ACEI for Hypertension; Can they all Prevent Myocardial Infarction?

Masrul Syafri, MD
Proportion of deaths attributable to leading risk factors worldwide (2000)

- High blood pressure
- Tobacco
- High cholesterol
- Underweight
- Unsafe sex
- High BMI
- Physical inactivity
- Alcohol
- Indoor smoke from solid fuels
- Iron deficiency

Systolic blood pressure greater than 115 mmHg

Hypertension: The Disease Continuum

Early Paradigm

Natural History of CVD Progression

- Elevated BP
- Target Organ Damage

More Recent Paradigm

- Vascular Dysfunction
- Elevated BP
- Target Organ Damage

A Proposed Future Paradigm

- Endothelial Dysfunction
- Vascular Dysfunction
- Elevated BP
- Target Organ Damage
- LVH
- Renal Damage
- MI
- Stroke
- Angina Pectoris
THE CARDIOVASCULAR CONTINUUM

Myocardial infarction
Arrhythmia & loss of muscle
Remodelling
Ventricular dilatation
Congestive heart failure
Death

Coronary thrombosis
Myocardial ischaemia
CAD
STROKE
Atherosclerosis
LVH

Risk factors
smoking, HYPERTENSION, cholesterol, diabetes

Sudden Death
Blood Pressure Reduction Is Critical: *the Lower, the Better*

Meta-analysis of 61 prospective, observational studies*
1 million adults
12.7 million person-years

2–mm Hg decrease in mean SBP

7% reduction in risk of ischemic heart disease

10% reduction in risk of stroke mortality

*Epidemiologic studies, not clinical trials of hypertension agents.
5/19/2012
**JNC 7 Re-Classification of SBP/DBP**

**JNC 6 (1997)**
- **Optimal**
  - < 120 and < 80
- **Normal**
  - < 130 and < 85
  - High-normal
    - 130-139 or 85-89
- **Hypertension**
  - **Stage 1**
    - 140-159 or 90-99
  - **Stage 2**
    - 160-179 or 100-109
    - **Stage 3**
      - ≥ 180 or ≥ 110

**JNC 7 (2003)**
- **Normal**
  - < 120 and < 80
- **Prehypertension**
  - 120-139 or 80-89
- **Stage 1**
  - 140-159 or 90-99
- **Stage 2**
  - ≥ 160 or ≥ 100

**References**
## Lifestyle Modifications

<table>
<thead>
<tr>
<th>Modification</th>
<th>Approximate SBP reduction (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight reduction</strong></td>
<td>5–20 mmHg/10 kg weight loss</td>
</tr>
<tr>
<td><strong>Adopt DASH eating plan</strong></td>
<td>8–14 mmHg</td>
</tr>
<tr>
<td><strong>Dietary sodium reduction</strong></td>
<td>2–8 mmHg</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td>4–9 mmHg</td>
</tr>
<tr>
<td><strong>Moderation of alcohol consumption</strong></td>
<td>2–4 mmHg</td>
</tr>
</tbody>
</table>
Hypertension-thrombosis via Ang II

Multiple mechanisms of ACEI

Vasculoprotective effects
- Direct antiatherogenic
- Enhance endogenous fibrinolysis
- Inhibit platelet aggregation
- Antimigratory for mononuclear cells
- ↓ Matrix formation
- Improve endothelial function
- Antioxidant
- Anti-inflammatory
- Protection from plaque rupture
- Improved arterial compliance and tone

Blood pressure lowering
Cardioprotective effects
- ↓ Preload and afterload
- ↓ LV mass
- ↓ Sympathetic stimulation
- ↓ Reperfusion injury
- Improved myocardial remodeling

Angiotensin II reduction / bradykinin increase

Selection of High Performance ACEIs

1. It should be a pro-drug, *which is absorbed efficiently in small intestine*
2. High penetration into tissue
3. Long-lasting activity & high T/P ratio
4. High Anti-Hypertensive effect ➞ *High Selectivity in RA System*

5. Patient friendly ➞ *Cough incidence lower than other ACE-I*
1. Pro-drug,

\[ \text{Imidapril} \rightarrow \text{M1(imidaprilat, active)} \]

→ which is absorbed efficiently in small intestine

IMIDAPRIL Proven Profile

2. High Tissue Penetration

Long-lasting ACE Inhibiting Action on the Vascular Wall

<table>
<thead>
<tr>
<th>Inhibition rate at 6 hours</th>
<th>Imidapril</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>93.7</td>
<td>85.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inhibition rate at 48 hours</th>
<th>Imidapril</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>83.6</td>
<td>57.4</td>
</tr>
</tbody>
</table>

Subject: Spontaneously hypertensive rat n=6~8/group
Method: 2 mg/kg/day of each drug was administered orally for 4 weeks

3. Long-lasting activity & high T/P ratio


<table>
<thead>
<tr>
<th>Drug</th>
<th>T/P Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>25%</td>
</tr>
<tr>
<td>Quinapril</td>
<td>27%</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>48%</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>51%</td>
</tr>
<tr>
<td>Enalapril</td>
<td>51%</td>
</tr>
<tr>
<td>Ramipril</td>
<td>56%</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>64%</td>
</tr>
<tr>
<td>Imidapril</td>
<td>84%</td>
</tr>
</tbody>
</table>

References:
IMIDAPRIL Proven Profile

4. High Anti-Hypertensive effect
   ➔ High Selectivity in RA System

- Dominant in RAA system
  - Efficient touching in Kalikrein System
  - Produce enough Bradikynin
  - Optimal Organ Protection
    - Improve Vascular Heart Renal
    - Very Low Cough
    - Patient Friendly
    - Very Low side effect

- Excellent BP lowering
  - Optimal BP Control
Double Digit BP Reduction of Imidapril in Europe (n=2942)

-25
-20
-15
-10
-5
0
Average SBP
Average DBP

Dews et al (2001), United Kingdom
Zweiker et.al (2002), Austria
R. van der Does & R Euer (2001), Germany
Imish (2004) Spain & Portugal

-25
-20
-15
-10
-5
0
Average SBP
Average DBP

Dews et al (2001), United Kingdom (n=354)
Zweiker et.al (2002), Austria (n=2224)
R. van der Does & R Euer (2001), Germany (n=231)
Imish (2004) Spain & Portugal (n=123)
IMIDAPRIL Proven Profile

5. Patient friendly

- Cough incidence lower than other ACE-I

<table>
<thead>
<tr>
<th>Incidence of Dry Cough (%)</th>
<th>Anti Hypertension efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMIDAPRIL (TANAPRESS)</td>
<td></td>
</tr>
<tr>
<td>71.3</td>
<td></td>
</tr>
<tr>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>55.3</td>
<td>8.1</td>
</tr>
<tr>
<td>Ramipril</td>
<td></td>
</tr>
<tr>
<td>66.6 / 9.7</td>
<td></td>
</tr>
<tr>
<td>Benezepril</td>
<td></td>
</tr>
<tr>
<td>Perindopril</td>
<td></td>
</tr>
<tr>
<td>Cilazapril</td>
<td></td>
</tr>
<tr>
<td>Lisinopril</td>
<td></td>
</tr>
<tr>
<td>Temocapril</td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td></td>
</tr>
<tr>
<td>Quinapril</td>
<td></td>
</tr>
<tr>
<td>Temocapril</td>
<td></td>
</tr>
<tr>
<td>Ceronapril</td>
<td></td>
</tr>
<tr>
<td>Trandorapril</td>
<td></td>
</tr>
</tbody>
</table>

ACE inhibitors Classification by Asc. Prof. SATO

**Class I**
- ACE inhibition
- Lowers Blood Pressure
- Lowers Proteinuria

- Captopril
- Enalapril
- Lisinopril
- Fosinopril
- Peindopril
- Ramipril
- IMIDAPRIL

**Class II**
- ACE inhibition
- Lowers Blood Pressure
- Lowers Proteinuria
- Reduces Mortality in CHF
- Reduces Nephropathy Progression

- Benazepril
- Captopril
- Enalapril
- IMIDAPRIL

**Class III**
- ACE inhibition
- Lowers Blood Pressure
- Lowers Proteinuria
- Reduces Mortality in CHF
- Reduces Nephropathy Progression

- Tissue Selectivity
- Bioavailability > 50%
- Once Daily Dosing
- Dual Mode of Excretion

**Class III plus Perfect**
- ACE inhibition
- Lowers Blood Pressure
- Lowers Proteinuria
- Reduces Mortality in CHF
- Reduces Nephropathy Progression

- Tissue Selectivity
- Bioavailability > 50%
- Once Daily Dosing
- Dual Mode of Excretion

**LOW COUGH INCIDENCE**

**High Performance ACE-I**
- Plus

**IMIDAPRIL**

**Patient Friendly**
Properties of Imidapril

1) **Higher Selectivity** to R-A system in comparison with other ACE inhibitors
   
   (R-A system > K-K system)
   
   Low incidence of cough & Excellent organ protection

2) **Well-balanced Bradykinin** accumulation
   
   (Cough < Organ protection)
   
   Increase in NO production by low Bradykinin accumulation
   → Retention of merits (Organ protection) based on Bradykinin activity

R-A : Renin-Angiotensin, K-K : Kallikrein-Kinin
Factors on thrombus formation

**tPA**
Tissue Plasminogen Activator
- Produced at endothelium
- Elicit thrombolytic effect due to converting plasminogen into plasmin

**PAI-1**
Plasminogen Activator Inhibitor-1
- Elicit thrombus formation effect due to inhibiting tPA
  (The production of PAI-1 is enhanced especially in plaque at the site of artherosclerosis.)
The Role of tPA/PAI-1 in Thrombus Formation

Endothelial Cells

Plasminogen \xrightarrow{\text{tPA}} \text{Plasmin} \xrightarrow{\text{tPA/PAI-1 complex}} \text{Disruption}\n
Lipid rich plaque

\text{tPA: Tissue Plasminogen Activator}
\text{PAI-1: Plasminogen Activator Inhibitor-1}
Factors Give Rise to Arteriosclerosis and Rupture by Ang II

- **BK/NO**
  - Improve endothelial function
  - Increase in coronary blood flow etc.

- **COX-2**
  - Inhibit platelet aggregation
  - Vasodilation etc.

- **PAI-1**
  - Thrombogenicity (t-PA suppression)
  - Cell proliferation
  - Extracellular matrix aggregation
  - Vascular smooth muscle migration

**Factors Give Rise to Arteriosclerosis and Rupture**

- Normal Vessel
- Early atherosclerosis
- Unstable Plaque
- Rapture

**Enhance rapture (Degradation of extracellular matrix)**

**Remodeling after MI**

**X by ACEi**
Imidapril directly inhibits both MMP and ACE activity

MMP and ACE both have Zn as active centers, and are inhibited by ACE-inhibitor

ACE and MMP belong the same family of metal enzyme. Imidapril stably bind to MMP, according to computer simulation.
Difference in MMP-9 Activity among ACE-inhibitors after MI
(Hamster MI model, 1 day after MI)

N : normal
P : placebo
L : lisinopril
I : imidapril

*P<0.05 vs placebo
**P<0.01 vs. placebo.
†P<0.05 vs. lisinopril.

The Effect of Imidapril on PAI-1 Activity in patients after AMI

Method: This study was designed to examine the levels of PAI-1 and serum ACE activity during the course of 2 weeks in 40 patients with AMI within 12 hours after the onsets of the symptom, and who randomly received early treatment with either Imidapril or a placebo.

Changes of plasma PAI activity between Imidapril and placebo

![Graph showing changes of plasma PAI activity between Imidapril and placebo](image)

- **Plasma PAI-1 activity (IU/mL)**
- **X-axis:** Admission, 8, 16, 24, 48, 3rd, 5th, 7th, 14th (hours and days)
- **Y-axis:** 0, 5, 10, 15, 20, 25, 30, 35 IU/mL
- **Legend:** Placebo, Imidapril
- **Annotations:**
  - * p<0.01 vs Placebo
  - † p<0.01 vs admission

Changes in PAI-1 antigen concentrations

Subjects: 20 insulin-resistant hypertensive patients
Method: Fibrinolytic variables were monitored before and after administration of losartan or ramipril with hydrochlorothiazide.

Changes in tPA activity

Nancy J. Brown, et al., Hypertension 2002; 40: 859-865
FISIC study

Fibrinolysis and Insulin Sensitivity in Imidapril and Candesartan

AIM

To compare the effects of the ACE-I imidapril and ARB candesartan on fibrinolytic balance and insulin sensitivity in normal weight mild to moderate hypertensive patients with at least another cardiovascular risk factor
Effect of IMIDAPRIL and CANDESARTAN on BP

SBP (mmHg)

- Imidapril
  - Baseline
  - Treatment

- Candesartan
  - Baseline
  - Treatment

p<0.001

DBP (mmHg)

- Imidapril
  - Baseline
  - Treatment

- Candesartan
  - Baseline
  - Treatment

p<0.001

Effect of IMIDAPRIL and CANDESARTAN on Insulin Sensitivity

**Glucose Infusion Rate (last 30 min.)**

- **Imidapril**
  - Baseline: 5.0 µmol/min/kg
  - Treatment: 6.0 µmol/min/kg
  - p < 0.01

- **Candesartan**
  - Baseline: 5.5 µmol/min/kg
  - Treatment: 5.5 µmol/min/kg
  - ns

Effect of IMIDAPRIL and CANDESARTAN on Plasma PAI-1 Antigen After 12 Week Treatment

Change in Plasma PAI-1 Antigen Over Time in Response to IMIDAPRIL or CANDESARTAN

*p< 0.05 vs baseline; ° p< 0.05 vs imidapril

Change in Plasma t-PA Activity Over Time in Response to IMIDAPRIL or CANDESARTAN

Δ IU/ml

* p< 0.05 vs baseline; ° p< 0.05 vs imidapril

Effect of IMIDAPRIL and CANDESARTAN on Plasma t-PA Activity After 12 Week Treatment

Summary of FISIC I

In mild to moderate hypertensive patients with normal weight
imidapril and candesartan chronic treatments have different
effects on insulin sensitivity and fibrinolytic balance, despite the
same antihypertensive effect:

- Insulin sensitivity is improved by imidapril
- PAI-1 antigen is reduced by imidapril and is increased by
candesartan
- t-PA plasma constitutive activity is reduced by candesartan while
  it is not changed by imidapril; however, after a specific
  endothelial provocative test plasma t-PA activity is increased
  significantly more by imidapril than by candesartan
FISIC-II Study

- **Background and aim**

  **FISIC-II Study**

  - **Background**

    While fibrinolysis and insulin sensitivity were evaluated in FISIC study, the relation between PAI-1 and Ang II was not evaluated. Therefore, it was observed in FISIC-II.

  - **Aim**

    To assess the role of Ang II in plasma PAI-1 changes induced by the ACE-I imidapril and the ARB candesartan.
Back ground of FISIC-II

- In FISIC study, relation among PAI-1 and t-PA, Insulin Sensitivity were evaluated. As a result, Imidapril decreased PAI-1 and improved Insulin Sensitivity. Although Ang II might play important role, Ang II was not evaluated. Therefore, relation between PAI-1 and Ang II was evaluated in FISIC-II.

- Further, subjects were changed to patients with Metabolic Syndrome, because they are subject to actual clinical practice.

- Study duration was longer in FISIC-II in order to see long-term effects of ACE-I and ARB
Study Design

-2 0 2 4 8 12 16 WEEK

IMIDAPRIL 10 mg (n=45)

CANDESARTAN 16 mg (n=45)

BP               BP                  BP                               BP                             BP

PAI-1                   PAI-1              PAI-1                          PAI-1                         PAI-1

Ag II                   Ag II               Ag II                            Ag II                          Ag II

TITRATION   TITRATION
Change in Plasma PAI-1 Level

* p< 0.05; ** p< 0.01 vs baseline
° p< 0.05; + p< 0.01 vs imidapril

Fogari et al., Hypertension Research; 2011;34, 1321-6
Change in Plasma Ang II Level

![Graph showing changes in plasma Ang II level over time with Imidapril and Candesartan comparisons.]

- Imidapril
- Candesartan

Week 2 | Week 4 | Week 8 | Week 12 | Week 16

* p < 0.05; ** p < 0.01 vs baseline
° p < 0.05; + p < 0.01 vs imidapril

Fogari et al., Hypertension Research; 2011;34, 1321-6
Relationships between Plasma PAI-1 and Ang II changes in Imidapril group

Fogari et al., Hypertension Research ; 2011;34, 1321-6
### Relationships between Plasma PAI-1 and Ang II changes in Candesartan group

<table>
<thead>
<tr>
<th>Week</th>
<th>PAI-1 (ng/ml)</th>
<th>Ag II (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>* °</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>** +</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>** +</td>
<td></td>
</tr>
</tbody>
</table>

- $r = 0.09$ ns
- $r = 0.27 \ p < 0.05$
- $r = 0.37 \ p < 0.005$

- $\cdot p < 0.05$; $** p < 0.01$ vs baseline
- * $p < 0.05$; + $p < 0.01$ vs imidapril

Fogari et al., Hypertension Research; 2011;34, 1321-6
Hypertensive patients with Metabolic Syndrome, Imidapril and the Candesartan equivalent antihypertensive efficacy

- Imidapril reduced plasma PAI-1 and Ang II levels
- Candesartan increased plasma PAI-1 and Ang II levels

- This suggests that the different effect of ACE-I and ARB on Ang II production has a role in their different influence on fibrinolysis

- Imidapril has better effect on fibrinolytic balance and might be contribute to preventive and reduce in coronary disease
### Comparison of FISIC and FISIC II

<table>
<thead>
<tr>
<th></th>
<th>FISIC</th>
<th>FISIC II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>imidapril, candesartan</td>
<td>imidapril, candesartan</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>hypertensive patients with normoweight</td>
<td>hypertensive patients with metabolic syndrome</td>
</tr>
<tr>
<td><strong>PAI-1</strong></td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Ang II</strong></td>
<td>Not Applicable</td>
<td>↓</td>
</tr>
<tr>
<td><strong>t-PA</strong></td>
<td>↑</td>
<td>Not Applicable</td>
</tr>
<tr>
<td><strong>Insulin Sensitivity</strong></td>
<td>↑</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>
## Differences Effects on Clotting and Fibrinolytic System between ACE inhibitor and ARB

<table>
<thead>
<tr>
<th>Effects</th>
<th>ACE inhibitors</th>
<th>ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endothelial function</strong></td>
<td>Stimulation Ang II Bradykinin release</td>
<td>Stimulation AT&lt;sub&gt;1&lt;/sub&gt; receptor stimulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fibrinolysis</strong></td>
<td>Stimulation t-PA PAI-1 (long-term)</td>
<td>Not established Short-term reduction in PAI-1 t-PA activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td>Suppression? TAT, monocyte TF production</td>
<td>Suppression? TF mRNA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Platelet aggregation</strong></td>
<td>Suppression PGI&lt;sub&gt;2&lt;/sub&gt; release NO release</td>
<td>Suppression TXA&lt;sub&gt;2&lt;/sub&gt; blocking NO release</td>
</tr>
</tbody>
</table>

TAT: thrombin-antithrombin complex  
TXA<sub>2</sub>: thromboxane A<sub>2</sub>  
TF: tissue factor

POSSIBLE CAUSES
May the different mechanism of action of ACE-Is and ARBs play a role?

- ARBs: Ang II increase (with AT1 blockade)
- ACE-I: Ang II decrease + bradykinin increase

POSSIBLE CONSEQUENCES
May these different effects affect the clinical outcomes, independently of blood pressure reduction?
COMPETITIVE EFFECT OF ANGIOTENSIN II AND BRADYKININ ON FIBRINOLYTIC BALANCE

KININOGEN → BRADYKININ

ANGIOTENSINOGEN → ANG I → ANG II → ANG IV

ACE → t-PA → PAI-1

EC VSMC
Possible Consequences of Different IMIDAPRIL and Candesartan Results

THE DIFFERENT EFFECTS OF IMIDAPRIL AND CANDESARTAN ON INSULIN SENSITIVITY AND ON FIBRINOLYTIC BALANCE COULD AFFECT THE CLINICAL OUTCOME, INDEPENDENTLY OF BLOOD PRESSURE REDUCTION.

AN INDIRECT SUPPORT TO THIS HYPOTHESIS COMES FROM TWO LARGE META-ANALYSIS:

– Blood pressure-dependent and independent effects of agents that inhibit the renin angiotensin system


– Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials

SUMMARY OF FINDINGS OF BPLTTC REGRESSION META-ANALYSIS

**ANGIOTENSIN CONVERTING ENZYME INHIBITORS**

- **Stroke**: RR = -1% (9% to -10%)
- **CHF**: RR = 10% (10% to 0%)
- **CHD**: RR = 9% (14% to 3%)

**ANGIOTENSIN II AT1 RECEPTOR ANTAGONISTS**

- **Stroke**: RR = 2% (33% to -3%)
- **CHF**: RR = 16% (36% to -5%)
- **CHD**: RR = -7% (7% to -24%)

**PROBABILITY OF CHD EVENTS WITH INTENSIVE GLUCOSE LOWERING VS STANDARD TREATMENT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Events</th>
<th>Weight of study size</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>3071/1549</td>
<td>426/259</td>
<td>8.6%</td>
<td>0.75 (0.54–1.04)</td>
</tr>
<tr>
<td>PROactive</td>
<td>2605/2633</td>
<td>164/202</td>
<td>20.2%</td>
<td>0.81 (0.65–1.00)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>5571/5569</td>
<td>310/337</td>
<td>36.5%</td>
<td>0.92 (0.78–1.07)</td>
</tr>
<tr>
<td>VADT</td>
<td>892/899</td>
<td>77/90</td>
<td>9.0%</td>
<td>0.85 (0.62–1.17)</td>
</tr>
<tr>
<td>ACCORD</td>
<td>5128/5123</td>
<td>205/248</td>
<td>25.7%</td>
<td>0.82 (0.68–0.99)</td>
</tr>
<tr>
<td>Overall</td>
<td>17267/15773</td>
<td>1182/1136</td>
<td>100%</td>
<td>0.85 (0.77–0.93)</td>
</tr>
</tbody>
</table>

**Blood pressure effect**
(OR reduction and 95%CI for 5 mmHg lower SBP):
- ACE-I: 16% (7.25)
- ARB: 17% (-49.27)

**Blood pressure independent effect**
(OR reduction and 95%CI at 0 mmHg lower SBP):
- ACE-I: 9% (3.14)
- ARB: -8% (-39.17)

Hypothesis of no difference between slopes: \( p=0.7 \)

Hypothesis of no difference in SBP-independent effects:
\( p=0.002^{**} \)

Beyond BP lowering effect!
What’s another new result?

The most benefit population among CAD patients?
**SPAIC study**

*Shiga Plasminogen Activator In Coronary circulation Study*

Background: Emerging role of Bradikinin


2. BK induce endogenous t-PA release in peripheral and this effect is enhanced by ACE inhibition (Protorius, M. et al. Circulation 2003; 107: 579-585)

3. However, effect on endogenous t-PA release in coronary artery remains unclear.

Objective

In hypertensive patients receiving coronary radiography, fibrinolytic balance in coronary artery was evaluated and the effects of an ACE inhibitor Imidapril and their gender-wise differences were analyzed.

# Clinical Characteristics of Study Group

<table>
<thead>
<tr>
<th></th>
<th>non ACE-I</th>
<th></th>
<th>ACE-I</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Man (n=27)</td>
<td>Woman (n=17)</td>
<td>Man (n=21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Woman (n=12)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 ± 2</td>
<td>63 ± 2</td>
<td>60 ± 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>64 ± 3</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>ns</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>12 (52%)</td>
<td>1 (6%)</td>
<td>11 (52%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>5 (22%)</td>
<td>5 (29%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 (25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>23.7 ± 0.4</td>
<td>24.4 ± 0.6</td>
<td>23.9 ± 0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24.0 ± 0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
<td>124±3</td>
<td>127±3</td>
<td>121±4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>124±5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
<td>65±3</td>
<td>68±2</td>
<td>65±3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>64±3</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>ns</td>
</tr>
<tr>
<td>Dyslipidemia (%)</td>
<td>7 (30%)</td>
<td>7 (41%)</td>
<td>7 (33%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 (42%)</td>
</tr>
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</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>184±7</td>
<td>203±7</td>
<td>197±7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>189±6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>115±5</td>
<td>128±7</td>
<td>128±7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>119±8</td>
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<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>46±4</td>
<td>51±4</td>
<td>44±4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>53±6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>142±28</td>
<td>122±18</td>
<td>156±35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>124±20</td>
</tr>
</tbody>
</table>

*Mean ± SEM

χ² test or 1-way ANOVA

Imidapril induce the release of t-PA from the coronary artery of Women

[Methods]
Hypertensive patients with myocardial ischemia were divided at random into the Imidapril treated group (5 mg/day) and the non-ACE inhibitor treated group (calcium antagonists in 35 cases or beta-blockers in 5 cases). After 4 weeks of treatment, the amount of t-PA produced in the coronary artery was analyzed by gender and compared between the two groups.

Relationship between plasma ACE activity and net t-PA release

Conclusion

- The different effects of imidapril and candesartan on insulin sensitivity and on fibrinolytic balance, which is related to their different mechanisms of action, could be one possible explanation of the greater CHD prevention showed by ACE-Is independently of blood pressure reduction.

- Imidapril, an ACE inhibitor, was shown to stimulate t-PA release in the coronary artery. It suggests that Imidapril is appropriate as first-line drug for postmenopausal hypertensive women.
Thank You