STAGE A
At high risk for HF but without structural heart disease or symptoms of HF
- e.g., Patients with:
  • hypertension
  • CAD
  • diabetes mellitus or Patients
  • Using cardiotoxins
  • With FHx CM

THERAPY
- Treat hypertension
- Encourage smoking cessation
- Treat lipid disorders
- Encourage regular exercise
- Discourage alcohol intake, illicit drug use
- ACE-inhibition in appropriate patients

STAGE B
Structural heart disease but without symptoms of HF
- e.g., Patients with:
  • Previous MI
  • LV systolic dysfunction
  • Asymptomatic valvular disease

THERAPY
- All measures under stage A
- ACE-inhibition in appropriate patients

STAGE C
Structural heart disease with prior or current symptoms of HF
- e.g., Patients with:
  • Know structural heart disease
  • Shortness of breath and fatigue, reduced exercise tolerance

THERAPY
- All measures under stage A
- Drugs for routine use:
  - Diuretics
  - ACE inhibitors
  - Beta-blockers
  - Digitalis
- Dietary salt restriction

STAGE D
Refractory HF requiring specialized interventions
- e.g., Patients with:
  - Marked symptoms at rest despite maximal therapy, who are recurrently hospitalized or cannot be safely discharged without specialized interventions

THERAPY
- All measures under stage A, B, C
- Mechanical assist devices
- Heart transplantation
- Continuous (not intermittent) IV inotropic infusion for palliation
- Hospice care

Development of symptoms of HF: Structural heart disease
Refactory symptoms of HF at rest
Histological section of myocardial specimen biopsy from a hypertensive patient with nonsevere myocardial fibrosis (A) and a hypertensive patient with severe myocardial fibrosis (B) before and after treatment with losartan. Picrosirius red stain; magnification

Left Ventricular Peak Filling Rate in Hypertensive Patients With Impaired Diastolic Function at Randomization

RESTING CONDITIONS

PEAK EXERCISE

Peak filling rate (EDV/sec)

$\text{p < 0.01}$

$\text{p < 0.05}$
LIFE: ECG-LVH Regression from Baseline

- Cornell Product
  - p < 0.0001
- Sokolow-Lyon
  - p < 0.0001

Losartan vs Atenolol

Prevalence of excessive fibrosis in atenolol- and losartan-treated patients at baseline and after 36-week treatment.

- **Atenolol**
  - Baseline: 57%
  - Therapy: 61%

- **Losartan**
  - Baseline: 69%
  - Therapy: 48%
RUOLO DEL SISTEMA RENINA-ANGIOTENSINA NEL POST-INFARTO: CRESCENTE CONCENTRAZIONE DI ACE NEL MIOCARDIO

SHAM

3 DAY

MYOCARDIAL INFARCTION

I 351A RADIOLIGAND

14 DAY

28 DAY

(Jackson, 1991)
Electron Microscopic Localization of HHMC (III)
<table>
<thead>
<tr>
<th>First Incubation</th>
<th>Second Incubation</th>
<th>Angiotensin II Formed (pmoles/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisinopril 100 μM</td>
<td>HHMC</td>
<td></td>
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<tr>
<td>Anti-Chymase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril 100 μM</td>
<td>ACE</td>
<td></td>
</tr>
<tr>
<td>Anti-Chymase</td>
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</table>
Targeted Disruption of NGFI-A

(a) Diagram showing the disruption of NGFI-A. The wild-type (wt) NGFI-A is disrupted by the introduction of a NEO gene (indicated by NEO) through homologous recombination. The targeted NGFI-A shows the integration of NEO.

(b) Gel electrophoresis with markers 1, 2, and 3. Lanes 1 and 2 show 25 kb and 19 kb markers, respectively. Lane 3 shows the wt, 25 kb, and 19 kb markers.

(c) Gel electrophoresis of samples 1 to 12, with markers 1 to 12. Lane 1 shows 25 kb markers, lane 2 shows 19 kb markers, and lane 3 shows the wt and ko (knockout) samples.
LEFT VENTRICULAR GROWTH DURING CHRONIC PRESSURE OVERLOAD

- Egr-1 +/+
- Egr-1 -/-

LV/W/BW (mg/g) vs. Systolic Pressure Gradient (mmHg)
MYOCYTE CROSS SECTIONAL AREA AFTER CHRONIC PRESSURE OVERLOAD

Myocyte cross sectional area ($\mu m^2$)

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>TAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egr-1+/+</td>
<td>175</td>
<td>200</td>
</tr>
<tr>
<td>Egr-1-/-</td>
<td>190</td>
<td>210</td>
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</tbody>
</table>

*p<0.05 vs Sham
Myocardial fibrosis (%) vs Egr-1 genotypes:

- Sham
- TAC

Egr-1+/+: *p<0.05 vs Sham; §p<0.05 vs TAC +/+
SURVIVAL RATES DURING PRESSURE OVERLOAD

![Graph showing survival rates over days after TAC for Egr-1 +/+ and Egr-1 -/- genotypes.](image-url)
Effect of antihypertensive therapy on ventricular–arterial mechanics, coupling, and efficiency

Carolyn S.P. Lam¹,²*,†, Amil M. Shah³†, Barry A. Borlaug⁴, Susan Cheng³, Anil Verma⁵, Joseph Izzo⁶, Suzanne Oparil⁷, Gerard P. Aurigemma⁸, James D. Thomas⁹, Bertram Pitt¹⁰, Michael R. Zile¹¹, and Scott D. Solomon³

¹National University Health System, Tower Block Level 9, 1E Kent Ridge Road, Singapore 119228, Singapore; ²Boston University School of Medicine, Boston, MA, USA; ³Brigham and Women’s Hospital, Boston, MA, USA; ⁴Mayo Clinic, Rochester, MN, USA; ⁵Ochsner Heart and Vascular Institute, New Orleans, LA, USA; ⁶State University of New York, Buffalo, NY, USA; ⁷University of Alabama, Birmingham, AL, USA; ⁸University of Massachusetts Medical School, Worcester, MA, USA; ⁹Cleveland Clinic Foundation, Cleveland, OH, USA; ¹⁰University of Michigan, Ann Arbor, MI, USA; and ¹¹RHJ Department of Veterans Affairs Medical Center and the Medical University of South Carolina, Charleston, SC, USA
Conclusion

Antihypertensive therapy reduces arterial and ventricular stiffness, enhances ventricular–arterial coupling, reduces cardiac work, and improves LV efficiency, systolic, and diastolic function. Attenuated responses in women and among obese subjects suggest that structure–function changes may be less reversible in these groups, possibly explaining their greater susceptibility to ultimately develop heart failure.
A differenza degli ACE-I e degli ARB, aliskiren riduce l’ Ang I, l’ Ang II e la PRA

<table>
<thead>
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<th>Ang I</th>
<th>Ang II</th>
<th>Renina</th>
<th>PRA</th>
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<tr>
<td><strong>ACEI</strong></td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td><strong>ARB</strong></td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td><strong>Aliskiren</strong></td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
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</table>

Azizi M et al. 2006
Rappresentazione schematica del meccanismo di attivazione del recettore della prorenina
Nonproteolytic Activation of Prorenin Contributes to Development of Cardiac Fibrosis in Genetic Hypertension
Atsuhiro Ichihara, Yuki Kaneshiro, Tomoko Takemitsu, Mariyo Sakoda, Fumiaki Suzuki, Tsutomu Nakagawa, Akira Nishiyama, Tadashi Inagami and Matsuhiko Hayashi

Hypertension 2006, 47:894-900: originally published online April 3, 2006
Mean arterial pressure (mmHg)

Cardiac prorenin receptor mRNA (ratio to GAPDH mRNA)

Hypertension. 2006;47:894-90)
L’ associazione aliskiren/losartan assicura una maggiore riduzione di ~20% dell’ IMVS rispetto a losartan in monoterapia

Variazione percentuale media (%) di IMVS dal basale dopo 36 settimane di trattamento

- **Aliskiren 300 mg**: n=132, -5.4%
- **Losartan 100 mg**: n=123, -4.7%
- **Aliskiren/losartan 300/100 mg**: n=136, -6.4%

*IMVS: indice di massa ventricolare sinistra
Analisi fra trattamenti basate su dati medi minimi quadrati:
* p<0.0001 vs basale
† p<0.0001 per non inferiorità vs losartan 100 mg; †p=0.52 vs losartan 100 mg

Prorenin Receptor Blockade Inhibits Development of Glomerulosclerosis in Diabetic Angiotensin II Type 1a Receptor–Deficient Mice

Atsuhiro Ichihara,* Fumiaki Suzuki,†† Tsutomu Nakagawa,† Yuki Kaneshiro,* Tomoko Takemitsu,* Mariyo Sakoda,* A.H.M. Nurun Nabi,‡ Akira Nishiyama,§ Takeshi Sugaya,‖ Matsuhiko Hayashi,* and Tadashi Inagami¶

*Department of Internal Medicine, Keio University School of Medicine, Tokyo, †Faculty of Applied Biological Sciences and ‡United Graduate School of Agricultural Science, Gifu University, Gifu, §Department of Pharmacology, Kagawa University School of Medicine, Kagawa, and ¶Nephrology Diseases Research Laboratory, Tanabe Seiyaku, Osaka, Japan; and ‖Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee
Aliskiren riduce significativamente il rapporto urinario albumina/creatinina (UACR) rispetto al placebo.

Riduzione media dell’UACR rispetto al basale (%)

-18% ***

Riduzione del 20% dell’UACR vs placebo

n=287

2%
n=289

Terapia ottimale + aliskiren 300 mg

Terapia ottimale + placebo

*** p = 0,0009 vs placebo

Effect of aliskiren treatment on endothelium-dependent vasodilation and aortic stiffness in essential hypertensive patients

Agostino Virdis*,†, Lorenzo Ghiadoni†, Ahmad Amedeo Qasem, Gianni Lorenzini, Emiliano Duranti, Giulia Cartoni, Rosa Maria Bruno, Giampaolo Bernini, and Stefano Taddei

Department of Internal Medicine, University of Pisa, Pisa, Italy

Received 22 November 2011; revised 1 February 2012; accepted 16 February 2012
Pulse wave velocity (m/s)

<table>
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<tr>
<th>Group</th>
<th>Aliskiren</th>
<th>Ramipril</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>7.5</td>
<td>7.2</td>
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Augmentation index

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<td>15</td>
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