Analytical and Clinical Evaluation of the Bayer ADVIA Centaur Automated B-Type Natriuretic Peptide Assay in Patients with Heart Failure: A Multisite Study

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Background: B-Type natriuretic peptide (BNP) is released from the left ventricle of the heart into the circulation in response to ventricular stretching and volume overload. Increased BNP concentrations are associated with heart failure (HF).

Methods: We evaluated the analytical and clinical performance of the Bayer ADVIA Centaur® BNP assay. Studies included precision, analytical correlation (against the Shionogi ShionoRIA™ and Biosite Triage® BNP assays), BNP results for blood collected in plastic tubes containing EDTA vs other collection tubes, high-dose hook effect, detection limits, and interferences. The clinical performance was tested on 2243 blood samples collected from 983 apparently healthy individuals, 538 patients with chronic disease but without HF (renal insufficiency, chronic obstructive pulmonary disease, diabetes, and hypertension), and 722 patients with HF (New York Heart Association classes I-IV).

Results: The ADVIA Centaur assay had total imprecision (CV) of 3.4%, 2.9%, and 2.4% at BNP concentrations of 48, 461, and 1768 ng/L, respectively. The Passing–Bablok correlations to the ShionoRIA and Triage were as follows: ADVIA Centaur/H11549 1.11(ShionoRIA)/H11546 1.19 ng/L (r = 0.98); ADVIA Centaur/H11549 0.78(Triage)/H11545 5.89 ng/L (r = 0.92), respectively. Of the different blood collection tubes, only EDTA plastic tubes (with and without the barrier gel) were acceptable. The lower detection limit was 0.5 ng/L, and there were no interferences from common analytes, other neuropeptides, or unusual antibodies. BNP exhibited different reference intervals according to age and gender. BNP concentrations increased progressively as the severity of HF increased.

Conclusions: The ADVIA Centaur is the first commercially available BNP assay for use on an automated immunochemistry platform. This assay has good analytical and clinical performance characteristics for diagnosing HF.

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B-Type natriuretic peptide (BNP)10 has emerged as a useful biomarker for diagnosing heart failure (HF). BNP is derived from a precursor peptide, proBNP, which is cleaved into the biologically active BNP hormone and the inactive amino-terminal fragment (NT-proBNP). Clinical studies have shown that BNP and NT-proBNP peptides are useful for the diagnosis of HF in patients evaluated in
the emergency department for dyspnea and shortness of breath (1, 2). The European Society of Cardiology has recommended analysis of these peptides along with chest x-rays and electrocardiograms when evaluating patients with suspected HF (3). BNP concentrations within the reference interval may negate the need for the more expensive and time-consuming procedures such as echocardiograms or 6-min walk tests (4).

Assays for BNP are currently available on a point-of-care testing platform (Triage®, Biosite Diagnostics,) and a manual RIA (ShionoRIA™, Shionogi & Co., Ltd.). The performance of these BNP assays has been reported (5, 6). Although the NT-proBNP assay is available on an automated platform (Roche Diagnostics), the ADVIA Centaur® BNP assay is the first totally automated assay for BNP.

**Materials and Methods**

**Analytical Evaluation**

We assessed the imprecision of the ADVIA Centaur BNP assay according to a modified NCCLS EP5-A protocol (7). Three levels of controls and two sample pools were tested for within-run (n = 21) and total (n = 26 runs) imprecision. The results for BNP collected into different types of phlebotomy tubes and anticoagulants were evaluated. Results were considered different if the BNP concentration was <10% of the value obtained from the EDTA-containing plastic tube (without a barrier gel).

The stability of BNP in whole blood and plasma was determined in plastic EDTA-containing tubes. Samples from 15 patients with HF were drawn at time 0. The primary tube was held uncentrifuged at room temperature (22 °C). At time points 0, 24, and 48 h, an aliquot of whole blood was removed into a plastic microcentrifuge tube, plasma was prepared by centrifugation, and the aliquots were frozen for simultaneous determination of BNP concentration at each time point. Additional stability studies were also performed on freshly prepared plasma stored at both 22 and 4 °C.

We evaluated the ADVIA Centaur assay for a high-dose hook effect by testing samples to which BNP concentrations up to 100 000 ng/L had been added. The minimum detectable concentration was determined from the mean of the relative light unit response of the zero calibrator plus 2 SD (over two reagent lots). The effects of the common interferents hemoglobin (up to 10 g/L), unconjugated bilirubin (250 mg/L), conjugated bilirubin (250 mg/L), triglycerides (8 g/L), cholesterol (10 g/L), urea (2 g/L), and immunoglobulin (53 g/L) on the BNP results were tested (BNP concentration range, 60–880 ng/L). The assay was also tested for several BNP fragments and other neuropeptides: α-atrial natriuretic peptide; NT-proBNP amino acids 1–21; NT-proBNP 22–46; NT-proBNP 1–46; NT-proBNP 1–76; NT-proBNP 47–76; urodilatin; C5, D7, and V-natriuretic peptides; adrenomedullin-52; angiotensin III; arg-vasopressin (all at 1.0 ng/L); angiotensin I and II (at 0.6 ng/L); and renin (50 ng/L). Ten patients with high titers of rheumatoid factor, 4 patients with heterophilic antibodies, and 5 patients with human anti-mouse antibodies were also evaluated. Samples containing BNP concentrations ranging from 350 to 450 ng/L were mixed 1:1 to specimens containing these endogenous interferents.

Medications administered for the treatment of hypertension, coronary heart disease, acute coronary syndromes, or other illnesses, including acetaminophen, caffeine, salicylates, antihypertensives, statins, diuretics, beta-blockers, and angiotensin-converting enzyme inhibitors, were tested at twice the maximum therapeutic dosage. Drugs were added to pools of plasma prepared with exogenous BNP at concentrations of ~350–450 ng/L. The control pools were samples without added drug but with an equivalent volume of drug diluent added. The percentage difference and recovery or cross-reactivity were calculated. Values exceeding 10% of the expected value were considered to have significant interference. For both the interference studies and tube types, the 10% cutoff was selected because it is well within the analytical goals for imprecision of 25% established from the biological variation of BNP (8).

**Donors and Samples**

Samples were collected from the following centers: Hartford Hospital (Hartford CT), Columbia Presbyterian Medical Center (New York, NY), University of Virginia Medical Center (Charlottesville, VA), Henry Ford Hospital (Detroit MI), Centre Hospitalier Universitaire de Sherbrooke (Sherbrooke, Quebec, Canada), Uppsala University Hospital (Uppsala, Sweden), Umeå University Hospital (Umeå, Sweden), Linköping University Hospital (Linköping, Sweden), Gothenburg University Hospital (Gothenburg, Sweden), Västerås Hospital (Västerås, Sweden), Falun Hospital (Falun, Sweden), University of Innsbruck (Innsbruck, Austria), Teragenex (Fl. Lauderdale, FL), and ProMedDx (Norton MA). The protocol was approved by the Institutional Review Board at each institution, and all donors signed an informed consent form before enrollment.

A total of 2581 individuals were enrolled in the clinical phase of the study, from September 2002 to March 2003. Of these, 217 were excluded for not meeting protocol criteria, and 121 were excluded for having incomplete information. The remaining 2243 donors were divided into three groups. Group 1 consisted of 983 healthy adults with no history, signs, or symptoms of HF, cardiovascular disease, myocardial infarction, unstable angina, hypertension, diabetes, chronic obstructive pulmonary disease, or renal insufficiency. Group 2 consisted of 538 patients who had one or more chronic diseases: 43 patients with renal insufficiency (serum creatinine ≥20 mg/L or creatinine clearance <60 L/min), 102 with chronic obstructive pulmonary disease, 166 with type II diabetes, and 228 with hypertension. The “reference group” used throughout this report consisted of 1521 individuals from both groups...
1 and 2. Group 3 consisted of 722 patients with HF with 72 in New York Heart Association (NYHA) class I, 242 in class II, 289 in class III, and 119 in class IV. The exclusion criteria were presence of acute coronary syndrome (unstable angina/non ST-elevation or ST-elevation myocardial infarction) within the previous 4 weeks, myocarditis, age <18 years, cardiac surgery within the previous 4 weeks, and presence of malignancies. The individuals with malignancies was excluded because some chemotherapies, such as anthracyclines and trastuzumab, are cardiotoxic (9, 10).

The following were recorded for each enrollee in the study: age, sex, race, smoking status, final discharge diagnoses, medications, and results of the diagnostic testing, including results of electrocardiograms, angiograms, nuclear ventriculography, myocardial perfusion imaging, pulmonary function tests, chest x-rays, exercise tolerance testing, and echocardiograms with a calculation of left ventricular ejection fraction. This information was used by the cardiologist in the staging of patients according to the NYHA. Class definitions were as follows: class I, no symptoms noticeable on typical physical activity; class II, typical activity leads to dyspnea, fatigue, or edema; mild activity limitations; class III, less than ordinary activity produces symptoms; moderate to marked activity limitations; class IV, symptoms at rest, severe activity restrictions. The assessments of NYHA classifications for patients enrolled in this study were not based on BNP concentrations. The ADVIA Centaur BNP results obtained from this study were not used or made known to the treating physicians. Overall, there were 1049 women and 1194 men ranging in age from 19 to 102 years. The majority were Caucasian (79.9%), with 8.5% African Americans, 8.1% Hispanics, and 3.5% Asians. Using a cutoff of 100 ng/L, we computed the clinical sensitivity, specificity, and negative predictive value for the different age and gender groups for the HF vs reference population. There were 1521 individuals in the reference group (48.4% males) and 772 patients in the HF group (63.4% males) broken into NYHA class I (10.0% of total; 65.3% male), NYHA class II (33.5% of total; 62.0% male), NYHA class III (40.0% of total; 67.1% male), and NYHA class IV (16.5% of total; 55.5% male).

For the clinical phase of the study, blood was collected by venipuncture into plastic evacuated tubes containing EDTA. Samples were stored for a maximum of 24 h at 2–8 °C before centrifugation and the separation of plasma. Plasma was stored frozen at −70 °C before analysis. For the optimum sample type studies, samples were centrifuged and processed within 1 h of collection. Pairs of blood samples were collected simultaneously into tubes containing EDTA (with and without a gel barrier) and either sodium citrate, lithium heparin, sodium fluoride, or no preservatives (serum); each pair was tested within 1 h in the same analytical run.

ADVIA CENTAUR BNP ASSAY
All samples were tested on the ADVIA Centaur Immunochemistry Analyzer (Bayer Healthcare LLC, Diagnostics Division). The Bayer ADVIA Centaur BNP assay is a two-site dual-monoclonal immunochemiluminescent assay. Both antibodies are supplied by Shionogi & Co., Ltd. and have been widely used in the ShionoRIA BNP assay to demonstrate the clinical efficacy of BNP measurements. The capture biotinylated antibody is directed to the C-terminal part of the peptide (amino acids 27–32) and is coupled to streptavidin paramagnetic particles. The acridinium ester-labeled F(ab′)2 antibody is directed against the ring portion of BNP (amino acids 14–21) (11). The analytical signal, in relative light units, is detected by release of chemiluminescent light. The assay has a sample volume of 100 μL, and the upper limit of the dynamic range is 5000 ng/L (data from the manufacturer). Concentrations up to 50 000 ng/L can be reported with appropriate dilutions. The time to first result is 18 min with the next result available in 15 s.

CORRELATION TO OTHER BNP ASSAYS
On the same day as testing on the ADVIA Centaur, a subset of these and other specimens were also tested by the ShionoRIA (Shionogi & Co. Ltd; n = 225) and Triage BNP (Biosite Diagnostics; n = 220). Samples exceeding 1300 ng/L were not included in the Triage correlation study because this exceeded the linearity of the Triage assay at the time the study was conducted. Using a cutoff of 100 ng/L, we computed the percentage of diagnostic agreement between the Triage and ADVIA Centaur BNP assays. This cutoff was selected so that laboratories using the Triage assay would not have to change their cutoff limits.

STATISTICS
An ANOVA was computed for all data with the SPSS system for Windows (Ver. 11; SPSS), Resampling Stats (Ver. 5; Resampling Stats), or Microsoft EXCEL 200 with Resampling (Ver. 3). P < 0.05 was considered significant.

Data analysis was conducted by the manufacturer, but the verification and interpretation were made by the principal investigator (A.H.B. Wu).

Results
The results of the imprecision study (summarized in Table 1) showed that the within-run and total imprecision (CV) was <3.5%. In the comparison of the various collection tubes, BNP concentrations were 60%, 39%, 70%, and 48% lower in blood collected into tubes containing citrate, heparin, fluoride, and no anticoagulants, respectively, compared with values for samples collected into EDTA-containing tubes. There was no difference in BNP results between EDTA tubes with and without gel barriers (98% of expected value). The results of sample stability studies using whole blood indicated that at room temperature, unprocessed blood could be held for up to 24 h if
necessary before centrifugation (Table 2). The mean measured concentration of BNP at 24 h was 96% of the measured value in the sample processed immediately and was 80% at 48 h. Plasma stored at 4°C was stable an additional 24 h; the mean measured value was 91% of the value obtained for the sample processed immediately.

The ADVIA Centaur BNP assay showed no high-dose hook effect up to 100 000 ng/L. Samples up to 20 000 ng/L gave linear results, whereas samples between 40 000 and 100 000 ng/L exhibited a plateau and did not hook to lower concentrations. The minimum detectable concentration was 0.5 ng/L (data not shown). The assay showed no interference from hemoglobin (mean difference in BNP results between samples with and without added hemoglobin, −0.7%), unconjugated (mean difference, 1.8%) and conjugated bilirubin (mean difference, −6.6%), triglycerides (mean difference, −3.9%), cholesterol (mean difference, 0.7%), urea (mean difference, 4.9%), or immunoglobulin (mean difference, −6.9%). There was no significant cross-reactivity of the ADVIA Centaur assay against other BNP fragments and neuropeptides (cross-reactivities ranging from 2.2% for adrenomedullin-52 to 1.6% for -atrial natriuretic peptide). There were no interferences from rheumatoid factor (mean measured value, 93.8% of the expected value), heterophile (94.6%), or human antimouse antibodies (96.3%). With respect to common drugs, the effect on measured values ranged from −8.1% (for 32 mg/L simvastatin) to 9.4% (for 320 mg/L sulfamethoxazole), all within the design limits for the ADVIA Centaur BNP assay.

The correlation between the ADVIA Centaur BNP and the Shiono RIA BNP and Biosite Triage BNP assays is shown in Fig. 1, panels A and B, respectively. The correlation between the ADVIA Centaur and the Shiono RIA was high (r=0.98), whereas the correlation between the ADVIA Centaur and the Triage was lower (r=0.92). The cutoff concentration for the Bayer ADVIA Centaur assay was set at 100 ng/L to maximize clinical specificity (97%) and to be greater than the upper confidence limit of the 95th percentile of the non-HF reference population. This cutoff matched the decision threshold recommended for the Biosite Triage assay. This produced a slope that was lower than that for the Triage assay. However, the diagnostic agreement between the two assays at the 100 ng/L cutoff was high at 94.7% (Table 3).

The distribution of BNP concentrations in reference groups 1 and 2 by gender and age is shown in Fig. 2. Results showed a gradual increase for each 10-year age

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**Table 1. Precision of the ADVIA Centaur BNP assay.**

<table>
<thead>
<tr>
<th>Material</th>
<th>Mean BNP concentration, ng/L</th>
<th>Within-run (n=21)</th>
<th>Total (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SD, ng/L</td>
<td>CV, %</td>
<td>SD, ng/L</td>
</tr>
<tr>
<td>Control 1</td>
<td>48</td>
<td>5.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Control 2</td>
<td>461</td>
<td>9.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Control 3</td>
<td>1768</td>
<td>32.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Pool 1</td>
<td>47</td>
<td>1.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Pool 2</td>
<td>414</td>
<td>7.2</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**Table 2. Stability of BNP in whole blood stored at room temperature.**

<table>
<thead>
<tr>
<th>Sample</th>
<th>BNP, ng/L (t=0)</th>
<th>Recovery, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t=0</td>
<td>t=24 h</td>
</tr>
<tr>
<td>1</td>
<td>493</td>
<td>83.5</td>
</tr>
<tr>
<td>2</td>
<td>336.4</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>584.1</td>
<td>91.5</td>
</tr>
<tr>
<td>4</td>
<td>1717.6</td>
<td>110</td>
</tr>
<tr>
<td>5</td>
<td>1133.6</td>
<td>114.7</td>
</tr>
<tr>
<td>6</td>
<td>173.1</td>
<td>100.4</td>
</tr>
<tr>
<td>7</td>
<td>731.8</td>
<td>93.2</td>
</tr>
<tr>
<td>8</td>
<td>441</td>
<td>103.7</td>
</tr>
<tr>
<td>9</td>
<td>668.9</td>
<td>108.2</td>
</tr>
<tr>
<td>10</td>
<td>1323.7</td>
<td>97.7</td>
</tr>
<tr>
<td>11</td>
<td>490.4</td>
<td>93.6</td>
</tr>
<tr>
<td>12</td>
<td>638.3</td>
<td>83.5</td>
</tr>
<tr>
<td>13</td>
<td>179.2</td>
<td>100.3</td>
</tr>
<tr>
<td>14</td>
<td>824.9</td>
<td>94.7</td>
</tr>
<tr>
<td>15</td>
<td>461.8</td>
<td>79.4</td>
</tr>
<tr>
<td>Mean</td>
<td>100</td>
<td>96.3</td>
</tr>
<tr>
<td>SD</td>
<td>10.2</td>
<td>10.7</td>
</tr>
</tbody>
</table>

* *p <0.05.*

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![Fig. 1. Passing and Bablok correlation for the ADVIA Centaur BNP assay.](image-url)
group. There appeared to be a larger concentration difference between age groups 65–74 and ≥75 years than between other adjacent groups (P < 0.005). This latter group contained individuals who were older than 85 years, i.e., more than 10 years older than the upper limit of the 65–74 years age group. Women had higher BNP concentrations than men in the corresponding age group (P < 0.05 for all age groups).

The distribution of BNP concentrations in HF patients broken down according to NYHA classification is shown in Fig. 3. There was no overlap between any of the groups with the exception of NYHA classes I and II. Given the subjective nature of the NYHA classifications, some overlap between groups is expected. There was a substantial increase in BNP concentrations from NYHA class III to class IV (P < 0.005) than from NYHA class I to class II (P < 0.05).

The results of the ROC curve analysis for the reference vs HF groups for patients are shown in Fig. 4. The area under the curve was 0.919 [95% confidence interval (CI), 0.904–0.934]. Table 4 shows the clinical sensitivity, specificity, and negative predictive value at a cutoff of 100 ng/L for different age and gender groups. For males and females combined, the negative predictive value of the ADVIA Centaur BNP assay at a cutoff of 100 ng/L was >98%, with an overall negative predictive value >99%. When we used the single cutoff of 100 ng/L, the clinical sensitivity was lower for younger individuals than for the older age groups (e.g., 55.3% for <45 years vs 87.8% for ≥75 years; P > 0.05).

The Bayer ADVIA Centaur assay had an imprecision (CV) <3.5% for all control levels tested. This is substantially improved relative to the Biosite Triage and ShionoRIA assays, which had total imprecisions exceeding 8–17% (5, 6, 8). We have previously demonstrated that the intra-individual (CV_I) and interindividual (CV_G) biological variations for the ADVIA Centaur BNP assay are 50% and 28%, respectively (8). These intra- and interindividual CV are similar to those reported for other assays for BNP and NT-proBNP (12). On the basis of the CV_I, the goal for analytical variation (CV_A) is ≤0.50CV_I, or 25% (13). The total imprecision of the ADVIA Centaur assay is less than the analytical goals for imprecision.

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The ADVIA Centaur assay correlates well with the ShionoRIA assay (r = 0.98). This is not unexpected given the fact that the two assays use the same antibodies. The epitopes for these antibodies are well characterized and are directed against the COOH terminus (antibody BC-203) and ring structure of BNP (antibody KYhBNP-II).
When we used a different pair of antibodies, the correlation between the ADVIA Centaur and Triage assays was not as high ($r = 0.92$). Analytical studies comparing the Triage and the ShionoRIA BNP assays have shown different regression equations and coefficients of $0.92–0.96$ (15–18). Although the ADVIA Centaur BNP assay was calibrated to match the same decision threshold as the Biosite Triage BNP assay, the slope for the difference between the ADVIA Centaur vs Biosite Triage assay was 0.78 (Passing and Bablok conversion). At a cutoff of 100 ng/L, however, the diagnostic agreement was very high (94.7%; Table 3). Thus the clinical impact of this lack of standardization would be expected to be minimal. Above the threshold of 100 ng/L, absolute values for BNP may deviate between the ADVIA Centaur and Triage BNP, with median values obtained by the ADVIA Centaur being ~20% lower in HF patients than those obtained with the Triage BNP assay.

This study on a reference population confirmed the results of Redfield et al. (19), who used the Triage and ShionoRIA BNP assays and showed that BNP concentrations are higher in females and increase with increasing age. Similar results have been observed for NT-proBNP (20). It may also be possible that these elderly individuals had a higher frequency of unrecognized heart disease. Given that HF is, to a large extent, a disease of aging and that the prevalence of HF in younger groups is low (<2%) compared with age groups >55 years (prevalence, 3.4–9.7%) (21), it is likely that the use of age- and gender-related cutoffs will improve the clinical sensitivity of all BNP assays while maintaining a high specificity. The age-related increase in BNP may be attributable to an age-related reduction in the glomerular filtration rate. McCollough et al. (22) found a weak correlation ($r = 0.29$) between the log estimated glomerular filtration rate (based on serum creatinine concentration and adjusted for age, sex, and race) and log BNP. Redfield et al. (19) suggested that estrogen use may be a cause for some differences between males and females. Obesity may also be a factor. In patients with HF, obesity is associated with lower BNP concentrations (23). Among men and women >50 years of age, the body mass index steadily decreases with each decade of age (24). We did not acquire the data in this study to address these questions, but the data in Fig. 2 show that separate age- and/or gender-specific reference intervals are appropriate.

Despite these differences, the package inserts for both the Bayer ADVIA Centaur BNP and the Biosite Triage BNP assays recommend the use of a single worldwide BNP cutoff of 100 ng/L for both genders (25, 26). In the package insert for the US, Roche has recommended two age-specific cutoffs for NT-proBNP: 125 (<75 years) and 450 (≥75 years) ng/L (27). The package insert for assays sold outside the US lists reference intervals for four different age and gender classifications for NT-proBNP. Although a single BNP cutoff of 100 ng/L optimizes for clinical specificity and negative predictive value (Table 4), the sensitivity for detection of HF is diminished, especially for younger age groups (<45–64 years). If BNP is to be used as a screening test for HF in a high-risk population, e.g., those with diabetes mellitus, lower cutoff concentrations may be necessary to optimize the assay for clinical sensitivity (28).

As shown in Fig. 3, the mean BNP concentrations

### Table 4. Clinical performance of BNP for diagnosis of HF.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Sensitivity, %</th>
<th>95% CI, %</th>
<th>Specificity, %</th>
<th>95% CI, %</th>
<th>NPV, a %</th>
<th>95% CI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 years</td>
<td>55.3</td>
<td>45.3–66.1</td>
<td>99.7</td>
<td>99.6–99.9</td>
<td>99.7</td>
<td>99.7–99.9</td>
</tr>
<tr>
<td>45–54 years</td>
<td>51.6</td>
<td>42.1–66.1</td>
<td>99.7</td>
<td>99.5–99.9</td>
<td>99.2</td>
<td>99.5–99.9</td>
</tr>
<tr>
<td>55–64 years</td>
<td>67.3</td>
<td>60.2–74.2</td>
<td>98.8</td>
<td>97.5–99.9</td>
<td>98.3</td>
<td>98.5–98.9</td>
</tr>
<tr>
<td>65–74 years</td>
<td>79.2</td>
<td>72.5–85.4</td>
<td>97.0</td>
<td>95.7–98.9</td>
<td>98.5</td>
<td>97.6–90.9</td>
</tr>
<tr>
<td>≥75 years</td>
<td>87.8</td>
<td>83.3–91.9</td>
<td>85.6</td>
<td>79.6–90.9</td>
<td>98.5</td>
<td>85.1–98.9</td>
</tr>
</tbody>
</table>

a Cutoff at 100 ng/L.

b NPV, negative predictive value.
roughly doubles with each increase in the NYHA classifications. This appears to be consistent with the reported biological variability of BNP being ~77–139% (12). Given that the NYHA classifications are based on clinical symptoms alone, these data further support the concept that BNP is a clinical marker of HF disease severity and not just left ventricular function.

In summary, the ADVIA Centaur BNP assay is a precise method for testing BNP, an emerging marker for the diagnosis and management of HF. The Bayer ADVIA Centaur BNP method was calibrated to achieve the same clinical decision threshold for rule-out of HF (100 ng/L) as the Triage BNP assay. The overall clinical specificity (>97%) and negative predictive value (>99%) for the ADVIA Centaur BNP assay are equivalent to those reported previously for other methods. The performance of the Bayer ADVIA Centaur BNP assay also supports its use in assessing the severity of HF because the proportional increase in BNP concentration was more than twofold as HF severity increased from NYHA class I to class II, from class II to class III, and from class III to class IV.

References