Multi-center Comparison of the Response Biomedical Corporation RAMP® NT-proBNP Assay against the Roche Diagnostics GmbH Elecsys® proBNP Assay

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Abstract

Background: NT-proBNP measurements aid in the evaluation of individuals with suspected heart failure (HF) and may facilitate risk stratification in patients with acute coronary syndromes (ACS), pulmonary embolism (PE) or coronary artery disease (CAD). Point-of-care (POC) assays can potentially provide more timely results.

Methods: In a multi-center study, we evaluated the analytical precision, sensitivity and specificity of the Response Biomedical Corporation RAMP NT-proBNP POC assay using EDTA whole blood samples in 606 subjects (335 reference and 271 with predominantly stable HF), and compared results to those obtained from the Roche Elecsys proBNP central-laboratory assay system using heparin plasma. EDTA and heparin samples from each subject were obtained from a single blood draw.

Results: Intra- and total NT-proBNP assay precision ranged from 5.5% to 10.3% at 140, 449 and 1675 ng/L. The 10% CV concentration from whole blood analyses was 123 ng/L. The upper limit of linearity was 35,000 ng/L with an average recovery of 95%. The lower limit of detection was 18 ng/L. Analytical correlation was: RAMP NT-proBNP = 1.005 x Elecsys proBNP + 14.83 (r=0.98, n=540 samples between 5 and 35,000 ng/L). Concordance of RAMP versus Elecsys results using age specific cut offs of 125 ng/L for subjects <75 years and 450 ng/L for subjects ≥75 years per Roche package insert was 92% (95% CI 89-94%) for the reference group, and 99% (95% CI 97-100%) for the HF group. The reference group was comprised of 127 apparently healthy individuals and 208 non-healthy subjects with dyspnea, CAD, ACS, hypertension, diabetes, pulmonary disease (including PE), and other diagnoses. In the 208 non-healthy reference subset, 50% of RAMP and 54% of Elecsys results were <125 ng/L for subjects <75 years, and 52% of RAMP and Elecsys results were <450 ng/L for subjects ≥75 years. In the 127 apparently healthy reference subset, 82% of RAMP and 89% of Elecsys results were <125 ng/L for subjects <75 years, and 100% of RAMP and Elecsys results were <450 ng/L for subjects ≥75 years. The HF group included individuals diagnosed with HF without regard to other medical co-morbidities. In this HF group, 90% of RAMP and 89% of Elecsys results were >125 ng/L for subjects <75 years, and 99% of RAMP and 97% of Elecsys results were >450 ng/L for subjects ≥75 years. HF subjects were also categorized according to the New York Heart Association (NYHA) functional classification. 80%, 87%, 97% and 100% of the RAMP results and 77%, 85%, 96% and 100% of the Elecsys results were greater than the age appropriate cut-off for HF subjects classified into NYHA I, II, III or IV groups. For both the RAMP and Elecsys results the median NT-proBNP level statistically correlated (increasing) with the NYHA I, II, III or IV groups respectively (p<.0001), with no difference between the two tests for this correlation.

Conclusions: Using EDTA whole blood, the POC RAMP NT-proBNP Assay provides comparable results to the FDA-cleared Roche central laboratory platform.

Methods and Materials

- All four sites used IRB approved protocols.
- EDTA and heparinized whole blood samples were collected from a single draw in 606 subjects (335 reference and 271 with predominantly stable HF).
- Results from the EDTA whole blood samples measured using the RAMP NT-proBNP assay were compared to the results from heparin plasma samples measured using the Roche Elecsys proBNP central laboratory assay.

Subject Demographics

Healthy Reference n=127, mean age=44.8yrs (18-83), 41% male, 59% female.

Non Healthy Reference (Non-CHF): n=208, mean age=60.5yrs (24-100), 51% male, 49% female.

Comorbidities; Diabetes 23.1%, Hypertension 35.5%, Pulmonary 8.2%, Other 33.2%

HF n=271, mean age=63.9yrs (19-95), 63% male, 37% female.

Comorbidities; Diabetes 32.1%, Hypertension 36.9%, Pulmonary 5.2%, Other 25.8%

Analytical Characteristics

Functional sensitivity, Lower Limit of Detection and Upper Limit of Linearity for the RAMP NT-proBNP assay are presented in the following table:

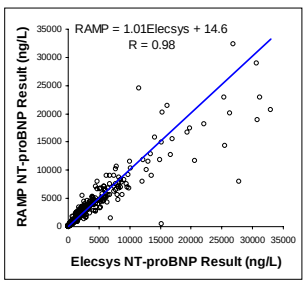
Characteristic	Performance
Functional Sensitivity	10% CV at 123 ng/L
	20% CV at 57 ng/L
Lower Limit of Detection	18 ng/L
Upper Limit of Linearity	35,000 ng/L

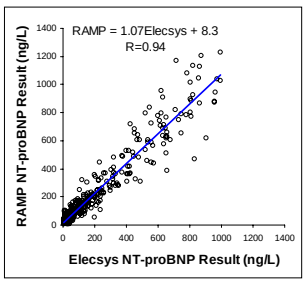
Intra - and total assay precision analysis results are presented in the table below for the RAMP NT-proBNP assay:

Precision	Standards NT-proBNP Mean Concentration (ng/L)		
	140	449	1675
Intra-assay CV	9.4%	6.4%	5.5%
Total assay CV	10.3%	9.8%	8.9%

Method Comparison

RAMP verus Roche Elecsys for samples with NT-proBNP of 5-35,000 ng/L on Elecsys (n=540) and for a subset of samples with NT-proBNP <1000 ng/L on Elecsys (n=336).

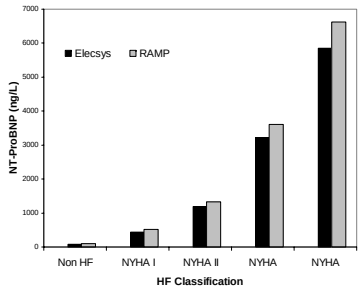




Passing Bablok analysis showed excellent correlation and slope for all samples (R=0.98, slope 1.01) and for a subset of samples with NT-proBNP concentrations of <1000 ng/L by Elecsys (R=0.94, slope 1.07).

Clinical Comparisons

Median NT-proBNP levels on both RAMP and Elecsys assays according to severity of heart disease are shown below:



Category	# Cases	RAMP (ng/L)	Elecsys (ng/L)
Non-CHF	335	99	77
NYHA I	35	514	442
NYHA II	87	1325	1197
NYHA III	83	3618	3207
NYHA IV	66	6628	5844

In patients grouped by NYHA classification (blinded to RAMP NT-proBNP results), RAMP provided equivalent results to the Roche Elecsys proBNP test (p>0.05, Mann-Whitney U-Test).

Concordance between the two methods using cut offs of 125 ng/L for subjects < 75 years and 450 ng/L for subjects ≥ 75 years (as per the Roche Elecsys proBNP package insert).

	Reference		Heart Failure	
	n	%	n	%
Sensitivity	110	94.55	247	100.00
Specificity	225	90.67	24	87.50
PPV	125	83.20	250	98.80
NPV	210	97.14	21	100.00
Concordance	335	91.94	271	98.89

The RAMP assay demonstrated equal clinical performance to Roche Elecsys in differentiating normal and non-healthy non-heart failure patients from those with acute heart failure.

Conclusions

Response Biomedical's point-of-care 15 minute RAMP NT-proBNP assay provides comparable results to those measured on the FDA cleared Roche proBNP assay run on the Roche Elecsys central laboratory platform.

*RAMP NT-proBNP Assay: CE self-certified. Licensed by Health Canada (country of origin approval). Test not yet cleared for sales in the US (FDA)