Horizon Scan Report 0019 **Date 27/09/2011**

Diagnostic Technology: Point of care B-type natriuretic peptide testing

Clinical Questions:

1. In adults with suspected heart failure how does point-of-care (POC) B-type natriuretic peptide (BNP) testing compare with current practice in ruling out heart failure in the primary care setting?
2. What is the impact on health outcomes when POC BNP is used for ruling in or ruling out heart failure in primary care?

Advantages over Existing Technology:

Recent National Institute for Health and Clinical Excellence (NICE) and European Society for Cardiology (ESC) guidelines on the initial diagnosis of chronic heart failure (CHF) and referral for echocardiography recommend the use of BNP in combination with clinical assessment [1, 2]. NICE guidelines recommend measurement of serum natriuretic peptides in patients with suspected heart failure without previous myocardial infarction (MI), and those with previous MI should be referred for an urgent echocardiogram [1]. Timely diagnosis and treatment of CHF may result in improved patient outcomes as has been demonstrated for acute decompensated heart failure (ADHF) [3]. Although several hospital laboratories carry out BNP testing, few return results within a day. POC BNP testing can considerably reduce turnaround time and could lead to earlier initial treatment, more timely referral and less uncertainty for patients. Moreover, using POC BNP levels to quickly rule out heart failure, could allow more rapid initiation of investigation of other causes of dyspnoea.

Details of Technology:

B-type natriuretic peptide is produced from heart muscle cells as a pro-hormone (proBNP) and released into the cardiovascular system in response to ventricular dilation and pressure overload [9]. The pro-hormone is split by a protease and secreted as the physiologically active C-terminal fragment (BNP) and the inactive N-terminal fragment (NT-proBNP). Several POC BNP testing devices have been identified and they either measure BNP or NT-proBNP (the latter has a longer half-life):

<u>BNP:</u>

1. Biosite Triage System BNP Test (Biosite Diagnostics Inc., San Diego, CA; Supplied in the UK by Alere, Stockport [previously Inverness Medical]). CE marked. Immunoassay that measures BNP concentration from capillary whole blood samples obtained by finger prick. Results are available in 12-15 minutes. The device has reported lower and upper detection limits of 5 pg/ml and 5000 pg/ml, respectively [4]. This is a desk-top device which weighs approximately 0.7kg and is portable. Initial studies claim the test has a 98% diagnostic accuracy at a cut-off value of 80 pg/ml in an urgent care setting [5].
2. Alere Heart Check System (Alere, Stockport, UK). CE marked. Measures BNP concentration from a 15µl sample (obtained by finger prick). Results are available in 15 minutes. The product is handheld.
3. Abbott iSTAT Analyser (Abbott Point of Care, IL, USA; Supplied in the UK by Axis-Shield). CE marked. Measures BNP concentration from a 17µl sample (obtained by finger prick). Results are available in 10 minutes. The device has reported lower and upper detection limits of 15 pg/ml and 5000 pg/ml, respectively [6]. The product is handheld.

<u>NT-proBNP:</u>

1. RAMP 200 Clinical System (Response Biomedical, BC, Canada; no UK distributor identified). CE marked. Measures NT-proBNP from an EDTA whole blood sample, results are available in 15 minutes. The device has a

reported lower limit of detection of18 pg/ml and an upper limit of linearity of 23,450 pg/ml [7]. The product weighs approximately 2 kg and is portable.

2. Cobas h 232/Cardiac Reader (Roche Diagnostics, Burgess Hill, UK). Measures NT-proBNP from a 150µl sample of heparinised venous blood. Results available in 12 minutes. The device has reported lower and upper limits of detection of 60 pg/ml and 3000 pg/ml, respectively [8]. The product is handheld.

Importantly, BNP levels have been found to vary with age, gender and certain diseases (e.g. renal failure) [9]. It has been suggested that higher cut-off values are used when individuals are >75 years, female or in renal failure [9].

Patient Group and Use:

- Patients in primary care with suspected heart failure [1, 14].

Importance:

Around 900,000 people in the UK currently have heart failure (HF) [10]. In a prospective community screening study, definitive HF according to European Society of Cardiology (ESC) criteria was present in 2.3% (95% CI 1.9%-2.8%) of the population [11]. The prevalence rose to 8% in individuals ≥75 years old [11]. The ageing population and improved survival of individuals with ischaemic heart disease are likely to lead to a continuing rise in the prevalence of heart failure. The incidence of HF in the UK is less clear but the crude rate has been estimated to be 1.3 cases per 1000 population per year for those ≥25 years. As expected the incidence increases with age reaching 7.4 cases per 1000 population per year for 75-84 years and 11.6 cases per 1000 population per year for ≥85 years [12]. The British Heart Foundation reported the incidence of heart failure in the UK in 2009 as 39.1 per 100 000 person years [29]. Overall a GP with a patient population of 2000 will care for approximately 40-50 patients with heart failure and see 2-3 new cases each year.

Since heart failure may be reversible in the early stages it is important that CHF is diagnosed as quickly as possible. However, because it has a low incidence, GPs are unlikely to have sufficient experience to identify more subtle presentations of CHF. For example, whilst CHF is frequently diagnosed by GPs, it is only confirmed by echocardiography in approximately a third of cases [13]. A recent health technology assessment of the use of BNP in the diagnosis of HF, compared with ECG and echocardiography found that a normal ECG can be used to exclude a diagnosis of heart failure but it is relatively non-specific. Whilst ECG is a sensitive test when performed by cardiologists (sensitivity = 89%; 95% CI 77%–95%) [14], its sensitivity was much lower (53%) when carried out by GPs [15]. It is for this reason that the most recent NICE guidelines on CHF have refined the diagnostic algorithm for heart failure, replacing ECG with serum BNP measurement [1]. POC BNP testing would enable GPs to rapidly refer the appropriate patients or, if CHF can be excluded, investigate alternative causes of dyspnoea.

Previous Research:

Accuracy compared to existing technology

A 2003 study compared Biosite Triage system to the Roche Elecsys 2010 laboratory based analyser, both operated in a laboratory setting, on 3 different sample concentrations of BNP or NT-proBNP generated from pooled patient plasma. Depending on the concentration of BNP or NT-proBNP, the POC test had a coefficient of variation (CV) of 9.9% to 12.2% whilst the laboratory based test had a CV of 2.9% to 6.1% [16]. This is similar to the total CV reported by the manufacturer.

The diagnostic accuracy of the Biosite Triage system compared to the Roche Elecsys analyser was tested in 306 consecutively presenting patients referred from their GP to rapid access heart failure clinics in the UK [13]. Echocardiography was used as the reference standard. At a cut-off BNP concentration of ≤100pg/ml recommended by the manufacturer, the Triage system had a sensitivity of 79%, a specificity of 72%, a positive predictive value (PPV) of 59% and a negative predictive value (NPV) of 87%. The positive likelihood ratio (LR+) was 2.8 and the negative likelihood ratio (LR-) 0.3. In contrast, when an alternative cut-off point of ≤65pg/ml was applied the Triage system displayed a sensitivity of 87%, a specificity of 57%, a PPV of 51% and a NPV of 90%. The LR+ becomes 2.02 and the LR- 0.23.

A 2009 Swiss study compared the diagnostic accuracy of BNP and NT-proBNP, using the Triage system and Roche Elecsys immunoassay respectively, to echocardiography in patients referred to outpatient clinics from primary care with suspected CHF [17]. Whilst sensitivity and specificity were not calculated, the area under the receiver operator curve (AuROC) was 0.691 for the BNP test and 0.742 for the NT-proBNP assay.

A 2010 study evaluated the diagnostic accuracy of POC Abbott iSTAT BNP assay and the laboratory based Abbott ARCHITECT BNP assay in 150 samples from patients presenting to the emergency department or as cardiology outpatients; analyses were all performed retrospectively in the laboratory [18]. The range of BNP values obtained on both the iSTAT and ARCHITECT varied from 5pg/ml to 5000pg/ml matching the manufacturer's reported range [6]. The study reports a correlation coefficient of 0.977 but an average bias of -36.01%. The precision of the iSTAT is also considerably poorer than its laboratory counterpart. The between day CV of 15 samples run over 15 days ranged from 9.8% to 14% for the iSTAT, whilst for the ARCHITECT it varied from 3.2% to 5.5%.. The investigators concluded that whilst the iSTAT demonstrates poor precision, it shows good clinical agreement relative to the lab based platform [18]. However, the sample population was from the Veterans Affairs Healthcare System of San Diego, 96% of which were male. In addition, the study reports a conflict of interest.

A 2007 study carried out a multicentre validation of the RAMP 200 NT-proBNP assay compared to the Roche Elecsys 2010 NT-proBNP immunoassay using whole blood samples, analysed by both methods retrospectively in the laboratory from 335 individuals of variable health and 271 cases of heart failure [7]. Between day CV was measured by duplicate analysis of 3 different sample concentrations over 10 days and ranged from 8.9% to 10.3% for the RAMP 200 System. Linear regression analysis of 540 samples gave a correlation coefficient of 0.98 but a Bland-Altman plot was not drawn. Using the available data, the RAMP 200 System has a sensitivity of 92%, specificity of 63%, PPV of 67% and NPV of 91%. The calculated LR+ is 2.5 and the LR- 0.12. The authors conclude that both the performance characteristics of the RAMP 200 System and its clinical performance compare favourably to those of the Roche Elecsys 2010 immunoassay and recommend its use in a variety of scenarios.

A Swedish study from 2008 compared the performance and clinical characteristics of the Roche Cobas h232 and Roche Elecsys 2010 NT-proBNP immunoassays using whole blood samples from 440 patients admitted to a cardiology ward or attending a heart failure clinic as outpatients, with the analysis performed in the clinical setting [19]. Total CV was between 8.6% and 12.8% for the Cobas h232. Regression analysis of the 440 samples gave a correlation coefficient of 0.96 and a Bland-Altman plot showed an average bias of -5.4%. The Cobas h232 provides limited information on NT-proBNP concentration; values below 60pg/ml are shown as <60 pg/ml and values higher than 3000 pg/ml as >3000 pg/ml. Values between 60pg/ml and 3000pg/ml are reported quantitatively. For each of these analytical ranges the authors report the sensitivity and specificity of the Cobas h232 compared to the Elecsys 2010. In the range <60pg/ml, the Cobas h232 had a sensitivity of 82%, a specificity of 99%, a PPV of 82% and a NPV of 99%. Between 60pg/ml and 3000pg/ml, the Cobas h232 had a sensitivity of 97%, a specificity of 83%, a PPV of 95% and a NPV of 89%. Finally in the range >3000pg/ml, the Cobas h232 had a sensitivity of 82%, a specificity of 99%, a PPV of 97% and a NPV of 92%. The study concludes that in spite of the imprecision relative to its laboratory counterpart, the Cobas h232 is sufficiently robust for clinical practice and should prove useful for the rapid diagnosis of heart failure in the hospital setting.

A UK Health Technology Assessment (HTA) carried out a comprehensive systematic review and meta-analysis of all studies comparing the diagnostic accuracy of BNP testing to clinical examination by cardiologists in heart failure in all settings until 2006 [14]. The review included 20 studies on the accuracy of BNP for the diagnosis of clinically defined heart failure, 16 of which took place in the emergency department and 13 used the point-of-care Triage system. The study of Zaphiriou et al [13] mentioned above was included in the analysis, however the study by Zuber et al [17] was not included as it was published after the cut-off date for inclusion. The review found that for a cut-off of ≥100pg/ml BNP assays had a sensitivity of 93% (95% CI 91%–96%), a specificity of 74% (95% CI 63%–83%), a LR+ of 3.57 (95% CI 2.44–5.21) and an LR- of 0.09 (95% CI 0.06–0.13). Four studies took place in primary care, one used the point-of-care test and three used laboratory-based tests. These demonstrated a slightly lower sensitivity (84% [95% CI 72%–92%]) but similar specificity (73% [95% CI 65%–80%]).

A total of 16 studies reported data on the accuracy of NT-proBNP for the diagnosis of clinically defined heart failure and showed a pooled sensitivity of 93% (95% CI 88%–96%) and specificity of 65% (95% CI 56%–74%), a LR+ of 2.70 (95% CI 2.12–3.43) and an LR- of 0.11 (95% CI 0.07–0.18). Eight of the studies were conducted on samples from patients presenting in primary care with similar findings – pooled sensitivity of 90% (95% CI 81%–96%), a specificity of 60% (95% CI 50%–70%), a LR+ of 2.28 (95% CI 1.82–2.86), and a LR- of 0.16 (95% CI 0.09–0.30). The HTA report also highlighted that the utility of BNP testing will depend on the pre test probability of CHF in the patient. An individual patient data analysis was used to derive and validate a simple clinical prediction rule (MICE score) that can be used to estimate the pre test probability [14]. When the pre-test probability is low but there is some clinical suspicion of heart failure (not accounted for by MICE score) and for situations where the MICE score is inconclusive (at a score of 5-8 the MICE has a specificity of 60-80% and sensitivity of 80-50%), BNP testing would contribute important diagnostic information as a negative test would reduce the post-test probability. A US technology assessment gave similar results [9].

One of the systematic reviews and meta-analyses of the diagnostic accuracy of BNP testing for heart failure in the emergency department, in which 9 of the 11 studies used the Triage system, showed that at a cut-off of ≤100pg/ml (the cut-off value used in most studies), BNP testing has a sensitivity of 0.93 and specificity of 0.66 [20]. This corresponded to a positive likelihood ratio (PLR) of 2.7 (95% CI = 2.0-3.9) and negative likelihood ratio (NLR) of 0.11 (95% CI = 0.07-0.16). The review concludes that BNP testing is effective in ruling out heart failure when the BNP concentration in a patient with suspected CHF is ≤100pg/ml. However, it also concludes this cut-off is ineffective at confirming heart failure because its PLR is only 2.7. Two other systematic reviews that included the same studies only pooled likelihood ratios and achieved similar results [21,22]. It is also worth noting that the majority of the studies on the Triage BNP system were performed in the emergency setting in the USA; cut off values for primary care may therefore be different.

Impact compared to existing technology

A systematic review and meta-analysis has evaluated the impact of BNP testing in the emergency department on a number of different outcomes, such as admission, length of stay in hospital and inpatient mortality [23]. Of the 5 studies included in the meta-analysis, 2 used the point-of-care Triage system, while the others used a laboratory-based assay. Combined results on hospital admission showed no significant difference between the BNP testing and usual care groups where no BNP testing was performed, although there was a trend towards reduced admission in the intervention group (combined risk ratio: 0.82; 95% CI 0.67-1.01; p = 0.06). This trend was weighted by the results from one study in which a 47% reduction in admission to hospital was seen, in contrast to the small reductions observed in other studies. Combined results from 5 studies that reported inpatient mortality and 4 studies that reported 30 day mortality also found no significant difference between the BNP testing and control groups (no BNP testing); in patient mortality combined risk ratio = 0.96; 95% CI = 0.65-1.41; p= 0.83 and 30 day mortality combined risk ratio = 0.82; 95% CI = 0.58-1.16; p = 0.27. However, synthesis of data from all five studies on length of hospital stay and four studies on length of critical care unit (CCU) stay found that patients in the BNP testing group spent approximately 1 less day in hospital (mean difference –1.22; 95% CI –2.31 to –0.14) and half a day less in CCU (mean difference –0.56; 95% CI –1.06 to –0.05). The review concludes that knowledge of BNP levels may reduce length of stay in hospital but again the authors acknowledge that only a limited number of heterogeneous studies were analysed. A second systematic review and meta-analysis, in which 1 of the 4 studies used the Triage system and all of which are included in the previous review, gave similar results [24].

Although a study investigating the impact of POC NT-proBNP testing with the Cobas h232 has yet to be carried out, feedback on its ease of use has been documented [19]. In this study the nurses on duty in the coronary care unit, who operated the device, found it simple to learn and handle.

A recent UK study has developed appropriateness ratings for the diagnostic application of BNP testing or echocardiography for heart failure in general practice [28]. The study concluded that BNP testing should be the routine test for suspected heart failure where referral for diagnostic testing is considered appropriate and that abnormal BNP testing should be followed up with referral for echocardiography.

Guidelines and Recommendations

NICE guidelines on the diagnosis of heart failure recommend using BNPs in place of ECG [1], although patients with previous MI should be referred urgently for ECG within 2 weeks. The ESC also promotes the use of BNP assays in the diagnosis of CHF [2] and both NICE and ESC recommended cut-off values for CHF referral are different for BNP and NT-proBNP and are as follows:

1. BNP>400pg/ml (>116pmol/L) or NT-proBNP>2000 pg/ml (>236 pmol/l): Refer for echocardiogram and specialist clinical assessment within 2 weeks of presentation.
2. BNP 100-400 pg/ml (29-116 pmol/l) or NT-proBNP 400-2000 pg/ml (47-236 pmol/l): Refer for echocardiogram and specialist clinical assessment within 6 weeks of presentation.
3. BNP <100 pg/ml (<29 pmol/l) or NT-proBNP <400 pg/ml (<47 pmol/l), in the absence of CHF therapy: CHF is an unlikely cause for the presentation.

An older SIGN guideline continues to recommend using either BNP testing or ECG in their diagnostic algorithm for CHF and suggest considering referral to echocardiography on a similar basis to NICE [25].

Combined AHA/ACC guidelines encourage the use of BNP assays in the urgent care setting in whom the clinical diagnosis of HF is uncertain [26]. It also states that BNP levels 'can be useful in risk stratification' in such patients.

Cost-effectiveness and economic impact of BNP testing:

Few economic evaluations and economic impact studies of BNP testing exist [30-36], with only one study focussed on POC BNP in a primary care setting [37]. This decision-tree based cost-consequences analysis concluded that the adoption of BNP in primary care is likely to lead to fewer delayed diagnoses for symptomatic heart failure patients at a very small increased cost relative to referring all patients for an ECG. The results were, however, subject to significant uncertainty relating to a number of key parameters such as the relative unit cost of the BNP test and ECG, and the accuracy and sensitivity of the assays. These uncertainties were tackled in the HTA systematic review and economic model of different diagnostic strategies for heart failure in primary care [14]. A rigorous analysis of the impact of varying the cut-off point for BNP and its resulting sensitivity/specificity on the cost-effectiveness of BNP versus echocardiography was reported. In the base-case analysis a BNP cut-off point above 150 resulted in the 'no-test' option being the preferred cost-effective option, while a BNP cut-off between 72 and 149, the cost-effective strategy is to perform a BNP test first, with echocardiography for positive test results, whereas, for cases where the BNP cut-off is below 72 the cost-effective strategy is for all patients to receive an echocardiogram.

QIPP Evidence has provided documentation to assist primary care organisations in implementing BNP or NTproBNP testing [38]. Heart failure referrals costs the NHS more than £5 million per annum, computer modelling using a 'Scenario Generator' of pathway costs for Lancashire, Cumbria and East Yorkshire showed a 30-40% reduction in referral to cardiology outpatient departments resulting in a 25-40% cost-saving [38]. NICE has recently provided an estimated whole pathway saving of £3.8 million after the introduction of the test [1].

Research Questions:

What is the diagnostic accuracy of the various POC BNP tests in primary care when operated by primary care staff?
What is the impact of POC BNP tests on diagnosis (rule out) and monitoring of heart failure in primary care?
How does the diagnostic accuracy of the MICE score compare to both that of a POC BNP assay and a combination of MICE score and a POC BNP assay in primary care?
What is the diagnostic accuracy of POC BNP tests when used for screening patients at risk of developing HF?
Which cut-off values should be used in the primary care setting?
What is the economic impact of using POC BNP testing in primary care?

Suggested next step:

a) Carry out a systematic review and meta-analysis of studies that investigate the diagnostic accuracy of POC BNP tests in patients with dyspnoea/suspected heart failure in primary care.
b) Examine how the use of POC BNP tests and/or MICE score impacts on the rate of referral to echocardiography and acute hospital or outpatient referral from primary care in a multi-centre study across the U.K.

c) Horizon Scanning Reports on the available evidence for using POC BNP tests both to screen for CHF and to guide CHF therapy.

Expected outcomes:

a) Many of the published studies have investigated the use of BNP in the ED or hospital setting, therefore more studies on the diagnostic accuracy of POC BNP tests in primary care are required.
b) POC BNP tests alone or combined with the MICE score may reduce referral rates by excluding some patients with a low post-test BNP level, who would otherwise have been referred on the basis of an intermediate pre-test probability of CHF and/or inconclusive ECG.
c) Studies using POC BNP tests for CHF screening and to guide therapy are limited and this may hinder such a report. However, there are currently at least five trials underway [27] that examine BNP guided therapy.

References:

1. National Institute for Health and Clinical Excellence Guideline 108: Chronic Heart Failure National clinical guideline for diagnosis and management in primary and secondary care. Aug 2010
2. European Society for Cardiology Guidelines: ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal. 2008 Aug;2388–2442
3. Peacock WF, Fonarow GC, Emerman CL, Mills RM, Wynne J: ADHERE Scientific Advisory Committee and Investigators and the ADHERE Study Group. Impact of Early Initiation of Intravenous Therapy for Acute Decompensated Heart Failure on Outcomes in ADHERE. Cardiology 2007 Jan;107:44-5
4. Triage BNP Test [product insert]. San Diego, Calif; Biosite Incorporated; 2005
5. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, Clopton P, Alberto J, Hlavin P, Maisel AS. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. Journal of the American College of Cardiology. 2001 Feb;37(2):379-85
6. Abbott Point of Care Inc (2008-2011). [Online]. Available from: http://www.abbottpointofcare.com/ [Accessed on: 2nd March 2011]
7. Lee-Lewandrowski E, Januzzi JL, Green SM, Tannous, Wu AHB, Smith A, Wong A, Murakami MAM, Kaczmarek J, Apple FS, Miller WL, Hartman K, Jaffe AS. 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. 2007 Jul;386:20–24
8. Roche Diagnostics Ltd (2011). [Online]. Available from: https://www.cobas-roche.co.uk/site/pointofcare.aspx# [Accessed on: 2nd March 2011]
9. Balion C, Santaguida PL, Hill S, Worster A, McQueen M, Oremus M, McKelvie R, Booker L, Fagbemi J, Reichert S, Raina P. Testing for BNP and NT-proBNP in the diagnosis and prognosis of heart failure. Evidence Report/Technology Assessment. 2006 Sep;(142):1-147
10. Petersen S, Rayner M, Wolstenholme J. Coronary heart disease statistics: heart failure supplement. 2002
11. Davis MK, Hobbs FDR, Davis RC, Kenkre JE, Roalfe AK, Hare R, Wosornu D, Lancashire RJ. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. The Lancet. 2001 Aug;358:439-444
12. Cowie MR, Wood DA, Coats AJS, Thompson SG, P. A. Poole-Wilson PA, Suresh V, Sutton GC. Incidence and aetiology of heart failure: A population-based study. European Heart Journal. 1999;20:421–428
13. Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T, Hardmam SMC, Dargie HJ, Cowie MR. 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. 2005;7:537– 541
14. Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, Mant D, McManus RJ, Holder R, Deeks J, Fletcher K, Qume M, Sohanpal S, Sanders S, Hobbs FDR. 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. 2009. Vol. 13: No. 32
15. Lim TK, Collinson PO, Celik E, Gaze D, Senior R. Value of primary care electrocardiography for the prediction of left ventricular systolic dysfunction in patients with suspected heart failure. Int J Cardiol. 2007;115:73–4.
16. Yeo KT, Wu AH, Apple FS, Kroll MH, Christenson RH, Lewandrowski KB, Sedor FA, Butch AW. Multicenter evaluation of the Roche NT-proBNP assay and comparison to the Biosite Triage BNP assay. Clinica Chimica Acta. 2003;338:107–15
17. Zuber M, Cuculi F, Attenhofer Jost CH, Kipfer P, Buser P, Seifert B, Erne P. Value of brain natriuretic peptides in primary care patients with the clinical diagnosis of chronic heart failure. Scandinavian Cardiovascular Journal. 2009;43(5):324-9

18. Shah K, Terracciano GJ, Jiang K, Maisel AS, Fitzgerald RL. Comparability of Results between Point-of-Care and Automated Instruments to Measure B-type Natriuretic Peptide. Western Journal of Emergency Medicine. 2010 Feb;11(1):44-8
19. Alehagen U, Janzon M. A clinician's experience of using the Cardiac Reader NT-proBNP point-of-care assay in a clinical setting. European Journal of Heart Failure. 2008 Mar;10(3):260-6
20. Wang, CS, FitzGerald M, Schulzer M, Mak E, Ayas NT. Does This Dyspneic Patient in the Emergency Department Have Congestive Heart Failure? JAMA. 2005 Oct;294(15):1944-1956
21. Korenstein D, Wisnivesky JP, Wyer P, Adler R, Ponieman D, McGinn T. The utility of B-type natriuretic peptide in the diagnosis of heart failure in the emergency department: a systematic review. BMC Emergency Medicine. 2007 Jun;7:6
22. Latour-Perez J, Coves-Orts FJ, Abad-Terrado C, Abraira V, Zamora J. Accuracy of B-type natriuretic peptide levels in the diagnosis of left ventricular dysfunction and heart failure: A systematic review. The European Journal of Heart Failure. 2006;8:390 – 399
23. Lam LL, Cameron PA, Schneider HG, Abramson MJ, Müller C, Krum H. Meta-analysis: effect of B-type natriuretic peptide testing on clinical outcomes in patients with acute dyspnea in the emergency setting. Annals of Internal Medicine. 2010 Dec ;153(11):728-35
24. Trinquart L, Ray P, Riou B, Teixeira A. Natriuretic peptide testing in EDs for managing acute dyspnea: a meta-analysis. American Journal of Emergency Medicine. 2010 Apr; [Epub ahead of print]
25. Scottish Intercollegiate Guidelines Network (SIGN) Guideline 95: Management of chronic heart failure. A national clinical guideline. Feb 2007
26. American Heart Association/American College of Cardiology. 2009 Focused Update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: Developed in Collaboration With the International Society for Heart and Lung Transplantation. Apr 2009
27. U.S. National Institutes of Health 2011. [Online] Available from: http://clinicaltrials.gov/ct2/home [Accessed on: 2nd March 2011]
28. Campbell SM, Fuat A, Summerton N, Lancaster N, Hobbs FR. Diagnostic triage and the role of natriuretic peptide testing and echocardiography for suspected heart failure: an appropriateness ratings evaluation by UK GPs. Br J Gen Pract. 2011; 61(588):427-35.
29. Scarborough P, Bhatnagar P, Wickramasinghe K, Smolina K, Mitchell C, Rayner M. Coronary hear disease statistics 2010 edition. British Heart Statistics Database, available at www.heartstats.org. Accessed on 20 September 2011.
30. 30. Breidthardt T, Laule K, Strohmeyer AH, Schindler C, Meier S, Fischer M et al. Medical and economic long-term effects of B-type natriuretic peptide testing in patients with acute dyspnea. Clin Chem 2007; 53(8):1415-1422.
31. Heidenreich PA, Gubens MA, Fonarow GC, Konstam MA, Stevenson LW, Shekelle PG. Cost-effectiveness of screening with B-type natriuretic peptide to identify patients with reduced left ventricular ejection fraction. J Am Coll Cardiol 2004; 43(6):1019-1026.
32. Mueller C, Laule-Kilian K, Schindler C, Klima T, Frana B, Rodriguez D et al. Cost-effectiveness of B-type natriuretic peptide testing in patients with acute dyspnea. Arch Intern Med 2006; 166(10):1081-1087.
33. Nielsen OW, McDonagh TA, Robb SD, Dargie HJ. Retrospective analysis of the cost-effectiveness of using plasma brain natriuretic peptide in screening for left ventricular systolic dysfunction in the general population. J Am Coll Cardiol 2003; 41(1):113-120.
34. Rutten JH, Steyerberg EW, Boomsma F, van Saase JL, Deckers JW, Hoogsteden HC et al. N-terminal pro-brain natriuretic peptide testing in the emergency department: beneficial effects on hospitalization, costs, and outcome. Am Heart J 2008; 156(1):71-77.
35. Sim V, Hampton D, Phillips C, Lo SN, Vasishta S, Davies J et al. The use of brain natriuretic peptide as a screening test for left ventricular systolic dysfunction- cost-effectiveness in relation to open access echocardiography. Fam Pract 2003; 20(5):570-574.
36. Chuck A, Jacobs P. Cost estimation of Point of Care B-Type Natriuretic Peptide for the Diagnosis of Heart Failure in the Emergency Department: Application to Alberta. Information Paper HTA. 2005. Alberta Heritage Foundation for Medical Research.
37. Scott MA, Price CP, Cowie MR, Buxton MJ. Cost-consequences analysis of natriuretic peptide assays to refute symptomatic heart failure in primary care. British Journal of Cardiology 2008; 15:199-206.
38. NHS Improvement. Heart Failure: Use of BNP/NTproBNP testing in primary care to facilitate early diagnosis. http://www.evidence.nhs.uk/QIPP. Accessed on 1 June 2011.

This report was prepared by the Primary Care Diagnostic Horizon Scanning Centre Oxford
Authors: Nick Denny, Dan Lasserson, Christopher P Price, Carl Heneghan, Matthew Thompson, Annette Plüddemann.
Contact details: Dr. Annette Plüddemann; Email: horizonscanning@phc.ox.ac.uk