INHIBITORS OF THE RENIN ANGIOTENSIN SYSTEM IN HEART FAILURE: II- Angiotensin Receptor Blockers

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Angiotensin II formation in normal and dysfunctional vessels
ANGIOTENSIN II RECEPTORS

AT1:
Vasoconstrictor, LV and vascular hypertrophy.

AT2:
Less clear function (fetal tissue, brain, reproductive tissue, heart, kidney)
Expression declines after birth.

AT1-7:
Vasodilator

Goodfriend et al. NEJM 1996; 334:1649
CARDIAC & VASCULAR HYPERTROPHY


• AT1 block:
  – Lower BP + regression of LVH.
  – Aortic hypertrophy not prevented.

• AT2 block (PD123319):
  – No effect on the hypertension
  – Protected against aortic injury.
  – Prevented arterial hypertrophy.

CONCLUSION: AT2 receptor promotes arterial injury in HT
Response to myocardial ischemia

- Effects of AT1 & AT2 antagonists on the recovery of mechanical function after 30 min. ischemia
  - AT2 block: Cardioprotective when given before ischemia.
  - AT1 block (losartan) delayed recovery of LV work.
    Ford et al Circulation 1996; 94:3087

- Coronary ligation in AT2 Knock-out mouse (AT2-KO)
  - BP response: Similar to wild-type mouse
  - LVEF at 20 W: Lower in AT-II-KO mouse
  - Response of EF to ACEI: Similar to wild-type mouse

CONCLUSION: AT2 receptor function associated with preservation of LVEF in response to ischemia

ISH. Sao Paulo, Feb. 2004
ACTION ON KININS

• Contribute to the hypotensive action of ACE inhibitors, releasing NO.

• Icateband (a bradykinin receptor antagonist) Blocked the increase of flow dependent VD by Quinaprilat.  
  Hornig et al. Circulation 1997; 95:1115

• Icateband blocked the hypotensive effect of Captopril, but not Losartan, in hypertensive patients  
  Gainer et al. NEJM 1998; 18:1285
HEART FAILURE

• ELITE II: Losartan (50) vs Captopril (150) for CHF. Total and sudden death. 
  
  Lancet 2000;355:1582
Valsartan + ACE-I in HF: Val-HeFT

5010 pts. EF <40% NYHA II–IV

Receiving standard therapy

ACE-I (93%)
Dig (67%)
Diuretic (86%)
β-blockers (36%)

Randomized to

Valsartan 40-160 mg bid

PBO

906 events

Figure 4. Relative Risks and 95 Percent Confidence Intervals for the Combined End Point (Death from Any Cause, Cardiac Arrest with Resuscitation, Hospitalization for Worsening Heart Failure, or Therapy with Intravenous Inotropes or Vasodilators), According to the Background Therapy at Base Line, as Calculated by Means of a Cox Regression Model.

ACE denotes angiotensin-converting enzyme, + the use of the drug, and − nonuse.
CHARM-Alternative: Primary outcome CV death or CHF hospitalization

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

Number at risk
Candesartan 1013 929 831 434 122
Placebo 1015 887 798 427 126

Placebo

Candesartan

406 (40.0%)
334 (33.0%)
CHARM-Added: Primary outcome
CV death or CHF hospitalisation

HR 0.85 (95% CI 0.75-0.96), p=0.011
Adjusted HR 0.85, p=0.010

Number at risk
- Candesartan: 1276, 1176, 1063, 948, 457
- Placebo: 1272, 1136, 1013, 906, 422

538 (42.3%)
483 (37.9%)

CHF: Congestive Heart Failure
POST-MI LV DYSFUNCTION
OPTIMAAL: Losartan vs Captopril in high-risk MI: mortality and morbidity

Lancet 2002;360:752

![Graph showing total mortality with endpoint rates and number at risk for Losartan and Captopril.](image)

Total Mortality

Relative risk 1.13
(95% CI 0.99–1.28) p=0.069

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Losartan</th>
<th>Captopril</th>
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<td>1309</td>
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<td>Category</td>
<td>Number of patients</td>
<td>Hazard ratio (95% CI)</td>
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<td><strong>Age</strong></td>
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<td><strong>Overall</strong></td>
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## Principal efficacy end-points in OPTIMAAL

<table>
<thead>
<tr>
<th>End-point</th>
<th>Losartan (n=2744)</th>
<th>Captopril (n=2733)</th>
<th>Hazard ratio</th>
<th>P value</th>
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<tbody>
<tr>
<td>All cause mortality</td>
<td>18.2%</td>
<td>16.4%</td>
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<td>Sudden cardiac death</td>
<td>8.7%</td>
<td>7.4%</td>
<td>1.19</td>
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<td>Re-infarction</td>
<td>14%</td>
<td>13.9</td>
<td>1.03</td>
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<tr>
<td>Cardiovascular death</td>
<td>15.3%</td>
<td>13.3%</td>
<td>1.17</td>
<td>0.03</td>
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</tbody>
</table>
VALIANT

- Post-MI pts
- Mean age 65y
- Females 31%
- Mean MI duration 4.9 D
- Diabetes 23%
- Mean LVEF 35%
- Clinical CHF: 15%

- Randomized to:
  - VAL: 4,909
  - CAP: 4,909
  - VAL+CAP: 4,885
  - TOTAL 14,703

- FU: 36 M.
- Mortality EP: 2878

VALIANT: Total Mortality

Valsartan vs Captopril: HR = 1.00; \( P = 0.982 \)

Valsartan + Captopril vs Captopril: HR = 0.98; \( P = 0.726 \)

VALIANT: Adverse Effects

- Hypotension: VAL 18.2, CAP+VAL 11.9, CAP 15.3
- Renal causes: VAL 4.8, CAP+VAL 3.0, CAP 4.1
- Cough: VAL 1.7, CAP+VAL 4.6, CAP 5.0
- Any ADE: VAL 34.8, CAP+VAL 28.4, CAP 30.5
Mortality in SAVE, TRACE, AIRE, VS. VALIANT

Hazard Ratio for Mortality

Favors Active Drug
Favors Placebo

SAVE
TRACE
AIRE
Combined

Imputed placebo

SUMMARY: WHAT DO ARB OFFER IN CHF BEYOND “NO COUGH”

- **Hypertrophy** (animal models): conflicting on reversal of vascular / ventricular hypertrophy, a well established effect of ACEI.

- **Clinical Heart Failure:**
  - Comparable or less effect than ACEI
  - Not recommended as first line.

- **Post-MI LV Dysfunction:** Equal or less effective

  [ELITE II, OPTIMAAL, VALIANT]