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# Prospective Validation of NT-proBNP Cut-off Concentrations for the Diagnosis of Acute Heart Failure

**Brief title:** NT-proBNP cut-off concentrations

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Acute heart failure (AHF) is the most common diagnosis in the emergency department (ED) leading to hospitalization.[1,2] In contrast to the enormous improvements achieved in the management of patients with chronic heart failure, morbidity and mortality remain unacceptably high in patients with AHF.[1–3] The dismal outcome of patients with AHF may at least in part be related to diagnostic uncertainty in the ED and the associated delay in diagnosis and initiation of effective treatment.[3]

The clinical introduction of natriuretic peptides as quantitative markers of hemodynamic stress and heart failure provided a novel and unique non-invasive window to the heart and has substantially improved the rapid detection of AHF among patients presenting with acute dyspnea.[1–3] Accordingly, the diagnostic use of natriuretic peptides has received a class I recommendation in both the European and the American practice guidelines.[1,2] While the cut-off concentrations of B-type natriuretic peptide (BNP) recommended in current guidelines were validated in a large, multicentre study,[4] only recently, the performance of the NT-proBNP cut-off concentrations has been tested in a North American and an Asian cohort of relatively young patients with low prevalence of AHF and less comorbidities as compared to that observed in European patients.[2,5–7] We therefore aimed to address this major gap in knowledge and prospectively validate NT-proBNP cut-off concentrations in the diagnosis of AHF in the European multicentre cohort Basics in Acute Shortness of Breath EvaLuation (BASEL V) *(NCT01831115).*

We enrolled unselected adult patients presenting to the ED of two Swiss University Hospitals (Basel and Zurich) with acute dyspnea as their chief complaint. While enrolment was independent of renal function, patients with terminal kidney failure on chronic dialysis were excluded. For this analysis, patients were also excluded if they did not have NT-proBNP plasma concentrations measured from study blood samples at ED presentation, if the final diagnosis remained unclear even after central adjudication, and if the patients were adjudicated

to have cardiac dyspnea due to acute coronary syndrome or arrhythmia without any other evidence for AHF. Two independent cardiologists/internists centrally adjudicated the final diagnosis using all individual patient's information including chest x-ray, natriuretic peptide, renal dysfunction (defined as estimated glomerular filtration rate <60 mL/min/1.73m² at presentation), echocardiography, pulmonary function test, and 90-day follow-up, in consistence with current guidelines.[1,2] Accordingly, in 1,633 (80%) patients the adjudication was performed blinded to NT-proBNP concentrations, in 420 (20%) patients NT-proBNP concentrations were part of extensive dataset available for the adjudication. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. All patients provided a written informed consent.

Specificity, positive predictive value (PPV), and the percentage of patients triaged towards rule-in were the primary outcome measures for the age-dependent NT-proBNP rule-in cut-off concentrations (450 pg/mL if <50 years, 900 pg/mL if 50-75 years, and 1,800 pg/mL if >75 years).[1,2,5–7] Sensitivity, negative predictive value (NPV), and the percentage of patients triaged towards rule-out were the primary outcome measures for the universal NT-proBNP rule-out cut-off concentration (300 pg/mL).[1,2,5–7] The relevant 95% confidence intervals (CIs) were defined by using the Wilson score method without continuity correction. Diagnostic accuracy of NT-proBNP plasma concentrations to diagnose AHF was quantified by using the area under the receiver operating characteristic curves (AUC). Comparison of AUC was performed as recommended by DeLong.

Among 2,053 patients eligible for analysis, 1,043 patients (51%) had an adjudicated diagnosis of AHF. For the rapid rule-in of AHF, the currently recommended age-dependent cut-off concentrations of NT-proBNP (450 pg/mL if <50 years old, 900 pg/mL if 50-75 years

old, and 1,800 pg/mL if >75 years old) achieved a specificity of 91% (95% CI, 87-95%), 84% (95% CI, 81-87%), and 81% (95% CI, 76-85%), a positive predictive value of 60% (95% CI, 45-73%), 79% (95% CI, 74-82%), and 90% (95% CI, 88-92%), allowing to rule-in AHF in 19%, 45%, and 62% of patients, respectively. For the rapid rule-out of AHF, the universal cut-off of 300 pg/mL achieved a sensitivity of 98% (95% CI, 97-99%), a negative predictive value of 97% (95% CI, 95-98%), and allowed to rule-out AHF in 29% of patients (Figure and Table). Compared to the clinical judgment in ED alone, its combination with NT-proBNP plasma concentrations showed significantly higher diagnostic accuracy as quantified by using the AUC (0.889 [95% CI, 0.863-0.915] vs. 0.935 [95% CI, 0.915-0.954], $p<0.001$).

Sensitivity analysis excluding the subgroup of patients in which among multiple other clinical variables also NT-proBNP plasma concentrations were available for the final adjudication revealed similar findings. Further separating the age-strata into patients with normal renal function versus renal dysfunction showed that the presence of renal dysfunction increased NT-proBNP plasma concentrations, reduced the specificity for AHF, while it tended to increase the sensitivity at the currently recommended NT-proBNP cut-off concentrations.

These findings extend and corroborate previous work on the best possible clinical use of natriuretic peptides in the early diagnosis of AHF.[1–3,5–7] **First**, natriuretic peptides should be interpreted as quantitative markers of hemodynamic cardiac stress and heart failure. **Low** concentrations provide a very high NPV for AHF and allow triaging patients towards rule-out. For patients presenting with acute dyspnea in the ED, concentrations below 300ng/L for NT-proBNP and below 100ng/L for BNP balance the safety and efficacy of rule-out well. **High** concentrations provide a high PPV for AHF and allow triaging patients towards rule-in.[6–8] **Second,** while patients with BNP or NT-proBNP plasma concentration in the 'grey zone' have a broad differential diagnosis and usually require full clinical work-up, most of them will finally be found to have mild heart failure.[8] **Third**, even in the presence of renal

dysfunction the utility of NT-proBNP in the rapid triage of dyspneic patients in the ED remains high.[5,6]

In conclusion, this large two-centre diagnostic study using central adjudication confirmed that currently recommended NT-proBNP cut-off concentrations perform well in the rapid diagnosis of AHF in elderly European patients with acute dyspnea in the ED.

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**Conflict of interest**

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**Figure legend**

**Figure.** NT-proBNP based diagnosis of AHF across the predefined age groups.
For AHF rapid rule-in, currently recommended NT-proBNP cut-off concentrations (450 pg/mL if <50, 900 pg/mL if 50-75, and 1,800 pg/mL if >75) achieved specificity of 91%, 84%, and 81%. For rapid rule-out, the universal cut-off concentration of 300 pg/mL achieved sensitivity of 98%.
AHF denotes acute heart failure; AUC denotes area under the curve; NT-proBNP denotes N-terminal pro-B-type natriuretic peptide; ROC denotes receiver operating characteristic.

**Table.** Optimal NT-proBNP cut-off concentrations for the diagnosis or exclusion of AHF among patients with acute dyspnea

| Category | Recommended cut-off concentration | Sensitivity, % (95% CI*) | Specificity, % (95% CI) | PPV, % (95% CI) | NPV, % (95% CI) | Accuracy, % (95% CI) |
|---|---|---|---|---|---|---|
| **Confirmatory ('rule-in') cut-off concentrations** | | | | | | |
| Rule-in, overall | | 84 (81-86) | 84 (82-87) | 85 (82-87) | 83 (81-85) | 84 (82-86) |
| <50 years old (n=224) | 450 pg/mL | 89 (73-96) | 91 (87-95) | 60 (45-73) | 98 (95-99) | 91 (87-94) |
| 50–75 years old (n=842) | 900 pg/mL | 88 (85-91) | 84 (81-87) | 79 (74-82) | 92 (89-94) | 86 (83-88) |
| >75 years old (n=987) | 1,800 pg/mL | 81 (78-84) | 81 (76-85) | 90 (88-92) | 66 (61-70) | 81 (78-83) |
| **Exclusionary ('rule-out') cut-off concentration** | | | | | | |
| All patients (n=2053) | 300 pg/mL | 98 (97-99) | 57 (54-60) | 70 (68-72) | 97 (95-98) | 78 (76-79) |

* The method used to calculate the confidence interval for a proportion is the Wilson score method without continuity correction.

AHF = acute heart failure; NPV = negative predictive value; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PPV = positive predictive value; CI = confidence interval