Criteria for Nonformulary Use of Ramipril in Veteran Patients

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. The manufacturer's labeling should be consulted for detailed information when prescribing ramipril.

I. General Recommendations

It is generally believed that the benefits of the angiotensin-converting enzyme inhibitors (ACEIs) are a class effect. However, recognizing that not every provider concurs with this viewpoint, and in light of the benefits observed in the large randomized controlled Heart Outcomes Prevention Evaluation (HOPE) trial, criteria for ramipril have been developed. The criteria are intended to assist those facilities and/or VISNs in determining who may be eligible for ramipril, when requested by VA clinicians. Clinical trials are available demonstrating the benefit of an ACEI in patients with hypertension (HTN),[1-3] chronic heart failure (HF),[4-8] diabetes mellitus (DM),[9-16] renal disease,[17-19] and post acute myocardial infarction (MI)[20,21] especially in patients with left ventricular (LV) dysfunction.[22-24] The ACEI, ramipril, was studied in patients at high risk for cardiovascular (CV) events in the Heart Outcomes Prevention Evaluation (HOPE) trial.[25]

It should first be noted that:

- These criteria do not apply to patients with a history of HF or left ventricular ejection fraction (LVEF) < 40% (i.e., these patients were excluded from the HOPE trial). Patients with HF should receive another ACEI (unless contraindicated or not tolerated) currently on the VANF.
- These criteria do not apply to patients requiring treatment for uncontrolled HTN (i.e., the HOPE trial was not a HTN trial in that patients were either normotensive or had their blood pressure controlled with antihypertensive medications at baseline). If an ACEI is indicated for the treatment of HTN, another ACEI that is currently on the VANF should be considered to attain goal blood pressure.
- These criteria do not apply to patients who require an ACEI for renal disease. Such patients should be considered for another ACEI (unless contraindicated or not tolerated) currently on the VANF.
- These criteria do not apply to patients with a creatinine clearance < 40 ml/minute since a maximum dose of 5mg is recommended in these patients (for the treatment of HTN). In addition, a target dose has not been established since the mean serum creatinine in the HOPE study was approximately 1.06mg/dL, therefore, it is likely that patients with a creatinine clearance < 40ml/minute were not included in the study.
- If the patient is unable to tolerate ramipril 10mg, the drug should be discontinued and the patient changed to another formulary agent (ramipril dosages higher or lower than 10mg/day are not considered appropriate medical justification for nonformulary use as they were not used in the HOPE study and have not been demonstrated to provide clinical benefit over formulary ACEIs).
- These criteria do not apply to patients under 55 years of age, as those patients were not included in the HOPE trial.

II. Recommendations for the Use of Ramipril

It is recommended that another ACEI currently listed on the VANF be considered for patients who meet one or more of the exclusion criteria listed above.

Ramipril 10mg/day[a] may be considered for use in patients 55 years of age or older[b] with the following medical problems as adjunct therapy to reduce the risk of CV death, MI, and stroke (refer to Table 1).

History of one or more of the following:

☐ Coronary artery disease (CAD)
☐ Stroke (also refer to the discussion in section IV)
☐ Peripheral vascular disease (PVD)
(refer to the discussion in section III for recommendations in patients with DM)

[a] The premise for using ramipril over another ACEI is that a target dose of 10mg was used in the HOPE trial. Since the outcomes were not based on blood pressure reduction (although patients in the ramipril group experienced a reduction of 3/1 mm Hg vs. placebo), it has been argued that the equivalent target dose for other ACEIs is unknown. If it is determined that the patient fits the above criteria, ramipril should be titrated to the target dose of 10mg according to the following instructions:

- 2.5mg once daily X 1 week *
- 5mg once daily X 3 weeks *
- 10mg once daily *

* *It is recommended that patients be scheduled for a return visit each time the dose is increased to evaluate for potential side effects, determine adherence to the medication regimen, and to monitor the patient's blood pressure. As is recommended with all ACEIs, the patient's potassium and renal function should be monitored.*

[b] Since a large majority of patients enrolled in the trial were Caucasian (almost 90%), there is not enough information to determine whether ramipril provides similar benefit in patients of other ethnic origins.[26,27]

III. Recommendations for Patients with DM

Patients with DM (39%), plus at least one additional CV risk factor [i.e., HTN, increased total cholesterol (> 200 mg/dl), low HDL cholesterol (≤ 35 mg/dl), cigarette smoking, documented microalbuminuria] were also included in the HOPE trial. According to subgroup analyses, the benefit was consistent in patients with or without DM, evidence of CV disease, HTN, or baseline microalbuminuria.[25]

The MICRO-HOPE was a subanalysis of 3,577 patients with DM who participated in the HOPE trial. The primary endpoint of composite CV death, MI, or stroke was significantly decreased by 25% in patients who received ramipril compared to placebo (P=0.0004; ARR=4.5%, NNT=22). It should be noted that 60% of patients with DM had a history of CAD and 56% had concomitant HTN. Baseline blood pressure for patients on ramipril was 141.7/80.0 mm Hg compared to 142.3/79.3 mm Hg in patients randomized to placebo. The difference in change from baseline to final blood pressure was statistically significant (SBP: ramipril ↓ 1.9 mm Hg vs. placebo ↑ 0.55 mm Hg, P=0.008; DBP: ramipril ↓ 3.3 mm Hg vs. placebo ↓ 2.3 mm Hg, P=0.0002). The reduction in the primary endpoint remained significant (P=0.0004) after adjustments for the changes in blood pressure. The benefit was noted regardless of whether the patient had HTN or microalbuminuria (although the authors note that the study was not adequately powered to detect different effects in the subgroups).[28]

Other trials have shown cardiovascular benefit with an ACEI in patients with DM, although these trials were in patients with concomitant HTN.[1,9,10,14-16] Given the collective evidence, it is recommended that another formulary agent be selected when therapy is deemed appropriate in patients with DM and HTN.

IV. Additional Discussion in Patients with a History of Stroke

A subanalysis of patients who participated in the HOPE trial was conducted to determine the effect of ramipril on stroke risk. The risk of stroke was significantly decreased by 32% in patients who received ramipril compared to placebo (P=0.0002; ARR=1.5%, NNT=66.7). Mean blood pressure of patients who experienced a stroke was 143/79 mm Hg compared to 139/79 mm Hg in patients who did not develop a stroke. After control for baseline blood pressures and change in blood pressure, there was a 28% reduction in the risk of stroke in the ramipril group. The conclusions of the subanalysis were that patients at high risk for stroke should be treated with ramipril, in conjunction with other measures such as antihypertensive agents or aspirin.[29]

In another trial, the perindopril protection against recurrent stroke study (PROGRESS) randomized 6,105 patients with previous stroke or transient ischemic attack (TIA) to active treatment (perindopril 4mg, with the addition of indapamide 2.5mg left to the discretion of the clinician) or placebo. The primary endpoint of fatal or nonfatal stroke was reduced by 25% (P<0.0001; ARR=3.7%, NNT=27.1). Blood pressure reduction was on average 9/4 mm Hg in patients on active therapy compared to placebo. Patients on combination therapy (58%) experienced a blood pressure reduction of 12/5 mm Hg and a reduction in stroke risk of 43%, whereas single drug therapy with perindopril 4mg reduced blood pressure by 5/3 mm Hg with a reduction in stroke similar to placebo. The benefit with combination therapy over single drug therapy was consistent in patients with or without HTN. Approximately half of patients were receiving concomitant antihypertensive agents and most patients were taking antiplatelet agents.[30]

Table 1. Data from HOPE[25]

<table>
<tr><th>Trial</th><th>Methods</th><th>Results</th><th>Comments</th></tr>
<tr>
<td>HOPE[25]

R, DB, PC, 2X2 factorial</td>
<td>9297 pts at high-risk for CV events: CAD (80%), stroke or TIA (42%), PVD (42%), DM (39%) and at least 1 of the following: HTN (48%), +TOB (14%), microalbuminuria (21%), ↑TC (65%), ↓HDL (18%)

Excluded pts w/HF, LVEF < 40%, uncontrolled HTN, nephropathy, MI or stroke w/in 4 wks

Mean age: 66 yrs

Mean F/U: 4.5 yrs

RAM 10mg qd vs. placebo (also randomized to vitamin E 400 IU vs. PL)

PEP: Composite CV death, MI, stroke</td>
<td>
<table>
<tr><th></th><th>RAM n=4645</th><th>PL n=4652</th><th>RR (CI)</th><th>P value</th><th>ARR</th></tr>
<tr><td>PEP</td><td>651 (14.0%)</td><td>826 (17.8%)</td><td>0.78 .70-.86</td><td><0.001</td><td>3.7%</td></tr>
<tr><td>CV death</td><td>282 (6.1%)</td><td>377 (8.1%)</td><td>0.74 .64-.87</td><td><0.001</td><td>2.0%</td></tr>
<tr><td>MI</td><td>459 (9.9%)</td><td>570 (12.3%)</td><td>0.80 .70-.90</td><td><0.001</td><td>2.4%</td></tr>
<tr><td>CVA</td><td>156 (3.4%)</td><td>226 (4.9%)</td><td>0.68 .56-.84</td><td><0.001</td><td>1.5%</td></tr>
</table>
NNT for PEP: 26.7
</td>
<td>Secondary outcomes: all-cause death (P=0.005), revascularization (P=0.002), hospitalization for unstable angina (NS) or HF (NS), DM related complications (P=0.03)
Other outcomes: worsening angina (P=0.004), HF (P<0.001), development of DM (P<0.001), cardiac arrest (P=0.02)

Mean BP
BL: 139/79 mm Hg
End: 136/76 mm Hg (RAM), 139/77 mm Hg (PL)
(↓3/1 mm Hg vs. PL)

Patients on 10mg qd at 1 yr (83%), 2 yrs (74.6%), 3 yrs (70.9%), 4 yrs (62.4%), last visit (65%)

29% of pts on RAM discontinued tx

BL Medications
BB (39%), Diuretic (15%), CCB (46%), ASA/AP (75%), Antillipemic (28%)</td>
</tr>
</table>

AP=antiplatelet; ARR=absolute risk reduction; ASA=aspirin; BB=beta-blocker; BL=baseline; BP=blood pressure; CAD=coronary artery disease; CCB=calcium channel blocker; CI=95% confidence interval; CV=cardiovascular; DB=double-blind; F/U=follow-up; HDL=high-density lipoprotein cholesterol; HF=heart failure; HTN=hypertension; LVEF=left ventricular ejection fraction; MI=myocardial infarction; NNT=number needed to treat; NS=not significant; PC=placebo-controlled; PEP=primary endpoint; PL=placebo; PVD=peripheral vascular disease; RAM=ramipril; RR=relative risk; TC=total cholesterol; TIA=transient ischemic attack; TOB=cigarette smoking; wks=weeks; yrs=years

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References:

[1] Hansson L, Lindholm LH, Niskanen L et al for the Captopril Prevention Project (CAPPP) study group. Effect of angiotensin-converting enzyme inhibition compared to conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomized trial. Lancet 1999;353:611-16.

[2] Hansson L, Lindholm LH, Ekbom T et al for the STOP-Hypertension-2 study group. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity. The Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999;354:1751-6.

[3] Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials. Lancet 2000;355:1955-64.

[4] The Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. JAMA 1988;259:539-44.

[5] The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991;325:293-302.

[6] Cohn JN, Johnson G, Ziesche S et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303-10.

[7] The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.

[8] Garg R, Yusuf S. Collaborative Group on ACE Inhibitor Trials. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995;273:1450-56.

[9] U.K. Prospective Diabetes Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998;317:703-13.

[10] Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993;329:1456-62.

[11] Viberti G, Morgensen CE, Groop LC et al. Effect of captopril on progression to clinical proteinuria in patients with insulin dependent diabetes mellitus and microalbuminuria. JAMA 1994;271:275-9.

[12] Laffel LM, McGill JR, Gans DJ. The beneficial effect of angiotensin-converting enzyme inhibition with captopril on diabetic nephropathy in normotensive IDDM patients with microalbuminuria: North American Microalbuminuria Study Group. Am J Med 1995;99:497-504.

[13] Ravid M, Savin H et al. Long term stabilizing effect of angiotensin-converting enzyme inhibitors on plasma creatinine and proteinuria in normotensive type II diabetic patients. Ann Intern Med 1993;118:577-81.

[14]Tatti P, Pahor M, Byington RP et al. Outcome results of the fosinopril versus amlodipine cardiovascular events randomized trial (FACET) in patients with hypertension and NIDDM. Diabetes Care 1998;21:597-603.

[15] Estacio RO, Jeffers BW, Hiatt WR et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 1998;338:645-52.

[16] Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A for the CAPPP study group. Reduced cardiovascular morbidty and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared with a diuretic/beta-blocker-based treatment regimen: a subanalysis of the Captopril Prevention Project. Diabetes 2001;24:2091-6.

[17] Maschino G, Alberti D, Janin G et al for the Angiotensin-Converting Enzyme Inhibition and Progressive Renal Insufficiency Study Group. Effect of angiotensin-converting enzyme inhibitor benazepril on the progression of chronic renal insufficiency. N Engl J Med 1996;334:939-45.

[18] Giatras I, Lau J, Levey AS for the Angiotensin-Converting Enzyme Inhibition and Progressive Renal Disease Study Group. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Ann Intern Med 1997;127:337-45.

[19]The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomized placebo-controlled trial of effect of ramipril on decline in glomerular filatration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet 1997;349:1857-63.

[20] ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. 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. Lancet 1995;345:669-85.

[21] Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet 1994;343:1115-22

[22] Pfeffer MA, Braunwald E, Moye LA et al on behalf of the SAVE Investigators. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1992;327:669-77.

[23] The Acute Infarction Ramipril (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993;342:821-8.

[24] Kober L, Torp-Pedersen C, Carlsen JE et al for the Trandolapril Cardiac Evaluation (TRACE) Study Group. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995;333:1670-6.

[25] The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145-53.

[26] Package insert. Altace® (ramipril). Monarch Pharmaceuticals, Inc. Bristol, TN;July 2001.

[27] *Altace* revasculaarization benefit is clear but inappropriate for label-cmte. FDC Rep. 2000; 62(May 8).

[28] Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000;355:253-59.

[29] Bosch J, Yusuf S, Pogue J et al on behalf of the HOPE Investigators. Use of ramipril in preventing strike: double blind randomized trial. BMJ 2002;321:1-5.

[30] PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood pressure lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033-41.

Criteria Checklist for Ramipril

Exclusion Criteria	**#1**
Any of the following: ☐ Chronic heart failure (HF) or left ventricular ejection fraction (LVEF) < 40% ☐ ACEI selected for treatment of uncontrolled hypertension (HTN) ☐ ACEI selected for the patient with diabetes (with proteinuria or nephropathy) ☐ ACEI required for management of renal disease ☐ Creatinine clearance < 40 ml/minute ☐ Under 55 years of age	(≥ 1 answer) ☐ yes ☐ no *If yes, patient is not eligible to receive ramipril; recommend another ACEI on VANF*
Approved Criteria for Use	**#2**
Ramipril should only be used as adjunctive therapy for patients who do not meet the exclusion criteria above, who require no additional blood pressure reduction, and who have any one of the following (check all that apply): ☐ Coronary artery disease (CAD) ☐ Stroke ☐ Peripheral vascular disease (PVD) ☐ High risk patients with type 2 diabetes mellitus (DM)	(≥ 1 answer) ☐ yes ☐ no *If yes (and no for #1), patient is eligible to receive ramipril*
Recommended Titration	**#3**
➢ 2.5mg once daily X 1 week * ➢ 5mg once daily X 3 weeks * ➢ 10mg once daily * * *It is recommended that patients be scheduled for a return visit each time the dose is increased to evaluate for potential side effects, determine adherence to the medication regimen, and to monitor the patient's blood pressure. As is recommended with all ACEIs, the patient's potassium and renal function should be monitored.* ☐ Unable to tolerate ramipril 10mg	☐ yes ☐ no *If yes, ramipril should be discontinued*

Approved by Physician: _____ **Date/Time:** _____