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.[1,2]

- 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].[3,4]

- 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.[5]

- Repeat NP testing is not indicated in the vast majority of in-patients with HF[3] and should be measured once, except for specific indications including clinical deterioration.

Key recommendations for Laboratories

Methods

- There is currently no difference in diagnostic and prognostic performance between BNP and NT-proBNP.[6,7,8]

- Provision of an NP assay by Near Patient Testing (NPT) 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 NPT should be considered, not least in the out-patient setting where the number of follow-up visits may be reduced.[4]. However NPT is only an option where requisite governance, implementation and regulatory frameworks exist to ensure safe and effective NPT. [50]. Numerous studies have compared NP assays available at NPT to those on central laboratory analytical platforms where the majority have shown good correlation in terms of performance and clinical characteristics.[5, 9,10,11]. There is a relative paucity of studies involving NP testing by NPT in primary care (especially for NT-proBNP), with variable diagnostic accuracy especially where prevalence of CHF is low. [51].

- As for all NP use in Ireland, and especially for NPT, 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.[3'4]. NT-proBNP testing is currently available to several commercial diagnostic providers, which affords opportunity for more widespread testing, regardless of the laboratory's diagnostic instrumentation, and greater result comparability across laboratories. This is less achievable with BNP, since standardisation is lacking across BNP manufacturers.

- Laboratories should consult manufacturer's kit inserts for all information relating to test performance and limitations including cross-reactivities with non-analyte.

Internal Quality Control (IQC)

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

[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 must 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.[18]

Reporting Units
BNP and NT-proBNP assay results should be reported in 'conventional' units: ng/L (or pg/mL).[17]

Background & Epidemiology

The prevalence of heart failure (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.[19]

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.[1]

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).[20]

BNP has multiple cardiac functions and is released in response to a variety of cardiac stresses but, 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.[4]

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.[4]

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 [ED}): BNP or NT–proBNP testing improves diagnostic accuracy in patients presenting to the ED with dyspnoea.[3]

[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].[21]

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

[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].[3]

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. *(13)*

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

[a]See Decision Cut-off Values, Algorithm for Testing & Confounding Factors (Appendix 2).

2. Risk stratification and prognosis (In-patients, Acute HF): BNP or NT-proBNP should be measured prior to discharge when optivolaemic (dry/baseline) status is achieved.

[This optivolaemic BNP or NT-proBNP level is likely to be most important in monitoring the patient in the first thirty days after discharge].[3]

3. Natriuretic peptide-driven collaborative care in a population at high risk of heart failure (e.g. post MI, diabetes, poorly controlled hypertension).
As clinically indicated and where laboratory resource permits, NT-proBNP may be used in primary care as part of the Integrated Model of Structured Chronic Disease Prevention and Management[45], for opportunistic case finding, disease prevention strategies for high risk patients e.g. ischaemic heart disease, diabetes, atrial fibrillation within the context of the structured treatment programme.

[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].[27]

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)[28] or those with shortness of breath consistent with other aetiologies (i.e. asthma, COPD), BNP is not likely to assist in the diagnostic workup.[27]

2. Screening for asymptomatic ventricular dysfunction in a low risk population.
[In a low risk population, lower pre-test probabilities render BNP and NT-proBNP sub-optimal for screening purposes].[28]

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 [25]].

[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].[24]

[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 [26]].

[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.[1,12,13] 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[3] and should be measured once. Re-testing may however be appropriate in the following circumstances:

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 [29] including patients with chronic disease (e.g. HF, DM, AFib, IHD) showing clinical deterioration.

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 once ovtivolaemic and in other 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][30]

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 (NPT) is the recommended sample type. Specimens for central laboratory testing should be referred within 4 hours to minimise analyte deterioration.

[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 4ºC, decreases of 5% and 12% are reported for 4 and 8 hours storage, respectively].[31]

NT-proBNP: Either serum or heparin/EDTA plasma and whole blood (NPT) can be used
[By comparison to BNP, NT-proBNP is more stable, for at least 24 hours storage at room temperature**.** NT-proBNP is the preferred laboratory-based test for primary care users, particularly where pre-analytical delays may be longer (>4h) and unavoidable and which would render BNP unsuitable].[32]

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, Upper Reference Limits, Algorithm for Testing & Confounding Factors

The decision cut-offs quoted below have been evaluated from previous study involving the use of natriuretic peptides in the acute (mainly) and non-acute settings, with respective estimation of diagnostic sensitivity and specificity.[10,19,22,46]. They are used to guide decisions on ruling out/in heart failure, adjudicating the need for ECHO and specialist referral. Laboratories may choose to incorporate such thresholds into Laboratory Information Managements Systems (LIMs), relevant to location (and age), for evaluating patient results. Alternatively such information may be given in the test report as an interpretative (auto or free text) comment as well as webpage links for any supplementary guidance. See example interpretative autocomments in **Appendix 2: Indication for NT-proBNP testing in the community**

Results may also be contextualised further in the report by the provision of reference ranges (2.5th and 97.5th percentiles), which are used for guiding clinicians on most biochemical test results. However, akin to troponin (99th percentile), the upper reference limit (URL: e.g. 95th /97.5th /-99th) is most relevant for evaluating NPs. Accordingly, age and gender specific URLs for each decade of life should be used where possible and appropriate, reflecting the increase in natriuretic peptides with age and the gender difference (Females>Males) seen particularly in younger individuals (e.g. <55 years). Ranges quoted in manufacturer's kit inserts should be evaluated carefully before considering their use. Those derived from the Gutenberg Health study[47], quoted current by Roche for NT-proBNP, currently appear most appropriate and transferable across most NT-proBNP providers. Reference range transference studies should however be undertaken as necessary. [48]

Rule-Out cut-offs

The following tables provide the decision thresholds/cut-off values for BNP and NT-proBNP for '**ruling-out'** HF in the acute and non-acute setting.**[19,22]**

	NT- proBNP cut-off	**BNP cut-off**
Non-Acute Setting	< 400 ([1]<125) pg/mL	< 35 pg/mL
Acute Setting	< 300 pg/mL	< 100 pg/mL

For the management of patients in primary care we recommend using an NT-proBNP threshold of 400 pg/ml for ruling out HF and avoiding the need to consider echocardiogram and specialist review. However, it is important to reiterate that NT-proBNP levels may be lowered by factors including obesity (50%) and drugs (e.g. diuretics etc.). Furthermore, such a threshold may exceed even the 99th percentile for a healthy population[47], particularly in younger male patients (<55y) where NP levels are considerably lower than for age-matched females and further contextualisation of results against age/gender related reference limits may be necessary. See Clinical care pathway for suspected non-acute heart failure (Appendix 1 & 3).

[1]The NT-proBNP threshold of 125 pg/ml is recommended by the ESC for ruling out HF.[(19)] However, applying this threshold in primary care is associated with a very low specificity (<50%) and a lower yield of heart failure diagnosis, whereas at a higher threshold of 400 pg/ml most patients with HF (~80%) are identified, with fewer patients (<10%) being referred without HF. The National Institute for Health and Care Excellence Clinical (NICE, 2018[35]) also state that NTproBNP < 400 pg/ml (or in 2010: BNP <100 pgml[33,34]) 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).[(22,33,34,35)] Elsewhere [(19,22,44)], a rule-out threshold of <300 pg/ml is advocated and also shown to improve diagnostic sensitivity.[(44)] On recognising the trade-off between sensitivity and specificity and the potential resource implications from using lower thresholds, our recommendation for the higher cut-off (400 pg/ml) is further supported by the observation that plasma NT-proBNP >125 ng/L is seen in more than 50% of patients with stable ischaemic heart disease or diabetes[49], a large group of patients in whom NPs will be measured as part of the Chronic Disease Management (CDM) programme. Furthermore, the phased implementation of the CDM programme indicates potential for increased testing initially amongst patients ≥75 years of age, for whom NP levels are higher. As the CDM programme continues to expand to younger ages, cut-offs maybe adjusted as necessary, pending in part upon the review of national activity and the CDM programme's outcomes.

[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 a Near Patient Testing BNP method (Triage BNP,Biosite Inc.).[(2)] However, despite methodological differences and bias observed amongst BNP assays (NPT and central laboratory), 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].[(5)]

Rule in cut-offs [(36)]

BNP >500	**All Ages**
[1]NT-proBNP:	Age (yrs)
>450 pg/Ml	<50
>900 pg/mL	50 – 75
>1800 pg/Ml	>75

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

For new diagnosis of HF in primary care, we recommend a threshold of >400 pg/ml for echocardiogram and specialist review. Such referral should be urgent where values are >2000 pg/ml. See Clinical care pathway for suspected non-acute heart failure (Appendix 1 & 3).

Defining ''rule in'' cut-offs for HF is complicated because multiple factors, including age, gender (M>F) 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.[1]. See Table 2 for cardiac and non-cardiac causes of increased NPs.

[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)]. [37]

Lower thresholds should be used to diagnose HF in obese patients. [39,49]

[There is an inverse linear relationship between obesity and circulating NPs, such that lowering the established cut-off concentrations by 50% in obese patients (BMI ≥30 kg/m^2 is considered reasonable to optimize diagnostic accuracy]. [39,49]

Due to the strong correlation between renal dysfunction and age, no additional adjustment is considered necessary for NT-proBNP once using age-adjusted rule-in cut-offs[49].

Factors affecting NP levels
*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 of age 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. [38]

Interpreting serial BNP measurements

The large biological variation for NPs must be considered when interpreting serial NP measurements.[26,40] [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 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.[41]

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[1,2,13,16] 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.

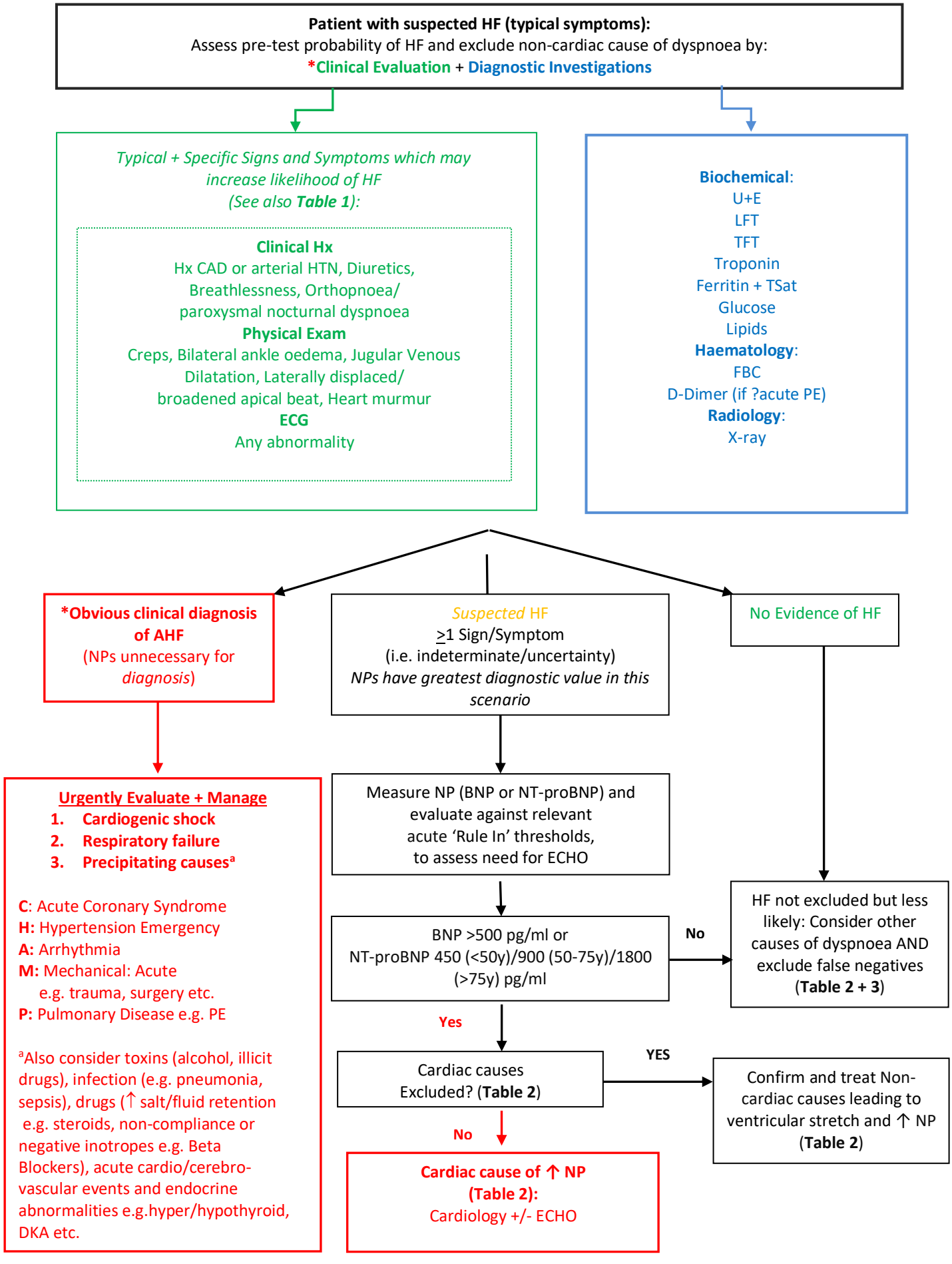
Patient with suspected HF (typical symptoms):
Assess pre-test probability of HF and exclude non-cardiac cause of dyspnoea by:
*Clinical Evaluation + Diagnostic Investigations
Typical + Specific Signs and Symptoms which may increase likelihood of HF
(See also Table 1):
Clinical Hx
Hx CAD or arterial HTN, 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
D-Dimer (if ?acute PE)
Radiology:
X-ray
*Obvious clinical diagnosis of AHF
(NPs unnecessary for diagnosis)
Suspected HF
≥1 Sign/Symptom
(i.e. indeterminate/uncertainty)
NPs have greatest diagnostic value in this scenario
No Evidence of HF
Urgently Evaluate + Manage
1. Cardiogenic shock
2. Respiratory failure
3. Precipitating causes[a]
C: Acute Coronary Syndrome
H: Hypertension Emergency
A: Arrhythmia
M: Mechanical: Acute e.g. trauma, surgery etc.
P: Pulmonary Disease e.g. PE
[a]Also consider toxins (alcohol, illicit drugs), infection (e.g. pneumonia, sepsis), drugs (↑ salt/fluid retention e.g. steroids, non-compliance or negative inotropes e.g. Beta Blockers), acute cardio/cerebro-vascular events and endocrine abnormalities e.g.hyper/hypothyroid, DKA etc.
Measure NP (BNP or NT-proBNP) and evaluate against relevant acute 'Rule In' thresholds, to assess need for ECHO
BNP >500 pg/ml or NT-proBNP 450 (<50y)/900 (50-75y)/1800 (>75y) pg/ml
No
HF not excluded but less likely: Consider other causes of dyspnoea AND exclude false negatives (Table 2 + 3)
Yes
Cardiac causes Excluded? (Table 2)
YES
Confirm and treat Non-cardiac causes leading to ventricular stretch and ↑ NP (Table 2)
No
Cardiac cause of ↑ NP (Table 2):
Cardiology +/- ECHO

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

Symptoms	Signs
Typical	***More Specific***
Breathlessness	Elevated jugular venous presssure
Orthopnoea	Hepatojugular reflux
Paroxysmal nocturnal dyspnoea	Thurd heart sound (gallop rhythm)
Reduced exercise tolerance	Laterally displaced apical impulse
Fatigue, tiredness, increased time	
to recover post-exercise	
Ankle swelling	
Less Typical	***Less Specific***
Nocturnal cough	Wright 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
Dizziness	percussion at lung bases (pleural effusion)
Syncope	Tachycardia
Bendopnea	Irregular pulse
	Tachypnoea
	Cheyne Strokes respiration
	Hepatomegaly
	Ascites
	Cold extremeties
	Oliguria
	Narrow pulse pressure

COLD **WET**

HYPOPERFUSION (+)
Cold sweat extremeties
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)

Cardiac	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
Non-cardiac	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

False negative: Low B-type natriuetic peptide with heart failure
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
- Chronic Disease Management (CDM) registration visit
- Specialist request
  -through cardiology consultation and other structured specialist and community based integrated care programmes (See National Clinical Programme for Heart Failure [Programme Progress]) https://www.hse.ie/eng/about/who/cspd/ncps/heart-failure/achievements
- Discussed with Laboratory.

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

Renal Function profile – ticked

Note NT-proBNP should only be considered if clinical deterioration.

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”.

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. [42, 43]

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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https://www.hse.ie/eng/services/list/2/primarycare/community-healthcare-networks/gp-diagnostics/

Appendix 1: 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 near patient testing (NPT, 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. 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), 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:

NP testing in Primary Care:
>Possible new onset of HF (Diagnostic aid)
> Chronic Disease Management Programme-At registration in those wth DM, IHD, HF, Afib
>Patient deteriorating where HF is part of the differnetial (unless clear clinical cardiac or respiratory cause)
NP testing in the Hospital setting:
>Emergency admission with breathlessness, likely cardiology origin (Diagnostic +Prognostic value)
>At discharge following treatment for HF (Prognostic value)
Deterioration or failure to respond to treatment durng 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.

Appendix 2: Indication for NT-proBNP testing in the community

Authors: Dr Graham Lee, Consultant Clinical Biochemist. Dr Joe Gallagher, General Practitioner

GROUP 1
Specialist guided management of existing HF.* NTproBNP request in consultation with specialist cardiology services.

GROUP 2
Suspected HF, case finding (non-acute onset).** Assess probability using "Clinical care pathway for suspected non-acute heart failure algorithm (overleaf) and refer to CDM consultation template.
Consider NT-proBNP if clinically indicated

GROUP 3
CDM: Treatment Programme***
Registration/first visit for patients with DM, AFib, IHD or HF. *Consider NT-proBNP if clinically indicated*

NT-proBNP interpretative notes (all patients)
Note: *Consider factors which decrease NT-proBNP (BMI >30, drugs e.g. diuretics) or increase NT-proBNP (e.g. renal failure, age and other cardiac/non-cardiac causes e.g. ACS, PH, COPD). For further information see "Natriuretic Peptide Testing Guideline"*
https://hse.ie/clinicaldesignandinnovation/nationalclinicalprogramme/pathology/programmedocuments&resources.
Note: *Your laboratory may report NT-proBNP in either pg/ml or ng/L (pg/ml = ng/L).*

Interpret current NT-proBNP levels against previous[#] (if available) and manage patient as *per* specialist advice

Use "Clinical care pathway for suspected non-acute heart failure" algorithm (overleaf) and the following interpretative guidance as appropriate when NTproBNP is:
(i) ≤125 pg/ml: Heart failure (HF) can be ruled out with high probability.
(ii) >125 pg/ml: Indicative of increased cardiovascular risk.
(iii) ≤400 pg/ml: HF is less likely, especially for patients >75 years.
(iv) >400 pg/ml: HF may be ruled in, if clinically supported and after excluding other causes of raised NT-proBNP. Suggest ECHO and specialist review as appropriate (see overleaf).
(v) >2000 pg/ml has a high probability of HF. Exclude other causes of a raised NT-proBNP and suggest urgent ECHO and specialist review as appropriatesee overleaf).
(vi) [#]Increasing by 50% from a recent stable value supports *worsening HF as a cause of deteriorating symptoms.*

**Group 1:* may include patients already part of existing (+regional) HF programmes e.g. structured services for management of ADHF, HF ICP project in the community (Carlow/Kilkenny) etc.
***Group 2:* will be symptomatic patients (i.e. suspected HF). NTproBNP testing will be taken only if clinically indicated. HF may be identified through opportunistic case finding as part of the Chronic Disease Management programme, when a patient attends for another issue whereby risk criteria can be applied (use the CDM programme consultation template).
****Group 3*: Outside of first registration, NTproBNP may be tested for such patients showing clinical deterioration in symptoms or suspected new onset heart failure. For Group 3 patients with known HF, NTproBNP testing may also be undertaken as per Group 1 patients.
[#] *A study of Irish subjects concluded that a NTproBNP change of ~50% indicates an altered clinical status in stable HF patients.* O'Hanlon R, O'Shea P, Ledwidge M, O'Loughlin C, Lange S, Conlon C, Phelan D, Cunningham S, McDonald K. 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. 2007; 13(1):50-55.

Appendix 3. Clinical Care pathway for suspected non-acute heart failure[52]