Impact of Angiotensin Receptor Nephrilysin Inhibition on Natriuretic Peptides

Christopher deFilippi, MD
Vice-Chair Academic Affairs
Inova Heart and Vascular Institute
Consulting/Honorarium: Roche Diagnostics, Siemens Diagnostics, Radiometer, Ortho Diagnostics, Thermo Fisher, Diadexus, MedScape

Grants: Roche Diagnostics, Critical Diagnostics, Abbott Diagnostics, Siemens Diagnostics
Objectives
Nephrolysin Inhibition and NP levels

• The evidence to support adding neprilysin inhibition to the management of ambulatory patients with HFrEF
• Impact of neprilysin inhibition on clinically measured BNP and NT-proBNP levels – *The simple view*
• Further insight into the interaction of nephrolysin and measured B-type natriuretic peptides – *A more complex story*
PARADIGM-HF
Kaplan–Meier Curves for Key Study Outcomes

A Primary End Point

Hazard ratio, 0.80 (95% CI, 0.73–0.87)
P<0.001

Cumulative Probability

No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236

Days since Randomization

B Death from Cardiovascular Causes

Hazard ratio, 0.80 (95% CI, 0.71–0.89)
P<0.001

Cumulative Probability

No. at Risk
LCZ696 4187 4056 3891 3282 2478 1716 1005 280
Enalapril 4212 4051 3860 3231 2410 1726 994 279

Days since Randomization

C Hospitalization for Heart Failure

Hazard ratio, 0.79 (95% CI, 0.71–0.89)
P<0.001

Cumulative Probability

No. at Risk
LCZ696 4187 3922 3663 3018 2257 1544 896 249
Enalapril 4212 3883 3579 2922 2123 1488 853 236

Days since Randomization

D Death from Any Cause

Hazard ratio, 0.84 (95% CI, 0.76–0.93)
P<0.001

Cumulative Probability

No. at Risk
LCZ696 4187 4056 3891 3282 2478 1716 1005 280
Enalapril 4212 4051 3860 3231 2410 1726 994 279

Days since Randomization

PARADIGM-HF

Differential findings with BNP vs NT-proBNP measures

Enalopril patients are grey boxes; LCZ696 patients are white boxes

Objectives
Nephrilysin Inhibition and NP levels

✓ The evidence to support adding neprilysin inhibition to the management of ambulatory patients with HFrEF

✓ Impact of nephrilysin inhibition on clinically measured BNP and NT-proBNP levels – *The simple view*

• Further insight into the interaction of nephrilysin and measured B-type natriuretic peptides – *A more complex story*
  
  • A large proportion of detected “BNP” is proBNP
  
  • Nephrilysin and degradation of BNP and proBNP
  
  • A possible bidirectional relationship between nephrilysin and B-type natriuretic peptides
Biology of the NP System

Synthesis and Release

Both BNP and NT-proBNP are released from myocytes in response to stretch – BNP is an active hormone, NT-proBNP is inactive.
ProBNP$_{1-108}$ levels in the failing heart
Patients undergoing BVICD implantation (n=21)

Costello-Boerrigter et al. JACC Heart Fail 2013;1:207–12
Cross-Reactivity of commercial BNP and NT-proBNP assays with proBNP$_{108}$

Table 1. Percentage recoveries and cross-reactivities by BNP and NT-proBNP assays for each peptide.

<table>
<thead>
<tr>
<th>Assay</th>
<th>S$^a$ BNP</th>
<th>P BNP</th>
<th>S proBNP</th>
<th>H proBNP</th>
<th>H NT-proBNP</th>
<th>R NT-proBNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architect</td>
<td>151 (142, 160)$^b$</td>
<td>98 (85, 110)</td>
<td>38 (37, 38)</td>
<td>6 (2, 11)</td>
<td>&lt;1 (0, 0.8)</td>
<td>4 (4, 5)</td>
</tr>
<tr>
<td>AxSYM</td>
<td>184 (164, 205)</td>
<td>124 (117, 130)</td>
<td>34 (28, 39)</td>
<td>9 (3, 15)</td>
<td>&lt;1 (0, 0.5)</td>
<td>4 (3, 5)</td>
</tr>
<tr>
<td>Centaur</td>
<td>194 (189, 199)</td>
<td>137 (133, 141)</td>
<td>17 (17, 18)</td>
<td>14 (10, 17)</td>
<td>&lt;1 (0, 0.3)</td>
<td>7 (5, 9)</td>
</tr>
<tr>
<td>Access</td>
<td>199 (192, 205)</td>
<td>130 (129, 130)</td>
<td>24 (24, 25)</td>
<td>13 (7, 19)</td>
<td>&lt;1 (0, 0.4)</td>
<td>6 (5, 7)</td>
</tr>
<tr>
<td>Triage</td>
<td>135 (115, 156)</td>
<td>79 (78, 80)</td>
<td>19 (18, 20)</td>
<td>5 (0, 12)</td>
<td>&lt;1 (0, 0.2)</td>
<td>3 (2, 4)</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimension</td>
<td>&lt;1 (0, 0)</td>
<td>&lt;1 (0, 0)</td>
<td>&lt;1 (0, 0)</td>
<td>249 (230, 267)</td>
<td>243 (235, 251)</td>
<td>95 (91, 99)</td>
</tr>
<tr>
<td>Vitros</td>
<td>&lt;1 (0.6, 0.8)</td>
<td>&lt;1 (0.03, 0.4)</td>
<td>2 (1.6, 2.2)</td>
<td>55 (52, 59)</td>
<td>127 (124, 130)</td>
<td>71 (68, 74)</td>
</tr>
<tr>
<td>Elecsys</td>
<td>&lt;1 (0.2, 0.8)</td>
<td>&lt;1 (0, 0.04)</td>
<td>1 (0.7, 2)</td>
<td>29 (28, 30)</td>
<td>131 (126, 137)</td>
<td>47 (45, 49)</td>
</tr>
</tbody>
</table>

$^a$ S indicates Scios; P, Peptide Institute; H, HyTest; R, Roche.

$^b$ 95th Percentile confidence intervals are in parentheses.
In-vitro degradation of BNP and proBNP by Nephrilysin

Objectives
Nephrilysin Inhibition and NP levels

✓ The evidence to support adding neprilysin inhibition to the management of ambulatory patients with HFrEF
✓ Impact of nephrilysin inhibition on clinically measured BNP and NT-proBNP levels – *The simple view*

• Further insight into the interaction of nephrilysin and measured B-type natriuretic peptides – *A more complex story*

✓ A large proportion of detected “BNP” is proBNP_{108} in patients with heart failure
✓ Nephrilysin and degradation of BNP and proBNP_{108}

• A possible bidirectional relationship between nephrilysin and B-type natriuretic peptides
Nephrilysin activity modulated by BNP level
In vitro Nephrilysin activity inhibited by both BNP$_{1-32}$ and proBNP$_{1-108}$

Vodovar N et al. JACC Heart Fail. 2015;3:629-36
Molecular Switch Induced by the BNP-Mediated Neprilysin Inhibition

Vodovar N et al. JACC Heart Fail. 2015;3:629-36
Conclusions

• Nephrilysin inhibition with Sacubitril results in modest elevations of BNP in ambulatory patients with HFrEF

• A large proportion of the immuno-reactive BNP in patients with heart failure is the intact proBNP1-108 which in-vitro is not degraded by nephrilysin

• High levels of BNP and proBNP appear to have their own counter regulatory role to nephrilysin by inhibiting its activity, potentially identifying an additional role for the B-type natriuretic peptide system to help compensate heart failure