Angiotensin Receptors – Neprilysin Inhibition (ARNI): Mechanisms of Action, Effects and Side Effects

Uri Elkayam, MD
Professor of Medicine
University of Southern California
Keck School of Medicine
elkayam@usc.edu
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*
• 1898 a Finnish physiologist and his Swedish medical students working in the Karolinska institute, discovered that saline extracts of rabbit renal cortex injected into rabbits, caused a pressor response. They named the active component of the extracts **Renin**.
"A [rabbit] kidney was pulverized with 21 ml of water. Injection into jugular vein. Within 80 s, there is a rise in mean arterial pressure from 62-67 mmHg to 100 mmHg, i.e. an increase by ca. 50%.

Robert Adolf Armand Tigerstedt (ca. 1910)

Experiment 1B, November 8, 1896
Tigerstedt and Bergman, Niere und Kreislauf
Skand. Arch. Physiol. 8: 223-271, 1898
1940 two groups, one in Argentina and the second in the US demonstrated that renin catalyzed the formation of a peptide pressor substance that was called Angiotensin.

They described 2 forms, the first an inactive decapeptide Angiotensin I that was cleaved by an enzyme (ACE) to the active octapeptide Angiotensin II.
Effects of Angiotensin II

- Retention of Na$^+$ and water by a direct proximal tubular effect and activation of aldosterone and vasopressin.
- Stimulates the thirst center of the brain.
- Stimulates cell proliferation, oxidative stress and fibrosis of the heart, kidneys and other organs.
- Stimulate the adrenal cortex to produce aldosterone.
- Stimulates cell proliferation, oxidative stress, and fibrosis.
Stimulates cell proliferation, oxidative stress, and fibrosis
RAAS Inhibitors

• 1977 the 1st ACE inhibitor, Captopril was developed and became a useful antihypertensive.

Gavras H et al NEJM 1978;298:991-5
Influence of Chronic Captopril Therapy on the Infarcted Left Ventricle of the Rat

Janice M. Pfeffer, Marc A. Pfeffer, and Eugene Braunwald

With the technical assistance of Cynthia R. Steinberg

From the Cardiovascular Division, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, Boston, Massachusetts

Stroke Volume Index

Ejection Fraction

End Diastolic Volume
The New England Journal of Medicine

EFFECT OF CAPTOPRIL ON MORTALITY AND MORBIDITY IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION AFTER MYOCARDIAL INFARCTION

Results of the Survival and Ventricular Enlargement Trial

Marc A. Pfeffer, M.D., Ph.D., Eugene Braunwald, M.D., Lemuel A. Moyé, M.D., Ph.D.,
Lofty Basta, M.D., Edward J. Brown Jr., M.D., Thomas E. Cutler, M.D.,
Barry R. Davis, M.D., Ph.D., Edward M. Geitman, M.D., Steven Goldman, M.D.,
Greg C. Flaker, M.D., Marc Klein, M.D., Gervasio A. Lamas, M.D., Milton Packer, M.D.,
Jaques Rouleau, M.D., Jean L. Rouleau, M.D., John Rutherford, M.D., John H. Wertheimer, M.D.,
and C. Morton Hawkins, Sc.D., on behalf of the SAVE Investigators*
253 class IV HF patients randomized to placebo or enalapril 5-20 mg BID
Figure 2. Cumulative Probability of Death in Patients Not Taking Vasodilators (Group I) and in Patients Taking Vasodilators (Group II) at the Time of Random Assignment.
EFFECT OF ENALAPRIL ON SURVIVAL IN PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS AND CONGESTIVE HEART FAILURE

The SOLVD Investigators*

Abstract  Background. Patients with congestive heart failure have a high mortality rate and are also hospitalized frequently. We studied the effect of an angiotensin-converting-enzyme inhibitor, enalapril, on mortality and hospitalization in patients with chronic heart failure and ejection fractions ≤0.35.

Methods. Patients receiving conventional treatment for heart failure were randomly assigned to receive either placebo (n = 1284) or enalapril (n = 1285) at doses of 2.5 to 20 mg per day in a double-blind trial. Approximately 90 percent of the patients were in New York Heart Association functional classes II and III. The follow-up averaged 41.4 months.

Results. There were 510 deaths in the placebo group (39.7 percent), as compared with 452 in the enalapril group (35.2 percent) (reduction in risk, 16 percent; 95 percent confidence interval, 5 to 26 percent; P = 0.0036).

Although reductions in mortality were observed in several categories of cardiac deaths, the largest reduction occurred among the deaths attributed to progressive heart failure (251 in the placebo group vs. 209 in the enalapril group; reduction in risk, 22 percent; 95 percent confidence interval, 6 to 35 percent). There was little apparent effect of treatment on deaths classified as due to arrhythmia without pump failure. Fewer patients died or were hospitalized for worsening heart failure (736 in the placebo group and 613 in the enalapril group; risk reduction, 26 percent; 95 percent confidence interval, 18 to 34 percent; P < 0.0001).

SOLVD Treatment Trial

**EF ≤ 35%**

- Placebo: 1284, 1159, 1085, 1005, 939, 819, 669, 487, 299
- Enalapril: 1285, 1195, 1127, 1069, 1010, 891, 697, 526, 333

**Progressive HF**

- Placebo
- Enalapril

**Arrhythmias**

- Placebo
- Enalapril

**HF Hospitalizations – 26%**

Figure 1. Mortality Curves in the Placebo and Enalapril Groups.

P = 0.0036

P = 0.0045
N=4228
Mortality – 8% P=0.30
CV mortality – 12% P=0.12
Death and HF hospitalizations -29% P<0.001
EFFECT OF ENALAPRIL ON MORTALITY AND THE DEVELOPMENT OF HEART FAILURE IN ASYMPTOMATIC PATIENTS WITH REDUCED LEFT VENTRICULAR EJECTION FRACTIONS

The SOLVD Investigators*

Abstract Background. It is not known whether the treatment of patients with asymptomatic left ventricular dysfunction reduces mortality and morbidity. We studied the effect of an angiotensin-converting–enzyme inhibitor, enalapril, on total mortality and mortality from cardiovascular causes, the development of heart failure, and hospitalization for heart failure among patients with ejection fractions of 0.35 or less who were not receiving drug treatment for heart failure.

Methods. Patients were randomly assigned to receive either placebo (n = 2117) or enalapril (n = 2111) at doses of 2.5 to 20 mg per day in a double-blind trial. Follow-up averaged 37.4 months.

Results. There were 334 deaths in the placebo group, as compared with 313 in the enalapril group (reduction in risk, 8 percent by the log-rank test; 95 percent confidence interval, −3 to 26 percent; P = 0.12). When we combined patients in whom heart failure developed and those who died, the total number of deaths and cases of heart failure was lower in the enalapril group than in the placebo group (630 vs. 818; risk reduction, 29 percent; 95 percent confidence interval, 21 to 36 percent; P < 0.001). In addition, fewer patients given enalapril died or were hospitalized for heart failure (434 in the enalapril group vs. 518 in the placebo group; risk reduction, 20 percent; 95 percent confidence interval, 9 to 30 percent; P < 0.001).

Conclusions. The angiotensin-converting–enzyme inhibitor enalapril significantly reduced the incidence of heart failure and the rate of related hospitalizations, as compared with the rates in the group given placebo, among patients with asymptomatic left ventricular dysfunction. There was also a trend toward fewer deaths due to cardiovascular causes among the patients who re-
SOLVD Prevention

N=4228

12% mortality from all causes (%)

Placebo

Enalapril

P = 0.30

29% death or hospitalization for CHF (%)

Placebo

Enalapril

P < 0.001

12% mortality from cardiovascular causes (%)

Placebo

Enalapril

P = 0.12

20% death or CHF (%)

Placebo

Enalapril

P < 0.001
V-HeFT II

Effect of Enalapril vs. HYD/ISDN on all cause mortality

P = 0.016 at 2 years (28%) and 0.08 overall mortality difference due to decreased sudden death

Mortality reduction
More prominent in class I-II patients

Sites of Action of ACEIs and ARBs

Major importance When level of Renin and Angiotensinogen Increased by use Of ACE-I

AT_1-receptor blocker

AT_1-receptor

Vasoconstriction, 
Cell Growth (Remodeling)
Aldosterone secretion (Salt/water retention)
Cathecholamine release

AT_2-receptor

Vasodilation,
Inhibition of cell Growth,
Natriuresis,
Bradykinin release/NO/PGE

Angiotensin I

ACEI

Angiotensin II

ACE-Kininase II

Bradykinin → BK II-receptor

Inactive degradation products

Vasodilation
Natriuresis
Anti-remodeling

Cough Angioedema

## Trials with ARBs in HF & Post-MI

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Drug</th>
<th>Comparator</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELITE-2</td>
<td>CHF Class II-IV &gt; 60 years</td>
<td>Losartan</td>
<td>Captopril</td>
<td>No benefit over captopril Less cough</td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>CHF Class II-III</td>
<td>Valsartan</td>
<td>Placebo</td>
<td>↓HF M&amp;M particularly in pts on no ACEi or BB. Worse in pts on both.</td>
</tr>
<tr>
<td>CHARM Alternative Added</td>
<td>CHF Class II-III</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>Reduced M&amp;M Alter P- 0.0004 Add-on P- 0.011</td>
</tr>
<tr>
<td>OPTIMAAL</td>
<td>Post MI HF</td>
<td>Losartan</td>
<td>Captopril</td>
<td>Both improve LV function, Trend favored Captopril</td>
</tr>
<tr>
<td>VALIANT</td>
<td>Post MI HF</td>
<td>Valsartan</td>
<td>Captopril</td>
<td>No benefit over Captopril alone or in combination</td>
</tr>
</tbody>
</table>
ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality.

(Class 1, Level of Evidence: A)
ARBs are recommended in patients with HFrEF with current or prior symptoms who are ACE inhibitor intolerant, unless contraindicated, to reduce morbidity and mortality. (Class 1, Level of Evidence: A)
ARBs are reasonable to reduce morbidity and mortality as alternatives to ACE inhibitors as first-line therapy for patients with HFrEF, especially for patients already taking ARBs for other indications, unless contraindicated. (Class IIa, Level of Evidence: A)
Natriuretic Peptide System

In 1898 Tigerstedt and Bergman showed that infusion of extracts of rat atrium caused hypotension, > 30 fold increase of Na excretion and 10 fold increase in urine output and called it Atrial Natriuretic Factor.
Natriuretic Peptide System

- In 1988 a peptide was identified in porcine brain that also caused hypotension, natriuresis and diuresis and was called Brain Natriuretic Peptide (BNP).

- BNP is also found in the heart and produced primarily from the ventricles.
Natriuretic Peptides

- **ANP**: 28aa peptide
- **BNP**: 32aa peptide
- **CNP**: 22aa peptide
Physiologic Effects of Natriuretic Peptides

Corticotropin = hormone secreted by the adenohypophysis, having a stimulating effect on the adrenal cortex.
BNP Concentration for the Degree of CHF Severity

The Natriuretic Peptide System is Overwhelmed in Acute Decompensated Heart Failure

A hallmark of HF is BNP resistance..

Angiotensin II
Epinephrine
Endothelin
Aldosterone
Angiotensin II
Epinephrine

BNP in HF biologically inactive
Much of BNP measured by contemporary assays is either nonprocessed (glycosylated) proBNP or degradation products of BNP 1-32 (BNP 3-32, 5-32, and 8-32).

Jaffe A. JACC 2015:65:666
Both furin and corin process proBNP to biologically active BNP and nonbiologically active NT-proBNP. BNP mediates its biological actions by binding to its receptor (pGC-A) and activating the second messenger cGMP. BNP is degraded into less biologically active BNP products by the enzyme nepriyisn that is highly expressed in the kidney. BNP = B-type natriuretic peptide; cGMP = 3'-5'-cyclic guanosine monophosphate; NT-proBNP = N-terminal pro-B-type natriuretic peptide.
The influence of neprilysin inhibitors on natriuretic peptides testing in heart failure (HF).

Central Illustration: Natriuretic Peptide Testing in Heart Failure: The Influence of Neprilysin Inhibitors

- **proBNP**: Pro-brain natriuretic peptide, a precursor of BNP.
- **NT-proBNP**: N-terminal pro-B-type natriuretic peptide, a degradation product of proBNP.
- **BNP**: Brain natriuretic peptide, an active hormone.
- **Tβ1**: 1.5 to 2.0 h, an inactive metabolite.
- **Tβ2**: 20 min, an active hormone.
- **Nephrilysin**: An enzyme that degrades BNP.
- **Sacubitril**: A neprilysin inhibitor.
- **LCZ696**: A combination of sacubitril and valsartan.

The use of LCZ696 (sacubitril/valsartan, also known as Entresto) will likely influence circulating natriuretic peptide levels in patients with heart failure. Because B-type natriuretic peptide (BNP), but not N-terminal pro-B-type natriuretic peptide (NT-proBNP), is a substrate of nephrilysin, levels of circulating BNP may reflect the action of the drug. BNP levels may rise in patients taking sacubitril/valsartan due to nephrilysin inhibition. However, circulating NT-proBNP levels may fall due to diminished left atrial and left ventricular wall stress.
Table 1. Measurements of Systemic and Renal Hemodynamic Parameters at Baseline and 15 min After Intravenous Infusion of Nesiritide in 16 Patients With HF

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Infusion</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>79 ± 16</td>
<td>81 ± 16</td>
<td>0.444</td>
</tr>
<tr>
<td>SRBP (mm Hg)</td>
<td>135 ± 28</td>
<td>123 ± 22</td>
<td>0.003</td>
</tr>
<tr>
<td>DRBP (mm Hg)</td>
<td>79 ± 12</td>
<td>71 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRBP (mm Hg)</td>
<td>99 ± 17</td>
<td>89 ± 13</td>
<td>0.002</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>9 ± 6</td>
<td>7 ± 5</td>
<td>0.061</td>
</tr>
<tr>
<td>SPA (mm Hg)</td>
<td>55 ± 19</td>
<td>49 ± 22</td>
<td>0.001</td>
</tr>
<tr>
<td>DPA (mm Hg)</td>
<td>26 ± 8</td>
<td>22 ± 9</td>
<td>&lt;0.001</td>
</tr>
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<td>MPA (mm Hg)</td>
<td>36 ± 12</td>
<td>31 ± 13</td>
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<tr>
<td>PCWP (mm Hg)</td>
<td>21 ± 8</td>
<td>15 ± 10</td>
<td>&lt;0.001</td>
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<tr>
<td>CO (l/min)</td>
<td>3.9 ± 1.2</td>
<td>4.6 ± 1.6</td>
<td>0.001</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>2.2 ± 0.5</td>
<td>2.5 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVR (dyne·s·cm⁻⁵)</td>
<td>1,995 ± 532</td>
<td>1,563 ± 504</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR (dyne·s·cm⁻⁵)</td>
<td>315 ± 157</td>
<td>305 ± 157</td>
<td>0.632</td>
</tr>
<tr>
<td>VTI (cm/beat)</td>
<td>27 ± 15</td>
<td>23 ± 15</td>
<td>0.008</td>
</tr>
<tr>
<td>RAD (mm)</td>
<td>6.2 ± 0.7</td>
<td>6.7 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RVR (dyne·s·cm⁻⁵)</td>
<td>14,568 ± 7,334</td>
<td>13,609 ± 6,654</td>
<td>0.45</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>623 ± 326</td>
<td>647 ± 412</td>
<td>0.15</td>
</tr>
</tbody>
</table>

CI = cardiac index; CO = cardiac output; DPA = diastolic pulmonary artery (pressure); DRBP = diastolic renal blood pressure; HF = heart failure; HR = heart rate; MPA = mean pulmonary artery (pressure); MRBP = mean renal blood pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RAD = renal artery diameter; RAP = right atrial pressure; RBF = renal artery blood flow; RVR = renal vascular resistance; SPA = systolic pulmonary artery (pressure); SRBP = systolic renal blood pressure; SVR = systemic vascular resistance; VTI = velocity-time integral.
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What is Neprilysin?

- A plasma membrane glycoprotein, a metalloendopeptidase (neuropeptide-metabolizing enzyme), and the principle mechanism for degradation of the natriuretic peptides.
Interaction of Individual NPs With Neprilysin

Pankow et al J Mol Biol 2009;393:469

The natriuretic peptides (NPs) enter the interior cavity of neprilysin (green). The shorter amino and carboxy terminal tails of atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP) (upper panel) allow optimal positioning and interaction with the catalytic site for primary cleavage of the NP ring structure at the cysteine-phenylalanine bond. The longer tails of B-type natriuretic peptide (BNP) (lower panel) cause spatial clashes at the entry to the cleft and hinder orientation for catalysis resulting in initial cleavage outside the ring structure at residues Met-Val. Modified with permission from Pankow et al. (14).
Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With HF


**FIGURE 4** NT-proBNP Values in Patients Treated With Sacubitril/Valsartan Versus Enalapril at Each Study Time Point

<table>
<thead>
<tr>
<th></th>
<th>V2/V2a</th>
<th>V3</th>
<th>V5</th>
<th>V7</th>
<th>V10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacubitril/Valsartan</td>
<td>1303 (781,2371)</td>
<td>1251 (652,2208)</td>
<td>917 (526,1653)</td>
<td>938 (511,1595)</td>
<td>859 (450,1708)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>1269 (762,2184)</td>
<td>1276 (698,2186)</td>
<td>882 (517,1693)</td>
<td>1203 (711,2061)</td>
<td>1102 (610,2073)</td>
</tr>
</tbody>
</table>

Median N-terminal pro-B-type natriuretic peptide (NT-proBNP) values in the sacubitril/valsartan-treated patients (blue circles, blue solid line) versus enalapril-treated patients (orange squares, orange dashed line) at each measurement time point are shown. Numeric values for median (interquartile range; Q1,Q3) in patients with values available at each time point are presented in the table below the figure. NT-proBNP was significantly lower in the sacubitril/valsartan-treated patients than in the enalapril-treated patients at 1 and 8 months after randomization.

*p < 0.05. V2/V2a = baseline before run-in; V3 = after enalapril run-in; V5 = at randomization; V7 = 1 month after randomization; and V10 = 8 months after randomization.
What is Neprilysin?

- Neprilysin also breaks down numerous other peptides including the vasodilators bradykinine, adrenomedullin, and but also angiotensin I, angiotensin II, endothelin-1 and amyloid - β.
Metabolism of NPs and Other Peptide Hormones by NEP

- Natriuretic peptide receptors (NPRs) are coupled to guanylyl cyclase.
- NPR-A activation increases intracellular cGMP, which in turn mediates biologic effects, including:
  - Vasodilation
  - Natriuresis and diuresis
  - Antifibrosis, antihypertrophic effects
  - Inhibition of the RAAS, endothelin and vasopressin

- NPs are cleared by NPR-C receptor.
- ANP through degradation by membrane bound nephrilysin (NEP).
- NEP also degrades other vasoactive peptides including vasodilators, e.g., substance P and bradykinin, and vasoconstrictors such as endothelin 1 (ET-1) and angiotensin II (Ang II).
Adrenomodulline

• A 52 amino acids peptide produced by the endothelium.

• Reduces myocyte hypertrophy, fibroblast proliferation, collagen synthesis and aldosterone secretion.
Adrenomodulline

• A strong peripheral and renal vasodilator, reduces vascular resistance and PCW pressure, increases CO, GFR, urine volume and Na excretion.

• Works by increasing cyclic AMP and activating NO.
Hemodynamic Effect Of Adrenomedullin in HF
Nagaya N et al Circulation 2000;101:498
Hemodynamic Effect Of Adrenomedullin in HF
Nagaya N et al Circulation 2000;101:498
Renal Effects of Adrenomedullin in HF
Nagaya N et al Circulation 2000;101:498

**Urin Volume**

**Urinary Na Excretion**

**Urinary K excretion**

**Creatinine Clearance**

*Figure 4.* Changes in urine volume (UV), urinary sodium excretion (UNaV), urinary potassium excretion (UKV), and creatinine clearance (CrCl) during infusion of AM or placebo. Data are mean±SEM. *P<0.05 vs Before; †P<0.05 vs CHF-placebo; ‡P<0.05 vs NL-placebo; §P<0.05 vs NL-AM; ||P<0.05 vs NL-placebo.*
Bradykinin

• Bradykinin is a powerful vasodilator.

• Its vasodilatory effects result partially from NO release.

• Improves endothelial function.

• ACE inhibition enhances endothelium-mediated dilation in humans by a bradykinin-dependent mechanism.
Radial Artery Diameter During Reactive Hyperemia

**Figure 1.**

Percentage change in radial artery diameter during reactive hyperemia (FDD) at control measurements 1 and 2 (C1 and C2) and during icatibant (IC), quinaprilat (QUIN), and coinfusion of both icatibant and quinaprilat (IC + QUIN).
Comparison of Omapatrilat and Enalapril in HF
The OVERTURE Study

Milton Packer, MD; Robert M. Califf, MD; Marvin A. Konstam, MD; Henry Krum, MBBS, PhD; John J. McMurray, MD; Jean-Lucien Rouleau, MD; Karl Swedberg, MD; for the OVERTURE Study Group*

Background—Combined inhibition of the angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP) may produce greater benefits in heart failure than ACE inhibition alone.

Methods and Results—We randomly assigned 5770 patients with New York Heart Association class II to IV heart failure to double-blind treatment with either the ACE inhibitor enalapril (10 mg BID, n=2884) or to the ACE-NEP inhibitor omapatrilat (40 mg once daily, n=2886) for a mean of 14.5 months. The primary end point—the combined risk of death or hospitalization for heart failure requiring intravenous treatment—was used prospectively to test both a superiority and noninferiority hypothesis (based on the effect of enalapril in the Studies of Left Ventricular Dysfunction [SOLVD] Treatment Trial). A primary end point was achieved in 973 patients in the enalapril group and in 914 patients in the omapatrilat group (hazard ratio 0.94; 95% CI: 0.86 to 1.03, P=0.187)—a result that fulfilled prespecified criteria for noninferiority but not for superiority. The omapatrilat group also had a 9% lower risk of cardiovascular death or hospitalization (P=0.024) and a 6% lower risk of death (P=0.339). Post hoc analysis of the primary end point with the definition used in the SOLVD Treatment Trial (which included all hospitalizations for heart failure) showed an 11% lower risk in patients treated with omapatrilat (nominal P=0.012).

Conclusion—Omapatrilat reduces the risk of death and hospitalization in chronic heart failure but was not more effective than ACE inhibition alone in reducing the risk of a primary clinical event. Between-group differences in favor of omapatrilat observed in secondary and post hoc analyses warrant further study. (Circulation. 2002;106:920-926.)
The omapatrilat group had a 9% lower risk of CV death or hospitalization (P=0.024)
Omapatrilat was superior to Enalapril in reducing BP. However, incidence of angioedema 3 times higher (0.7% v 2.2%). Incidence higher in AA (1.6% v 5.5%). FDA declined to approve based on safety.
Angioedema Risk Increased with Omapatrilat which inhibits 3 enzymes in the Bradykinin Breakdown Pathway

4X risk of angioedema compared with ACE inhibitor in hypertension trials

Omapatrilat

Natriuretic peptides

Bradykinin

Angiotensin I

Aminopeptidase P

APP

Angiotensin II

APP-Aminopeptidase

NEP

DEGRADATION PRODUCTS

DEGRADATION PRODUCTS
Sites of Action of ACEIs and ARBs

Angiotensinogen

- Renin

Angiotensin I

- ACEI

Angiotensin II

- ACE-Kininase II

- Bradykinin

- BK II-receptor

Chymase

Trypsin

Peptidase

AT₁-receptor blocker

- AT₁-receptor

- AT₂-receptor

Vasoconstriction,
Cell Growth (Remodeling)
Aldosterone secretion (Salt/water retention)
Cathecolamine release

- Vasodilation,
Inhibition of cell Growth,
Natriuresis,
Bradykinin release/NO/PGE

- Vasodilation
Natriure-/diuresis
Anti-remodeling

Major importance When level of Renin and Angiotensinogen increased by use of ACE-I

All can undergo Further proteolysis To All I and All II which Promote vaso-constriction

Cough
Angioedema

NO

Interaction of Individual NPs With Neprilysin
Pankow et al J Mol Biol 2009;393:469

The natriuretic peptides (NPs) enter the interior cavity of neprilysin (green). The shorter amino and carboxy terminal tails of atrial natriuretic peptide (ANP) and C-type natriuretic peptide (CNP) (upper panel) allow optimal positioning and interaction with the catalytic site for primary cleavage of the NP ring structure at the cysteine-phenylalanine bond. The longer tails of B-type natriuretic peptide (BNP) (lower panel) cause spatial clashes at the entry to the cleft and hinder orientation for catalysis resulting in initial cleavage outside the ring structure at residues Met-Val. Modified with permission from Pankow et al. (14).
LCZ696 – A first-in-class Angiotensin Receptor Neprilysin Inhibitor – Simultaneously Inhibits NEP and the RAS

Vasoactive Peptide System

Heart Failure

Renin Angiotensin System

Sacubitril (AHU377)

Vasodilation
- ↓ blood pressure
- ↓ sympathetic tone
- ↓ aldosterone levels
- ↓ fibrosis
- ↓ hypertrophy
- Natriuresis/Diuresis

LCZ696 is a novel crystalline complex consisting of the molecular moieties of valsartan and sacubitril in an equimolar ratio.
Neprilysine in Heart Failure

Bayes-Genis JACC HF 2015;3:637

**NEP INHIBITION**

- ANP
- BNP
- CNP

**Endogenous**
- BNP
- BNP
- BNP
- BNP
- BNP

- ANP
- BNP

- CNP

- sNEP

- sNEP

- sNEP

- sNEP

- BK
- ET-1
- ANP
- AT II
- ANP
- sBP
- CNP

- sNEP

**Exogenous**
- Sacubitril

- LCZ696

- Valsartan

- ANG II

**Signaling cascades**

- GTP
- GTP
- cGMP

**Vasodilation**

- Inactive peptides

- Cardiac fibrosis / hypertrophy

- Natriuresis / diuresis

**Vasoconstriction**

- Cardiac fibrosis / hypertrophy

- Sodium / water retention
Angiotensin Receptors – Neprilysin Inhibition (ARNI): Mechanisms of Action, Effects and Side Effects

Uri Elkayam, MD
Professor of Medicine
University of Southern California
Keck School of Medicine
elkayam@usc.edu