Overview & Update on the Utilization of the Natriuretic Peptides in Heart Failure

Linda C. Rogers, PhD, DABCC, FACB
Agenda

- Overview of the Natriuretic Peptides and Efficacy studies
- Similarities and Differences
- Confounders
- Clinical Studies of Entresto and Implications for Measurement of the Natriuretic Peptides
Cardiac Natriuretic Peptides

Physiological role:
- Natriuresis, i.e., discharge of sodium by urinary excretion
- Regulates blood volume through osmotic hemodynamics

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Stimulus for Release</th>
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<tbody>
<tr>
<td>ANP</td>
<td>Atrial Distension</td>
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<tr>
<td>BNP</td>
<td>Ventricular Overload</td>
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<tr>
<td>CNP</td>
<td>Endothelial Stress</td>
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</tbody>
</table>

Physiology of BNP control

Natriuretic Peptides

Hemodynamic Stress
Ischemia
Cardiotoxicity
Sepsis

Signal peptide
(26 aa)

Pre-proBNP (134 aa)

ProBNP (108 aa)

Cardiac myocyte

Blood stream

Enzymatic cleavage

Martinez-Rumayor et al. Am J Cardiol 2008;101[suppl]:3A-8A
Elimination Paths of BNP and NT-proBNP Impacts Half Life

Half-Life = 20 minutes

Half-Life = 60 – 120 minutes

Decision Cut Points for Ruling Out Heart Failure

<table>
<thead>
<tr>
<th>NT-proBNP</th>
<th>BNP</th>
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<tbody>
<tr>
<td>Age &lt; 75 yrs: ≤ 125 pg/mL</td>
<td>&lt; 100 pg/mL</td>
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<tr>
<td>Age ≥ 75 yrs: ≤ 450 pg/mL</td>
<td>&lt; 100 pg/mL</td>
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</table>

These are the only accepted cut points, regardless of manufacturer.

Source: Siemens IFU’s
Dilation of the left ventricle increases cardiac pre-proBNP gene expression.

The amount of pre-proBNP released into the circulation is directly proportional to the extent of heart wall stretch.

Thus, natriuretic peptide levels are an accurate reflection of the severity of heart failure.
BNP is a useful test to distinguish patients with heart failure from those without heart failure.

BNP is useful for both systolic and nonsystolic heart failure, even though nonsystolic heart failure diagnosis is more difficult to make and is often incorrectly excluded in the presence of normal left ventricular systolic function.

BNP cannot reliably distinguish systolic dysfunction from nonsystolic dysfunction: a measurement of left ventricular dysfunction is required to make this distinction and guide therapy accordingly.

PRIDE Study Supports the Clinical Utility of NT-proBNP

- NT-proBNP testing alone was superior to clinical judgment alone for diagnosing acute CHF.
- NT-proBNP plus clinical judgment was superior to NT-proBNP or clinical judgment alone.
- NT-proBNP measurement is a valuable addition to standard clinical assessment for the identification and exclusion of CHF in the emergency department setting.

Januzzi, Am J Cardiol 2005;95:948-954
**ROC Curves Estimating Clinical Probability of Heart Failure**

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<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>1 - Specificity</th>
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</thead>
<tbody>
<tr>
<td><strong>BNP Study</strong></td>
<td></td>
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<tr>
<td>BNP + clinical assessment, AUC = 0.93</td>
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<td></td>
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<tr>
<td>BNP alone, AUC = 0.90</td>
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<tr>
<td>Clinical assessment alone, AUC = 0.86</td>
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<tr>
<td><strong>PRIDE Study</strong></td>
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Clinical Confounders to NP Interpretation

- Age-associated increases
- CKD
- High BMI
- AFib
NP’s in CKD

- BNP and NT-proBNP were elevated in kidney dysfunction even in the absence of systolic heart failure (SHF).

- NT-proBNP elevated more than BNP.

- Further research and association guidelines are necessary for clinical guidance.

Impact of NPs in Patients with Renal Dysfunction and Dyspnea


Manufacture decision cut-points are unchanged
Natriuretic Peptides in Obese Patients with CHF


Manufacture decision cut-points are unchanged.
Association Between Natriuretic Peptides and 1-Year Mortality

N = 383

### Comparing BNP versus NT-proBNP

<table>
<thead>
<tr>
<th>Similarities</th>
<th>Differences</th>
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<tr>
<td>Both show similar clinical diagnostic performance for HF.</td>
<td>NT-proBNP appears more impacted by age (requiring age-specific cut-points).</td>
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<tr>
<td>Both demonstrate prognostic performance (although NT-proBNP may outperform BNP).</td>
<td>NT-proBNP has greater analytical stability (24 hours at room temp vs. 4 hours for BNP and NT-proBNP may have greater stability when stored frozen).</td>
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<tr>
<td>Studies for both suggest potential utility for therapeutic monitoring.</td>
<td>Absolute values are very different due to alternate mechanisms of clearance.</td>
</tr>
<tr>
<td>Performance of both may be impacted by CKD (although NT-proBNP perhaps more so).</td>
<td>BNP values are typically in the hundreds while NTproBNP can be in the thousands.</td>
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<td>Both may have clinical utility outside of HF (like ACS).</td>
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LCZ696*

A combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker, indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II–IV) and reduced ejection fraction. Usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

*trade name Entresto
**Mechanism of Action of LCZ696**

**Valsartan**
Blocks the angiotensin II type-1 (AT₁) receptor, inhibiting angiotensin II and the release of aldosterone.

**Neprilysin**
An endopeptidase that breaks down vasoactive peptides (BNP, bradykinin, and adrenomedullin); its inhibition may therefore reduce remodeling, vasoconstriction, and renal sodium retention and improve outcomes in HFrEF.

Inhibition of neprilysin by LBQ657, the active metabolite of sacubitril, increases the levels of these peptides, decreasing vasoconstriction, sodium retention, and maladaptive remodeling.
The PARAMOUNT Trial

The angiotensin receptor-neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomized controlled trial.

Prospective comparison of ARNI (angiotensin receptor-neprilysin inhibitor) with ARB (angiotensin receptor blocker) on Management Of heart failure with preserved ejection fraction (PARAMOUNT).

PARAMOUNT Trial: Inclusion and Exclusion Criteria

Key Inclusion Criteria

- Age ≥40 years
- Documented stable chronic heart failure (NYHA II–IV) with signs and symptoms of HF (dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema)
- LVEF ≥45%
- Plasma NT-proBNP >400 pg/mL at screening
- On diuretic therapy prior to visit 1, controlled systolic BP (<140 mmHg, or <160 mmHg if on three meds)
- eGFR ≥30 mL/min/1.73 m² (MDRD)
- Patients with a K ≤5.2 mmol/L at visit 1

Key Exclusion Criteria

- Patients with a prior LVEF <45% at ANY time
- Patients who required treatment with both an ACE inhibitor and an ARB
- Isolated right HF due to pulmonary disease
- Dyspnea and/or edema from noncardiac causes, such as lung disease, anemia, or severe obesity
- Presence of valvular heart disease, hypertrophic cardiomyopathy, infiltrative cardiomyopathy, restrictive cardiomyopathy, or pericardial disease
- Coronary disease requiring revascularization during the study
PARAMOUNT Trial
Primary Endpoint: Significant Reduction of NT-proBNP at 12 Weeks

- Patients with HFpEF taking ENTRESTO reduced NT-proBNP to a greater extent than valsartan after 12 weeks of therapy.

- This reduction became evident at 4 weeks and was sustained to 36 weeks, although the between-group difference was no longer significant.

- There was also a reduction in left atrial size, indicative of reverse left atrial remodeling and improvement in NYHA class in patients randomly assigned to ENTRESTO after 36 weeks compared with those randomly assigned to valsartan.

- ENTRESTO was well tolerated.

- These findings suggest that ENTRESTO may have beneficial effects in patients with HFpEF and that further testing of this drug may be warranted in patients with this condition.
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
Aim of the PARADIGM-HF Trial

**Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial (PARADIGM-HF)**

LCZ696 400 MG DAILY

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Enalapril 20 MG DAILY

Specifically designed to replace current use of ACE inhibitors and angiotensin receptor blockers as the cornerstone of the treatment of heart failure.

ARNI: Angiotensin receptor-neprilysin inhibition; ACEI: angiotensin-converting enzyme inhibition
PARADIGM-HF Trial Was Designed to Show Incremental Effect on Cardiovascular Death

**Primary Endpoint**

- Primary endpoint was cardiovascular death or hospitalization for heart failure, but PARADIGM-HF was designed as a cardiovascular mortality trial.
- The sample size of the trial was determined by effect on cardiovascular mortality, not the primary endpoint.
- The Data Monitoring Committee was allowed to stop the trial only for a compelling effect on cardiovascular mortality (in addition to the primary endpoint).
- Difference in cardiovascular mortality of 15% between LCZ696 and enalapril was prospectively identified as being clinically important.

**Secondary Endpoints**

- All-cause mortality.
- Change from baseline in the clinical summary score of the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 8 months.
- Time to new onset of atrial fibrillation.
- Time to first occurrence of a protocol-defined decline in renal function.
PARADIGM-HF

HR = 0.80 (0.73–0.87)  
P = 0.0000002  
Number needed to treat = 21

HR = 0.80 (0.71–0.89)  
P = 0.00004  
Number needed to treat = 32
PARADIGM-HF

C Hospitalization for Heart Failure

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

D Death from Any Cause

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

PARADIGM-HF: Cause of Death and Hospitalization Data

PARADIGM-HF Cause of Death and Hospitalization Data vs. Current Standard of Care ACEi Enalapril

- Death from CV causes: -20%
- Sudden death: -19%
- Death from any cause: -16%
- First hospitalization for HF: -21%
- Total number of ER visits for HF: -30%
- Total number of hospitalizations for HF: -23%

LCZ696 improved the symptoms and physical limitations of heart failure more than enalapril, $p = 0.001$. 
PARADIGM-HF: Conclusions

In comparison with guideline-recommended doses of an ACE inhibitor, combined inhibition of both the angiotensin receptor and neprilysin was more effective not only in reducing all-cause and cardiovascular mortality, but also in reducing the risks and rates of multiple manifestations of clinical deterioration of surviving patients with heart failure. The effect of LCZ696 to stabilize the course of heart failure is likely to have important ramifications for both quality of life and resource utilization in this disorder.
Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure

Milton Packer, MD*; John J.V. McMurray, MD*; Akshay S. Desai, MD, MPH; Jianjian Gong, PhD; Martin P. Lefkowitz, MD; Adel R. Rizkala, PharmD; Jean L. Rouleau, MD; Victor C. Shi, MD; Scott D. Solomon, MD; Karl Swedberg, MD, PhD; Michael Zile, MD; Karl Andersen, MD, PhD; Juan Luis Arango, MD; J. Malcolm Arnold, MD; Jan Bělohlávek, MD, PhD; Michael Böhm, MD; Sergey Boytsov, MD; Lesley J. Burgess, MB BCH, PhD; Walter Cabrera, MD; Carlos Calvo, MD; Chen-Huan Chen, MD; Andrej Ducat, MD; Yan Carlos Duarte, MD; Andrejs Erglis, MD, PhD; Michael Fu, MD; Efrain Gomez, MD; Angel Gonzalez-Medina, MD; Albert A. Hagège, MD, PhD; Jun Huaag, MD; Tzvetana Katova, PhD; Songsak Kiatschoosakun, MD; Kee-Sik Kim, MD, PhD; Ömer Kozan, Prof Dr; Edmundo Bayram Lamas, MD; Felipe Martinez, MD; Bela Merkely, MD; Iván Mendoza, MD; Arend Mosterd, MD, PhD; Marta Negrusz-Kawecka, MD, PhD; Ketjo Peukkonen, MD, Felix J.A. Ramires, MD, PhD; Jens Refsgaard, MD, PhD; Arvo Rosenthal, MD, PhD; Michele Senini, MD; Antonio S. Sibulo Jr, MD; José Silva-Cardoso, MD, PhD; Iain B. Squire, MD; Randall C. Starling, MD, MPH; John R. Teclink, MD; Johan Vanhaecke, MD, PhD; Dragos Vincereanu, MD, PhD; Raymond Ching-Chiew Wong; MBBS on behalf of the PARADIGM-HF Investigators and Coordinators†
In contrast, in comparison with enalapril, patients receiving LCZ696 had consistently lower levels of NT-proBNP (reflecting reduced cardiac wall stress) and troponin (reflecting reduced cardiac injury) throughout the trial.

The contrasting effects of LCZ696 on the two types of natriuretic peptides represent an important finding, because the levels of the two peptides characteristically parallel each other during the course of heart failure.

However, because BNP (but not NT-proBNP) is a substrate for neprilysin, levels of BNP will reflect the action of the drug, whereas levels of NT-proBNP will reflect the effects of the drug on the heart.
Summary

PARAMOUNT Trial

- Patients with HFpEF taking ENTRESTO as compared to valsartan reduced NT-proBNP to a greater extent than valsartan after 12 weeks of therapy.
- This reduction became evident at 4 weeks and was sustained to 36 weeks, although the between-group difference was no longer significant.
- There was also a reduction in left atrial size, indicative of reverse left atrial remodeling and improvement in NYHA class in patients randomly assigned to ENTRESTO after 36 weeks compared with those randomly assigned to valsartan.
- ENTRESTO was well tolerated.
- These findings suggest that ENTRESTO may have beneficial effects in patients with HFpEF and that further testing of this drug may be warranted in patients with this condition.
- ENTRESTO is not currently approved for treatment of patients with HFpEF.

PARADIGM-HF Trial

- LCZ696 was more effective than enalapril for patients with HFrEF in reducing the risk of CV death and HF hospitalization, reducing the risk of CV death, reducing the risk of HF hospitalization, reducing all-cause mortality, and incrementally improving symptoms and physical limitations.
- LCZ696 was better tolerated than enalapril and less likely to cause cough, hyperkalemia, or renal impairment.
- Less likely to be discontinued due to an adverse event.
- More hypotension, but no increase in discontinuations.
- Not more likely to cause serious angioedema.
- However, because BNP (but not NT-proBNP) is a substrate for neprilysin, levels of BNP will reflect the action of the drug, whereas levels of NT-proBNP will reflect the effects of the drug on the heart.
- ENTRESTO was FDA-approved to treat chronic HF patients with reduced HFrEF.
Contact

- Linda C. Rogers, PhD, DABCC, FACB
  Senior Clinical Consultant

- Siemens Healthcare

- Scientific & Clinical Affairs

- Phone: (949)421-9101
  Email: rogers.linda@siemens.com