The Beneficial Role of Angiotensin-Converting Enzyme Inhibitor in Acute Myocardial Infarction

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Introduction

1. Cardiovascular disease is one of the leading causes of mortality in the world and most of the deaths are originated from the coronary artery disease.

2. Despite the proven beneficial effect of other drugs including aspirin, statin and β-blockers on the coronary heart disease, still the cardiovascular complications remains high.
ACE Inhibitors

3. Angiotensin-converting-enzyme (ACE) inhibitors have been introduced for an effective secondary preventive strategy to minimize these cardiovascular morbidity and mortality.

4. Traditionally, ACE inhibitors are known to be effective in reducing morbidity and mortality among patients with heart failure, left ventricular (LV) dysfunction, post myocardial infarction (MI), hypertension and other high risk patients.
Role of ACEI in AMI

** Two randomized trials involved patients with moderate to severe LV dysfunction

1) The SOLVD trial (Studies of Left Ventricular Dysfunction)
2) The SAVE trial (Survival And Ventricular Enlargement)

Post hoc analysis showed a reduction in the rate of AMI in patients who were treated with an ACE inhibitor.

HOPE - (Heart Outcomes Prevention Evaluation)

1. **Objective**

To investigate the effect of **Ramipril (Tritace)** on the **prevention of CV events in high-risk patients**

2. **Study Design**

2x2 factorial, double blind, randomized, placebo-controlled

9,297 patients enrolled

3. **Follow-up**

4.5 years (visits at 6 months)

HOPE - Patients

1. Inclusion Criteria

Patients (age ≥55) at high risk for cardiovascular events because of
- any evidence of **vascular disease (CHD, Stroke, PVD)**

*diabetes with one other risk factor*

2. Exclusion Criteria

1) Low EF

2) Current use of ACE-I or Vitamin E
1. **Primary Endpoint**

**Composite of MI/Stroke/CV death**
(+ separate analysis of each)

2. **Secondary Endpoint**

Total Mortality, Revascularization, **Diabetes Complications**

3. **Other Endpoint**

**Onset of New Diabetes**, Worsening angina/unstable angina,
HF(including hospitalisations), Cardiac arrest

HOPE – *Result I: Primary Outcomes*

**RRR(%)**

- **CV death**: -26%
- **MI**: -20%
- **Stroke**: -32%

All differences *p*<0.001

HOPE – Result II: Secondary Outcomes

RRR(%)  Revascularization  Diabetes Complications

-15  p=0.002

-16  p=0.03

Effect of Ramipril in HOPE
- increasing divergences with time

- Patients reaching composite endpoint [MI, stroke, CV death] (%)
- Risk reduction 22%
- $p < 0.001$

**HOPE-Result III**

- significant reduction of new diagnosis of diabetes

Role of 10 mg Ramipril:

- Direct dose dependent action of Ramipril on the RAS

* Based on the Clinical Results of the HOPE-Study

# In Patient with Recommended Dose-Modification (ex. Renal Dysfunction.)
CV Protective Effect was *more than by BP Reduction*

1. Totally different from other clinical trials in the same effect in both *Normotensives* and *Hypertensives*

2. Much higher risk reduction than expected from general BP reduction
ACEI Ramipril 10mg
- the recent understanding of mechanism
• Across the spectrum of risk
• Efficacy beyond blood pressure control
Risk assessment

In patients with stable coronary disease, after 4.2 years mean follow up, major cardiac events (death, MI) : 8 - 10%

- Risk assessment in these patients?
- Perindopril benefit at all levels of risk?
Primary endpoint

% CV death, MI or cardiac arrest

Placebo annual event rate: 2.4%

RRR: 20%
p = 0.0003

EUROPA Study Investigators *Lancet* 2003;362:782-788
**Diabetes**

<table>
<thead>
<tr>
<th>Total death / MI</th>
<th>PERSUADE diabetes</th>
<th>No diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRR 20%</td>
<td>RRR 19%</td>
<td>RRR 21%</td>
</tr>
<tr>
<td>9,9% placebo</td>
<td>15,5% placebo</td>
<td>9,0% placebo</td>
</tr>
<tr>
<td>8,0% perindopril</td>
<td>12,6% perindopril</td>
<td>7,4% perindopril</td>
</tr>
</tbody>
</table>
Risk factors in stable CAD:

- male
- age
- weight
- smoker
- diabetes
- BP
- cholesterol
- creatinine
- family history CAD
- stroke/TIA/PAD
- no revascularization
### Risk model

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0 - 8</td>
<td>PAD/CVD 3</td>
</tr>
<tr>
<td>Chol</td>
<td>0 - 6</td>
<td>Male 2</td>
</tr>
<tr>
<td>Weight</td>
<td>0 - 3</td>
<td>Diabetes 2</td>
</tr>
<tr>
<td>Creat</td>
<td>0 - 3</td>
<td>Smoker 2</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0 - 2</td>
<td>Fam Hist 1</td>
</tr>
<tr>
<td><strong>Revasc</strong></td>
<td></td>
<td><strong>-1</strong></td>
</tr>
<tr>
<td>Risk level</td>
<td>low</td>
<td>mid</td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>n=</td>
<td>3976</td>
<td>3975</td>
</tr>
<tr>
<td>age (year)</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>Male (%)</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>Pre-MI (%)</td>
<td>41</td>
<td>71</td>
</tr>
<tr>
<td>Revasc. (%)</td>
<td>73</td>
<td>50</td>
</tr>
<tr>
<td>Syst. BP (mmHg)</td>
<td>133</td>
<td>137</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Creatinin level (µmol/l)</td>
<td>99</td>
<td>94</td>
</tr>
</tbody>
</table>
Consistent risk reduction with perindopril

Treatment effect
Conclusion

Risk factors in stable CAD:

- male
- age
- weight
- smoker
- diabetes
- BP
- cholesterol
- creatinin
- family history CAD
- stroke/TIA/PAD
- no revascularization

Perindopril treatment benefit consistent across all risk levels
ACE inhibition for secondary prevention of CAD

Rationale

- Anti-atherosclerotic effects
- Plaque rupture reduction
- Improvement in vascular endothelial function
- Enhanced fibrinolysis
- Modulation of neurohormonally-induced arterial vasoconstriction
- LV hypertrophy reduction
- Blood pressure reduction
Blood pressure

**Perindopril 8mg**

- **SBP:** 5 mmHg
- **DBP:** 2 mmHg

![Graph showing blood pressure changes over 60 months with Perindopril 8mg compared to Placebo.](image-url)
Are the cardiovascular benefits observed in EUROPA the result of blood pressure lowering or could more specific anti-atherosclerotic effects be involved?
Effect of baseline systolic blood pressure on primary endpoint

Primary endpoint-risk reduction

No interaction between treatment and SBP: p=0.141
**Effect of baseline diastolic blood pressure on primary endpoint**

Primary endpoint-risk reduction

No interaction between treatment and DBP

p=0.130

<table>
<thead>
<tr>
<th>DBP Range</th>
<th>Placebo</th>
<th>Perindopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;80 mmHg</td>
<td>3226</td>
<td>3263</td>
</tr>
<tr>
<td>&gt;80 and &lt;90 mmHg</td>
<td>2187</td>
<td>2183</td>
</tr>
<tr>
<td>&gt;90 mmHg</td>
<td>695</td>
<td>664</td>
</tr>
</tbody>
</table>
EUROPA Conclusion

- Perindopril’s benefit in EUROPA cannot be explained by blood pressure at baseline or blood pressure reduction alone.

- Other mechanisms including direct vascular, anti-atherosclerotic effects and improvement of endothelial function of perindopril may play a role.

- PERTINENT (a substudy of EUROPA): PERindopril - Thrombosis, InflammatioN, Endothelial dysfunction and Neurohormonal activation Trial.
1. **PEACE Trial** (Prevention of Events with Angiotensin Converting Enzyme Inhibition)
   ; Trandolapril

2. Study population
   1) In patients with stable coronary heart disease and preserved LV function who are receiving current standard therapy
   2) In whom the rate of cardiovascular events is lower than in previous ACE inhibitor trials in patients with vascular disease
In pts with stable coronary heart disease and preserved LV function who are receiving “current standard” therapy and in whom the rate of cardiovascular events is lower than in previous trials of ACEI in pts with vascular disease, ACE inhibitor provides no further benefit in terms of death from cardiovascular causes, MI or coronary revascularization.
Effect of ACEI in AMI Setting

1. Blood Pressure?
2. Cardiovascular protective effects?
3. LV remodeling?
4. Baroreflex sensitivity?
5. QT dispersion and tachyarrhythmia?
6. Angiogenesis?
7. No-reflow?
Angiotensin II

1. increases lipid peroxidation
2. increases oxyradical formation
3. stimulates the expression of proinflammatory genes (chemoattractant protein and leukocyte adhesion molecules)
   → endothelial dysfunction
4. improves vascular smooth-muscle proliferation
5. stimulates the production of PAI-I.
Bradykinin

1. counteracts the negative action of angiotensin II
2. improves endothelial function by increasing expression and activity of the constitutive nitric oxide synthase
3. antiproliferative effect; inhibits the expression of monocyte and adhesion molecules
4. stimulates the synthesis of tissue plasminogen activator
ACEI and LV remodeling in AMI

1. Inflammatory cytokines play an important role in the pathophysiology of LM remodeling and hs CRP is a predictor of LV remodeling in patients with AMI.

2. ACEI to AMI patients showing increased hs CRP levels during the early stage of the disease could prevent LV remodeling.

3. Early initiation of ACE inhibitor (Perindopril) reduces collagenase activity.

ACEI and Baroreflex Sensitivity in AMI

1. Depressed barorelex sensitivity after AMI is considered an indication of decreased vagal and/or increased sympathetic tone.

2. ACE inhibitor Captopril (Capril®) appears to improve baroreflex sensitivity in the early phase of AMI.

## ACE Inhibitors, Angiotensin II Antagonists, and Platelet Function

<table>
<thead>
<tr>
<th><strong>ACE inhibitors</strong></th>
<th><strong>Angiotensin II antagonists</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Captopril 25 mg BID</strong></td>
<td><strong>Losartan 50–100 mg</strong></td>
</tr>
<tr>
<td>Someya et al(^{78})</td>
<td>Li-Saw-Hee et al(^{81})</td>
</tr>
<tr>
<td>ADP-induced aggregation</td>
<td>Soluble P-selectin</td>
</tr>
<tr>
<td><strong>Captopril 25–50 mg BID</strong></td>
<td><strong>Losartan 50–100 mg</strong></td>
</tr>
<tr>
<td>Birkebaek et al(^{79})</td>
<td>Pathansali et al(^{91})</td>
</tr>
<tr>
<td>ADP-induced aggregation, PF4</td>
<td>Megakaryocyte size and ploidy</td>
</tr>
<tr>
<td><strong>Quinapril 20 mg BID</strong></td>
<td><strong>Losartan 100 mg</strong></td>
</tr>
<tr>
<td>Gupta et al(^{80})</td>
<td>Levy et al(^{84})</td>
</tr>
<tr>
<td>ADP-induced aggregation, PF4</td>
<td>Platelet aggregation</td>
</tr>
<tr>
<td><strong>Enalapril 10–20 mg</strong></td>
<td><strong>Losartan and valsartan</strong></td>
</tr>
<tr>
<td>Li-Saw-Hee et al(^{81})</td>
<td>Kalinowski et al(^{77})</td>
</tr>
<tr>
<td>ADP-induced aggregation</td>
<td>NO release in vitro</td>
</tr>
<tr>
<td><strong>Captopril 25–50 mg</strong></td>
<td><strong>Collagen-induced aggregation</strong></td>
</tr>
<tr>
<td>Muller et al(^{82})</td>
<td>Decreased</td>
</tr>
<tr>
<td>Platelet (-)-adrenoceptors</td>
<td>No change</td>
</tr>
<tr>
<td><strong>Enalapril 20 mg</strong></td>
<td><strong>Increased</strong></td>
</tr>
<tr>
<td>Hernandez-Hernandez et al(^{83})</td>
<td><strong>Decreased</strong></td>
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<tr>
<td>ADP-induced aggregation</td>
<td></td>
</tr>
</tbody>
</table>

PF4 indicates platelet factor 4; NO, nitric oxide.

## Indication for ACE-Is (US)

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>HF</th>
<th>LVD/HF after MI</th>
<th>MI</th>
<th>Reduction in Risk of MI Stroke and Death from Cardiovascular Cause</th>
<th>Reduction in mortality/morbidity for the indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benazepril</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>X</td>
<td>X*</td>
<td>X*</td>
<td>X*</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Enalapril</td>
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<td>√</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X*</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Moexipril</td>
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<tr>
<td>Ramipril</td>
<td>X</td>
<td>X*</td>
<td></td>
<td>X*</td>
<td></td>
<td>√</td>
</tr>
<tr>
<td>Perindopril</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Trandolapril</td>
<td>X</td>
<td>X*</td>
<td></td>
<td></td>
<td></td>
<td>√</td>
</tr>
</tbody>
</table>

| No of Agents | 10 | 7 | 1 | 5 |

* includes documentation of improved long-term survival and clinical outcomes compared with placebo

ACEI and QT dispersion in AMI

1. A prolonged QT dispersion is a marker of electrical instability predisposing to ventricular arrhythmia and sudden cardiac death.

2. ACE inhibitor *Enalapril* reduces the degree of ventricular dispersion of repolarization following AMI and sudden cardiac death can be reduced.

ACEI and angiogenesis in AMI

1. Intravenous bFGF (basic fibroblast growth factor) may increase VEGF (vascular endothelial growth factor) and bFGF significantly, thus promoting the angiogenesis in the infarct zone and border zone in cardiac infarction as VEGF and bFGF are the potent angiogenic growth factors.

2. ACE inhibitor Benazepril may promote angiogenesis in the infarct zone and border zone in cardiac infarction.

ACEI and No-reflow in AMI

1. No-reflow phenomenon has been associated with severe myocardial injury, progressive LV remodeling, CHF and poor prognosis.

2. Pretreatment with ACE inhibitor (Captopril-M/C, Enalapril, Fosinopril) could preserve the microvascular integrity after AMI.

Role of ACEI in AMI - Summary -

1. BP lowering effect
2. Direct cardiovascular protective effects
3. Decreasing LV remodeling
4. Improve Baroreflex sensitivity
5. Decrease QT dispersion
6. Increase Angiogenesis
7. Reduce No-reflow
Conclusion

1. The beneficial effects of ACE inhibitors in addition to other preventive measures including aspirin, β-blockers and lipid-lowering drugs were consistent for the patients with AMI in all the previously published literature.

2. These results provide strong support for considering ACE inhibitors in all patients with AMI irrespective of cardiac function or risk factors.
Thank You for your attention!!

1. We have learned an incredible amount.
2. We are only limited by our imagination.