

Plasma growth hormone is a strong predictor of risk at one year in acute heart failure

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Abstract

Aim

We sought to compare the prognostic utility of growth hormone (GH) with N-terminal B-type natriuretic peptide (NTproBNP) and the ADHERE score in a large cohort of acute heart failure (HF) patients, subcategorised into HF with reduced ejection fraction <50% (HFrEF) and preserved ejection fraction \geq 50% (HFpEF).

Methods and results

GH and NTproBNP levels were measured in 537 patients (HFrEF N=415; HFpEF N=122) with acute HF recruited into this prospective cohort study. The main outcome measure was death or HF readmission at one year. GH levels were higher in both HFrEF (1.26 [0.54 to 2.62] vs. 0.8 [0.26 to 1.94] ng/ml, $p<0.001$) and HFpEF (1.04 [0.48 to 2.92] vs. 0.53 [0.18 to 1.94] ng/ml, $p=0.020$) patients with the outcome compared to event-free survivors. GH levels were independently predictive for the outcome at 1 year in the entire cohort (HR=1.47 [1.16 to 1.86], $p=0.001$) and those with HFrEF (HR=1.54 [1.19 to 1.99], $p=0.001$) in multivariate Cox hazard analysis.

GH improved risk classification as measured by continuous net reclassification improvement (NRI) when added to the ADHERE multivariate logistic model of age, sex, urea, HR and systolic BP, for all patients (NRI=29.6 [12.1 to 47.1], $p=0.001$) and HFrEF NRI=21.7 [1.9 to 41.6], $p=0.034$) patients, as well as in addition to the ADHERE model combined with NTproBNP for all patients (NRI=25.4 [7.8 to 43.1], $p=0.005$).

Conclusion

GH offers incremental prognostic information over the ADHERE score clinical predictors and NTproBNP for risk stratification of acute HF patients.

Keywords: Growth hormone, N-terminal B-type natriuretic peptide, ADHERE score, acute heart failure

Introduction

Heart failure (HF) is an increasingly important global issue especially when considering an ageing population. The mortality from acute decompensated HF is high. A number of clinical variables have been shown to be related to risk of adverse outcome including age, anaemia, blood pressure, and plasma sodium and creatinine (1,2). The acute decompensated heart failure national registry (ADHERE) score, which was derived from the patient's blood urea nitrogen, systolic blood pressure and creatinine, provides a means of assessing individual patient risk of inpatient mortality in acute HF (3). Despite this, better risk stratification tools are required to differentiate high risk from low risk patients, to help guide management in a developing era of precision medicine. Biomarkers have their role in this clinical syndrome as exemplified by N-terminal B-type natriuretic peptide (NTproBNP) which offers both diagnostic and incremental prognostic utility over conventional variables (4-7)

Other pathways may be informative and may further help to understand the complex pathophysiology of acute HF. This clinical syndrome is dominated by disturbances in various neuroendocrine pathways which impacts on survival (8).

The growth hormone (GH) axis has been explored in chronic HF with deficiency reported in up to 40% of patients (9)(10). Low levels of its effector hormone, insulin like growth factor 1 (IGF-1) has been shown to be independently predictive of death in chronic HF (11). In severe chronic HF associated with cardiac cachexia, patients exhibit an acquired GH resistance characterised by high GH levels and low levels of IGF-1(12). This mechanistic deficiency in chronic HF has served as a potential therapeutic target with the expectation of increased myocardial contractility and muscle mass. However the results of therapeutic correction have been inconsistent, with studies reporting no improvements in cardiac indices of function (13)

whilst others have shown improvements in ejection fraction and reductions in NTproBNP (10). Despite the controversy regarding its therapeutic effects, the predictive utility of GH in illness is more robust. Elevated levels of GH have been shown to be independently related to mortality and offer additive value to validated risk scoring tools in critically ill patients(14,15).

We sought to investigate GH as a marker of risk in acute HF. The objective of this study was to compare the prognostic utility of endogenous GH with NTproBNP and the ADHERE score for the prediction of death and HF readmission at one year in a large cohort of acute HF patients.

Methods

Study population

This observational cohort study enrolled 537 patients with decompensated HF admitted to the University Hospitals of Leicester as part of a broad-based research programme examining the prognostic value of a number of biomarkers in patients hospitalised with heart failure. Patients were enrolled between February 2006 and May 2011. This study complied with the declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all patients. Diagnosis of decompensated HF was made on the basis of progressive worsening or new onset of shortness of breath along with clinical signs of pulmonary oedema, peripheral oedema or elevated jugular venous pressure. Medical notes were reviewed for information relating to the index admission and past medical history. Patients with a history of cancer or surgery in the previous month were excluded from the study. The modified diet in renal disease (MDRD) formula was used to estimate glomerular filtration rate (16).

Plasma Sampling

Following provision of consent and with the patient recumbent, 20mls of venous blood was withdrawn and collected in pre-chilled sterilins containing EDTA and aprotonin. Blood was centrifuged at 1500g for 20mins at 4°C. Plasma was siphoned, aliquoted and stored at -80°C until analysis. At the time of analysis plasma samples were defrosted at room temperature and analysed in a single batch.

Echocardiography

Transthoracic echocardiography was performed using a Sonos 5500 instrument (Philips Medical Systems). The biplane method of disc formula was used to calculate left ventricular (LV) ejection fraction (EF). HF with reduced EF (HFrEF) was defined as LVEF < 50% and HF with preserved LVEF (HFpEF) as EF \geq 50%. Pulse wave Doppler was used to measure the early diastolic inflow E wave and tissue Doppler to measure the diastolic velocity e' at the medial and lateral edge of the mitral valve annulus which were then used to calculate medial and lateral E/e' ratios. The medial and lateral E/e' ratios were averaged to give an overall measure of diastolic dysfunction.

GH assay

A sensitive chemiluminescent sandwich assay, which has been described previously (17), was used for quantification of GH levels. In brief, polystyrene tubes were coated using the solid phase antibody (1.5µg antibody/ 0.3ml 100mmol/l NaCl, 50mmol/l Tris/HCL, pH 7.8 for 18hours). Tubes were blocked with 5% BSA then washed with PBS, pH7.4 and subsequently vacuum dried. 50 µl of sample/standards and 200µl of purified labelled antibody tracer were added to the tubes and incubated for 2 hours at 22°C. Dilutions of GH were used as standards. Tubes were washed 5 times with wash solution and bound chemiluminescence was measured on an AutoLumat LB 953 (Berthold Technologies GmbH

& Co. KG). The analytical assay sensitivity was 2 pg/ml GH. The functional assay sensitivity (<20% interassay coefficient of variation) was 10 pg/ml. The normal range for GH levels using this assay was 0.11ng/ml (IQR 0.06 to 0.33) for males and 1.22ng/ml (IQR 0.40 to 3.15) for females (18).

NTproBNP assay

Concentrations of NTproBNP were quantified using a sandwich immunoassay as described previously (19). Monoclonal mouse antibodies directed against the C-terminal of NTproBNP were used to coat the wells and served as the capture antibody. Biotinylated sheep antibody directed against the N-terminal was used for detection. Bound chemiluminescence was measured on a luminometer (Dynex Technologies) following the addition of methylacridinium ester labelled streptavidin. The lower limit of detection was 0.3pmol/L. The median for normals was 28.4 (IQR 5.7 to 82.1) pmol/L. Interassay and intraassay coefficients of variations were under 5%. There was no cross reactivity with atrial natriuretic peptide (ANP), BNP or C-type natriuretic peptide (CNP).

Endpoints

The primary endpoint was the combination of death or HF readmission at 1 year. Endpoints were obtained from hospital records. All surviving patients were followed up for 1 year post initial hospitalisation. In cases where the patient had multiple events, the time to first event was counted as the outcome.

Statistical Analyses

Data were analysed using R 3.0.2. Concentrations of GH and NTproBNP were log transformed prior to analysis. The independent t test and chi squared test were used to

compare variables between HFrEF and HFpEF subgroups. Cox regression models were created using those variables showing univariate association ($p \leq 0.10$) with the endpoint. The hazard ratio presented for each biomarker refers to 1 standard deviation (SD) increments in the log transformed value. The hazard ratios for all other variables were as per unit change. Kaplan-Meier plots were used to visualise association between GH levels and outcome, with the log rank test to assess the difference. The comparative utility of the biomarkers was assessed by two methods; comparison of area under curve (AUC) of receiver operating characteristic (ROC) curves and continuous net reclassification improvement (NRI) as described by Pencina (20). Patients were assigned to risk groups 1 (lowest) to 5 (highest) using the ADHERE classification and regression tree (CART) model as follows: 1 (Urea < 15.35 mmol/l and SBP \geq 115mmHg), 2 (Urea < 15.35 mmol/l and SBP < 115mmHg), 3 (Urea \geq 15.35 mmol/l and SBP \geq 115 mmHg), 4 (Urea \geq 15.35 mmol/l, SBP < 115 mmHg, and creatinine level < 243.1 μ mol/l) and 5 (Urea \geq 15.35 mmol/l, SBP < 115 mmHg, and creatinine level \geq 243.1 μ mol/L) (3). A p value of <0.05 was deemed statistically significant for all comparisons.

Results

Patient characteristics

Baseline characteristics are shown in Table 1. Of 537 patients recruited, 351 (65.5%) were men and median age 76.5 [67 to 82.5] (Table 1). Median time between admission and blood sampling was 1 day and between blood sampling and ECHO was 3 days. Samples were taken after treatment was initiated and independent of the patients fasting status or at any particular time of day. Three hundred and forty one (63.5%) patients had a de novo diagnosis of HF whilst 196 (36.5%) had decompensated chronic HF.

During the index admission 20 patients (3.7%) received CPAP and 135 (25.1%) were treated with a GTN infusion. Nine (1.7%) patients were treated with inotropes for blood pressure

support and 3 had percutaneous coronary intervention. LVEF was measured in all patients. Median LVEF was 35 [25 to 48] %, with LVEF \geq 50% (HFpEF) in 122 (22.7%) and LVEF < 50% (HFrEF) in 415 (77.3%). A greater proportion of patients with HFpEF compared to HFrEF were female.

Urea, creatinine, QRS duration, LV internal diameter in diastole (LVIDD) and NTproBNP were higher in those with HFrEF compared to those with HFpEF (Table 1). GH levels were similar in the two subcategories. Prior histories of HF ischaemic heart disease and AF were more prevalent in HFrEF. Pre-admission rates of prescription of cardiovascular medication were statistically similar in the two subgroups.

At 1 year, 215 (40%) patients had reached the primary end point of death or readmission with HF, equating to an event rate of 57.2 per 100 person years for all patients, 58.1 per 100 person years in HFrEF and 53.9 per 100 person years in HFpEF. Of these, 139/537 (25.9%) patients died, an overall event rate of 41.1 per 100 person years (41.6 per 100 person years in HFrEF and 39.4 per 100 person years in HFpEF). The risk of adverse outcome was numerically higher for patients with HFrEF, although statistically similar to HFpEF (Table 1).

GH levels in patients in ADHERE score group 4 were significantly greater than those in groups 1 and 2 ($p < 0.001$ and $p = 0.046$ respectively), while NTproBNP levels in patients in ADHERE score group 5 were significantly greater than in those in ADHERE score groups 1 to 4 ($p = 0.005$, $p < 0.001$, $p < 0.0001$ and $p = 0.028$ respectively), with p values adjusted for multiple comparisons using the Bonferroni correction (Figure 1).

Table 2 shows selected baseline characteristics of all patients by GH tertiles. Overall significant differences between GH tertiles were found with age, urea, EF and systolic blood pressure and NTproBNP. In post hoc tests using the Bonferroni correction, urea and NTproBNP were significantly greater in the 3rd tertile compared to the 1st (both $p<0.001$), while systolic blood pressure and EF was significantly lower ($p=0.010$ and $p=0.002$ respectively). A greater proportion of those in the third tertile for GH met the combined endpoint compared to those in the 1st ($p<0.001$).

GH concentrations – Association with clinical and laboratory covariates

GH concentrations were similar in males and females ($p=0.971$), and lower in patients with diabetes mellitus, compared to those without diabetes mellitus (DM) ($p=0.001$). There was no significant difference in GH levels between patients presenting with de novo HF compared to those with decompensated chronic HF ($p=0.354$).

GH levels correlated directly with increasing age ($r=0.09$, $p=0.037$), urea ($r=0.19$, $p<0.001$) creatinine ($r=0.10$, $p=0.018$) and NTproBNP ($r=0.29$, $p<0.001$). GH was inversely related to EF ($r=-0.15$, $p=0.001$) and systolic blood pressure ($r=-0.10$, $p=0.023$).

GH levels were higher in patients with the combined endpoint of death or HF readmission at 1 year than in event free survivors (1.26 [0.52 to 2.73] vs 0.72 [0.24 to 1.94] ng/ml respectively, $p<0.001$). This was evident for both HFrEF (1.26 [0.54 to 2.62] vs 0.8 [0.26 to 1.94] ng/ml, $p<0.001$) and HFpEF (1.04 [0.48 to 2.92] vs 0.53 [0.18 to 1.94] ng/ml, $p=0.020$).

Variables showing univariate association with GH concentration at $p\leq 0.10$ were entered into a multivariate linear regression to establish the independent predictors of GH levels. In the entire cohort, greater admission urea and NTproBNP levels, and the absence of a history of DM, were independently associated with higher GH levels. In patients with HFrEF, higher

admission urea, lower EF and greater NTproBNP, as well as the absence of a history of DM, were independently associated with GH levels. In patients with HFpEF only increasing age and NTproBNP levels were independently related to GH levels.

Death or heart failure hospitalisation

Cox regression analysis

Variables showing univariate association with the combined end point ($p \leq 0.1$) were entered into multivariate analysis (Figure 2). A history of AF was significantly associated with the endpoint in all patients (HR=1.57 [1.10 to 2.24], $p=0.013$) but not in HFrEF (HR=1.49 [0.99 to 2.23], $p=0.054$) or HFpEF patients (HR=2.01 (0.90 to 4.47), $p=0.089$) in univariate Cox Hazards analysis. A greater QRS duration was associated with the endpoint in all patients (HR=1.01 [1.00 to 1.01], $p<0.001$) and HFrEF patients (HR=1.01 [1.00 to 1.01], $p<0.001$) but not in HFpEF (HR=0.99 [0.98 to 1.01], $p=0.334$). A history of AF was only predictive of the combined endpoint in HFpEF patients (HR=3.16 [1.13 to 8.81], $p<0.028$) in multivariate analysis. The QRS duration was not associated with the outcome in multivariate analysis in any patient group. The mean E/e' was not significantly associated with the combined endpoint in univariate analysis for any patient group.

For all patients, past history of IHD (HR=1.99 [1.14 to 3.48], $p=0.016$), NYHA IV status (HR=1.89 [1.10 to 3.27], $p=0.021$), a lower systolic BP (HR=0.99 [0.98 to 1.00], $p=0.035$) as well as greater GH levels (HR=1.47 [1.16 to 1.86], $p=0.001$) were independently associated with the combined end point.

For HFrEF patients, only greater GH levels remained an independent predictor in multivariate analysis (HR=1.54 [1.19 to 1.99], $p=0.001$).

For patients with HFpEF, GH levels did not retain independent association with the combined endpoint in a multivariate model. The only independent predictors of the endpoint in HFpEF were a past history of IHD (HR=3.72 [1.28 to 10.8], p=0.016) and AF (HR=3.16 [1.13 to 8.81], p=0.028).

Kaplan-Meier analysis

Above median GH levels were associated with worse outcomes at 1 year in both HFpEF and HFrEF (Figure 3).

Receiver Operating Characteristic (ROC) curve analysis

Estimated risk of death or HF readmission at 1 year was calculated using the ADHERE logistic regression model clinical variables (admission urea, systolic BP, heart rate and age) with either GH or NTproBNP added as a covariate. Model predictive accuracy was compared using area under the curve (AUC) of ROC curves.

For the entire cohort, neither the addition of GH (AUC combined = 0.68 [0.64 to 0.73]) nor NTproBNP (AUC combined = 0.67 [0.63 to 0.72]) significantly increased the AUC of the baseline clinical model (AUC= 0.67 [0.62 to 0.72]), p values = 0.400 and 0.461 respectively.

Neither GH nor NTproBNP significantly increased the AUC of the ADHERE clinical variables logistic model in the sub cohorts of HFrEF and HFpEF patients.

Furthermore, GH failed to significantly improve the AUC of a baseline model consisting of the ADHERE predictors, mean E/e', QRS duration and past history of AF.

Reclassification analysis

The net effect of addition of GH added to four different baseline models for prediction of death or HF readmission at 1 year was assessed using category free (continuous) net reclassification improvement (NRI) (Table 3). For the entire cohort and in HFrEF patients

GH added to the baseline clinical model using the ADHERE logistic regression variables (admission urea, systolic BP, heart rate and age) improved overall patient classification (NRI=29.6 [12.1 to 47.1], $p=0.001$ and NRI=21.7 [1.9 to 41.6], $p=0.034$ respectively). NTproBNP when added to the ADHERE logistic regression clinical variables also improved classification for all patients (NRI= 25.2 [7.5 to 42.8], $p=0.006$) and HFpEF patients (NRI= 42.2 [8.2 to 76.1], $p=0.032$) but not for HFrEF patients (NRI= -2.4 [-21.1 to 16.2], $p=0.813$).

GH produced a significant improvement in reclassification when NTproBNP was used alone as the baseline model in all patients (NRI=27.4 [10.2 to 44.5], $p=0.002$) and HFrEF patients (NRI=27.1 [7.7 to 46.4], $p=0.007$). Furthermore, the addition of GH to a baseline model comprising the ADHERE risk predictors and NTproBNP, also improved reclassification in all patients (NRI=25.4 [7.8 to 43.1], $p=0.005$).

Adding GH to a baseline model consisting of the ADHERE predictors, mean E/e', QRS interval and history of AF, significantly improved reclassification HFrEF patients (NRI=45.2 [1.9 to 88.5], $p=0.047$) (Table 3).

Discussion

The majority of de-novo HF diagnosis occurs in the acute setting; hence many admitted patients will be either drug naïve or on suboptimal therapy which probably contributes to their high mortality. The ability to identify high risk patients would facilitate earlier investigation and more aggressive treatment leading to a better use of finite health care resources. Risk stratification tools such as the ADHERE score go some way in identifying high risk patients but this relies predominantly on measures of renal dysfunction (3). Biomarkers such as NTproBNP confer both complementary diagnostic and prognostic information to the conventional tools in HF (5). Reduced levels of the anabolic hormones have been associated with adverse outcomes in chronic HF (8). We therefore sought to

explore the pathophysiology of the GH axis in the acute HF setting and assess its prognostic capacity. We quantified GH levels using a highly sensitive immunoassay, exceeding the detection capabilities conferred by standard GH assays, thereby providing a more accurate representation of the true GH levels and potentially identifying new relationships (17).

In multivariate analysis, the independent determinants for GH levels in all patients were greater urea and NTproBNP levels, along with a past history of DM, which showed an inverse association with GH levels. The relationship between GH and NTproBNP may be confounded by the acute event, ventricular wall stress being the precipitant for NTproBNP release and adrenergic drive being the precipitant for GH secretion. Median GH levels were similar between males (1.01ng/ml (IQR 0.32- 2.29) and females (0.84ng/ml (IQR 0.35 to 2.11), $p=0.971$) in this cohort, consistent with previous findings (21).

To our knowledge, this is the first study to demonstrate a strong relationship between plasma GH concentration at admission and prognosis in acute HF. Levels of GH were higher in those that endured the composite endpoint of death or HF readmission at 1 year when analysing the entire cohort and both subcategories of HF. Furthermore, elevated GH levels were predictive of the combined endpoints in Cox Hazard regression analyses for models comprising of all patients and for patients in the HFrEF subcategory. This compared favourably to NTproBNP which was eliminated from the final models. The association between plasma GH levels and the adverse outcomes may be a reflection of stress, enhancing hypothalamic pituitary secretion in settings of multi-organ failure.

The addition of either GH or NTproBNP to the ADHERE logistic model failed to improve the AUC for the prediction of the composite endpoint for all patients and subcategories of HF. The conservative nature of ROC for the assessment of potential biomarkers has led to the adoption of category-free net reclassification improvement (20). For all patients and for

HFrEF patients, GH significantly reclassified patients with endpoints after initial ADHERE risk modelling, enabling identification of high-risk patients who would potentially benefit from more aggressive treatments or closer monitoring in the acute and convalescent period. The use of GH may lie as an adjunct with current tools, as the addition of GH to a baseline model comprising of the ADHERE score clinical predictors and NTproBNP conferred additional prognostic information for the entire cohort, which is dominated by high morbidity and mortality. Furthermore, the addition of GH to a baseline model comprising of the ADHERE risk predictors, E/e' a robust echocardiographic marker of cardiac performance, along with the incorporation of QRS duration and AF also improved reclassification for HFrEF patients. The lack of prognostic capability for GH in the HFpEF subcategory was likely to be due to the small cohort size.

GH exhibits a pulsatile secretory pattern, with frequent high peaks in acute illness and a diminished oscillatory pattern in more protracted chronic critical illness (22). It is therefore plausible that the secretory patterns of GH in the acute de-novo HF patients may be higher than decompensated chronic HF patients; however this was not the case, as there was no difference in GH levels between the two types of presentations despite using a high sensitivity assay.

While measurement of individual biomarkers may help in estimating prognosis, the ideal biomarker would help guide treatment. To date, no single biomarker has shown such utility in routine clinical practice, and the scientific community continues to search for novel or additional entities which might aid clinical management of patients. Our demonstration of the association with adverse outcome of elevated GH levels reinforces the well-recognised nature of heart failure as a systemic condition associated with perturbation of multiple physiological pathways.

This was a single centre study therefore further multicentre studies are required for validation

of these findings. The measurement of GH in isolation rather than in combination with IGF-1 and in unfasted patients may be deemed as limitations. Although the ADHERE score contains important prognostic variables, it is not exhaustive and neglects to take into consideration adverse patient performance indicators such as low exercise capacity, slow walk speed and decrease in lean body mass.

In conclusion, the measurement of plasma GH using a highly sensitive immunoassay in acute HF confers incremental prognostic utility to the ADHERE score clinical predictors and to NTproBNP, when either are used in isolation or in combination. The identification of high risk patients using plasma GH may lead to a better allocation of resources, especially at a time of precision medicine.

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Conflict of interest

Dr. Bergmann holds ownership in Sphingotec AG, which manufactures the GH assay; and is a member of the board of directors of Sphingotec GmbH. Dr. Struck is an employee of Sphingotec GmbH. The other authors declare no conflict of interest.

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Legends

Figure 1 GH (a) and NTproBNP (b) levels in all patients by ADHERE score group.....

Figure 2 Forrest plots for univariate and multivariate Cox hazard regression for the prediction of death/HF readmission at 1 year for All (a & d) HFrEF (b & e) and HFpEF (c & f) patients. Variables with a p value ≤ 0.1 in univariate analysis were entered into multivariate analysis. Significant hazard ratios ($p < 0.05$) are indicated with an *.

Figure 3 Kaplan-Meier plots of showing outcome death or HF readmission at 1 year by median GH levels in a) Patients with an EF $< 50\%$ b) Patients with an EF $\geq 50\%$. p values are shown for the log rank test.

Tables

Table 1 Baseline characteristics of patients at admission. Number after oblique indicates number of available observations. p values are for independent t test or chi squared test.

	Median (IQR) or number/observations available and (% observations available)			
	All (N=537)	HFrEF (N=415)	HFpEF (N=122)	p (HFrEF vs HFpEF)
Demographics				
Age (years)	76.5 (67 to 82.5)	76 (67 to 82)	77 (67.9 to 84.9)	0.188
Sex (% male)	351/536 (65.5)	293/414 (70.8)	58/122 (47.5)	<0.001
Admission physiological parameters				
eGFR	54 (40 to 69.06)	53.5 (38.8 to 70)	54 (43.2 to 68)	0.571
Urea (mmol/l)	8.8 (6.6 to 12.55)	9.3 (6.9 to 13.3)	7.5 (5.8 to 10.9)	0.001
Creatinine (μmol/l)	112 (89 to 140.5)	114 (90 to 145.5)	105 (84.8 to 127.5)	0.008
Na (mmol/l)	138 (135 to 141)	138 (135 to 141)	138 (135 to 140.2)	0.569
QRS (ms)	107 (92 to 136)	113 (95 to 139)	96 (84 to 106)	<0.001
EF (%)	35 (25 to 48)	30 (22.5 to 38)	60 (54 to 65)	<0.001
LVIDD (cm)	5.3 (4.7 to 6)	5.5 (5 to 6.2)	4.7 (4.3 to 5.2)	<0.001
Mean E/e'	15.6 (11.5 to 21.0)	15.5 (12.0 to 20.9)	18.1 (10.4 to 24.6)	0.339
Systolic BP (mmHg)	132 (116 to 149)	130 (115.2 to 147)	138 (119 to 153)	0.039
Diastolic BP (mmHg)	75 (65 to 86)	75 (66 to 87)	75 (62 to 85)	0.354
NTproBNP (pmol/l)	3056 (1500 to 5702)	3319 (1664 to 5781)	1911 (716.8 to 3992)	<0.001
GH (ng/ml)	0.94 (0.32 to 2.17)	1 (0.4 to 2.2)	0.7 (0.3 to 2.1)	0.131
Past medical history				
MI	142/425 (33.4)	125/346 (36.1)	17/79 (21.5)	0.019
DM	179/537 (33.3)	135/415 (32.5)	44/122 (36.1)	0.536
HF	196/537 (36.5)	162/415 (39)	34/122 (27.9)	0.032
(Ex-) Smoker	154/325 (47.4)	124/258 (48.1)	30/67 (44.8)	0.732
HTN	315/537 (58.7)	240/415 (57.8)	75/122 (61.5)	0.539
AF	117/324 (36.1)	85/257 (33.1)	32/67 (47.8)	0.037
Admission medications				
Aspirin	190/425 (44.7)	158/346 (45.7)	32/79 (40.5)	0.48
BetaBlocker	205/425 (48.2)	171/346 (49.4)	34/79 (43)	0.368
ACEi/ARB	262/425 (61.6)	214/346 (61.8)	48/79 (60.8)	0.959
Statin	221/425 (52)	182/346 (52.6)	39/79 (49.4)	0.693
CCB	87/425 (20.5)	65/346 (18.8)	22/79 (27.8)	0.100
Diuretic	273/425 (64.2)	223/346 (64.5)	50/79 (63.3)	0.949
ARA	21/213 (9.9)	18/189 (9.5)	3/24 (12.5)	0.923
Management				

GTN Infusion	135/537 (25.1)	96/415 (23.1)	39/122 (32)	0.063
CPAP	20/537 (3.7)	14/415 (3.4)	6/122 (4.9)	0.603
Inotropes	9/537 (1.7)	7/415 (1.7)	2/122 (1.6)	1.000
PCI	3/213 (1.4)	2/189 (1.1)	1/24 (4.2)	0.766
CABG	2/213 (0.9)	2/189 (1.1)	0/24 (0)	1.000
CRT	1/213 (0.5)	1/189 (0.5)	0/24 (0)	1.000
ICD	1/213 (0.5)	1/189 (0.5)	0/24 (0)	1.000
Outcomes at 1 year				
Death	139/537 (25.9)	109/415 (26.3)	30/122 (24.6)	0.800
Death or HF readmission	215/537 (40)	170/415 (41)	45/122 (36.9)	0.482

MI=Myocardial infarction, DM= Diabetes Mellitus, HTN= Hypertension, ACEi=Angiotensin II inhibitor, ARB=Aldosterone receptor blocker, CCB=Calcium channel blocker, ARA=Aldosterone receptor antagonist, Na=Sodium level, LVIDD=Left ventricle internal diameter in diastole, sBP=Systolic BP, PCI=Percutaneous coronary intervention, CABG=Coronary arterial bypass graft, CRT= Cardiac resynchronisation therapy.

Table 2 Baseline characteristics of all patients by GH tertile. Number after oblique indicates number of available observations. p values are for ANOVA.

	Median (IQR) or number/observations available and (% observations available) by tertiles of GH			p*
	1st tertile	2nd tertile	3rd tertile	
Age	73 (65.7 to 80.5)	78 (70.5 to 83.9)	77 (67.4 to 83)	0.004
eGFR	56.5 (42.8 to 71.2)	54 (38.9 to 67.2)	52 (40 to 69)	0.213
Urea (mmol/l)	8 (6.3 to 10.9)	8.8 (6.6 to 12.5)	9.8 (7.1 to 15)	0.001
Creatinine (μmol/l)	110 (88 to 135)	111.5 (88.8 to 140.2)	118 (91.2 to 145)	0.148
Na (mmol/l)	139 (136 to 141)	138 (134 to 141)	138 (134 to 140)	0.092
QRS (ms)	106 (90 to 138)	106 (95.5 to 132)	108 (92 to 137)	0.741
EF (%)	38 (28.5 to 50)	35 (26 to 46.5)	32 (21 to 45)	0.003
LVIDD (cm)	5.1 (4.6 to 5.8)	5.4 (4.9 to 6)	5.5 (4.8 to 6.2)	0.086
Mean E/e'	16.6 (11.2 to 20.5)	14.6 (11 to 21)	16 (13 to 21.7)	0.635
Systolic BP (mmHg)	134.5 (118 to 154.2)	135 (119 to 150)	127.5 (110 to 143.2)	0.008
Diastolic BP (mmHg)	75 (65 to 85)	75 (68.2 to 85)	75 (65 to 88.5)	0.856
NTproBNP	2061 (633.3 to 3712)	3262 (1442 to 5235)	4390 (2609 to 7363)	<0.001
Sex	117/178 (65.7)	111/179 (62)	123/179 (68.7)	-
Death at 1 year	24/179 (13.4)	54/179 (30.2)	61/179 (34.1)	-
Death or Heart failure at 1 year	49/179 (27.4)	79/179 (44.1)	87/179 (48.6)	-

*p value for ANOVA

Table 3 Continuous reclassification showing change in classification for prediction of outcome death or HF readmission at 1 year with the addition of GH or NTproBNP to different baseline predictive models.

Baseline model	Additional	All (n=537)		HFrEF (n=415)		HFpEF (n=122)	
		NRI	P	NRI	p	NRI	p
ADHERE predictors	+ GH						
	Without Endpoint	9.4	0.105	2.2	0.740	9.9	0.406
	With Endpoint	20.2	0.004	19.5	0.012	0.0	1.000
	Total	29.6	0.001	21.7	0.034	9.9	0.607
ADHERE predictors	+ NTproBNP						
	Without Endpoint	6.1	0.294	-39.0	<0.001	69.0	<0.001
	With Endpoint	19.0	0.006	36.6	<0.001	-26.8	0.086
	Total	25.2	0.006	-2.4	0.813	42.2	0.032
NTproBNP	+ GH						
	Without Endpoint	7.6	0.178	7.1	0.273	16.9	0.138
	With Endpoint	19.8	0.004	20.0	0.009	14.3	0.355
	Total	27.4	0.002	27.1	0.007	31.2	0.104
ADHERE predictors + NTproBNP	+ GH						
	Without Endpoint	5.4	0.351	2.2	0.738	4.2	0.722
	With Endpoint	20.0	0.004	17.1	0.029	2.4	0.876
	Total	25.4	0.005	19.3	0.060	6.7	0.734
ADHERE predictors + E/e'+QRS + AF	+ GH						
	Without Endpoint	18.0	0.159	18.5	0.174	-*	-
	With Endpoint	17.7	0.303	26.7	0.144	-*	-
	Total	35.7	0.096	45.2	0.047	-*	-
ADHERE predictors = Age, sex, urea, HR and systolic BP							
* Complete separation of logistic regression model occurs							

**Figure
1**

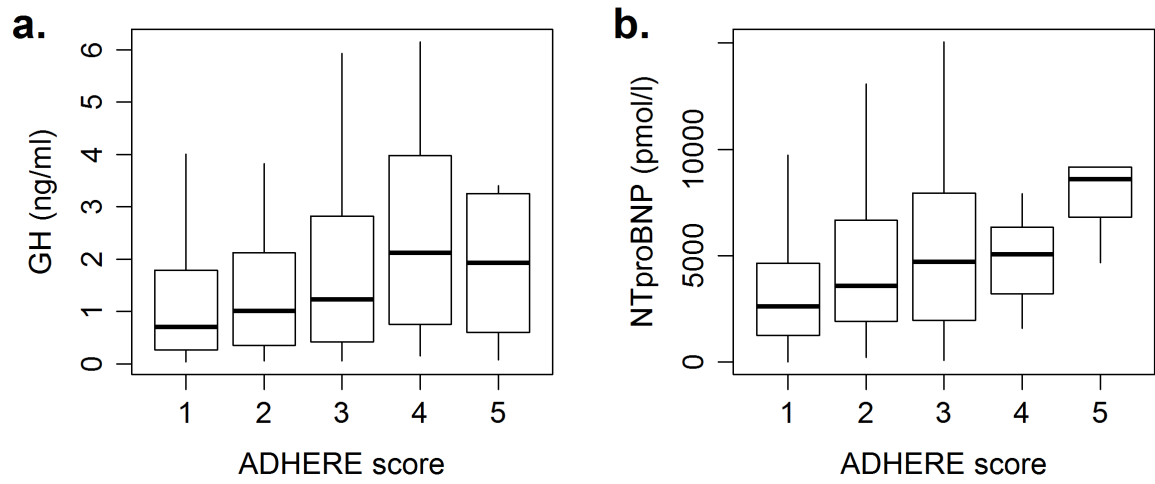


Fig 2

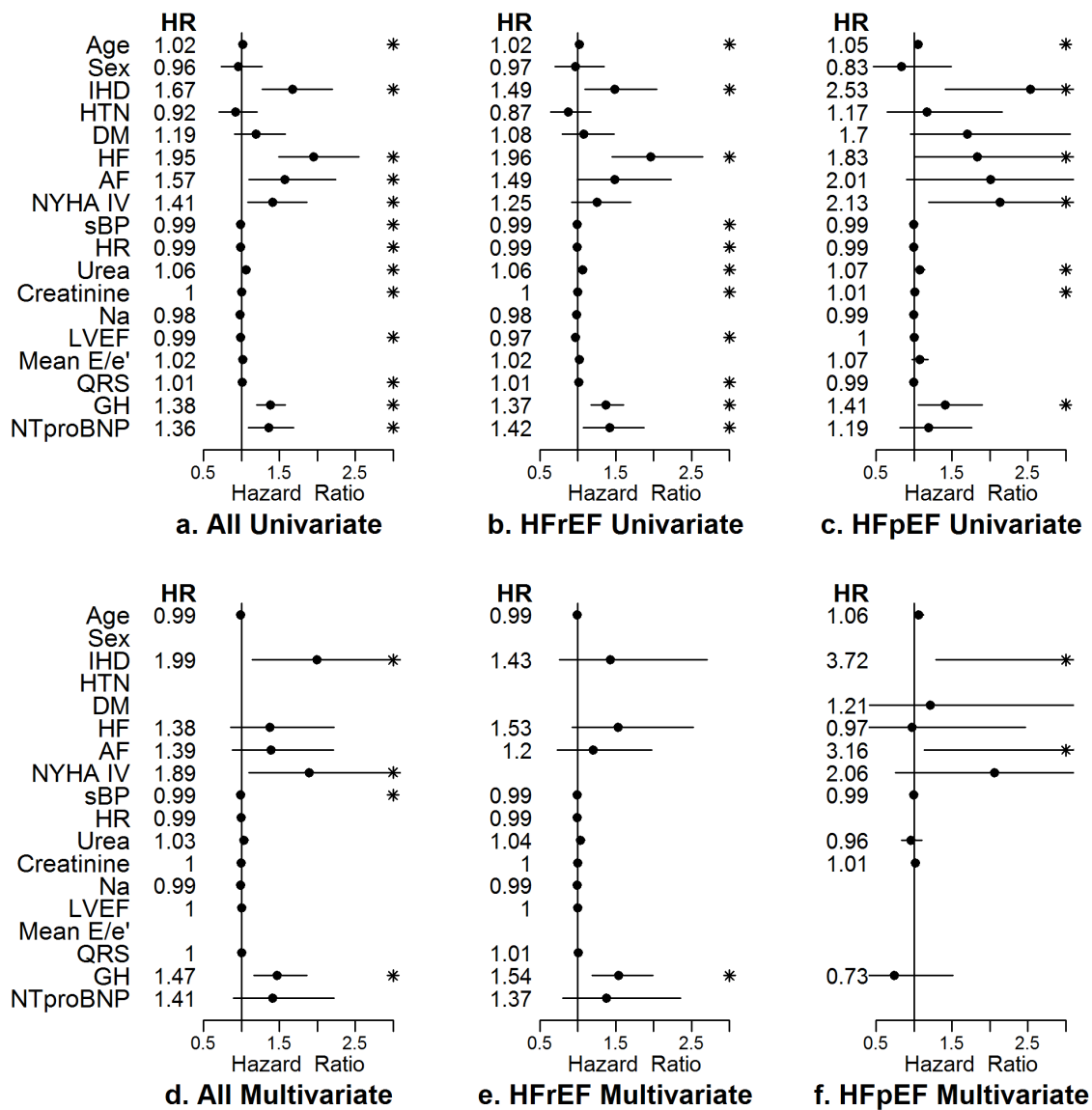


Fig 3

