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Prospective evaluation and long term follow up of patients referred to secondary care based upon natriuretic peptide levels in primary care.

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Abstract

Objectives: The UK National Institute for Health and Care Excellence (UK-NICE) and European Society of Cardiology (ESC) guidelines advise natriuretic peptide (NP) assessment in patients presenting to primary care with symptoms possibly due to chronic heart failure (HF), to determine need for specialist involvement. This prospective service evaluation aimed to describe the diagnostic and prognostic utility of these guidelines.

Methods: We prospectively collected clinical, echocardiography and outcomes data (minimum 5yrs) from all patients referred to the Leeds HF Service for 12m following the initiation of the NP-guideline-directed pathway.

Results: Between May 1st 2012 and August 1st 2013, 1020 people with symptoms possibly due to HF attended either with a raised NT-pro-BNP or a previous myocardial infarction (MI) with an overall rate of LVSD of 33%. Of these, 991 satisfied the ESC criteria (NT-pro-BNP ≥125pg/mL) in whom the rate of LVSD was 32%, and 821 the UK-NICE criteria in whom the rate of LVSD was 49% in those with a previous MI, 25% in those with NT-pro-BNP concentration 400-2000pg/mL and 54% in those with NT-pro-BNP concentration of >2000pg/mL. An NT-pro-BNP concentration 125-400pg/mL had a 12% risk of LVSD. Specificity was poor in women >70yrs, who made up the largest proportion of attendees. Elevated NT-pro-BNP levels were associated with lower survival even in the absence of LVSD.

Conclusion: In people referred through the ESC and UK-NICE guidelines, elevated NT-pro-BNP is a marker of increased mortality risk, but there is wide variation in specificity for LVSD. Age- and sex-adjusted criteria might improve performance.

Introduction

Chronic heart failure due to left ventricular systolic dysfunction (LVSD) is a major cause of death and disability worldwide and a significant financial burden on global healthcare systems. Early diagnosis and institution of evidence-based medical therapies, in patients with chronic heart failure due to LVSD, has been shown to substantially reduce mortality[1] and unplanned hospitalisation,[2][3] the major contributor to the cost of chronic heart failure.[4] In primary care the accurate diagnosis of chronic heart failure remains difficult,[5][6] and the need to develop approaches to improve diagnosis is therefore important.

Elevated B-type natriuretic peptide (BNP) concentrations are associated with an adverse prognosis in the general population,[7][8] and in people with [9][10][11] and without [12][13][14] LVSD and in heart failure, a reduction in NP concentrations with treatment is associated with an improvement in prognosis.[15] A series of screening studies in higher risk people have demonstrated that those with elevated BNP levels have a higher rate of LVSD.[7][16][17][18][19] Since 2008 and 2010 respectively, the European Society of Cardiology (ESC) and United Kingdom (UK) National Institute of Health and Care Excellence (UK-NICE) guidelines [20][21] have advocated measurement of serum concentrations of natriuretic peptides (NP), specifically BNP or NT-pro-BNP, to aid in the clinical assessment of people presenting in primary care with symptoms possibly due to chronic heart failure. The guidelines differ in their cut-off values for NT-pro-BNP above which referral should be considered (ESC: ≥125pg/mL [22] and UK: >400pg/mL). The UK guidelines (but not those

from the ESC) suggest that a measurement of BNP is unnecessary in people with a history of myocardial infarction and also suggest that an NT-pro-BNP level >2000pg/mL should trigger a more urgent referral. The ESC guidelines were updated in 2016 and the UK-NICE guidelines have been updated in 2018, but the cut-offs for referral are unchanged.[23]

However, despite widespread adoption of BNP measurement as a diagnostic and prognostic marker in patients presenting with acute and chronic symptoms suggestive of heart failure, the positive and negative predictive values of BNP measurement within a management pathway based on the ESC or UK-NICE guidelines have, until now, remained unexplored. The aim of this prospective service evaluation was to define the diagnostic and prognostic value of the ESC and UK-NICE NP-based guidelines in unselected patients presenting to primary care with symptoms suggestive of chronic heart failure.

Methods

As part of a comprehensive *a priori* determined service evaluation of the ESC and UK-NICE guidelines referral algorithms we collected data on all patients referred to the Leeds Heart Failure Clinic following a raised NP test performed due to clinical suspicion of heart failure in primary care between 1st May 2012 and 1st May 2013. Prior to the initiation of the NP-guided pathway, primary care teams had referred based upon clinical suspicion alone. In order to avoid false 'negative' tests during the first year, we used the ESC cut-off of NT-pro-BNP level ≥125pg/mL as the lower threshold for referral which allowed us to

explore clinical features and outcomes when using both ESC and UK-NICE thresholds. The clinic covers a mostly urban and suburban catchment area of 750,000 people, and the clinic provided the only route for further investigation during the period in question.

Upon arrival at the clinic, demographic details, medical history, and medical therapy were recorded and patients underwent clinical assessment by specialist nurses. A history of previous myocardial infarction was confirmed from the patient-reported history, the general practitioners' letters and the hospital medical notes. Blood pressure was taken (right arm recumbent), electrocardiography and echocardiography performed, and patients were reviewed by one of two consultants with a specialist interest in CHF (KKW, MTK). At the end of their visit, a primary diagnosis was assigned to each patient.

All NT-pro-BNP samples from practices referring to the Leeds Heart Failure Clinic were analysed in the biochemistry laboratory at Leeds Teaching Hospitals NHS Trust using the Immulite 2000 assay (Siemens Healthcare Diagnostics, Camberley, UK). The interbatch coefficient of variation was 8.9% at 350pg/mL and 5.9% at 4100pg/mL. Results were described numerically but included a commentary stating whether referral was recommended based upon the cut-off as described.

Twelve lead electrocardiography

Standard 12-lead electrocardiographs (ECGs) recorded at 25mm/s were analysed by one of two cardiologists (MTK and KKW), who recorded rhythm (sinus rhythm or atrial fibrillation), heart rate and QRS duration.

Echocardiography

Two-dimensional echocardiography was performed according to American Society of Echocardiography recommendations by echocardiographers (JG, MP, JEL) without reference to NT-pro-BNP measurements. Left ventricular (LV) dimensions and ejection fractions were calculated according to recommended guidelines.[24] According to guidelines and the indications for therapy for heart failure in place at the time of data collection, LVSD was defined as an ejection fraction (EF) of <50%.[25]

Mortality data

Vital status data were collected using linked Hospital Episode Statistics and Office of National Statistics mortality data following S251 ethical approval (CAG 8-03(PR1)/2013). All patients had a minimum follow-up of 5 years.

Statistical analysis

All data items were recorded on case report forms and transferred to a bespoke database for statistical analysis. Patient characteristics were summarized according to the ESC NT-pro-BNP cut off (≥125pg/mL) or UK-NICE pathway (previous MI, 400pg/mL-2000pg/mL, and >2000pg/mL).

The positive predictive value of the test was calculated as the number of true positive diagnoses of LVSD and therefore heart failure with reduced ejection fraction (HFrEF) divided by the number of patients attending clinic, separately by guideline category, after positive test result.

Although neither guideline includes an adjustment for age or sex, other datasets suggest that these variables have an influence on NT-pro-BNP concentration.[26][27] We therefore also undertook an exploratory analysis to examine the performance of NT-pro-BNP as a diagnostic tool in subgroups divided by age (<70 and ≥70), sex (male versus female) and the presence of atrial fibrillation (AF), (yes or no) for both ESC and UK-NICE cohorts using Chi-squared analysis to explore differences between NT-pro-BNP category, age, sex and the presence of AF and renal dysfunction as covariates for the presence of LVSD.

Survival analyses by guideline and category were performed to the censor date of 20th May 2018 and presented using Kaplan-Meier curves. Differences in survival between cohorts, categories of patients, and between those with and without LVSD, were analysed by log-rank survival tests.

Analysis was performed using Staview 5.0, SAS Institute, USA. All statistical tests were two-sided and described as 'significant' if $p<0.05$. Throughout the present report, our methodology and results are reported according to the STROBE guidelines for observational studies.[28]

Results

1020 adults with symptoms possibly due to heart failure were referred. The referral pathway for most was as a result of an elevated NT-pro-BNP, although 156 were referred on the background of previous myocardial infarction of whom 29 did not undergo an NT-pro-BNP measurement.

Demographic data, medical history, symptomatic status and the results of investigations are shown in Table 1, divided by groups according to the guideline-directed criteria. A large proportion of patients (900/1020; 88%), were >70 years of age. More than 60% in each cohort self-reported symptom levels at New York Heart Association classes I or II. Overall, 49% and 55% were already taking a beta-blocker or RAAS antagonist (Table1).

Diagnostic outcomes

Overall, 334/1020 (33%) had evidence of LVSD confirming a diagnosis of HFrEF, although the proportion varied across the criteria.

European Society of Cardiology criteria

In this analysis we excluded patients referred via the MI pathway without an NT-pro-BNP level (n=29). This left 991 patients that fulfilled the ESC criteria for consideration of referral for echocardiography (NT-pro-BNP ≥125pg/mL),[20] of whom 89% (878/991) were >70 years of age and 319/991 (32%) had LVSD (Table 1).

United Kingdom – NICE criteria

Table 1 also shows the clinical and imaging variables for the cohort divided by the categories in the UK-NICE guidance. We excluded those with a previous MI from the UK-NICE NT-pro-BNP categories.

The cohort with a previous MI (n=156) had a male preponderance, and most (136/156 (87%)) were >70years of age. Of these, 49% had evidence of LVSD on echocardiogram.

Patients referred with an intermediate NT-pro-BNP level (400-2000pg/mL) had a female preponderance and most (395/436; 91%) were >70 years of age. In this cohort, 110/436 (25%) had evidence of LVSD. Patients referred with a 'high' NT-pro-BNP level according to the UK-NICE criteria (>2000pg/mL) were not older than those in the intermediate group (212/229; 93% >70years; p=0.39) but did have a higher rate of LVSD than those in the intermediate group (123/229; 54%; p<0.0001).

Overall, an NT-pro-BNP >400pg/mL was associated with LVSD in 233/665 (35%) of patients without a previous MI. Therefore, whilst the positive predictive value of 400pg/mL is better than the ESC level of 125pg/mL, in our population we would have missed 24 cases of LVSD in 199 people (12%) without a previous MI.

The influence of age, sex, renal dysfunction and atrial fibrillation on diagnostic outcomes

Neither the ESC nor UK-NICE guidelines include age or sex in their criteria. We found variable evidence of heterogeneity in the positive predictive value of a raised NT-pro-BNP by age and sex (Figures 1a and b). Specifically, in those with an NT-pro-BNP≥125pg/mL, 38% (n=43/113) of patients <70 years compared with 32% (n=276/878) in those ≥70 years had LVSD (X^2=2.00; p=0.15). In the UK-NICE 4000-2000pg/mL cohort the positive predictive value in the younger and older patients were 41% and 27% respectively (X^2 = 6.32; p=0.012) and in the >2000pg/mL cohort, younger patients were also more likely to have LVSD than those ≥70 years (88% v 51%; X^2=8.80; p=0.003). Using the ESC criteria overall 44% (n=187/426) of men compared with 24% (n=132/565) of women had LVSD. These differences in performance were also present at both UK-NICE categories with men more likely to have LVSD at both NT-pro-BNP categories (400-2000pg/mL: 34% v 19%; X^2=11.78; p=0.0006, and 2000pg/mL: 64% v 45%; X^2=8.65; p=0.0033). Whilst only 19% of elderly women with a NT-pro-BNP 400-2000pg/mL had LVSD, they represented 40% of all referred patients (Figures 1a and b).

For patients satisfying the ESC guidelines, 31% of patients in sinus rhythm had LVSD (217/703) compared with 35% of those in atrial fibrillation (102/288). Regarding UK-NICE groups, in the 'intermediate' group, 27% of people in sinus rhythm had LVSD (80/300), compared with 23% of people in atrial fibrillation (30/130); in the 'high' group 59% of people in sinus rhythm had LVSD (66/112), compared with 49% of people in atrial fibrillation (57/117). None of these positive predictive values were statistically significant between groups with sinus rhythm and atrial fibrillation.

For patients satisfying the ESC guidelines, 31% of patients with an estimated glomerular filtration rate (eGFR) ≥60 had LVSD (204/656) compared with 34% of those with an eGFR<60 (114/331). Regarding UK-NICE groups, in the 'intermediate' group, 27% of people with an eGFR ≥60 had LVSD (76/287), compared with 23% of people with an eGFR<60 (33/146); in the 'high' group 57% of people with an eGFR ≥60 had LVSD (68/120), compared with 51% of people with eGFR<60 (55/108). None of these positive predictive values were statistically significant between groups with preserved and impaired renal function.

Prognostic outcomes

We had vital status in all except 2 attendees to the censor date of 20th May 2018 with a minimum of 5 years of follow-up (in total >6340 patient-years). Compared with patients with a 'low' NT-pro-BNP concentration according to the UK-NICE guidelines, patients with both a 'high' NT-pro-BNP (>2000pg/mL) (HR 5.98, 95% CI 4.33-8.25) and those with an intermediate result (400-2000pg/mL) (HR 3.08, 95% CI 2.25-4.20) had a significantly higher mortality rate at 5 years (Figure 2). The overall 5 year survival rate of those with a 'high' NT-pro-BNP level was 41.9 (95% CI 35.4-48.4) whilst the survival of the ≥125pg/mL group, at 60.8% (95% CI 57.9-63.7) was similar to that of the UK-NICE 400-2000pg/mL (intermediate) (61.8 (95% CI 57.3-66.3) and 'MI' cohorts (55.8, 95% CI 48.0-63.6). Although the absence of LVSD in those with elevated NT-pro-BNP levels according to the ESC criteria was an independent predictor of good outcome (HR 0.70, 95% CI 0.57-0.81) the presence of LVSD was not additive in any of the UK-NICE criteria (Figures 3a

and b). No patient with a previous MI and only 2 in the >2000pg/mL group died within the first 6 weeks after the referral or blood test.

Discussion

This is the first prospective study to report the diagnostic and prognostic value of two diagnostic pathways for possible heart failure that include natriuretic peptide (NP) measurement in primary care. We demonstrate in unselected consecutive patients referred from primary care with symptoms or signs possibly due to heart failure *and* a raised NT-pro-BNP that 32% and 35% of those investigated and referred according to the current ESC and UK-NICE guidelines will have LVSD. Importantly however, we also found that 12% of people with symptoms but an NT-pro-BNP level 125-400pg/mL have LVSD.

Diagnosing chronic heart failure due to LVSD in primary care is difficult. Symptoms such as breathlessness and fatigue have poor specificity, while those such as orthopnoea and lung crepitations are rare and have low sensitivity.[5][29] Chest radiography is often also unhelpful.[30] Hence more refined approaches are required to improve the diagnosis of chronic heart failure in primary care, and pathways to achieve this form a central part of the UK-NICE and European Society of Cardiology guidelines for the diagnosis and management of chronic heart failure.[20][21] For almost a decade, these pathways have included an assessment of NP concentrations. In contrast to the US guidelines, which suggest that a measurement of NP can be helpful,[31] the ESC and UK-NICE guidelines describe cut-offs for NP above which referral is advised.

Much of the historical work on the utility of NP testing in the diagnosis of chronic heart failure is based either on screening studies of people at higher risk of heart failure,[7][16][17][18][19] studies of acute destabilised heart failure[32] or acute breathlessness presenting to the emergency room.[33][34][35][36][37][38] The data describing the positive predictive value of NP for LVSD stem from modestly sized cohorts of people referred from primary care with sub-acute breathlessness in whom a test was done at the heart failure clinic following a referral based upon clinical suspicion.[39][40][41][42][43][44] Only one published study has described a pathway where the NP measurement was done in primary care at the clinic, but in this study, the protocol mandated referral for echocardiography in each subject limiting the usefulness of this work to clarify the utility or cost-effectiveness of the pathway in usual practice.[45]

Despite widespread adoption of NP-based care pathways, we could find no data exploring the utility of NP testing performed *in primary care*, and specifically whether including the test in the clinical assessment of a symptomatic patient improves the specificity of a referral to a secondary care heart failure service for heart failure due to LVSD over clinical suspicion alone. In the studies described above, where referral was based upon clinical suspicion, the median prevalence of heart failure due to LVSD was 28% of attendees (range 23%-60%). Since the prevalence of attendees in our dataset with LVSD is similar, one interpretation of our dataset could be that adding the NP test to clinical suspicion may not improve the positive predictive value of a NT-pro-BNP test done in primary care for a diagnosis of LVSD, although the

denominator might be different. The REFER dataset mentioned above,[45] which mandated referral in people assessed with a NP test, found a low prevalence in their 304 attendees of whom only 13 had LVSD (LVEF <50%) with only 3 presenting with an LVEF <40%).[45]

The UK-NICE guidelines also include a recommendation that patients with particularly high concentrations (NT-pro-BNP>2000pg/mL) and those with a prior MI should receive an urgent outpatient appointment (within two weeks). Our data demonstrate that around half of these patients will not have CHF due to LVSD, that around 70% have no signs or symptoms of clinical instability and by the time of clinic attendance a proportion will have no ongoing symptoms (NYHA class I).

Although there are data suggesting that NP concentrations are influenced by age and sex,[46] neither ESC nor UK-NICE guidelines propose age-sex specific thresholds. Our data support previous work [27][47] suggesting that these variables influence the performance of NT-pro-BNP in identifying patients with heart failure due to LVSD. Although the test performed better in high risk groups, these patients made up a small proportion of referred patients. Specifically, only 19% of elderly women with a NT-pro-BNP 400-2000pg/mL, which make up 40% of all referred patients, have LVSD. It is possible therefore that age and sex adjusted guidelines would improve specificity without affecting sensitivity of the test in primary care.

Prognostic utility of a raised NP

Our unique dataset allow us to clarify clearly in a well characterised cohort of patients that a raised NT-pro-BNP is a marker of adverse prognosis even in people without LVSD as previously described.[14] Our data highlight that despite contemporary medical therapy coordinated by a secondary care clinic with a high rate of optimal doses,[48] the prognosis for consecutive, unselected elderly patients with HFrEF remains poor.

Limitations of study

Our dataset is highly relevant to day to day clinical practice as it assessed in an unbiased fashion all consecutive and unselected patients referred using the ESC and UK-NICE guidelines. Moreover, vital status to at least 5 years is also a significant strength of our report. There are however, some limitations that should be discussed. Our report describes a single centre experience so it would be useful to examine the utility of an NP-guided pathway in different settings. Our data suggest that an elevated NT-pro-BNP level is associated with a poor prognosis even in those without LVSD. Although we recorded images for future analyses, the assessment of diastolic function was not part of the *a priori* aims of this particular piece of work. We have therefore not addressed other causes of elevated NT concentrations including HFpEF in this manuscript as these form part of a separate project. Furthermore, although optimal medical and device therapy can reduce mortality and morbidity in patients with heart failure due to LVSD,[1] to our knowledge no therapy has yet been shown to improve prognosis in people with chronic heart failure without LVSD,[20] possibly limiting the benefit on prognosis of a diagnostic pathway for this group. Whilst it is true that many interventions

possibly of benefit to people without LVSD, for example dietary advice and diuretic therapy have not been formally tested they might nevertheless improve both symptoms and important outcomes such as mortality and hospitalisation rates. Furthermore, a raised NP level that stimulated a referral may lead to a diagnosis of other conditions such as atrial fibrillation for which earlier treatment might be beneficial. A formal assessment of an NP-guided pathway would be able to describe the benefits in people with and without LVSD.

A further limitation of the observational cohort design of our service evaluation, is that we did not mandate referral of all patients undergoing the blood test, restricting our ability to comment on the negative predictive value of low NT-pro-BNP values in either pathway. However, our prospective use of the ESC guidelines for referral allows us to describe a 12% false negative rate in those with NT-pro-BNP levels between 125-400pg/mL.

Conclusion

In patients with suspected chronic heart failure referred using the ESC guidelines 32% had chronic heart failure secondary to LVSD whilst using 2010 UK-NICE guidelines 35% had chronic heart failure secondary to LVSD but there was wide variation in specificity in subgroups with the test performing poorly in older women. Overall, these positive predictive value rates are similar to those historically seen in the literature following referral based upon clinical judgement alone. Furthermore, 12% of people with an NT-pro-BNP between the ESC and 2010 UK-NICE guidelines have LVSD. Our

analysis highlights the critical importance of performing outcome studies of pathways before their widespread introduction.

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Data sharing: All data collected have been included in the analysis and presented in the manuscript. Patient level anonymised data are available from the corresponding author.

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References

1 Cubbon RM, Gale CP, Kearney LC, Schechter CB, Brooksby WP, Nolan J, et al. Changing characteristics and mode of death associated with chronic heart failure caused by left ventricular systolic dysfunction: a study across therapeutic eras. *Circ Heart Fail* 2011**; 4:** 396-403

2 Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N Engl J Med* 1991; **325:**293–302

3 The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353:** 9–13

4 Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. *Eur J Heart Fail* 2002;**4:**361-71

5 Mant J, Doust J, Roalfe A, Barton P, Cowie MR, Glasziou P, et al. Systematic review and individual patient data meta-analysis of diagnosis of heart failure, with modelling of implications of different diagnostic strategies in primary care. *Health Technol Assess* 2009;**13:**1-207

6 Davie AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. Assessing diagnosis in heart failure: which features are any use? *QJM* 1997;**90:**335–9

7 Groenning BA, Raymond I, Hildebrandt PR, Nilsson JC, Baumann M, Pedersen F. Plasma N–terminal Pro–brain Natriuretic peptide concentrations in a large sample of the general population. *Heart* 2004;**90:**297–303

8 Wallén T, Landahl S, Hedner T, Nakao K, Saito Y. Brain natriuretic peptide predicts mortality in the elderly. *Heart* 1997;**77:**264-7

9 McDonagh TA, Cunningham AD, Morrison CE, McMurray JJ, Ford I, Morton JJ et al. Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population. *Heart* 2001;**86:**21-6

10 Tsutamoto T, Wada A, Maeda K, Hisanaga T, Mabuchi N, Hayashi M, et al. Plasma brain natriuretic peptide level as a biochemical marker of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction. Comparison with plasma angiotensin II and endothelin-1. *Eur Heart J* 1999;**20:**1799-807

11 Gustafsson F, Steensgaard-Hansen F, Badskjaer J, Poulsen AH, Corell P, Hildebrandt P. Diagnostic and prognostic performance of N-terminal ProBNP in primary care patients with suspected heart failure. *J Card Fail*. 2005;**11**(5 Suppl):S15-20

12 Valle R, Aspromonte N, Feola M, Milli M, Canali C, Giovinazzo P et al. B-type natriuretic peptide can predict the medium-term risk in patients with acute heart failure and preserved systolic function. *J Card Fail* 2005;**11:**498-503

13 Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT et al. Systolic and diastolic heart failure in the community. *JAMA* 2006;**296:**2209-16

14 York MK, Gupta DK, Reynolds CF, Farber-Eger E, Wells QS, Bachmann KN et al. B-Type natriuretic peptide levels and mortality in patients with and without heart failure. *J Am Coll Cardiol* 2018;**71:**2079-2088

15 Zile MR, Claggett BL, Prescott MF, McMurray JJ, Packer M, Rouleau JL et al. Prognostic implications of changes in N-terminal pro–B-type natriuretic peptide in patients with heart failure. *J Am Coll Cardiol* 2016;**68:**2425–36

16 McDonagh TA, Robb SD, Murdoch DR, Morton JJ, Ford I, Morrison CE et al. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1998;**351:**9-13

17 Hobbs FDR, Davis RC, Roalfe AK, Hare R, Davies MK. Reliability of N-terminal pro-BNP assay in diagnosis of left ventricular systolic dysfunction within representative and high risk populations. *Heart* 2004;**90**:866–70

18 Rutten FH, Moons KG, Cramer MJ, Grobbee DE, Zuithoff NP, Lammers JW, et al. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. *BMJ* 2005;**331**:1379

19 Mueller T, Gegenhuber A, Dieplinger B. Capability of B-type natriuretic peptide (BNP) and aminoterminal proBNP as indicators of cardiac structural disease in asymptomatic patients with systemic arterial hypertension. *Clin Chem* 2005;**51**:2245–1

20 Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;**29:**2388-442

21 Available from http://www.nice.org.uk/cg108 (accessed 27th May 2018)

22 Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37:**2129-2200

23 Available from: https://www.nice.org.uk/guidance/ng106/chapter/Recommendations#diagnosing-heart-failure (accessed 13th October 2018)

24 Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;**18:**1440-63

25 McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14:**803-698

26 Loke I, Squire IB, Davies JE, Ng LL. Reference ranges for natriuretic peptides for diagnostic use are dependent on age, gender and heart rate. *Eur J Heart Fail* 2003; **5:** 599-606

27 Hildebrandt P, Collinson PO, Doughty RN, Fuat A, Gaze DC, Gustafsson F, et al. Age-dependent values of N-terminal pro-B-type natriuretic peptide are superior to a single cut-point for ruling out suspected systolic dysfunction in primary care. Eur Heart J. 2010;31:1881–1889

28 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;**147:**573-7

29 Davie AP, Francis CM, Caruana L, Sutherland GR, McMurray JJ. Assessing diagnosis in heart failure: which features are any use? *QJM* 1997; **90:** 335–9

30 Clark AL, Coats AJ. Unreliability of cardiothoracic ratio as a marker of left ventricular impairment: comparison with radionuclide ventriculography and echocardiography. *Postgrad Med J* 2000; **76:** 289-91

31 Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017;**70:**776-80

32 Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J* 2006;**27:**330–337

33 Wang CS, FitzGerald JM, Schulzer M, Mak E, Ayas NT. Does this dyspneic patient in the emergency department have congestive heart failure? *JAMA* 2005;**294:**1944–1956

34 Maisel AS, Krishnaswamy P, Nowak RM, Mak E, Ayas NT. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;**347:**161–167

35 Januzzi JL, Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005;**95:**948–954

36 McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* 2002;**106:**416–422

37 Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. *J Am Coll Cardiol 2*003;**42**:728–35

38 Davis M, Espiner E, Richards G, Billings J, Town I, Neill A, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. *Lancet* 1994;**343**:440–4

39 Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. *Lancet* 1997;**350**:1349–53

40 Zaphiriou A, Robb S, Murray-Thomas T, Mendez G, Fox K, McDonagh T, et al. The diagnostic accuracy of plasma BNP and NTproBNP in patients referred from primary care with suspected heart failure: results of the UK natriuretic peptide study. *Eur J Heart Fail* 2005;**7**:537–41

41 Wright SP, Doughty RN, Pearl A, Gamble GD, Whalley GA, Walsh HJ, et al. Plasma amino-terminal pro-brain natriuretic peptide and accuracy of heart failure diagnosis in primary care: a randomized, controlled trial. *J Am Coll Cardiol* 2003;**42**:1793–800

42 Nielsen LS, Svanegaard J, Klitgaard NA, Egeblad H. N-terminal pro-brain natriuretic peptide for discriminating between cardiac and non-cardiac dyspnoea. *Eur J Heart Fail* 2004;**6**:63–70

43 Zuber M, Cuculi F, Attenhofer Jost CH, Kipfer P, Buser P, Seifert B et al. Value of brain natriuretic peptides in primary care patients with the clinical diagnosis of chronic heart failure. *Scand Cardiovasc J* 2009;**43:**324-9

44 Fuat A, Murphy JJ, Hungin AP, Curry J, Mehrzad AA, Hetherington A, et al. The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure. *Br J Gen Pract* 2006;**56:**327-33

45 Taylor CJ, Roalfe AK, Iles R, Hobbs FR; REFER investigators, Barton P, Deeks J, McCahon D, Cowie MR, Sutton G, Davis RC, Mant J, McDonagh T, Tait L. Primary care REFerral for EchocaRdiogram (REFER) in heart failure: a diagnostic accuracy study. *Br J Gen Pract* 2017;**67:**e94-e102

46 Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC et al. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002;**40:**976–982

47 Savarese G, Orsini N, Hage C, Dahlström U, Vedin O, Rosano GMC et al. Associations with and prognostic and discriminatory role of N-Terminal Pro-B-Type Natriuretic Peptide in heart failure with preserved versus mid-range versus reduced ejection fraction. *J Card Fail* 2018;pii:S1071-9164(18)30123-4

48 Witte KK, Drozd M, Walker AMN, Patel PA, Kearney JC, Chapman S, et al. Mortality reduction associated with β-adrenoceptor inhibition in chronic heart failure is greater in patients with diabetes. *Diabetes Care* 2018;**41:**136-142

Legends

Figures 1a and b	The performance of European Society of Cardiology (ESC) (panel a), and United Kingdom Institute for Health and Care Excellence (UK-NICE) NT-pro-BNP concentrations (panel b) to identify people with heart failure due to left ventricular systolic dysfunction, divided by age and sex
Figure 2	All cause mortality of attendees by European Society of Cardiology (ESC) and United Kingdom Institute for Health and Care Excellence (UK-NICE) referral category
Figures 3a and b	All cause mortality of attendees by European Society of Cardiology (ESC) (panel a) and United Kingdom Institute for Health and Care Excellence (UK-NICE) (panel b) referral category by presence of left ventricular systolic dysfunction

Table

Referral variables		All patients (n=1020)	ESC criteria (≥125pg/mL) (n=991)	NICE criteria (n=821)		
				Previous MI (n=156)	400-2000pg/mL (n=436)	>2000pg/mL (n=229)
Age (years)		82 (10)	82 (10)	81 (10)	83 (9)	85 (9)
Sex	male (%)	445 (44)	426 (43)	89 (57)	181 (42)	106 (46)
	female (%)	575 (56)	565 (57)	67 (43)	255 (58)	123 (54)
NT-pro-BNP (pg/mL) (median, IQR)		882 (1712)	891 (1712)	999 (1727)	813 (643)	3685 (4552)
NYHA class	I (%)	55/346 (16)	52/336 (15)	13/84 (15)	27/115 (23)	12/124 (10)
	II (%)	185/346 (51)	171/336 (51)	44/84 (52)	59/115 (51)	74/124 (60)
	III (%)	107/346 (30)	99/336 (29)	27/84 (32)	24/115 (21)	31/124 (25)
	IV (%)	10/346 (3)	10/336 (3)	0/84 (0)	2/115 (2)	7/124 (6)
Previous myocardial infarction (%)		156 (15)	127 (13)	156 (100)	-	-
Hypertension (%)		578 (57)	563 (57)	72 (46)	259 (59)	136 (59)
Previous stroke (%)		88 (9)	85 (9)	15 (9)	40 (10)	25 (11)
Diabetes mellitus (%)		212 (21)	206 (21)	44 (28)	94 (22)	40 (17)
Previous cardiac surgery (%)		74 (7)	69 (7)	28 (18)	30 (7)	9 (4)
On examination						
HR (beats/min)		75 (17)	75 (17)	71 (17)	75 (16)	81 (20)
Systolic blood pressure (mmHg)		141 (24)	141 (23)	136 (26)	142 (22)	137 (24)
Diastolic blood pressure (mmHg)		74 (12)	74 (12)	72 (13)	73 (12)	74 (13)
Weight (kg)		79 (20)	79 (20)	77 (18)	78 (20)	76 (19)
Height (cm)		163 (10)	163 (10)	164 (10)	163 (11)	163 (10)
Electrocardiogram						
Atrial fibrillation (%)		292 (29)	288 (29)	36 (23)	136 (31)	117 (51)
QRS duration (ms)		100 (24)	99 (24)	102 (25)	98 (23)	108 (26)
Echocardiogram						
LVEF <50% (%)		334 (33)	319 (32)	77 (49)	110 (25)	123 (54)
LVEF (%)		50 (11)	50 (11)	44 (14)	52 (9)	44 (13)
Baseline treatment						
Beta-blockers (%)		504 (49)	480 (48)	115 (74)	196 (45)	129 (56)
RAAS inhibitors (%)		568 (55)	543 (55)	117 (75)	238 (55)	120 (52)
MRA (%)		39 (4)	35 (4)	14 (9)	11 (3)	13 (6)
Regular loop diuretic (%)		397 (39)	385 (39)	61 (39)	151 (35)	133 (58)

Summary data are presented as means (SD) for continuous variables unless indicated, and as frequency (%) for categorical variables.
ESC; European Society of Cardiology, NICE; National Institute for Health and Care Excellence, MI; myocardial infarction,
NYHA; New York Heart Association, LVEF; left ventricular ejection fraction, RAAS; renin angiotensin aldosterone system.

Figure 1a – Positive predictive value of the ESC guidelines

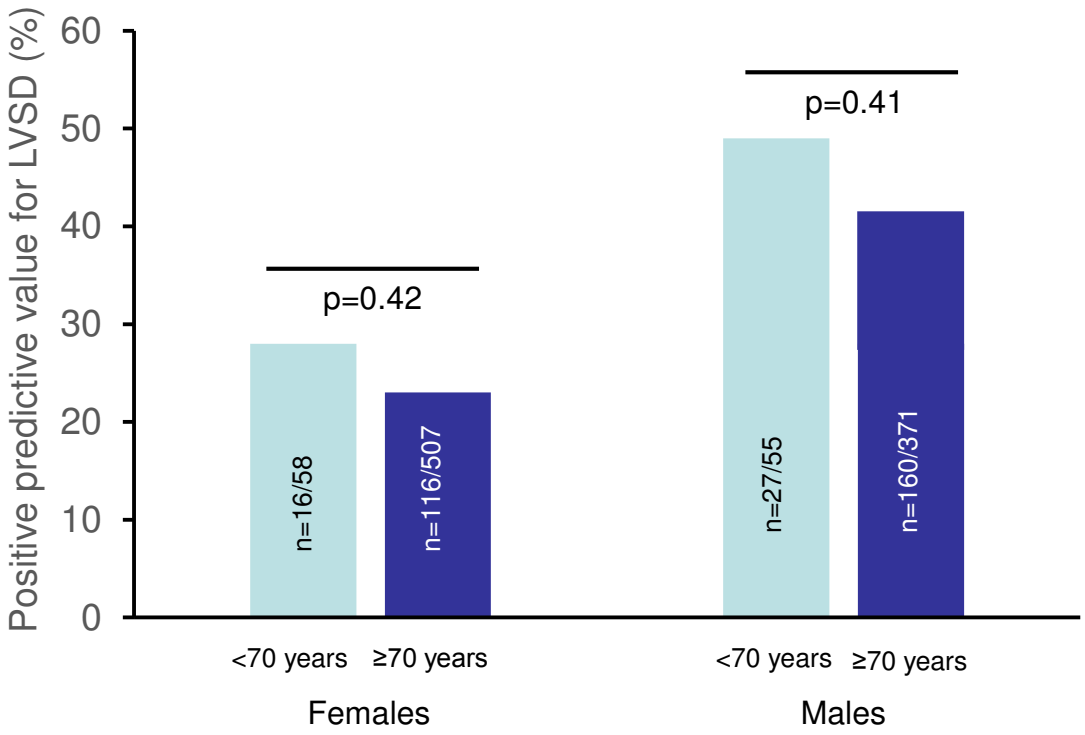


Figure 1b – Positive predictive value of the UK-NICE guidelines

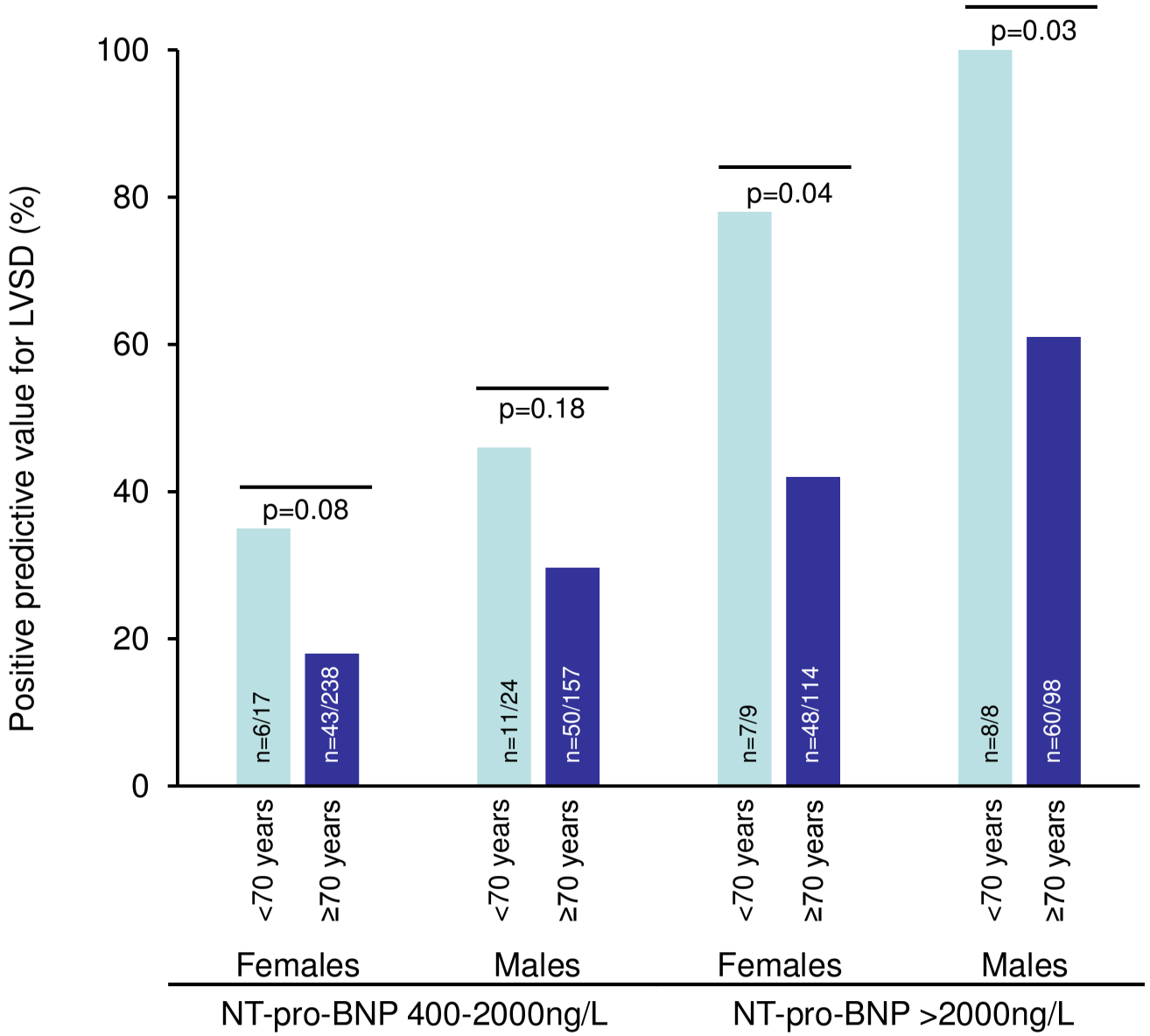
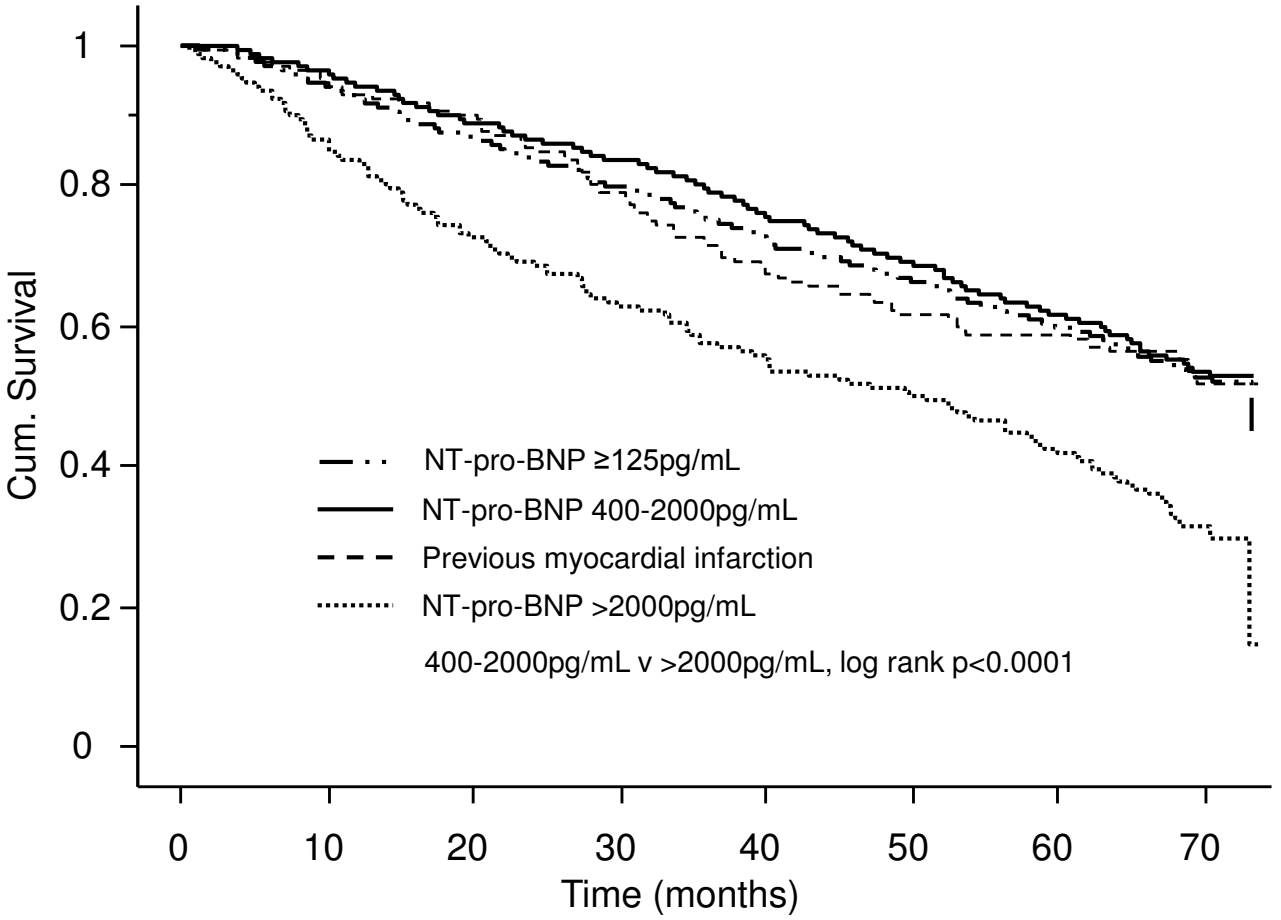
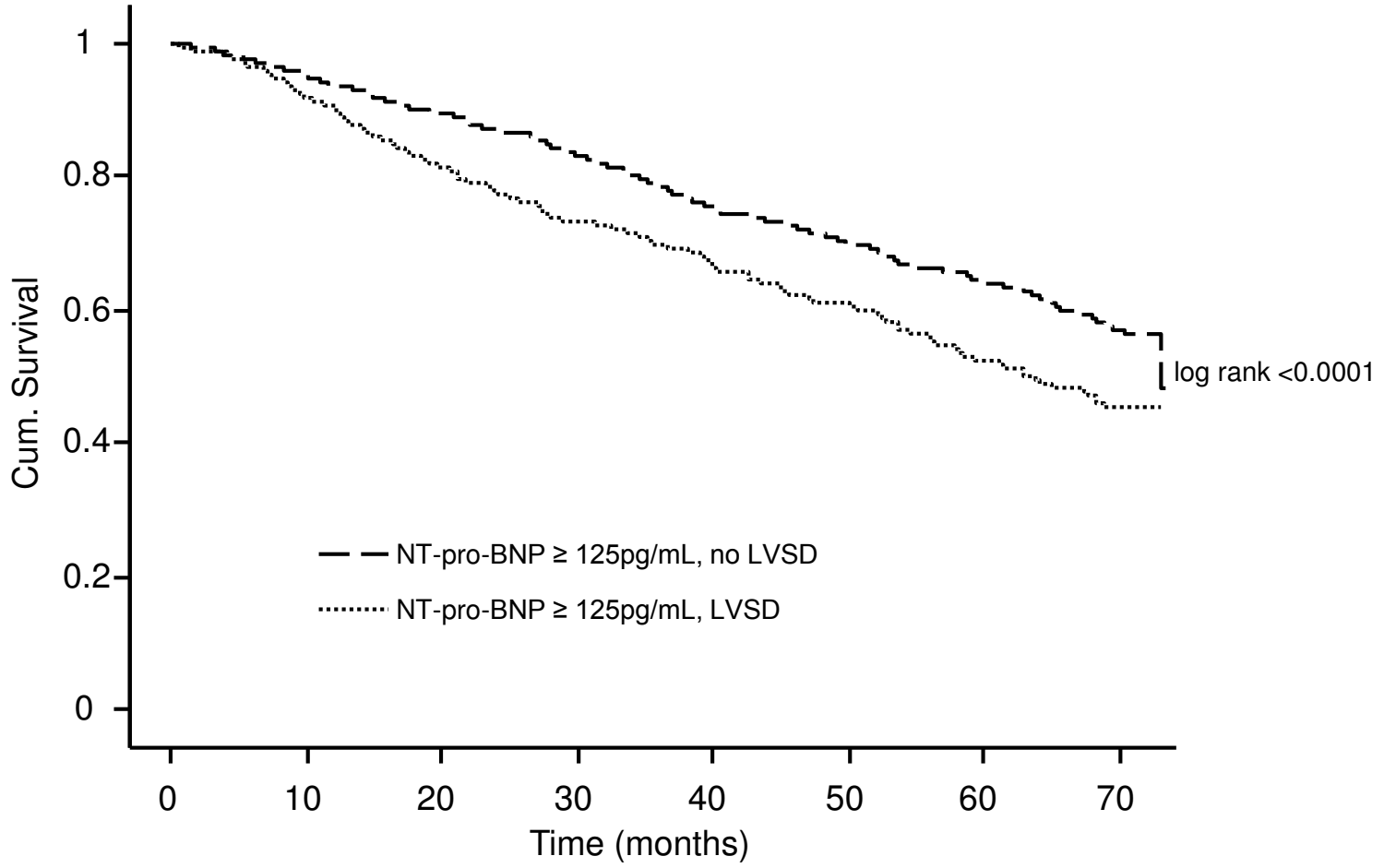


Figure 2 – Survival by cohort defined by the ESC and UK-NICE guidelines



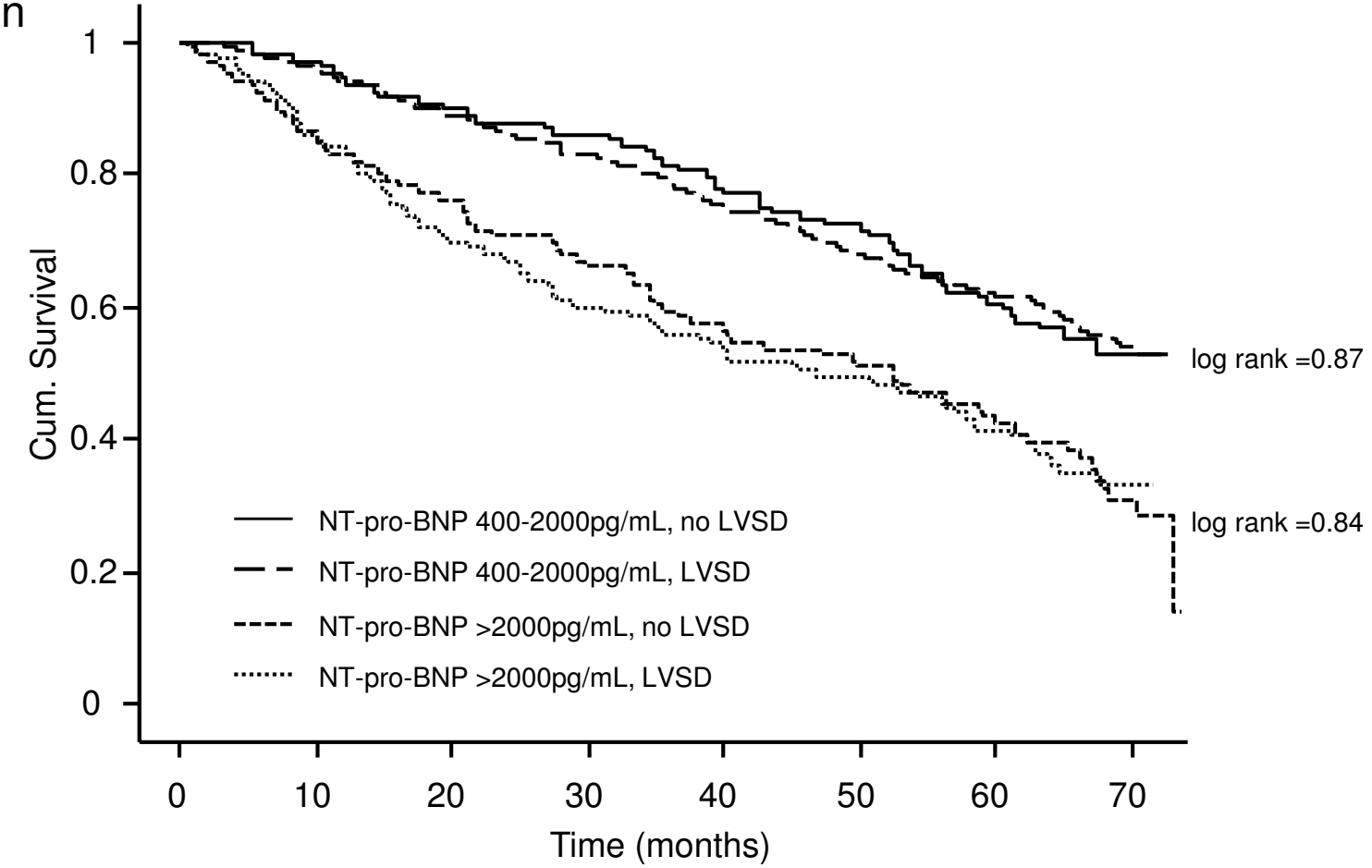
Time (months)	0	10	20	30	40	50	60	70
≥125pg/mL	991	936	862	794	720	666	262	47
400-2000pg/mL	435	418	387	364	329	300	268	72
>2000pg/mL	229	198	167	144	126	115	96	17
Previous MI	156	145	137	121	104	93	87	29

Figure 3a – Survival by ESC cohort and presence of left ventricular systolic dysfunction



Time (months)	0	10	20	30	40	50	60	70
≥125pg/mL, no LVSD	671	641	601	559	507	470	433	167
≥125pg/mL, LVSD	318	293	259	233	211	194	167	29

Figure 3b – Survival by UK-NICE cohort and the presence of left ventricular systolic dysfunction



Time (months)	0	10	20	30	40	50	60	70
400-2000pg/mL, no LVSD	326	312	289	270	245	221	202	62
400-2000pg/mL, LVSD	109	105	98	94	84	79	66	10
>2000pg/mL, no LVSD	106	92	81	70	60	54	46	13
>2000pg/mL, LVSD	123	106	86	74	66	61	51	4