ACE, DPP4 and NEP inhibitors

Understanding Mechanisms to Optimize Cardiovascular Benefit
Disclosures

Grant support: NIH, AHA, Novo Nordisk, Shire Pharmaceuticals
Consulting: Novartis Pharmaceuticals, Shire Pharmaceuticals, Selenity Pharmaceuticals, Alnylam Pharmaceuticals
Institutional: Bayer/Vanderbilt Alliance

I will reference unlabeled or unapproved uses of drugs or other products: bradykinin, icatibant, substance P, brain-type natriuretic peptide, neuropeptide Y
Three peptidase inhibitors

- Angiotensin-converting enzyme
- Dipeptidyl peptidase-4
- Neutral endopeptidase

Captopril 1981
Sitagliptin 2006
Sacubitril/Valsartan 2015

Losartan 1995
Peptidase Inhibitors: Common themes

- The enzymes these drugs inhibit are “promiscuous.” Beneficial and adverse effects of the inhibitors often result from blocking the degradation of more than one biologically active peptide.
- The peptidases share many substrates, creating the possibility of drug-drug interactions among inhibitors.
- The peptide substrates of the enzymes are difficult to measure and degraded through multiple pathways.
Angiotensin-converting enzyme (ACE) inhibitors

Diagrams illustrating the renin-angiotensin system and the effects of ACE inhibitors (DRI), aldosterone receptor blockers (ARB), and mineralocorticoid receptor antagonists (MR antag).

[Image: Diagram showing the renin-angiotensin system and the effects of various inhibitors on blood pressure regulation.]
Comparative effectiveness of ACEi vs ARB in ischemic heart disease

### TABLE 3

**General Summary of Outcomes and Strength of Evidence Addressing Key Questions 1 and 2**

<table>
<thead>
<tr>
<th>Key Question 1: ACE Inhibitors vs Placebo&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>Key Question 1: ARBs Versus Placebo</th>
<th>Key Question 2: Combined Therapy Versus ACE Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>↓↓↓</td>
<td>--</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>↓↓</td>
<td>--</td>
</tr>
<tr>
<td>MI&lt;sup&gt;c&lt;/sup&gt;</td>
<td>↓↓↓</td>
<td>NE</td>
</tr>
<tr>
<td>Stroke</td>
<td>↓↓</td>
<td>--</td>
</tr>
<tr>
<td>Composite of cardiovascular mortality, nonfatal MI, and stroke</td>
<td>--</td>
<td>↓↓</td>
</tr>
<tr>
<td>Study withdrawal due to adverse events</td>
<td>↑</td>
<td>NE</td>
</tr>
<tr>
<td>Hypotension</td>
<td>--</td>
<td>NE</td>
</tr>
<tr>
<td>Syncope</td>
<td>↑</td>
<td>NE</td>
</tr>
<tr>
<td>Cough</td>
<td>↑</td>
<td>NE</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data from Raptopoulos et al., 2008.

<sup>b</sup> Data from Raptopoulos et al., 2009.

<sup>c</sup> MI indicates myocardial infarction.
Bradykinin contributes to the blood pressure response to ACE inhibition

Gainer et al. *NEJM* 1998
Endogenous bradykinin stimulates t-PA release during ACE inhibition

Assessing effect of peptidase (ACE) inhibitors on responses to vascular peptides

Arterial Line (brachial artery) & Adjacent Peripheral IV

Forearm Blood Flow Readings

Strain Gauge Plethysmography
During ACE inhibition, endogenous bradykinin increases vascular t-PA release

Brown et al, Circulation 2000

Pretorius et al, Circulation 2003
Forearm t-PA release reflects coronary endothelial fibrinolytic function

Coronary t-PA release parallels forearm t-PA release

Minai et al *JACC* 2001

Forearm t-PA release predicts cardiovascular events

Robinson et al *ATVB* 2007
Cardiovascular risk factors are associated with impaired endothelial fibrinolysis

**Hypertension**

Ridderstrale et al *Hypertension*

**Obesity and insulin resistance**

Carnassi et al *Thromb Res*

**Smoking**

Pretorius et al *ATVB*

**Male sex**

Pretorius et al *Circulation, ATVB, Hypertension*

**Exposure to diesel exhaust**

Tornquist et al *Am J Resp Crit Care*
• ACE inhibitors decrease the degradation of peptides such as angiotensin I to II and bradykinin to inactive products

• Endogenous bradykinin contributes to favorable effects of ACE inhibitors on blood pressure and endothelial t-PA release

• But...
Bradykinin Is a Double-Edged Sword
ACE inhibitor-associated angioedema: an effect of bradykinin?
## Angiotensin-converting enzyme inhibitor-associated angioedema: risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American race</td>
<td>2.97 (2.24, 3.92)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2.49 (1.86, 3.34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.49 (1.16, 1.91)</td>
<td>0.002</td>
</tr>
<tr>
<td>Seasonal allergies</td>
<td>1.52 (1.12, 2.06)</td>
<td>0.008</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.47 (1.09, 1.99)</td>
<td>0.013</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.58 (0.38, 0.90)</td>
<td>0.014</td>
</tr>
</tbody>
</table>
Hypothesized mechanism of ACE inhibitor-associated angioedema

Inactive metabolites

ACE

DPP IV

APN

NEP

ACE

NEP

APP

Substance P

BK

Increased vascular permeability

Des-Arg^9^-BK

B^1

NK^1

B^2

Increased vascular permeability
Angioedema during combined ACE/neutral endopeptidase (NEP) inhibition

WALL STREET JOURNAL APRIL 2000

...the FDA raised questions about four patients on the drug who had a severe reaction that closed down their airways. The patients were among 7,000... The four patients had a severe form of angioedema, which is typically characterized by a mild, temporary swelling of the lips, cheeks or tongue.

Some 40 other patients developed the milder angioedema....

Among the four patients with the severe reaction, two were white and two were black, but the overall incidence of angioedema, though low, was four times higher among blacks....
A Variant in XPNPEP2 Is Associated with Angioedema Induced by Angiotensin I–Converting Enzyme Inhibitors

Qing Ling Duan,1,2* Borzoo Nikpoor,1* Marie-Pierre Dubé,3 Giuseppe Molinaro,4
Inge A. Meijer,5 Patrick Dion,5 Daniel Rochefort,5 Judith Saint-Onge,5 Leah Flury,9
Nancy J. Brown,9 James V. Gainer,9 Jean L. Rouleau,9 Angelo Agostoni,7 Massimo Cugno,7
Pierre Simon,6 Pierre Clavel,9 Jacky Potier,11 Bassem Wehbe,11 Seddik Benrabia,15
Julien Marc-Aurélo,14 Jacques Chanard,10 Tatiana Foroud,5 Albert Adam,9
and Guy A. Rouleau9

Table 2
C-2399A SNP Genotypes in ACEI-Associated AE Cases and Matched Controls

<table>
<thead>
<tr>
<th>C-2399A SNP GENOTYPE</th>
<th>AE-ACEI CASES (n = 20)</th>
<th>CONTROLS (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Males</td>
<td>No. of Females</td>
</tr>
<tr>
<td>CG or CC</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>CA</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>AA or A</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>All</td>
<td>16</td>
<td>14</td>
</tr>
</tbody>
</table>

NOTE.—Mean APP activity is represented as units of arginine released per minute per milliliter of plasma sample.
Aminopeptidase P deficiency contributes to anaphylactoid reactions but less likely to ACE inhibitor-associated angioedema.

Adam et al Lancet 2002
Woodard-Grice 2010
Hypothesized mechanism of ACE inhibitor-associated angioedema

In the diagram:
- **ACE** (Angiotensin Converting Enzyme)
- **DPPIV** (Dipeptidyl Peptidase IV)
- **APN** (Aminopeptidase N)
- **NEP** (Neprilysin)

**Inactive metabolites**
- **B₂**

**Increased vascular permeability**
- **Des-Arg⁹-BK**

**Substance P**
- **NK₁**

**Increased vascular permeability**

**Des-Arg⁹-BK**

**ACE NEP APP**

**BK**

**CPN**
DPP4 activity is decreased in plasma during ACEI-associated angioedema

Byrd et al Hypertension 2008
DPPIV deficiency increases susceptibility to ACE inhibitor-induced peritracheal edema through NK1

Byrd et al J Allergy Clin Immunol 2008
DPP4 inhibitor use is associated with increased risk of ACEi angioedema

Increased angioedema in saxagliptin-treated in SAVOR-TIMI 53

Brown et al Hypertension 2009
Comparisons of clinical trials of B2 receptor antagonist in ACE inhibitor-associated angioedema

<table>
<thead>
<tr>
<th>Study</th>
<th>Baş et al</th>
<th>Straka et al</th>
<th>Sinert et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>27 per protocol</td>
<td>30</td>
<td>121</td>
</tr>
<tr>
<td>Patient Characteristics</td>
<td>37% female</td>
<td>63% female</td>
<td>61.2% female</td>
</tr>
<tr>
<td>Comparator group</td>
<td>0% African descent</td>
<td>67% African descent</td>
<td>69.4 % African descent</td>
</tr>
<tr>
<td>Comparator group</td>
<td>500 mg prednisolone, Clemastine 2 mg</td>
<td>Both groups received standard therapy</td>
<td>Both groups received standard therapy</td>
</tr>
<tr>
<td>Symptoms to treatment (hr)</td>
<td>6.1 (3.0 to 10.0)</td>
<td>10.3 ± 0.56</td>
<td>7.8 (5.5 to 9.6)</td>
</tr>
<tr>
<td>Finding</td>
<td>Icatibant superior</td>
<td>No difference</td>
<td>No difference</td>
</tr>
<tr>
<td></td>
<td><em>NEJM 2015</em></td>
<td><em>J All Clin Immunol 2017</em></td>
<td><em>J All Clin Immunol Pract 2017</em></td>
</tr>
</tbody>
</table>
Bradykinin and bradykinin: BK1-5 ratio increased in ACE inhibitor-associated angioedema compared to ACE inhibitor-treated controls

Hubers et al *J Allergy Clin Immunol* 2018
Interim Summary

• ACE and DPP4 share many peptide substrates.
• In patients taking an ACE inhibitor, use of a DPP4 inhibitor increases the risk of angioedema.

Could there be a favorable interactive effect of ACE inhibitors and DPP4 inhibitors on blood pressure?
Dipeptidyl peptidase 4 (CD26)


GLP-1 causes vasodilation through GLP-1 receptor-dependent and -independent pathways

GLP-1 (7-36) → DPP4 → GLP-1 (9-36)

GLP-1 receptor dependent

NO – independent vasodilation
(not blocked by NOS inhibitor)

GLP-1 receptor independent
(see in GLP-1R -/- mice)

NO-dependent vasodilation
(blocked by L-NNA)

Ban et al Circulation 2008
GLP-1 receptor stimulation increases blood pressure and heart rate

Yamamoto et al J Clin Invest 2002
GLP-1R stimulation activates autonomic regulatory neurons

Yamamoto et al J Clin Invest 2002
GLP-1 increases blood pressure and heart rate during intra-duodenal (ID) glucose

Trahair et al J Clin Endocrinol Metab 2014  Wu et al Diabetic Med 2014
GLP-1 does not cause direct vasodilation in human forearm

Devin et al JAHA 2014
Interim Summary

• In rodents, GLP-1 causes vasodilation through GLP-1 receptor-dependent and -independent mechanisms.
• GLP-1 also activates the sympathetic nervous system.
• GLP-1 does not cause vasodilation in the human forearm vasculature.
• Acute GLP-1 administration may increase blood pressure and heart rate when given during caloric intake.
• With chronic administration of GLP-1 analogues, blood pressure decreases, but this may be due to weight loss.
Vasoactive substrates of DPP4

**Substance P**
RPKPQQFFGLM

**Brain natriuretic peptide**
SPKMVQGSGCFGRKMDRISSSSGLGCKVLRRH

**Neuropeptide Y**
NPYYPSKPDNPOEDAPAEDLARYYSALRHYINLITRQRY

**Peptide YY**
YPSKPEAPGEDASPEELNRYYASLRHYLNLVTRQRY
Effect of DPP4 inhibitor on acute response to ACE inhibitor

Marney et al *Hypertension* 2010
DPP4 inhibition attenuates BP response to acute maximal ACE inhibition

Marney et al Hypertension 2010
Full-dose ACE inhibition increases sympathetic activity when DPP4 is inhibited

Marney et al *Hypertension* 2010
DPP4 inhibition increases post-prandial catecholamines

Boschmann et al. *J Clin Endocrinol Metab* 2009
No effect of DPP4 inhibition on vasodilation in response to bradykinin or substance P

Devin et al Hypertension 2014
Substance P stimulates local NE release during ACE and DPP4 inhibition
Effect of ACE and DPP4 inhibition on t-PA release in response to substance P
Potential mechanism for decreased t-PA release during combined ACE and DPP4 inhibition

During ACEi+DPP4i substance P accumulates and stimulates SNS

Stimulation of the SNS results in depletion of t-PA
Working Hypothesis
Study Protocol: Effect of DPP4 inhibition on neuropeptide Y (NPY)-mediated vasoconstriction
DPP4 increases vasoconstrictor response to NPY during ACEi in healthy subjects

Hubers et al Hypertension 2018
DPP4 inhibition increases vasoconstrictor response to NPY during ACEi in T2DM

Hubers et al Hypertension 2018
Sitagliptin decreases degradation of NPY
DPP4 inhibition increases vasoconstrictor response to NPY during ARB

Hubers et al Hypertension 2018
Protocol: Contribution to endogenous substance P to effects of combined DPP4 and chronic ACE inhibition
Metabolic effects of sitagliptin similar during ACEi, ARB and CCB
Sitagliptin increases post-prandial norepinephrine during inhibition of the renin-angiotensin-aldosterone system
Sitagliptin decreases the conversion of Y1 to Y2 agonists.
DPP4 inhibition increases GHRH-stimulated growth hormone secretion in women

Wilson et al. JAHA 2018
DPP4 inhibition increases GH-stimulated forearm vasodilation in women

Wilson et al JHA 2018
Interim Summary

• DPP4 inhibition attenuates the blood pressure response to acute ACE inhibition and increases catecholamines
• During concurrent DPP4 and ACE inhibition substance P increases forearm release of catecholamines
• DPP4 inhibition potentiates the effect of NPY during either ACE inhibition or ARB treatment
• During interruption of the renin-angiotensin-system, DPP4 inhibition increases circulating catecholamines through an NK1 receptor-dependent mechanism
• These findings have implications for mechanism of increased risk of heart failure with DPP4 inhibition
Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes
Saxagliptin use associated with increased risk of heart failure

<table>
<thead>
<tr>
<th>Table 2. Prespecified Clinical End Points.*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End Point</strong></td>
</tr>
<tr>
<td>Cardiovascular death, myocardial infarction, or stroke: primary efficacy end point</td>
</tr>
<tr>
<td>Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or coronary revascularization: secondary efficacy end point</td>
</tr>
<tr>
<td>Death from any cause</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Ischemic stroke</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
</tr>
<tr>
<td><strong>Hospitalization for heart failure</strong></td>
</tr>
<tr>
<td>Hospitalization for coronary revascularization</td>
</tr>
<tr>
<td>Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine &gt;6.0 mg/dl (530 μmol/liter)</td>
</tr>
<tr>
<td>Hospitalization for hypoglycemia</td>
</tr>
</tbody>
</table>

* Event rates and percentages are 2-year Kaplan–Meier estimates.
Concomitant medications and risk of heart failure with saxagliptin

<table>
<thead>
<tr>
<th>Baseline Medications</th>
<th>Yes</th>
<th>No</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>6786</td>
<td>9706</td>
<td>1.19</td>
<td>(0.95, 1.50)</td>
<td>0.42</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>6997</td>
<td>9895</td>
<td>1.27</td>
<td>(0.92, 1.75)</td>
<td>0.93</td>
</tr>
<tr>
<td>Metformin</td>
<td>11415</td>
<td>5077</td>
<td>1.39</td>
<td>(1.06, 1.77)</td>
<td>0.38</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>972</td>
<td>15520</td>
<td>1.64</td>
<td>(0.64, 4.47)</td>
<td>0.78</td>
</tr>
<tr>
<td>Beta-Blocker</td>
<td>10162</td>
<td>6330</td>
<td>1.18</td>
<td>(0.97, 1.43)</td>
<td>0.56</td>
</tr>
<tr>
<td>Statin</td>
<td>12917</td>
<td>3575</td>
<td>1.28</td>
<td>(1.06, 1.56)</td>
<td>0.77</td>
</tr>
<tr>
<td>ACE/ARB</td>
<td>12990</td>
<td>3497</td>
<td>1.21</td>
<td>(1.00, 1.47)</td>
<td>0.28</td>
</tr>
<tr>
<td>Calcium Antagonist</td>
<td>3378</td>
<td>11114</td>
<td>1.08</td>
<td>(0.80, 1.46)</td>
<td>0.57</td>
</tr>
<tr>
<td>Diuretic</td>
<td>7198</td>
<td>9294</td>
<td>1.25</td>
<td>(1.03, 1.53)</td>
<td>0.76</td>
</tr>
<tr>
<td>Overall</td>
<td>16492</td>
<td></td>
<td>1.27</td>
<td>(1.07, 1.51)</td>
<td></td>
</tr>
</tbody>
</table>

Hazard Ratio: 0.2 to 5

Favors Saxagliptin

Favors Placebo

Data from Scirica et al Circulation 2014
Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial

Faiez Zannad, Christopher P Cannon, William C Cushman, George L Bakris, Venu Menon, Alfonso T Perez, Penny R Flick, Cyrus R Mehta, Stuart Kugler, Craig Wilson, Hung Lam, William B White, for the EXAMINE Investigators

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>History of heart failure at baseline</th>
<th>No history of heart failure at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alogliptin (n=2701)</td>
<td>Placebo (n=2679)</td>
<td>Alogliptin (n=771)</td>
</tr>
<tr>
<td>Cardiovascular death and hospital admission for heart failure</td>
<td>201 (7.4)</td>
<td>201 (7.5)</td>
<td>107 (13.9)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.00 (0.82-1.21)</td>
<td>0.976</td>
<td>0.90 (0.70-1.17)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P&lt;0.0001 for treatment and history of heart failure</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cardiovascular death*</td>
<td>112 (4.1)</td>
<td>130 (4.9)</td>
<td>55 (7.1)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.85 (0.66-1.10)</td>
<td>0.212</td>
<td>0.77 (0.54-1.09)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P&lt;0.0001 for treatment and history of heart failure</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hospital admission for heart failure</td>
<td>106 (3.9)</td>
<td>89 (3.3)</td>
<td>63 (8.2)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>1.19 (0.90-1.58)</td>
<td>0.220</td>
<td>1.00 (0.71-1.42)</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P&lt;0.0001 for treatment and history of heart failure</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Analysis includes all cardiovascular deaths, including those that followed heart failure that were not counted in the analysis of the composite endpoint.

Table 8: Risk of events assessed in the post-hoc analysis, by history of heart failure
Figure 1. Changes from baseline in blood pressure, heart rate, and body weight at the final visit according to angiotensin-converting enzyme inhibitor (ACEi) use. BP indicates blood pressure.
Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes


![Graphs showing the effect of Sitagliptin on cardiovascular outcomes in Type 2 Diabetes.](image)

Figure 1. Kaplan-Meier Curves for Primary and Secondary Outcomes (Intention-to-Treat Population). The graphs illustrate the primary cardiovascular outcomes for each group: composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (Panel A), and hospitalization for heart failure (Panel B). Kaplan-Meier. The curves are shown for the sitagliptin and placebo groups. The inset graphs show the same curves on a log scale. The 100% confidence intervals. This figure provides a visual representation of the study results.
<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number initiating chronic</td>
<td>542/5608</td>
<td>744/5655</td>
<td>0.7 (0.63-0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>insulin therapy</td>
<td>(9.7%)</td>
<td>(13.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number initiating additional</td>
<td>1591/7332</td>
<td>2046/733</td>
<td>0.72 (0.68-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hypoglycemic agents</td>
<td>(21.7%)</td>
<td>2 (27.9%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
LCZ696 – A first-in-class Angiotensin Receptor Neprilysin Inhibitor

Vasoactive Peptide System

Heart Failure

Renin Angiotensin System

Angiotensinogen (liver secretion)

Angiotensin I

Angiotensin II

AT₁ receptor

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

Vasoconstriction

- blood pressure
- sympathetic tone
- aldosterone
- fibrosis
- hypertrophy

Provided by M.D. Scott Solomon
PARADIGM: ARB/NEP inhibitor superior to ACE inhibition in heart failure

PIONEER: ARB/NEP inhibitor reduces readmissions after acute heart failure decompensation

<table>
<thead>
<tr>
<th>Table 2. Secondary Efficacy and Safety Outcomes.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
</tr>
<tr>
<td>Key safety outcomes — no. (%)</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Asthenia</td>
</tr>
<tr>
<td>Secondary biomarker outcomes — % (95% CI)</td>
</tr>
<tr>
<td>Change in high-sensitivity troponin T concentration</td>
</tr>
<tr>
<td>Change in B-type natriuretic peptide concentration</td>
</tr>
<tr>
<td>Change in ratio of B-type natriuretic peptide to NT-proBNP</td>
</tr>
<tr>
<td>Exploratory clinical outcomes — no. (%)</td>
</tr>
<tr>
<td>Rehospitalization for heart failure</td>
</tr>
<tr>
<td>Implantation of left ventricular assist device</td>
</tr>
<tr>
<td>Unplanned outpatient visit leading to use of intravenous diuretics</td>
</tr>
<tr>
<td>Increase in dose of diuretics of &gt;50%</td>
</tr>
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</table>

*NA denotes not available.
†Worsening renal function was defined by an increase in the serum creatinine concentration of 0.5 mg per deciliter or more (44 μmol per liter) and a decrease in the estimated glomerular filtration rate of 25% or more.
‡Shown are data on the time-averaged proportional change, from the baseline value to the geometric mean of values obtained at weeks 4 and 8.
§Hazard ratios and associated 95% confidence intervals were calculated with a Cox proportional-hazards model. Confidence intervals have not been adjusted for multiple comparisons, and therefore, inferences drawn from these intervals may not be reproducible.
¶The outcome of a composite of serious clinical events was added to the list of exploratory clinical outcomes in May 2013, before the database was locked and unblinding occurred. This end point included death, rehospitalization for heart failure, implantation of a left ventricular assist device, and inclusion on the list of patients eligible for heart transplantation.
ACE and neprilysin share substrates

**Bradykinin**

\[ \text{APP}^{\text{DPP4}} \rightarrow \text{NEP} \rightarrow \text{ACE} \]

\[ \text{RPPGFSFPFR} \]

**Substance P**

\[ \text{DPP4} \rightarrow \text{NEP} \rightarrow \text{ACE} \]

\[ \text{RPKPQFFGLM} \]

**BNP**

\[ \text{IDE} \rightarrow \text{NEP} \rightarrow \text{DPP4} \]

\[ \text{SKMVKQGSGLKLRHRH} \]
Peptide concentrations in patients treated with sacubitril/valsartan

“Venous blood samples were collected in tubes containing EDTA.”

Nougué et al Eur J Heart Fail 2018
Closing Thoughts

Understanding how a drug works matters.

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers have different efficacy in preventing thrombotic events in part because ACE inhibitors alter the degradation of bradykinin as well as the formation of angiotensin II.

Similarly, DPP4 inhibitors have effects distinct from GLP-1 analogues due to effects on the degradation of vasoactive peptide substrates.

Understanding the contribution of decreased degradation of peptides such as bradykinin and substance P, as well as the natriuretic peptides, would enhance the use of sacubitril/valsartan in patients with heart failure.
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