B-type natriuretic peptide (BNP) was first identified in porcine brain in 1988 and originally was termed brain natriuretic peptide. Subsequently, it was detected in ventricular cardiomyocytes and the ventricular myocardium was later recognized as the major source of circulating BNP. The main stimulus for increased BNP synthesis and secretion is wall stress and BNP is synthesized as a proBNP comprising 108 amino acids. Upon release into the circulation, it is cleaved in equal proportion into the biologically active 32 acid BNP and the biologically inactive 76 amino acid N-terminal fragment, NT-proBNP. BNP relaxes vascular smooth muscle, dilates arteries and veins, lowers blood pressure and ventricular preload, and inhibits sympathetic activity and the renin–angiotensin–aldosterone system. It also increases glomerular filtration and inhibits sodium reabsorption by the kidney, promoting natriuresis and diuresis [1,2]. BNP is mainly cleared from plasma by binding to the natriuretic peptide receptor type C (NPR-C) and through proteolysis by neutral endopeptidases. In contrast, NT-proBNP is cleared by renal clearance. This finding led to the incorrect hypothesis that NT-proBNP is dependent on renal function whereas BNP is not dependent on renal function. However, studies have shown correlation coefficients between BNP and estimated glomerular filtration rate (eGFR) [3,4].

BNP and NT-proBNP are mostly used as diagnostic biomarkers of acute heart failure (HF). The contributions of blood BNP or NT-proBNP measurements in the initial evaluation of patients presenting with acute HF have been confirmed. In the multicenter Breathing-Not-Properly Study, the use of a 100 pg/ml BNP (Triage, Biosite, San Diego, CA, USA) concentration as a diagnostic “cut-off”, identified HF as the cause of acute dyspnea with a 90% sensitivity, 76% specificity, and an 83% diagnostic accuracy, in 1586 patients presenting to the emergency department, which was superior to a clinical assessment alone [5]. The similar contributions made by the measurements of NT-proBNP were confirmed in the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study, in 600 patients presenting with acute dyspnea. NT-proBNP concentrations >450 pg/ml at <50 years of age, and >900 pg/ml at ≥50 years of age, were highly sensitive and specific for the diagnosis of acute HF, while <300 pg/ml was optimal to exclude acute HF, with a negative predictive value of 99% [6]. From these observations, the National Academy of Clinical Biochemistry (NACB) laboratory medicine practice guidelines stated that “the use of BNP or NT-proBNP testing in an acute setting to rule out or to confirm the diagnosis of heart failure among patients with ambiguous signs and symptoms”, and was assigned a class I, level of evidence A [7]. From the PRIDE study, the use of NT-proBNP is valuable for the evaluation of the dyspneic patient, irrespective of renal function. With receiver-operating characteristic (ROC) curves, the performance of NT-proBNP for the diagnosis of acute HF in breathless subjects with normal-to-mild renal insufficiency (glomerular filtration rate [GFR] ≥ 60 ml/min/1.73 m², n = 393) versus moderate-to-severely impaired renal function (GFR < 60 ml/min/1.73 m², n = 206) were compared and the difference between the two curves was not statistically significant (p = 0.34) (Fig. 1) [8].

![Fig. 1. Receiver-operating characteristic curves comparing the performance of amino-terminal pro-brain natriuretic peptide for the diagnosis of acute congestive heart failure in breathless subjects with normal-to-mild renal insufficiency (glomerular filtration rate [GFR] ≥ 60 ml/min/1.73 m², n = 393) versus moderate-to-severely impaired renal function (GFR < 60 ml/min/1.73 m², n = 206) [8]. The difference between the two curves was not statistically significant (p = 0.34).](http://dx.doi.org/10.1016/j.jjcc.2013.01.015)
BNP and NT-proBNP are also used as prognostic markers in patients with HF. It is particularly noteworthy that, by multiple variable analysis, in theValsartan Heart Failure Trial (Val-HeFT), norepinephrine, BNP, aldosterone, plasma renin activity, big endothelin (ET)-1, and ET-1 were assayed at baseline in 4300 patients. By multiple variable analysis, BNP was most closely correlated with mortality [9]. A sub-study of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) examined the prognostic value of NT-proBNP in a large population of patients presenting with severe chronic HF [10]. Therefore, NACB laboratory medicine practice guidelines state that “Blood BNP or NT-proBNP testing can provide a useful addition to clinical assessment in selected situations when additional risk stratification is required” and assigned it a class IIa, Evidence level A [7].

In this issue, Horii reports that the area under the receiving operating characteristic curve (AUC) of BNP and NT-proBNP for mortality and cardiovascular events were similar for chronic kidney disease (CKD) stage 1–3. However, for CKD stage 4–5, AUC of NT-proBNP was higher than AUC of BNP. It was concluded that NT-proBNP is a superior prognostic marker to BNP for CKD stage 4–5. Calculated optimal cutoff values of BNP for all-cause death were 87.0 pg/ml in patients with an eGFR ≥ 30 ml/min/1.73 m², and 114.5 pg/ml in patients with an eGFR < 30 ml/min/1.73 m², so the optimal cutoff values differed by 30%. However, the optimal cutoff values of NT-proBNP for all-cause death were 258 pg/ml in patients with an eGFR ≥ 30 ml/min/1.73 m², and 5809 pg/ml in patients with an eGFR < 30 ml/min/1.73 m². From a clinical point of view, it was concluded that it should be noted that the optimal cutoff of NT-proBNP varied quite widely based on renal function [11].

In a sub-analysis of 720 patients presenting with acute decompensated HF from the International Collaborative on NT-proBNP (ICON) study, NT-proBNP level was predictive of 60-day outcome in the setting of impaired renal function. Both an eGFR < 60 ml/min per 1.73 m² and an NT-proBNP level above the median (4647 ng/l) predicted a poor outcome. Intriguingly, these investigators identified that it was the combination of both that carried the greatest risk (Fig. 2) [12]. Another study has also compared BNP and NT-proBNP for all-cause mortality in emergency department patients presenting with dyspnea and an eGFR < 60 ml/min per 1.73 m². NT-proBNP levels were superior predictors of 1-year mortality after adjustment for comorbidities, renal function, and diagnosis of decompensated HF [13].

In conclusion, NT-proBNP is as useful as BNP for the prognostic and diagnostic evaluation of patients with HF irrespective of renal function. Particularly in patients with severe CKD, NT-proBNP is a superior prognostic marker than BNP, although the optimal cutoff of NT-proBNP varied quite widely based on renal function.

References


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