The 'Peptide for Life' Initiative: a call for action to provide equal access to the use of natriuretic peptides in the diagnosis of acute heart failure across Europe

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After the first proof of principle for B-type natriuretic peptide (BNP) as a diagnostic aid for acute heart failure (AHF) was reported by Davis *et al.* in 1994,[1] the Breathing Not Properly (BNP) study, published in 2002, ushered in a new era for natriuretic peptides (NPs) as companion biomarkers for the diagnosis of heart failure (HF).[2] More than just a clinical trial with novel and favourable results, it revolutionized a whole field and introduced biomarkers and the molecular phenotyping of the heart to algorithms in use for HF diagnosis and management. Ever since, the use of biomarkers to predict the onset of future HF, identify its presence when fully developed, and risk-stratify affected patients has gathered much attention and inspired a tsunami of studies. Indeed, the introduction of objective, non-invasive, biologically meaningful biomarkers into clinical assessment has considerably changed the way HF is diagnosed and monitored.[3]

The setting of AHF diagnosis is where the evidence for the use of NPs is most robust. Twenty years after the BNP study using BNP, with similar evidence reported for N-terminal proBNP (NT-proBNP), NPs have a central position in international guidelines for the diagnostic evaluation of AHF, and have been incorporated into the biomarker portfolios of a growing number of hospitals across Europe and the rest of the world.

Given the wealth of evidence, and the consensus in the HF community, one would assume that the use of NPs is widespread and that testing capacity is omnipresent. The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) recently published the first edition of the HFA Atlas. It provides a contemporary description of HF epidemiology, resources, and management, and of the activities of the National Heart Failure Societies (NHFS) in ESC member countries, which comprise a total population of over 800 million people.[4] The HFA Atlas identified a median of 3.58 hospitals offering NP measurement in the emergency department per million people. Remarkably however, none of the ESC countries reported access to NP testing in all its Emergency Departments. The highest numbers were reported in Germany (with 19.82 hospitals per million people with NPs used in emergency departments),

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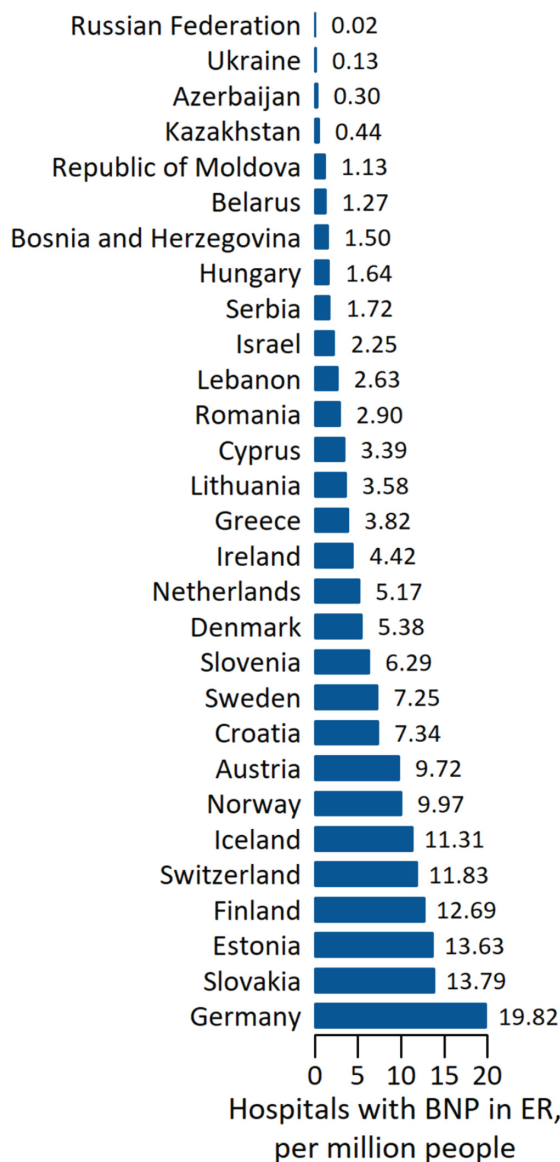
Figure 1 Hospitals with availability of natriuretic peptides [B-type natriuretic peptide (BNP) or N-terminal proBNP] in the emergency department per million people. Data not available: Belgium, Bulgaria, Czech Republic, Italy, Latvia, Poland, Portugal, Republic of Georgia, Spain, Turkey, United Kingdom. No resources: Kyrgyzstan, North Macedonia. ER, emergency room. Adapted from Seferović et al.[4]

Central Europe, and Scandinavia. The countries with lower use of NPs in emergency departments per million people were Kyrgyzstan and North Macedonia with none, followed by the Russian Federation (with 0.02 hospitals per million people using NPs in emergency departments), with similarly low numbers in other countries from the former Soviet Union and Southeast Europe (*Figure 1*).

In this viewpoint article, the biomarkers working group of the HFA discusses the scientific evidence that supports the use of NPs

to diagnose AHF in the emergency department, followed by the recommendations of international guidelines, and conclude with a call for action to increase awareness to promote equal access to NP analysis in HF diagnosis across Europe.

What does the science say?

The gene encoding NPs (NPPB) is constitutively expressed as a 'housekeeping' process; however, in normal healthy individuals production of its products is minimal. For example, among healthy individuals, BNP concentrations average ≤ 10 pg/mL; interestingly, while NT-proBNP concentrations are often much higher than BNP in the presence of prevalent HF, in healthy individuals NT-proBNP is often as very low as BNP. However, in conditions of myocardial stretch, the induction of the NPPB gene results in substantial production and secretion of prohormone proBNP$_{1-108}$. This is cleaved into the biologically active BNP$_{1-32}$ (usually referred to as BNP) and the biologically inert but biochemically more stable NT-proBNP$_{1-76}$ (usually referred to as NT-proBNP). Both fragments and the precursor, proBNP$_{1-108}$, are detected in the circulation.[5] The majority of studies regarding the use of B-type class peptides have focused on the measurement of either BNP or NT-proBNP.

The Breathing Not Properly study led by Maisel et al.[2] enrolled 1586 patients presenting to the emergency department with acute dyspnoea and evaluated the ability of BNP for diagnosis or exclusion of AHF. Investigators found that patients with clinically diagnosed AHF had higher BNP levels compared with those without AHF (mean 675 vs. 110 pg/mL, $P < 0.001$). BNP was the best single predictor of a final diagnosis of AHF compared with individual history, physical examination, chest x-ray, and laboratory findings. The area under the curve (AUC) for BNP in receiver operating characteristic curve testing was 0.91 for the diagnosis of AHF. A BNP cut-off value of 100 pg/mL had a sensitivity of 90% and a specificity of 76%. BNP was more accurate (83%) than either the National Health and Nutrition Examination Survey (NHANES) criteria (67%) or the Framingham criteria (73%), two established sets of criteria for HF diagnosis. Importantly, the best method of AHF diagnosis combined BNP and clinical findings.

NT-proBNP is cleared via different mechanisms and has a longer half-life than BNP (70 min vs. 20 min), but it is equivalent for the diagnostic evaluation of patients with suspected AHF, and likely more accurate in patients treated with neprilysin inhibitors (i.e. sacubitril/valsartan). The use of NT-proBNP in the diagnosis of AHF was first demonstrated by Lainchbury et al.,[6] and soon confirmed by Bayés-Genís et al.[7] and Januzzi et al.[8] Subsequently, the International Collaborative of NT-proBNP (ICON) study[9] examined optimal applications of NT-proBNP in 1256 acutely dyspnoeic patients. Patients with AHF had considerably higher NT-proBNP concentrations compared with those without AHF (mean 4639 vs. 108 pg/mL, $P < 0.001$), and symptom severity correlated with NT-proBNP concentrations ($P = 0.008$). Optimal negative and positive predictive values were obtained by use of an age-independent rule-out cut-off at 300 pg/mL and three age-stratified rule-in cut-off points (NT-proBNP ≥ 450 pg/mL for age < 50 years, ≥ 900 pg/mL
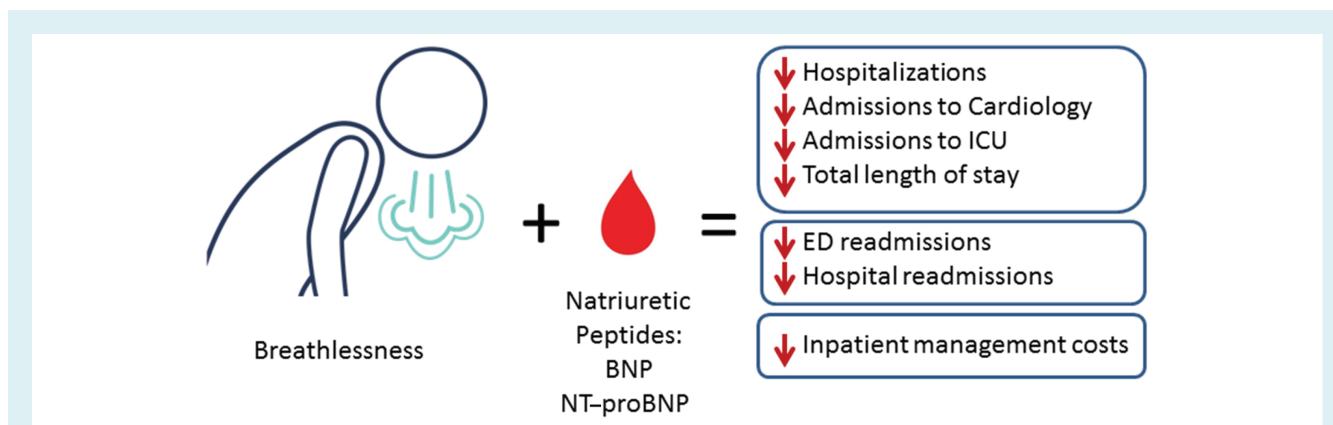
Figure 2 Incorporation of natriuretic peptides in the diagnosis of acute breathlessness results in clinical and economic benefit. BNP, B-type natriuretic peptide; ED, emergency department; ICU, intensive care unit; NT-proBNP, N-terminal pro B-type natriuretic peptide.

for age 50–75 years, and ≥1800 pg/mL for age >75 years.). These cut-offs remain equally useful in AHF across the full spectrum of left ventricular ejection fraction. More recently, the ICON RELOADED (ICON: Re-evaluation of Acute Diagnostic Cut-Offs in the Emergency Department)[10] and BASEL-V[11] studies validated the age-specific NT-proBNP cut-offs in contemporary cohorts. They found that the NT-proBNP-supported strategy led to 14.5% fewer initial hospitalizations, 16.0% fewer admissions to cardiology, 12.5% fewer admissions to intensive care units, 3.2% fewer emergency department readmissions, and 21.6% fewer hospital readmissions[12] (*Figure 2*).

It is of major importance to highlight that the use of NPs in this indication is also supported by randomized controlled trials documenting more rapid initiation of the appropriate therapy, more rapid discharge from the emergency department, and lower total treatment cost in the emergency department in the NP-guided group.[12–16]

What do the guidelines and the universal definition of heart failure say?

Natriuretic peptide testing aids in the diagnosis of AHF, and the use of these biomarkers is now embedded as a class I, level of evidence A, recommendation in the ESC and American College of Cardiology/American Heart Association (ACC/AHA) clinical practice guidelines.[17,18] A class IA indication is the highest recommendation in international guidelines.

The 2016 guidelines on HF from the ESC[17] state the following: 'Upon presentation to the emergency department or coronary care unit, a plasma NP level should be measured in all patients with acute dyspnoea and suspected AHF to help in the differentiation of AHF from non-cardiac causes of acute dyspnoea. NPs have high sensitivity, and normal levels in patients with suspected AHF makes the diagnosis unlikely'.

The 2017 focused update of the 2013 guidelines of the ACC/AHA[18] states the following: 'In emergency settings, NP

biomarker levels usually have higher sensitivity than specificity and may be more useful for ruling out than ruling in HF. Although lower values of NP biomarkers exclude the presence of HF, and higher values have reasonably high positive predictive value to diagnose HF, clinicians should be aware that elevated plasma levels for both NPs have been associated with a wide variety of cardiac and primarily non-cardiac causes'.

The recent publication of the universal definition of HF proposes the incorporation of an objective measurement (elevated NP levels and/or imaging or haemodynamic derangements) in addition to symptoms in the HF definition for making the diagnosis of HF more accessible to non-specialists and more reliable and consistent between observers, hospitals, and health care systems.[19]

A call for action

European Society of Cardiology member countries differ in their organization, delivery, and funding of health care, all of which ultimately lead to the uneven use of NP in the emergency department. With ample and consistent scientific evidence, and the highest recommendation by clinical guidelines, it is time to build strategies to help identify specific barriers to guideline implementation and to define actions to ensure that the majority of patients with acute dyspnoea have access to NP measurement in the emergency department. A timely and accurate diagnosis is crucial to enable early initiation of key lifesaving therapies. NPs should allow clinicians to choose the best diagnostic and treatment strategy more rapidly and to triage patients more confidently.

We present two additional pieces of evidence to support such a call for action initiative. First, the majority of patients are initially diagnosed with HF in the emergency department. An audit of the National Health Service in England showed that 80% of people diagnosed with HF receive the diagnosis following an acute hospital admission, despite half of them having had HF symptoms for up to 5 years before admission.[20] Second, the use of NPs has favourable effects not only on health outcomes, but also on costs. Contemporary data show that the use of NT-proBNP decreases

Figure 3 The 'Peptide for Life' Initiative logo.

average inpatient management costs by 10.3% and reduces the total length of stay in the emergency department and hospital[12] (*Figure 2*).

The use of BNP or NT-proBNP to aid in the diagnosis of acute HF in the emergency department saves lives, time and money.

It is the right time for HFA to launch the 'Peptide for Life' Initiative (*Figure 3*) coordinated by the ESC, the HFA, and the NHFS. The aim is to build confidence in biomarkers (with emphasis in NPs) as diagnostic tools in HF management in regions/countries where NP use in the emergency department is currently negligible. Country and site coordinators, in conjunction with the HFA and the NHFS will conduct educational activities and clinical case mentoring, with follow-up surveillance to identify good clinical practices.

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