

# Angiotensin Converting Enzyme Inhibitors (ACEIs) Clinical Pearls for the Washington Rx Therapeutic Interchange Program (TIP)

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## Background

In 2003, the Washington State Pharmacy and Therapeutics Committee (P&T), the agency directors of the Department of Social and Health Services-Medical Assistance Administration (DSHS-MAA), Labor and Industries (L&I), and the Health Care Authority-Uniform Medical Plan (UMP) declared captopril, enalapril, lisinopril and ramipril to be the “preferred” ACE inhibitors for patients covered by their prescription insurance. Patients currently using “non-preferred” agents” must be evaluated for conversion to a preferred agent. Furthermore, patients covered by these state agencies presenting with prescriptions for non-preferred agents from “endorsing practitioners” (i.e., providers that have signed the TIP agreement) may be automatically converted to preferred agents by pharmacists once this program is operational.

## Purpose

The purpose of this document is to inform pharmacists of the clinical, safety and cost rationale for these policy changes and to optimize their ability to assure safe and effective conversion of patients to the appropriate agents.

## Overview:

Angiotensin Converting Enzyme Inhibitors (ACEI) is a drug class that has been defined by a specific mechanism of action within the renin-angiotensin-aldosterone system. However, these agents have wide ranging physiologic effects and benefits including lowering of blood pressure, reduction in ventricular remodeling following myocardial infarction, and slowing the progression of heart failure and diabetic nephropathy. These attributes have made provision of ACE inhibitors a key component in standards of care for numerous diseases and conditions.

## Current ACE Inhibitors available in the US

Benazepril (Lotensin®)	Captopril** (generic)	Enalapril* (generic)	Fosinopril (generic)	Lisinopril* (generic)
Moexipril (Univasc®)	Perindopril (Aceon®)	Quinapril (Accupril®)	Ramipril* (Altace®)	Trandolapril (Mavik®)

\* Washington State Evidence Based Preferred Drug List Agents

## 1. Clinical Efficacy

- Hypertension:
  - All ACEI have an FDA indication for treatment of hypertension.
  - All the DSHS preferred ACE inhibitors have been studied in large, randomized control trials, demonstrating the benefit of ACEI in hypertensive patients against placebo and other drug classes.
  - ACE inhibitors have been proven to be effective in patients with compelling indications, such as diabetes, renal insufficiency and post myocardial infarction.
  - There is consensus that all drugs in this class have equal efficacy in treating patients with hypertension.
- Cardiovascular risk
  - Based on results of the HOPE trial, ramipril is the only ACEI to demonstrate a decrease in all cause mortality in patients 55 years or older at high risk of developing a major cardiovascular event because of a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes accompanied by at least one other cardiovascular risk factor.
  - Ramipril’s benefits were not seen in patients without a history of cardiovascular disease. Also, the HOPE trial did not include patients with left ventricular dysfunction (i.e., EF < 40%, CHF or post-MI).
  - Perindopril, through the EUROPA trial, demonstrated a reduction in cardiovascular endpoints in patients with stable cardiovascular disease. This trial was unable to demonstrate a reduction in all cause mortality seen in the HOPE trail.

- Recent Myocardial Infarction
  - In post-myocardial infarction patients, ramipril (AIRE), lisinopril (GISSI-3), and captopril (SAVE) have demonstrated a reduction in mortality and heart failure.
  - Enalapril has demonstrated some superiority over captopril for the reduction in all-cause mortality. However, these results were not duplicated in the primary outcomes of a follow up study.
- Congestive Heart Failure
  - Benazepril, captopril, lisinopril, enalapril, perindopril, quinapril and ramipril have demonstrated the ability to reduce morbidity and mortality from heart failure. (Note: benazepril and perindopril do not currently have FDA-approval for this indication.)
  - Captopril, lisinopril, fosinopril, enalapril, quinapril and ramipril have demonstrated improvement in the NYHA functional class and exercise tolerance.
  - Head to head studies show no superiority among studied ACEI in the treatment of CHF, although benazepril, trandolapril, moexapril, and perindopril have not been studied in head to head trial.
- Nephropathy
  - In a meta-analysis by Kshirsagar demonstrated ACE inhibitors, as a class effect, have demonstrated a decreased incidence of microalbuminuria.
  - The EMCSG and the NAMSG have shown captopril to prevent the onset of proteinuria, hypertension, and worsening of renal function in Type 1 DM with microalbuminuria.
  - Post-hoc analysis of the HOPE (ramipril) and SOLVD (enalapril) trial indicate a reduction in the development of diabetes.

## 2. Safety

- ACEI adverse effects include; hypotension, dry cough, hyperkalemia, rash, hepatotoxicity, dysgeusia, renal impairment, and angioedema (rare).
- Head to head hypertension trials show no differences in quality of life, rates of cough or hyperkalemia among ACEI.
- Data does not support superior safety of any particular ACE inhibitors in the treatment of post MI or CHF.

## 3. Cost and Dosing Considerations

- Captopril, enalapril, and lisinopril are currently available as generic agents and are therefore, low cost options. Costs for the branded product, ramipril, are considerably higher than the other preferred ACEI.

ACEI Agent(s)	Cost of 30-Day Supply
<b>Preferred, generic ACEI agents</b> (capto-, enala-, lisinopril)	\$16 - 23
<b>Preferred, branded agent: Ramipril</b>	\$39
<b>Non-preferred, branded ACEI Agents</b> (benaza-, fosino-, moexi-, perindo-, quina-, trandolapril)	\$22 - 38

\*Costs based on DSHS reimbursement formulas

## 4. Special Patients Populations

- There is no difference in therapeutic response among ACE inhibitors in women
- There are no differences among ACE inhibitors in the elderly.
- While African American patients may have less robust anti-hypertensive response to ACEI compared to non-African Americans, the AASK trial demonstrated the value of ramipril in the treatment of left ventricular dysfunction (post-MI, CHF) and kidney disease. Similar benefits were seen in the ALLHAT trial, although there was an increase incidence of stroke in patients treated with lisinopril.
- Angioedema, a rare side effect of ACEI, is two to four times more likely to occur African American patients than with other Americans.

## 5. Conversion of Patients to Preferred ACEI Agents

### Steps and Considerations in Managing the ACEI Conversion

#### **#1. Select the appropriate agent and dose of a preferred ACEI agent based on the current agent and dose (using the conversion guide).**

- In selecting an agent keep in mind that captopril must be dosed multiple times a day and that ramipril is more costly. For traditional ACEI indications (hypertension, CHF, post-MI, renal protection), enalapril and lisinopril are agents that offer known effectiveness in low-cost, generic formulations that can generally be dosed once daily.
- For patients with the non-traditional indication of CV risk (i.e., HOPE criteria), ramipril offers an evidence-based choice. While some clinicians support the idea of an ACEI class effect with regard to these benefits, this is a matter of discretion that cannot be resolved in this guide.
- When using the conversion guide remember that captopril is generally dosed three times a day, while enalapril, lisinopril and ramipril are generally given once daily. Doses of enalapril > 20mg/day may need to be given twice daily to assure 24-hour effectiveness. In treatment of CHF, ACE inhibitors are generally dosed twice daily (captopril dosed TID).

#### **ACEI Conversion Guide\* (Note: All doses are once-daily unless otherwise stated)**

Agent	Conversion Doses <sup>^</sup>				
Captopril	6.25mg tid	12.5mg tid	25-37.5mg tid	50mg tid	100-150mg tid
Enalapril <sup>#</sup>	5mg	10mg	20mg	20mg bid	
Lisinopril	5mg	10mg	20mg	40mg	40mg bid
Ramipril	1.25mg	2.5mg	5mg	10mg	
Benazepril	5mg	10mg	20mg	40mg	80mg
Fosinopril	5mg	10mg	20mg	40mg	80mg
Moexipril	3.75 mg	7.5mg	15mg	30mg	60mg
Perindopril	2mg	4mg	6mg	8mg	16mg
Quinapril	5mg	10mg	20mg	40mg	
Trandolapril	0.5mg	1mg	2mg	4mg	

\*This table does not represent exact or equivalent dosing conversions. It is based on FDA approved dosing ranges and comparative doses from clinical trials used in the treatment of hypertension. Practitioners should exercise common sense in the practical application of this guide, including consideration for a patient's current cardiovascular status and other clinical variables.

<sup>^</sup>In the treatment of CHF and left-ventricular dysfunction most ACEIs are administered twice daily.

<sup>#</sup>Enalapril may require administration on a BID schedule, especially at doses > 20mg/day.

#### **#2. Patient Education and Consultation**

- The patient should be counseled on the rationale behind this conversion.
- The patient should be specifically instructed to stop the previous ACEI agent and begin taking the new agent with emphasis on the risk of using both medications.
- Counseling should include advising the patient on adverse reactions that may occur with all ACEI medications and what to do should they experience any significant reactions (ie. cough)
- The patient should be advised to contact the pharmacy for any questions related to the medication therapy or to contact their physician/prescriber for any health-related concerns

#### **#3. Notification of Prescriber Regarding Conversion**

- The pharmacist/pharmacy is legally obligated to communicate information regarding medication changes that occur via the TIP for all patients to ensure continuity of care.

### References and Resources

#### **General Resources**

- Oregon Health Policy and Research (OHPR) Evidenced-based Drug Reviews (<http://www.ohppr.state.or.us/index.html>)
- Micromedex; ACE inhibitor dosage conversion table
- Medline Plus: <http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202044.html>

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