



# NATIONAL LABORATORY HANDBOOK

## Laboratory Testing for Natriuretic Peptides (NP)-BNP / NT- proBNP

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## Scope

This guidance is intended to guide clinicians and clinical laboratories on the appropriate use, result interpretation, performance (diagnostic + analytical) and limitations of testing involving Natriuretic Peptides (NP), BNP or NT-proBNP, in adult non-pregnant patients.

## Key Recommendations for Clinical Users

- Measurement of either BNP or NT-proBNP is most useful to support the diagnosis of ambulatory and acute decompensated heart failure (HF), especially in the setting of clinical uncertainty.<sup>(1,2)</sup>
- NP levels should always be interpreted within the clinical context and should consider factors which either increase (age, gender [F>M] and other co-morbidities [e.g. renal function]) or decrease levels (obesity, drug therapy [diuretics, beta blockers, ACEi, ARNI etc]).<sup>(3,4)</sup>
- BNP/NT-proBNP is not a 'stand-alone' test – it is of greatest value when it complements clinical judgement along with other available diagnostic tools. Therefore, to confirm a diagnosis of HF, BNP or NT-proBNP values above their respective 'rule-out' thresholds should be correlated with clinical and imaging assessment and non-cardiac causes of increased NP levels excluded.<sup>(5)</sup>

## Key Recommendations for Laboratories

### Methods

- There is currently no difference in diagnostic and prognostic performance between BNP and NT-proBNP.<sup>(6,7,8)</sup>
- Provision of an NP assay by point-of-care testing (POCT) e.g. emergency department (ED) or out-patient clinic will depend primarily on whether or not the turnaround time of NP testing by the central laboratory is meeting clinical need. Where this is not met, NP measurement by POCT should be considered, not least in the out-patient setting where the number of follow-up visits may be reduced.<sup>(4)</sup> Numerous studies have

compared NP assays available at POCT to those on central laboratory analytical platforms where the majority have shown good correlation in terms of performance and clinical characteristics.<sup>(9,10,11)</sup> As for all NP use in Ireland, and especially for POCT testing, models of clinical governance and appropriate reimbursement should be implemented wherever such testing is offered.

- BNP and NT-proBNP test results are not interchangeable and they cannot be directly compared. They have different half-lives, different modes of degradation and critically, different decision cut-off values. <sup>(3,4)</sup>
- Laboratories should consult manufacturer's kit inserts for all information relating to test performance and limitations including cross-reactivities with non-analytes.

### **Internal Quality Control (IQC)**

Each Laboratory should implement an IQC programme for BNP or NT-proBNP, in accord with expert opinion including national recommendation.<sup>(14-16)</sup> There are no unique requirements for NP IQC procedures. Imprecision targets (total CV) <15% at relevant diagnostic threshold (see later) should be achievable. <sup>(17)</sup>

[In a survey of Irish Laboratories the current state of the art imprecision (CV, %) for BNP (Abbott Laboratories + Beckman Coulter) and NT-proBNP (Roche Diagnostics) assays was determined. Overall, the CVs obtained across the analytical range was 2.8 - 11.5 % and 2.2 – 8.0 % for NT-proBNP (50 - 5774 ng/L) and BNP (30 - 2185 ng/L) respectively, as assessed from routine analysis of IQC material (n = 600 - 790). (Micheál Ryan, personal communication, August 2017) ].

### **External Quality Assurance (EQA)**

Each laboratory should participate in an EQA scheme (programme) for BNP or NT-proBNP such as to assure the quality of testing; one which evaluates not only method and participant performance but also provides education, training and support to its participants.<sup>(18)</sup>

### **Reporting Units**

BNP and NT-proBNP assay results should be reported in 'conventional' units: ng/L (or pg/mL).<sup>(17)</sup>

## **Background & Epidemiology**

The prevalence of HF depends on the definition applied, but is approximately 1–2% of the adult population in developed countries, rising to ≥10% among people > 70 years of age. <sup>(19)</sup>

Numerous prognostic markers of death and/or HF hospitalization have been identified in patients with HF. However, their clinical applicability is limited and precise risk stratification in HF remains challenging. <sup>(1)</sup>

BNP is synthesised as a pre-hormone (proBNP) comprising 108 amino acids. Upon release into the circulation it is cleaved in equal proportions into the biologically active 32 amino acid BNP, which represents the C-terminal fragment, and the biologically inactive 76 amino acid N-terminal fragment (NT-proBNP). <sup>(20)</sup>

BNP has multiple cardiac functions and is released in response to a variety of cardiac stresses, most particularly cardiac stretch.

The severity of HF is usually classified into four classes defined by the New York Heart Association (NYHA) classification system. Plasma BNP and NT-proBNP concentrations are elevated in patients with HF in line with the NYHA class. <sup>(4)</sup>

NP testing is used currently in the differential diagnosis of dyspnoea, screening for asymptomatic left ventricular dysfunction, risk stratification/prognostication and treatment monitoring in selected patients with HF. <sup>(4)</sup>

## Testing

### Who to Test

Testing for BNP or NT-proBNP may have clinical value in the following circumstances:

1. Differential diagnosis of dyspnoea where NPs are important adjuncts to clinical assessment, ECG, chest X-ray and echocardiography in patients of suspected HF:

*Acute (emergency department): BNP or NT-proBNP testing improves diagnostic accuracy in patients presenting to the emergency department (ED) with dyspnoea.* <sup>(3)</sup>

[In the Breathing Not Properly (BNP) Multinational Study, B-type natriuretic peptide levels by themselves were more accurate than any other finding in the history, physical finding, or laboratory value in delineating the cause of dyspnoea – B-type natriuretic peptide performed better than either the NHANES or Framingham criteria for diagnosis of congestive HF]. <sup>(21)</sup>

[A single measurement of serum NPs (BNP or NT-proBNP) is recommended to ‘rule out’ diagnosis in patients presenting with new suspected acute HF]. <sup>(22)</sup>

[BNP or NT-proBNP levels may guide the intensity of ED treatment, aid in the decision to admit or not admit a patient to the hospital, and clarify the urgency of post-discharge follow-up]. <sup>(3)</sup>

*Non-Acute (out-patient, primary care): BNP or NT-proBNP can be used as an initial diagnostic test in the non-acute setting when echocardiography is not immediately available.* <sup>(13)</sup>

Elevated natriuretic peptides help establish an initial working diagnosis, identifying those who require further cardiac investigation; patients with values below the cut-point <sup>(a)</sup> for the exclusion of important cardiac dysfunction do not require echocardiography. <sup>(19)</sup>

<sup>(a)</sup> See Decision Cut-off Values, Algorithm for Testing & Confounding Factors.

2. Risk stratification and prognosis (in-patients): BNP or NT-proBNP should be measured routinely at the time of admission and prior to discharge when optimolaemic (dry/baseline) status is achieved.

[This baseline BNP or NT-proBNP level is likely to be most important in monitoring the patient in the first thirty days after discharge]. <sup>(3)</sup>

3. Natriuretic peptide-driven collaborative care in a population at high risk of heart failure (e.g. post MI, diabetes, poorly controlled hypertension).

[In the Irish based STOP-HF Randomized Trial, BNP-based screening and collaborative care among selected patients at high risk of HF resulted in a reduction in the combined rates of left ventricular systolic dysfunction, diastolic dysfunction and HF].<sup>(27)</sup>

### Who not to test

BNP or NT-proBNP testing is not recommended in the following patient cohorts:

1. Patients with classic signs of acute decompensated HF (i.e. prior episodes of ADHF, volume overload, dyspnoea and orthopnoea)<sup>(28)</sup> or those with shortness of breath consistent with other aetiologies (i.e. asthma, COPD), BNP is not likely to assist in the diagnostic workup.<sup>(27)</sup>

2. Screening for asymptomatic ventricular dysfunction in a low risk population. [In a low risk population, lower pre-test probability renders BNP and NT-proBNP sub-optimal for screening purposes].<sup>(28)</sup>

3. Monitoring treatment for HF. In general, NPs should not be used to monitor or guide treatment. However for specific patients where monitoring NPs may have value (e.g. <75 years), clinicians should consider the large biological variability when interpreting result changes. For any monitoring of patients on ARNIs, we recommend NT-proBNP. Any such monitoring decisions should be through cardiology consultation.

[For patients >75 years, NP-guided therapy may not be better than symptom-guided therapy<sup>(25)</sup>].

[The BATTLESCARRED study concluded that NT-proBNP-guided treatment was associated with a lower mortality rate (and hospitalization rate) at 3 years compared with either intensive clinical management or usual care for patients <75 years of age].<sup>(24)</sup>

[Biologic variability must be considered on the occasion where NPs are measured serially for monitoring and titrating HF treatments. From a study of Irish subjects, it was concluded that changes of approximately 50% and 66% for NT-proBNP and BNP, respectively, are needed to indicate an altered clinical status in stable HF patients<sup>(26)</sup>].

[Use of the angiotensin receptor and neprilysin inhibitor (ARNI) Entresto, is reported to cause a modest initial increase in BNP (median BNP: 200 to 250 ng/L) but not NT-proBNP which decreases rapidly during this period. However the magnitude of any such effect of ARNIs on BNP measurement across different BNP assays is currently unknown. Whilst any BNP increase might itself suggest compliance and/or response to treatment, baseline values after one month of treatment should be obtained, whenever monitoring is considered appropriate. Dual use of BNP and NT-proBNP (and with a BNP:NT-proBNP ratio) have been proposed when using ARNIs, to concomitantly monitor progression of HF and provide a comprehensive biological and clinical picture.<sup>(1,12,13)</sup> However, until such information is available including data from prospective randomised studies involving ARNIs, we currently recommend NT-proBNP measurements (only) in such patients.

### Who to Re-Test

Repeat NP testing is not indicated in the vast majority of inpatients with HF<sup>(3)</sup> and should be measured once, with the following exceptions:

1. Primary Care – there is a repeat episode of suspected HF with a change in clinical presentation and the diagnosis of HF has been excluded previously.<sup>(29)</sup>

2. Secondary Care (per acute episode) – unless there is clinical deterioration or failure to respond to therapy. It is reasonable to expect such requests to be discussed and justified.

3 Pre-discharge in specified cases (e.g. potential transplant candidates) when the question of prognosis might be of clinical importance, or where the result may impact on follow-up arrangements.

[Pre-discharge repeat measurement has prognostic significance but has not been shown to alter outcome].<sup>(30)</sup>

## Specimen and Ordering Information

All requests (electronic and paper) and specimens must adhere to the laboratories standard requirements and contain all necessary demographics and should provide the indication for testing and relevant clinical information including date and time of venepuncture, to enable accurate result interpretation. In order to comply with accreditation standards (ISO: 15189:2012), laboratories cannot accept or process samples which do not meet their defined minimum standards.

### Specimen pre-requisites for each test are given below:

BNP: EDTA plasma or whole blood (POCT) is the recommended sample type.

[Time between venepuncture and analysis should be minimized particularly for BNP, which shows concentration decreases (mean) of 10% (range: 6-12%) after storage of whole blood for 4 hours (room temperature). After 8 hours under the same conditions, the average decrease is 12% (9-15%) and thereby creating greater potential to confound analysis and generate false negative results. At 4°C, decreases of 5% and 12% are reported for 4 and 8 hours storage, respectively].<sup>(31)</sup>

NT-proBNP: Either serum or heparin/EDTA plasma and whole blood (POCT) can be used.

[By comparison to BNP, NT-proBNP is more stable, for at least 24 hours storage at room temperature. If resource exists to offer NP analysis to primary care, NT-pro-BNP is the preferred laboratory-based test particularly where pre-analytical delays may be longer (>4h) and unavoidable].<sup>(32)</sup>

Laboratories should consult manufacturer's product specification sheets for their specific BNP/NT-proBNP assay to obtain further information related to sample handling and stability studies.

## Decision Cut-off Values, Algorithm for Testing & Confounding Factors

The following tables provide the decision thresholds/cut-off values for BNP and NT-proBNP for 'ruling-out' HF.<sup>(19,22)</sup>

	<sup>1</sup> BNP cut-off	NT- proBNP cut-off
Non-Acute Setting	< 35 pg/mL	< 125 pg/mL
Acute Setting	< 100 pg/mL	< 300 pg/mL

<sup>1</sup> The National Institute for Health and Care Excellence (NICE) state that BNP < 100 pg/mL or NTproBNP < 400 pg/mL in an untreated patient make heart failure unlikely. Above these levels,

serum NPs carry poorer prognosis and can be used to guide the selection of patients for transthoracic Doppler 2D echocardiography (ECHO).<sup>(22, 33,34,35)</sup> Elsewhere<sup>(19,22,44)</sup>, a lower threshold (<300 pg/mL) is advocated and shown to improve diagnostic sensitivity.<sup>(44)</sup>

[In the Breathing Not Properly study involving patients presenting to ED with acute dyspnoea, a BNP cut-off of 100 pg/mL gave the highest sensitivity (90%) and specificity (73%). This study involved the Triage BNP test (Biosite Inc.).<sup>(2)</sup> Despite methodological differences and bias observed amongst BNP assays, there is comparable ability across BNP (and NT-proBNP) assays to exclude HF (sensitivity, BNP: 95% [95% CI 93-96], NT-proBNP: 99% [95% CI 96-100] using the above cut-offs however specificity is variable).<sup>(5)</sup>

### Rule in cut-offs <sup>(36)</sup>

<b>BNP &gt;500</b>	<b>All Ages</b>
<sup>1</sup> NT-proBNP:	Age (yrs)
>450 pg/mL	<50
>900 pg/mL	50 – 75
>1800 pg/mL	>75

<sup>1</sup>At the time of guideline preparation age related thresholds for HF were quoted with the Alere NT-proBNP for Architect assay for patients <75 years (>125 pg/mL) and ≥75 years (>450 pg/mL) respectively.

Defining “rule in” cut-offs for HF is complicated because multiple factors, including age, gender (F>M) and medications influence NP levels (see table below). However, their overall impact is less significant compared with comorbidities such as cardiac, pulmonary and renal disease which are likely to increase NP levels above current thresholds for HF.<sup>(1)</sup>

[The International Collaborative of NT-proBNP (ICON) study concluded that for diagnosis of HF (“ruling in”), age-dependent cut-points improve the positive predictive value (PPV)].<sup>(37)</sup>

<b>Factors affecting NP levels</b>
*Age (↑)
Gender (F>M)
High sodium diet (↑)
Exercise prior to sampling (↑)
Obesity (↓)
Drugs [Diuretics, ACEi, ARBs, Aldosterone Receptor Antagonists, Beta Blockers] (↓)

\*Not for all assays. Where observed, effect is greater for BNP vs NT-proBNP in HF patients (*vice versa* for healthy individuals), though effect of age (and gender) is modest compared to other factors in HF patients.<sup>(38)</sup>

Lower thresholds should be used to diagnose HF in obese patients.<sup>(39)</sup> [There is an inverse relationship between obesity and circulating NPs].

### Interpreting serial BNP measurements

The large biological variation for NPs must be considered when interpreting serial NP measurements.<sup>(26,40)</sup> [See above section on Who Not to Test: “Monitoring Treatment for HF”.]

Across healthcare regions in Ireland, NP testing has become available to hospital clinicians and in some cases to GPs however audit of its use as a biomarker to rule out HF show a lack of compliance and inappropriate result interpretation by clinical users.<sup>(41)</sup>



Where NPs are available in the non-acute setting and are elevated, full investigation of precipitating factors and/or alternative diagnoses (e.g. ACS, PE) may be precluded where diagnostic tests for such conditions are not routinely available (e.g. troponin, d-dimers). The use of NPs in this setting is therefore largely limited to ruling out HF, assessing the need for ECHO where NPs are raised and stratified testing as part of collaborative in patients at high risk of HF. Patients with suspected acute HF should therefore be referred immediately for acute care and management.

Algorithms involving the use of NPs in the diagnosis of HF is reported in a number of published guidelines <sup>(1,2,13,16)</sup> from which we have extracted and synthesised into the following algorithm, encompassing the above diagnostic considerations, to guide appropriate use and interpretation of NPs in the investigation of patients presenting with suspected acute HF.

**Patient with suspected HF (typical symptoms):**  
 Assess pre-test probability of HF and exclude non-cardiac cause of dyspnoea by:  
**\*Clinical Evaluation + Diagnostic Investigations**

*Typical + specific signs and symptoms which may increase likelihood of HF (see also Table 1):*

**Clinical Hx**  
 Hx CAD or arterial HTN, diuretics, breathlessness, orthopnoea/paroxysmal nocturnal dyspnoea

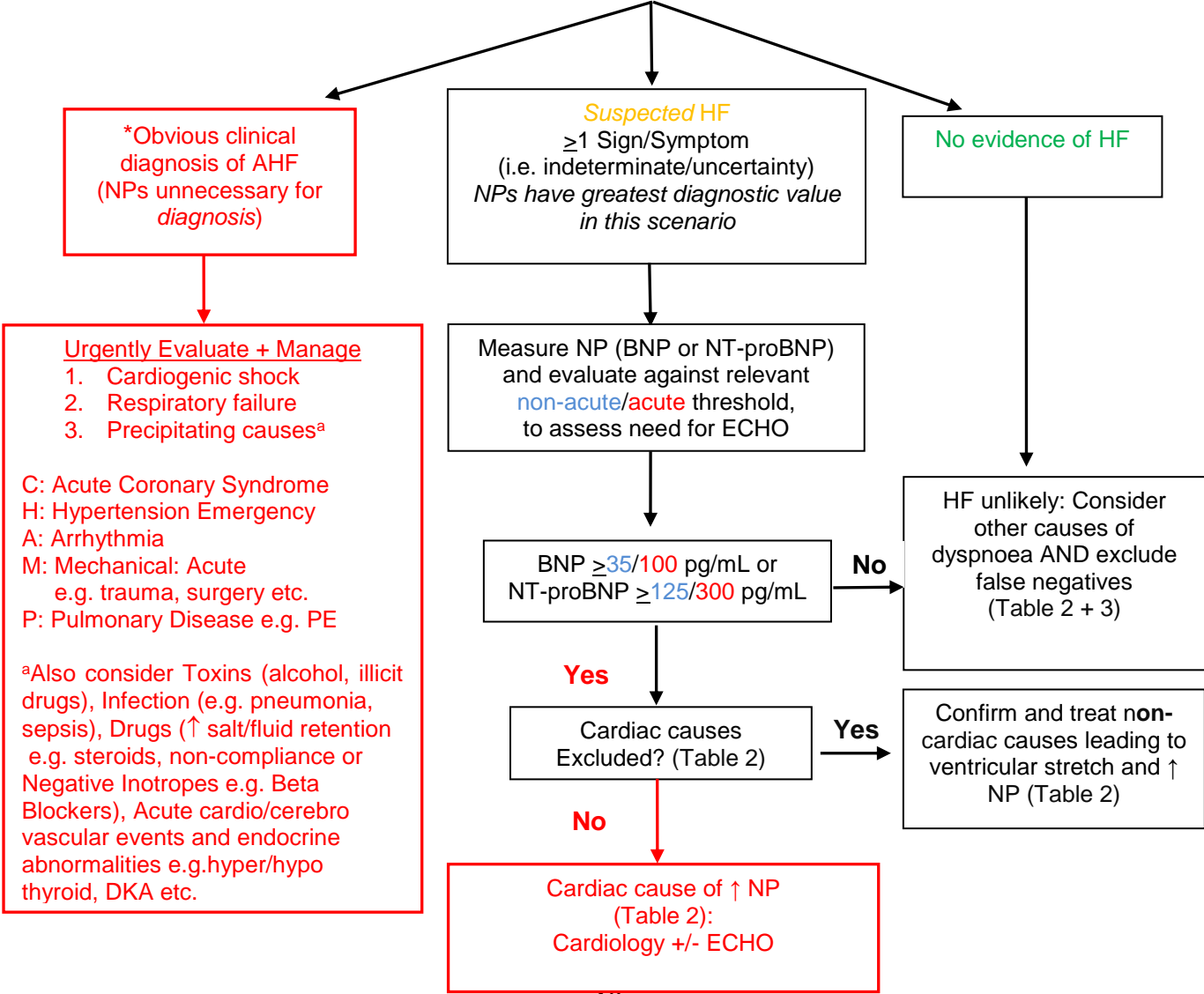
**Physical Exam**  
 Creps, bilateral ankle oedema, jugular venous dilatation, laterally displaced/broadened apical beat, Heart murmur

**ECG**  
 Any abnormality

**Biochemical:**  
 U+E  
 LFT  
 TFT  
 Troponin  
 Ferritin + TSat  
 Glucose  
 Lipids

**Haematology:**  
 FBC

**Radiology:**  
 D-Dimer (if ?acute PE)  
 X-ray



**Table 1: Signs and Symptoms typical of HF (Ref. 13).**

Symptoms	Signs
<i>Typical</i>	<i>More Specific</i>
Breathlessness	Elevated jugular venous pressure
Orthopnoea	Hepatojugular reflux
Paroxysmal nocturnal dyspnoea	Third heart sound (gallop rhythm)
Reduced exercise tolerance	Laterally displaced apical impulse
Fatigue, tiredness, increased time to recover post-exercise	
Ankle swelling	
<i>Less Typical</i>	<i>Less Specific</i>
Nocturnal cough	Weight gain (>2kg/week)
Wheezing	Weight Loss (advanced HF)
Bloating feeling	Tissue wasting (cachexia)
Loss of appetite	Cardiac murmur
Confusion (especially in elderly)	Peripheral oedema (ankle, sacral, scrotal)
Depression	Pulmonary crepitations
Palpitations	Reduced air entry and dullness to percussion at lung bases (pleural effusion)
Dizziness	
Syncope	Tachycardia
Bendopnea	Irregular pulse
	Tachypnoea
	Cheyne Strokes respiration
	Hepatomegaly
	Ascites
	Cold extremities
	Oliguria
	Narrow pulse pressure

**COLD**

**WET**

**HYPOPERFUSION (+)**

Cold sweat extremities
Oliguria
Mental confusion
Dizziness
Narrow pulse pressure

**CONGESTION (+)**

Pulmonary congestion
Orthopnoea/paroxysmal nocturnal dyspnoea
Peripheral (bilateral) oedema
Jugular venous dilatation
Congested hepatomegaly
Gut congestion, ascites
Hepatojugular reflux

**Note:** Patients most commonly present Warm + Wet (Well perfused + Congested). Reduced cardiac output with peripheral hypoperfusion (Cold) occurs less often.

**Note:** Likelihood of HF increased in patients with abnormal ECG and/or previous AMI.

**Note:** A normal ECG has a high Negative Predictive Value and is rarely normal in AHF

**Note:** Increased JVP + displacement of apical impulse are harder to detect and lack reproducibility.

**Note:** Above signs and symptoms are difficult to ID in obese, elderly and patients with chronic lung disease.

**Table 2: Cardiac and Non-cardiac causes of elevated natriuretic peptides (Ref. 13)**

<b>Cardiac</b>	Heart Failure
	Acute Coronary Syndromes
	Myocarditis
	Left Ventricular Hypertrophy
	Hypertrophic or restrictive cardiomyopathy
	Valvular heart disease
	Congenital heart disease
	Arterial and ventricular tachyarrhythmias
	Heart contusion
	Cardioversion, ICD shock
	Surgical procedures involving the heart
	Pulmonary hypertension
<b>Non-cardiac</b>	Advanced age
	Ischaemic stroke
	Subarachnoid haemorrhage
	Renal dysfunction
	Liver dysfunction (mainly liver cirrhosis with ascites)
	Paraneoplastic syndrome
	Chronic obstructive pulmonary disease
	Severe infections (including pneumonia and sepsis)
	Severe burns
	Anaemia
	Severe metabolic and hormone abnormalities

**Table 3: Causes of Falsely Low Natriuretic Peptides**

<b>False negative: Low B-type natriuretic peptide with heart failure</b>
Failure to adjust cut-off values for:
Age
Gender
Flash pulmonary oedema
Acute mitral regurgitation
Mitral stenosis
Atrial myxoma
Fully treated low-grade heart failure

**Note:** Low BNP may also be seen in patients with obesity, right-sided AHF or decompensated end-stage HF.

## Recommendations for National Laboratory Information System (MedLIS)

An order entry form has been developed to facilitate test ordering in line with this national guideline, agreed with the National Clinical Programme for Heart Failure as follows:

**Order Entry form for GPs:** Clinical details field – mandatory free text field.

Indication for testing – drop down menu:

- Possible new HF
- Deterioration ?cause
- Discussed with Lab.

**Order entry form for in-patients:** Clinical details field – mandatory free text field.

Indication for testing – drop down menu:

- Cardiac Admission
- Discharge
- Other (specify).

### Heart Failure Annual Review Care Set:

FBC – ticked

U&E – ticked

BNP or NT-proBNP – unticked.

Rule to be built: If care set ordered within the last 11 months pop-up to state “This care set cannot be ordered within 11 months of previous annual review”.

A suite of interpretive comments will be developed with the National Clinical Programme for Heart Failure.

## Information for Patients

There is no special patient preparation required prior to blood testing for BNP or NT-proBNP. NPs are not affected by posture or circadian rhythm and therefore timing of appointments for venepuncture is not as important as it might be for other tests e.g. testosterone. <sup>(42,43)</sup>

BNP or NT-proBNP testing assists the general practitioner or hospital physician to diagnose, monitor and risk stratify patients with either known or suspected HF.

BNP or NT-proBNP may be used along with a chest x-ray, ECG, and Doppler echocardiography in the clinical assessment for suspected HF both in outpatient and in the emergency care settings.

## Guideline Development Methodology - Consultation Plan and History

The guideline was drafted by the authors, followed by expert consultation with the National Clinical Programme for Heart Failure. Following incorporation of feedback the guideline was submitted to the full National Clinical Programme for Pathology consultation process.

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## References

1. A Scientific Statement from the American Heart Association (2017). Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure. *Circulation*. 135:1054–1091.
2. McCullough PA. et al. (2002). B-Type Natriuretic Peptide and Clinical Judgement in Emergency Diagnosis of Heart Failure: Analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation*. 106:416-422.
3. Maisel AS. et al. (2008). State of the art: Using natriuretic peptide levels in clinical practice. *European Journal of Heart Failure*. 10:824-839.
4. Cowie M.R. et al. (2003). Clinical applications of B-type natriuretic peptide (BNP) testing. *European Heart Journal*. 24: 1710 – 1718.
5. Roberts E. et al. (2015). The diagnostic accuracy of the natriuretic peptides on heart failure: systematic review and diagnostic meta-analysis in the acute care setting. *BMJ*. 350:h910.
6. Pfister R. et al. (2004) Use of NT-proBNP in routine testing and comparison to BNP. *The European Journal of Heart Failure*. 6:289–293.
7. Richards M. et al. (2006) Comparison of B-Type Natriuretic Peptides for Assessment of Cardiac Function and Prognosis in Stable Ischemic Heart Disease. *Journal of the American College of Cardiology*. 47 (1): 52-60.
8. Mant J. et al. (2009) Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. *Health Technology Assessment*. 13(32):1-207.
9. Shah K. et al. (2010) Comparability of Results between Point-of-Care and Automated Instruments to Measure B-type Natriuretic Peptide. *Western Journal of Emergency Medicine*. 11(1):44-8.
10. Zaphiriou A. (2005).The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: Results of the UK natriuretic peptide study. *The European Journal of Heart Failure*. 7:537-541.
11. Lee-Lewandrowski E. et al. (2007) Multi-center validation of the Response Biomedical Corporation RAMP® NT-proBNP assay with comparison to the Roche Diagnostics GmbH Elecsys® proBNP assay. *Clinica Chimica Acta*. 386:20-24.

12. Lippi G. Sanchis-Gomar F. (2016) Monitoring B-type natriuretic peptide in patients undergoing therapy with neprilysin inhibitors. An emerging challenge? *Internal Journal of Cardiology*. 219; 111-4.
13. Semenov AG., Katrukha AG. (2016) Analytical Issues with Natriuretic Peptides – has this been Overly Simplified. *The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine*. 27(3):189 – 207.
14. Joint Working Group on Irish Laboratory Accreditation (JWG ILA) Sub-group on IQC Procedures. (2016) *Internal Quality Control Survey – Results and Recommendations*.
15. Lee G.R. Fitzgibbon M.C. O'Shea P. (2016) “In Control? IQC consensus and statutory regulation”. *International Journal of Health Care Quality Assurance*. 29 (5):492-506.
16. Lee G.R. Fitzgibbon M.C. O'Shea P. (2016) “Laboratory services: regaining and maintaining control”. *International Journal of Health Care Quality Assurance*. 29 (5):507-522.
17. Apple F. et al. (2007) National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage Laboratory Medicine Practice Guidelines: Analytical Issues for Biomarkers of Heart Failure. *Circulation*. 116: e95-e98.
18. James, D. et al., 2014. External quality assessment: best practice. *Journal of clinical pathology*, 67(8), pp.651–5.
19. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *European Heart Journal*. 37: 2129–2200.
20. Tietz NW. Burtis CA. Ashwood ER. Bruns DE. (2006) *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*. 4<sup>th</sup> Edition.
21. Maisel AS. et al. (2002). Rapid Measurement of B-type Natriuretic Peptide in the Emergency Diagnosis of Heart Failure. *The New England Journal of Medicine*. 347(3):161-167.
22. National Institute for Health and Care Excellence Clinical Guideline 187. (2014) Acute heart failure. Diagnosing and managing acute heart failure in adults. [www.nice.org.uk/guidance/cg187](http://www.nice.org.uk/guidance/cg187)
23. Januzzi JL. Troughton R. (2013). Serial Natriuretic Peptide Measurements are Useful in Heart Failure Management. *Circulation*. 127:500-508.
24. Lainchbury JG. et al. (2010) N-Terminal Pro-B-Type Natriuretic Peptide-Guided Treatment for Chronic Heart Failure - Results From the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) Trial. *Journal of the American College of Cardiology*. 55 (1): 53-60.
25. Maisel AS. (2010) Natriuretic Peptide-Guided Therapy for Heart Failure - Ready for “Battle” or Too “Scarred” by the Challenges of Trial Design? *Journal of the American College of Cardiology*. 55 (1): 61-64.
26. O'Hanlon R. et al (2007). The biologic variability of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide in stable heart failure patients. *Journal of Cardiac Failure*. 13(1):50-55.

27. Ledwidge M. et al. (2013) Natriuretic Peptide-Based Screening and Collaborative Care for Heart Failure. The STOP-HF Randomized Trial. The Journal of the American Medical Association (JAMA). 310(1):66-74.
28. Kosowsky JM. Chan JL. (2006). Acutely Decompensated Heart Failure: Diagnostic and Therapeutic Strategies. Emergency Medicine Practice. 8(12).
29. Redfield MM. et al. (2004). Plasma brain natriuretic peptide to detect pre-clinical ventricular systolic or diastolic dysfunction: a community-based study. Circulation. 109: 3176-3181.
30. Lang T. (2013) National Minimum Re-testing Interval Project: A final report detailing consensus recommendations for minimum re-testing intervals for use in Clinical Biochemistry Prepared for the Clinical Practice Group of the Association for Clinical Biochemistry and Laboratory Medicine and supported by the Royal College of Pathologists.
31. Gruson et al. (2006). Influence of Sampling and Storage Conditions on B-Type Natriuretic Peptide Immunoreactivity for 3 Automated Assays Clinical Chemistry 52(4):766-767.
32. Barnes SC et al., Evaluation of N-terminal pro-B type natriuretic peptide analysis on the Elecsys™ 1010 and 2010 analysers. Ann Clin Biochem; 41: 459–463.
33. National Institute for Health and Care Excellence Clinical Guideline 108. (2010) Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. [www.nice.org.uk/guidance/cg108](http://www.nice.org.uk/guidance/cg108)
34. National Institute for Health and Care Excellence Clinical Guideline 108. (2010) Chronic heart failure: management of chronic heart failure in adults in primary and secondary care. Quick reference guide. [www.nice.org.uk/guidance/cg108](http://www.nice.org.uk/guidance/cg108)
35. National Institute for Health and Care Excellence Guideline 106. (2018) Chronic heart failure in adults: diagnosis and management. [www.nice.org.uk/guidance/ng106](http://www.nice.org.uk/guidance/ng106)
36. Moe GW et al. (2015) The 2014 Canadian Cardiovascular Society Heart Failure Management Guidelines Focus Update: anaemia, biomarkers, and recent therapeutic trial implications. Canadian Journal of Cardiology. 31(1): 3-16.
37. Januzzi JL et al. (2006). NT-proBNP testing for diagnosis and short-term prognosis in acute destabilised heart failure: an international pooled analysis of 1,256 patients: the International Collaborative of NT-proBNP Study. European Heart Journal. 27:330-337.
38. Hogenhuisa et al (2005). Influence of age on natriuretic peptides in patients with chronic heart failure: a comparison between ANP/NT-ANP and BNP/NT-proBNP. The European Journal of Heart Failure 7;2005: 81– 86.
39. Madamanchia C. (2014) Obesity and Natriuretic Peptides, BNP and NT-proBNP: Mechanisms and Diagnostic Implications for Heart Failure. Internal Journal of Cardiology. 176(3): 611–617.
40. Rehman S.U. Januzzi JL Jr. (2008) Natriuretic Peptide Testing in Primary Care. Current Cardiology Reviews. 4 (4):300-308.
41. McKillop D, Brennan P, Sharpe P (2013). NT-proBNP audit to determine compliance with assay use as a “rule out” marker for Heart Failure under current working guidelines. Annals Clin Biochem; 50 (Suppl. 1).

42. Sagnella GA (2001). Measurement and importance of plasma brain natriuretic peptide and related Ann Clin Biochem; 38: 83-93.
43. Penney MD (2005). Natriuretic peptides and the heart: current and future implications for clinical biochemistry. Ann Clin Biochem; 42: 432-440.
44. Verdú *et al* (2012). Rapid Point-of-Care NT-proBNP Optimal Cut-off Point for Heart Failure Diagnosis in Primary Care. Rev Esp Cardiol;65(7):613–619.



## Appendix: Quick Reference Card

- Testing for Natriuretic Peptides (NPs) involves the analysis of either BNP (EDTA plasma) or NT-proBNP (serum or plasma), by the central laboratory or through point of care testing (POCT, whole blood). NPs are most useful in supporting the diagnosis of ambulatory and acute decompensated heart failure (HF), especially in the setting of clinical uncertainty.
- There is currently no difference in diagnostic and prognostic performance between BNP and NT-proBNP. Central laboratory and POCT testing show comparable performance.
- BNP and NT-proBNP test results are not interchangeable and cannot be directly compared.

### Indications for NP testing:

- Differential diagnosis of dyspnoea in patients of suspected HF, especially when echocardiography is not immediately available. NPs should be used and interpreted along with clinical assessment (including confounding factors), ECG, chest X-ray and echocardiography. A single measurement is adequate for 'rule out'.
- Risk stratification and prognosis (in-patients), on admission + prior to discharge.
- Screening for HF in high risk populations (e.g. post MI, diabetes, hypertension).

These indications are in line with the National Heart Failure Programme:

<b>NP testing in Primary Care:</b>
>Possible new onset of HF (Diagnostic aid)
>Patient deteriorating where HF is part of the differential (unless clear clinical cardiac or respiratory cause)
<b>NP testing in the Hospital setting:</b>
>Emergency admission with breathlessness, likely of cardiac origin (Diagnostic+Prognostic value)
>At discharge following treatment for HF (Prognostic value)
>Deterioration or failure to respond to treatment during admission (Justification required)

### Circumstances where NP testing is not recommended:

- Patients with classic signs of acute decompensated HF or those with shortness of breath consistent with other aetiologies.
- Screening for asymptomatic ventricular dysfunction.
- Widespread monitoring of treatment for HF.
- Daily monitoring of NP is inappropriate.

*Refer to the full guideline for Decision Thresholds and Algorithm for guiding appropriate Use and Interpretation of NPs in the Investigation of patients presenting with suspected HF.*