Background: We compared the performance of different natriuretic peptides to diagnose mild forms of left ventricular dysfunction (LVD) and investigated the influence of measuring B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) with different assays on the diagnostic performance of these markers.

Methods: We measured BNP (Triage® BNP), NT-proBNP (Biomedica), and N-terminal pro-A-type natriuretic peptide (NT-proANP; Biomedica) in 130 consecutive patients (age range, 28–83 years) with clinically suspected mild LVD. In patients with sufficient sample volume, we measured BNP and NT-proBNP with additional assays (Shionoria and Roche, respectively).

Results: For identifying patients with mild systolic LVD, BNP and NT-proBNP were the best markers, with mean (95% confidence interval) areas under the curves (AUC) of 0.78 (0.63–0.89) and 0.75 (0.58–0.87), respectively. However, the diagnostic performance of NT-proANP [AUC, 0.64 (0.48–0.77)] was significantly worse than that of BNP (P = 0.014). Both BNP assays (Triage and Shionoria) and both NT-proBNP assays (Biomedica and Roche) performed equally well for the diagnosis of systolic LVD despite the poor agreement between NT-proBNP assays. In patients with isolated diastolic LVD, the diagnostic performance of the Triage BNP [AUC, 0.70 (0.56–0.81)] was significantly better (P = 0.006) than that of Biomedica NT-proBNP [0.49 (0.34–0.65)]. Furthermore, the performance of the Biomedica NT-proBNP assay was significantly worse (P = 0.03) than that of the Roche NT-proBNP assay for diagnosis of isolated diastolic LVD.

Conclusions: The performance of BNP for the diagnosis of systolic or diastolic LVD is not affected by the assay used, whereas the performance of NT-proBNP for the diagnosis of isolated diastolic LVD is assay dependent.

Heart failure (HF) is an important clinical problem with significant morbidity, mortality, and socioeconomic impact. The natural history of HF is as bad as those of many cancers, and the 5-year mortality for mild HF is as high as ~50% (1). The prevalence of the disease in the elderly is high (2). Most patients with HF are diagnosed as New York Heart Association (NYHA) class I and II (asymptomatic or mildly symptomatic patients) (3). This is clinically relevant because the majority of these patients are currently underdiagnosed. However, it has been shown that treatment of these patients with angiotensin-converting enzyme inhibitors or beta-blockers substantially delays disease progression (4, 5). Therefore, screening for HF in high-risk populations would be of clear benefit.

Among all investigated neurohormones and natriuretic peptides, B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) (6–12) are the best markers to rule out left ventricular dysfunction (LVD). Some studies have also proposed NT-pro-A-type natriuretic peptide (NT-proANP) as a useful marker for the diagnosis of LVD.
(13–16). Yamamoto et al. (9) demonstrated that BNP is a more powerful marker of either left ventricular systolic dysfunction, left ventricular diastolic dysfunction, or left ventricular hypertrophy than is ANP or NT-proANP. A consistent finding of all reports is the excellent negative predictive value of BNP. Furthermore, BNP has a good negative likelihood ratio for diagnosis of LVD compared with standard clinical indices, such as clinical history, electrocardiogram, and chest x-ray (17). These clinical results led to the development of numerous commercially available assays to determine different natriuretic peptide hormones (18). However, different epitopes and fragments of the same analyte are detected by different assays, and cross-reactivities of antibodies with prohormone fragments may vary. Because natriuretic peptide assays are not standardized at present, clinical study results must be interpreted with caution when different assays are used.

The aims of this study were (a) to investigate which of the natriuretic peptides, BNP, NT-proBNP, or NT-proANP, performs best in the diagnosis of mild forms of LVD and (b) to investigate the impact of using different assays on the diagnostic performance of these natriuretic peptides.

**Materials and Methods**

**Patients**

We investigated 130 consecutive patients (median age, 63.5 years; age range, 28–83 years) with clinically suspected mild LVD, which could be caused by either isolated diastolic or systolic LVD. Patients were classified according to the NYHA classification (19) and according to the recommendations of the task force of the American College of Cardiology and the American Heart Association (four stages) (20). All patients were referred for routine coronary angiography between December 2000 and January 2001 to rule out substantial coronary artery disease. Patients gave written informed consent for blood sampling for natriuretic peptide measurements, and this study is consistent with the Declaration of Helsinki. All patients underwent left heart catheterization with left ventriculography. Additionally, a complete echocardiographic examination assessed all clinically relevant routine indices such as left ventricular ejection fraction (LVEF), regional systolic left ventricular function, diastolic function, left ventricular mass, and systolic pulmonary artery pressure. These examinations were performed by experienced cardiologists who were blinded to the natriuretic peptide results. Isolated diastolic LVD was defined according to the guidelines of the European Society of Cardiology (21) as an age-adjusted pathologic mitral valve diastolic inflow pattern on Doppler echocardiography together with an increased left ventricular end-diastolic pressure ≥16 mmHg in the presence of a normal LVEF (>50% in two-dimensional echocardiography). This precluded misclassification based on higher age alone. All patients with diastolic dysfunction showed the pattern of impaired relaxation in echocardiography. Systolic dysfunction was graded by use of the echocardiographically determined LVEF. Patients were grouped into three classes based on the following criteria: mild systolic LVD was defined as a LVEF of 40–50% on two-dimensional echocardiography, moderate LVD was defined as a LVEF of 30–40% on echocardiography; and severe LVD was defined as a LVEF <30%. Forty-seven patients with neither systolic nor diastolic LVD served as age- and sex-matched controls.

For the clinical study on the diagnostic performance of markers in suspected mild LVD, 44 patients were excluded for the following reasons: 6 patients had moderate to severe LVD; 31 patients had a myocardial infarction within 2 weeks of blood withdrawal; 5 patients presented with renal diseases; and 2 patients underwent a high-dose corticosteroid pretreatment for contrast-agent allergy. The final study population for this clinical investigation comprised 86 individuals (Table 1). All patients of this population had calculated systolic right ventricular pressures (by echocardiography) within the reference interval (<35 mmHg) and no evidence of right ventricular dysfunction on echocardiography. However, samples from all 130 patients were used for testing assay agreement of the different natriuretic peptides.

Blood was drawn into EDTA-containing plastic tubes after a standardized period of rest (10 min) in a supine position. After blood withdrawal, samples were stored at 4 °C (up to 1 h) until measurement of BNP in whole blood (Triage® BNP); subsequently samples were centrifuged at 2000g for 10 min at 4 °C, and the plasma was stored below −20 °C for up to 1 month for later determination of BNP, NT-proBNP, and NT-proANP by the different assays. The study design was prospective with respect to measurement of BNP, NT-proBNP, and NT-proANP for the clinical evaluation of the diagnostic performances of these different natriuretic peptides and retrospective with respect to the measurement of these peptides with different assays for assay comparison. Because of limited sample volumes, not every sample could be tested with all assays (see the Results). All patient samples were analyzed with the Triage BNP, Biomedica NT-proBNP, and Biomedica NT-proANP assays; subsequently, if the sample volume was sufficient, samples were analyzed with the Roche NT-proBNP and finally with the Shionoria BNP assay.

**Assays**

BNP was measured with the Triage BNP Test (Biosite Diagnostics) as described previously (22). This assay uses a murine Omniclonal® antibody bound to the fluorescent label and a murine monoclonal antibody against the mono-disulfide bond-mediated ring structure of BNP-32. This monoclonal antibody is bound to the solid phase (personal communication by the manufacturer).

In addition, BNP was measured by a commercially available IRMA (cat. no. IC-1049; Shionoria), which does not need plasma extraction procedures as described pre-
The assay uses an antibody specific to the C-terminal structure (amino acids 27–32) immobilized on a bead and a 125I-labeled antibody specific to the intramolecular ring structure of human BNP-32 (amino acids 14–21), respectively (24).

NT-proBNP(8–29) was assayed by a competitive enzyme immunoassay (cat. no. BI-20852; Biomedica) that uses an antibody specific against NT-proBNP(8–29) as described previously (25).

Additionally, NT-proANP(1–76) was measured by a sandwich enzyme immunoassay (cat. no BI-20892; Biomedica), which uses antibodies specific for distinct epitopes of proANP(1–98), as described previously (26, 27).

**Table 1. Patient characteristics.**

<table>
<thead>
<tr>
<th></th>
<th>Controls (group 1)</th>
<th>Isolated diastolic LVD (group 2)</th>
<th>Mild systolic LVD (group 3)</th>
<th>P values between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>47</td>
<td>20</td>
<td>19</td>
<td>NS</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>30 (64)</td>
<td>15 (75)</td>
<td>14 (74)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) age years</td>
<td>60.2 (12.1)</td>
<td>65.6 (8.7)</td>
<td>67.7 (9.6)</td>
<td>NS</td>
</tr>
<tr>
<td>NYHA 0–2</td>
<td>20 (43)</td>
<td>6 (30)</td>
<td>1 (5)</td>
<td>1 vs 3: P &lt; 0.001</td>
</tr>
<tr>
<td>NYHA class 1, n (%)</td>
<td>26 (55)</td>
<td>10 (50)</td>
<td>11 (58)</td>
<td></td>
</tr>
<tr>
<td>NYHA class 2, n (%)</td>
<td>1 (2)</td>
<td>4 (20)</td>
<td>7 (37)</td>
<td></td>
</tr>
<tr>
<td>Stages A–D</td>
<td>A</td>
<td>B and C</td>
<td>B and C</td>
<td>1 vs 2: P &lt; 0.001</td>
</tr>
<tr>
<td>Stage A, n (%)</td>
<td>47 (100)</td>
<td>17 (85)</td>
<td>12 (63)</td>
<td>1 vs 3: P &lt; 0.001</td>
</tr>
<tr>
<td>Stage B, n (%)</td>
<td></td>
<td>3 (15)</td>
<td>7 (37)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) diseased vessels</td>
<td>0.8 (0.9)</td>
<td>1.2 (1.2)</td>
<td>1.3 (1.2)</td>
<td>NS</td>
</tr>
<tr>
<td>No significant CAD, n (%)</td>
<td>23 (49)</td>
<td>8 (40)</td>
<td>6 (32)</td>
<td></td>
</tr>
<tr>
<td>1-Vessel disease, n (%)</td>
<td>14 (30)</td>
<td>5 (25)</td>
<td>7 (37)</td>
<td></td>
</tr>
<tr>
<td>2-Vessel disease, n (%)</td>
<td>8 (17)</td>
<td>3 (15)</td>
<td>1 (5)</td>
<td></td>
</tr>
<tr>
<td>3-Vessel disease, n (%)</td>
<td>2 (4)</td>
<td>4 (20)</td>
<td>5 (26)</td>
<td></td>
</tr>
<tr>
<td>History of AMI, n (%)</td>
<td>10 (21)</td>
<td>7 (35)</td>
<td>12 (63)</td>
<td>1 vs 3: P = 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus type 2, n (%)</td>
<td>5 (11)</td>
<td>1 (5)</td>
<td>5 (26)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>26 (55)</td>
<td>15 (75)</td>
<td>13 (68)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SD) creatinine, μmol/L</td>
<td>93.2 (17.0)</td>
<td>90.3 (15.8)</td>
<td>102.5 (22.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Drugs, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>44 (94)</td>
<td>19 (95)</td>
<td>16 (84)</td>
<td>NS</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>21 (45)</td>
<td>9 (45)</td>
<td>11 (58)</td>
<td>NS</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>14 (30)</td>
<td>11 (55)</td>
<td>15 (79)</td>
<td>1 vs 3: P &lt; 0.001</td>
</tr>
<tr>
<td>AT II receptor antagonists</td>
<td>0</td>
<td>2 (10)</td>
<td>2 (11)</td>
<td>1 vs 2: P = 0.028;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 vs 3: P = 0.024</td>
</tr>
<tr>
<td>Diuretics</td>
<td>7 (15)</td>
<td>4 (20)</td>
<td>7 (37)</td>
<td>1 vs 3: P = 0.048</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>6 (13)</td>
<td>5 (25)</td>
<td>1 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Statins</td>
<td>22 (47)</td>
<td>10 (50)</td>
<td>11 (58)</td>
<td>NS</td>
</tr>
<tr>
<td>Echocardiographic and hemodynamic data, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%; left ventriculography)</td>
<td>68 (5)</td>
<td>69 (6)</td>
<td>51 (6)</td>
<td>1 vs 3: P &lt; 0.001</td>
</tr>
<tr>
<td>Myocardial mass, g/m² BSA</td>
<td>118 (30)</td>
<td>141 (44)</td>
<td>146 (43)</td>
<td>1 vs 3: P = 0.015</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>49 (7)</td>
<td>51 (7)</td>
<td>54 (6)</td>
<td>1 vs 3: P = 0.006</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>38 (5)</td>
<td>41 (5)</td>
<td>43 (7)</td>
<td>1 vs 3: P = 0.004</td>
</tr>
<tr>
<td>RVEDD, mm</td>
<td>25 (3)</td>
<td>24 (4)</td>
<td>27 (3)</td>
<td>1 vs 3: P = 0.008</td>
</tr>
<tr>
<td>+dP/dt, mmHg/s</td>
<td>2100 (464)</td>
<td>2387 (511)</td>
<td>1841 (646)</td>
<td>1 vs 2: P = 0.023</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 vs 3: P = 0.008</td>
</tr>
</tbody>
</table>

**a** Values in parentheses indicate percentage of total number of cases.

**b** NS, not significant; CAD, coronary artery disease; AMI, acute myocardial infarction; ASA, acetosalicylic acid; ACE, angiotensin-converting enzyme; AT II, angiotension II; BSA, body surface area; LVEDD, left ventricular end-diastolic diameter; LAD, left atrial diameter; RVEDD, right ventricular end-diastolic diameter.

**c** In these patients, HF symptoms were mimicked by noncardiac diseases.
pressure was estimated by measurement of the systolic
deceleration time of the E-wave. Right ventricular systolic
Doppler measurement of velocities of early and late
volumes were normalized to body surface area. Left
calculate left ventricular mass. Left ventricular mass and
M-mode technique, and the Penn formula was used to
were measured in a parasternal short-axis view using the
son method). The end-diastolic thicknesses of the intra-
chamber view by the area-length method (modified Simp-
tained. Left ventricular volumes and ejection fraction
frames. The ventriculogram was analyzed by 4, 2, and 3 long-axis chamber views were ob-
with the smallest ventricular volume was taken to
calculate the end-systolic volume. Left ventricular vol-
ary diagnostic performances (Fig. 2) with mean [95%
Echocardiography
Each patient underwent a complete standardized echocar-
diographic examination using an Acuson ultrasound im-
aging system (Acuson Sequoia C256; Siemens) equipped
with a 3.5-MHz transducer suitable for second harmonic
imaging. Parasternal long- and short-axis views as well as
four, two, and three long-axis chamber views were ob-
tained. Left ventricular volumes and ejection fraction
were measured from the two-dimensional apical four-
chamber view by the area-length method (modified Simp-
don method). The end-diastolic thicknesses of the intra-
ventricular septum and the left ventricular posterior wall
were measured in a parasternal short-axis view using the
M-mode technique, and the Penn formula was used to
calculate left ventricular mass. Left ventricular mass and
volumes were normalized to body surface area. Left
ventricular diastolic filling was evaluated by pulsed-wave
Doppler measurement of velocities of early and late
ventricular diastolic filling (E- and A-wave), as well as the
deceleration time of the E-wave. Right ventricular systolic
pressure was estimated by measurement of the systolic
retrograde blood flow velocity into the right atrium by the
continuous wave Doppler technique.

Statistics
ROC plot analysis (29) was carried out to illustrate and
compare the diagnostic performance of the different na-
triuretic peptides and assays. Spearman rank correlation
coefficients were calculated. The Mann–Whitney U-test
was used for group comparisons. Data are given as the
mean (SD), or as median and interquartile range (25th and
75th percentiles) if more appropriate, and natriuretic
peptide concentrations are given in ng/L. Assays were
compared by use of Bland–Altman plots (30) with Ana-
yze-it of the software package Microsoft Excel (Ver. 1.63).
A P value < 0.05 was considered to indicate statistical
significance.

Results
Natriuretic Peptide Concentrations
BNP, NT-proBNP, and NT-proANP increased signifi-
cantly with the clinical severity of HF symptoms (Table 2).
BNP as measured by the Triage BNP assay [median, 146
ng/L (interquartile range, 47–209 ng/L)] and NT-proBNP
as measured by the Biomedica NT-proBNP assay [median,
(2023–4517) ng/L] were significantly increased in patients
with mild systolic LVD compared with controls (BNP,
P = 0.001; NT-proBNP, P = 0.002) and patients with
isolated diastolic LVD (Triage BNP, P = 0.026; Biomedica
NT-proBNP, P = 0.011; Fig. 1A and B). Additionally, in
patients with isolated diastolic LVD Triage BNP concen-
trations [37 (22–81) ng/L; P = 0.018; Fig. 1A] showed
significant increases compared with controls. By contrast,
NT-proANP concentrations were not significantly in-
creased in either patients with mild LVD or patients with
isolated diastolic LVD (Fig. 1C).

Comparison of Markers
Mild systolic LVD. In patients with mild systolic LVD, the
Triage BNP and Biomedica NT-proBNP showed compara-
table diagnostic performances (Fig. 2) with mean [95%

Table 2. Natriuretic peptide concentrations according to the NYHA classification and to the A–D stages of HF according to
the American College of Cardiologists/American Heart Association task force.

<table>
<thead>
<tr>
<th></th>
<th>NYHA</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic</td>
<td>Class 1</td>
</tr>
<tr>
<td>BNP (Triage), ng/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>22</td>
<td>45</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>8–39</td>
<td>12–133</td>
</tr>
<tr>
<td>NT-proBNP (Biomedica), ng/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1595</td>
<td>2023</td>
</tr>
<tr>
<td>NT-proANP (Biomedica), pmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2510</td>
<td>3489</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>2080–3696</td>
<td>2638–5518</td>
</tr>
</tbody>
</table>

* P ≤ 0.03 between NYHA class 1 or 2 and asymptomatic individuals or between stage B or C and stage A of HF.

* P ≤ 0.03 between NYHA class 1 and 2 or between stage B and C of HF.
confidence interval (CI)] areas under the curves (AUC) of 0.78 (0.63–0.89) and 0.75 (0.58–0.87), respectively. However, NT-proANP gave a significantly ($P = 0.014$) smaller AUC [0.64 (0.48–0.77)] than Triage BNP; the AUC for NT-proANP was not significantly different from the AUC for NT-proBNP. The negative predictive values (95% CI)
at optimal cutoff values (see Fig. 2) were 90 (76–97)% for BNP, 83 (67–94)% for NT-proBNP, and 77 (61–88)% for NT-proANP, respectively.

Isolated diastolic LVD. In patients with isolated diastolic LVD, the mean (95% CI) AUC for the Triage BNP (Fig. 3) of 0.70 (0.56–0.81) showed significantly better (P < 0.001) diagnostic performance than the AUC for the Biomedica NT-proBNP [0.49 (0.34–0.65)]. At the optimal cutoff value of 25 ng/L for Triage BNP, the sensitivity was 70 (46–88)%, the specificity was 57 (42–72)%, the positive predictive value was 41 (25–59)%, the negative predictive value was 82 (65–93)%, and the efficiency was 61 (49–73)%. NT-proANP had a smaller mean AUC of 0.63 (0.48–0.76), but was not significantly different from the Triage BNP.

Correlations of natriuretic peptides with each other and with hemodynamic data
We found close correlations between the Triage BNP and Roche NT-proBNP (r = 0.88; P < 0.001), between the Shionoria BNP and Biomedica NT-proBNP (r = 0.82; P < 0.001), and between the Shionoria BNP and Roche NT-proBNP (r = 0.88; P < 0.001). The Triage BNP and Biomedica NT-proBNP correlated as well (r = 0.78; P < 0.001). Correlations between NT-proANP and the other natriuretic peptides were weak (r = 0.34–0.51; P < 0.001).

There were only weak correlations between natriuretic peptides and myocardial mass, atrial and ventricular dimensions, or hemodynamic data (r = −0.052 to 0.337; P < 0.001–0.96). The closest correlations were between the natriuretic peptides and LVEF obtained from left ventriculography (Triage BNP, r = −0.459; Biomedica NT-proBNP, r = −0.376; P < 0.001).

Comparison of assays
BNP. In 81 individuals, the Triage BNP and Shionoria BNP assays showed a close correlation (r = 0.96; P < 0.01). Nevertheless, absolute BNP values measured with both assays differed markedly (P < 0.001), with concentrations measured by the Triage BNP being, on average, 110 ng/L higher (mean value of difference). However, there was better agreement of test results below concentrations of 100 ng/L (mean value of difference, 9.2 ng/L; Fig. 4A).

NT-proBNP. In 113 individuals, the NT-proBNP(8–29) assay (Biomedica) showed a moderate correlation with the NT-proBNP(1–76) assay (Roche; r = 0.73; P < 0.01). These assays also showed a marked concentration difference (see Fig. 4B) with a mean difference of 1803 ng/L (mean value of difference, 9.2 ng/L; Fig. 4A).

Influence of measuring with different assays on the diagnostic performance of BNP and NT-proBNP
In a subgroup analysis, we compared the diagnostic performance of the Triage BNP and Shionoria BNP assays. There was equal diagnostic performance for both assays [mean (95% CI) AUC, 0.68 (0.49–0.84) for Triage BNP and 0.74 (0.56–0.88) for Shionoria; P = 0.09; Table 3].
for the diagnosis of mild systolic LVD. In a further subgroup analysis, the diagnostic performance of the Biomedica and Roche NT-proBNP was compared. There was no statistically significant impact of assays on the ability of NT-proBNP to differentiate between controls and patients with mild systolic LVD (Table 4). However, in the comparison of the diagnostic performances of NT-proBNP in patients with isolated diastolic LVD, the diagnostic performance of the Biomedica NT-proBNP assay was significantly worse compared with the Roche NT-proBNP assay \( P = 0.03; \) mean (95% CI) AUC, 0.44 (0.29–0.59) vs 0.58 (0.42–0.73); Table 4).

**Discussion**

In the present study, in contrast to several earlier published studies, we used a very exact definition of mild systolic LVD and isolated diastolic LVD based on several objective measurements (19–21). Our controls were matched for age and sex and were very well characterized, showing normal echocardiographic, left ventriculo-

Table 3. Comparison of the diagnostic performances of Triage and Shionoria BNP assays to identify patients with mild systolic LVD (n = 15 patients with mild systolic LVD and 27 controls).\(^a\)

<table>
<thead>
<tr>
<th>BNP</th>
<th>Triage</th>
<th>Shionoria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity, %</td>
<td>73 (45–92)</td>
<td>73 (45–92)</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>85 (66–96)</td>
<td>74 (54–89)</td>
</tr>
<tr>
<td>PPV,(^b) %</td>
<td>73 (45–92)</td>
<td>61 (36–83)</td>
</tr>
<tr>
<td>NPV, %</td>
<td>85 (66–96)</td>
<td>83 (63–95)</td>
</tr>
<tr>
<td>Efficiency, %</td>
<td>83 (65–91)</td>
<td>74 (58–86)</td>
</tr>
<tr>
<td>Mean AUC</td>
<td>0.68 (0.49–0.84)</td>
<td>0.74 (0.56–0.88)</td>
</tr>
<tr>
<td>Cutoff, ng/L</td>
<td>70</td>
<td>34</td>
</tr>
</tbody>
</table>

\(^a\) Values in parentheses are the 95% CI.
\(^b\) PPV, positive predictive value; NPV, negative predictive value.

In agreement with our previous study (8), BNP and NT-proBNP were interchangeable as diagnostic markers in patients with mild systolic LVD, whereas the diagnostic performance of NT-proANP was significantly worse than that of BNP. BNP and NT-proBNP concentrations were significantly increased in patients with mild systolic LVD compared with controls, independent of the assay used. In contrast, NT-proANP concentrations did not differ significantly from concentrations in controls. The lack of a significant increase in NT-proANP in mild systolic LVD is in contrast to some previous reports (13, 15, 16). One explanation for this discrepancy is that there was less severe impairment of LVEF in our patients with systolic LVD. In the present study, the grading of the severity of LVD was not based solely on subjective individual symptoms, where LVEF can vary considerably in patients of a given NYHA class; objective data obtained from echocardiography and cardiac catheterization were also used to classify the severity of LVD. Furthermore, measurement of natriuretic peptide by less precise RIAs, which require extraction of plasma samples, may have influenced the results of earlier studies. However, our results agree very well with previous studies showing good performance of BNP and NT-proBNP compared with other natriuretic peptides or their second messenger, cGMP, in patients with impaired LVEF (8, 9, 11, 12, 31, 32). In contrast to the results reported by Prontera et al. (33), in our study the diagnostic performance of BNP and NT-proBNP was comparable. However, Prontera et al. could not exclude whether the differences in marker performance were just an effect of differences in assay precision. Our results showing the high negative predictive values of BNP and NT-proBNP confirmed results obtained in previous studies and indicate that these markers may be suitable tools to rule out mild systolic LVD in high-risk patients.

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**Fig. 4.** Bland–Altman difference plots between the Triage and Shionoria BNP assays (A) and the Roche and Biomedica NT-proBNP assays (B). Concentrations were log-transformed to exclude relationships between difference and magnitude and to achieve a gaussian distribution of values.
tion of isolated diastolic dysfunction based on echocardiographic and hemodynamic data, we confirmed the significant increase in BNP, as measured by the Triage BNP assay, reported previously by Lubien et al. (34), who used only echocardiographic criteria. However, we did not observe a similarly high diagnostic performance of Triage BNP, which may be explained by the fact that our cohort did not include patients with restrictive filling patterns. The high negative predictive value of BNP (82%) in the present study confirms the results of a previous report (35) and underlines the accuracy of BNP as a rule-out marker even for isolated diastolic LVD. Thus, BNP is a promising marker for the diagnosis of isolated diastolic LVD as well. We found no significant difference in the diagnostic performance of BNP and NT-proANP for the diagnosis of isolated diastolic LVD, which confirms a previous report of increased ANP and BNP concentrations in diastolic LVD (36).

We found significant correlations among all tested natriuretic peptides. In accordance with previous studies, we found only weak inverse correlations of LVEF and BNP (7–9, 12, 37). There are only two published studies (in which LVEF was determined by magnetic resonance imaging) showing a close correlation between BNP and LVEF \((r = -0.78)\) (38) and between NT-proBNP (Roche) and LVEF \((r = -0.75)\) (39) in patients in NYHA classes II–IV. The more severely reduced LVEF than in our study population and the more precise method for the calculation of LVEF likely account for the closer correlations.

There was a close correlation between BNP measured by Biosite Triage and by Shionoria assay. However, Bland–Altman plots showed an acceptable agreement between methods only at concentrations <100 ng/L. There was no influence of the BNP assay used on the diagnostic performance of the marker. By contrast, the correlation between NT-proBNP measured by the Biomedica and Roche methods was only moderate, and Bland–Altman plots revealed only poor test agreement over the whole measuring range. Nevertheless, NT-proBNP assays were not significantly different in identifying patients with mild systolic LVD. However, in patients with isolated diastolic LVD, the AUC were significantly different. The epitopes detected by the different assay antibodies in the NT-proBNP molecule are different, which may influence diagnostic endpoints in very mild forms of LVD.

There are very limited data on the influence of measuring natriuretic peptides with different assays on diagnostic performance. In accordance with our results, Tjeerdsma et al. (40) and Fischer et al. (22) found a close correlation between Triage BNP and Shionoria BNP results, with Triage BNP values being higher than Shionoria values. However, the AUC for the assays were higher in both studies compared with our AUC for BNP, which can be explained in part by either the more severely diseased patient cohort or by a younger control group not age-matched to the LVD patient group. Our data confirm the lack of influence of the assay used on the diagnostic performance of BNP in less severe LVD. Data regarding the recently Food and Drug Administration-cleared Centaur (Bayer) BNP assay showed a high correlation with the Shionoria as well as with the Triage BNP assays in a large multisite study (24). The close correlation with the Shionoria assay is not surprising because the antibodies are identical in both assays (24). However, the slope of 0.78 between the Centaur (Bayer) and the Triage (Biosite) BNP assays showed that these assays did not agree very well. Nevertheless, similar to our results, there was a high agreement at a cutoff value of 100 ng/L. For the Roche and Biomedica methods, a recent report demonstrated a similar lack of assay and analytical agreement with a large mean concentration difference between the NT-proBNP assays similar to that seen in our study (41).

Our results for differentiating patients with isolated diastolic LVD from controls showed better performance of the Roche assay compared with the Biomedica assay, similar to that seen in the previous study for differentiating patients with asymptomatic structural heart disease

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**Table 4. Comparison of the diagnostic performance of Biomedica and Roche NT-proBNP assays to identify patients with mild systolic LVD and with isolated diastolic LVD.**

<table>
<thead>
<tr>
<th></th>
<th>Mild systolic LVD</th>
<th>Isolated diastolic LVD</th>
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<tbody>
<tr>
<td></td>
<td>Biomedica</td>
<td>Roche</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>60 (32–84)</td>
<td>73 (45–92)</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>63 (47–78)</td>
<td>78 (62–89)</td>
</tr>
<tr>
<td>PPV, %</td>
<td>38 (19–59)</td>
<td>55 (32–77)</td>
</tr>
<tr>
<td>NPV, %</td>
<td>81 (64–93)</td>
<td>89 (74–97)</td>
</tr>
<tr>
<td>Efficiency, %</td>
<td>62 (49–75)</td>
<td>77 (63–87)</td>
</tr>
<tr>
<td>Mean AUC</td>
<td>0.70 (0.49–0.85)</td>
<td>0.74 (0.56–0.87)</td>
</tr>
<tr>
<td>Cutoff, ng/L</td>
<td>2123</td>
<td>251</td>
</tr>
<tr>
<td>No. of cases</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>1531</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

* Values in parentheses are the 95% CI.

**Note:** PPV, positive predictive value; NPV, negative predictive value.
from individuals without. Both assays did not differ significantly in their diagnostic performances for the diagnosis of symptomatic LVD. The commercially available Triage BNP and NT-proBNP (Roche) assays were compared with different locally developed in-house RIAs for BNP and NT-proBNP (42). Close correlations between all assays were found, but data on analytical assay agreement were not published. We found higher diagnostic efficiency of BNP and NT-proBNP than did the authors of that study (42), although we included only patients with mild forms of LVD who consequently had lower BNP and NT-proBNP concentrations.

In conclusion, our study confirms the usefulness of BNP and NT-proBNP and extends previous findings by directly comparing commercially available BNP and NT-proBNP assays in the same study population. Furthermore, our results highlight the diversity of the natriuretic peptide assays on the market. Thus it is difficult to compare study results that are based on different assays. Published decision limits are valid only for the particular assay used. Our study population was too small for additional subgroup analysis to calculate age- and sex-dependent decision limits, but from our results a cutoff of 50 ng/L (14 pmol/L) for the Triage BNP assay could be a good screening value to exclude LVD in high-risk patients.

The BNP Triage tests and NT-proBNP Elecsys assays were gifts from Biosite (Velizy, France) and Roche (Penzberg, Germany), respectively. BNP Shionoria assays were a gift from Bayer Diagnostics (Tarrytown, NY), and NT-proBNP Elecsys was provided free of charge from Biomedica (Vienna, Austria). The assay manufacturers had no influence on the study design, data analysis or interpretation, or the content of this report.

References

5. Packer M, Cohn JN. Consensus recommendations for the management of chronic heart failure. Am J Cardiol 1999;83:1A–32A.


