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BNP assays from Siemens Healthcare Diagnostics: Analytical performance and comparison to commercially available BNP assays

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BNP assays from Siemens Healthcare Diagnostics: Analytical performance and comparison to commercially available BNP assays

by Jennifer Snyder, PhD, DABCC

Abstract

B-type natriuretic peptide (BNP) is routinely used in the emergency department for differential diagnosis of heart failure. The TRIAGE® BNP Test from Biosite Diagnostics, Inc. (now Alere) was the first clinical assay for BNP testing available for routine use. It has been used extensively in clinical studies assessing the value of BNP testing to aid clinical judgment in the diagnosis of heart failure. Since its initial limited launch in 1999, other BNP assays have been developed and harmonized to the TRIAGE BNP test, including fully automated TRIAGE BNP tests for use on the Beckman Coulter immunoassay systems. Even with harmonization, the performance characteristics of BNP assays are not identical. To better understand the nuances in performance of different BNP assays, we conducted external studies to compare the BNP assays developed by Siemens Healthcare Diagnostics to the TRIAGE BNP test and commercially available BNP assays from other manufacturers. The results of these studies indicate that there are BNP analyte recovery differences between manufacturers with the potential to affect clinical results.

Introduction

Heart failure (HF) is a common cardiac condition that poses a significant burden on healthcare services around the globe. Heart failure was recorded as one of the highest disease burdens of any medical condition in 2006, and in 2010 the direct and indirect costs for HF treatment in the United States alone were estimated at $39.2 billion. The risk of developing HF increases as a person ages, and as a result, HF is the most frequent cause of hospitalization and rehospitalization in the developed world.[1,2]

HF occurs when the heart is unable to pump blood at a rate sufficient for metabolic requirements. Causes of HF include coronary artery disease, hypertension, valvular heart disease, diabetes, and cardiomyopathy. Accurate and early diagnosis is important, since effective therapeutic interventions can improve both morbidity and mortality.

Natriuretic peptides are a family of structurally similar but genetically distinct peptides, which include atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) of myocardial cell origin, and C-type natriuretic peptide (CNP) of endothelial cell origin. The cardiac natriuretic peptides are naturally occurring antagonists of the renin-angiotensin-aldosterone system and of the sympathetic nervous system. They promote natriuresis and diuresis, act as vasodilators, and exert antimitogenic effects on cardiovascular tissues.[3] ANP and BNP are secreted by the heart in response to hemodynamic stress. Increased levels of BNP are produced mainly in response to left ventricular wall stretch and volume overload. ANP and BNP are expressed predominantly in the atria and ventricles, respectively, and are important in regulation of blood pressure, electrolyte, and volume homeostasis.[2-7]

The active hormone BNP and its related prohormone NT- proBNP are routinely measured as an aid in the diagnosis, monitoring, and prognosis of heart failure. Many manufacturers have developed BNP assays, and fully automated and semiautomated solutions are available for BNP testing in the central laboratory and point-of-care settings. Siemens Healthcare Diagnostics currently offers natriuretic peptide testing across its instrument portfolio, including BNP assays on the ADVIA Centaur® Systems and NT-proBNP assays on the Dimension® EXL™ with LM System, Dimension Vista® Systems, IMMULITE® Systems*, and the Stratus® CS Acute Care™ Diagnostic System. BNP assays for the Dimension EXL™ with LM are currently available only in Japan* and BNP for Dimension Vista systems* is currently available outside the U.S. To better understand the performance characteristics of the two Siemens BNP assays, external studies were conducted to compare precision, method comparison, clinical concordance, and sample stability. Performance

 *Not available for sale in the U.S. Product availability may vary from country to country and is subject to varying regulatory requirements.

Table 1. Five-day precision results

Platform	Lot	N	Mean (pg/mL)	Repeatability %CV (SD)	Total %CV (SD)
EDTA Plasma Sample 1 (Target ~50 pg/mL)					
Dimension Vista BNP Assay	1	15	38	3.4% (1.3)	3.4% (1.3)
	2	15	42	2.4% (1.0)	2.4% (1.0)
	3	15	39	5.4% (2.1)	5.4% (2.1)
ADVIA Centaur BNP Assay	1	15	50	3.5% (1.7)	3.5% (1.7)
	2	15	47	4.3% (2.0)	5.6% (2.6)
TRIAGE BNP Test (TRIAGE Meter)	1	15	48	9.1% (4.4)	9.1% (4.4)
	2	15	63	13.5% (8.5)	14.4% (9.0)
TRIAGE BNP Test (ACCESS 2 system)	1	15	69	2.4% (1.7)	3.8% (2.6)
	2	15	72	3.7% (2.6)	4.0% (2.9)
EDTA Plasma Sample 2 (Target ~100 pg/mL)					
Dimension Vista BNP Assay	1	15	103	1.0% (1.1)	1.7% (1.8)
	2	15	113	2.5% (2.8)	2.5% (2.8)
	3	15	107	1.7% (1.8)	1.7% (1.8)
ADVIA Centaur BNP Assay	1	15	119	3.3% (2.7)	3.3% (2.7)
	2	15	110	2.8% (3.0)	3.7% (4.1)
TRIAGE BNP Test (TRIAGE Meter)	1	14*	119	7.2% (8.6)	7.2% (8.6)
	2	15	147	7.9% (11.5)	7.9% (11.5)
TRIAGE BNP Test (ACCESS 2 system)	1	15	161	1.9% (3.1)	2.8% (4.5)
	2	15	167	3.2% (5.3)	4.0% (6.6)
EDTA Plasma Sample 3 (Target ~500 pg/mL)					
Dimension Vista BNP Assay	1	15	461	1.2% (5.7)	1.8% (8.3)
	2	15	475	1.6% (7.5)	2.3% (11.0)
	3	15	459	1.7% (7.7)	2.3% (10.7)
ADVIA Centaur BNP Assay	1	15	448	3.7% (16.5)	3.7% (16.5)
	2	15	410	3.0% (12.3)	3.2% (12.9)
TRIAGE BNP Test (TRIAGE Meter)	1	15	519	10.1% (52.7)	11.4% (59.0)
	2	15	606	7.7% (46.9)	9.2% (55.4)
TRIAGE BNP Test (ACCESS 2 system)	1	15	600	2.0% (12.1)	3.1% (18.5)
	2	15	622	1.7% (10.7)	2.2% (13.7)

*One result (>10 SD) was removed; when included, mean recovery changes to 124 pg/mL, with 18.8% repeatability and total CV.

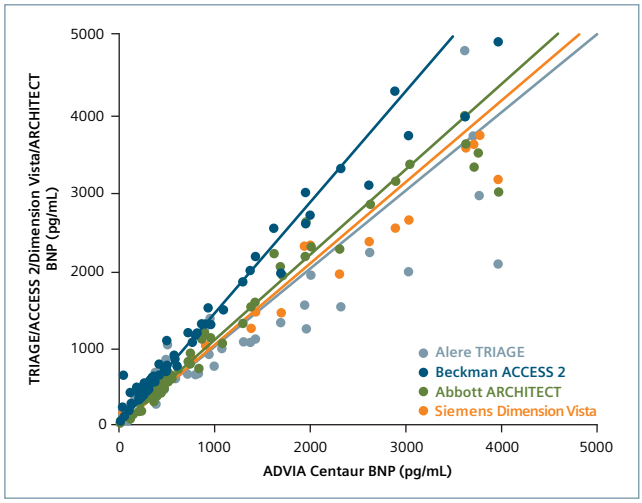
characteristics were also assessed and compared to the Siemens BNP assays for the commercially available TRIAGE BNP test on the TRIAGE® Meter (Alere, Waltham, MA, U.S.), the ACCESS® 2 Immunoassay System, Unicel® DxI 800 System (Beckman Coulter, Inc, Brea, CA, U.S.), and the ARCHITECT® BNP assay (Abbott Laboratories, Abbott Park, IL).

Precision comparison between the Siemens BNP assays and BNP assays from other manufacturers

To assess precision across multiple lots of reagents, a five-day precision study in accordance with CLSI EP15-A2[8] was performed on two or more BNP reagent lots for each of the BNP assays tested. The same three EDTA plasma pools with targets of ~50 pg/mL, ~100 pg/mL, and ~500 pg/mL were utilized to perform BNP testing on the ADVIA Centaur System, Dimension Vista System, TRIAGE, and ACCESS 2 systems.

Recovery and coefficient of variation (CV) between lots were consistent within-assay for the fully automated ADVIA Centaur, Dimension Vista, and ACCESS 2 systems, but were more variable for the TRIAGE Meter point-of-care (POC) device. Sample recovery varied between manufacturers and between lots for the Alere TRIAGE Meter. Results are shown in Table 1.

Figure 1. Results were collected at an external site within the U.S. for all instruments except ARCHITECT system; ARCHITECT BNP results were generated at an external site in the Netherlands. The same samples were used in testing across all platforms, and only results within the assay range were used in the comparison.



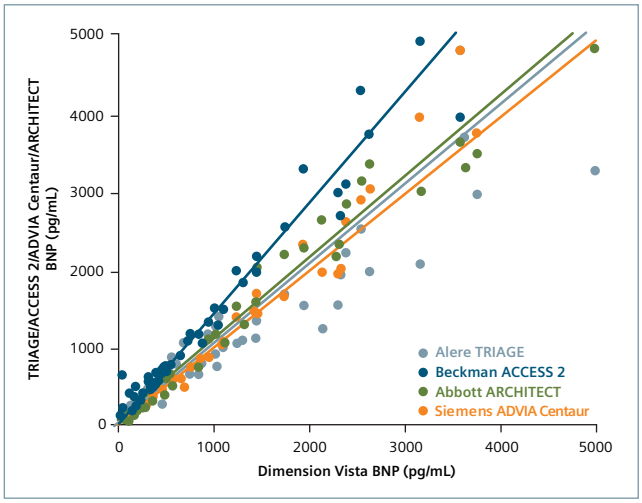


Table 2. Comparison statistics across manufacturers[†‡]

Siemens Method	Comparison (y-axis)	Slope	Intercept	N	R*
ADVIA Centaur BNP Assay (x-axis)	Alere TRIAGE	1.01	3.6	116	0.94
	Beckman ACCESS 2	1.44	13.5	114	0.99
	Abbott ARCHITECT	1.07	-2.8	110	0.98
	Siemens Dimension Vista	1.04	-6.6	114	0.99
Dimension Vista BNP Assay (x-axis)	Alere TRIAGE	0.98	9.7	115	0.95
	Beckman ACCESS 2	1.38	26.0	112	0.98
	Abbott ARCHITECT	1.01	4.0	110	0.99
	Siemens ADVIA Centaur	0.96	6.4	114	0.99
	Beckman DxI – TRIAGE BNP	1.57	16.96	96	0.99

[†] ADVIA Centaur, Dimension Vista, ACCESS 2, ARCHITECT, and Alere TRIAGE comparisons shown graphically in Figure 1.
[‡] Dimension Vista/DxI comparisons shown graphically in Figure 2.
*R=Pearson correlation

Table 3. BNP clinical concordance at the 100 pg/mL cutoff

Comparison System	Comparison System BNP Result	TRIAGE Meter	ACCESS 2	ARCHITECT	Beckman DxI	Dimension Vista	ADVIA Centaur
ADVIA Centaur BNP Assay	≥ 100 pg/mL	99%	100%	95%		96%	
	< 100 pg/mL	86%	59%	98%		96%	
	Total	93%	82%	96%		96%	
Dimension Vista BNP Assay	≥ 100 pg/mL	100%	100%	98%	100%		97%
	< 100 pg/mL	87%	55%	100%	69%		94%
	Total	94%	80%	99%	90%		96%

Method comparison

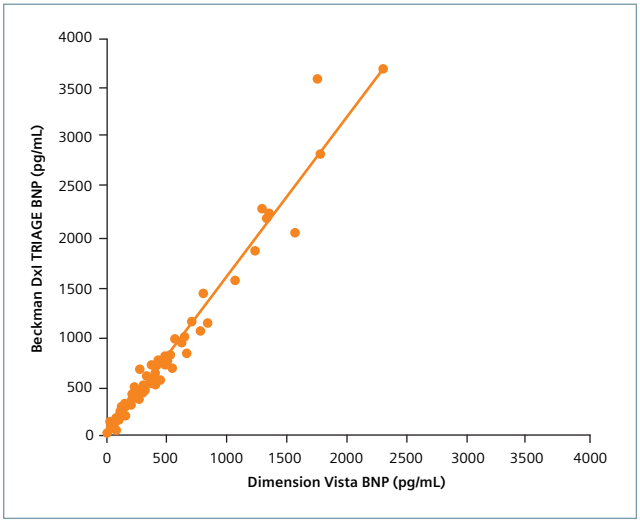
Patient sample comparison testing was performed between the BNP assays on the Siemens Dimension Vista and ADVIA Centaur systems, the Alere TRIAGE Meter, Beckman ACCESS 2 system, and the Abbott ARCHITECT i2000 system. The same set of approximately 120 patient EDTA plasma samples spanning the range of the various assays was tested on each system. One lot of reagent was used for each method. Figure 1 and Table 2 demonstrate method comparison between manufacturers. The ADVIA Centaur and Dimension Vista BNP assays align well with the TRIAGE BNP test performed on the TRIAGE Meter. As seen previously in the precision study, there are sample recovery differences between manufacturers.

A comparison between the Dimension Vista BNP assay and the TRIAGE BNP test on the Unicel DxI 800 System was performed on a separate set of patient samples. One lot of reagent was used for each method. Figure 2 confirms sample recovery differences between the BNP assays performed on the Dimension Vista and the Unicel DxI 800 platforms.

Clinical Concordance of BNP Assays

The TRIAGE BNP was the first clinical assay for BNP available for routine use, and the decision threshold for diagnosis of heart failure was determined to be 100 pg/mL. Other manufacturers have developed automated assays to be equivalent to the TRIAGE BNP test on the TRIAGE Meter; all recommend the same 100 pg/mL clinical cutoff. The results shown in Table 3 demonstrate clinical concordance at the 100 pg/mL cutoff of the BNP assays on the ADVIA Centaur and Dimension Vista to the BNP assays on the ARCHITECT i2000, ACCESS 2, TRIAGE Meter, and DxI.

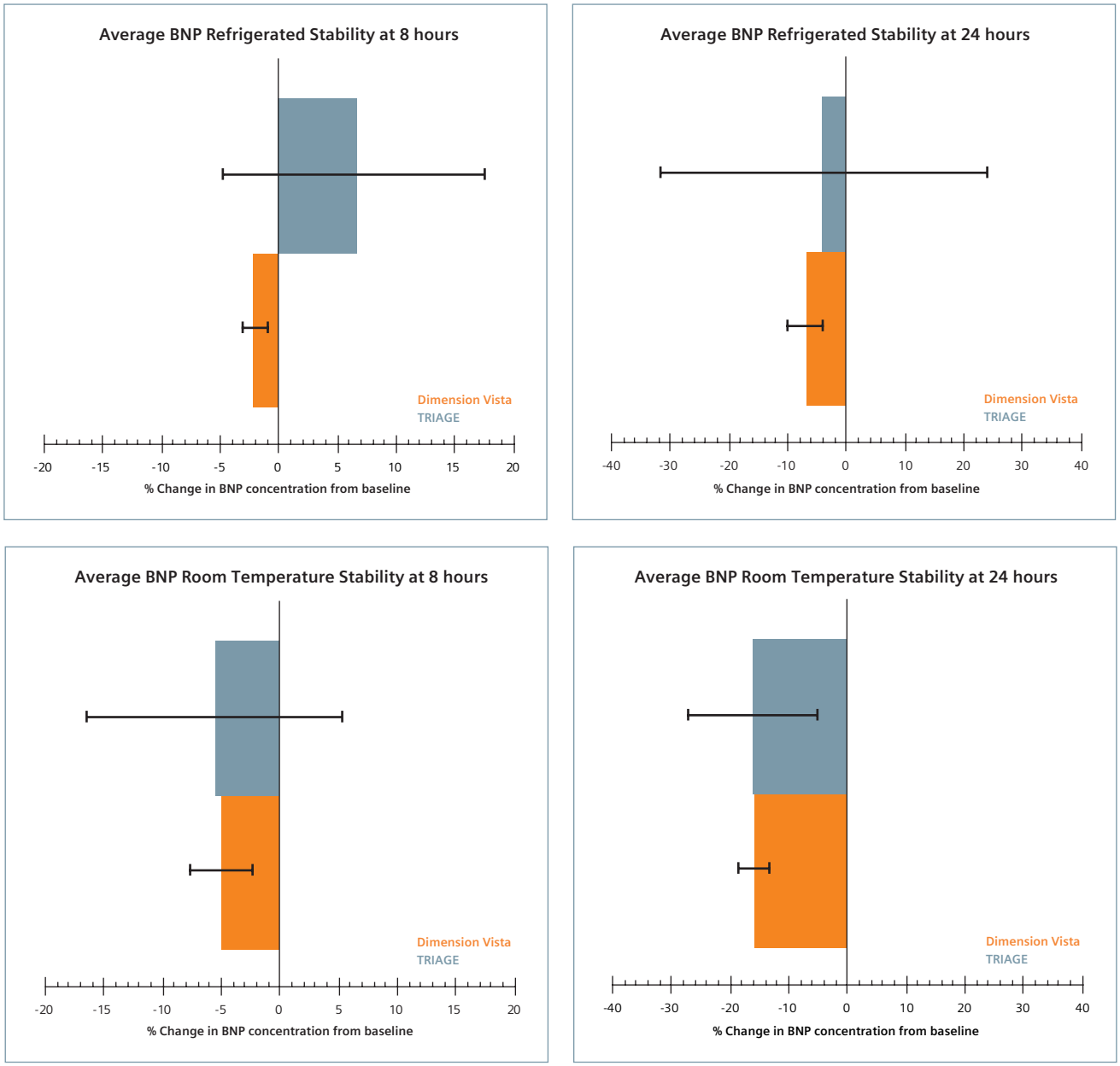
Figure 2. Dimension Vista BNP assay vs. TRIAGE BNP test on the Beckman Unicel DxI 800 system. Results were collected at an external site within the U.S.; samples were different than used in Figure 1.



Sample Stability for the Dimension Vista BNP Assay vs. the TRIAGE BNP Test

EDTA plasma sample stability for the Dimension Vista BNP assay and TRIAGE BNP test on the TRIAGE Meter was examined by testing 12 samples at both 8 and 24 hours post-collection. Due to the limited amount of sample available for the study, testing of additional BNP assays was not possible. The experiment was performed under room temperature and refrigerated conditions. The

Figure 3. Sample stability as tested using the Dimension Vista and TRIAGE BNP assays. Clockwise from top left is: 8-hour refrigerated stability, 24-hour refrigerated stability, 24-hour room-temperature stability, and 8-hour room-temperature stability. Error bars indicated standard deviation for average % change in BNP concentration from baseline.



average sample decay from baseline for each method is shown in Figure 3. The results demonstrate similar room-temperature and refrigerated sample stability for both assays, although the standard deviation between results (shown by the error bars in Figure 3) varied significantly by assay.

Discussion

This study looked at precision performance of BNP assays across two lots of reagents. For the TRIAGE BNP reagents on the Alere TRIAGE Meter, recovery was significantly different between the two reagent lots used in the study. One lot exhibited similar recovery to the ADVIA Centaur and Dimension Vista systems; the other lot showed similar recovery to the Beckman ACCESS 2 system. Only one lot was used in method comparison studies; for the Alere TRIAGE Meter, the lot that more closely matched the ADVIA Centaur and Dimension Vista systems was used.

Although the number of lots utilized in this study was relatively small, the results indicate that fully automated test systems for BNP have lower imprecision than the assay performed on the TRIAGE Meter point-of-care device. Precision across the fully automated platforms was similar, with within-lab %CVs of <6%, ≤4%, and <4% for plasma pools at ~50 pg/mL, ~100 pg/mL, and ~500 pg/mL respectively. The within-lab %CVs were higher for the Alere TRIAGE BNP assay, with <15%, <8%, and <12% for the same plasma pools. Since the TRIAGE BNP assay employs the same reagent formulation for use on an automated system (Beckman ACCESS or DxI) and point-of-care device (Alere TRIAGE Meter), one likely explanation is that the instrumentation itself plays a large role in imprecision.

As shown in the method comparison studies, differences in recovery exist between the various BNP assays. Since no standardization exists and the antibodies used in the various assays differ, this result is not entirely unexpected. However, all automated methods with the exception of the Dimension Vista claim the Alere TRIAGE Meter as predicate to some degree (Dimension Vista uses the ADVIA Centaur assay as a predicate). Since substantial recovery differences exist between lots of TRIAGE reagents on the TRIAGE Meter, the recovery differences between automated manufacturers may reflect variability in the predicate device during automated method development. It is especially interesting that the Beckman systems, which utilize the same TRIAGE reagents as the Alere TRIAGE Meter, exhibit perhaps the greatest recovery differences.

Not surprisingly, differences in recovery translate to differences in clinical concordance at the cutoff. As shown in Table 3, the Beckman ACCESS 2 has significantly lower negative concordance. This results clinically in a higher number of false positives as compared to the Alere TRIAGE Meter. However, it is interesting to note that if the other lot of reagents for the TRIAGE Meter had been utilized, the ARCHITECT, ADVIA Centaur, and Dimension Vista BNP assays would have a higher percentage of false negatives.

Conclusions

Natriuretic peptides are routinely measured in the clinical laboratory for diagnosis, monitoring, and prognosis of heart failure. The clinically accepted cutoff for BNP in diagnosis of heart failure is 100 pg/mL. All manufacturers of BNP tests claim this cutoff despite the fact that no accepted standardization of the BNP analyte exists. Significant lot-to-lot differences for the Alere TRIAGE meter may affect clinical performance and concordance at the cutoff in light of the fact that the Alere TRIAGE Meter was used as the predicate for the automated methods.

Siemens BNP assays demonstrate excellent precision and recovery from lot to lot. Room-temperature and refrigerated sample stability between the Dimension Vista and the TRIAGE BNP assays are similar.

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Global Siemens Headquarters
Siemens AG
Wittelsbacherplatz 2
80333 Muenchen
Germany

Global Siemens Healthcare Headquarters
Siemens AG
Healthcare Sector
Henkestrasse 127
91052 Erlangen
Telephone: +49 9131 84-0
Germany
www.siemens.com/healthcare

Global Division
Siemens Healthcare Diagnostics Inc.
511 Benedict Avenue
Tarrytown, NY 10591-5005
USA
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