A Fresh Look at ARBs
: Focus on HF survival data

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ARBs, are they really same?

- Pharmacodynamic : Half-life ?
- Binding affinity : Binding half-life ?
- Hydrophilicity vs. Lipophilicity ?
- Clinical study design?
- Patient type?
Correlation between the degree of insurmountability (i.e. the \([\text{IR}^+]/(\text{IR}+[\text{IR}^+])\) ratio) and the corresponding experimental half-lives \((t_{1/2} \text{ in min})\) of sartan dissociation from the human AT\(_1\) receptor stably expressed in recombinant CHO-hAT\(_1\) cells. Data are from Table 1; \(t_{1/2}\) was arbitrarily set to 1 min for losartan. The curve was drawn according to a hyperbolic function with GraphPad Prism software (GraphPad Software Inc., San Diego, CA)
Candesartan and losartan have significant pharmacological differences:

- Atacand binds harder to the AT₁-receptor
- Atacand binds longer to the AT₁-receptor

Correlation between the degree of insurmountability (i.e. the [IR⁺]/([IR]+[IR⁺]) ratio) and the corresponding experimental half-lives (t 1/2 in min) of sartan dissociation from the human AT1 receptor stably expressed in recombinant CHO-hAT1 cells. t1/2 was arbitrarily set to 1 min for losartan.

Candesartan compared with losartan has higher binding affinity for the AT₁ receptor, is more effective at lowering blood pressure, and is associated with less de novo HF when used in hypertension.
## Small pill of ARBs

<table>
<thead>
<tr>
<th>ARB</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>16 mg</td>
<td>16/12.5</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>600 mg</td>
<td>600/12.5</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>300 mg</td>
<td>300/12.5</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>80 mg</td>
<td>80/12.5</td>
</tr>
<tr>
<td>Losartan</td>
<td>100 mg</td>
<td>100/25</td>
</tr>
<tr>
<td>Valsartan</td>
<td>160 mg</td>
<td>160/12.5</td>
</tr>
</tbody>
</table>
ARBs, are they really same?

- BP control efficacy
- Beyond BP control effect in HF
  - Existence of Clinical Evidence
  - Difference in Result
Reduction in diastolic BP (mmHg)

-10 -8 -6 -4 -2 0

0 25 50

Losartan
Valsartan
Irbesartan
Candesartan

0 250 500 mg Losartan
0 800 1600 mg Valsartan
0 750 1500 mg Irbesartan
0 8 16 mg Candesartan

Blood pressure-lowering efficacy of olmesartan relative to other angiotensin II receptor antagonists: an overview of randomized controlled studies

Changes from baseline in casual diastolic blood pressure in comparative studies. *p<0.05 vs. olmesartan

Changes from baseline in casual systolic blood pressure in comparative studies. *p<0.05 vs. olmesartan

Response rates from ARB studies

Respecters: DBP <90 mm Hg or Decrease ≥10 mm Hg

1. CAESAR, data on file
2. Chrysant SG et al, AJH 2004;17:252-9
## Blood pressure before and 2 years after switching from losartan to candesartan

<table>
<thead>
<tr>
<th></th>
<th>Systolic</th>
<th>Diastolic</th>
<th>Systolic</th>
<th>Diastolic</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before switch</td>
<td></td>
<td></td>
<td>2 years post-switch</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n=42)</td>
<td>142 ± 12.1</td>
<td>81 ± 6.6</td>
<td>133 ± 11.5</td>
<td>79 ± 5.5</td>
<td>0.0002 0.06</td>
</tr>
<tr>
<td>Diabetes (n=19)</td>
<td>137 ± 12.5</td>
<td>78 ± 5.2</td>
<td>128 ± 10.6</td>
<td>73 ± 5.7</td>
<td>0.007 0.00005</td>
</tr>
<tr>
<td>CVD (n=20)</td>
<td>132 ± 13.2</td>
<td>76 ± 6.3</td>
<td>129 ± 17.5</td>
<td>75 ± 10.7</td>
<td>0.48 0.81</td>
</tr>
<tr>
<td>All (n=81)</td>
<td>138 ± 12.9</td>
<td>79 ± 6.6</td>
<td>131 ± 13.1</td>
<td>77 ± 7.6</td>
<td>0.00004 0.0069</td>
</tr>
</tbody>
</table>

* Paired Student’s t-test, CVD, cardiovascular disease

Duration of blood pressure lowering effect
100 mg Losartan vs. 16 mg Candesartan

Missed dose

Change in SBP (mm Hg)

Hours after dose

Losartan

Candesartan

$p=0.004$

ARBs, Are they really Same?

- BP control efficacy → Different

- Beyond BP control effect
  - Existence of Clinical Evidence
  - Difference in Result
ARBs, Are they really Same?

- BP control efficacy → Different

- Beyond BP control effect
  - Existence of Clinical Evidence
  - Difference in Result
Angiotensin II Plays a Central Role in Organ Damage

A II $\rightarrow$ AT$_1$ receptor

- Atherosclerosis*
- Vasoconstriction
- Vascular hypertrophy
- Endothelial dysfunction

- LV hypertrophy
- Fibrosis
- Remodeling
- Apoptosis

- GFR
- Proteinuria
- Aldosterone release
- Glomerular sclerosis

$\Rightarrow$ Stroke
$\Rightarrow$ Hypertension
$\Rightarrow$ Heart failure
$\Rightarrow$ MI
$\Rightarrow$ Renal failure
$\Rightarrow$ DEATH

*preclinical data
LV = left ventricular; MI = myocardial infarction; GFR = glomerular filtration rate

<table>
<thead>
<tr>
<th></th>
<th>Candesartan</th>
<th>Irbesartan</th>
<th>Losartan</th>
<th>Olmesartan</th>
<th>Telmisartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>LVH</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td></td>
<td>O</td>
<td>O</td>
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<tr>
<td>AF</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td></td>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
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<td></td>
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<tr>
<td>Kidney</td>
<td></td>
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<tr>
<td>Nephropathy</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td></td>
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<tr>
<td>DM</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Is there Clinical Studies for Target Organ Protection?

CHARM CASE-J SCOPE SMART DIRECT
IRMA IDNT I-PRESERVE
LIFE OPTIMAL RENAAL ELITE
ONTARGET DETAIL PROFESS
Val-Heft VALUE VALIANT ABCD-2V
ARBs in Heart Failure

All-cause mortality

Captopril/Losartan Hazard Ration (95% CI): 0.88 (0.75, 1.05) \( P = 0.16 \)

Captopril, (n=1574), 250 events
Losartan, (n=1578), 280 events

Pitt B et al: Lancet 2000
Considerations in ELITE-2 Study

• Primary endpoint: all-cause mortality

• ACEI – naive patients

• Low dose of ARB (losartan, 44 mg)?

• High prevalence of ACEI (captopril) discontinuation?

• How about long-acting ACEI?
ARBs in Heart Failure

All-cause mortality

Val-HeFT

Valsartan
320mg

Placebo

Cohn et al: NEJM 2001

27 mos

Event-free Survival

p = 0.80
Considerations in Val-HeFT Study

• Two primary endpoints
  1) all-cause mortality
  2) combined endpoints of all-cause mortality/CV morbidity

• ACEI – tolerant patients

• High dose of ARB (valsartan, 254 mg) ?

• Beta-blockers (35 %), ACEI (93 %)

• Safety for high-dose of ARB ?
  : 9.9 % of discontinuation
CHARM Programme

3 component trials comparing candesartan to placebo in patients with symptomatic heart failure

- **CHARM Alternative**: n=2028, LVEF ≤40%, ACE inhibitor intolerant
- **CHARM Added**: n=2548, LVEF ≤40%, ACE inhibitor treated
- **CHARM Preserved**: n=3025, LVEF >40%, ACE inhibitor treated/not treated

Primary outcome for each trial: CV death or HF hospitalisation
Primary outcome for Overall Programme: All-cause death

Lancet. 2003;362(9386):759-66
**CHARM-Overall**

**All cause death**
- HR 0.91 (95% CI 0.83-1.00), \( p=0.055 \)
- Adjusted HR 0.90, \( p=0.032 \)

**CV death**
- HR 0.88 (95% CI 0.79-0.97), \( p=0.012 \)
- Adjusted HR 0.87, \( p=0.006 \)

**Non-CV death**
- \( p=0.45 \)

Number at risk
- **Candesartan**:
  - 3803, 3563, 3271, 2215, 761
- **Placebo**:
  - 3796, 3464, 3170, 2157, 743

Lancet. 2003;362(9386):759-66
ARBs in Heart Failure

CHARM-Alternative

Placebo

Candesartan 32 mg

Granger et al: Lancet 2003

CV Death or HF Hosp

0

.5

42 mos

HR 0.77 (95% CI 0.67-0.89), p=0.0004
Adjusted HR 0.70, p<0.0001

23 %↓
Considerations in CHARM-Alternative Study

- ACEI – naïve patients
- HF patients on optimal standard therapy
- Relatively low CV risk factors
- Different primary endpoints: (CV death or HF hospitalization)
## ARBs in Heart Failure
### Candesartan vs Placebo

<table>
<thead>
<tr>
<th>Event</th>
<th>Candesartan (n=1278)</th>
<th>Placebo (n=1272)</th>
<th>Unadjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or hospital admission for CHF</td>
<td>37.9%</td>
<td>42.3%</td>
<td>0.85 (0.75 - 0.96)</td>
<td>0.011</td>
</tr>
<tr>
<td>CV death</td>
<td>23.7%</td>
<td>27.3%</td>
<td>0.84 (0.72 - 0.98)</td>
<td>0.029</td>
</tr>
<tr>
<td>Hospital admission for CHF</td>
<td>24.2%</td>
<td>28.0%</td>
<td>0.83 (0.71 - 0.96)</td>
<td>0.014</td>
</tr>
</tbody>
</table>
Considerations in CHARM-Added Study

• ACEI – tolerant patients

• 96 % of ACEIs optimal dose

• Beta-blockers (55%), spironolactone (17%)

• Different primary endpoints: (CV death or HF hospitalization)
Add-on therapy for heart failure patients

CHARM-Added ¹)

<table>
<thead>
<tr>
<th>Candesartan</th>
<th>Placebo</th>
<th>Candesartan better</th>
<th>placebo better</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB Yes</td>
<td>223/702 274/711</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>260/574 264/561</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi Yes</td>
<td>232/643 275/648</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>251/633 263/624</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All pts</td>
<td>483/1276 538/1272</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Val-HeFT ²)

- Combined mortality/CV morbidity
  - ACEi + BB: 3,034
  - ACEi + BB+: 1,610
  - ACEi - BB-: 226
  - ACEi - BB+: 140

- All cause mortality
  - ACEi + BB: 3,034
  - ACEi + BB+: 1,610
  - ACEi - BB-: 226
  - ACEi - BB+: 140

Favors valsartan
Favors placebo

Recommended dose

Candesartan: better
Placebo: better

Cox regression model
**Preserved heart failure patients**

**CHARM-Preserved**

- **Placebo**: 366 (24.3%)
- **Candesartan**: 333 (22.0%)

**HR 0.89 (95% CI 0.77-1.03), p=0.118**

**Adjusted HR 0.86, p=0.051**

Number at risk:
- **Candesartan**: 1514, 1458, 1377, 833, 182
- **Placebo**: 1509, 1441, 1359, 824, 195

**I-Preserved**

- **Placebo**
- **Irbesartan**

**HR (95% CI) = 0.95 (0.86-1.05)**

*Log-rank p=0.35*

Number at Risk:
- **Placebo**: 2067, 1812, 1640, 1513, 1088, 497
- **Irbesartan**: 2061, 1808, 1618, 1466, 1051, 446

### Heart Failure Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Candesartan</th>
<th>Valsartan</th>
<th>Irbesartan, Losartan, Olmesartan, Telmisartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi 내약성이 좋지 않은 경우</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>ACEi에 추가요법이 필요한 경우</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td><strong>용법 용량</strong></td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>1일 1회 4~32mg</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>1일 2회 80~160mg</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>주의사항</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>• ACEi, BB, Valsartan의 3종 요법은 권장되지 않는다.</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>• 중증 심부전 환자에게 ACEi 또는 ARB로 치료하는 것은 반 노력, 진행성 질소혈증, 급성심부전 또는 사망과 관련이 있다.</td>
<td>☑</td>
<td>☑</td>
<td>☑</td>
</tr>
</tbody>
</table>

**ACEi**에 불내성인 심부전

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Severance Cardiovascular Hospital

Yonsei University College of Medicine
Different ARBs have NOT been tested head to head in HF patients!
Association of Candesartan vs Losartan with All-cause Mortality in Patients with Heart Failure

JAMA 2011;305:175-82.
Backgrounds

- ARBs reduce combined mortality and hospitalization in patients with HF with reduced LVEF.

- Different agents have different affinity for the AT$_1$ receptor and may have different clinical effects.

- RCTs have NOT been performed to test difference of ARBs efficacy in HF patients.
Objective

- To determine whether candesartan is associated with all-cause mortality than losartan in a large cohort of unselected patients with HF
Methods

Swedish Heart Failure Registry (RisksSvikt, S-HFR)

- Inclusion criteria are clinician-judged HF.
- Approximately 70 variables are recorded at discharge from hospital or after clinic visit on a case record form.
- Main outcome: all-cause mortality

Statistical analysis
- To adjust for selection bias, propensity scores for each patient were estimated with logistic regression.
- Kaplan-Meier survival analysis and log-rank test by LVEF.
S-HFR
- 30,254 patients registration,
- 5,823 received an ARBs
- From 2000–2009, 62 hospitals and 60 clinics

**Design**

- **Losartan**
  - N=2,500
  - Main outcome: All-cause mortality

- **Candesartan**
  - N=2,639
  - Mean age: 74 years, 39% women

**Valsatan** (n=357) and other ARBs (n=327) were excluded due to small numbers
Results: Overall Survival

- 1 year survival
  Candesartan group 90% vs. losartan group 83%

- 5 year survival
  Candesartan group 61% vs. losartan group 44% (log-rank P< .001)
# Results: HRs for all-cause mortality

Proportional hazard regression models for all-cause mortality for Losartan vs Candesartan

<table>
<thead>
<tr>
<th>Losartan vs. Candesartan</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate model</td>
<td>1.77 (1.58-1.99)</td>
</tr>
<tr>
<td>Multivariate model</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>1.56 (1.39-1.75)</td>
</tr>
<tr>
<td>Adjusted for duration of heart failure</td>
<td>1.71 (1.52-1.92)</td>
</tr>
<tr>
<td>Adjusted for hypertension</td>
<td>1.77 (1.58-1.99)</td>
</tr>
<tr>
<td>Adjusted dose of 50 mg/d&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.53 (2.22-2.88)</td>
</tr>
<tr>
<td>Adjusted dose of 150 mg/d&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.91 (1.67-2.18)</td>
</tr>
<tr>
<td>Adjusted for ACE inhibitor, β-blocker, and aldosterone antagonist</td>
<td>1.71 (1.52-1.93)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Losartan vs. Candesartan</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariate final model</td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>1.43 (1.23-1.65)</td>
</tr>
<tr>
<td>With propensity scores covariate</td>
<td>1.41 (1.22-1.64)</td>
</tr>
<tr>
<td>With propensity scores strata</td>
<td>1.43 (1.23-1.65)</td>
</tr>
</tbody>
</table>

- **Univariate HR: 1.77 (95% CI 1.58-1.99)**
- **Multivariate HR including stratification for propensity score: 1.43 (95% CI 1.23-1.65, P < .001), HR= 0.70 for candesartan vs losartan**
Results: HRs after adjustment

Multivariate final analysis with propensity score strata and interaction for patients receiving losartan vs candesartan

<table>
<thead>
<tr>
<th>Multivariate Final Analysis</th>
<th>HR (95% CI)</th>
<th>P Value Main Effect</th>
<th>P Value Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Blocker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.90 (1.39-2.60)</td>
<td>&lt;.001</td>
<td>.04</td>
</tr>
<tr>
<td>Yes</td>
<td>1.35 (1.15-1.57)</td>
<td>&lt;.001</td>
<td>.04</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>1.45 (1.25-1.68)</td>
<td>&lt;.001</td>
<td>.09</td>
</tr>
<tr>
<td>Yes</td>
<td>0.82 (0.42-1.58)</td>
<td>.55</td>
<td>.09</td>
</tr>
<tr>
<td>Duration of heart failure, mo</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>1.72 (1.35-2.20)</td>
<td>&lt;.001</td>
<td>.05</td>
</tr>
<tr>
<td>Yes</td>
<td>1.33 (1.12-1.56)</td>
<td>&lt;.001</td>
<td>.05</td>
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<tr>
<td>Creatinine</td>
<td>1.51 (1.18-1.93)</td>
<td>&lt;.001</td>
<td>.07</td>
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<tr>
<td>Lung disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.52 (1.29-1.79)</td>
<td>&lt;.001</td>
<td>.06</td>
</tr>
<tr>
<td>Yes</td>
<td>1.17 (0.90-1.51)</td>
<td>.24</td>
<td>.06</td>
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</tbody>
</table>

Losartan remained associated with increase mortality compared with candesartan for all categories except cardiac resynchronization therapy and lung disease.
Results: HRs in subgroup

HRs for all-cause mortality from multivariate model after adjustment with selected subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Deaths/Total No.</th>
<th>Candesartan</th>
<th>Losartan</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td></td>
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</tr>
<tr>
<td>2001-2005</td>
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<td>86/214</td>
<td>406/701</td>
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<tr>
<td>2006-2009</td>
<td></td>
<td>355/2425</td>
<td>482/1799</td>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Women</td>
<td></td>
<td>177/1006</td>
<td>348/1017</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td>264/1633</td>
<td>540/1483</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤70</td>
<td></td>
<td>100/1014</td>
<td>153/706</td>
</tr>
<tr>
<td>&gt;70</td>
<td></td>
<td>341/1625</td>
<td>735/1794</td>
</tr>
<tr>
<td><strong>Creatinine, µmol/L</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>≤100</td>
<td></td>
<td>156/1416</td>
<td>267/1080</td>
</tr>
<tr>
<td>&gt;100</td>
<td></td>
<td>285/1223</td>
<td>621/1420</td>
</tr>
<tr>
<td><strong>NYHA class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td></td>
<td>186/1587</td>
<td>304/1262</td>
</tr>
<tr>
<td>III-IV</td>
<td></td>
<td>255/1052</td>
<td>548/1238</td>
</tr>
<tr>
<td><strong>LVEF, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td></td>
<td>243/1519</td>
<td>541/1398</td>
</tr>
<tr>
<td>≥40</td>
<td></td>
<td>198/1120</td>
<td>347/1102</td>
</tr>
</tbody>
</table>

| Diabetes mellitus | Yes | No | 169/767 | 272/1872 | 325/848 | 563/1652 |
| β-Blocker         | Yes | No | 379/2298 | 62/341   | 697/2057 | 191/443 |
| Aldosterone antagonist | Yes | No | 151/807 | 351/910 |
| ACE inhibitor     | Yes | No | 61/421  | 867/2423 |
| Target dose, mg/d | ≤50 | >50 | 341/1684 | 268/534 |
| Target dose at 150 mg/d | ≤50 | >50 | 341/1684 | 100/955 |

SEVERANCE CARDIOVASCULAR HOSPITAL
YONSEI UNIVERSITY COLLEGE OF MEDICINE
## Results: HRs in subgroup

HRs for all-cause mortality from multivariate model after adjustment with selected subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Deaths/Total No.</th>
<th>Favors Candesartan</th>
<th>Favors Losartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≥40% patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>243/1519</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Losartan</td>
<td>541/1398</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>LVEF &lt;40% patients</td>
<td></td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Candesartan</td>
<td>199/1120</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Losartan</td>
<td>343/1202</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Candesartan vs losartan group in LVEF ≥40% patients
- 1 year Survival: 91% (95% CI 89-92%) vs 82% (95% CI 80-85%)
- 5 year Survival: 68% (95% CI 60-76%) vs 44% (95% CI 40-49%)

Candesartan vs losartan group in LVEF <40% patients
- Univariate HR: HR 2.08 (95% CI 1.76-2.46% P<.001)
- Multivariate HR including stratification for propensity score: 1.41 (95% CI 1.14-1.76% P=.002)
Candesartan compared with losartan was associated with a lower mortality risk in this registry of patients with HF
Limitations

- The study was registry study not randomized controlled trial and had potential biases and confounders.

- Diagnosis of HF in S-HFR is clinical and does not require objective evidence of HF

- Different ARB agents should be tested against each other in RCTs
ARBs Treatment in HF patients

- Angiotensin II receptor blockers (ARBs) are widely used to treat heart failure (HF)
- ARBs vary in their affinity for the AT_1_ receptor and in their effects on blood pressure
- Reduction of mortality and hospitalization in patients with HF with reduced left ventricular ejection fraction.
ARBs, Are they really Same?

- BP control efficacy → Different

- Beyond BP control effect
  - Existence of Clinical Evidence → Different
  - Difference in Result → Different
경청해 주셔서 감사 합니다.