Effect of Compensated Renal Dysfunction on Approved Heart Failure Markers

Direct Comparison of Brain Natriuretic Peptide (BNP) and N-Terminal Pro-BNP

Andreas Luchner, Christian Hengstenberg, Hannelore Löwel, Günter A.J. Riegger, Heribert Schunkert, Stephan Holmer

Abstract—Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are markers of heart failure. Although renal dysfunction may increase plasma concentrations, the magnitude of this effect has not been assessed in a head-to-head comparison between the clinically approved tests. We assessed the effect of compensated renal dysfunction on BNP (Triage BNP; Biosite) and NT-proBNP (elecsys proBNP; Roche) in 469 randomly selected stable outpatients after myocardial infarction (MI; Monitoring Trends and Determinants in Cardiovascular Diseases [MONICA] register Augsburg) who were characterized with respect to renal function (glomerular filtration rate [GFR]; Cockroft method) and left ventricular (LV) ejection fraction (EF) and mass (2D echocardiography). BNP and NT-proBNP were elevated in MI patients with LV dysfunction (LVD; EF < 55%) compared with MI patients with preserved EF (>45%; BNP 139 ± 27 pg/mL versus 75 ± 6; NT-proBNP 816 ± 237 pg/mL versus 243 ± 20; both P < 0.03). Among all MI patients, the prevalence of renal dysfunction (GFR < 85 mL/min) was 24%. BNP and NT-proBNP were significantly elevated in MI patients with renal dysfunction (BNP 132 ± 17 pg/mL versus 68 ± 4 without renal dysfunction; NT-proBNP 535 ± 80 pg/mL versus 232 ± 19; both P < 0.05), and both markers were correlated with GFR in univariate and multivariate analyses (all P < 0.01). When binary cut-off values were stratified according to the absence or presence of renal dysfunction (BNP 75 pg/mL and 125 pg/mL, respectively; NT-proBNP 100 pg/mL and 350 pg/mL, respectively), the predictive power of both markers for the detection of LVD increased substantially. BNP and NT-proBNP are almost similarly influenced by mild-to-moderate renal dysfunction. Renal dysfunction is a potential cause of elevated marker concentrations in the absence of LVD, and cut-off concentrations should be stratified according to renal function. (Hypertension. 2005;46:118-123.)

Key Words: myocardial infarction ■ ventricular function ■ hypertrophy ■ kidney ■ natriuretic peptides
tion with a slightly greater effect on NT-proBNP. Furthermore, we hypothesized that adjustment of the current cut points might improve the predictive values of BNP and NT-proBNP to detect LV dysfunction (LVD) in this important patient population at risk for the subsequent development of cardiac events and CHF.

Methods

Study Population
All subjects experiencing premature MI (first MI at <60 years of age) in the urban and surrounding rural areas of Augsburg, Germany, from 1984 through 1996 were identified through the Augsburg MONICA MI register. The diagnosis of MI was established according to the MONICA diagnostic criteria. Patients alive (elapsed time since MI 1 to 10 years; mean 5.6 years) were invited to participate in this study. Subjects were examined in a study center and provided information regarding medication and medical history. The questionnaire included a question regarding the presence of heart failure. Possible answers were “yes”, “no,” and “I do not know.” Patients were assigned to self-reported heart failure if they had agreed with “yes” to that question. Blood pressure was measured according to MONICA guidelines using the random-zero method, and standard mercury sphygmomanometers and body weight and height were determined. Body mass index (BMI) was calculated as weight divided by the square of height. An echocardiogram was obtained for assessment of LV function and mass, and blood was drawn for biochemical measurements. Patients were classified according to the results of the interview data, which were confirmed by medical reports from their general practitioners, cardiologists, or hospitals. A complete data set including measurement of BNP and NT-proBNP, echocardiographic assessment of LV function and mass, and assessment of renal function was available for 469 of 649 (73%) patients.

Echocardiography
A 2D-guided M-mode echocardiogram was performed on each subject by an expert sonographer. Left atrial and LV diameters (end diastolic diameter and end systolic diameter) as well as septal and posterior wall thickness were measured according to the guidelines of the American Society of Echocardiography.11 LV mass in grams was calculated from M-mode echocardiograms according to the formula described by Devereux et al.12 LV mass was indexed to body surface area as LV mass index (LVMI) in g/m² body surface area. LV hypertrophy by M-mode criteria was considered when LVMI was ≥2 SDs above the mean of a gender control group (women >138 g/m²; men >145 g/m²). An additional 2D echocardiogram from the apical view was used for the determination of systolic ejection fraction (EF) by planimetry of the LV (modified Simpson method).

Biochemical Measurements
Blood was drawn in a supine resting position. Glomerular filtration rate (GFR) as parameter of renal function was calculated from serum creatinine concentration, age, and body weight according to Cockcroft.13 As a singular cut off for renal functional impairment, a GFR of 85 mL/min was chosen. EDTA plasma was chilled, immediately centrifuged at 4°C, and stored at −80°C until measurement of the approved heart failure markers BNP (Triage BNP; Biosite) and NT-proBNP (elecsys-proBNP; Roche Diagnostics).

Statistics
Differences in mean concentrations between subgroups were tested for statistical significance by Mann–Whitney U test because both markers are not normally distributed. Marker concentrations in Figures 1 and 2 are depicted as box and whiskers plots on which the center horizontal line is drawn at the sample median; the bottom and the top edges of the box are drawn at the sample 25th and 75th percentiles (interquartile range), and the vertical lines extend from the box as far as the data extend to a distance of up to 1.5

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**Figure 1.** Subgroup analysis for BNP according to renal function (white boxes indicate normal GFR; gray boxes, impaired GFR). MI, EF >45% denotes patients with previous MI and preserved LV function; MI, 35% <EF <45%, patients with previous MI and moderate LVD; MI, EF <35%, subjects with previous MI and severe LVD. *P<0.05 vs EF >45%; **P<0.05 vs 35% <EF <45%; §P<0.05 vs normal GFR. See Methods for a description of the “box and whiskers” plot.

**Figure 2.** Subgroup analysis for NT-proBNP according to renal function (white boxes indicate normal GFR; gray boxes, impaired GFR). MI, EF >45% denotes patients with previous MI and preserved LV function; MI, 35% <EF <45%, patients with previous MI and moderate LVD; MI, EF <35%, subjects with previous MI and severe LVD. *P<0.05 vs EF >45%; **P<0.05 vs 35% <EF <45%; §P<0.05 vs normal GFR.
identify independent correlation between both markers and anthropometric and cardiac structural and functional parameters. Together with the multivariate correlation coefficients, the corresponding $\beta$-coefficients were computed. The $\beta$-coefficient is a standardized regression coefficient and adjusted measure for the increase or decrease in NT-proBNP that can be attributed to a change in one unit of the corresponding independent variable. Logistic regression analysis was used to calculate the relative risk for LVD associated with elevated marker concentrations. $P$ values <0.05 were assumed as statistically significant and $P$ values <0.01 as highly significant.

### Results

#### Study Population

Anthropometric, hemodynamic, and echocardiographic characteristics as well as medical history are depicted in Table 1 according to renal function status. The overall rate of impaired renal function after MI was 24%. Patients with renal dysfunction were older, had a more frequent history of arterial hypertension, used diuretics more often, and had a slightly lower diastolic blood pressure. No significant differences were observed on echocardiography, and most notably, the prevalence of heart failure symptoms as well as LV EF were equal in both groups. In patients designated to renal dysfunction (GFR <85 mL/min), the degree of renal dysfunction was moderate, with a mean GFR of 71 mL/min and a mean creatinine plasma concentration of 1.2 mg/dL.

Post-MI patients with significant LVD (EF <35%) were characterized by a higher prevalence of renal dysfunction (35%). Renal impairment in patients with concomitant LVD and renal dysfunction (EF <35% and GFR <85 mL/min) was more pronounced when compared with patients with preserved EF and renal dysfunction (EF >35% and GFR <85%). Specifically, GFR was 62±7 mL/min versus 72±1, and creatinine was 1.6±0.2 mg/dL versus 1.2±0.03 (both $P$<0.02). Similarly, LV mass was higher in patients with concomitant LVD and renal dysfunction when compared with patients with preserved EF and renal dysfunction (159±14 g/m² versus 121±3; $P$<0.02). The greater impairment in renal function and the confounding increase in LV mass work to magnify the increase in marker concentrations assigned to renal dysfunction in patients with significant LVD (EF <35% and GFR <85 mL/min) compared with patients with renal dysfunction but preserved EF (EF >35% and GFR <85%).

#### Univariate and Multivariate Analysis

BNP was significantly correlated (all $P$<0.01) with age ($r$=0.17), diastolic blood pressure ($r$=0.16), LV EF ($r$=0.19), LVMi ($r$=0.20), and GFR ($r$=0.28) in univariate analysis. BNP was increased significantly in MI subjects with CHF (98.4±11.6 pg/mL versus 74.8±7.0; $P$<0.01) as well as in female MI subjects (130.7±23.9 pg/mL versus 75.7±5.1; $P$<0.01). Heart rate, systolic blood pressure, and BMI displayed no significant relationship (all $P$=NS). When the statistically significant univariate predictors as well as gender and CHF were included into a multivariate model, gender, diastolic blood pressure, LV EF, LVMi, and GFR displayed a significant and independent relationship with BNP (Table 2).

NT-proBNP was significantly (all $P$<0.05) correlated with BMI ($r$=−0.09), heart rate ($r$=−0.11), age ($r$=0.14), diastolic blood pressure ($r$=−0.16), LV EF ($r$=−0.25), LVMi ($r$=0.22), and GFR ($r$=−0.29) in univariate analysis. NT-proBNP was increased significantly in MI subjects with CHF (384.6±62.8 pg/mL versus 259.9±26.7; $P$<0.01) as well as in female MI subjects (406.7±80.9 pg/mL versus 289.8±26.0; $P$<0.01). Systolic blood pressure displayed no significant relationship (P=NS). When the statistically significant univariate predictors as well as gender and CHF were

### Table 1. Study Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MI</th>
<th>Preserved GFR</th>
<th>Impaired GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>355 (76)</td>
<td>114 (24)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55±8</td>
<td>61±6†</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>88</td>
<td>81*</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>84</td>
<td>92*</td>
<td></td>
</tr>
<tr>
<td>CHF (%)</td>
<td>21</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>ACE-I (%)</td>
<td>25</td>
<td>34; $P$=0.06</td>
<td></td>
</tr>
<tr>
<td>β-Blocker (%)</td>
<td>67</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>19</td>
<td>36†</td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>67±12</td>
<td>67±12</td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>133±17</td>
<td>133±17</td>
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<tr>
<td>DBP (mm Hg)</td>
<td>85±10</td>
<td>82±10†</td>
<td></td>
</tr>
<tr>
<td>LA (mm)</td>
<td>40±6</td>
<td>40±7</td>
<td></td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>56±7</td>
<td>55±7</td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>50±9</td>
<td>50±9</td>
<td></td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>121±28</td>
<td>124±36</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.9±0.1</td>
<td>1.2±0.3†</td>
<td></td>
</tr>
<tr>
<td>GFR (mL/min)</td>
<td>115±23</td>
<td>71±12†</td>
<td></td>
</tr>
</tbody>
</table>

Mean±SD. Preserved GFR indicates GFR >85 mL/min; impaired GFR, 30 mL/min < GFR < 85 mL/min; hypertension, blood pressure >160/95 mm Hg or therapy; CHF, self-reported heart failure; ACE-I, medication with angiotensin-converting enzyme inhibitor; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LA, left atrial diameter; LVEDD, LV end-diastolic diameter. *$P$<0.05 vs GFR >85 mL/min; †$P$<0.01 vs GFR >85 mL/min.

### Table 2. Predictors of BNP and NT-proBNP in Regression Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β-Coefficient</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female vs male)</td>
<td>56.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>HR (min−1)</td>
<td>6.7</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>−2.1</td>
<td>0.06</td>
</tr>
<tr>
<td>EF (10%)</td>
<td>−19.8</td>
<td>0.001</td>
</tr>
<tr>
<td>LVMi (20 g/kg)</td>
<td>13.4</td>
<td>0.001</td>
</tr>
<tr>
<td>GFR (10 mL/min)</td>
<td>−9.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Significant univariate predictors were included into the multivariate model as continuous and gender and CHF as binary variables.

CHF indicates self-reported heart failure; HR, heart rate; DBP, diastolic blood pressure.
included into a multivariate model, heart rate, diastolic blood pressure, LV EF, LVMI, and GFR remained statistically significant and independent predictors of NT-proBNP (Table 2).

**Effect of Renal Dysfunction**

BNP and NT-proBNP were significantly increased in the presence of renal dysfunction and increased further stepwise and inversely to LV EF (Figures 1 and 2). The relative increase in BNP and NT-proBNP associated with impaired renal function was virtually equal in the presence of preserved or moderately impaired LV function (EF > 35%). Specifically, median BNP and NT-proBNP concentrations were increased 2-fold in these patients (Figure 3). In subjects with severe LVD (EF < 35%), the relative increase in NT-proBNP associated with impaired renal function was slightly more pronounced than that of BNP. Specifically, median BNP concentrations were increased by 480% and median NT-proBNP concentrations by 640% in these patients (Figure 3).

The relative contribution toward increased BNP and NT-proBNP concentrations was calculated after the continuous variables LV function, LVMI, and renal function were dichotomized and again entered into a multivariate model. The adjusted increase of BNP assigned to renal dysfunction was 57 pg/mL and that of NT-proBNP 267 pg/mL (both P < 0.001). Next, binary cutoff values were stratified according to the presence or absence of renal dysfunction. The currently approved cutoff values for heart failure are 100 pg/mL BNP and 125 pg/mL NT-proBNP. For practical reasons, the results of multivariate analysis were rounded, and renal dysfunction was assumed to increase BNP by 50 pg/mL and NT-proBNP by 250 pg/mL. The proposed binary cutoff values were nested around the approved cutoff values and were 75 pg/mL BNP for subjects without renal dysfunction and 125 pg/mL for subjects with renal dysfunction (difference of 50 pg/mL assigned to renal dysfunction). For NT-proBNP, the proposed binary cutoff values are 100 pg/mL for subjects without renal dysfunction and 350 pg/mL for subjects with renal dysfunction (difference of 250 pg/mL assigned to renal dysfunction). When these stratified cutoff values were applied, the predictive power of both markers increased substantially. Specifically, the relative risk for impaired LV function (EF < 45%) increased from 1.61 to 2.13 in the presence of pathologically elevated BNP concentrations and from 1.63 to 2.49 in the presence of pathologically elevated NT-proBNP concentrations (Figure 4). The predictive values also improved, and the specificity of BNP to detect severe LVD (EF < 35%) in the presence of concomitant renal dysfunction (GFR < 85 mL/min) increased from 67% to 73% when the adjusted cut points were used, while sensitivity remained at 88%. Similarly, the specificity of NT-proBNP increased from only 20% at the 125 pg/mL cut point to 70% when the adjusted cut points were used, whereas sensitivity only slightly decreased from 100% to 88%.

**Discussion**

The current study is the first to directly compare the 2 approved heart failure markers BNP and NT-proBNP with respect to their susceptibility to compensated renal dysfunction. It demonstrates that both markers are profoundly affected by renal dysfunction, particularly in the presence of dysfuction (GFR < 85 mL/min). **Proposed binary cutoff values for NT-proBNP are 100 pg/mL for subjects without and 350 pg/mL for subjects with renal dysfunction.**
more severe LVD (EF <35%). The strong effect of renal dysfunction on BNP and NT-proBNP suggests that clinical cutoff concentrations for the detection of LVD should be stratified according to renal function.

Importance of Renal Dysfunction

The current study demonstrates that renal dysfunction is a strong predictor of BNP and NT-proBNP concentrations. Because of the cross-sectional and population-based study design, our study population represents typical outpatients with previous MI. This is a highly relevant study population because BNP and NT-proBNP are evolving not only as markers of acutely decompensated CHF but also as risk markers in patients after MI and for the biochemical diagnosis of LVD in symptomatic patients. Just recently, the prognostic power of BNP as risk marker after MI has been reiterated by Suzuki et al.\textsuperscript{14} and Anavekar et al demonstrated in >14,000 patients from the VALIANT database that the risk of MI patients with LV systolic dysfunction markedly increases when concomitant renal dysfunction is present.\textsuperscript{15} These reports will fuel the use of the cardiac markers but also the confusion with individual test results if the user is unaware of extracardiac influences such as renal dysfunction.

In our study population, the overall prevalence of renal dysfunction was 24% in the total study population and even 35% in patients with more severe LVD (EF <35%). Despite the high prevalence of renal dysfunction, the severity of renal impairment was only mild to moderate. In clinical routine, such an impairment might be underestimated or even neglected. Nevertheless, the strong effect of renal dysfunction on marker concentrations has direct practical implications in these patients, particularly with respect to false testing and optimal cutoff concentrations.

With respect to false testing, there is a substantial potential for both tests to assign subjects with renal dysfunction but without LVD to pathologically elevated marker concentrations (false-positive) and to miss subjects with LVD but without renal dysfunction because of not yet significantly elevated concentrations (false-negative) when the approved cut points are used. With respect to optimized cutoff concentrations, our multivariate analyses assigned an adjusted increase of ≈50 pg/mL BNP and 250 pg/mL NT-proBNP to renal dysfunction alone. We could demonstrate that the probability of LVD can be markedly increased when cutoff concentrations are stratified under additional consideration of renal function. Particularly, the specificity of a positive test result increased for BNP and NT-proBNP when the adjusted binary cut points were used, whereas sensitivity remained high.

In contrast to other important predictors (eg, EF and LVMl), renal function is easy to assess together with BNP or NT-proBNP, and therefore, stratification of cut points according to renal dysfunction is clinically feasible. In addition to renal function, gender, heart rate, and diastolic blood pressure were also significantly correlated with marker concentrations. Although the effects of blood pressure and heart rate appear rather small, a gender dependency of BNP and NT-proBNP has also been demonstrated previously\textsuperscript{16–18} and would be attractive for additional adjustments. However, because of the limited number of females with impaired GFR and severe LVD in our cohort, the current data do not allow for valid dual adjustments of renal dysfunction and gender, and much larger studies would be needed to address this issue.

Recently, the heart failure markers were not only discussed for the diagnosis of heart failure and LVD but also as prognostic markers in subjects with established LVD.\textsuperscript{19–22} Concomitant renal dysfunction is an important predictor of poor prognosis in these subjects\textsuperscript{15,23,24} and markedly influences BNP and NT-proBNP concentrations. Therefore, it is tempting to speculate that part of the prognostic information of the cardiac markers might be derived not only from the association with heart failure or LVD but also with renal dysfunction. Additional studies that also collect follow-up information are warranted to dissect the contribution of LVD and renal dysfunction on the prognostic value of these markers.

Direct Comparison Between BNP and pro-BNP

As a result of the current head-to-head comparison, it appears that there is no fundamental difference between both markers with respect to relative increases associated with mild-to-moderate renal dysfunction. Indeed, no difference in mean concentrations was observed in the absence of severe LVD (both markers double with moderate renal dysfunction), and only a modest difference was observed in the presence of severe LVD, with a slightly greater effect of renal dysfunction on NT-proBNP. Furthermore, the overall correlation with renal function was similar for BNP and NT-proBNP, and therefore, both heart failure markers are indeed indicators of cardiorenal function.

This finding extends previous studies and challenges the notion that the susceptibility of NT-proBNP concentrations to renal dysfunction is generally much greater than that of BNP. To date, it has been shown that NT-proBNP concentrations are excessively elevated in terminal renal failure, do not correlate with LV hypertrophy or function in these patients, and may even increase after hemodialysis.\textsuperscript{10} In contrast, BNP has been shown to correlate with intravascular volume, LV hypertrophy, and function and still provides reasonable sensitivity and specificity as a predictor of LV hypertrophy in patients with terminal renal failure.\textsuperscript{9,10} Nevertheless, BNP concentrations also strongly depend on renal function, and in the Breathing Not Properly study,\textsuperscript{7} BNP concentrations were consistently elevated above the current cut off value (100 pg/mL) in subjects with moderate or more severe renal impairment. Furthermore, when optimal cut points for the diagnosis of acute heart failure were calculated, they were lower for patients without renal impairment and higher for subjects with renal impairment, and further increased according to renal dysfunction class. Of notice, optimal cutoff concentrations for the correct diagnosis of heart failure were on average 2-fold higher in patients with renal impairment compared with patients without renal impairment. This finding is very similar to our finding in which patients with renal dysfunction were characterized by a 2-fold increase in BNP as long as LVD was not severe.

In patients with more severe LVD (EF <35%), we observed a much greater relative increase in BNP (+480%) and NT-proBNP (+640%) associated with renal dysfunction than in those with EF >35%. The underlying reason is that in
patients with EF <35% and concomitant renal dysfunction, GFR was decreased to a greater extent, and a greater degree of concomitant LV hypertrophy was present than in patients with EF >35% and concomitant renal dysfunction. These 2 effects work to magnify the relative increase in marker concentrations assigned to renal dysfunction. The slightly greater susceptibility of NT-proBNP for renal dysfunction compared with BNP, which was observed in subjects with EF <35%, is most likely also related to the lower GFR in these patients. This observation would imply that below a GFR of \( \approx 65 \) mL/min, the differential clearance of the 2 markers might become evident and result in a greater relative elevation of NT-proBNP. Because the degree of renal dysfunction was only mild to moderate in our patients, our study does not allow conclusions to be drawn regarding a head-to-head comparison in more severe renal dysfunction. Therefore, further studies are warranted and should also allow the defining of optimal cut points in these patients.

In summary, BNP and NT-proBNP are markedly influenced by renal dysfunction. Whereas mild-to-moderate renal dysfunction leads to \( \approx 2 \)-fold increases of both markers in the absence of severe LVD, increases are \( >4 \)-fold in subjects with severe LVD, with a slightly greater effect of renal dysfunction on NT-proBNP. Adjusting cutoff concentrations according to renal function increases the predictive value of both markers for LVD and also might increase their clinical benefit.

Acknowledgments

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References

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