Table 5) have evaluated the effect of ACE inhibitors with respect to mortality and morbidity in patients who have had an acute MI. The trials can be grouped into two categories: ACE inhibition within 24 to 36 hours post-MI and ACE inhibition at least 3 days after the MI. Trials involving ACE inhibitors within 24 to 36 hours include: the International Study of Infarct Survival (ISIS-4)[31] which studied captopril; the Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS II)[32]; and the Gruppo Italiano per lo Studio della Sopravivenza nell'Infarcto Miocardio III (GISSI-3)[33] studied lisinopril. Trials involving ACE inhibitors at least 3 days post-MI include: the Survival and Ventricular Enlargement (SAVE)[34] which studied captopril; the Acute Infarction Ramipril Efficacy (AIRE)[35]; and the Trandolapril Cardiac Evaluation (TRACE)[36].

ACE inhibition within 36 hours:

In the major clinical trials that evaluated mortality, only enalapril has been associated with a (nonsignificant) increase in mortality, and the CONSENSUS II trial was stopped early (Table 5). This trial differed from the other trials as enalapril was given very early and intravenously. All other studies have used oral ACE inhibitors.

The early use (<24 hours) of oral lisinopril and captopril, in GISSI-3 and ISIS-4 respectively, showed significantly that the use of these agents had a desirable effect on mortality (Table 5). The 18 895 and 58 050 patients in these respective trials were randomized to lisinopril or open control and, captopril or placebo. The study designs basically tested nonselective use of ACE inhibitors. Results demonstrate a small, but significant beneficial effect on survival by treating all patients for a period of approximately 1 month. In ISIS-4 the effect is still visible after 1 year.

Table 5: Selected trials of ACE inhibitors initiated within 24 hours of myocardial infarction

CONSENSUS II: Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction[32]		
# of Patients	6090	Published: N Engl J Med 1992
Study Design	Randomized, double-blind, placebo controlled trial.	
Patient Population	AMI and blood pressure above 105/65 mm Hg	
Study Length	follow-up to a maximum of 6 months	
Treatment	Enalapril or placebo was given: ● enalaprilat 1mg infusion given ● six hours after end of infusion, enalapril 2.5 mg bid given on day 1; 5 mg bid given on day 2; 10 mg daily on day 3; and 20 mg daily therafter nb. the dose was only titrated up based on blood pressure	
Endpoints	all cause mortality within six months	
Findings	The trial was stopped early by the safety committee due to increase mortality in the enalapril arm of the trial. ● all cause mortality was 10.2% vs. 9.4% (p=0.26) with enalapril and placebo respectively, at a maximum of 6 months follow-up ● death due to progressive heart failure was 4.3% vs 3.4% with enalapril and placebo respectively	
Authors' Conclusion	Enalapril therapy started within 24 hours of the onset of acute myocardial infarction does not improve survival during the 180 days after infarction.	
GISSI-3: Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction[33]		
# of Patients	18895	Published: Lancet 1994
Study Design	Randomized, 2x2 factorial, open label trial.	
Patient Population	AMI within 24 hours of symptom onset and no clear indications for or against the study treatments.	
Study Length	Follow-up for 6 months	
Treatment	● Oral lisinopril 5 mg at randomization and 10 mg/d for 6 weeks, or open control ● Intravenous GTN for 24 hours, started at a rate of 5 μg/min and increased until systolic blood pressure fell by 10% or below 90 mm Hg for 24 hours than transdermal GTN 10 mg/d for 14 hours each day for 6 weeks, or placebo	

Continued

Endpoints	All cause mortality
Findings	● Mortality was lower in the lisinopril group when compared to open control: 6.3% vs 7.1% (p=0.03) ● Combined end point of mortality, heart failure beyond day 4 of infarction, left ventricular ejection fraction ≤35%, or ≥45% myocardial segments with abnormal motion occurred in 15.6% and 17% (p=0.009) with lisinopril and open control respectively ● GTN did not alter mortality or the combined end points above
Authors' Conclusion	The results with the open design of GISSI-3 are highly consistent in terms of both efficacy and safety with those of the larger and blinded ISIS-4 study… (these) results can be directly translated into recommendations for treating confidently all hemodynamically stable patients who have had AMI within the previous 24 hours.

ISIS-4: A randomized factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction[31]

# of Patients	58 050	Published: Lancet 1995
Study Design	Randomized "2 x 2 x 2 factorial", double-blind, placebo controlled (captopril and mononitrate); (magnesium vs open control) trial	
Patient Population	Suspected AMI admitted within 24 hours of onset with no clear indications, or contraindications to the study medications.	
Study Length	5 week follow-up	
Treatment	• Captopril 6.25 mg initial dose; 12.5 mg 2 h later; 25 mg 10-12 h later and therafter 50 mg bid for 28 days vs matching placebo • One month of oral controlled-release mononitrate (30 mg initial dose titrated up to 60 mg daily) vs placebo • Twenty-four (24) hour of IV magnesium sulphate (8 mmol initial bolus followed by 72 mmol/24 hours) vs open control	
Endpoints	All cause mortality	
Findings	● Captopril reduced 5 week mortality by 7% (p=0.02); 7.19% vs 7.69% in the captopril and placebo groups respectively ● Mononitrate did not alter 5 week mortality ● IV magnesium therapy did not reduce 5 week mortality; 7.64% vs 7.24% (p=NS) in the magnesium and control groups respectively	
Authors' Conclusion	Because of its size, ISIS-4 provides reliable evidence about the effects of adding each of these three treatments to established treatments for acute MI. IV magnesium was ineffective, and although oral nitrate therapy appeared safe it did not produce a clear reduction in 1-month mortality. Other trials have shown that starting long-term converting enzyme inhibitor (CEI) therapy in the weeks or months after MI in patients with impaired ventricular function avoids about 2 deaths per 1000 patients per month of treatment. ISIS-4, GISSI-3, and smaller studies now collectively demonstrate that, for a wide range of patients without clear contraindications, ACEI therapy started early in acute MI prevents about 5 deaths per 1000 in the first month (2p=0.006), with somewhat greater benefits in higher-risk patients. This benefit from 1 month of early ACEI treatment seems to persist for at least the first year.	

ACE inhibition after 3 days:

Three clinical trials have evaluated mortality when using ACE inhibitors 3 days after an acute myocardial infarction: SAVE, AIRE and TRACE (Table 6). All three of these trials had a significant effect on decreasing mortality post-MI. However, the patient population, average time for treatment after MI and average follow-up differ in these trials.

The SAVE trial enrolled 2231 patients who did not have overt heart failure but who had an ejection fraction of ≤ 40%. All patients were required to have tolerated a test dose of captopril 6.25 mg before being randomized. Also, patients could not have residual overt ischemia, which was not the case in the AIRE and TRACE trials. Average time for treatment from myocardial infarction was 11

days and average follow-up was 42 months. Results showed a significant risk reduction of mortality and cardiovascular mortality of 19% and 21% respectively.

The AIRE trial enrolled 1986 patients who exhibited signs or symptoms of heart failure, so they may have been sicker than those patients in the SAVE trial. Average time for treatment from myocardial infarction was 5 days and average follow-up was 15 months. Results showed a significant risk reduction of mortality by 27% over placebo. Unlike the SAVE and TRACE trials, AIRE did not determine the impact of heart failure deaths on total mortality, which was a main contributor to the mortality benefit in those trials.

TRACE enrolled 1749 patients with electorcardiographic evidence of left ventricular dysfunction. Fourty-two percent (42%) of patients had signs and symptoms consistent with NYHA class I heart failure. Average time for treatment from myocardial infarction was 4.5 days, which is similar to the AIRE trial, and follow-up was between 24 and 50 months. Four-year mortality significantly decreased with the use of trandolapril over placebo, 34.7% vs. 42.3% respectively. Progression to severe heart failure had a statistically significant reduction with trandolapril over placebo, 9.3% vs. 11.8% respectively.

Table 6: Selected trials of ACE inhibitors used after 3 days in myocardial infarction

SAVE: Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction[34]	
# of Patients	2231
Published:	N Engl J Med 1992
Study Design	Randomized, double-blind, placebo controlled trial
Patient Population	Myocardial infarction with ejection fraction ≤ 40% but without overt heart failure or symptoms of myocardial ischemia
Study Length	Follow-up from 24-60 months, average 42 months
Treatment	● Within 3 to 16 days post-MI captopril 12.5 mg as an initial dose and increased gradually to 50 mg tid, or placebo ● Average time since MI: 11 days
Endpoints	All cause mortality + several other prospectively defined outcomes
Findings	● Total mortality was lower with captopril when compared to placebo: 20% vs 25% respectively, relative risk reduction 19% (p=0.019) ● Cardiovascular mortality: 17% vs 21%, risk reduction 21% (p=0.014) ● Mortality due to progressive heart failure: 3% vs 5%, risk reduction 36% (p=0.032)
Authors' Conclusion	In patients with asymptomatic left ventricular dysfunction after myocardial infraction, long-term administration of captopril was associated with an improvement in survival and reduced morbidity and mortality due to major cardiovascular events. These benefits were observed in patients who received thrombolytic therapy, aspirin, or beta-blockers, as well as those who did not, suggesting that the treatment with captopril leads to additional improvement in outcome among selected survivors of myocardial infarction.
AIRE: Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure[35]	
# of Patients	1986
Published:	Lancet 1993
Study Design	Randomized, double-blind, placebo controlled trial.
Patient Population	Definite myocardial infarction and signs of heart failure (even transient) in some period after the infarction. Patients with heart failure due to valvular heart disease, unstable angina, severe and resistant heart failure were excluded.
Study Length	Clinical follow-up for >6 months, average 15 months

Continued

Treatment	● Within 3 to 10 days post-MI patients received ramipril 2.5 mg increased to 5 mg bid (or 2.5 mg bid in case of intolerance) or placebo ● Average time since MI: 5 days
Endpoints	All cause mortality
Findings	● Total mortality was lower with ramipril when compared to placebo: 17% vs 23%, risk reduction 27% (p=0.002) ● Development of severe heart failure: 14% vs 18% (p=NS) ● No difference between the rates of stroke and reinfarction ● Combined end points of death, severe heart failure, myocardial infarction, or stroke developed in 28% vs 34%, risk reduction 19% (p=0.008) respectively of the ramipril and placebo groups,
Authors' Conclusion	Oral administration of ramipril to patients with clinical evidence of either transient or ongoing heart failure, initated between the second and ninth day after myocardial infarction, resulted in substantial reduction in premature death from all causes. This benefit was apparent as early as 30 days and was consistent across a range of subgroups.

TRACE: A clinical trial of the angiotensin-converting enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction[36]

# of Patients	1749	Published: N Engl J Med 1995
Study Design	Randomized, prospective, double-blind, placebo controlled trial	
Patient Population	Acute myocardial infarction with echocardiographic proof of left ventricular dysfunction without a definite need for ACE inhibition were included	
Study Length	Follow-up 24-50 months	
Treatment	● Within 3-7 days post-MI patients received trandolapril 1mg/day or placebo. The trandolapril dose was gradually increased to 1-4 mg/day ● Average time since MI: 4.5 days	
Endpoints	All cause mortality	
Findings	● Total mortality after 4 years was 34.7% in the trandolapril group and 42.3% in the placebo group, relative risk reduction 0.78 (p=0.001) ● Cardiovascular mortality: 25.8% vs. 33% risk reduction 0.75 (p=0.001) ● Rate of sudden death: 12% vs. 15.2%, risk reduction 0.76 (p=0.03) ● Progression to severe hearth failure: 9.3% vs. 11.8%, risk reduction 0.71 (p=0.003)	
Authors' Interpretation	Long-term treatment with trandolapril in patients with reduced left ventricular function soon after myocardial infarction significantly reduced the risk of overall mortality, mortality from cardiovascular causes, sudden death, and the development of severe heart failure. That mortality was reduced in a randomized study enrolling 25 percent of consecutive patients screened should encourage the selective use of ACE inhibition after myocardial infarction.	

The impressive results of ACE inhibitor trials in both groups: ACE inhibition within 36 hours and ACE inhibition after 36 hours have left debate over which approach is best.[30] A consensus of investigators in this field agreed that if the hemodynamics were satisfactory, patients with acute MI could benefit from earlier treatment. There was still some disagreement whether all patients should be treated or patients at clinically high risk.[30,37]

Adverse Reactions and Contraindications:

All ACE inhibitors share common adverse reactions and contraindications. Differences arise on the extent and severity of the adverse reactions. The most common side effects are cough and hypotension. Less common, but severe reactions, include hyperkalemia (in renal failure or with high doses of potassium retaining diuretics), acute renal failure (rare), angioedma (rare) and skin

reactions. Contraindications for using ACE inhibitors are bilateral renal artery stenosis, severe aortic stenosis or obstructive cardiomyopathy, and pregnancy.[3,4]

Drug Interactions

Most drug interactions with ACE inhibitors are aimed at preventing adverse reactions. Hypotensive agents and diuretics should be used cautiously in patients who are on ACE inhibitors (or vice versa) to prevent hypotension as there is an additive effect on blood pressure. Drugs that increase serum potassium concentrations (e.g., amiloride, spironolactone, triamterene) should also be used with caution since hyperkalemia may occur. Nonsteroidal Anti-inflammatory drugs (NSAIDs) may reduce the blood pressure response to ACE inhibitors. Lithium toxicity has occurred following concomitant administration of ACE inhibitors and lithium carbonate. Lithium levels should be monitored regularly and the dose adjusted accordingly while patients are receiving ACE inhibitors.

Dosage and Administration:

Comparative chart on ACEI dosing and pharmacokinetics is included in the Appendix.

Table 7

Dosage and Administration for ACE inhibitors[1,3,4]

		Heart Failure		
	Hypertension	**initial**	**maintenance**	**Post AMI**
Benazepril	10-80 mg od-bid			
Captopril	25-50 mg bid-tid	6.25 mg	up to 50 mg tid	50 mg tid
Cilazapril	2.5-5 mg od	0.5 mg	1-2.5 mg od	
Enalapril	5-20 mg od-bid	2.5 mg	up to 20 mg bid	
Fosinopril	10-40 mg od-bid	10 mg	20-40 mg od	
Lisinopril	10-40 mg od	5 mg	10-40 mg bid	10 mg od
Perindopril	4-8 mg od			
Quinapril	10-40 mg od-bid			
Ramipril	2.5-10 mg od-bid			2.5-5 mg bid
Trandolapril	0.5-4 mg od then 4 mg bid			1-2 mg od

Cost Comparison:

Table 8

Available Dosage Forms and Costs[1,38]

	Dosage Form	Cost ($)	Cost/day low[a] (high)[b]	Cost/Year low[a] (high)[b]		Dosage Form	Cost ($)	Cost/day low[a] (high)[b]	Cost/Year low[a] (high)[b]
Benazepril	5 mg 10 mg 20 mg	0.60 0.71 0.82	**$0.71** (**$3.28** for 80 mg od)	**$259** (**$1197**)	**Lisinopril**	5 mg 10 mg	0.51 0.83	**$0.83** (**$6.64** for 40 mg bid)	**$303** (**$2427**)
Captopril	12.5 mg 25 mg 50 mg	0.30 0.35 0.83	**$0.70** (**$2.49** for 50 mg tid)	**$255** (**$909**)	**Perindopril**	2 mg 4 mg	0.61 0.76	**$0.76** (**$1.52** for 8 mg od)	**$277** (**$554**)
Cilazapril	1 mg 2.5 mg 5 mg	0.30 0.35 0.41	**$0.35** (**$0.41** for 5 mg od)	**$128** (**$150**)	**Quinapril**	5 mg 10 mg 20 mg 40 mg	0.84 0.84 0.84 0.84	**$0.84** (**$1.68** for 40 mg bid)	**$306** (**$613**)
Enalapril	2.5 mg 5 mg 10 mg 20 mg	0.48 0.57 0.69 0.83	**$0.57** (**$1.66** for 20 mg bid)	**$208** (**$606**)	**Ramipril**	1.25 mg 2.5 mg 5 mg 10 mg	0.47 0.53 0.54 0.68	**$0.53** (**$1.36** for 10 mg bid)	**$193** (**$496**)
Fosinopril	10 mg 20 mg	0.80 0.96	**$0.80** (**$3.84** for 40 mg bid)	**$292** (**$1400**)	**Trandolapril**	not available	not available	-	-

a) based on lowest dose for use in hypertension (Table 7)
b) based on highest dose for hypertension or heart failure (Table 7)

Discussion:

All ACE inhibitors have been approved and studied for use in hypertension. All agents available will have an effect with blood pressure and in prolonging renal function in diabetics. However, unlike hypertension, only captopril, cilazapril, enalapril, fosinopril, lisinopril and quinapril are indicated for use in heart failure. Likewise, only captopril, lisinopril, ramipril and trandolapril are indicated for use in post-MI patients.

Enalapril has been exhaustedly studied in the use of heart failure in large, clinical, randomized placebo-controlled trials with favourable outcomes. No other ACE inhibitor has been subject to such large and numerous trials.

Captopril, lisinopril, ramipril and trandolapril have trials involving patients after myocardial infarctions. Both captopril and lisinopril have been studied for use in patients who have suffered a myocardial infarction within 24 hours, while ramipril, trandolapri and captopril have been studies for patients who have suffered a myocardial infarction between 3 and 10 days prior to treatment. Results in these trials are favourable for each category and each agent.

There is no question that ACE inhibitor therapy is a necessity for diabetic patients in order to prevent the many complications that occur with this disease process. Many ACE inhibitors have been studied with this patient population with impressive results. Selected studies of captopril, enalapril, fosinopril and ramipril used in diabetics have been presented in this evaluation. The

MICRO-HOPE trial is the most recent diabetic trial with favourable results, even when compared to the patients in the HOPE trial that were not diabetic.

Based on pharmacokinetics only enalapril, fosinopril, lisinopril, perindopril, ramipril and trandolapril should be dosed once daily based on trough-peak ratios. However, enalapril, lisinopril and ramipril are bordering on twice daily dosing base on the above ratio (trough-peak ratio > 50%). All ACE inhibitors need to be adjusted for renal dysfunction with the exception of fosinopril, which doesn't need to be adjusted in renal or hepatic failure and/or dialysis. Captopril and enalaprilat (intravenous form of enalapril) has the fastest onset of action, while captopril's time to peak effect is the quickest among all oral agents, and it also has the shortest duration of action.

Recommendations

It is recommended that captopril, enalapril, ramipril and fosinopril be kept on formulary based on the evidence presented in this evaluation.

Captopril is need for it's short half life and quick onset of action, as well it can be used post-MI.

Enalapril has been studied extensively in heart failure patients and should be used for this indication in all patients.

Ramipril, with the results of the AIRE trial, is effective and should be used in post-MI patients. Additionally, and albeit that this evaluation was not particularly aimed at evaluating treatment for diabetic patients, ramipril with the evidence from the MICRO-HOPE sub-study should be used for this population.

Fosinopril for it favourable pharmacokinetic properties of dual hepatic and renal excretion routes should be used in patients with either dysfunction so that dose adjustment and/or change in disease status does not need to be considered for appropriate dosing.

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Comparative Angiotensin Converting Enzyme Inhibitors Dosing and Pharmacokinetics

	Approved Indication	Dose (hypertension)†‡ a. Frequency b. Starting	Dose (hypertension)†‡ c. Maintenance d. Maximum	Onset of Action[a] Initial (h)	Onset of Action[a] Peak (h)	Duration of Action (h)[a]	Half Life[a] Parent (h)	Half Life[a] Metab-olite (h)	Metabolism	% renal excretion	Adjustment in Renal Failure	Adjustment in Liver Failure	Adjustment in HD/PD
Benazepril	Hypertension	a. od or bid b. 10 mg/d	c. 20-40 mg/d d. 80 mg/d	-	2-6	24	0.6	22	Liver	33	Yes	No	No
Captopril	Hypertension Heart Failure Post AMI Diabetic Nephrophaty	a. bid or tid b. 25 mg bid/tid	c. 25-150 mg/d d. 450 mg/d	15-30 min	1-1.5	8-12	2	NA	Liver (50%)	95	Yes	No	Yes[h]
Cilazapril	Hypertension Heart Failure	a. od or bid b. 2.5 mg/d	c. 2.5-5 mg/d d. 10 mg/d	1-2[b]	2-5[c]	24	1.3	30-50	Liver	53	Yes	Yes	No
Enalapril	Hypertension Heart Failure	a. od or bid b. 2.5-5 mg/d	c. 10-40 mg/d d. 40 mg/d	1-4[d]	8-18[e]	24[f]	1.3	11	Liver (70%)	61	Yes	Yes/No[i]	Yes[h]
Fosinopril	Hypertension Heart Failure	a. od b. 10 mg/d	c. 20-40 mg/d d. 80 mg/d	1	2-7	24	minutes	12	Liver	44	No[j]	No	No
Lisinopril	Hypertenision Heart Failure Post AMI	a. od b. 10 mg/d	c. 10-40 mg/d d. 80 mg/d	1	6	24	12	NA	Liver (7%)	29	Yes	No	Yes[h]
Perindopril	Hypertension	a. od b. 4 mg/d	c. 4-8 mg/d d. 8 mg/d	1.5	3-7	24	1	5-10	Liver (90%)	75	Yes	No	Yes[h]
Quinapril	Hypertension Heart Failure	a. od or bid b. 10 mg/d	c. 20 mg/d d. 80 mg/d	1	2-4	12-24	0.8	2-25	Liver (extensive)	55	Yes	Yes/No[i]	Yes[h]
Ramipril	Hypertension Post AMI	a. od b. 2.5 mg/d	c. 2.5-10 mg/d d. 20 mg/d	1-2	3-6	24	1-5	13-17	Liver (extensive)	40-60	Yes	No	Yes[h]
Trandolapril	Hypertension	a. od b. 1 mg/d	c. 1-2 mg/d d. 4 mg/d	-	-	24	0.6-1.3	16-24	Liver (extensive)	33	Yes	Yes	-

† These doses may vary from those recommended by the manufacturer. There is no exact dosage conversion when switching from one ACEI to another. It is suggested that patients be started on the lowest recommended initial dosage with subsequent adjustments based on the patient's response.
‡ If a patient is also receiving a diuretic, the starting dose of the ACEI should be lower and initiated under close medical supervision.
- = unknown or no data available; NA = not applicable; HD = hemodialysis; PD = peritoneal dialysis
a) for PO route of administration and for hypertension only, unless otherwise stated
b) 3-5 hours in CHF
c) 6 hours in CHF
d) IV administration = 30 minutes
e) IV administration = 0.5-4 hours
f) IV administration = 8-12 hours after single dose only
g) for PO route of administration and for hypertension only, unless otherwise stated
h) supplement 25% of dose post HD; no adjustment necessary for PD
i) questionable depending on severity of liver dysfunction. Monitor BP (expect ↓ efficacy of drug with ↑ liver dysfunction)
j) only in severe renal dysfunction should the dose be reduced by 25%

Appendix