

Criteria for Formulary 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 non-formulary 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}

July 2002; February 2003; February 2004

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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 (\leq 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 \downarrow 1.9 mm Hg vs. placebo \uparrow 0.55 mm Hg, P=0.008; DBP: ramipril \downarrow 3.3 mm Hg vs. placebo \downarrow 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 HOPE²⁵

Trial	Methods	Results					Comments																										
HOPE ²⁵ R, DB, PC, 2X2 factorial	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	<table border="1"> <thead> <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> </thead> <tbody> <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> </tbody> </table> <p>NNT for PEP: 26.7</p>		RAM n=4645	PL n=4652	RR (CI)	P value	ARR	PEP	651 (14.0%)	826 (17.8%)	0.78 .70-.86	<0.001	3.7%	CV death	282 (6.1%)	377 (8.1%)	0.74 .64-.87	<0.001	2.0%	MI	459 (9.9%)	570 (12.3%)	0.80 .70-.90	<0.001	2.4%	CVA	156 (3.4%)	226 (4.9%)	0.68 .56-.84	<0.001	1.5%	<p><u>Secondary outcomes:</u> all-cause death (P=0.005), revascularization (P=0.002), hospitalization for unstable angina (NS) or HF (NS), DM related complications (P=0.03)</p> <p><u>Other outcomes:</u> worsening angina (P=0.004), HF (P<0.001), development of DM (P<0.001), cardiac arrest (P=0.02)</p> <p style="text-align: center;"><u>Mean BP</u></p> <p>BL: 139/79 mm Hg End: 136/76 mm Hg (RAM), 139/77 mm Hg (PL) (↓3/1 mm Hg vs. PL)</p> <p>Patients on 10mg qd at 1 yr (83%), 2 yrs (74.6%), 3 yrs (70.9%), 4 yrs (62.4%), last visit (65%)</p> <p>29% of pts on RAM discontinued tx</p> <p style="text-align: center;"><u>BL Medications</u></p> <p>BB (39%), Diuretic (15%), CCB (46%), ASA/AP (75%), Antilipemic (28%)</p>
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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

HOPE was funded by the Medical Research Council of Canada, Hoechst-Marion Roussel, AstraZeneca, King Pharmaceuticals, Natural Source Vitamin E Association and Negma, and the Heart and Stroke Foundation of Ontario

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Criteria Checklist for Ramipril

<p>Exclusion Criteria</p> <p>Any of the following:</p> <ul style="list-style-type: none"> <input type="checkbox"/> Chronic heart failure (HF) or left ventricular ejection fraction (LVEF) < 40% <input type="checkbox"/> ACEI selected for treatment of uncontrolled hypertension (HTN) <input type="checkbox"/> ACEI selected for the patient with diabetes (with proteinuria or nephropathy) <input type="checkbox"/> ACEI required for management of renal disease <input type="checkbox"/> Creatinine clearance < 40 ml/minute <input type="checkbox"/> Under 55 years of age 	<p align="center">#1</p> <p>(≥ 1 answer)</p> <p><input type="checkbox"/> yes <input type="checkbox"/> no</p> <p align="center"><i>If yes, patient is not eligible to receive ramipril; recommend another ACEI on VANF</i></p>
<p>Approved Criteria for Use</p> <p>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):</p> <ul style="list-style-type: none"> <input type="checkbox"/> Coronary artery disease (CAD) <input type="checkbox"/> Stroke <input type="checkbox"/> Peripheral vascular disease (PVD) <input type="checkbox"/> High risk patients with type 2 diabetes mellitus (DM) 	<p align="center">#2</p> <p>(≥ 1 answer)</p> <p><input type="checkbox"/> yes <input type="checkbox"/> no</p> <p align="center"><i>If yes (and no for #1), patient is eligible to receive ramipril</i></p>
<p>Recommended Titration</p> <ul style="list-style-type: none"> ➤ 2.5mg once daily X 1 week* ➤ 5mg once daily X 3 weeks* ➤ 10mg once daily* <p><i>* 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.</i></p> <p><input type="checkbox"/> Unable to tolerate ramipril 10mg</p>	<p align="center">#3</p> <p><input type="checkbox"/> yes <input type="checkbox"/> no</p> <p align="center"><i>If yes, ramipril should be discontinued</i></p>

Approved by Physician: _____

Date/Time: _____