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B-TYPE NATRIURETIC PEPTIDES AS POWERFUL MARKERS IN CARDIAC DISEASES – ANALYTICAL AND CLINICAL ASPECTS[1)]

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Summary: Among all natriuretic peptides and neurohormones, B-type natriuretic peptide (BNP) and its N-terminal prohormone fragment (NT-proBNP) have been shown to be the best and most powerful markers to identify patients with acute and chronic heart failure (HF). The fully automated BNP and NT-proBNP assays require only 15–20 min to achieve a test result so that a turn-around time of less than 60 min is possible, as requested by the guidelines of the cardiological societies. The in-vitro stabilities of BNP and NT-proBNP are sufficient for routine use. Most of the commercially available assays, except if they are sublicensed, use different antibodies. This may explain that in general, BNP and NT-proBNP assays show close correlations, but do not agree in absolute values. The assays have not been standardized so far and the application of various calibration materials may contribute to different results. Thus, reference ranges are dependent on the assay used, and reference ranges have to be determined for each assay separately. The increasing values with age may be related to the increasing frequency of subclinical renal or cardiac dysfunction in the elderly. Estrogens stimulate the natriuretic peptide production in females, and reference ranges depend on sex from adolescence to menopause. Immediately after birth, BNP and NT-proBNP levels are substantially higher in neonates than in their mothers. The high biological variation of natriuretic peptides must be considered when interpreting serial BNP and NT-proBNP results. Therefore, only marked BNP or NT-proBNP changes during follow-up are related to changes in the clinical HF status. A conclusion of all major studies is that in patients with chronic HF BNP and NT-proBNP are rather rule-out than rule-in markers because of limited cardiac specificities. Patients with acute HF usually show higher BNP and NT-proBNP levels than patients with chronic HF. The greatest efficiency of BNP and NT-proBNP testing was demonstrated in patients presenting to the emergency department with acute dyspnoea or in outpatients with symptoms suggesting chronic HF. Many studies indicate that short- and long-term prognosis in HF can be assessed by BNP or NT-proBNP determination. These hormones are independent predictors of death or HF hospitalizations. Natriuretic peptides are increased in all diseases affecting the cardiac or renal function and fluid balance. BNP and NT-proBNP are markers of cardiac dysfunction in patients with renal failure as well, but higher decision limits have to be used. Decreased BNP and NT-proBNP concentrations in obesity are not fully understood and controversial reports are found in the literature. In summary, BNP or NT-proBNP determination is a powerful test for ruling out HF. Furthermore, these markers are a useful addition to the standard clinical investigations of patients with suspected ventricular dysfunction.

Key words: assays, B-type natriuretic peptide (BNP), diagnosis, monitoring, NT-proBNP, risk stratification

Introduction

During the last few years the natriuretic peptides, particularly B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP), have emerged as powerful biochemical markers in cardiac diseases. The most widely studied application of natriuretic peptides is in heart failure (HF), a disease which poses an important clinical problem with a significant morbidity, mortality, and socioeconomic impact. At present, 15 million people of the western industrialized countries suffer from congestive HF, in the US, 5 million people are affec-

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ted with nearly 500,000 new cases per year. The prevalence increases with age from 0.5% in persons younger than 55 years to more than 10% in persons older than 80 years (1). Every second German citizen dies because of cardiovascular disease (global cardiovascular infobase of WHO: http://www.cvdinfobase.ca/default_1.htm). Currently, echocardiography is most frequently used to identify patients with left ventricular (LV) dysfunction or structural heart diseases. However, echocardiography is not always readily available. Thus, it is obvious that a simple, reliable biochemical test to diagnose HF would be cost-effective and clinically useful. The natriuretic peptides A-type natriuretic peptide (ANP) and BNP have been shown to be cardiac neurohormones located on chromosome 1 and to be released upon distinct stimuli from the heart. ANP secretion occurs from storage in atrial granules in response to increased atrial wall tension, whereas BNP is mainly newly synthesized upon increased ventricular stretch or wall tension. Since this discovery was made, several studies have reported increased natriuretic peptide concentrations in patients with HF. However, BNP emerged as the superior marker in HF because of its superior in-vitro stability and diagnostic performance. Nevertheless, it took 12 years from the discovery of BNP until the first BNP assay received clearance from the Food and Drug Administration (FDA) in 2000. Several point-of-care and automated laboratory assays are now commercially available for BNP testing and also for the measurement of NT-proBNP, which is a split product of its precursor hormone proBNP. Both BNP and NT-proBNP are increasingly gaining acceptance by clinicians and laboratorians for the exclusion of HF. Recent studies also indicate their usefulness for risk assessment in patients with HF or acute coronary syndromes (ACS) and for disease monitoring in HF patients. However, confounding factors such as biological variability, limited cardiac specificity, and differences between BNP and NT-proBNP assays have to be considered. The following review will focus on approved automated or point-of-care assays for BNP and NT-proBNP testing and is intended to give some useful background information and hints for the interpretation of measurement results in daily clinical practice.

BNP and NT-proBNP assays

The commercially available assays for routine application are immunometric assays, which are usually characterized by a lower limit of detection and a superior precision and specificity compared with com-

Table I Imprecision and sensitivity of the natriuretic peptide assays

Assay	Levels, ng/L	Intra-assay CV, %	Inter-assay CV, %	Analytical sensitivity, ng/L; (mean of zero standard + 3 SD)	References
BNP					
Biosite Triage	40–800	9.4–15.0	11.0–16.0	6.0	Fischer et al. (3)
	88–733	11.2–12.6	9.9–12.5		Yeo et al. (4)
Beckman Coulter	88–2080	1.6–2.9	0.8–2.3	0.4 (mean + 2 SD)	Rawlins et al. (5)
BNP (Biosite)					
Bayer Centaur	45–1572	1.8–2.3	0.0–1.7	0.8 (mean + 2 SD)	Rawlins et al. (5)
	47–1768	1.7–3.1	2.4–3.4	0.5 (mean + 2 SD)	Wu et al. (6)
	82–1525	1.5–1.6	4.4–4.8		Mueller et al. (7)
Abbott AxSYM	108–2117	5.1–6.0	8.1–10.3	11.9	Mueller et al. (7)
	21–319	5.7–18.4	14.0–19.8	5.6	Storti et al. (5)
	101–1423	3.8–5.1	0.8–2.3	9.0 (mean + 2 SD)	Rawlins et al. (5)
Shionoria	10–2000	<15.0	5.4–11.6	2.6	Del Ry et al. (9)
NT-proBNP					
Roche Elecsys	105–5616	1.3–2.4	2.9–6.1	n.d.	Yeo et al. (4)
	104/602	1.7/1.5	4.0/3.8	4.2	Prontera et al. (10)
	246–10000	0.9–1.7	2.2–4.7	n.d.	Mueller et al. (11)
	200–25000	0.5–3.3	1.0–4.8	n.d.	Sokoll et al. (12)
	350–13000	0.7–1.6	4.4–6.7	n.d.	Collinson et al. (13)
Roche E170	260–6039	0.4–0.7	0.0–0.2	3.0 (mean + 2 SD)	Rawlins et al. (5)

CV, coefficient of variation; SD, standard deviation; n.d., not determined.

petitive immunoassays (2). In general, the fully automated commercially available BNP and NT-proBNP assays require only 15–20 min per test result so that a turn-around time of less than 60 min, as required by the guidelines of the European Society of Cardiology (ESC) and the American Heart Association (AHA), should be achievable in a routine laboratory (http://www.nacb.org/lmpg/main.stm). Alternatively, point-of-care assays for whole blood measurement are available which produce results within 20 min. The total imprecision of all these assays should be less than 10% at the cut-off value to avoid misclassification due to poor assay precision. Currently, five BNP and three NT-proBNP assays are approved for HF diagnosis. The first FDA-cleared assay was the Triage BNP point-of-care assay from Biosite Diagnostics, which shows a slightly higher imprecision of less than 17% at 800 ng/L (*Table I*). The subsequently developed BNP assays by Bayer Healthcare (ADVIA Centaur, ADVIA IMS, ACS:180) and Abbott Laboratories (AxSYM, ARCHITECT, IMx) were adjusted to the FDA-cleared point-of-care assay by harmonizing the results around the suggested HF cut-off value for Biosite's Triage at 100 ng/L. Further, the Bayer Centaur BNP assay was licensed by Shionogi & Co., Ltd (immunoradiometric assay, Japan), which otherwise had no FDA-cleared assay, and the Abbott BNP assay runs with one Shionogi antibody as well. Additionally, Biosite Diagnostics developed, together with Beckman Coulter, an automated version of the point-of-care assay. Referring to NT-proBNP assays, Roche Diagnostics offered the first automated NT--proBNP assay and also launched a point-of-care test on the Cardiac Reader in August 2005. Further, Roche Diagnostics sublicensed their antibodies and antigens to Dade Behring and Diagnostic Products Corporation (DPC). The Dade Behring and DPC NT-proBNP assays are now commercially available. In Europe, a competitive enzyme immunoassay for NT-proBNP is also available from Biomedica Diagnostics which uses antibodies (NT-proBNP 8–29) different from those used by Roche.

Table II Specific antibodies (AB) and standard material of the natriuretic peptide assays

Assay	Capture antibody	Detection antibody	Standard material	Detected BNP forms	References
BNP					
Biosite Diagnostics	NH_2 terminus and part of the ring structure (Scios), murine monoclonal AB, aa 6–14	BNP (Biosite), murine Omniclonal® AB, aa 3–32	Recombinant BNP	BNP 1–32/4–32/7–32 (proBNP 1–108)*	Hammerer-Lercher et al. (14) Apple et al. (15)
Beckman Coulter BNP (Biosite Diagnostics)	NH_2 terminus and part of the ring structure (Scios), murine monoclonal AB, aa 6–14	BNP (Biosite), murine Omniclonal® AB, aa 3–32	Recombinant BNP	BNP 1–32/3–32/4–32 1–31; (proBNP 1–108)*	Rawlins et al. (5) Personal communication
Abbott Laboratories	NH_2 terminus and part of the ring structure (Scios), murine monoclonal AB, aa 5–13	COOH terminus (BC-203), murine monoclonal AB, aa 26–32	Synthetic BNP 32	BNP 1–32/3–32/4–32 (proBNP 1–108)*	Rawlins et al. (5) Mueller et al. (11) Personal communication
Bayer Healthcare	COOH terminus (BC-203), murine monoclonal AB, aa 27–32	Ring structure (KY-hBNP-II), murine monoclonal AB, aa 14–21	Synthetic BNP	BNP 1–32/3–32/4–32/ 10–32 (proBNP 1–108)*	Belenky et al. (16) Rawlins et al. (5) Personal communication
Shionogi	Ring structure (KY-hBNP-II), murine monoclonal AB, aa 14–21	COOH terminus (BC-203), murine monoclonal AB, aa 27–32	Synthetic BNP	BNP 1–32/4–32/7–32/ 10–32 (proBNP 1–108)*	Ry et al. (17) Apple et al. (15)
NT-proBNP					
Roche Diagnostics	NH_2 terminus, polyclonal sheep AB, aa 1–21	Central molecule, polyclonal sheep AB, aa 39–50	Synthetic NT-proBNP 1–76	NT-proBNP 1–76, (proBNP 1–108, truncated NT-proBNP)*	Mueller et al. (18) Apple et al. (15)
Dade Behring	NH_2 terminus, polyclonal sheep AB, aa 1–21	Central molecule, polyclonal sheep AB, aa 39–50	Synthetic NT-proBNP 1–76	NT-proBNP 1–76, (proBNP 1–108, truncated NT-proBNP)*	Di Serio et al. (19) Personal communication
DPC	NH_2 terminus, polyclonal sheep AB, aa 1–21	Central molecule, polyclonal sheep AB, aa 39–50	Synthetic NT-proBNP 1–76	NT-proBNP 1–76, (proBNP 1–108, truncated NT-proBNP)*	Personal communication

Aa, amino acids; *possible cross-reactivity; DPC, Diagnostic Products Corporation.

Analytical assay comparison

Most of the commercially available assays, except if they were sublicensed, use different antibodies that also detect different epitopes and fragments of the respective peptide (*Table II*). This may explain that in general, BNP and NT-proBNP assays show close correlations, but do not agree in absolute values (*Table III*). It is surprising that Biosite Triage and Biosite Beckman Coulter BNP assays are not in absolute agreement (95.9%) (5), since Biosite and Beckman partnered to manufacture an automated version of the point-of-care BNP assay. Similarly, Bayer Centaur and Abbott AxSYM, both using at least one Shionogi antibody, showed excellent correlations, but with a mean difference of 226 ng/L (7.9%) and higher values for the Abbott AxSYM BNP (7). The highest BNP concentrations are produced by the Abbott assay, followed by Triage, Bayer, and Shionogi. Also, the two automated NT-proBNP assays on the market showed a disagreement of 15 to 22%, although both assays use the same antibodies and standards (19). The Roche Elecsys assay yielded lower NT-proBNP results than the Dade Dimension assay, and this NT-proBNP difference was even higher when lithium heparin samples instead of serum samples were used for the Roche assay (19).

When comparing BNP and NT-proBNP assays for concordance, the Triage BNP assay is often used as the reference BNP assay, mainly because this was the first FDA-cleared natriuretic peptide assay. However, this point-of-care assay shows a higher imprecision (CV <17%) than the fully automated analysers (CV <11%, *Table I*). BNP assays correlate with NT-proBNP assays moderately to excellently between 0.54 and 0.95 (*Table III*). The high slopes are partly due to the NT-proBNP concentrations that exceed

Table III Comparison of BNP and NT-proBNP assays

Assays	Correlation coefficient (r)	Slope	Intercept, ng/L	Mean difference between first and second assay	Sample size	References
BNP						
Biosite–Shionoria	0.96	1.58*Shionoria	–2.95	n.d.	145	Fischer et al. (3)
Biosite–Shionoria	0.95	1.69*Shionoria	3.61	n.d.	108	Tjeerdsma et al. (20)
Biosite–Shionoria	0.96	n.d.	n.d.	110 ng/L	81	Hammerer-Lercher et al. (14)
Biosite–Abbott	0.92	1.43*Biosite	2.80	n.d.	348	Tang et al. (21)
Biosite–Abbott	0.94	1.13*Biosite	–6	–7 ng/L	197	Rawlins et al. (5)
Biosite–Abbott	0.93	0.96*Biosite	46.90	n.d.	215	Clerico et al. (22)
Biosite–Bayer	0.92	0.78*Biosite	5.89	n.d.	220	Biosite–Bayer Wu et al. (6)
Biosite–Bayer	0.92	0.57*Biosite	23.10	n.d.	121	Biosite–Bayer Sykes et al. (23)
Biosite–Bayer	0.92	0.77*Biosite	–3	26 ng/L	197	Rawlins et al. (5)
Biosite–Access 2 BNP	0.95	0.96*Biosite	–6	10 ng/L	197	Rawlins et al. (5)
Bayer–Shionoria	0.98	1.11*Shionoria	–1.19	n.d.	225	Wu et al. (6)
Bayer–Abbott	0.99	1.55*Bayer	–10.40	–226 ng/L	177	Mueller et al. (7)
Bayer–Abbott	0.97	1.31*Bayer	16.60	n.d.	354	Clerico et al. (22)
Bayer–Abbott	0.93	1.79*Bayer	n.d.	n.d.	60	Barak et al. (24)
NT-proBNP						
Roche–Dade Behring	n.d.	0.84*Roche	–0.43	230 ng/L	100	Di Serio et al. (19)
Roche: Elecsys–CARDIAC Reader	0.95	1.02*Elecsys	n.d.	n.d.	271	Manufacturer information
Roche–Biomedica	n.d.	8.4*Roche	20.10 pmol/L	–224 pmol/L	180	Mueller et al. (18)
Roche–Biomedica	0.73	n.d.	n.d.	–1803 ng/L	113	Hammerer-Lercher et al. (14)
Roche–Biomedica	0.57	n.d.	n.d.	n.d.	150	Mikkelsen et al. (25)
BNP vs. NT-proBNP						
Biosite–Roche	0.95	1.20*Roche	1.419 pmol/L	n.d.	145	Fischer et al. (3)
Biosite–Roche	0.54	5.99*Biosite	1107	n.d.	327	Yeo et al. (4)
Biosite–Roche	0.57	4.95*Biosite	7.50	n.d.	254	Sokoll et al. (12)
Biosite–Roche	0.80	8.90*Biosite	–225	n.d.	197	Rawlins et al. (5)
Biosite–Roche	0.75	6.09*Biosite	women: +1132 men: –220	n.d.	131	Sykes et al. (23)
Biosite–Roche	0.93	1.10*Biosite	0.57 (log_{10})	n.d.	160	Alibay et al. (26)
Bayer–Roche	0.48	15.34*Bayer	2401	n.d.	150	Sykes et al. (23)
Abbott–Roche	0.70	7.23*Abbott	2.53	n.d.	68	Chien et al. (27)
Shionoria–Roche	0.74	4.53*Shionoria	3.70	n.d.	956	Sokoll et al. (12)
Shionoria–Roche	0.95	n.d.	n.d.	n.d.	150	Mikkelsen et al. (25)

n.d., not determined.

the BNP concentrations found in human blood samples. NT-proBNP concentrations were demonstrated to be 4- to 20-fold higher than BNP concentrations (depending on the sample range and regression analysis used) (4, 28–30). These discrepancies between BNP and NT-proBNP values are not fully clarified but may partly be explained by the greater mass of NT-proBNP, by the longer half-life time of NT-proBNP (estimated to be 1–2 h) than that of BNP (approximately 20 min.), and by different clearance mechanisms (31, 32). A further issue is that assays have not been standardized so far and the application of various calibration materials may contribute to the differences in the BNP or NT-proBNP results as well. Therefore, the absolute concentration of BNP or NT-proBNP in a patient sample will vary depending on the assay used, and for follow-up investigations the same assay should always be used.

Blood sampling and stability of sample

Blood samples for BNP must be drawn using ethylenediamine-tetraacetic-acid (EDTA)-containing plastic tubes, whereas for NT-proBNP, serum or heparin plasma is applicable. For NT-proBNP, EDTA plasma results are 6–10% lower than serum values (12). Recent studies indicate no mandatory need of a 10-min rest upon arrival of the patient for BNP or NT-proBNP blood sampling because of the low influence of minor exercise such as walking (33). In contrast to ANP, the natriuretic peptides BNP and NT-proBNP are less affected by exercise and body posture. In healthy subjects or HF patients, no significant influences on BNP and NT-proBNP were seen for blood sampling by either supine or sitting posture (12, 33, 34), by posture change (12, 35, 36), or by exercise (12, 37). One study found significantly decreased BNP concentrations after prolonged orthostatic stress (38). In chronic HF patients, significant increases in BNP were shown by treadmill exercise, and peak exercise natriuretic peptide values were better related to left ventricular parameters than resting BNP concentrations (39). Similar findings were demonstrated for patients with permanent atrial fibrillation and in healthy subjects, although the latter study showed smaller BNP increases (40). Severe exercise such as marathon running or biking increased NT-proBNP in obviously healthy athletes as well (41, 42). Thus, BNP and NT-proBNP are affected by heavy physical exercise in healthy subjects or by moderate exercise in HF patients. Therefore, to be on the safe side, in clinical practice it is recommended that patients with suspected cardiac diseases should be allowed to rest for 10 min before blood sampling. Drugs such as glucocorticoids, thyroid hormones, diuretics, angiotensin converting enzyme inhibitors, and adrenergic agonists and antagonists may influence the plasma levels of natriuretic peptides (43). Decreased diagnostic performances of BNP and NT-proBNP were demonstrated after 6 and 12 months of HF therapy (25). Therefore, blood samples should ideally be drawn before the start of HF therapy. Recently, a recombinant BNP (nesiritide) was cleared by the FDA for treatment of acute HF, and nesiritide was shown to influence BNP and NTproBNP measurements (44). Plasma BNP concentrations increased during a 24-h nesiritide infusion period (recombinant

Table IV In-vitro stabilities of BNP and NT-proBNP

Assay	Sample type	Room temperature	4 °C	–20 °C	References
Biosite Triage	EDTA whole blood	4 h	24 h		Personal communication
	EDTA plasma	4 h	24 h		Yeo et al. (4)
Abbott AxSYM	EDTA whole blood	4 h	24 h		Daghfal et al. (45)
	EDTA plasma	4 h	24 h		Daghfal et al. (45)
	EDTA plasma			Not recommended	Mueller et al. (11)
	EDTA plasma	6 h	6 h tested		Chien et al. (27)
	Separated serum	Not recommended	Not recommended		Chien et al. (27)
Bayer Centaur	EDTA whole blood	24 h			Wu et al. (6)
	EDTA plasma		48 h		Wu et al. (6)
	EDTA plasma	6 h	24 h		Belenky et al. (16)
Roche	EDTA whole blood	3 days	3 days		Sokoll et al. (12)
	Serum, heparinized or EDTA plasma		3 days		Sokoll et al. (12)
	EDTA plasma	3 days	>6 days	>10 days	Yeo et al. (4)
	EDTA plasma			3 months	Mueller et al. (11)
	Serum on clot-activation gel	7 days	11 days		Collinson et al. (13)
	Clotted whole blood	24 h			Collinson et al. (13)
	EDTA plasma	3 days	3 days		Chien et al. (27)
	Separated serum	3 days	3 days		Chien et al. (27)
Dade Behring	Heparin plasma	3 days	15 days	60 days	Di Serio et al. (19)

BNP is detected by the available BNP assays) and decreased below the baseline values six hours after the infusion was stopped, whereas NT-proBNP decreased during this period. Additionally, eating habits, such as sodium intake, or clinical conditions, especially renal failure and anemia, can increase NP levels. Influences on natriuretic peptide values by renal function and obesity will be discussed in detail later. The in-vitro stabilities of BNP or NT-proBNP are sufficient for routine application. For sample delivery, NT-proBNP is preferred because of its longer stability compared to BNP. Depending on the assay used, the invitro stabilities vary (*Table IV*), partly due to the different antibodies used which recognize different epitopes and fragments of the same analyte. For longer storage of BNP or NT-proBNP samples they should be centrifuged and the serum or plasma should be stored at or below –20°C. However, plasma BNP concentrations measured by Abbott AxSYM were reported to decrease by 30% after only one day of storage at –20°C, and to decrease to less than 50% after two months at –20°C (11). In contrast, EDTA plasma containing aprotinin was stable for one year at –20°C when measured by the Shionoria assay (17). It is recommended to measure BNP immediately after the arrival of the sample in the laboratory. NT-proBNP, by contrast, is not affected by several freezethaw (frozen at –20°C) cycles (12, 13, 19, 46).

Reference ranges and biological variability

As with in-vitro stabilities, reference ranges are also dependent on the assay used, and reference ranges have to be determined for each assay separately (*Table V*). Although some assays are harmonized with each other around a certain peptide concentration (e.g. 100 ng/L for Abbott and Biosite BNP) (7), absolute values above and below this concentration need not necessarily be in exact agreement. Therefore, for all follow-up examinations, the same assay should be used for peptide measurement. Several reports documented the age and sex dependence of both BNP and NT-proBNP with higher concentrations in women than in men from adolescence to menopause (6, 19, 47–50). Nevertheless, most studies on patients with chronic stable HF propose only one cut-off concentration not adjusted for age and sex, and only a few studies used age- and sex-adjusted cut-off values (see chapter chronic HF). The peptide values, which increase with age, are probably related to the more frequent occurrence of mild renal, systolic, and diastolic dysfunction and cardiac hypertrophy in the elderly (51). Estrogen levels have been thought to stimulate natriuretic peptide production in females, which may explain the sex dependence of the reference ranges (52). In women, increased plasma levels have also been reported in the last trimester of pregnancy and in the immediate puerperium (53, 54).

Table V Reference ranges for BNP and NT-proBNP in adults

BNP, ng/L						References
Age groups	<45 years	45–54 years	55–64 years	65–74 years	≥75 years	
Biosite (n=1286)						Manufacturer information 2000
Males	23.8	39.0	72.4	62.7	77.9	
Females	47.4	71.7	80.5	95.4	179.5	
Bayer (n=1521)						Manufacturer information 2005
Males	29.4	32.8	38.8	67.6	121.0	
Females	35.9	56.7	75.5	72.9	167.0	Manufacturer information 2005
Abbott (n=890)						
Males	73.0	40.0	80.0	150.0	121.0	
Females	89.0	111.0	155.0	159.0	266.0	
NT-proBNP, ng/L						References
Roche* (n=1981)						Hess et al. 2005 (47)
Age groups	18–29 years	30–39 years	40–49 years	50–59 years	60–69 years	
Males	65.0	88.0	95.0	172.0	278.0	
Females	130.0	132.0	169.0	249.0	303.0	
Dade (n=308)						Manufacturer information 2004
Age groups		<55 years	55–64 years	65–74 years	≥75 years	
Males		134.0	114.0	76.0	1476.0	
Females		76.0	163.0	203.0	1081.0	
DPC (n=217)						Manufacturer information 2005
Age groups				<75 years	≥75 years	
All				110.0	589.0	

Values are given as the 97.5th percentiles.

Recent studies demonstrated high NT-proBNP and BNP concentrations in healthy neonates with a subsequent rapid decrease within several days (55–60). Immediately after delivery, NT-proBNP concentrations were substantially higher (6.8- to 11-fold) in neonates than in the respective mothers (61, 62). This is partly due to the perinatal circulatory changes from fetal to neonatal life, which lead to an increased LV volume and pressure load. Additionally, BNP may be involved in the postnatal extracellular fluid volume contraction (58, 63), which occurs in the first week of life. Finally, kidney maturation requires approximately one year and may affect natriuretic peptide levels of infants, because BNP and NT-proBNP may be cleared by the kidneys (64–66). The contradictory results concerning NT-proBNP reference ranges in children were shown to be partly assay-dependent (67). The Roche assay displayed the influence of age in a pediatric population between 1 to 18 years showing high values in infants of up to six years of age (67). Similarly, age-and sex-dependent reference values were reported for the Biosite and Dade Behring assays (68). A gender-related difference seems to start during adolescence (59, 69).

The biological variation of natriuretic peptide secretion must be considered when interpreting serial natriuretic peptide results. Although no significant circadian rhythm was found for NT-proBNP (12), substantial intra-individual weekly biological variations of up to 59% were reported for NT-proBNP and BNP in healthy subjects (70, 71). Indeed, Wu et al. (70) suggested a serial change of 92–169% in BNP or NT-proBNP concentrations to be significant for follow-up investigations, which will not be clinically practicable, whereas Melzi d'Eril et al. (71) claimed a more realistic NT-proBNP change of more than 26%. Therefore, for BNP (Biosite), at least a 7-day interval for serial blood sampling is recommended to reflect significant increases or decreases and to avoid misinterpretations (72). In clinical studies, BNP or NT-proBNP changes of >50% during follow-up were related to changes in clinical HF status or mortality (73, 74).

Chronic heart failure

Studies comparing the diagnostic performances of various natriuretic peptides or their second messenger cyclic guanosine monophosphate to identify an impaired left ventricular systolic function revealed the superiority of BNP and NT-proBNP (75–81). Both have been shown to correlate moderately with LV ejection fraction (14, 76–78, 81–85) and with measures of diastolic LV function and to increase with the clinical severity of HF (6, 10, 29, 30). For BNP, this upward shift was demonstrated in female as well as in male patients even with mild forms of HF of either systolic or diastolic LV dysfunction (86). The markedly lower area under curve (AUC) in patients younger than 65 years compared to older ones presenting with LV ejection fractions F50% did not reach statistical significance (86). In the Framingham Heart Study (87), a gender-specific difference was reported for the detection of LV ejection fractions <50%, with a significantly ($p<0.005$) higher AUC in men than in women using the Shionoria BNP assay (*Table VI*). In moderate or severe systolic LV dysfunction (ejection fraction <40%), this gender-specific difference was not observed anymore (AUC women: 0.85 [0.67–1.00] and AUC men: 0.79 [0.71–0.86]). Using the Bayer Centaur assay, neither gender nor different age groups affected the negative predictive values (6). The negative predictive values were remarkably high (>98%) at a cut-off of 100 ng/L to discriminate patients of all NYHA classes from healthy subjects, and the clinical sensitivity increased with age (6). Furthermore, AUCs for the detection of moderate to severe diastolic dysfunction were substantially higher (approximate CI between 0.60 and 0.99) than for the detection of LV ejection fraction ≤50% (CI between 0.40 and 0.80) (86).

In chronic HF patients, the different BNP assays seem to be comparably useful for ruling out HF despite the lack of test agreement. The Biosite Triage and Abbott AxSYM showed comparable AUCs (0.983 vs. 0.967, respectively) to differentiate between patients with and without HF comprising NYHA classes I–IV patients (21). At a cut-off of 100 ng/L, the Abbott AxSYM demonstrated a significantly higher sensitivity in minimally symptomatic HF patients than the point-of-care assay (74 vs. 56%, respectively; $p<0.01$), whereas in moderate to severe HF patients, sensitivities were similar (21). Also the Biosite Triage (AUC mean (CIs): 0.91 [0.83–0.98] and the Shionoria assays (AUC: 0.88 [0.77–0.94]) performed similarly to identify impaired LV function (LV ejection fraction ≤50%) (3). NT-proBNP and BNP were found to be comparably useful in discriminating mild HF patients from healthy subjects as well (14, 76, 91).

There is evidence that BNP and NT-proBNP are also of diagnostic value in patients with isolated diastolic LV dysfunction. Significantly increased BNP (Triage) concentrations compared to controls were found in isolated diastolic LV dysfunction patients (14, 86, 88), with highest concentrations in patients with restrictive filling patterns (88, 90). BNP and NT-proBNP concentrations in isolated diastolic LV dysfunction patients do not normally exceed concentrations in mild systolic LV dysfunction patients (14, 25, 88). The diagnostic performances of BNP and NT-proBNP are only fair in mild diastolic LV dysfunction (14, 88) and give better results in moderate to severe diastolic LV dysfunction (88). Because of the low prevalence of preclinical systolic or diastolic LV dysfunction and a specificity between 64–93%, screening in the community would lead to a large number of required echocardiograms for diagnosis confirmation, which is cost-intensive and not recommended

Table VI Natriuretic peptide performance for the detection of stable chronic HF

References	Assay	AUC (CIs)	Number (men in %)	Mean age, years	HF patients	Echocardiographic diagnostic criteria
Chronic HF						
Krishnaswamy et al. (88)	Biosite	0.95 (0.93–0.97)	400 (96)	65		EF < or >50%
Redfield et al. (86)	Biosite	Women: 0.74 (no CI) Men: 0.82 (0.71–0.93)	396 (50)	74	hypertension, coronary artery disease, ≥65 years	EF ≤40%
Fischer et al. (3)	Biosite	0.91 (0.83–0.98)	95 (67)	63	NYHA I–IV	EF ≤50%
Tang et al. (21)	Biosite Abbott	0.98 (0.97–0.99) 0.97 (0.95–0.99)	348	57	NYHA I–IV	
Wu et al. (6)	Bayer	0.92 (0.90–0.93)	2243 (57)	19–102	NYHA I–IV	
Vasan et al. (87)	Shionoria	Women: 0.56 (0.50– 0.65) Men: 0.72 (0.67–0.77)	3177 (46)	58		FS <29% (≅ EF <50%) females vs. men: p<0.005
McDonagh et al. (50)	Roche ELISA	0.85	3051 (55)	56	HF	
Pfister et al. (29)	Roche Shionoria	0.83 (0.75–0.90) 0.87 (0.75–1.00)	339 (72) 149	66	NYHA I–IV NYHA I–IV	EF <40% EF <40%
Mueller et al. (18)	Roche	0.84 (0.77–0.90)	137 (89)	53	Stage B	
Prontera et al. (89)	Roche	0.96 (0.93–0.98)	206 (68)	61	NYHA I–IV	EF <55%
Prontera et al. (10)	Roche	0.96 (0.93–0.98)	278 (64)	58	NYHA I–IV	Mean EF 33%
Mikkelsen et al. (25)	Roche	0.95 (0.91–0.99)	150 (55)	65	NYHA II–IV	EF < or > 45%
Mild systolic HF						
Hammerer-Lercher et al. (14)	Biosite	0.78 (0.63–0.89)	66 (67)	64	NYHA I–II	EF <50%
Tang et al. (21)	Biosite Abbott	0.74 (0.59–0.87) 0.56 (0.40–0.71)			NYHA I	
Prontera et al. (89)	Roche	0.93 (0.88–0.97)	152		NYHA I–II	EF <55%
Prontera et al. (10)	Roche	0.93 (0.89–0.97)	201		NYHA I–II	
Mild diastolic HF						
Krishnaswamy et al. (88)	Biosite	0.95 (0.92–0.98)	245			Impaired relaxation + restrictive filling + pseudonormal pattern.
Lubien et al. (90)	Biosite	0.92 (0.89–0.95)	294 (90)	66		EF <50%; Impaired relaxation + restrictive filling + pseudonormal pattern.
		0.97 (0.95–1.00)				Restrictive filling pattern.
		0.94 (0.88–1.00)				Pseudonormal pattern.
		0.87 (0.82–0.93)				Impaired relaxation.
Hammerer-Lercher et al. (14)	Biosite	0.70 (0.56–0.81)	67 (68)	63		LVEDP ≥16 + pathological mitral valve diastolic inflow pattern

CIs, confidence intervals; EF, left ventricular ejection fraction; NYHA, New York Heart Association classification; LVEDP, left ventricular end diastolic pressure.

(86). However, a common conclusion of all major studies is that in patients with chronic HF NT-proBNP and BNP are rather rule-out than rule-in markers, as shown by the high negative predictive values (92).

Acute heart failure

Patients with acute HF usually show significantly higher natriuretic peptide concentrations than patients with stable chronic HF (93–96). BNP and NT-proBNP concentrations were found to be independent of age, gender, or body mass index in patients presenting with acute dyspnoea to the emergency department (*Table VII*) (94, 101, 102, 108). Nevertheless, the PRIDE (ProBNP Investigation of Dyspnoea in the Emergency Department) investigators (104) suggested to categorize patients into age groups below 50 and above 50 years using a higher cut-off value for the elderly (NT-proBNP Roche: 450 vs. 900 ng/L). The greatest value of natriuretic peptide testing was demonstrated in patients with an intermediate probability of having HF presenting with acute dyspnoea to the emergency department, because in these patients, a low natriuretic peptide value (Biosite BNP <100 ng/L) correctly excluded having HF in 93% of patients (99). However, in patients with intermediate BNP concentrations (Biosite 80–300 ng/L), BNP measurement added no value to the clinical diagnosis, and in these patients, confirmation of HF by echocardiography was recommended (93). Although natriuretic peptide values can be increased in chronic lung disease due to right ventricular stress, BNP was useful to identify patients with a history of chronic lung disease but acute dyspnoea from HF. These patients had significantly higher BNP concentrations than patients with a history of HF but acute dyspnoea from lung disease (97). Patients suffering from terminal parenchymal lung disease but with normal LV function did not show increased NT-proBNP values (109). Renal function affected BNP and to a greater extent NT-proBNP values in acute congestive HF patients (106). Particularly patients with moderate to severe renal impairment require an adjustment of the decision limit (NT-proBNP of 1200 ng/L) (*Table VII*) (106, 107).

Also in acute HF, both hormones, BNP and NT-proBNP, seem to perform similarly well, at least when comparing the Biosite to the Roche assay (94, 101). Natriuretic peptide measurement was shown to be superior to standard clinical assessment for HF diagnosis (98, 99, 104, 110). The AUCs to differentiate patients with and without acute HF are high (0.81–0.99, *Table VII*) and the respective natriuretic peptide cut-off values show high negative predictive

Table VII Decision limits for patients presenting with acute dyspnoea to the emergency department

References	Assay	Cut-off, ng/L age-dependent	Taken from the ROC: one	AUC (CIs)	Mean age, y	Numbers (men %)
Morrison et al. (97)	Biosite		94	0.99 (0.96–0.99)	n.d.	321 (95)
Maisel et al. (95)	Biosite		100	0.91 (0.90–0.93)	64	1586 (56)
Steg et al. (98)	Biosite		100	0.89	66	709 (43)
McCullough et al. (99)	Biosite		100	0.90 (0.88–0.91)	66	1586 (56)
Logeart et al. (93)	Biosite		<80 (rule out) >300 (rule in)	0.93	67	163 (67)
Ray et al. (100)	Biosite		250	0.87 ± 0.08	80	308 (49)
Mueller et al. (7)	Abbott Bayer		137 110	0.94 (0.87–0.98) 0.93 (0.86–0.97)	N.D.	100 (n.d.)
Alibay et al. (10)	Biosite Roche		150 1000	0.82 0.84	80	160 (48)
Lainchbury et al.	Biosite Roche		208 2875	0.89 0.89	70	205 (49)
Mueller et al.	Abbott Roche		295 825	0.92 (0.87–0.95) 0.90 (0.86–0.94)		251 (93)
Bayes-Genis et al.	Roche		254 (rule out) 973 (rule in)	0.96 (0.92–1.0)	70	89 (59)
Januzzi et al.	Roche	<50 year: 450 ≥50 year: 900 (rule in)	300 (rule out)	<50 year: 0.98 ≥50 year: 0.93	65	599 (51)
Januzzi et al. (105)		<50 year: 450 50–75 year: 900 >75 year: 1800 (rule in)	300 (rule out)	n.d. (accuracy 83–95%)	n.d.	1256 (n.d.)
Anwaruddin et al.	Roche		GFR <60: 1200	0.88	76	207 (71)
McCullough et al.	Biosite		GFR >90: 71 GFR 60–89: 104 GFR 30–59: 201 GFR <30: 225	GFR >90: 0.91 GFR 60–89: 0.90 GFR 30–90: 0.81 GFR <30: 0.86	65	1452 (56)

CIs, confidence intervals; y, years; GFR, glomerular filtration rate in mL/min/1.73 m^2; n.d., not determined.

values between 83 and 99%. When combining both, natriuretic peptide measurement and clinical assessment, the diagnostic performance was improved significantly. Thereby, the management of patients with acute dyspnoea was improved and resulted in a significantly shorter median time of discharge and hospital admission, and in the elderly patients, in addition to a shorter discharge time, in reduced admission to intensive care and mortality (110, 111).

Prognostic value of natriuretic peptides in heart failure

Chronic heart failure

Recent studies indicate that short- and long-term prognosis can be assessed by BNP or NT-proBNP determination. These hormones were shown to be independent predictors of death or HF hospitalizations when compared with other neurohormones and markers such as ANP, norepinephrine, plasma renin activity, aldosterone, endothelin-1, cardiac troponin T, or LV ejection fraction in multivariate analysis calculations (112, 113). Non-survivors with chronic congestive HF showed 3.4 to 5.6 times higher BNP (Shionoria) concentrations than survivors who were followed up for two or four years (114, 115). NT-proBNP (Roche) concentrations above a median were predictive for a 50% risk of death alone (116) and a 70% risk of death or HF (117) over a one-year period. Additionally, patients with the highest NT-proBNP levels had a very poor short-term prognosis (116). In moderate to severe HF patients (LV ejection fraction <25%), both BNP and NT-proBNP (Biomedica) were independently related to death within four years, and survivors showed increasing LV ejection fractions and in parallel decreasing NT-proBNP values (118). The prognostic power of neurohormones was found to depend on the clinical stage of HF and the observation period (74, 119, 120). One of the largest trials, the Valsartan Heart Failure Trial (Val-HeFT), demonstrated that baseline BNP (Shionoria) concentrations divided into quartiles showed a significant quartile-dependent increase in all-cause mortality and first morbidity event (74). Absolute changes were yet found to be useless, whereas percent changes revealed a direct relationship to the mortality rate; a decrease in BNP of more than 45% within four months was associated with a 13.6% mortality rate, whereas an increase in BNP greater than 30% was associated with a 19.1% mortality rate (74). Similar results were found in a smaller study (119), in which patients were classified according to the severity of HF. Patients in the group of most severe HF required heart transplantation more often or had more deaths than patients with moderate or mild HF. Recently, the combined one-year risks for all-cause mortality or hospitalization for HF were reported to be 14% in the lowest NT-proBNP tertile and 46.7% in the highest tertile in severe chronic HF patients (120). Furthermore, high NT-proBNP concentrations were more specific predictors for major adverse cardiac events such as decrease in LV ejection fraction <35%, valvular heart disease, myocardial infarction, cardiac death, etc. in patients younger than 75 years compared to older ones (121). Elderly patients showed a more gradual increase in adverse events with a less distinctive threshold (121).

Acute heart failure

There is increasing evidence for a role of BNP and NT-proBNP testing for risk stratification in acute HF. In patients with dyspnoea and suspect of acute HF, rising BNP concentrations were associated with progressively worse prognosis for the following six months (122). Patients with BNP (Biosite) concentrations above 480 ng/ L were at 51% risk of death, hospital readmissions, or repeat emergency department visits for HF within six months. On the other hand, patients with less than 230 ng/L BNP concentrations had an event rate of only 2.5% (122). BNP at discharge (Biosite discriminator concentration of 321 ng/L), but not on admission was found to be related to hospital readmission or death within six months (123). However, BNP levels decreased not only in event-free patients, but also in patients without adverse events, though to a lesser extent (123). Also NT-proBNP (Roche) was a strong predictor of short-term mortality (60 days) irrespective of renal impairment in dyspnoeic patients with a hazard ratio of 1.57 (106).

Disease monitoring of heart failure

Preliminary studies suggest that the course of HF disease can be monitored according to the changes of natriuretic peptide concentrations. However, most studies report mean natriuretic peptide changes in parallel with different criteria for the improvement of HF without showing the individual course of a patient. Criteria such as cardiothoracic ratio and left ventricular end-diastolic diameters (124) or increases in maximal exercise capacity during the bicycle exercise stress test and improvement in NYHA class were associated with decreases in BNP concentrations during follow-up of congestive HF patients (125). Lee et al. (126) demonstrated a 45% – reduction of BNP (Shionoria) concentrations in patients whose NYHA class improved, whereas in patients without improvement BNP remained unchanged. Although the overall mean values indicated a significant decrease in BNP concentrations in parallel to an improvement of the disease, not each patient did actually respond with a BNP reduction when the NYHA class was improved (126). In moderately diseased HF patients treated with carvedilol, BNP (Shionoria) levels fell from 453 ng/L to 223 ng/L and LV ejection fraction and NYHA class improved at six months (127). After

four months of spironolacton treatment of patients with mild-to-moderate congestive HF, BNP Shionoria concentrations decreased by approximately 55% (mean 200 vs. 90 ng/L) from baseline when NYHA class, left ventricular volume, or mass ameliorated (128). In patients with severe HF, an approximate 70%-decrease in Shionoria BNP (mean 917 vs. 285 ng/L) was found within three months of successful treatment (115). Using the FDA-cleared point-of-care BNP assay, mean increases from 239 ng/L to a final mean of 1800 ng/L were shown in patients with decompensated HF who died or were readmitted after one month of treatment (129). In case of successful treatment, BNP concentrations declined significantly by mean –216 ng/L of the baseline. NT-proBNP (Roche ELISA) concentrations increased slightly in patients treated with carvedilol by less than 5% at the end of carvedilol uptitration, but decreased by more than 25% after six months and were again only slightly decreased after the long-term follow-up period of 29 months (120). In acute HF patients, NT-proBNP values (Roche) were reduced by about 56% in patients with complete resolution and by about 37% in patients with clinical stabilization, whereas patients with persistent decompensated HF had only a mean reduction of 21% after seven days of treatment (103).

Furthermore, patients with mild forms of HF may benefit from disease monitoring with natriuretic peptides. However, only moderate but equal diagnostic performances of changes in BNP and NT-proBNP to differentiate between HF patients with and without improvement in the clinical HF status were found during a 3-month follow- up, and therefore, natriuretic peptides cannot replace established methods (73). Only NT-proBNP concentration decreases of at least 50% and of BNP concentration decreases of 40% were strongly related to clinical improvement.

Treatment guidance according to natriuretic peptide concentrations in heart failure patients

Since BNP and NT-proBNP decrease in parallel with hemodynamic or clinical improvement, a treatment tailoring according to these natriuretic peptides should be beneficial to the patient. Moreover, it was shown that HF treatment with angiotensin converting enzyme inhibitors (124, 130), beta-blockers (118, 131), or valsartan (132) can reduce natriuretic peptide concentrations. Nevertheless, there is only a limited number of studies. Murdoch et al. (130x randomized 20 patients with mild to moderate congestive HF into patients who received stable conventional therapy (clinical group) and into patients who received treatment intended to achieve BNP levels <50 ng/L (Shionoria, BNP group). In the BNP group, more favorable hemodynamic changes were observed, and BNP decreased earlier and to a greater extent than in the clinical group with a mean reduction of –42.1% at four weeks and a lesser reduction after eight weeks (–34.2%), which was still higher than in the clinical group (–27.5%). If HF patients were treated to achieve NTproBNP concentrations <1691 ng/L (in-house assay), total cardiovascular events were reduced, the time to the first event was delayed, and NT-proBNP concentrations were decreased compared with intensive clinically guided treatment during a 6-month follow-up (133). However, in a recent study (134), only a trend to better quality of life was found in patients treated according to their BNP levels compared to patients on standard care. LV ejection fractions were improved in both groups after three months of bisoprolol treatment. All above-mentioned studies were relatively small and the usefulness of tailoring treatment according to natriuretic peptide levels remains to be determined in larger trials.

Acute coronary syndrome-risk stratification

According to the new guidelines, ACS include unstable angina pectoris, non ST-elevation myocardial infarction (non-STEMI) and STEMI (135, 136) (http://www.acc.org/clinical/guidelines/unstable/update_index.htm). In patients with acute STEMI, both BNP and to a greater proportion NT-proBNP increased rapidly and peaked at 12 to 24 h after the onset of chest pain, decreased slightly thereafter, but remained increased for up to 12 weeks (137). It was shown that patients with larger infarcts and lower ejection fractions presented a biphasic increase in BNP with a second peak on day 5 after admission, whereas patients with smaller infarcts had a monophasic BNP increase (138). Moreover, the magnitude of natriuretic peptide increases was related to the infarct size (139, 140). In case of remodeling sustained BNP elevations until 90 days post myocardial infarction were reported with a subsequent decrease at day 180, whereas a significant decrease from day 2 to 90 indicated no remodeling (141). A BNP concentration one month after myocardial infarction was predictive for the subsequent degree of LV dilation, which was higher in the remodeling group (142).

The value of natriuretic peptide measurement for risk stratification after ACS was reported in several large trials. Patients with unstable angina or non-STEMI showed the highest mortality in the highest NT-proBNP quartile or tertile, and NT-proBNP was an independent predictor or one of the most important predictors of death during the long-term follow-up (between one year and 40 months) in the Fast Assessment in Thoracic Pain (FAST) (143), the Assessment of Safety and Efficacy of a New Thrombolytic (ASSENT) trial (144), the Global Utilization of Strategies To Open Occluded arteries-IV (GUSTO-IV) (145), and the FRISC II trial (146). A significant dif-

ference in NT-proBNP quartile-dependent mortality risk was seen already within two days in the GUSTO-IV trial (145). At one year, an exponentially increasing mortality was found in the whole spectrum of NT-proBNP (Roche) levels of the GUSTO-IV trial with mortalities of 0.4% in the lowest decile (–98 ng/L) and 27.1% in the highest decile (>4634 ng/L) (145). No significant difference in the prognostic value of BNP or NT-proBNP was found for either short- (OR [95% CIs]: 4.31 [3.77–4.94]) or longterm mortality (OR: 3.38 [2.44–4.68]), without any significant influence whether the sample collection occurred on admission or within several hours (OR: 4.42 [3.83–5.10]) or days after admission (OR: 3.51 [2.64–4.67]) (147). Furthermore, the prognostic value of natriuretic peptide determination was similar in STEMI and non-STEMI patients with increasing mortality rates across NT-proBNP quartiles (148, 149).

Natriuretic peptides in other diseases

Natriuretic peptides are not increased exclusively in patients suffering from acute or chronic HF. They are also increased in several diseases affecting the cardio-renal homeostasis and fluid balance as listed in *Table VIII*. Anemia is associated with increased severity of HF, although the cause is still unknown (150, 151). Haemoglobin concentrations were shown to be significantly inversely correlated with NT-proBNP ($r=-0.408$; $p<0.0001$) concentrations in non-HF patients (152) and with BNP concentrations in men, but not in women without HF ($r=0.081$; $p<0.001$) (153) as well as in patients with mild HF ($r^2=0.15$; $p<0.0001$) (154). Additionally, recent studies indicate an impact of atrial fibrillation (155), type of pacemaker (156), and diabetes (157) on natriuretic peptide levels. The usefulness of natriuretic peptide measurement in patients with arterial hypertension or stable angina pectoris is still a matter of debate. In patients with arterial hypertension, natriuretic peptides were moderately correlated with LV mass (158, 159), thus limiting the diagnostic value for LV mass in these patients, but were strong prognostic risk markers for cardiovascular events (159, 160). Also in patients with stable coronary heart disease, natriuretic peptides are of limited diagnostic value for LV systolic function, which may be due to the greater prevalence of competing diseases such as ischemia, LV hypertrophy, and diastolic LV dysfunction with increased natriuretic peptide levels (161). Nevertheless, in these patients, the natriuretic peptides still seem to be strong prognostic markers (162). A recent epidemiologic study revealed that NT-proBNP is a strong predictor (OR [95% CIs]: 3.24 [1.18–8.85]) of coronary events in a middle- aged population of men at work, independent of body mass index, smoking, diabetes, systolic blood pressure, total and HDL cholesterol, creatinine, and previous coronary heart disease (163). However, in the Framingham study (87) and in a community-based study (86), BNP was shown to be suboptimal as a mass screening tool for the detection of increased LV mass or preclinical ventricular systolic or diastolic dysfunction.

Table VIII Natriuretic peptides in diseases other than heart failure.

- Acute coronary syndrome, acute myocardial infarction
- Left ventricular hypertrophy
- Myocarditis
- Systemic arterial hypertension
- Pulmonary hypertension
- Acute or chronic renal failure
- Liver cirrhosis with ascites
- Endocrine disorders (primary hyperaldosteronism, hyperthyroidism, cushing syndrome)
- Anemia
- Central nervous system diseases (subarachnoidal hemorrhage, stroke)

Renal function

First evidence of higher arterial BNP and NT-proBNP concentrations than in the renal veins indicates that both hormones are extracted by the kidneys in healthy men (164) as well as in patients with essential hypertension or cirrhosis but preserved renal function (66). Extraction rates were comparable between the two hormones without any influence of body mass index (66). Small concentrations of BNP and NT-proBNP were also found in the urine of patients with renal failure (165) or HF (166). In patients with renal dysfunction (<85 mL/min/1.73 m^2), the magnitude of BNP and NT-proBNP increase was reported to be two-fold higher in those with preserved or moderately impaired LV function (ejection fraction >35%) and was much greater in patients with severe HF (167). In these latter patients, also renal function was worse, and BNP and NT-proBNP showed a different clearance pattern with markedly higher NT-proBNP (+ 640%) than BNP increases (+ 480%). Both markers were shown to increase in line with the decline in the glomerular filtration rate and thereby to influence the optimal decision limits, particularly in patients with a glomerular filtration rate less than 30 mL/min/1.73 m^2 (107, 168). Both markers are highly increased in patients with end stage renal failure on hemodialysis. Hemodialysis treatment was reported to drop BNP concentrations by approximately 20% in end-stage renal disease patients (169–171). However, NT-proBNP clearance by hemodialysis was shown to depend on the membrane used, resulting in a NT-proBNP reduction similarly to BNP with high-flux membranes and in an elevation of NT-proBNP (17%) with low-flux membranes (170). This finding can be explained by the fact that the molecular weight of NTproBNP was too high to be filtered through the low-flux membrane and retained in the

blood. In summary, BNP and NT-proBNP are markers of cardiac dysfunction in patients with renal failure as well, but the decision limits are higher than in patients with normal renal function.

Obesity

The effect of obesity on natriuretic peptide levels has not been fully understood so far and controversial reports are found in the literature. Several studies showed decreased BNP (172–174) and NT-proBNP concentrations (175) with increased body mass index irrespective of the cardiac function (176, 177). In contrast, Grandi et al. (178) did not find any correlation of BNP with body mass index in hypertensive patients, and Hermann-Arnhof et al. (179) demonstrated NT-proBNP concentrations that were similarly high in healthy obese subjects and in mild HF patients. One explanation for lower BNP concentrations in obese subjects than in lean subjects could be the enhanced BNP clearance by adipose tissue, which expresses natriuretic peptide clearance receptors (NPRC). However, greater lean mass, but not fat mass was demonstrated to be associated with low BNP and NT-proBNP concentrations, which does not support the theory of enhanced natriuretic peptide clearance in adipose tissue (176).

Conclusion

BNP and NT-proBNP are now well-established acute and chronic HF markers. Both hormones are comparably useful to exclude HF in patients with HF symptoms presenting to the general practitioner, or in patients with acute dyspnoea in whom acute lung disease has to be differentiated from acute HF (*Table IX*). In chronic HF patients, high BNP and NT-proBNP concentrations indicate a very poor prognosis, and there is evidence that these markers are of prognostic value in acute HF patients as well. In case of complicated myocardial infarction (MI), sustained natriuretic peptide concentrations are expected, and in patients with unstable angina or non-STEMI, BNP and NT-proBNP are independent predictors or one of the most important short- or long-term predictors of mortality. If the course of HF disease is monitored using natriuretic peptides, biological variations of these hormones must be considered, and only substantial changes of the concentrations measured at intervals of at least one week or better longer periods are indicative of clinical changes. Several commercial assays, which are not standardized, are available producing different absolute concentrations or are harmonized only around a certain cut-off value. Therefore, for all follow-up investigations, the same assays should be used to avoid misinterpretation. Furthermore, there are several confounding factors that influence natriuretic peptide concentrations. In renal disease, for example, the cut-off values have to be raised. Ongoing studies will clarify how to interpret BNP and NT-proBNP concentrations in patients taking influencing medications (nesiritide, beta-blockers, etc.) or suffering from diseases such as atrial fibrillation, obesity, or anemia.

Table IX Evidence-based clinical applications of natriuretic peptide testing.

	BNP	NT-pt
HF Screening		
ED patients with dyspnoea	Yes	Yes
Symptomatic patients at the GP	Yes	Yes
General population	No	No
Risk stratification		
HF	Yes	Yes
ACS (including MI)	Yes	Yes
HF monitoring	No	No
Biological variation!		

HF, heart failure; ED, emergency department; GP, general practitioner; ACS, acute coronary syndrome; MI, myocardial infarction.

B-TIP NATRIURETSKIH PEPTIDA KAO MOĆNIH MARKERA U KARDIOLOŠKIM BOLESTIMA – ANALITIČKI I KLINIČKI ASPEKTI

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Kratak sadržaj: Među svim natriuretskim peptidima i neurohormonima, za B-tip natriuretski peptid (BNP) i njegov N-terminalni prohormonski fragment (NT-proBNP) je pokazano da su najbolji i najmoćniji markeri za identifikaciju pacijenata sa akutnom i hroničnom srčanom insuficijencijom (SI). Potpuno automatizovana određivanja BNP i NT-proBNP ahtevaju samo 15–20 minuta za dostizanje rezultata testa tako da je moguće »turn-around« vreme manje od 60 minuta, kao što se zahteva od strane vodiča kardioloških društava. In vitro stabilnosti BNP i NT-proBNP su dovoljne za rutinsku upotrebu. Većina komercijalno dostupnih testova, sem ako su sublicencirani, koriste različita antitela. Ovo se može objasniti da uopšteno, BNP i NT-proBNP određivanja sa različitim testovima pokazuju bliske korelacije, ali se ne slažu u apsolutnim vrednostima. Ova određivanja nisu dosada standardizovana i primena različitih kalibracionih materijala može doprineti različitim rezultatima. Prema tome, referentni opsezi zavise od testa koji se koristi, i moraju biti određeni za svaki test posebno. Povećanje vrednosti sa godinama možda je u vezi sa rastućom frekvencijom subkliničke renalne ili kardiološke disfunkcije kod starijih osoba. Estrogeni stimulišu produkciju natriuretskih peptida kod žena, a referentni opsezi zavise od pola od adolescencije do menopauze. Odmah nakon rođenja, nivoi BNP i NT-proBNP su znatno viši kod novorođenčadi nego kod njihovih majki. Visoka biološka varijacija natriuretskih peptida mora se uzeti u obzir pri interpretaciji serije rezultata BNP i NT-proBNP. Prema tome, samo znatne promene BNP i NT-proBNP u toku praćenja pacijenta su u vezi sa promenama kliničkog statusa SI. Zaključak svih vodećih studija je da su BNP i NT-proBNP kod pacijenata sa hroničnom SI pre markeri za »isključenje« nego za »potvrdu« zbog ograničenih kardioloških specifičnosti. Pacijenti sa akutnom SI obično pokazuju više nivoe BNP i NT-proBNP nego pacijenti sa hroničnom SI. Najveća efikasnost testiranja BNP i NT-proBNP je pokazana kod pacijenata prisutnih na urgentnom odeljenju sa akutnom dispneom ili kod pacijenata sa simptomima koji ukazuju na hroničnu SI. Mnoge studije ukazuju da kratkoročna i dugoročna prognoza kod SI može biti procenjena određivanje BNP i NT-proBNP. Ovi hormoni su nezavisni prediktori letalnog ishoda ili hospitalizacije zbog SI. Natriuretski peptidi su povećani kod svih bolesti koje utiču na kardijalnu ili renalnu funkciju i ravnotežu tečnosti. BNP i NT-proBNP su takođe markeri kardijalne disfunkcije i kod pacijenata sa renalnom insuficijencijom, ali se tu moraju koristiti više vrednosti granica odlučivanja. Smanjene koncentracije BNP i NT-proBNP kod gojaznih nisu potpuno razumljive i kontraverzni izveštaji su nađeni u literaturi. U zaključku, određivanje BNP i NT-proBNP je moćan test za isključenje SI. Osim toga, ovi markeri su korisna dopuna standardnim kliničkim ispitivanjima pacijenata sa suspektnom ventrikularnom disfunkcijom.

Ključne reči: procedure određivanja, B-tip natriuretski peptid (BNP), dijagnoza, praćenje, NT-proBNP, stratifikacija rizika

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