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Chapter 5.

Natriuretic Peptides – a resume of the literature

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5.1 Introduction

Since the introduction of echocardiography in the 1970s, there have been few significant advances in diagnosing heart failure. Currently clinicians rely on physical examination and sometimes on an ECG and a chest X-ray in initial assessment of these patients³⁷⁹. However, the information derived from these methods is often subjective, resulting in over-diagnosis or under-diagnosis of the disease⁷³. A blood test could play an important role in improving early detection of heart failure and enable more timely treatment of this progressive and ultimately terminal disease. Recently, measurement of natriuretic peptides in particular B-type natriuretic peptide (BNP) is gathering momentum as an adjunct to the diagnosis of heart failure. A development that may be attractive to GPs in assessing patients with suspected HF. There are also potential uses for natriuretic peptides in screening, predicting prognosis and treatment of heart failure.

I have undertaken a resume of the relevant literature. This is not a formal systematic review. This review was done as a prelude to the following two chapters.

5.2 Methods

5.2.1 Search Strategy

Search of bibliographic databases including Medline (1966 – 2002), Embase (1980-2002) and Cinahl (1982 – 2002) and the evidence based database (Cochrane Library). Identification of studies from conferences attended and by consultation with experts in the field of HF research. Search terms used included brain natriuretic peptide, B-type natriuretic peptide, natriuretic peptides, sensitivity and specificity, cardiac failure, congestive cardiac failure, heart failure, congestive heart failure, left ventricular dysfunction, general practice and primary care.

5.2.2 Describing diagnostic tests

The diagnostic accuracy of a particular test is determined by construction of a 2 x 2 table which require numbers of patients with and without a disease (in

this chapter HF, LVSD, LVD or DD), as determined by a “gold standard” investigation (usually echocardiography) and numbers of patients with positive and negative test results. From this 2 x 2 table sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) can be determined^{385, 386}. These parameters are defined as:

- Sensitivity = proportion of people with the disease who are correctly identified by a positive test (“true positive rate”)
- Specificity = proportion of people free of disease who are correctly identified by a negative test (“true negative rate”)
- PPV = proportion of people with positive test results who have the target disease
- NPV = proportion of people with negative test results who are free of the target disease

The concept of a negative test ruling out disease and a positive result ruling in a disease has become popular recently³⁸⁵⁻³⁸⁷.

However, Pewsner and colleagues cogently argue that the ability to rule out does not depend on sensitivity alone, but also on its specificity. Similarly, the ability to rule in depends not only on specificity, as suggested by the SpPIn rule, but also on sensitivity³⁸⁷. It is important to look at all these test results before drawing conclusions as to the diagnostic accuracy of a specific test. A sensitivity or specificity of greater than 85% would be considered to be acceptable for a screening test³⁸⁶.

5.2.3 Receiver operating characteristic (ROC) curves

A ROC curve gives a visual picture of the trade off between sensitivity and specificity with changing thresholds. By displaying ROC curves for different tests on the same graph, the performance of different tests can be compared.

The diagonal on a ROC curve represents the null hypothesis; a curve which follows this line would show that a test had no more potential of producing a correct answer than one selected by chance. An ideal test would follow the ordinate (100% specificity) and at a particular threshold (the cut-off) would

follow the top of the graph (100% sensitivity). Visually the nearer to the top left hand corner of the graph the elbow of the curve appears, the better the diagnostic test accuracy. This type of analysis provides a good reflection of diagnostic ability of a test throughout the range of decision thresholds whereas reporting only one sensitivity and specificity result could be misleading^{388,389}.

The area under the curve (AUC) gives a measure of how good a diagnostic test is; the diagonal line (null hypothesis) gives AUC=0.5 and a perfect test (with a clear threshold) gives AUC=1.

5.3 Physiological perspectives

5.3.1 Natriuretic peptides subtypes and physiology

The natriuretic peptide family consists of three structurally related peptides that participate in the integrated control of renal and cardiovascular homeostasis³⁹⁰. The family members that are of relevance in cardiovascular diseases are atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) previously called brain natriuretic peptide. C-type natriuretic peptide (CNP) is the third but seems to have little clinical significance in cardiovascular disease. The name brain natriuretic peptide was felt to be misleading because circulating BNP originates mainly from the heart ventricle and highest concentrations are found in the myocardium³⁹¹. BNP was first isolated from porcine brain tissues, which explained its original name³⁹². Both ANP and BNP act mainly as cardiac hormones and are produced predominantly by the atrium and ventricle respectively. CNP does not act as a cardiac hormone, being largely produced from the endothelium, and seems to have no role to play in congestive heart failure with levels being unchanged in chronic heart failure compared with normal subjects³⁹³. Both ANP and BNP are involved in sodium and water homeostasis in healthy humans. It has been demonstrated that secretion patterns of both ANP and BNP are pulsatile in most healthy humans³⁹⁴. Whether pulsatile or circadian secretion also occurs in heart failure is not clear and it has been suggested that further studies are needed to determine this in order to obtain the most informative

predictive values, both in the differential diagnosis of dyspnoea and in the evaluation of the severity of the disease³⁹⁴.

BNP is a naturally occurring hormone in the body which is excreted by the ventricles of the heart as one of the body's natural responses to heart failure³⁹⁵. When the heart is unable to pump blood efficiently, BNP is produced to ease its workload³⁹⁶. BNP appears to relax blood vessels (vasodilatation), increase the excretion of sodium (natriuresis) and fluid (diuresis) and decrease neurohormones that lead to vessel constriction, fluid retention and elevated blood pressure. A hallmark of congestive cardiac heart failure is the activation of the cardiac endocrine system in particular ANP and BNP³⁹⁷ and early studies confirmed that plasma levels of BNP were raised in hypertrophic cardiomyopathy³⁹⁸ and in congestive heart failure³⁹⁹. Subsequent studies have shown that amongst all neuropeptides, BNP is the most promising candidate for routine diagnosis. It has been shown to be superior to other neuro hormones for both diagnosis of left ventricular dysfunction and estimating prognosis in left ventricular dysfunction or during the sub-acute phase of myocardial infarction⁴⁰⁰. Cleavage of the precursor protein (proBNP) produces BNP and the biologically inactive peptide N terminal fragment proBNP (NT proBNP). Recent work has shown that the NT proBNP may have potential benefits over BNP^{116,401} although this needs further evaluation.

5.3.2 Factors other than heart failure affecting natriuretic peptide levels

Indications and usefulness of natriuretic peptide assays have been studied extensively for use in cardiovascular disease but especially in patients with various degrees of heart failure^{402,403}. However, it must be emphasised that because cardiac peptides are raised in a variety of clinical conditions a normal value has only negative predictive value whereas increased values usually call for further diagnostic investigations in patients with cardiovascular diseases.

Natriuretic peptides values should be considered in the context of the patient's presentation, as other factors can affect BNP and NT proBNP levels⁴⁰⁴. Older people have higher BNP levels than younger people⁴⁰⁵⁻⁴⁰⁷. This could be explained by physiological changes in ventricular mass and decrease in

myocardial function, declining renal function with subsequent reduction in renal clearance. Women tend to have slightly higher levels than men⁴⁰⁵. Patients in renal failure had markedly elevated BNP levels in two studies^{405,408}.

Natriuretic peptides levels are also raised in patients with diastolic dysfunction⁴⁰⁹, hypertension⁴¹⁰, atrial fibrillation⁴¹¹, aortic stenosis⁴¹², cor pulmonale⁴¹³, acute coronary syndromes⁴¹⁴ and stable angina⁴¹⁵. While some studies found higher BNP levels with hypertension⁴¹⁰, others did not unless patients also had LVH⁴⁰⁷. It could be argued that NT proBNP or BNP is a general indicator of cardiac structural disease rather than a specific indicator of left ventricular systolic dysfunction⁴¹⁵.

Studies have shown that diuretics may lower BNP levels in patients with acute heart failure⁴¹⁶, and beta-blockers⁴¹⁷ and angiotensin converting enzyme inhibitors⁴¹⁸ in chronic heart failure. However, the diuretic study was conducted in severe heart failure using an intravenous therapy and therefore may not be applicable to patients presenting in primary care often with mild heart failure⁴¹⁶. Also there is no clear-cut evidence that any of these agents lower natriuretic peptide levels below cut off levels likely to be used in ruling out heart failure.

5.3.3 Cardiac natriuretic peptide assay methodology

Clerico and colleagues reviewed the measurement of cardiac natriuretic hormones (ANP, BNP and related peptides) in clinical practice⁴¹⁹. They reviewed all recent studies concerning competitive and non-competitive immunoassays for the different cardiac natriuretic peptides to compare the analytical characteristics and clinical relevance of assays.

Studies comparing the clinical uses of different NP assays in patients with different degrees of heart failure have produced conflicting results. In some studies the assay for N-terminal pro-BNP peptides was shown to be equally or even more clinically useful than other natriuretic peptide assays whereas in others, BNP was found to be the best marker of myocardial involvement.

Although these conflicting results could be explained partly by the heterogeneous nature of groups studied, different specificities of methods

used to measure the cardiac peptides could also play an important role. Unfortunately a comparison of analytical and clinical performances of these assays is difficult because the analytical characteristics and methods used are not always specified in clinical studies. Several methods for natriuretic peptide assays have been described but all have some problems concerning lack of sensitivity, precision and /or accuracy (specificity). Furthermore, these methods, even when measuring similar or identical peptides, show different clinical results in reference values so that each laboratory has to determine its own reference interval⁴¹⁹.

5.3.4 Stability of natriuretic peptides in blood

The widespread applicability of BNP would be greatly diminished if the blood sample required special storage or handling. There have been several studies that look at the stability of BNP⁴²⁰⁻⁴²³, as well as NT-proBNP⁴⁰¹ and NT-ANP⁴²⁴. Murdoch and colleagues showed that in a mixed population including patients with LVSD and healthy volunteers that endogenous BNP remains stable in whole blood at room temperature for 3 days⁴²⁰. Other study findings supported the stability of BNP^{422,423,425}. However, other groups have published conflicting results⁴²⁶. Therefore, the above results have not gained universal acceptance⁴²⁷⁻⁴²⁹. Murdoch and colleagues set about repeating the original study to confirm their original findings and suggested that the disparity may have arisen because other groups have looked at the stability of exogenous rather than endogenous BNP⁴³⁰. Using blood from the forearm vein of 10 healthy volunteers, their findings confirmed the previous observations that only a minor decline in endogenous BNP concentrations occurred over 72 hours at room temperature in whole blood and they concluded that these results continued to support the feasibility of the assay of BNP for diagnosis of LVSD in routine clinical practice⁴³⁰. Previously samples had to be frozen prior to assay. The fact that they are now stable at room temperature increases potential utility in primary care.

5.3.5 Available commercial assays

Clerico et al point out that NP and related peptides are generally measured with competitive immunoassay methods that use radioactive labels (i.e.

RIA)⁴¹⁹. In late 2001 two assays became commercially available, a point-of-care BNP fluorescence immunoassay using the Biosite™ Triage System (Biosite Diagnostics, Velizy, France) and an automated laboratory ECLIA assay NT proBNP system developed from a standard microtitre plate system from Roche Diagnostics and run on the Elecsys™ analyser.

Both companies presented assay reference ranges based on 97.5 percentiles in healthy volunteers up to age 65. As the average age of patients with heart failure is around 75 this presented difficulties in use of the assays in our population of patients with suspected heart failure. There have been no comparative studies of the two assays in patients suspected of having heart failure by their general practitioners.

5.4 The role of cardiac peptides in clinical practice

Several authors have reviewed the diagnostic, prognostic and therapeutic uses of cardiac peptides in clinical practice^{397,431-439}. Most have concluded that the best cardiac peptides to measure cardiac function in heart failure appear to be BNP or NT proBNP. These cardiac peptides could be used in several ways including in diagnosis, prognostic prediction and risk stratification, screening of general and high risk populations, therapy and monitoring of therapy.

5.4.1 Diagnosis of Heart Failure

Measurements of cardiac peptides have shown promise in determining whether symptomatic patients have a cardiac cause for their condition⁴³⁴. The majority of comparative studies of BNP and NT-pro ANP have shown BNP to be superior in diagnosis of LVSD⁴⁴⁰⁻⁴⁴³. These studies have failed to reproduce the high diagnostic accuracy of NT-pro ANP observed by Lerman and colleagues⁴⁴⁴. Furthermore, BNP appears to be a reliable marker of left ventricular diastolic dysfunction^{445,446}. However, there are some conflicting data on the validity of BNP as a potential diagnostic aid in primary care.

Table 5.1 below summarises 15 trials that support the diagnostic utility of BNP and/or NT proBNP in HF and table 5.2 the 4 trials that do not support this utility.

Tables 5.1 and 5.2 summarise recent studies attempting to determine the accuracy of BNP or NT proBNP measurement in diagnosing or excluding heart failure in patients' representative of those likely to be referred from primary care for echocardiography or secondary care assessment.

Table 5.1 Summary of studies supporting diagnostic use of natriuretic peptides

Author	Year	Setting	Participants	Reference Standard	Condition of Interest	Index test	BNP cut- off (pg/ml)	Results	Disease prevalence
Yamamoto ⁴⁴²	1996	Rochester, Minnesota USA	94 consecutive referrals for cardiac catheterisation (60% male, mean age 62, no active ischaemia or renal failure)	Echo LVEF \leq 0.45 Cardiac catheter (DD)	LVSD DD	BNP Biosite	124.3	Sensitivity 83% Specificity 77% AUC 0.85 Sensitivity 63% Specificity 76% AUC 0.822	26%
Davidson ⁴⁴⁷	1996	Dundee UK	Random sample of 87 referrals for Radionuclide Ventriculography (66% male, mean age 64)	Radio-nuclide Ventriculography LVEF \leq 0.35	LVSD	BNP Peninsula	33.8	Sensitivity 100% Specificity 58% PPV 42% NPV 100% AUC 0.88	-
Cowie ⁴⁴³	1997	Hillingdon, UK	122 consecutive suspected cases of new heart failure (48% male, age 24-87)	Clinical criteria & echo	Heart Failure	BNP Peninsula	187.7	Sensitivity 97% Specificity 84% PPV 70% NPV 98% AUC 0.96	27%
McDonagh ⁴⁴⁰	1998	Glasgow UK	1252 randomly screened from general population	Echo LVEF \leq 0.30	LVSD	BNP Peninsula	17.9	Sensitivity 77% Specificity 87%	3%
Talwar ¹¹⁶	1999	Leicester UK	243 consecutive echo referrals (53% male, median age 73; no recent myocardial infarction)	Echo WMI \leq 1.2	LVSD	NTpro-BNP Local assay	275	Sensitivity 94% Specificity 55% PPV 58% NPV 93% AUC 0.85	40%

Table 5.1 Continued

Author	Year	Setting	Participants	Reference Standard	Condition of Interest	Index test	BNP cut-off (pg/ml)	Results	Disease prevalence
Koon ⁴⁴⁸	2000	San Diego USA	76 echo referrals with suspected LVD	Echo	LVD	BNP Biosite	100	Sensitivity 91% Specificity 100% PPV 100% NPV 93%	-
Bettencourt ⁴⁴⁹	2000	Portugal	100 consecutive referrals to heart failure clinic with suspected heart failure	Clinical diagnosis & echo LVEF≤0.45	Heart Failure LVSD DD	BNP Shionori a	39.7	AUC 0.92 PPV 95.5% AUC 0.78 AUC 0.89	66%
Yamamoto ⁴⁴²	2000	Rochester, Minnesota USA	466 consecutive echo referrals with symptoms of heart failure or risk factors for LVSD (55% male, median age 65 years)	Echo LVEF ≤ 0.45	LVSD	BNP	37	Sensitivity 79% Specificity 64% PPV 21% NPV 96% AUC 0.79	11%
Smith ⁴⁵⁰	2000	Poole England	155 randomly selected patients (mean age 76)	Echo	LVSD	BNP Peninsula a	18.7	Sensitivity 92% Specificity 65% PPV 18% NPV 99% AUC 0.85	8%
Krishnaswamy ⁴⁵¹	2001	San Diego USA	400 echo referrals (96% male, mean age 60 (no LVD), 69 (LVD))	Echo LVEF<0.50	LVD (LVSD and LVDD)	BNP Biosite	75	Sensitivity 85% Specificity 97% PPV 98% NPV 79% AUC 0.95	56%

Table 5.1 Continued

Author	Year	Setting	Participants	Reference Standard	Condition of Interest	Index test	BNP cut- off (pg/ml)	Results	Disease prevalence
Valli ⁴³²	1999	France	153 consecutive referrals for radionuclide ventriculography with suspected LVD (75% male, mean age 55 years)	Radio-nuclide Ventriculography LVEF≤40%	LVD	BNP Cis Bio	52	Sensitivity 85% Specificity 82% PPV 74% NPV 90% AUC 0.89	38%
Maisel ⁴⁵²	2001	San Diego USA	200 consecutive echo referrals with suspected LVD (95% male, mean age 65)	Echo	LVD	BNP Biosite	38.5	Sensitivity 95% Specificity 66% PPV 71% NPV 93% AUC 0.959	47%
Lubien ⁴⁰⁹	2002	San Diego USA	294 echo referrals with suspected DD and normal systolic function (90% male, mean age 60 (no DD), 71 (DD))	Echo	DD	BNP Biosite	17.5	Sensitivity 97% Specificity 45% PPV 54% NPV 95% AUC 0.91	40%
Hobbs ⁴⁵³	2002	West Midlands UK	Clinical heart failure (n=103) On diuretic (n=87) High risk (n=134) (54% male, mean age 66 years)	Clinical criteria & echo	Heart Failure	NTpro-BNP	304.5	Sensitivity 93-100% Specificity 18-44% PPV 12-39% NPV 97-100% AUC 0.8-0.87	7-34%
Hutcheon ¹¹⁴	2002	Dundee UK	299 patients referred to elderly day hospital (65% female, mean age 79)	Echo Semi-quantitative	LVSD	BNP Peninsula	49	Sensitivity 87% Specificity 54% PPV 18% NPV 97%	10% (50% had cardiac disease)

Table 5.2 Studies not supporting diagnostic use of natriuretic peptides

Author	Year	Setting	Participants	Reference Standard	Condition of Interest	Index test	BNP cut- off (pg/ml)	Results	Disease Prevalence
Omland ⁴⁵⁴	1996	Norway	254 consecutive referrals for cardiac catheterisation (76% male, mean age 59 years)	Cardiac catheter LVEF≤45%	LVD DD LVSD	BNP Shionoria	-	AUC 0.789 AUC 0.698 AUC 0.738	-
Muders ⁴⁵⁵	1997	Germany	221 consecutive referrals for cardiac catheterisation (70% male; mean age 60 years)	Cardiac catheter LVEF≤45%	LVSD	BNP NT-pro BNP	65 80	AUC 0.718 AUC 0.553	17%
McClure ⁴⁵⁶	1998	Glasgow UK	134 myocardial infarction survivors (63% male; mean age 67, 27% symptomatic)	Echo Semi-quantitative	LVSD	BNP	46	Sensitivity 27% Specificity 88% PPV 69% NPV 55% AUC 0.54	49%
Landray ¹¹³	2000	Oxford UK	126 referrals to study clinic with suspected heart failure (54% male, mean age 74 years)	Echo Semi-quantitative	LVSD	BNP Shionoria	17.9	Sensitivity 88% Specificity 34% PPV 38% NPV 85%	32%

5.4.1.1 “Positive” studies

Three studies looking at UK GP populations are noteworthy of further discussion as they support the potential use of BNP in HF diagnosis in a UK setting. However, none were conducted in a pragmatic GP setting.

The landmark Hillingdon heart study demonstrated that only 35 out of 122 referrals to a rapid access clinic with a new diagnosis of heart failure by primary care physicians had the diagnosis confirmed on further assessment (echocardiography)⁴⁴³. Limiting referral for assessment of possible heart failure of those patients with a plasma BNP concentration greater than 22 pg/ml would have reduced the number of patients assessed by more than a half with 70% of those being assessed having the diagnosis confirmed and only one patient with heart failure being ‘missed’. In this study BNP testing had a sensitivity of 97%, specificity of 84%, PPV of 70% and a NPV of 98%. Even though this study that has led to guidance³⁷⁹ for use of BNP or NT proBNP in primary care, it was not conducted in primary care but in patients referred from primary care.

McDonagh and colleagues conducted a study using NT-ANP and BNP concentrations in determination of LVSD in a random sample of the general population in Glasgow⁴⁴⁰. Two thousand participants aged 25-74 were selected from GP lists. All were sent questionnaires and 1653 respondents had echocardiography and ECG. LVSD was defined by an ejection fraction of 30% or less. One thousand two hundred and fifty two had analysable ECG, echocardiograms, completed questionnaires and blood samples. Using a BNP cut off level set at 17.9 pg/ml demonstrated a sensitivity of 77% and a specificity of 87% in all participants. It was suggested that measurement of BNP could be a cost effective method of screening for LVSD in the general population especially if its use was targeted to individuals at high risk. The authors proposed that this could potentially lead to more economical use of further investigations such as echocardiography.

Smith and colleagues measured BNP in 155 elderly patients aged 70 to 84 years⁴⁵⁰. At a cut-off point set at 18.7 pmol/l, the test sensitivity was 92%, specificity 65%, PPV 18%, NPV 99% and area under the ROC 0.85. This

would suggest that although BNP may not be a good test to “rule in” the diagnosis, it could be used effectively as an initial test to “rule out” LVSD.

5.4.1.2 “Negative” studies

There are four studies that do not support the use of BNP or NT proBNP in diagnosing or excluding heart failure:

Omland and colleagues reported a selected cohort of patients with CHD referred for cardiac catheterisation and patients with severe symptoms (NYHA II-IV) were excluded⁴⁵⁴. They reported an AUC of 0.789 which is low compared to most studies and the authors suggest that it is too modest to be useful clinically. This degree of selection bias is likely to affect test performance and limit generalisability to an unselected primary care population.

Muders and colleagues⁴⁵⁵ studied a similar cohort to Omland⁴⁵⁴ and found that neither BNP nor NT proBNP were independent predictors of LVSD. They used higher cut off values (60 and 80 pg/ml) than those used in other studies. Furthermore, these cut-off values were derived from a small cohort (n=23) of normal controls rather than from ROC curve analysis⁴⁵⁵. This methodological flaw could have limited the ability of BNP or NT proBNP to act as markers for LVSD.

McClure and colleagues studied 134 patients from a GP population in Glasgow who were stable after a myocardial infarction and compared BNP concentrations with echocardiographic assessment of left ventricular dysfunction⁴⁵⁶. The results suggested that BNP could not discriminate between patients with moderately severe LVSD and preserved left ventricular dysfunction (area under ROC for moderate or severe dysfunction = 0.54). Possible reasons for this could include the fact that this was a selected population with all patients having had an MI and therefore unlikely to have a “normal” heart; patients were older and many of them had hypertension, both factors increasing the likelihood of LVH and diastolic dysfunction. All these factors increase natriuretic peptide levels and make it harder to differentiate between normal and impaired left ventricular systolic function^{416,457,458}. Furthermore, more patients were on beta-blockers than in other studies, a

treatment known to increase natriuretic peptide levels initially⁴⁵⁹ and plasma was stored at -20 C rather than -70 C in other studies, which may have affected sample quality.

Landray and colleagues studied a relatively elderly GP population (n=126) referred to a diagnostic clinic¹¹³. They reported that addition of a negative BNP test to a negative history of MI, normal ECG and normal chest X-ray reduced the probability of having LVSD from 20% to 15%. They argued that this was still an unacceptably high risk. A cut-off value derived from a large study conducted on a different population was used in this study. This could explain the low specificity of this study compared to other studies.

5.4.1.3 Possible reasons for variations in diagnostic accuracy

The performance of a diagnostic test often varies considerably from one setting to another, which may be due to differences in the definition of the disease, the exact nature of the test, and its calibration and the characteristics of those with and without the disease in a given setting³⁸⁷. For example, patients attending in general practice will generally have disease at an earlier stage than patients in secondary or tertiary care, which may reduce the test sensitivity. Patients free of the disease in tertiary care will tend to have other conditions that raise natriuretic peptide levels, which could reduce the specificity of a diagnostic test³⁸⁷. Even when we assume that sensitivity and specificity do not change between settings and patient populations, test results will have different interpretations depending on whether a test is performed in a low risk population, such as primary care, or high risk patients in tertiary care³⁸⁷.

Several confounding factors could contribute to differences in the results of these studies. Some have already been outlined when describing the “negative studies”:

1. The prevalence of HF (when reported) varied from 3% to 66% in the populations studied. The negative studies tended to be in highly selected populations (CHD awaiting cardiac catheterisation^{454,455} or MI survivors⁴⁵⁶) with fairly high prevalence of HF.

2. The definitions of the condition of interest varied between studies. With those using more specific definitions of LVSD and DD having lower AUC than those adopting a broader diagnosis of HF or LVD.
3. The diagnostic criteria were not uniform across studies with defining LVEF varying from $\leq 35\%$ to $\leq 50\%$ and others using semi-quantitative measurements of left ventricular function or clinical criteria alone or in combination with echocardiography. Generally studies using lower ejection fractions reflecting more severe LVSD, reported higher diagnostic accuracy for natriuretic peptide tests.
4. Use of cardio-active pharmacotherapy (diuretics, ACEi, ARB and beta-blockers) and co-morbid conditions (CHD, diabetes, hypertension) which can all affect natriuretic peptide levels may contribute to test utility and accuracy.
5. Variations in mean age between studies (55 to 79) and the fact that male or female predominance also varied could also have affected results. 3 studies^{409,451,452} had a very high male predominance of between 90-96%. Natriuretic peptide levels tend to be higher in females and rise with increasing age.
6. Some studies applied exclusion criteria (e.g. no recent MI or renal failure) to reduce the effects of confounding, whilst others applied no exclusion criteria. The latter would make those studies more representative of real life clinical practice.
7. Different assays with different methods of deriving cut-off points

All these factors will need to be considered when seeking to analyse and generalise the results from these studies.

5.4.1.4 Potential diagnostic utility of natriuretic peptides in primary care

The wide clinical and methodological heterogeneity between studies makes it difficult to compare them like for like, and would make meta-analysis difficult. Most studies (15 of the 19 studies) show a generally high sensitivity, negative predictive value and favourable area under the Receiver Operating Curve (ROC) characteristics. However, specificity and positive predictive value tend

to be poor except in the two studies using the new point-of-care assay^{448,451}. This suggests that an elevated BNP level does not give a conclusive diagnosis of HF but is useful at excluding heart failure and identifies patients who should undergo echocardiography. If BNP were normal it would seem that there is no need for further tests of cardiac function, and alternative causes for dyspnoea should be sought¹³⁷. In other words a negative BNP or NT proBNP test rules out HF. The low specificity also means that natriuretic peptides could not replace echocardiography or be used as an indication to start treatment for HF.

5.4.1.5 Possible impact of BNP test introduction and future research.

The impact of introducing natriuretic peptide testing in primary care on the demand for echocardiography and/or cardiology outpatient assessment may be low due to the low specificity of the tests and the high prevalence of confounding factors in the referred population. Those patients likely to be tested will be elderly with co-morbidities (e.g. hypertension with LVH, renal impairment, mitral regurgitation) which may raise natriuretic peptide levels. This could result in a high number of patients with suspected HF and high BNP/NT proBNP being referred for further investigation. Abovementioned doubts about the utility of BNP in identifying systolic HF and lack of data for its place in the diagnosis of true 'diastolic dysfunction' have led to calls for research in a pragmatic primary care setting^{460,461}.

5.4.2 Prognosis and Risk Stratification in HF

Several studies have shown that BNP levels can also be used to predict prognosis when heart failure has been diagnosed. An elevated BNP level is a consistently strong predictor of a poor prognosis in patients with LVSD post-MI^{454,462-465}, in acute or decompensated HF⁴⁶⁶⁻⁴⁷¹, in stable HF of varying grades^{449,472,473} and in acute coronary syndromes⁴¹⁴. Even in elderly subjects without any known cardiovascular disorder, BNP was a strong and independent predictor of total mortality⁴⁷⁴.

The BNP level is better at predicting prognosis than at providing a diagnosis possibly because it responds to an increase in cardiac filling pressure regardless of its cause. At present post MI patients with elevated BNP but a

normal LVEF do not always receive an ACE inhibitor. Recent evidence however, suggests that such patients have a worse prognosis (death and development of heart failure) than those with normal LVEF and normal BNP^{195,475}. The elevated BNP is therefore a marker of increased risk even when LVEF is normal⁴⁷⁶. It may be appropriate to measure BNP routinely in post MI patients, especially when echocardiography is not readily available. The use of ACE inhibitors and beta-blockers at optimal doses in these patients is likely to be beneficial.

5.4.3 Treatment

Several studies have shown that infusions of BNP^{477,478} and ANP³⁹⁵ have beneficial haemodynamic and neurohormonal effects in patients with HF. Unfortunately ANP and BNP cannot be given orally⁴³³.

An understanding of natriuretic peptides has led to the development of endopeptidase inhibitors that prevent the degradation of natriuretic peptides. Several of these endopeptidase inhibitors (including candoxatril and omapatrilat) are orally active and seem to offer promise in the treatment of HF^{479,480}. Further investigation of these and similar agents in the treatment of heart failure are currently underway.

5.4.4 Monitoring the efficacy of therapy

Heart failure treatment is usually monitored subjectively (e.g. by signs and symptoms). This is a marked contrast to modern treatment of hypertension or diabetes, which is guided by objective measurements (blood pressure and haemoglobin A1C respectively)⁴⁸¹. A recent review suggested the prospect that monitoring BNP might become 'the same to heart failure as thyroid function tests are to hypothyroidism'⁴³⁶.

An objective measurement to show whether heart failure therapy should be intensified could ensure that each patient receives optimal therapy and improves the outcome of treatment. The feasibility of titration of vasodilator therapy according to plasma BNP had been demonstrated⁴⁸² before Troughton et al⁴⁸³ recently published a trial heralding a "new step in the quest for biomarkers to serve as surrogate endpoints for the treatment of HF"⁴⁸⁴. In

this study HF patients were divided into two groups. One group received standard therapy. In the other, the NT-proBNP level was monitored and therapy was intensified according to a strict and pre-determined protocol if NT-BNP was greater than or equal to 200 pmol/l. (This protocol consisted of: maximisation of ACE inhibitors; increase in loop diuretic and/or additional diuretic; addition of digoxin; additional vasodilator). Patients who received BNP-monitored intensification of therapy had fewer total cardiovascular events than those on usual treatment⁴⁸³. If this observation is confirmed, measuring BNP levels might become standard practice to monitor heart failure therapy. However, as natriuretic peptides are considerably more expensive than thyroid function tests cost effectiveness analyses will be needed in future research projects.

5.4.5 Screening for cardiac dysfunction in an asymptomatic population.

Mass screening of the entire population is unlikely to be cost effective, although there are no such cost effectiveness studies^{440,441,485}. The generally low positive predictive value of most tests would preclude its use in screening healthy populations (see table). However, screening of asymptomatic patients or individuals at high-risk of developing left ventricular systolic dysfunction by measurement of BNP or NT proBNP could lead to a more economical use of further investigations such as echocardiography^{440,442,485-489}. Patients at risk include those with cardiovascular risk factors (hypertension, peripheral vascular disease) and previous vascular events (MI, Stroke, Transient ischaemic attacks) or diabetes.

5.5 Summary and Future Research

5.5.1 The current situation

Echocardiography is currently considered to be the investigation of choice for confirming LVSD^{72,127}. It is, however, not uniformly available to all GPs and may be an expensive option for a first line investigation. Even if open access echocardiography is available its use is variable and many GPs have difficulties with interpretation of the results³⁶⁶. Furthermore, the capacity for

performing the test is limited by lack of availability of suitably trained technicians, and cardiologists to give a clinical interpretation of results. Additional limiting factors are that some patients are either too frail or unwilling to travel to hospital for an echocardiogram or outpatient appointment, or are not good candidates for optimal echocardiographic assessment e.g. obese or with COPD. Audit data suggests that only about 25% of those referred for an echocardiogram have CHF due to LVSD¹⁴⁰.

GPs have difficulty in diagnosing HF in those presenting with non-sensitive symptoms and non-sensitive signs⁷¹. This is even more difficult in elderly patients with multiple co-morbidities³⁶⁶. Furthermore there are a significant number of patients in general practice with a historical "label" of HF who have not had echocardiographic confirmation of the diagnosis of LVSD. These patients would benefit from introduction of evidence-based pharmacotherapy if LVSD was confirmed or withdrawal of current treatment if LVSD deemed unlikely.

5.5.2 Potential future developments using natriuretic peptides

BNP has been shown to have reproducible value as a test to "rule out" CHF. Research evidence suggests a negative predictive value of up to 99% i.e. if BNP is normal a diagnosis of CHF is extremely unlikely. A positive test would point to CHF, but would need confirmation (LVSD or Diastolic dysfunction) by further investigation (usually echocardiography). The use of BNP as a screening test for patients may be a cost effective and convenient test for GP patients¹³² and a welcome diagnostic aid for GPs. This test has the potential to act as an aid to the diagnosis of CHF in primary care. However, "BNP should not replace imaging techniques in the diagnosis of CHF because these methods provide complementary information"⁴⁵¹.

5.5.3 Future research

Mair and colleagues concluded that there is sufficient evidence for physicians to gain experience with BNP as a supplement in the diagnosis suspected of having heart failure⁴³⁴. The research needs for primary care are well summarised by Alan Struthers⁴⁶¹ "Despite most of the data being very positive, the use of BNP or N-BNP has not yet entered routine clinical practice. The

reasons for this are that there are virtually no studies yet of GPs using BNP/NT-proBNP in routine practice and before diuretic treatment or referral; in addition the cost-effectiveness of such a strategy still needs to be established. Future studies should clarify these important issues which may lead to GPs using BNP/NT-proBNP to pre-select symptomatic patients for echocardiography.” Furthermore, there have been calls for a prospective, randomised controlled trial in the primary care setting looking at “the use of natriuretic peptides by GPs on a consecutive, unselected cohort of symptomatic patients recruited from the community”⁴⁶⁰.

In light of National Service Framework recommendations¹³² for CHF, the utility of BNP testing in a primary care setting is in need of urgent evaluation. A project that aims to marry the areas of development, research evidence implementation and evaluation of a service that will deliver one of the goals of the National Service Framework for Coronary Heart Disease¹³² needs to be developed and tested in general practice.

However, as doubts remain around appropriate cut-offs and the utility and practicality of using either a laboratory based (NT proBNP) or a point of care assay (BNP) studies are needed to compare these assays and derive cut-offs from a primary care population. These cut-offs can then be piloted in a pragmatic primary care setting to study their impact on secondary care services and estimate cost effectiveness.

Chapter 6.

The diagnostic accuracy and utility of natriuretic peptides in a community population of patients with suspected heart failure, using near patient and laboratory assay methods.

Abstract

Objective

To test and compare the diagnostic accuracy and utility of B-type natriuretic peptide (BNP) and N-terminal proB-type natriuretic peptide (NT proBNP) in diagnosing heart failure due to left ventricular systolic dysfunction in patients with suspected heart failure referred by general practitioners to one-stop diagnostic clinics.

Design

Community cohort, prospective, diagnostic accuracy study.

Setting

One-stop diagnostic clinics in Darlington Memorial and Bishop Auckland General Hospitals and general practices in South Durham.

Participants

Two hundred and ninety seven consecutive patients with symptoms and signs suggestive of heart failure referred from general practice.

Main outcome measure

Sensitivity, specificity, positive and negative predictive values (PPV, NPV), and area (AUC) under receiver operating characteristic (ROC) curve for BNP (near patient assay) and NT proBNP (laboratory assay) in the diagnosis of heart failure due to left ventricular systolic dysfunction. The negative predictive value of both assays was determined as a potential method of reducing the number of referrals for echocardiography and/or cardiology assessment.

Results

One hundred and fourteen of the 297 patients had left ventricular systolic dysfunction (38%). The area under the curve (AUC) was 0.79 and 0.81 for BNP and NT proBNP respectively. At the manufacturers' recommended cut-off of 100pg/ml, BNP gave a NPV of 82%. BNP performed better at a cut off of 40pg/ml with a NPV of 88%. At a cut-off of 150pg/ml NT proBNP gave a NPV

of 92%. Using manufacturers' cut-off of 100pg/ml for males gave NPV of 89% with 150pg/ml cut off for females producing NPV of 94%. Using cut-offs of 40pg/ml and 150pg/ml for BNP and NT proBNP respectively could have prevented 24% and 25% of referrals to the clinic respectively.

Conclusions

In this setting, NT proBNP performed marginally better than BNP, and would be easier to use practically in primary care. A satisfactory cut-off has been identified, which needs validating in general practice. NT proBNP could be used to select referrals to a heart failure clinic or for echocardiography. This process needs testing in real life general practice.

6.1 Introduction

Echocardiography is currently considered to be the investigation of choice for confirming left ventricular systolic dysfunction. It is, however, not uniformly available to all general practitioners and may be an expensive option for a first-line investigation^{146,147,366}. Even if open access echocardiography is available, its use is variable and many general practitioners have difficulties with interpretation of the results³⁶⁶. Furthermore, the capacity for performing the test is limited by lack of availability of suitably trained technicians, and cardiologists to give a clinical interpretation of results. Observational studies of open access echocardiography services have shown that only 14-23% of patients referred have left ventricular systolic dysfunction¹⁵⁸.

B-type natriuretic peptide (BNP) is one of a family of structurally similar peptide hormones. The major site of BNP production is the left ventricle³⁹⁵. Cleavage of the precursor protein (proBNP) produces BNP which causes diuresis, natriuresis, vasodilatation and smooth muscle relaxation⁴⁹⁰ and the biologically inactive peptide NT proBNP. Both are readily detectable in plasma and rise with increased ventricular and atrial stretch and pressure overload³⁹⁵. Plasma levels are raised in heart failure, rising in line with severity⁴⁹¹ and New York Heart Association functional class⁴⁹².

It has been proposed that BNP or NT proBNP, tests that can be performed using venous blood, can be used by general practitioners to identify patients with heart failure^{105,379,402}. Small, single centre studies have suggested that BNP or NT proBNP has reproducible value as a test to rule out heart failure due to left ventricular systolic dysfunction and potentially pre-select patients for referral for echocardiography^{443,450,453}. However, other studies have questioned the accuracy of BNP in excluding heart failure^{113,456,493}. Most studies used "in house" assays and echocardiography, radionuclide ventriculography or cardiac catheterisation as the gold standard comparison and examined selected groups undergoing these investigations, which were not representative of "all comers" presenting to general practice.

In late 2001 two assays became commercially available, a point-of-care BNP fluorescence immunoassay using the Biosite™ Triage System (Biosite

Diagnostics, Velizy, France) and an automated laboratory ECLIA assay NT proBNP system developed from a standard microtitre plate system from Roche Diagnostics and run on the Elecys™ analyser.

Both companies presented assay reference ranges based on 97.5 percentiles in healthy volunteers up to age 65. As the average age of patients with heart failure is around 75 this presented difficulties in use of the assays in our population of patients with suspected heart failure. Furthermore, the relative merits of using a point of care assay versus a laboratory assay have not been studied in this diagnostic arena. A systematic review by Hobbs and colleagues found little evidence to support the use of point of care testing in primary care⁴⁹⁴. A further review concluded that point of care testing was more expensive than laboratory testing and required trained operators to ensure a good quality service⁴⁹⁵.

There have been no comparative studies of the two assays in patients suspected of having heart failure by their general practitioners. Our primary study aim was to test and compare the diagnostic accuracy and utility of BNP and NT proBNP in diagnosing heart failure due to left ventricular systolic dysfunction in patients with suspected heart failure referred by general practitioners to one-stop diagnostic clinics.

6.2 Methods

All 109 local general practitioners from 23 Darlington and Durham Dales practices were invited to refer patients with symptoms and signs suggestive of heart failure to a one-stop diagnostic clinic within their local hospital⁴⁹⁶. All practices covering a population of 190,000 patients agreed to participate and 94 general practitioners (86%) referred at least one patient to the clinics. The 15 general practitioners who did not refer did not differ from the 94 who did refer on the basis of age, gender, geographical location, ethnicity, practice partnership size or length of time in practice. Practices received an educational session on current diagnosis and management of heart failure from study clinicians and were given a locally produced guideline on the diagnosis and management of heart failure due to left ventricular systolic

dysfunction. A referral template was issued to all general practitioners and their secretaries (Appendix 3). The study ran over a 12 month period.

All patients referred were clinically assessed by clinicians with routine biochemistry, haematology, chest X-ray and 12 lead electrocardiogram results available. Spirometry was conducted where considered appropriate. Patients were given a patient information sheet as they arrived at the clinic and consented following discussion with the clinician.

6.2.1 Sampling for BNP and NT proBNP

Venous blood samples were drawn by clinicians under standard clinic conditions. For the Triage BNP assay, whole blood was drawn into an EDTA tube and the sample assayed within 1 hour. For the Roche Diagnostics NT proBNP assay the sample was taken into vacutainer tubes containing a sample separating gel and placed on ice. The sample was transferred to the lab where it was spun, separated and frozen at -20 degrees Celsius. Samples were then assayed in batches using the Elecys™ analyser with laboratory staff blinded to the clinical assessments. The results were not used by clinicians in diagnostic or management decision-making. Quality controls were carried out for both BNP and NT proBNP assays before each run of assays. The use of a venous sample for the point of care assay rather than a capillary sample was discussed with a consultant biochemist who did not feel that this would have a significant impact on the results achieved. Reasons he gave for this conclusion were that both venous and capillary blood are whole blood samples and deoxygenation should have no effect on BNP levels.

6.2.2 Statistical Analysis

Concentrations of BNP and NT pro BNP both exhibited skewed distributions and were log transformed before analysis. The diagnostic performance of the assays were assessed using receiver operating characteristic (ROC) curves, formed by plotting sensitivity on y axis and 1-specificity on x axis for all possible cut-off values of each diagnostic test³⁸⁸.

In addition to the area under the curve (AUC), the cut-off value was identified that maximised sensitivity without unacceptable loss of specificity, ensuring high negative predictive values.

The McNemar test was used to assess the significance of differences between sensitivity and specificity. Differences between AUCs were tested using the method developed by Hanley and McNeil^{388,389}.

6.2.3 Echocardiography and Electrocardiography

Full standard echocardiography was performed and reported by British Society of Echocardiography accredited clinical physiologists blinded to the clinical details, clinical assessment and BNP/NT proBNP results. Siemens Sequoia C256 and GE Vivid 7 echocardiogram machines were used at Bishop Auckland and Darlington Memorial hospitals respectively. Left ventricular function was assessed by “eyeball” assessment, by left ventricular ejection fraction calculated by Simpson's rule and by wall motion index using the American Society of Echocardiography 16 segment model⁴⁹⁷. Doppler studies were also carried out and other cardiac abnormalities that may have led to breathlessness or a raised BNP/NT proBNP result were documented.

Fifteen percent of echocardiograms were independently assessed by a cardiologist as a measure of quality control. Left ventricular systolic dysfunction was defined as mild, moderate or severe by “eyeball” assessment¹³¹. Ejection fraction²⁰ was measured in patients in sinus rhythm if adequate images were obtained and left ventricular ejection fraction < 0.40 was considered to represent left ventricular systolic dysfunction. A wall motion index of > 1.2 was taken to be abnormal. As it was not possible to measure ejection fraction or wall motion index in all subjects, clinicians diagnosed heart failure due to left ventricular systolic dysfunction if one or more parameter was abnormal.

Electrocardiograms were independently reported by two experienced doctors (AF and JJM) as being either normal or abnormal using the Minnesota criteria¹¹⁷. ECGs were coded abnormal if they showed pathological Q waves, atrial fibrillation or flutter, bundle branch block pattern, ST/T segment

abnormality, or voltage criteria for LVH. Where there was disagreement in coding, both doctors reviewed the ECG and reached a consensus opinion.

6.3 Results

Three hundred and five consecutive patients referred by their general practitioner to one-stop diagnostic clinics⁴⁹⁶ at two hospital sites (Darlington Memorial and Bishop Auckland General) were invited to participate; 297 patients gave informed consent to be included and 8 patients either declined study entry or were considered incapable of giving informed consent.

One hundred and fourteen patients (38%) had left ventricular systolic dysfunction as assessed by eyeball measurement. It was only possible to measure a low LVEF in 67 and abnormal wall motion index in 66 patients with LVSD. Table 6.1 lists the differences in baseline characteristics and demographics of the left ventricular systolic dysfunction and non-left ventricular systolic dysfunction populations. Significantly more patients in the left ventricular systolic dysfunction group were male, were receiving ACE inhibitors, had previous myocardial infarction or had atrial fibrillation, reflecting individuals with high cardiovascular risk factors for development of left ventricular systolic dysfunction. Significantly more patients with hypertension did not have left ventricular systolic dysfunction. However, many of these had left ventricular hypertrophy and diastolic dysfunction and would have been classified as having heart failure with preserved systolic function in other studies⁴⁹⁸. These conditions have been shown to raise natriuretic peptide levels^{409,410}.

All 297 patients had a natriuretic assay but due to technical reasons only 263 BNP and 273 NT proBNP assays were completed. These reasons included malfunction of the triage machine and supply problems with diagnostic kits. This was random and was not related to the presence or severity of heart failure. Figure 6.1 shows the ROC curves for both assays. Table 6.2 lists the areas under the ROC curves for both assays by gender.

Table 6.1 Baseline patient characteristics

	Left ventricular systolic dysfunction		Difference (95% confidence interval)
	Yes (n=114)	No (n=183)	
Mean age	73.5	74.0	-0.5 (-2.8, 2.0)
Age range	34-94	43-94	—
Gender	Male 47% (54)	Male 30% (55)	17.3% (6.0%, 28.6%)
Diuretics	70% (80)	63% (115)	7.4% (-3.6%, 18.3%)
Acei or A2RB	46% (53)	33% (60)	13.7% (2.3%, 25.1%)
Beta-blocker	18% (20)	21% (39)	-3.8% (-12.9%, 5.4%)
Hypertension	27% (31)	39% (71)	-11.6% (-22.4%, -0.8%)
Ischaemic Heart Disease	33% (38)	27% (49)	6.5% (-4.2%, 17.3%)
Previous myocardial infarction	24% (27)	7% (12)	17.1% (8.5%, 25.7%)
Atrial Fibrillation	25% (29)	15% (27)	10.6% (1.2%, 20.2%)
Diabetes	8% (9)	10% (18)	-1.9% (-8.5%, 4.6%)
Chronic Obstructive Pulmonary Disease	19% (22)	26% (47)	-6.4% (-16.0%, 3.2%)

Figure 6.1 ROC curve of BNP and NT proBNP prediction of LVSD

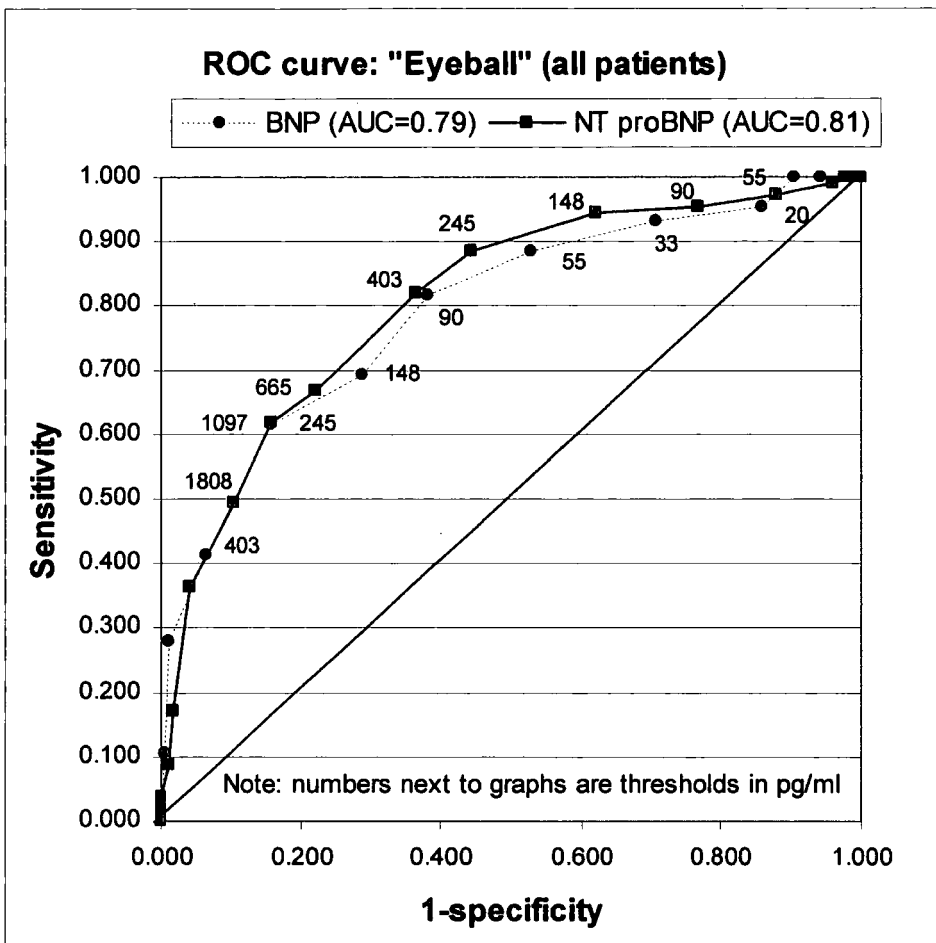


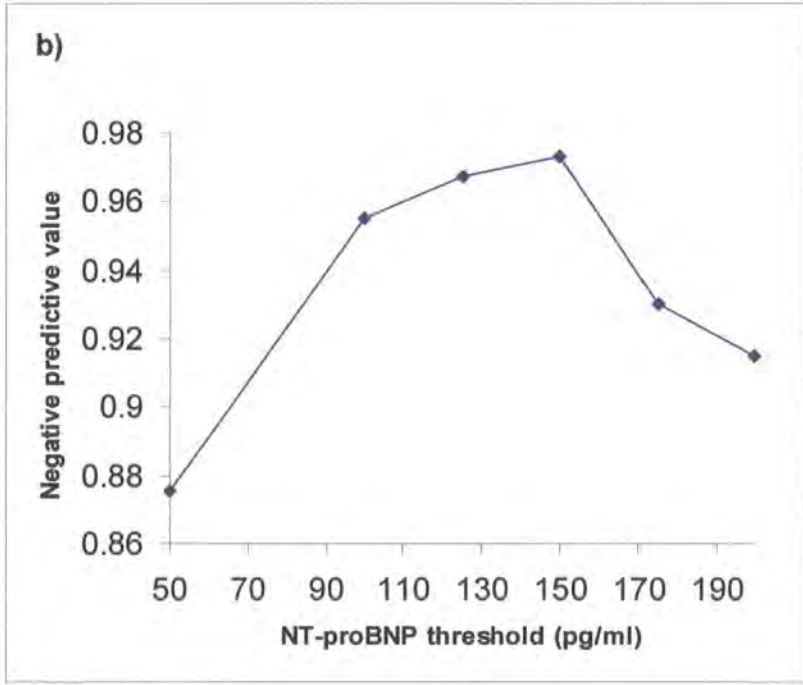
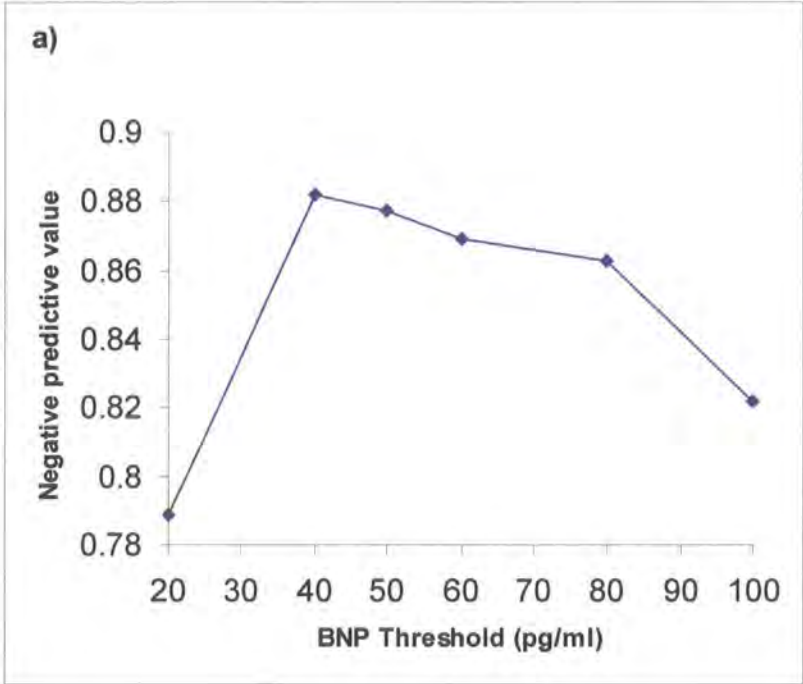
Table 6.2 Area under ROC curve

Peptide	Gender	Area under curve
BNP	All	0.79
	Male	0.79
	Female	0.80
NT proBNP	All	0.81
	Male	0.79
	Female	0.82

The shape of the ROC curves for both test were very similar. Areas under the curve for both tests were high but did not differ significantly from each other.

It was not possible to determine an optimum threshold from the ROC curves alone. Therefore, the NPV of the two tests were calculated at different thresholds and the results plotted graphically as shown in figure 6.2 below.

Figure 6.2 Graphical representation of the change in NPV at different thresholds for (a) BNP and (b) NT proBNP.



There was a clear optimum threshold for both tests. For BNP, the optimum negative predictive value (NPV) was at 40 pg/ml. For NT proBNP the optimum value was 150pg/ml.

During the period of study, the manufacturers made cut-off recommendations: Biosite (BNP) recommend 100pg/ml and Roche diagnostics (NT proBNP) recommend 125pg/ml for both sexes in the USA and 100pg/ml and 150pg/ml for males and females respectively in Europe and the UK. Table 6.3 compares the NPV for both BNP and NT proBNP using the recommended cut-offs with our own results.

Table 6.3. Negative predictive values at different cut-off points

Peptide	Cut-off point		NPV (95% CI)
BNP All	40 pg/ml		0.88 (0.80-0.96)
BNP All	100 pg/ml	<i>Manufacturers' recommendation</i>	0.82 (0.76-0.89)
NT proBNP All	150 pg/ml		0.92 (0.86-0.98)
NT proBNP All	125 pg/ml	<i>Manufacturers' recommendation (USA)</i>	0.92 (0.85-0.99)
NT proBNP Male	100 pg/ml	<i>Manufacturers' recommendation (Europe)</i>	0.89 (0.74-1.00)
NT proBNP Female	150 pg/ml	<i>Manufacturers' recommendation (Europe)</i>	0.94 (0.88-1.00)

Table 6.4 shows the overall performance characteristics of the two assays at our chosen cut-off. The differences between BNP and NT proBNP were not statistically significant. The cut-off points of 40pg/ml for BNP and 150pg/ml for NT proBNP both offer a high NPV of (0.88 and 0.92) respectively but specificity is poor (0.38 and 0.40 respectively). However 61% of patients with false positive results (38% of total patients) had other significant cardiac or related abnormalities that could have raised natriuretic peptide levels. These included left ventricular hypertrophy (n=37)⁴¹⁰, atrial fibrillation (n=17)⁴¹¹, mitral

regurgitation (n=17), pulmonary hypertension (n=17), diastolic dysfunction (n=14)⁴⁰⁹, aortic stenosis (n=3)⁴¹², aortic regurgitation (n=2), atrial flutter (n=2), right ventricular hypertrophy (n=2), cardiac amyloidosis (n=1), lupus and paraproteinaemia, paraproteinaemia (n=1), lung carcinoma (n=1) and cor pulmonale (n=1)⁴¹³. There were some patients who had more than one of these pathologies co-existing.

Table 6.4 Diagnostic utility of BNP and NT proBNP at optimal cut-off values

Peptide	Cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
BNP	40pg/ml	0.92 (0.87-0.97)	0.38 (0.30-0.45)	0.49 (0.42-0.57)	0.88 (0.80-0.96)
NTproBNP	150pg/ml	0.94 (0.90-0.99)	0.40 (0.33-0.47)	0.48 (0.41-0.55)	0.92 (0.86-0.98)

A high sensitivity was demonstrated for both BNP and NT proBNP, which suggests a low false negative rate i.e. they have LVSD. However, specificity is low suggesting that more patients will be referred for investigation than ruled out.

Table 6.5 Utility of the ECG in diagnosing LVSD.

Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95% CI)
0.82 (0.74-0.89)	0.58 (0.51-0.65)	0.55 (0.47-0.62)	0.83 (0.77-0.90)

There were 21 patients with LVSD who had normal ECGs. Of these 14 had mild, 1 mild to moderate, 2 moderate and 4 moderate to severe LVSD.

6.4 Discussion

6.4.1 Summary of main findings

This is the first study, using consecutive patients referred from primary care to one-stop diagnostic clinics that has compared a point-of-care assay of BNP with a laboratory NT proBNP assay and demonstrated high NPV for both methods. The patient group was representative of patients suspected of having heart failure by general practitioners. One hundred and fourteen of the 297 patients had left ventricular systolic dysfunction (38%). The area under the curve (AUC) was 0.79 and 0.81 for BNP and NT proBNP respectively. At the manufacturers' recommended cut-off of 100pg/ml, BNP gave a NPV of 82%. BNP performed better at a cut off of 40pg/ml with a NPV of 88%. At a cut-off of 150pg/ml NT proBNP gave a NPV of 92%. Using manufacturers' cut-off of 100pg/ml for males gave NPV of 89% with 150pg/ml cut off for females producing NPV of 94%. Using cut-offs of 40pg/ml and 150pg/ml for BNP and NT proBNP respectively could have prevented 24% and 25% of referrals to the clinic respectively.

In this setting, NT proBNP performed marginally better than BNP, and would be easier to use practically in primary care. A satisfactory cut-off has been identified, which needs validating in general practice. NT proBNP could be used to select referrals to a heart failure clinic or for echocardiography. This process needs testing in real life general practice.

6.4.2 Comparison with existing literature

The definition of heart failure due to left ventricular systolic dysfunction varies between mortality studies^{11,20} and between specialist guideline bodies^{105,379}. All guidelines suggest echocardiography as the gold standard for confirmation of left ventricular systolic dysfunction^{105,379}. However, it is not always possible to measure left ventricular ejection fraction, especially in patients with obesity or chronic obstructive pulmonary disease. In this situation "eyeball" assessment of left ventricular function has been shown to be an accurate measure¹³¹. This is often a "real life" assessment technique employed by experienced clinical physiologists and we felt it important to conduct this study using this measure. This the first study to compare BNP and NT proBNP

against this standard, and demonstrate high negative predictive values for ruling out left ventricular systolic dysfunction.

Nine patients were false negatives, where BNP or NT proBNP were below the cut-off points. All were on cardio-active therapy (9 on diuretics, 3 on ACE inhibitors and 1 on a beta-blocker) which could have lowered natriuretic peptide levels⁴¹⁶⁻⁴¹⁸. If natriuretic peptide assays were readily available such patients would have been tested before starting treatment. However, natriuretic peptide assays are not readily available in the NHS yet, largely due to the fact that there are unanswered questions and funding issues around use of natriuretic peptides in primary care. It would not have been ethical to stop treatment before assaying patients due to the risk of inducing decompensated heart failure. However, we should be reassured that individuals with low natriuretic peptide levels have a good prognosis and most were on appropriate therapy already^{499,500}.

For the NT proBNP measurement, Roche diagnostics suggest cut-offs of 125pg/ml for both sexes in the USA, but 100pg/ml for males and 150pg/ml for females in Europe and the UK. Our results showed NPV of 92% at 125pg/ml, 89% for males at 100pg/ml and 94% for females at 150pg/ml compared to 92% for both sexes at our optimum cut-off of 150pg/ml (see Table 6.3). Since our study was initiated, Biosite have suggested a cut-off point of 100pg/ml for BNP to rule out heart failure. Our results show that this gave a NPV of 82% compared to 88% at our optimum level of 40pg/ml. Our data therefore suggest that 40pg/ml is a better cut-off for BNP than the manufacturer recommendations and Val-HeFT data suggests that a BNP > 40pg/ml is associated with increased all-cause mortality⁵⁰¹. In this study 13 patients with BNP levels between 40-100 pg/ml who had left ventricular systolic dysfunction would have been denied evidence-based therapy.

Although point-of-care BNP may be useful when a rapid result is needed, for example in the emergency room⁵⁰² or medical assessment unit, it is likely to be impractical in general practice. Furthermore, it would not be practical for individual or even groups of practices to own a Biosite Triage machine costing around £2,000; each test is costly at around £15 each, kit shelf lives are short and performing quality controls are not a familiar task for general practitioners.

Laboratory assays are simple and familiar to general practitioners, samples are stable at room temperature for up to 72 hours⁴²⁰ and quality controls are stringent. This makes the laboratory assay an ideal test for use by general practitioners.

Using cut-offs of 40pg/ml and 150pg/ml for BNP and NT proBNP respectively could have prevented 24% and 25% of referrals to the clinic respectively. This could potentially free up valuable echocardiography capacity and clinician time in a health care system in which availability of both is limited. Obviously this is dependent on whether GPs would have referred all patients in whom they suspected HF and demonstrated a raised natriuretic peptide level. However it needs to be stated that the low specificity of these tests means that we would only send home 38 to 40% of patients who do not actually have the disease as definitely disease free. It follows that between 60 to 62% would need further investigation. This may have cost implications that need exploration in a pragmatic primary care study.

Guidelines and National Institute for Clinical Excellence (NICE) guidance for the diagnosis and management of heart failure due to left ventricular systolic dysfunction suggest that if an electrocardiogram is normal then left ventricular systolic dysfunction is very unlikely, with NPV of 97% in some studies^{105,106}. However, a NPV of 83% in this study suggests that significant left ventricular systolic dysfunction can be present in the presence of a normal electrocardiogram. If current guidance had been adhered to in referral of patients for echocardiography 17% (n21) patients with left ventricular systolic dysfunction would have been missed. Previous studies that suggested a normal electrocardiogram effectively ruled out left ventricular systolic dysfunction may not have been representative of the type of patients referred by general practitioners with suspected heart failure¹⁰⁶. In this study BNP and NT proBNP both performed better than electrocardiogram in selection of patients for further assessment of left ventricular function.

Despite inclusion in guidelines¹⁰⁵, the uptake of BNP or NT proBNP use has been slow in the NHS. Clinicians and Primary Care Trusts still harbour concerns about appropriate cut offs, the extra cost of BNP assays, lack of

expedient referral pathways for patients with a raised BNP level and absence of cost benefit/effectiveness data.

Recently, Wright and colleagues demonstrated in a small randomised controlled trial that NT proBNP measurement significantly improves the diagnostic accuracy of heart failure by general practitioners over and above customary clinical review⁵⁰³. However, this was a trial situation, is not necessarily representative of UK general practitioners using NT proBNP in patients with suspected heart failure and then deciding whether or not to refer for echocardiography.

6.4.3 Study Strengths and Limitations

Consecutive patients referred to the clinics from primary care were studied, hence reducing selection bias. However, we did not study practices to check if there were any patients not being referred to clinics. Since most general practitioners know that echocardiography is needed for patients with suspected heart failure and that the clinics were well advertised we feel it is likely that we captured all patients that general practitioners were worried about. Measurement bias was reduced by utilising the same high quality echocardiography equipment operated by British society of echocardiography accredited cardiac physiologists, reported to a uniform standard and quality checked by one cardiologist. Disease progression bias was reduced by all tests being taken at a one stop diagnostic clinic.

Thirty eight percent is an unexpectedly high prevalence rate for left ventricular systolic dysfunction in this population and it is possible that selection of patients could have been influenced by the education sessions given to practices. This may impact on the generalisability of this study.

These diagnostic values have been derived in one cohort, but require validation in a second cohort with different subjects and clinicians

6.4.4 Implications for future clinical practice and future research

Further research is urgently needed to study the use of BNP or NT proBNP with or without electrocardiography as screening tests in patients with suspected heart failure in an everyday NHS primary care environment. A cut-

off point of 150pg/ml for NT proBNP could be used to select referrals to a one-stop diagnostic clinic or for echocardiography but this process needs testing in “real life” general practice. General practitioners would have NT proBNP available to use in triage of patients with symptoms and signs suggestive of heart failure. An assay result of $\geq 150\text{pg/ml}$ would prompt general practitioners to refer for echocardiography. An assay result of $< 150\text{pg/ml}$ would effectively rule out heart failure and prompt the general practitioner to seek an alternative cause for the patients’ symptoms and signs. This would test the validity of this cut off and provide cost benefit data to inform further use of NT proBNP in primary care.

Such a future validation study could also recruit general practitioners with and without the educational program to see whether this has an effect on diagnostic pick up rates and appropriate referral for echocardiography.

Ethical Approval

The study was approved by South Durham Local Ethics Committee.

Chapter 7.

N-terminal pro B-type natriuretic (NT proBNP) to screen for heart failure referral: a pragmatic primary care study

Abstract

Introduction: Correct diagnosis of heart failure in primary care is problematic. To screen patients with suspected heart failure, national guidelines recommend using N-terminal pro B-type natriuretic peptide (NT-proBNP) although test performance in primary care is not well understood.

Objective: To describe the practicality, impact and cost of using NT-proBNP testing in a pragmatic primary care setting.

Design: A prospective observational study.

Setting and Participants: 600 primary care patients with suspected heart failure tested in 34 South Durham practices (population 282,000). General practitioners were asked to refer patients with raised NT-proBNP (≥ 150 pg/ml) to a one-stop diagnostic clinic.

Main outcome measures: Clinician-reported changes to the care pathway of patients with raised and normal NT-proBNP, final diagnosis, and analysis of NT-proBNP and hospital referral costs.

Results: 396 (66%) of assays were at or above the referral threshold of 150pg/ml: 343 (87%) of these patients were assessed in clinics. Of those assessed only 24% had left ventricular systolic dysfunction. Of the 76% without left ventricular systolic dysfunction the majority had cardiovascular causes for a raised NT-proBNP level. The use of NT-proBNP increased waiting times for clinics from 1-2 weeks to 3-8 weeks.

Conclusions: Due to its high false positive rate, NT-proBNP testing in primary care had an adverse impact on referral. A cut-off of 300 pg/ml would have reduced referrals by 25% but missed 5% of cases. Further research should identify sustainable and cost effective use of NT-proBNP within primary care setting.

7.1 Introduction

Diagnosis of heart failure in patients presenting to general practice is difficult, and up to 70% of cases do not have systolic dysfunction when investigated by echocardiography^{39,71,158}. Confirmation of left ventricular dysfunction (systolic or diastolic) is only possible by cardiac imaging^{105,379}. Echocardiography is currently considered to be the investigation of choice for confirming left ventricular systolic dysfunction^{105,379}. It is, however, not uniformly available to all general practitioners and may be an expensive option for a first-line investigation^{146,147,366}. Furthermore, the capacity for performing the test is limited by lack of availability of suitably trained technicians, and cardiologists to give a clinical interpretation of results. Observational studies of open access echocardiography services have shown that only 14-23% of patients referred have left ventricular systolic dysfunction¹⁵⁸. Even if open access echocardiography is available its use is variable and many general practitioners have difficulties with interpretation of the results³⁶⁶.

B-type natriuretic peptide (BNP) is one of a family of structurally similar peptide hormones released from the heart in direct proportion to ventricular stretch and pressure overload. Several studies have suggested that it may be used to rule out heart failure due to its high negative predictive value⁴³⁶. The major site of BNP production is the left ventricle³⁹⁵. Cleavage of the precursor protein (proBNP) produces BNP and the biologically inactive peptide NT proBNP. Both are readily detectable in plasma and rise with increased ventricular and atrial stretch and pressure overload³⁹⁵. Plasma levels are raised in heart failure, rising in line with severity⁴⁹⁰ and New York Heart Association functional class⁴⁹¹.

It has been proposed that BNP or NT proBNP tests performed using venous blood, can be used by general practitioners to identify patients with heart failure^{402,443,492}. Small, single centre studies have suggested that BNP or NT proBNP has reproducible value as a test to rule out heart failure due to left ventricular systolic dysfunction and potentially pre-select patients for referral for echocardiography^{443,450,453}. However, other studies have questioned the accuracy of BNP in excluding heart failure^{113,456,493}. Most studies used "in house" assays and echocardiography, radionuclide ventriculography or

cardiac catheterisation as the gold standard comparison and examined selected groups undergoing these investigations, which were not representative of “all comers” presenting to general practice.

Recent guidelines from the European Society of Cardiology and National Institute for Clinical Excellence (NICE) have suggested that BNP/NT proBNP and electrocardiography be used as a diagnostic tool to support general practitioners in their assessment of patients with suspected heart failure^{105,379}. Despite inclusion in guidelines^{105,379} uptake of BNP or NT proBNP use has been slow in the NHS. Clinicians and Primary Care Trusts still harbour concerns about appropriate cut offs, the extra cost of BNP/NT proBNP assays, which assay to use³⁸², and lack of expedient referral pathways for patients with a raised BNP/NT proBNP level.

There have been 4 recent cost effectiveness/benefit studies. However, these have been either retrospective analyses⁵⁰⁴, decision model estimates for screening⁵⁰⁵, small cohort studies of breathless patients using BNP and open access echocardiography referral⁵⁰⁶ or analysis of use of BNP in evaluation and management of acute dyspnoea in a US secondary care setting⁵⁰⁷. Although all suggest BNP or NT proBNP is cost effective there are no data from prospective primary care studies.

In a study of 297 consecutive patients with symptoms and signs suggestive of heart failure referred by general practitioners to a one-stop diagnostic clinic, NT proBNP gave a NPV of 92% at a single cut point of 150pg/ml³⁸².

To address primary care concerns and obtain real world implementation data we conducted a pragmatic study to assess the health impact and resource implications of primary care use of NT proBNP for suspected left ventricular systolic dysfunction, using our previously identified cut-off point as a referral threshold.

7.2 Methods

7.2.1 Setting and subjects

All local general practitioners from 34 Darlington, Dales and Sedgefield general practices were invited to contribute patients (Appendix 6). All practices received an educational session on current diagnosis and management of heart failure. We provided general practitioners with guidance on how to use NT proBNP in triaging patients with suspected heart failure. A referral template was issued to all general practitioners and their secretaries (Appendix 3).

GPs were encouraged to refer patients with suspected HF and raised NT proBNP (≥ 150 pg/ml) to one stop diagnostic clinics at Darlington Memorial and Bishop Auckland General Hospitals⁵⁰⁸. A management plan for further care was communicated to the patient's general practitioner and the patient followed up as per normal clinical practice (Appendix 7). All notes of patients with NT proBNP ≥ 150 pg/ml were scrutinised by a research nurse (GB) and the lead clinician (AF).

Patients with NT proBNP < 150 pg/ml were managed by their general practitioner as deemed appropriate. The clinical notes of these patients were surveyed by AF at the end of the recruitment period to determine whether a diagnosis was established and whether a secondary care referral was made during the four weeks subsequently.

All patients referred were clinically assessed by clinicians (AF [GP specialist in cardiology] and AM [Consultant physician]) with routine biochemistry, haematology, chest X-ray and 12 lead electrocardiogram results available. Spirometry was conducted where considered appropriate. Waiting times for patients to be seen in the one stop diagnostic clinics were surveyed before and during the course of the introduction of NT proBNP.

7.2.2 Exploratory Cost Analysis Methodology

Rather than assuming that general practitioners would refer all patients with suspected heart failure we asked them to indicate their preferred course of action if NT proBNP had not been available to them by completing a tick box

option list on the laboratory request form. We felt this reflected the real world decision making process general practitioners would follow. They were asked “What would you have done with this patient if you did not have NT proBNP available?” Options included treat with diuretic without echocardiogram, treat with diuretic and ACE inhibitor without an echocardiogram, referred to one stop diagnostic clinic, referred to cardiologist, referred to other physician, admit to hospital or other action. All patient records were surveyed within 6 months of NT proBNP assay to determine secondary care referral patterns. These were used to conduct a cost benefit analysis. Costs of referral were derived from the National Tariff (2004/2005)⁵⁰⁹.

7.2.3 Sampling for NT proBNP

Venous blood samples were drawn by clinicians, practice nurses or phlebotomists under standard clinic conditions. Blood samples were stored at room temperature and transferred to the laboratory within 10 hours. Standard laboratory quality controls were carried out before each run of NT proBNP assays. NT proBNP was assayed on a Roche Elecys 2010 analyser using an electro-chemo-illuminescence immunoassay principle (Roche Diagnostics). We calculated the cost of the NT proBNP assay to include costs for quality controls. If result $\geq 150\text{pg/ml}$ the laboratory comment was “BNP raised, refer patient to heart failure clinic”. If result $< 150\text{pg/ml}$ comment was “BNP below action limit, heart failure unlikely”.

7.2.4 Statistical Analysis

Concentrations of NT proBNP exhibited skewed distribution and were log transformed before analysis. Estimation of assay performance assumed that no false negatives occurred at a cut-off of 150pg/ml . The diagnostic performance of the assay was assessed using receiver operating characteristic (ROC) curves, formed by plotting sensitivity on y axis and 1-specificity on x axis for all possible cut-off values of each diagnostic test^{388,389}.

In addition to the area under the curve (AUC), we identified the cut-off value that maximised sensitivity without unacceptable loss of specificity, ensuring high negative predictive values.

7.2.5 Echocardiography and Electrocardiography

General practitioners were asked to provide an electrocardiogram with the NT proBNP assay. These were collected by a research nurse and copies distributed to all 3 clinicians (AF, JJM and AM). Electrocardiograms were independently reported by the 3 clinicians as being either normal or abnormal using the Minnesota criteria¹¹⁷. An ECG was considered abnormal in the presence of pathological Q waves, T wave changes, left or right axis deviation, left or right bundle branch block, left ventricular hypertrophy or atrial fibrillation or flutter. The ECG result was not used in determining whether the patients were referred or not. The 3 clinicians met to discuss electrocardiograms where there was a difference in coding (n=63) and a code was agreed in all cases.

Full standard echocardiography was performed and reported by British Society of Echocardiography accredited clinical physiologists blinded to the clinical details, clinical assessment and NT proBNP results. Siemens Sequoia C256 and GE Vivid 7 echocardiogram machines were used at Bishop Auckland and Darlington Memorial hospitals respectively. Left ventricular function was assessed by “eyeball” assessment¹³¹, by left ventricular ejection fraction calculated by Simpson’s rule using m-mode and by wall motion index using the American Society of Echocardiography 16 segment model⁴⁹⁷. Doppler studies were also carried out and other cardiac abnormalities that may have led to breathlessness or a raised BNP/NT proBNP result were documented.

15% of echocardiograms were independently assessed by a cardiologist as a measure of quality control. Left ventricular systolic dysfunction was classed as none, mild, moderate or severe by “eyeball” assessment¹³¹.

7.3 Results

7.3.1 The impact on secondary care referrals

All practices covering a population of 282,000 patients agreed to participate and 75 % of 179 general practitioners used NT proBNP at least once.

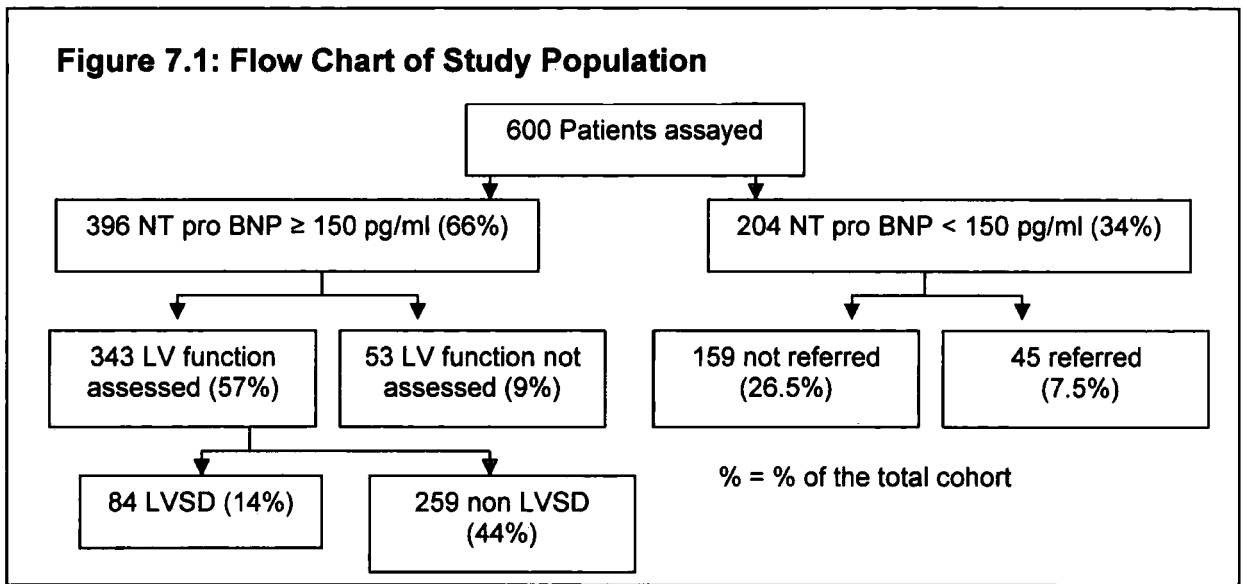
Six hundred patients were tested between August 2003 and June 2004. There were 367 women (61%) and ages ranged from 35 to 99 (mean 74). Table 7.1 outlines the baseline characteristics of the NT proBNP positive group who under went further assessment. The NT proBNP “negative” group had a lower mean age of 68 (age range 35 to 92) and 41% were male. We did not ascertain the baseline medications or co-morbidities in the NT proBNP “negative” group.

Table 7.1 Baseline characteristics of BNP positive patients attending clinics

	LVSD (n=84)	Non LVSD (n=259)
Mean age	78	78
Age range	53-91	43-94
Gender	Male 62%	Male 29%
Diuretics	90%	71%
ACEi or ARB	82%	47%
Beta-blocker	42%	37%
Hypertension	49%	59%
IHD	37%	29%
MI	26%	12%
AF	27%	20%
Diabetes	17%	10%
COPD	19%	22%

Figure 7.1 shows NT proBNP results and subsequent referral patterns for all 600 patients.

Figure 7.1: Flow Chart of Study Population



Of all the subjects 396 (66%) had an NT proBNP level ≥ 150 pg/ml, ranging from 150pg/ml to 33805 pg/ml. 343 of the NT proBNP “positive” group had echocardiographic assessment and 84 of those had left ventricular systolic dysfunction. This represents 14% of the total 600 patients assayed. A further 4 NT proBNP “negative” patients were referred to the one-stop diagnostic clinic, with none having LVSD. 42 patients in this group were either not referred or refused referral, 3 did not attend clinics despite 2 invitations and 8 died in the 15 day interim (range 7 to 15 days, mean 10 days) between NT proBNP assay and clinic attendance. Causes of death were recorded from death certificates and included acute myocardial infarction (n=4), cardio-respiratory failure (n=1), metastatic liver disease/carcinomatosis (n=1), ruptured aortic aneurysm (n=1), head injury and polycythaemia rubra vera (n=1). Of the 42 patients not referred or refusing referral 12 died within 2 to 8 months after NT proBNP testing but only one of these from congestive heart failure and atrial fibrillation. Of the 76% (n=259) patients with raised NT proBNP but no evidence of left ventricular systolic dysfunction the majority had other cardiac conditions that could have raised NT proBNP (Table 7.2)

Table 7.2: NT proBNP “positive” (+ 4 NT proBNP “negative” seen in OSDC) with no left ventricular systolic dysfunction – alternative diagnoses (n263)

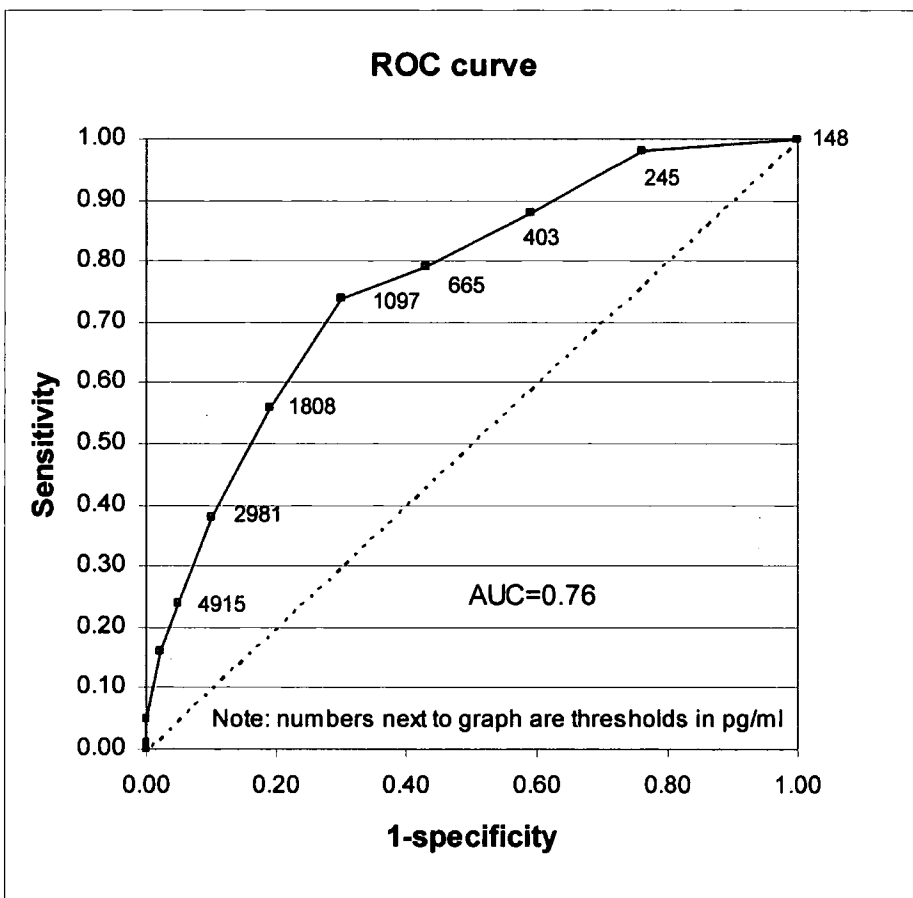
Hypertension	(n154)	58%
IHD	(n76)	29%
MI	(n34)	13%
Atrial Fibrillation	(n52)	20%
Valve disease	(n40)	15%
LVH	(n35)	13%
LVDD	(n18)	7%
Diabetes	(n27)	10%
COPD	(n59)	22%
Morbid Obesity	(n21)	8%
Anaemia	(n13)	5%
Pulmonary HT	(n10)	4%
Lung disease	(n7)	3%
Asthma	(n6)	2%
Other	(n39)	15%

Of the 204 NT proBNP “negative” group 45 were referred to secondary care despite an assay level below the referral threshold, but none of these had left ventricular systolic dysfunction. 5 were admitted to elderly care wards, and 40 referred to the following outpatient clinics; respiratory (n=13), one stop diagnostic clinic (n=4), general medicine (n=14), rapid access chest pain (n=3), general cardiology (n=5) and ENT (n=1). Alternative diagnoses that may have accounted for symptoms or signs that led a general practitioner to undertake NT proBNP assay were extracted from patient clinical notes and uncertain cases discussed with the appropriate general practitioner. These included chronic obstructive pulmonary disease (21%), ischaemic heart disease (13%), hypertension (8%), dependent peripheral oedema (6%), obesity (6%), anxiety (5%) and asthma (5%). No definite diagnosis was found in 11% and another 25% had other diagnoses including lower respiratory tract infection, ACE inhibitor cough, thyrotoxicosis, pulmonary fibrosis, anaemia, emphysema, lung cancer, sleep apnoea, NSAID induced wheeze and hyponatraemia.

Waiting times for the one stop diagnostic clinics rose from between one to two weeks for the year preceding the study to between three to eight weeks during the course of the study.

The receiver operating curve (ROC) gave an area under the curve (AUC) of 0.76 for NT proBNP using left ventricular systolic dysfunction diagnosis as the diagnostic “gold standard” (Figure 7.2). The diagnostic utility of NT proBNP was determined at several cut offs assuming a negative predictive value (NPV) of 100% for a cut-off of 150pg/ml based on previous studies⁵⁰⁸ and manufacturer’s recommended cut-offs for excluding left ventricular systolic dysfunction (Table 7.3). At an NT proBNP cut-off of 300pg/ml a NPV of 95% would have avoided 101 referrals of whom 86 had echocardiography and only missed 4 patients with left ventricular systolic dysfunction (3 mild and 1 moderate).

Figure 7.2: Receiver operating curve for NT proBNP (assuming no false negatives at a cut-off of 150pg/ml)



In this study if a normal electrocardiogram had been used to screen patients with suspected heart failure 14 patients with left ventricular systolic dysfunction would have been missed, with a NPV of 91% (Table 7.3).

Table 7.3: Diagnostic Utility of NT proBNP and Electrocardiography

	Cut-off pg/ml	TNs	FPs	FNs	TPs	Sens	Spec	PPV	NPV	95% CI for NPV
	150	0	259	0	84	1	0	0.26	-	-
	300	82	177	4	80	0.95	0.32	0.31	0.95	0.91-1
	450	119	140	12	72	0.86	0.46	0.34	0.91	0.86-0.96
	600	141	118	16	68	0.81	0.54	0.37	0.9	0.85-0.95
	750	157	102	19	65	0.77	0.61	0.39	0.89	0.85-0.94
	900	170	89	21	63	0.75	0.66	0.41	0.89	0.85-0.93
ECG		139	120	14	70	0.83	0.54	0.37	0.91	0.86-0.95

7.3.2 Exploratory cost analysis results

We calculated the predicted costs based on GP intentions (box 7.1) and the actual costs of care incurred by each individual patient based on 2004/2005 National Tariff costs for clinic referral episodes and hospital admissions (Table 7.4). OSDC clinics and RACPC were costed as a cardiology referral at £136 per episode; elderly care £233; general medicine £183; domiciliary visit £100; chest clinic £178 and ENT £221. GPs did not indicate an intended course of action for 24 patients and did not intend to refer 77 patients. We did not attach a referral cost to these patients. NT proBNP assays were cost £21 each. We did not include costs of GP care, drugs or follow up clinic attendances.

Review of all NT proBNP “negative” patients showed that 22% ended up in secondary care within 1 month of the assay date. These patients were included in the calculations.

Box 7.1: Initial cost benefit analysis based on GPs intended action

What would you have done with this patient if you did not have NT proBNP available?		
1. Treat with diuretic without echocardiogram		n46
2. Treat with diuretic and Ace without echocardiogram		n31
3. Referred to one stop heart failure clinic		n395
4. Referred to a cardiologist		n63
5. Referred to other physician (please specify)		n36
6. Admit to hospital		n5
7. Other (please specify)		n20
	no tick	n4
	total	n600

Table 7.4: Comparison of predicted versus actual costs

Actual costs	Predicted costs
NT proBNP "positive" (n=396) 344 referred	n=600
312 OSDC = £42976	395 OSDC = £53720
11 Elderly care = £ 2563	63 Cardiology = £ 8568
6 General medicine = £ 1093	36 Medicine = £ 6588
6 Admissions = £10926	5 Admissions = £ 9105
6 Cardiology = £ 816	24 Others = £ 0
2 Domiciliary visit = £ 200	77 Not referred = £ 0
1 Private referral = £ 0	
396 NT proBNP = £ 8316	
Sub Total = £66890	
NT proBNP "negative" group (n=204) 45 referred	
4 OSDC = £ 544	
14 General medicine = £ 2562	
13 Chest Clinic = £ 2314	
5 Admissions = £ 9105	
5 Cardiology = £ 680	
3 RACPC = £ 408	
1 ENT = £ 221	
204 NT proBNP = £ 4284	
Subtotal = £20118	
Total = £87008	Total = £77981

We calculated the predicted costs of raising the NT proBNP referral threshold to 300pg/ml as £73, 408. This would have represented a cost saving of £4,573 over GP predicted costs and £13, 600 over actual costs using NT proBNP at a referral threshold of 150pg/ml. It must be stressed that these are only cost estimates rather than costs based on what actually happened in this study.

We also estimated the potential costs of using NT proBNP if open access echocardiography had been the diagnostic referral strategy of choice rather than the one stop diagnostic clinic. The open access echocardiography costs were drawn from the recent NHS Quality Improvement Scotland Assessment report⁵¹⁰. We also used the electrocardiogram strategy suggested in this report to estimate costs of using an abnormal electrocardiogram, and if normal electrocardiograms with raised NT proBNP test to refer to either a one stop diagnostic clinic or open access echocardiography service (Table 7.5).

Table 7.5: Alternative Diagnostic referral strategies

Predicted costs if no NT proBNP (GP intentions)	= £77,981
Actual costs in real life study	= £87,008
Alternative strategies	
Open Access Echo all patients (@ £109)	= £65,400
NT proBNP and OAE all positive NT proBNP	= £55,764
Abn ECG/ N ECG-Abn NT proBNP then OSDC	= £66,366*
Abn ECG/ N ECG-Abn NT proBNP then OAE	= £51,157*
*Add £7200 if Consultant led ECG @ £12 per ECG	
All calculations exclude costs of drugs, GP care and follow up at clinics	

It is important to point out that based on previous work³⁶⁶ if OAE was the diagnostic model of choice there is no guarantee that patients would get full clinical assessment or evidence-based therapy for those recognised as having LVSD.

7.4 Discussion

Recently Wright and colleagues demonstrated in a small randomised controlled trial that NT proBNP measurement significantly improves the

diagnostic accuracy of heart failure by general practitioners over and above customary clinical review⁵⁰³. However, this was a trial situation and was not necessarily representative of UK general practitioners using NT proBNP in patients with suspected heart failure and then deciding whether or not to refer for echocardiography. Ours is the first reported study of NT proBNP use by general practitioners in real life assessment of patients with suspected heart failure.

7.4.1 The impact on secondary care referrals

The majority of patients tested in primary care have raised NT proBNP. This led to a high number of patients with high NT proBNP (including many false positives) being referred to secondary care with a resultant rise in diagnostic clinic waiting times from between one to two weeks to between three to eight weeks, generating increased workload for these services. Furthermore, there was a low strike rate with 24% of those seen having left ventricular systolic dysfunction and only 14% of the total cohort had left ventricular systolic dysfunction confirmed by echocardiography. The diagnosis yield for left ventricular systolic dysfunction was very similar to that experienced with open access echocardiography¹⁴⁰ and less than that for one stop diagnostic clinics that we have previously surveyed⁵⁰⁸. This variation could be explained by the fact that the provision of services in the same geographical area, with a fairly stable population, may have meant that GPs validated their lists of patients with suspected heart failure when the one-stop diagnostic clinics were introduced in 2002. This was advised by the National Service Framework for Coronary Heart Disease, and may have reduced the potential number of left ventricular systolic dysfunction patients. Another explanation could be increased uptake of ACE inhibitors and beta blockers for high risk patients (IHD, hypertension and diabetes) in light of guideline recommendations, leading to prevention and a reduced incidence of left ventricular systolic dysfunction.

Natriuretic peptides levels are also raised in patients with diastolic dysfunction⁴⁰⁹, hypertension⁴¹⁰, atrial fibrillation⁴¹¹, aortic stenosis⁴¹², cor pulmonale⁴¹³, acute coronary syndromes⁴¹⁴ and stable angina⁴¹⁵. It could be

argued that NT proBNP or BNP is a general indicator of cardiac structural disease rather than a specific indicator of left ventricular systolic dysfunction⁵¹¹. It is noteworthy that of the 76 % assessed who did not have left ventricular systolic dysfunction, many had other cardiac or pulmonary conditions that raised NT proBNP and these individuals benefited from further investigation, specialist referral or advice on treatment changes. Many of the patients with raised NT proBNP but no evidence of left ventricular systolic dysfunction benefited from establishment of a new diagnosis by initiation of further cardiac or respiratory investigations. This occurred either within the clinic or by appropriate referral to other secondary or tertiary care clinics, and a review of previously known conditions. Furthermore, many of these patients benefited from initiation and optimisation of evidence based therapies, advice on lifestyle measures and access to other health care professionals (e.g. cardiac and pulmonary rehabilitation specialist nurses and smoking cessation services).

The introduction of a new test may have lowered general practitioner threshold for testing patients that they may have previously treated without further investigation. When asked about their intentions if NT proBNP had not been available there were 77 patients (13%) that general practitioners stated they would treat with diuretics or diuretics and an ACE inhibitor without echocardiography. Of these patients 54 had an NT proBNP level over 150pg/ml and 52 underwent echocardiography with 11 (21%) having left ventricular systolic dysfunction. Without referral, and confirmation of LVSD, these patients could have been denied evidence based therapy, especially beta-blockers²³⁵. Therefore, use of NT proBNP benefited this group of patients.

Although 22% of the NT proBNP negative cohort was referred to secondary care general practitioners felt that they were able to refer many of these patients to a more appropriate secondary care specialist, rather than overloading the one stop diagnostic clinics.

7.4.2 Referral thresholds for NT proBNP

Previous work based on diagnostic clinic cohorts had suggested that an NT proBNP level below 150 pg/ml exhibited a high negative predictive value for ruling out heart failure due to left ventricular systolic dysfunction^{382,512}. The manufacturers (Roche Diagnostics) recommended an NT proBNP cut-off below 150 pg/ml for males and 125 pg/ml for females. We found that in this consecutive primary care cohort raising the action limit for referral to 300pg/ml would have avoided a further 101 referrals. This would have missed only four patients with left ventricular systolic dysfunction, all of whom were already on some cardio-active treatments and therefore unlikely to be denied appropriate evidence-based therapy. It has to be pointed out that only 86 of the 101 patients in the NT proBNP range 150 to 300pg/ml were assessed in clinics and it is not possible to say whether the 15 not assessed had LVSD or not. Despite this we believe that the optimum cut-off has yet to be resolved. It is possible that using higher cut offs adjusted for age and gender or a higher single dichotomous cut-off rather than the currently recommended cut-off may reduce referrals and minimise costs.

Many of the patients were taking drugs used for the treatment of heart failure, but prescribed for other cardiovascular indications (hypertension, angina and atrial fibrillation). Studies have shown that diuretics may lower BNP levels in patients with acute heart failure⁴¹⁶, and beta-blockers⁴¹⁷ and angiotensin converting enzyme inhibitors⁴¹⁸ in chronic heart failure. However, this is a real life study and it would be difficult and unrealistic to measure natriuretic peptides in only patients on no active cardiac therapies. Stopping treatment before NT proBNP testing would have been unethical as this discontinuation of cardio-active therapies may have led to decompensation of heart failure or increased cardiac ischaemic episodes. Furthermore, the diuretic study was conducted in patients with severe heart failure using an intravenous therapy and therefore is not applicable to patients presenting in primary care often with mild heart failure⁴¹⁶. Also there is no clear-cut evidence that any of these agents lower natriuretic peptide levels below cut off levels likely to be used in ruling out heart failure.

7.4.3 Electrocardiography in screening for left ventricular systolic dysfunction

Guidelines for the diagnosis and management of heart failure due to left ventricular systolic dysfunction suggest that if an electrocardiogram is normal then left ventricular systolic dysfunction is very unlikely^{105,379}. Such conclusions are dependent on case selection and the prevalence of left ventricular systolic dysfunction in the population studied. Our experience in assessment of patients with suspected left ventricular systolic dysfunction in primary care is that this statement is not always accurate⁵¹³. A previous study showed that if current guidance was adhered to in referral of patients for echocardiography 18 (22%) of patients with left ventricular systolic dysfunction would have been missed⁵¹³.

In a systematic review researchers have previously shown that significant left ventricular systolic dysfunction can be present in the presence of a normal electrocardiogram and suggested limitations to the usefulness of the electrocardiogram in identifying patients with suspected heart failure who would proceed to echocardiography¹¹⁸. Previous studies that suggested that a normal electrocardiogram effectively rules out left ventricular systolic dysfunction may not have been representative of the type of patients referred by general practitioners with suspected heart failure¹⁰⁶.

Recently a NHS Quality Improvement Scotland Assessment report⁵¹⁰ recommended that general practitioners could triage patients with suspected heart failure by initially using an electrocardiogram. If this was abnormal the patient would be referred for secondary care assessment. If the electrocardiogram was normal then use of BNP/NT proBNP was advised and if this was raised above the recommended action limit referral was again advised. There are problems with this approach in that general practitioners are frequently not confident in interpreting the electrocardiogram and our study suggests that numbers referred are dependent on the recommended cut off or action limit of BNP/NT proBNP. If this approach had been used with the present study cohort the potential number of referrals would have risen from 396 (raised NT proBNP) to 436 (abnormal electrocardiogram n263 +

normal electrocardiogram/abnormal NT proBNP n173), adding further pressure to diagnostic clinic waiting times.

7.4.4 Exploratory Cost Analysis

Cost effectiveness analysis allows decision makers to improve efficiency by spending the limited healthcare budget on those activities that generate the greatest health benefits per pound spent⁵¹⁴. Cost efficiency considerations are a key part of UK National Institute for Clinical Excellence (NICE) technology appraisals⁵¹⁵ and Primary Care Trusts have been reluctant to introduce BNP or NT proBNP without such information. We employed an exploratory cost analysis method. Although this kind of analysis is not as rigorous as an analysis based upon a properly controlled study design (cost effectiveness) it provides a useful exploratory cost analysis of the costs of care received in patients with suspected heart failure. Since each patient provides a putative cost with and without NT proBNP test the design removes interpersonal variance and chance bias.

Unlike previous studies and the recent NHS Quality Improvement Scotland Assessment report⁵¹⁰ that suggested that use of natriuretic peptides would be cost effective, this study based on real life patients identified in primary care concluded that use of NT proBNP using currently recommended cut-offs to pre screen before referral to a one stop diagnostic clinic or secondary care does not result in cost savings.

It is possible that if used in a region where the diagnostic model was open access echocardiography it could have resulted in cost savings but this is an estimation relying on extrapolation from our study cohort rather than based on a real life study in such a region. Furthermore, a recent qualitative study suggested that GPs have a problem with interpretation of echocardiography results and may not initiate evidence based therapies (especially beta blockers) or if even if they do may not up titrate these agents to effective target doses³⁶⁶.

7.5 Strengths and limitations of this study

A limitation of our study is that costs were based on the current service delivery models favoured in our locality. One stop diagnostic clinics are favoured by the majority of general practitioners over open access echocardiography and have been shown to deliver evidence based therapy at target doses to a high percentage of patients with left ventricular systolic dysfunction⁵⁰⁸. Our usually short waiting times (one to two weeks for a patient to be seen) at baseline made it difficult to demonstrate a favourable outcome on the impact on referrals. It is possible that if this study had been conducted in a setting where waiting times for secondary care referral or open access echocardiography were long a more positive outcome on impact and cost analysis may have been seen. Whilst services based on open access echocardiography services may be cheaper and offer some cost benefit over one stop clinics we are only able to estimate this from this study population. Obviously this limits the generalisability of our results to other areas in the NHS with different diagnostic services.

I accept that this exploratory cost analysis has significant limitations and feel that I have learnt to involve a health economist at the study design phase in any future studies of cost effectiveness or benefit. The fact that medication and patient borne costs, the number of GP and secondary care clinic visits are not included is a limitation of the study.

This study used a laboratory based NT proBNP assay (Roche Diagnostics) and it is unclear how other BNP assays (Bayer, Abbott) may perform. However, for any natriuretic peptide assay to be used efficiently within primary care there must be expedient diagnostic services available for patients with raised levels to be referred to. We have previously suggested that in most primary care NHS areas the use of point of care BNP assays (BioSite) are impractical⁵⁰⁸ due to difficulties in short kit shelf life and quality control issues.

The introduction of a new test is likely to have meant that general practitioners investigated more patients than they would have previously and possibly in those with milder symptoms and signs. The introduction of the new General Medical Services contract⁵¹⁶ for general practice that advised all patients with

a label of heart failure or incident symptoms be investigated may have had an impact in lowering general practitioner threshold for using NT proBNP in assessment of these patients. The free availability of the assay may also have increased use by general practitioners. Whilst our study ran over a nine month period we are unable to say whether continued availability of the test beyond this period may have led to a levelling off or reduction in numbers of patients assayed.

The strengths of our study are that it is based on real life decision making by general practitioners and a robust analysis of what actually happened to these patients. Retrospective analyses^{504,514} or decision model estimates^{505,514} do not necessarily give us accurate cost benefit figures for use by primary care trusts in deciding whether to commission the use of natriuretic peptides. We have shown in this study of all comers to general practitioners that rather than reduce referrals, as suggested by guidelines and advisory documents, the use of NT proBNP increased secondary care workload within our local service model. A weakness is that we did not substantiate this further with use of a control group against which assessment of subsequent referrals and care for all patients would have been studied.

7.6 Conclusions and future research implications

Whilst 34% of potential referrals to diagnostic services may have been avoided (in reality 65% [57% NT proBNP “positive” + 8% NT proBNP “negative] were referred), the high number of false positives increased clinic waiting times. The impact of introducing NT proBNP in primary care had an adverse impact on demand for outpatient diagnostic services largely due to the low specificity of the test and the high prevalence of confounding factors in the referred population.

The high false positive rate suggests that in this patient population the cut off may be too low to maximise the cost benefit of NT proBNP use. Furthermore, it would appear to be that NT proBNP levels are a marker of cardiovascular disease and not only left ventricular systolic dysfunction. Also it is apparent that general practitioners have a low threshold for using the assay in patients

with mild symptoms or signs suggestive of heart failure. Using a cut-off of 300 pg/ml would have avoided a further 101 referrals and in the 86 patients in this group assessed by echocardiography only missed 4 patients with left ventricular systolic dysfunction. Further analysis and discussion is needed to identify a cut-off that delivers the most cost effective use of NT proBNP within a primary care setting.

Using a higher single dichotomous cut-off of 300pg/ml or higher cut-offs based on age and gender adjustment along with general practitioner education and strict guidelines for NT proBNP use may be of cost benefit but further real life studies in separate cohorts and various diagnostic service delivery models are needed before widespread introduction of this assay.

Chapter 8.

Discussion and Conclusions

8.1 Background

This work has been placed within the context of primary care and the primary-secondary care relationship. General practitioners are by definition generalists. Research into a specific field such as cardiology, and then the highly specialised area of heart failure management represents a considerable journey for a general practitioner researcher, who, in the everyday course of events will need to deal with a wide range of problems from nappy rash to schizophrenia.

However, heart failure is a significant clinical area not only because of its high morbidity and mortality but also because of new diagnostic and treatment opportunities which have revolutionised patient outcomes. Exploiting these opportunities is dependent on general practitioners having an awareness of current scientific advances and access to facilities for early accurate diagnosis and state of the art management.

This thesis has explored the attitudes and perceptions of general practitioners and specialists regarding heart failure, ascertained the barriers that prevented optimal management and tested strategies to overcome these barriers. Invariably a number of methodologies, both qualitative and quantitative were used in the projects in this thesis. A major feature of the interventions and services provided was that these were necessarily dependent on close cooperation between primary and secondary care. An important by-product of the projects in this thesis is the recognition that the delivery of high quality cardiac services is dependent on a wide range of individuals – general practitioners, nurses, cardiac physiologists and specialists.

8.2 Summary of the studies

8.2.1 Study 1

The first study (chapter two) utilised a qualitative, focus group methodology to ascertain the beliefs, current practices and decision-making of general practitioners in the diagnosis and management of patients with suspected heart failure in primary care, with a view to identifying barriers to good care.

Three categories of reasons were identified contributing to variations in medical practice and why general practitioners experienced difficulties in diagnosing and managing heart failure: (a) **Clinical practice uncertainty** with GPs expressing a lack of confidence in establishing an accurate diagnosis of left ventricular systolic dysfunction, even if open access echocardiography was available. Diagnostic uncertainty led to poor uptake of evidence based treatment strategies for heart failure patients; despite some awareness there was reluctance to initiate modern therapies, especially beta blockers; (b) GPs expressed a **lack of awareness of relevant research evidence** and guidelines about diagnosis and management of heart failure; (c) **Local organisational factors** around NHS provision of diagnostic services, resources and the primary/secondary care interaction influences GP behaviour in heart failure management. Study participants suggested that locality specific and multifaceted implementation strategies for heart failure management across primary and secondary care were needed to overcome these barriers.

The qualitative methodology for this research lent itself to discovering the barriers to optimal care. Rigour was enhanced by multiple coding and respondent validation; the personal and intellectual bias of the principal investigator was minimised by using a co-moderator in three groups, by allowing discussions to develop naturally and by reporting the wide range of perspectives. Deviant case analysis enhanced the validity of the findings by questioning widely accepted practice. As the aim was to get a spectrum of views rather than quantification of the extent to which GPs felt proportionately about one factor or another I did not think questionnaires or structured interviews would have been appropriate methodologies for this study. Generalisability from qualitative research remains an issue with some. However, the concept of transferability has been proposed as an alternative to generalisability. This implies that the onus is on the reader to evaluate the methods, setting and results and decide if these are transferable to their own situation. I believe that the findings of this study can be transferred to the majority of settings in the United Kingdom.

8.2.2 Study 2

This study (chapter three) used a qualitative approach with semi-structured interviews to explore specialists' attitudes and practices in the diagnosis and management of heart failure with a view to identifying barriers to provision of uniformly high standards of care. Twelve clinicians in northern England participated in a study using a purposive sampling strategy.

Three major themes were identified that contributed to variations in practice. (a) diagnostic difficulties, including lack of access to echocardiography, failure in establishing the aetiology of heart failure, and difficulties in the assessment and management of increasingly elderly patients with co-morbidities (b) treatment issues, dependent on consultant experience and interest in heart failure, and barriers to initiation of evidence-based therapies (c) service delivery problems influenced locally by NHS resources, competing clinical priorities and a lack of speciality responsibility for heart failure.

The findings of this study confirm that there is a lack of uniformity in the diagnostic and management services for heart failure in the secondary care sector between clinicians and between institutions. This suggests that there is a pressing need for the exploration of conjoint service provision encompassing the possibility of a non-cardiologist centred service. From this research, exploring the views and experiences of specialists, there was much variation in practice within secondary care itself; a specific heart failure service would benefit patients across the interface.

Semi-structured interviews were used in preference to focus groups or a questionnaire survey. In this setting this methodology was useful in understanding the complex behaviour of clinicians; it did not impose any pre-determined categorisation limiting the field of inquiry and allowed the participants to introduce their own agendas. This proved to be effective in this research. The rigour of the study was increased by multiple coding and respondent validation. Although the number of participants was small, purposive sampling generated rich data from the interviews. The characteristics of the participants were felt to be broadly similar to specialists across British hospitals. The personal and intellectual bias the principal

investigator (AF) may have exerted on the interviews was minimised by allowing discussion to develop naturally, tape recording the procedures for independent coding and by ensuring a wide range of different perspectives from all twelve interviews.

8.2.3 Study 3

Chapter four was an observational study of the introduction and evaluation of a one stop diagnostic clinic for suspected heart failure and the Darlington integrated heart failure service. This service was created to overcome barriers to accurate diagnosis and the management of heart failure identified in studies one and two.

A GP specialist led diagnostic clinic facilitated the accurate diagnosis of LVSD in a single clinic visit rather than after repeated visits for further diagnostic tests, and was well received by GPs and patients. The majority of patients received evidence based therapy and attained target doses of ACE inhibitors and beta-blockers. Contrary to perceived anxieties regarding use of beta blockers in outpatients we achieved a high level of use (70%), even in patients with severe LVSD, without observation of clinical parameters at treatment initiation.

Weaknesses of this study were that it was an observational study of only one service in the north of England. Our model of care may not be transferable to other geographical localities. This is largely due to the fact that clinical services are dependent on local resources, the presence of local clinicians with an interest in heart failure, geographical location (urban, semi-urban or large rural locations will have differing priorities and needs) and availability of diagnostic services. There are no comparative studies of traditional outpatient care by a cardiologist or general physician "usual care", open access echocardiography or heart failure diagnostic clinics. Further research is needed to determine the optimal service delivery model for both patients with LVSD and LVDD or heart failure with preserved left ventricular ejection fraction (PLVEF).

In retrospect the study could have been strengthened by the use of a reliable and valid quality of life measure such as the Minnesota Living with Heart

Failure⁵⁹ or the left ventricular dysfunction questionnaire (LVD-36)⁵⁸. We had considered this but were limited by time in a busy heart failure clinic and the licensing costs of using the questionnaires.

8.2.4 Study 4

This study (chapter six) was designed to test the utility and diagnostic accuracy of natriuretic peptides in a community population of patients with suspected heart failure, using near patient and laboratory assay methods. There have been no comparative studies of BNP (near patient) and NT proBNP (laboratory) assays in patients suspected of having heart failure by general practitioners. Our primary study aim was to test and compare the diagnostic accuracy and utility of BNP and NT proBNP in diagnosing heart failure due to left ventricular systolic dysfunction in patients with suspected heart failure referred by general practitioners to one-stop diagnostic clinics.

This is the first study, using consecutive patients referred from primary care to one-stop diagnostic clinics, that compared a point-of-care assay of BNP with a laboratory NT proBNP assay and demonstrated high NPV for both methods. The patient group was representative of patients suspected of having heart failure by general practitioners. One hundred and fourteen of the 297 patients had left ventricular systolic dysfunction (38%). The area under the curve (AUC) was 0.79 and 0.81 for BNP and NT proBNP respectively. At the manufacturers' recommended cut-off of 100pg/ml, BNP gave a NPV of 82%. BNP performed better at a cut off of 40pg/ml with a NPV of 88%. At a cut-off of 150pg/ml NT proBNP gave a NPV of 92%. Using manufacturers' cut-off of 100pg/ml for males gave NPV of 89% with 150pg/ml cut off for females producing NPV of 94%. Using cut-offs of 40pg/ml and 150pg/ml for BNP and NT proBNP respectively could have prevented 24% and 25% of referrals to the clinic respectively.

The role of the electrocardiogram in diagnosis of LVSD was also analysed in this study. Guidelines suggest that HF is very unlikely in the presence of a normal ECG. However, a NPV of 83% in this study suggests that significant left ventricular systolic dysfunction can be present in the presence of a normal electrocardiogram. If current guidance had been adhered to in referral of

patients for echocardiography 18% (n21) patients with left ventricular systolic dysfunction would have been missed. Previous studies that suggested a normal electrocardiogram effectively ruled out left ventricular systolic dysfunction may not have been representative of the type of patients referred by general practitioners with suspected heart failure.

In this setting, NT proBNP performed marginally better than BNP, and would be easier to use practically in primary care. A satisfactory cut-off has been identified, which needs validating in general practice. NT proBNP could be used to select referrals to a heart failure clinic or for echocardiography. This process needs testing in real life general practice.

Consecutive patients referred to the clinics from primary care were studied, hence reducing selection bias. However, we did not study practices to check if there were any patients not being referred to clinics. Since most general practitioners know that echocardiography is needed for patients with suspected heart failure and that the clinics were well advertised we feel it is likely that we captured nearly all patients that general practitioners were worried about. Measurement bias was reduced by utilising the same high quality echocardiography equipment operated by British Society of Echocardiography accredited cardiac physiologists, reported to a uniform standard and quality checked by one cardiologist. Disease progression bias was reduced by all tests being taken at a one stop diagnostic clinic.

Thirty eight percent is an unexpectedly high prevalence rate for left ventricular systolic dysfunction in this population and it is possible that selection of patients could have been influenced by the education sessions given to practices. This may impact on the generalisability of this study.

These diagnostic values have been derived in one cohort, but require validation in a second cohort with different subjects and clinicians

8.2.5 Study 5

The final study (chapter 7) was conducted as a prospective observational study to determine the practicality, impact and provide an exploratory cost analysis of using NT proBNP as a pre-screening test, or filter, to secondary care referral in a pragmatic primary care setting. GPs were encouraged to

refer all patients with suspected HF and an NT proBNP level at or above 150pg/ml as identified in study 5.

Of the assays done 396 (66%) were at or above the referral threshold of 150pg/ml, with 204 (34%) below 150 pg/ml. 343 were assessed in clinics, of which only 24% (n84) had left ventricular systolic dysfunction (14% of the total cohort). Of the remaining patients, 42 were either not referred or refused referral, eight had died within 15 days of test and three did not attend clinics. Of the 259 without left ventricular systolic dysfunction the majority had cardiovascular causes for a raised NT proBNP level. The use of NT proBNP increased waiting times for clinics to between 3 to 8 weeks (normally 1-2 week waiting time).

Whilst 34% of potential referrals to diagnostic services were avoided, the high number of false positives increased clinic waiting times. The impact of introducing NT proBNP in primary care had an adverse impact on demand for outpatient diagnostic services largely due to the low specificity of the test and the high prevalence of confounding factors in the referred population.

The high false positive rate suggests that in this patient population the cut off is too low to maximise the cost benefit of NT proBNP use. Using a higher single, dichotomous cut-off of 300pg/ml or higher cut-offs based on age and gender adjustment along with general practitioner education and strict guidelines for NT proBNP use may be of cost benefit but further real life studies in separate cohorts and various diagnostic service delivery models are needed before widespread introduction of this assay.

A limitation of our study is that costs were based on the current service delivery models favoured in our locality. One stop diagnostic clinics are favoured by the majority of general practitioners over open access echocardiography and have been shown to deliver evidence based therapy at target doses to a high percentage of patients with left ventricular systolic dysfunction. Our usually short waiting times (one to two weeks for a patient to be seen) at baseline made it difficult to demonstrate a favourable outcome on the impact on referrals. It is possible that if this study had been conducted in a setting where waiting times for secondary care referral or open access

echocardiography were long a more positive outcome on impact and cost analysis may have been seen. Whilst services based on open access echocardiography services may be cheaper and offer some cost benefit over one stop clinics we are only able to estimate this from this study population. Obviously this limits the generalisability of our results to other areas in the NHS with different diagnostic services.

Introduction of a new test is likely to have meant that general practitioners investigated more patients than they would have previously and possibly in those with milder symptoms and signs. The introduction of the new General Medical Services contract for general practice that advised all patients with a label of heart failure or incident symptoms be investigated may have had an impact in lowering general practitioner threshold for using NT proBNP in assessment of these patients. The free availability of the assay may also have increased use by general practitioners. Whilst our study ran over a nine month period we are unable to say whether continued availability of the test beyond this period may have led to a levelling off or reduction in numbers of patients assayed.

The strengths of this study were that it was based on real life decision making by general practitioners and a robust analysis of what actually happened to these patients. Retrospective analyses or decision model estimates do not necessarily give us accurate cost benefit figures for use by primary care trusts in deciding whether to commission the use of natriuretic peptides. We have shown in this study of all comers to general practitioners that rather than reduce referrals, as suggested by guidelines and advisory documents, the use of NT proBNP increased secondary care workload within our local service model. A weakness is that we did not substantiate this further with use of a control group against which assessment of subsequent referrals and care for all patients would have been studied.

8.3 Conclusions

The following conclusions can be drawn from the 5 studies in this thesis.

1. Reasons behind GP lack of confidence and variability in diagnosing and managing HF were complex and included clinical practice uncertainty in diagnosis and treatment, lack of resources including diagnostic services and lack of awareness of relevant research evidence.
2. Variable opinions and practice in diagnosis and management of HF in hospitals and across primary-secondary care were confirmed by specialists and centred on diagnostic difficulties, treatment issues and service delivery problems.
3. A GP specialist led one-stop diagnostic clinic facilitated expedient, accurate diagnosis of LVSD.
4. An integrated HF service across primary-secondary care delivered evidence based therapy, and is likely to have contributed to reduction in hospitalisations and length of hospital stay for HF locally.
5. In a consecutive cohort of patients with suspected HF referred from primary care NT proBNP and BNP demonstrated high NPV for ruling out LVSD.
6. Contrary to previous guidance that a normal ECG effectively ruled out HF, the ECG was normal in a significant number of patients (17%) with LVSD in our cohort of patients referred from primary care. This suggests the ECG should not be used in isolation to rule out HF.
7. Use of NT proBNP as a pre-screening test to secondary care referral may have reduced potential referrals, but the low specificity of the test and high prevalence of confounding factors in the screened population increased demand on one-stop diagnostic services and did not lead to cost savings.

8.4 Implications of this research

The findings of this thesis have raised some important and practical issues for the optimal diagnosis and management of heart failure in primary care and across the primary-secondary care interface. The diagnostic and treatment difficulties identified by GPs and hospital specialists are dependent on a complex interplay of patient, clinician and organisational factors. The barriers

identified by qualitative studies need to be overcome in locality specific and multi-faceted implementation strategies across primary-secondary care. This thesis describes an integrated heart failure diagnosis and management system that overcomes these barriers and in so doing delivers accurate diagnosis, modern evidence based treatment and end of life care that is valued by patients, carers and clinicians.

The ongoing changes in the NHS call for research into models of care or strategies that either shift services from secondary to primary care, or reduce referrals to secondary care diagnostic or clinical services. Much of the work contained in this thesis has been directed at exploring such models of care or strategies. One of the strategies proposed by European Society of Cardiology and NICE guidelines has been the primary care use of the ECG and or natriuretic peptides in the diagnostic triage of patients with suspected heart failure. But despite inclusion in guidelines uptake of BNP and NT proBNP has been slow in the National Health Service. Clinicians and health care purchasers (Primary Care Trusts in the UK) still harbour concerns about appropriate cut offs, which assay to use, lack of expedient referral pathways for patients with a raised levels and absence of cost benefit/effectiveness data from a "real life" primary care study.

Landmark studies such as the Hillingdon heart failure study confirmed the high negative predictive value of BNP/NT proBNP for excluding heart failure but were not conducted in primary care, rather in patients referred from primary care. These studies do not address the role played by the general practitioners' decision making within the dynamics of patient consultation, the real life availability (or lack) of varied diagnostic facilities across the primary-secondary care divide, high co-morbidities and the widespread use of cardio-active drugs (ACE inhibitors and diuretics for hypertension, beta-blockers for angina) in elderly patients in the community. All of these have an impact on the utility of natriuretic peptide use in primary care. Furthermore, the poor positive predictive value and low specificity of this test in real life practice mean that large numbers of patients with raised BNP/NT proBNP do not have heart failure due to left ventricular systolic dysfunction. In my opinion companies marketing these assays have rushed the test into clinical practice

before adequate studies in community based patients. Work in this thesis concludes that the optimum cut-point for use in real life primary care prior to referral for echocardiography has yet to be resolved. Furthermore, there are potential problems with GPs using the ECG to rule out HF. Apart from GP lack of confidence in interpretation of the ECG, results from chapters six and seven question the previously reported high NPV of the ECG and suggest that those studies may not have been representative of the type of patients referred by GPs with suspected HF.

This thesis demonstrates that the prognostic power of BNP/NT proBNP extends beyond LVSD to most cardiac conditions. Ideally all patients with raised natriuretic peptides deserve a full cardiac assessment including echocardiography, followed by optimal use of evidenced based pharmacotherapy and health professional support. We need to find ways of providing expedient diagnostic and treatment services to these patients especially in health care rationed systems such as the NHS. Until this issue in particular is addressed widespread natriuretic peptide use is unlikely within the UK and other European Health care systems.

8.5 Future research

This thesis identifies several areas in need of further investigation.

1. Despite the success of our model (chapter 4) and other heart failure clinics, and the importance of accurate diagnosis of heart failure the NHS is still largely only offering traditional cardiology clinic referral or open access echocardiography. There are no comparative studies of traditional outpatient care (usual care), open access echocardiography or heart failure diagnostic clinics. Further research is needed to determine the optimal service delivery model.
2. Heart failure due to preserved left ventricular ejection fraction or left ventricular diastolic dysfunction is difficult to diagnose but such patients have poor quality of life and are frequently admitted to hospital. There is little known about appropriate treatment and management strategies. Further research is needed in this area.

3. The optimum referral threshold for use of natriuretic peptides has yet to be determined. At a higher single dichotomous cut-off of 300pg/ml or higher cut-offs based on age and gender adjustment along with general practitioner education and strict guidelines, NT proBNP use may be of cost benefit. The role of natriuretic peptide assay in care pathways (both diagnostic and treatment monitoring) is also in need of further evaluation. Further real life studies in separate cohorts and various diagnostic service delivery models are needed before widespread introduction of this assay.
4. Many patients in primary care with LVSD are still not on a beta blocker. Further research into GP education, initiation and up titration of beta blocker therapy for this group of patients is needed.
5. Newer models of care in heart failure management including the place for dedicated heart failure clinics and BHF specialist nurses need formal evaluation.

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Appendix 1: Respondent validation form for focus group study

Name:

Comments sheet

Please circle one of the statements below that most accurately describes your overall level of agreement with the enclosed study summary:

I strongly agree

I disagree

A neither agree nor disagree

I agree

I strongly agree

Please add any other comments below or overleaf:

|

Appendix 2: Discussion points for specialist semi-structured interviews

1. Do you think GPs can diagnose HF accurately (a) on clinical grounds and (b) by using open access investigation?
2. Do you think consultant cardiologists can diagnose HF accurately (a) on clinical grounds and (b) by using open access investigation?
3. What are the problems in the management of HF in the community?
4. What is the most accurate way of making this diagnosis?
5. If it is by using an investigation, what investigation should be used?
6. Who might order this investigation?
7. Who should conduct the investigation?
8. Do you offer an open access echo service in your hospital? If not why not?
9. What do you feel about its effectiveness and its use?
10. Do you think GPs can interpret echo results?
11. Do you think that non-cardiology consultants can interpret echo results?
12. What do you think can be done to improve the accuracy of HF diagnosis?
13. Do you think that HF is treated properly in the community?
14. Do you think that GPs are capable of giving optimal treatment to patients with HF?
15. Do you think consultants are capable of giving optimal treatment to patients with HF?
16. What do you think can be done to improve the optimal treatment of patients with HF?
17. Do you think patients with HF should be referred to a consultant, considering that there have been recent changes in the way patients with HF are treated?
18. Do you think patients should have to wait for an accurate diagnosis of HF to be made and be treated in some interim way?
19. What would you regard as a reasonable length of time for which a patient should have to wait without experiencing adverse quality of life or prognostic factors before investigation and then optimal treatment?
20. Can you suggest any models of care that are different from existing models for the diagnosis and management of patients with HF from general practice?
21. Would you be prepared to be part of a scheme that might contain an alternative method of delivering HF diagnosis and management in the community?
22. If you had HF would you rather be seen by your GP or be referred to a consultant?
23. Do you have any views about what you think GPs think about their cardiology colleagues in terms of services for managing HF?
24. Are there any other areas in HF diagnosis and management that you wish to discuss?

Appendix 3: One-stop heart failure clinic referral form

ONE STOP HEART FAILURE CLINIC REFERRAL FORM

Darlington Memorial Hospital
 Hollyhurst Road
 Darlington
 DL3 6HX

Tel: (01325) 743333
 Fax: (01325) 743601

Patient Details

Surname _____
 Forename _____
 Address _____

 Tel No. _____
 DOB _____
 Unit Number _____

Doctor Details

Name _____
 Surgery _____

 Tel No. _____
 (Practice stamp may be used)

Relevant Past History

Past MI Angina/IHD Atrial Fibrillation Hypertension
 Diabetes Mellitus Alcohol Abuse Valvular Heart Disease

Other _____

Current Medication (Please Specify drug and dose in relevant box)

Diuretic	ACE inhibitor	Digoxin	B Blocker	Nitrate
Spirololactone	AII antagonist	Calcium channel blocker		
Other Agents				

Other Relevant Information

Referring Doctor Signature Date

Appendix 4: Patient information sheet for heart failure diagnosis clinic

Heart Failure Diagnosis Clinic

Darlington Memorial Hospital

Directorate of General Medicine

Patient Information

What is the Heart Failure Diagnosis Clinic?

The Heart Failure Diagnosis Clinic is a one-visit clinic which aims to provide an accurate explanation (diagnosis) for the symptoms that you are experiencing.

The clinic is held on a Thursday morning in the medical out-patients department of Darlington Memorial Hospital.

The clinic is supported by a Nurse Specialist who will be available to answer any questions you may have.

Why have I been referred to the Heart Failure Diagnosis Clinic?

Your GP has requested that you are referred to the clinic, in order to find an explanation for the symptoms that you have reported to your GP.

You may have been experiencing symptoms that include, breathlessness, tiredness and swelling in your feet and ankles. These can be due to a condition called Heart Failure.

What is Heart Failure?

Heart Failure is a condition in which the pumping chamber of the heart (the left ventricle) does not function as efficiently as normal.

This can lead to a variety of symptoms, including breathlessness, chest pains, swelling in the lower limbs, tiredness, and other symptoms. Heart Failure is one of the most common heart problems in the country. Although not curable, there is a very effective treatment available. Mostly in the form of medications, although there are other options in some cases.

What can I expect to happen at the Heart Failure Clinic?

At the clinic you can expect

- To be examined by a Doctor with a specialist interest in Heart Failure.
- You may have had some blood taken by your GP and an X-ray of your chest. These results will be discussed with you at your appointment.
- You will also have an ECG (a heart tracing) taken.
- You will also have an Echocardiogram (a heart scan), which is an ultrasound scan of the chest area (similar to the scans pregnant women have).

After your tests, you will be seen again by the clinic doctor and informed of the results.

What do the results mean?

Heart Failure is diagnosed by the Echocardiogram. If this reveals that you have some impaired function of the pumping chamber, then a diagnosis of heart failure will be made.

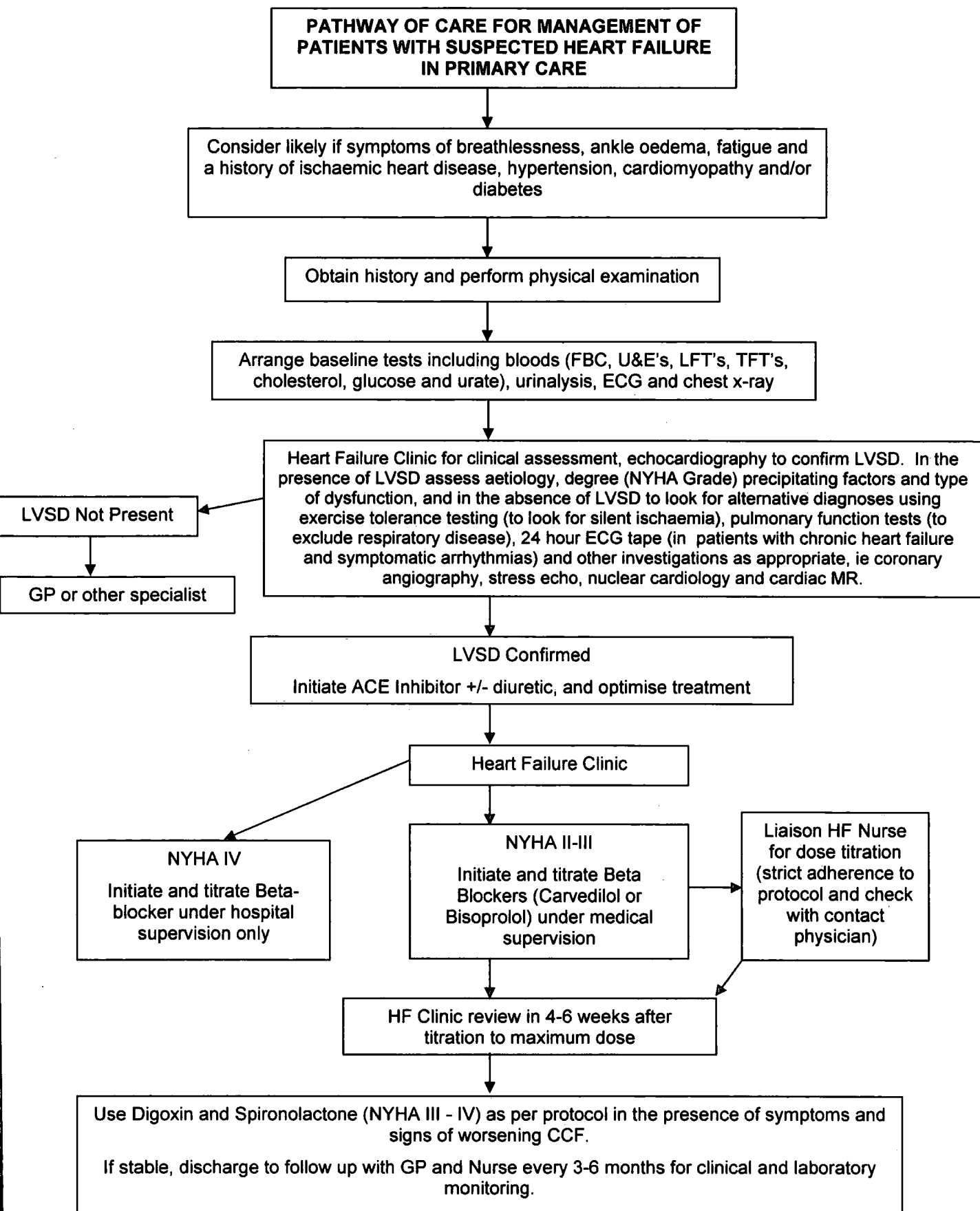
What next?

If the scan confirms that you have heart failure, the doctor in the clinic will discuss this with you and start you on some medication to control your symptoms. You will then be seen by a specialist nurse in heart failure who will be available to answer any questions you may have.

What if I don't have Heart Failure?

If you don't have heart failure, you will be referred back to your GP for further investigation.

Appendix 5: GP guidance for referral to heart failure clinic



Appendix 6: Letter to GPs launching NT proBNP use in primary care

DR GJG METCALFE

DR A FUAT

DR BF PENNEY

DR E MOORE

CARMEL MEDICAL PRACTICE

NUNNERY LANE

DARLINGTON

CO DURHAM

DL3 8SQ

Telephone: (01325) 463149/462398

Facsimile: (01325) 381834

Dear Colleague,

We plan to introduce a novel new blood test - N-Terminal pro-B Type Natriuretic Peptide (NP Pro-BNP) as a pre-screening test, or filter to secondary care referral for patients with suspected heart failure.

Recent evidence and work we have been doing over the last 18 months suggest that NT pro-BNP has a role in ruling out heart failure. In other words if NT Pro-BNP is below a certain cut off level (less than 150 pg/ml) heart failure is very unlikely (with a negative predictive value of 97.5%).

Although research has been done in various settings, NT pro-BNP needs to be made available to GPs and the practicality and cost effectiveness of its use studied in a "real life" GP setting. As each test costs around £15 we need further evidence to convince NHS providers to make the test widely available. The NHS Workforce Development Confederation fund has kindly given us a grant for 600 tests and a research nurse to study this important development in the diagnosis of suspected heart failure.

We would like your support in this venture. You may start to order NT Pro-BNP but please only use the test when heart failure is suspected in a newly presenting patient. We do not have enough tests initially for practices to use for all their patients on a heart failure register but have not had an echo. However if these patients become breathless and you have a doubt about the diagnosis then NT Pro-BNP use would be appropriate.

If the level is at or over 150 pg/ml you will be advised to consider referral to the heart failure clinic. If below 150 pg/ml heart failure NT Pro-BNP is very unlikely so please consider an alternative diagnosis. All patients on whom BNP has been ordered will be followed up by a survey of patient notes and we would be grateful if you would allow access to our research nurse who will contact your practice manager.

Please use the sticky labels to order the tests. These boxes must be ticked before the test will be done and are the basis of our cost effectiveness analysis. One yellow topped (SST II) vacutainer tube is needed for the NT Pro-BNP assay. An ECG sent with the blood would be very welcome as we are planning a parallel study of the value of ECG in suspected heart failure.

Cont/d...

2

You will be visited soon by your PCT CHD Lead Nurses (led by Caroline Levie) to discuss this further. However, if you have questions please contact Dr Ahmet Fuat on 01325 462883 or 07740 775127.

We appreciate your cooperation in this matter which we believe will make us the first area in the United Kingdom to allow GPs the use of this valuable test.

With kind regards,

Yours sincerely,

2.2 Dr A Fuat, Dr J J Murphy, Dr A Mehrzad

2.3 Dr A Hetherington, Jenny Johnson & Dr S Smellie

Appendix 7: Revised referral pathway for one stop diagnostic clinics

GP Guidelines for Referral to Heart Failure Diagnosis Clinic

Patient presents with symptoms suggestive of heart failure

Obtain history and perform physical examination

Arrange baseline tests:

- BNP, U+E, LFT, TFT, FBC, Glucose. Cholesterol. (ESSENTIAL)
- Chest X-ray. (ESSENTIAL)
- ECG. (DESIRABLE)

NT proBNP Normal (<150 pg/ml). Consider other pathologies.

NT proBNP Raised (≥ 150 pg/ml). Refer to diagnosis clinic for Echo and assessment.

Complete referral form with relevant details to ensure patient receives appointment within the correct clinic.

Inform patients of referral:

- ❖ Patients will receive a Thursday Morning appointment within 4 weeks of referral.
- ❖ Patients will also receive an information pack telling them what to expect in the clinic and how long their appointment will be (approx 3 hours for new patient).

Patient seen in clinic and heart failure ruled out:

Patient will be referred back to GP for further management, unless there is an urgent clinical need for other consultant involvement.

Patient seen in clinic and heart failure confirmed:

Treatment plan and medications required will commence in clinic. Review for up-titration of medications will be undertaken in the clinic. When stable on medication, patient will be referred back to GP.

Further advice and information can be obtained from Victoria Duffy. Specialist Nurse Practitioner– Heart Failure on 01325 746186.

Appendix 8: Focus groups – advice and tips for facilitators.

Focus groups are used as a research method to find out what groups of people think and how they discuss issues and ideas together.

A focus group is:

- A group discussion
- Focused on a particular topic
- Usually has members who have something in common
- Led by a facilitator
- Time limited
- Task limited

Strengths

- A good way of discovering people's attitudes, beliefs and perceptions on a particular subject (not only what people think, but also how they think and why they think that way).
- Data rich in human experience. A reflection of real life and experience of group members.
- Able to collect data "beyond the quantitative"/ "beyond the tick-box".
- Encourages spontaneity and candour.
- Can be used as a preliminary/preparatory method for gathering ideas for further research.
- Able to tape-record and transcribe (so data not missed).
- A group task can be completed in a short time.
- Do not discriminate against people that cannot read or write.
- Can encourage participation from those who are reluctant to be interviewed on their own.
- Can encourage contributions from people who feel they have nothing to say (but engage in the discussion generated by other group members).

Weaknesses

- Needs good facilitator who can encourage people to talk about experiences and ideas.
- May be dominated by 1 or 2 people.
- May be threatening to some individuals.
- May put "words in people's mouths".
- May get bogged down in power structures, hierarchies and politics.
- Time consuming to arrange and analyse – need good time management.
- Expensive if group members' expenses to be covered.

Sampling and sample size

- 8-12 members ideal
- Can have multiple groups to improve sample size and potentially strength of research.

- Can be generalisable if groups chosen carefully and are representative of the study population e.g. age, gender, ethnicity, experience etc.
- Triangulation can help by applying comparison with other sources of evidence.

Running Focus Groups

The focus group has a beginning, middle and an end:

- Beginning – getting people talking, relating experiences and ideas.
- Middle – helping people to focus by asking more specific questions.
- End – completing the group task.
- Keep a topic guide to help structure the discussion while allowing the interaction between the members of the group to develop.

Tips on dealing with potential problems

- If a person is not taking part try to draw them in by asking if they have anything to add. Try to remember something they have said so that you can do this at an appropriate time.
- If one person is dominating the discussion, it is acceptable to say politely: 'Thank you for that; now I think we need to hear what other people think'.
- If two or more people are talking at once, deal with it immediately: 'Can.... make her point first and then please?'.
- If two or more people are having their own conversation, deal with it at once: 'Do you want to say something to the group?'
- If two or more people are arguing about something and excluding others, step in with: 'There are clearly different points of view on this; can I check Feels this way ... and ... feels that way ...? What do other people think?'
- Do not assume that you understand what someone is saying; encourage people to say more and explain or describe their point, using phrases like: 'Can you tell us a bit more about that ...?'
'How did you feel when that happened?'
'Is this something that other people feel/have experienced?'

Note these phrases on the topic guide so that you can remind yourself if necessary.

Appendix 9: Facilitators guide of points to consider in GP focus groups.

“Suspected Heart Failure” Focus Groups with GPs – points to consider.

Diagnosis:

- Are they more likely to consider HF in high-risk patients e.g MI, IHD, DM?
- Which symptoms are considered?
- What examination do they conduct & which signs are considered important?
- Do they use any scoring systems?
- What tests are utilised (bloods, ECG, CXR, Echo) & are they always ordered?
- If tests not done, why not?
- What open-access facilities exist? Are they used every time?
- Are they aware of the difference between Systolic and diastolic HF? Does this influence the treatment choice?
- How comfortable are they with interpreting results? ECG, CXR, Bloods & Echo.
- Do they investigate themselves or refer (all patients or selected groups)?
- What influences decision to refer?
- Who do they refer to? Cardiologist, general physician, geriatrician?

Guidelines:

- Are they aware of any guidelines for HF?
- Do they use them?
- How useful do they find them?
- Would they welcome guidelines? In any particular format?

Treatment:

- How do they normally manage HF?
- Awareness of current evidence on the use of ACE inhibitors, B-blockers, Digoxin and AIIAntagonists?
- Would they use these agents?
- Do they have any worries about initiating them in GP?
- What dosages of ACE are aimed for? Do they reach them? How do they decide final dose? What monitoring is undertaken?
- What experiences of ACEi side-effects?
- Do they consider alternatives if ACE intolerance? If so, which agents?
- Do they recommend any lifestyle changes?
- Are co-morbid conditions treated any differently e.g. AF, HT, DM, IHD?
- Do you offer any literature to patients or carers on HF? Would availability of this be welcome?

Services:

- What change in current services would they like?
- Open- access facilities? Cardiologist services? Liaison nurse?

Education:

- Do they see education as being of assistance in their diagnosis and management of HF in GP?
- What sort of educational programs would they find useful?

Appendix 11: BNP/NT proBNP study patient information and consent form

Primary Care Group
Valley House
Valley Street
Darlington
DL1 1TJ

Darlington Memorial Hospital
Hollyhurst Road
Darlington
DL3 6HX

Darlington 
Primary Care Group

FINDING A BLOOD TEST TO HELP IN THE DIAGNOSIS OF BREATHLESSNESS

PATIENT INFORMATION SHEET

You are being invited to take part in a research project. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study

A condition called heart failure can cause breathlessness, ankle swelling and fatigue. Heart failure is a condition where the heart is not pumping as efficiently as it should. It is treatable by many currently available drugs. The current best way to diagnose it is with a heart scan called an echocardiogram. This is a painless procedure but only a quarter of patients referred for this test have heart failure. Recently a blood test (BNP) has been developed which may point to the diagnosis and may reduce referrals to hospital if a GP finds the test is normal. The purpose of this study is to study the accuracy of the test.

Why have I been chosen?

Your GP has decided you need further investigation of your health and has referred you to this new specialist clinic. All patients with symptoms similar to yours will be referred and we hope to study 300 patients over the next few months.

Do I have to take part?

Is it up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

We will take an extra tube of blood (about a tablespoons worth) in addition to the other routine tests you will have. You will then be asked to have an echocardiogram so that we can compare the results.

Your routine care will not be affected in anyway. A specialist with a view to establishing an accurate diagnosis will still assess you. Treatment will then be offered to you in line with current best clinical practice. You do not have to take any investigational drugs. A specialist nurse may also see you to offer advice on lifestyle and treatment.

What are the alternatives for diagnosis?

You would still be offered a referral to the clinic and would have the standard blood tests and heart scan but no extra blood test for BNP.

What are the possible disadvantages and risks of taking part?

As you are being treated in line with current best practice you are not being subjected to any additional risks. If you have heart failure you will be offered certain drug treatments, which may cause side effects, but these will be explained to you.

What are the possible benefits of taking part?

The benefits are that you will be thoroughly examined and investigated by a specialist team with the aim of establishing an accurate diagnosis. You will then be offered treatment to improve your health.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you, which leaves the hospital/surgery, will have your name and address removed so that you cannot be recognized from it. Your own GP will be notified of your involvement and details of the test results and treatments will be sent to them.

What will happen to the research results?

The results of the study will be written up for publication in medical and educational journals and for presentation at scientific meetings. You will not be identified in any report or publication.

Who is organizing and funding the research?

The study is being organized by Dr Ahmet Fuat (a local GP and NHS Research Training Fellow) and Dr Jerry Murphy (a local Consultant Cardiologist). Darlington Primary Care Group, South Durham NHS Trust and Northern & Yorkshire NHS R&D are funding the study.

Contact for Further Information

If you require further information you can contact Dr Ahmet Fuat at Carmel Medical Practice, Darlington Tel number 01325 463149/462398.

**THANK YOU VERY MUCH FOR READING THIS AND TAKING PART IN
THIS IMPORTANT STUDY**

