Newer imaging modalities to identify high-risk ambulatory patients with heart failure

Volume I

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Author's declaration

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Publications portfolio

1) **Pellicori P**, Carubelli V, Zhang J, Castiello T, Sherwi N, Clark AL, Cleland JG. IVC diameter in patients with chronic heart failure: relationships and prognostic significance. JACC Cardiovasc Imaging. 2013;6:16-28. *Impact factor: 7.188*

2) **Pellicori P**, Kallvikbacka-Bennett A, Khaleva O, Carubelli V, Costanzo P, Castiello T, Wong K, Zhang J, Cleland JG, Clark AL. Global longitudinal strain in patients with suspected heart failure and a normal ejection fraction: does it improve diagnosis and risk stratification? Int J Cardiovasc Imaging. 2014;30:69-79. *Impact factor: 1.81*

3) **Pellicori P**, Zhang J, Lukaschuk E, Joseph AC, Bourantas CV, Loh H, Bragadeesh T, Clark AL, Cleland JG. Left atrial function measured by cardiac magnetic resonance imaging in patients with heart failure: clinical associations and prognostic value. Eur Heart J. 2015;36:733-42. *Impact factor: 15.20*

4) **Pellicori P**, Joseph AC, Zhang J, Lukaschuk E, Sherwi N, Bourantas CV, Loh H, Clark AL, Cleland JG. The relationship of QRS morphology with cardiac structure and function in patients with heart failure. Clin Res Cardiol. 2015;104:935-45. *Impact factor: 4.56*

5) **Pellicori P**, Kallvikbacka-Bennett A, Zhang J, Khaleva O, Warden J, Clark AL, Cleland JG. Revisiting a classical clinical sign: jugular venous ultrasound. Int J Cardiol. 2014;170:364-70. *Impact factor: 4.036*

6) **Pellicori P**, Kallvikbacka-Bennett A, Dierckx R, Zhang J, Putzu P, Cuthbert J, Boyalla V, Shoaib A, Clark AL, Cleland JG. Prognostic significance of ultrasound-assessed jugular vein distensibility in heart failure. Heart. 2015;101:1149-58. *Impact factor: 5.59*

For all the publications included in the portfolio my contribution was: generating the original hypotheses, data collection, including retrospective off-line analysis of stored echocardiograms and measurement of left atrial volumes from cardiac magnetic resonance imaging, data interpretation, statistical analysis, manuscript drafting, article submission, and liaising with editors and reviewers as corresponding author. For publications (5) and (6), I developed and prospectively studied a novel ultrasound method to measure the internal jugular vein diameter and its changes with respiratory manoeuvres and I recruited the patients in the studies.

The full text of the publications listed above is attached at the end of this thesis.

Abbreviations

HF: heart failure
HFNEF: heart failure with normal ejection fraction
HFREF: heart failure with reduced ejection fraction
LBBB: left bundle branch block
RBBB: right bundle branch block
IVCD: indeterminate ventricular conduction delay
LV: left ventricle
LVSD: left ventricular systolic dysfunction
LVEF: left ventricular ejection fraction
GLS: global longitudinal strain
cMRI: cardiac magnetic resonance imaging
NTproBNP: N-terminal pro-B-type natriuretic peptide
RV: right ventricle
IVC: inferior vena cava
JV: jugular vein
LAEF: left atrial emptying fraction
LAD: left atrial diameter
LAVI: left atrial volume was indexed to body surface area.
AF: atrial fibrillation
TAPSE: tricuspid annular plane systolic excursion.
ACE-I: angiotensin converting enzyme Inhibitor
ARB: angiotensin receptor blocker
CI: confidence interval
ESC: European society of cardiology

Newer imaging modalities to identify high-risk ambulatory patients with heart failure

Summary

The lack of widely accepted objective measures of cardiac dysfunction other than left ventricular ejection fraction (LVEF) has hampered, and continues to hamper, clinical research in patients with heart failure (HF). Identifying patients at higher risk of adverse outcome would allow better targeting of therapy to those with most to gain.

The thesis is divided in three parts.

In the first part, I report the results of studies of the association between echocardiographic measures of right atrial pressure (by measuring the inferior vena cava (IVC) diameter) and outcome in ambulatory patients with HF. I also studied the associations with prognosis of a newer echocardiographic method (global longitudinal strain, GLS) to assess left ventricular systolic function in patients with normal LVEF on conventional imaging.

In the second part, I report the results of studies of the associations of left atrial function by cardiac magnetic resonance (cMRI) with outcome in ambulatory patients with HF. I also studied the relationship between QRS morphology on ECG with cardiac structure and function measured by cMRI in ambulatory patients with HF.

In the third part, I report the results of developing and prospectively evaluating an ultrasound method to measure the internal jugular vein diameter (as an objective estimate of the right atrial pressure) and its changes with respiratory manoeuvres.

I studied the association between the jugular vein diameter, clinical and echocardiographic variables, and its relations with outcome in ambulatory patients with HF and controls.

My results showed that upstream consequences of a dysfunctional left ventricle, such as impaired left atrial function measured by cMRI, a distended IVC or internal jugular vein by ultrasound, provide powerful prognostic information, similar to that obtained by measuring N-terminal pro-B-type natriuretic peptide plasma levels, in individuals with HF regardless of whether they have a reduced or normal LVEF.

As residual congestion (dilated IVC or jugular vein) and impaired left atrial function appear strongly related to an adverse outcome, tailoring treatment to minimise congestion or improving left atrial function is an attractive concept worth testing.

CHAPTER I. Introduction

Heart failure (HF) is a common and growing problem and its prognosis is extremely poor whether or not the left ventricular systolic function is reduced [1, 2]. The lack of widely accepted objective measures of cardiac dysfunction other than left ventricular ejection fraction (LVEF) has hampered, and continues to hamper, clinical research in patients with heart failure.

Decreased compliance of the left ventricle frequently causes an increase in left atrial pressure, which in turn leads to increased pressure in the right heart. One of the major consequences is that peripheral congestion develops. Once developed, congestion contributes to the severity of symptoms reported by patients with HF, and is responsible for a substantial number of hospital admissions and deaths[3, 4].

Currently, there is no accurate method to determine the degree of congestion; in addition, its presence is not specific for cardiac dysfunction and its clinical assessment is highly subjective and influenced by clinical experience and skills[5-7]. It is rare, nowadays, that a patient with HF presents to a clinician with obvious and widespread peripheral oedema; in the vast majority of cases, congestion is subclinical and might not be clinically recognised despite the presence of symptoms (such as breathlessness), particularly in the elderly [8, 9]. In those not known to have HF, the identification of subclinical congestion (and underlying cardiac dysfunction) at an earlier stage might change the clinical history of the disease. However, in patients who are already known to have HF, whether subclinical congestion is important or not is unclear. Moreover, the impact of the

structural and functional alterations leading to (and indicative of) congestion on the prognosis of patients with HF has not been widely studied [10].

1.1 Which markers could be used to identify congestion in ambulatory patients with HF?

Clinical examination remains the cornerstone of assessing patients with heart failure and an accurate evaluation of the clinical signs secondary to fluid overload identifies those patients with HF who have a more severe disease and a higher risk of adverse outcome[4]. However, due the widespread use and ability of echocardiography, blood tests and modern technology to provide detailed information regarding heart function and cardiovascular haemodynamics, and with the increasing number of patients being seen in ambulatory patient clinics, a comprehensive clinical examination in not often routinely performed[11].

A raised jugular venous pressure (JVP) reflects high right atrial pressure. It is the most reliable clinical sign indicating volume overload and carries powerful prognostic information[12]; its clinical assessment is, however, extremely challenging and subjective [6]. The evaluation of fluid status can be performed by measuring the diameter of the inferior vena cava (IVC) by echocardiography which also offers a fairly reliable estimate of right atrial pressure [13].

Preliminary reports have also shown that the ultrasound evaluation of the internal jugular vein area and its response to respiratory manoeuvres is possible, and might allow the identification of those patients in whom a high right atrial pressure can be excluded [14].

A raised right atrial pressure is usually a late consequence of an elevated left ventricular (LV) filling pressure, which initially affects the left atrium (LA) [15]. As a consequence of a chronic exposure to a high LV filling pressure, the LA increases in dimension and volume, and thus left atrial indices offer reliable prognostic information in patients with heart failure. With the development of sophisticated imaging modalities, such as speckle tracking echocardiography, which allow more accurate measurements of chamber deformation, the focus of study of the LA has shifted toward its function, as well as simply its size [16, 17].

An electrocardiogram (ECG) is a simple and cheap clinical investigation usually performed in patients with suspected HF; when abnormal, it increases the likelihood of the diagnosis. A prolonged duration of the QRS segment at the ECG is a common abnormality identified in patients with HF. It may indicate uncoordinated left ventricular contraction ("dyssynchrony") but could also be a marker of the underlying severity of cardiac disease. In the general population, the presence of a prolonged QRS segment with a right bundle branch block (RBBB) morphology is often considered a benign finding. However, some observational studies suggested that structural heart disease is more common in the presence of RBBB, which indicates an increased cardiovascular and mortality risk amongst asymptomatic individuals [18, 19]. Whether differences in QRS morphology reflect differences in the aetiology, pattern or severity of ventricular dysfunction in patients with HF is not clear and it requires further studies.

Previous and current European Society of Cardiology (ESC) guidelines advise the use of natriuretic peptides (NPs) to rule out, or to diagnose, HF [20, 21]. Natriuretic peptides are one of the body's defences against congestion (22) and any stretch of the muscle of the heart (myocardium) leads to an increase in their plasma level. Thus, a raised NP level in a patient with HF suggests that there is residual congestion, regardless of LVEF, although their levels should be adjusted for age and the presence of co-morbidities, such as atrial fibrillation (AF), renal dysfunction and obesity [22].

1.2 First objectives

1.2.1 Associations of inferior vena cava and outcome in ambulatory patients with heart failure

During the past decade some reports begun to show evidence that right ventricular (RV) dysfunction is an important determinant of outcome in HF [23, 24]. However, many of these studies have focused on RV systolic function rather than on the upstream consequences of ventricular dysfunction and tricuspid regurgitation. The measurement of the inferior vena cava (IVC) diameter by echocardiography is simple in trained hands, and it offers a quantifiable, objective estimation of right atrial pressure and fluid status. Its relationships with other clinical variables and its potential prognostic role have only received little attention. In a preliminary study, Nath and colleagues [25] reported the relationship between IVC diameter and outcome in around 3500 patients, almost exclusively men, who had an echocardiogram at one of three US Veterans hospitals: around 12% of the studied population had a dilated IVC (2 cm or more). Furthermore, patients with a dilated

IVC were older, were more likely to have HF and had a greater risk of dying than those who did not have a dilated IVC. This was, however, a study conducted in patients undergoing echocardiography for different reasons.

I aimed to study the associations between IVC diameter, natriuretic peptides and outcome in ambulatory patients with HF. I also studied the associations of novel measures of left (global longitudinal strain, GLS) and right ventricular function with the outcome of patients with suspected HF who had apparently normal LVEF on conventional echocardiography.

1.2.2 Associations of left atrial function and outcome in ambulatory patients with heart failure

An increased left atrial (LA) dimension and volume are associated with higher risk of adverse outcomes for patients with HF, regardless of LVEF [26-28]. Recent reports suggest that left atrial function might deteriorate before its size or structure change in conditions that increase cardiovascular risk, such as hypertension or diabetes [29], and it might identify individuals at higher risk of developing HF [30]. Thus, I aimed to measure the LA function using cardiac magnetic resonance imaging (cMRI) in patients with suspected or confirmed HF, to study its relationship with other clinical variables and with different measures of outcome.

1.2.3 Relationship between QRS morphology and cardiac structure and function in ambulatory patients with heart failure

A prolonged QRS is associated with a worse cardiovascular outcome in patients with chronic heart failure [31] and is also an important criterion for the selection of

patients for cardiac resynchronization therapy (CRT) [32]. A recently published individual patient meta-analysis of >3500 patients in sinus rhythm found that the benefits of CRT were associated with longer QRS duration [33], but it is less clear whether QRS morphology has an important influence on prognosis or whether it predicts the response to CRT [34]. Differences in QRS morphology might reflect differences in the aetiology or severity of ventricular dysfunction in patients with heart failure. Thus, the aim of my research was to evaluate the left and right heart structure and function in relation to QRS morphology in patients with HF, by cardiac MRI.

1.3 Second objective

1.3.1 Development of a newer ultrasound method to measure the jugular vein diameter in ambulatory patients with heart failure

There are several reasons, other than relevant clinical experience and subjective skills, that make the clinical assessment of jugular venous pressure (JVP) difficult: they might include obesity, the use of accessory muscles in patients with severe dyspnoea, poor lighting or poor positioning of the patient, as well as the difficulty in distinguishing between the carotid and the jugular pulse [6, 35]. More importantly, there is no objective method that measures JVP in a way that can serve as a permanent record to be shared with other colleagues [7], to assess either the response to a treatment or the clinical course of an ill patient.

The jugular vein is a compliant vessel, which size varies with changes in intravascular pressure and volume. The use of ultrasound gives a potential method of assessing and, importantly, providing a precise and objective record of JV

diameter (JVD) and its response to physiological manoeuvres. I developed and tested a method to measure the respiratory variation of internal JVD by ultrasound, using a high frequency probe. I prospectively assessed the relationship of JV diameter and clinical, biochemical and other echocardiographic characteristic in ambulatory patients with a spectrum of severity of HF and in control subjects without important myocardial or valve disease. I also studied the prognostic value of ultrasound assessment of JVD in ambulatory patients with HF.

CHAPTER II. Methods

All investigations conformed to the principles outlined in the Declaration of Helsinki and all the studies mentioned below were approved by relevant ethical bodies. All subjects enrolled gave their written informed consent.

For all the studies mentioned below, patients provided a detailed clinical history and clinical examination, blood tests (including haematology, biochemistry profile and NTproBNP)**,** ECGs and echocardiograms (when performed), including ultrasound assessment of jugular vein diameter, were conducted on the same day. Cardiac MRI was scheduled within a few weeks of the ambulatory visit.

Clinical congestion was assessed by constructing a novel congestion score, based on lung auscultation (normal, presence of basal, mid zone or diffuse crepitations), JVP (not visible, raised 1-4 cm, raised to earlobe), peripheral oedema (none, ankles, below or above knees) and liver examination (not palpable, palpable) with one point attributed for each degree of severity. Patients with a score of three or more out of a possible score of nine were defined as congested.

Our hospital is the only one in the region that offers acute medical services and data regarding hospitalizations, pacemaker implantation and death were collected from the hospital's electronic systems, supplemented by information from patients and their family doctors. Hospitalisations were considered to be HF related if the discharge letter suggested HF as a key reason for admission.

All the analyses were performed using SPSS and Stata software. A 2-sided p-value < 0.05 was considered statistically significant.

2.1 Echocardiographic measurements

Echocardiography was performed by an experienced operator using a Vivid Five, Seven or Nine (GE Health Care, UK) system. LVEF was measured using Simpson's biplane method. Left atrial diameter (LAD) was measured in parasternal long axis; LA volume was indexed to body surface area (LAVI). Tricuspid annular plane systolic excursion (TAPSE) was used to assess RV systolic function. The trans-tricuspid systolic gradient was also measured. With the patient supine, the maximum IVC diameter during the respiratory cycle was measured approximately three centimetres before merger with the right atrium. A digital loop was acquired from apical 2, 3 and 4-chamber views at frame rates of 40-80 frames/s to assess LV longitudinal strain. Peak systolic strain was defined as the peak negative value on the strain curve during the entire cardiac cycle. An 18 segment model of the LV was used and values from basal, medium and apical segment of each wall were then averaged. Global longitudinal strain values were reported if 12 or more segments could be analysed.

2.2 Cardiac MRI measurements

Cardiac MRI was performed on a 1.5 T scanner (either Sigma CV/I, GE Medical Systems or Achieva, Philips Medical Systems) equipped with a phased-array coil placed over the praecordium. Participants lay in the supine position, and after localizing scans, ECG-gated cine images of the heart were acquired during breath-

hold (in expiration). The images were acquired using steady-state free precession pulse sequences in two standard long axes and multiple short-axis slices, with slice thickness of 8 mm and inter-slice distance of 2 mm from the base to the apex of the heart.

Images were analysed offline using QMass MR software (MEDIS, Leiden, The Netherlands). The multi-slice, short-axis cine data-sets were analysed to calculate LV and RV volumes and masses. Endocardial and epicardial borders were traced manually using end-diastolic and end-systolic frames in contiguous short-axis slices. LV end-diastolic (EDV) and end-systolic (ESV) volumes were calculated using summation of area × [slice thickness + interslice gap] for each slice (Simpson's method), which were then used to calculate LVEF and LV mass. Papillary muscles were excluded from LV volume measurements and included in mass calculations. The interventricular septum was considered as part of the LV. RV volumes, mass and EF were calculated in a similar fashion. Left atrium (LA) maximum volume was measured at the frame just before mitral valve opening in 4 chamber long axis view. Mitral and tricuspid regurgitation volume was visually graded as none or trivial (0), mild (1) or moderate or worse (2).

2.3 Associations of IVC diameter and GLS with outcome in ambulatory patients with heart failure (part 1; paper 1 and 2)

2.3.1 Study population

Consecutive ambulatory patients with chronic HF attending a specialist community clinic between November 2008 and March 2010 were enrolled (paper

1). The cohort was further extended with patients who attended until May 2010 (paper 2).

2.3.2 IVC and outcome in HF. Definition of heart failure and main outcome (paper 1)

HF was defined as the presence of symptoms or signs of HF, supported by objective evidence of cardiac dysfunction: either LVEF ≤45% or the combination of both left atrial dilation (≥4 cm diameter in the parasternal long axis) and a plasma concentration of NTproBNP ≥400 pg/ml.

The primary outcome was a composite of admission for worsening HF or cardiovascular (CV) death. In order to avoid errors due to the attribution of cause of death, I also considered the secondary endpoint of all-cause mortality.

2.3.3 GLS and outcome in HFNEF. Definition of heart failure and main outcome (paper 2)

Patients were included in the analysis if their LVEF was ≥50% and they had symptoms or signs suspicious of HF. Three different subgroups were defined:

- Group A: Patients with no substantial cardiac dysfunction (LVEF≥50%, left atrial diameter (LAD) <4 cm in parasternal long axis, NTproBNP <400 ng/l): N= 76;
- Group B: Patients with LVEF ≥50%, but LAD ≥4 cm **or** NTproBNP ≥400 ng/l, defined as "possible HFNEF": N=99;

• Group C: Patients with LVEF ≥50%, LAD ≥4 cm **and** NTproBNP ≥400 ng/L, defined as "definite HFNEF": N=138.

The primary outcome of interest was a composite of admission for worsening HF or CV death (due to terminal HF or sudden death out of hospital not explained by cancer or other non-cardiovascular disease). To avoid errors due to the attribution of cause of death, a second end point of all-cause mortality was also considered.

2.3.4 Statistical methods

2.3.4.1 IVC and outcome in HF

50 IVC measurements were randomly selected and measured separately by myself and another experienced operator blind to each other's results. The reproducibility and internal consistency of the IVC measurements were tested using Bland-Altman plots and Cronbach's alpha method respectively. The relations between IVC diameter and other variables were assessed by Pearson, Spearman and point-biserial correlation coefficients. Patients were grouped as: those without evidence of cardiac dysfunction and, for patients with HF, by IVC diameter tertile. One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups, and chi-squared tests for categorical variables. Simple and multiple linear regression models were used to identify variables associated with IVC diameter. Only variables significantly associated with IVC diameter in univariable analysis ($p<0.05$) were entered into the multivariable analysis. Associations between variables and prognosis were assessed using Cox proportional hazards models. Because there were only 158 primary outcome

events, I chose eight candidate variables of interest in addition to IVC diameter and NTproBNP in order to avoid over-fitting. To investigate the prognostic value of IVC diameter compared to a more extensive list of prognostic variables, we repeated the exercise with a more robust dataset, recognising the risk of over-fitting. Three different multivariable models were tested. The first included both Log [NTproBNP] and IVC diameter and then each of them separately. Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome. C-statistics (area under receiver operating characteristic (ROC) curves) was used to compare Log [NTproBNP] and IVC diameter as predictors of prognosis at one year for the primary and secondary end points. The method also was used to compare IVC diameter and other key echocardiographic measures as predictors of prognosis at one year for the primary outcome.

2.3.4.2 GLS and outcome in HFNEF

16 GLS measurements and 276 individual segments were randomly selected and measured separately on two different occasions by the applicant. The reproducibility of the GLS measurements, as well as of each segment, was tested using Bland-Altman plots. One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi-squared test was used for categorical variables.

Associations amongst demographic, clinical, echocardiographic and biochemical variables with prognosis were assessed using the Cox proportional hazards models.

Because there were relatively few primary outcome events, two different multivariable models were tested to prevent over-fitting. In Model A, I chose, prospectively, eight candidate variables of interest in addition to GLS and diagnostic category; for Model B, I selected the eight variables most strongly associated with prognosis in univariable analysis. For the second model (Model B), given the high correlation between IVC diameter and TR systolic gradient ($R=0.529$, $p<0.001$), I selected the IVC diameter.

Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome. Assumptions of the models were tested, such as multicolinearity and proportional hazards.

2.4 Associations of left atrial function and outcome in ambulatory patients with heart failure (Part 2, paper 3)

2.4.1 Study population, definition of heart failure and main outcome

Consecutive ambulatory patients referred with suspected HF to a community HF clinic who had undergone cMRI as part of their investigation were followed up prospectively, but the analysis plan was developed post-hoc.

Patients in atrial fibrillation or atrial flutter or those who had no available measurement of NTproBNP were excluded from the analysis (Figure 1).

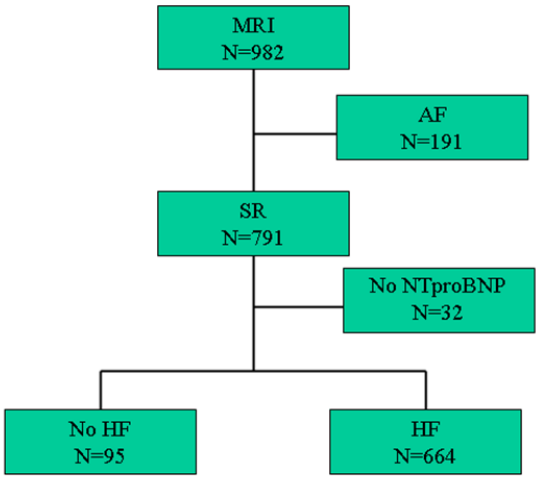

***Figure 1**: Consort diagram showing the disposition of patients enrolled. Of 982 patients who had a cardiac magnetic resonance imaging (MRI), 20% had atrial fibrillation (AF); plasma NTproBNP was not available in 3%. Of the remaining 759 in sinus rhythm (SR), 664 were considered to have heart failure (HF), 95 were not.*

HF was defined by the presence of symptoms or signs of HF supported by objective evidence of cardiac dysfunction: either a LVEF <50% on cMRI or raised plasma concentration of NTproBNP >400 pg/ml (or >125pg/ml if patients were taking loop diuretics).

The primary outcome of interest was a composite of hospitalisation for HF and all-cause mortality. Secondary endpoints were total mortality and cardiovascular mortality. A further secondary endpoint of incident AF, electrocardiographically documented, was also considered. We did not attempt to distinguish between persistent and permanent AF.

2.4.2 cMRI measurements for left atrium

Images were analysed offline using QMass MR software (MEDIS, Leiden, The Netherlands). LA maximum, the frame just before mitral valve opening, and

minimum, the frame just after mitral valve closure, volumes were measured in both 2 and 4 chamber views by the candidate and another experienced operator. The LA endocardial border was manually traced. The anterior border was at the mitral annular plane and the posterior border at the ostia of the pulmonary veins, excluding the LA appendage. LA volumes were calculated using the area-length method (Volume = $0.85 \times Area^2 / Length$) and LA emptying function (LAEF) was calculated using the formula: [(LA max - LA min)/LA max] × 100 %. We also calculated LA total emptying volume (reservoir function; (LA max-LA min) and LA conduit volume as (LV stroke volume – LA total emptying volume) [36].

2.4.3 Statistical methods

The relations between LAEF and other variables were assessed by Pearson, Spearman and point-biserial correlation coefficients. Patients were grouped as: those without evidence of cardiac dysfunction; and, for patients with HF, by LAEF quartiles. One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups, and chi-squared or Fisher's exact tests for categorical variables.

Simple and multiple linear regression models were used to identify variables associated with LAEF. Only the variables associated with LAEF in univariable analysis ($p<0.1$) were entered into the multivariable analysis. Two separate models were tested, one including and one excluding measurements of RV size and function, as a substantial proportion of patients did not have measurements of RV function available.

Associations between variables and prognosis were assessed using Cox proportional hazards models. In order to prevent over-fitting, variables included in prognostic models were restricted to age, sex, NYHA (III/IV versus I/II), IHD, congestion score 2 or less versus ≥3, creatinine, albumin, haemoglobin and left ventricular end-diastolic volume. To these were added log [NTproBNP] and LAEF together and then separately. RV measurements were not included in the multivariable analysis because these were available for only 549 patients with HF. The proportional hazards assumption was checked by the scaled Schoenfeld residual plot [37] and a global test of any proportional hazards violations were evaluated based on the method proposed by Grambsch and Therneau [38]. The overall model fit were evaluated by likelihood-ratio test and using the Cox-Snell residuals. The models fitted the data well. The discrimination of the model was accessed by Harrell's C. Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome.

2.5 The relationship of QRS morphology with cardiac structure and function in patients with heart failure (part 2, paper 4)

2.5.1 Study population, definition of heart failure and main outcome

Consecutive ambulatory patients referred with suspected HF (2001-2011) to a community HF clinic who had undergone cMRI as part of their investigation were followed up prospectively but the analysis plan was developed post-hoc. HF was defined by the presence of symptoms or signs of HF supported by objective evidence of cardiac dysfunction: either a LVEF ≤50% on cMRI or raised plasma

concentration of NTproBNP > 400ng/l (or >125pg/ml despite taking loop diuretics). The primary outcome of interest was of all-cause mortality.

2.5.2 Definition of different QRS morphologies at ECG

A surface 12-lead ECG was recorded at rest, at a speed of 25 mm/s, and 10 mm/mV gain. QRS morphology and duration reported by ECG software were confirmed by the doctor assessing the patient using standard criteria [39]. For patients who had QRS $\geq$120 msec, QRS morphology was defined as LBBB in the presence of broad notched or slurred R wave in leads I, aVL, V5, and V6 and the absence of a Q wave in leads I, V5 and V6; and as right bundle branch block (RBBB) when rsr′, rsR′, or rSR′ complexes were found in leads V_1 or V_2. Cases that did not fulfil these criteria were designated indeterminate ventricular conduction delay (IVCD).

2.5.3 Definition of ischaemic heart disease

Ischaemic heart disease (IHD) was defined as a previous history of MI or a >70% narrowing in at least one major epicardial artery on angiography, or evidence of significant scar on late-enhancement gadolinium contrast cMRI in a well-defined coronary artery territory. If there was no evidence of important coronary artery disease at angiography and no evidence of scar on late-enhancement gadolinium scans, the patients were considered to have non-ischaemic dilated cardiomyopathy. Those patients who had neither an angiogram, nor previous history of MI nor late-enhancement gadolinium at cMRI were left unclassified (n = 144 in total).

2.5.4 Statistical methods

Independent samples t-tests, one-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups, and chi-squared tests used for categorical variables. Associations between variables and prognosis were assessed using Cox proportional hazards models. Only variables associated with outcome ($p<0.1$) in univariable analysis were entered into multivariable models. Different multivariable models were tested, including and excluding measurements of RV function (RVEF), as they were not available for a substantial proportion of patients enrolled (24%). When RVEF was entered into the models, multiple imputation method was used for imputing missing values of RVEF. To impute the missing values of RVEF, age, hypertension, QRS duration, congestion, creatinine, NYHA class, BSA, albumin, bilirubin, haemoglobin, LVEDV and log(NTproBNP) were chosen for the imputation model (linear regression) because of their correlation with RVEF. Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome.

2.6 Development of a newer ultrasound method to measure the jugular vein diameter in ambulatory patients with heart failure (part 3, paper 5 and 6)

2.6.1 Study population, definition of heart failure and main outcome

Control subjects and ambulatory patients with HF enrolled in the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF) [40], an international observational study of the prevalence, incidence and impact of key co-morbidities in ambulatory patients with a clinical diagnosis of chronic HF who either had a LVEF <40% or a plasma concentration of NTproBNP >400ng/L or

both, were invited to participate. Patients were assessed after attempts to optimise their medical therapy.

Two reports were produced: the first explored the association of JVD ultrasound measurements and other clinical characteristics in 211 patients and 20 controls (paper 5); this cohort was extended enrolling more patients (until May 13) and analysing the relationship between JVD measured by ultrasound and outcome (paper 6).

The minimum follow up period was four months. The primary outcome of interest was a composite of all-cause mortality or HF hospitalization. All data regarding admissions and deaths were entered into a dedicated online database, and were adjudicated at regular intervals by different researchers blind to any other measurement collected at the time of the clinical visit.

2.6.2 Jugular vein measurements

With the patient reclining and head and neck elevated at 45°, the probe was placed below the angle of the jaw and then moved inferiorly toward the angle of Louis until the left internal JV was identified.

JV diameter and its changes were then measured continuously by M-mode or by two dimensional ultrasound using a linear high frequency probe (10 MHz) at rest (expiratory phase), during a Valsalva manoeuvre (performed by forceful expiration against a closed glottis) and, finally, during deep inspiration (Figure 2).

The ratio between maximum JV diameter during Valsalva and diameter at rest was also calculated (JVD ratio).

Because in our laboratory the echocardiographic machine is situated on the left side of the bed it was easier to measure left internal jugular vein diameter changes as opposed to the right. Veins are easily compressible and it is important to apply only very light pressure on the neck to avoid inaccurate vein measurements.

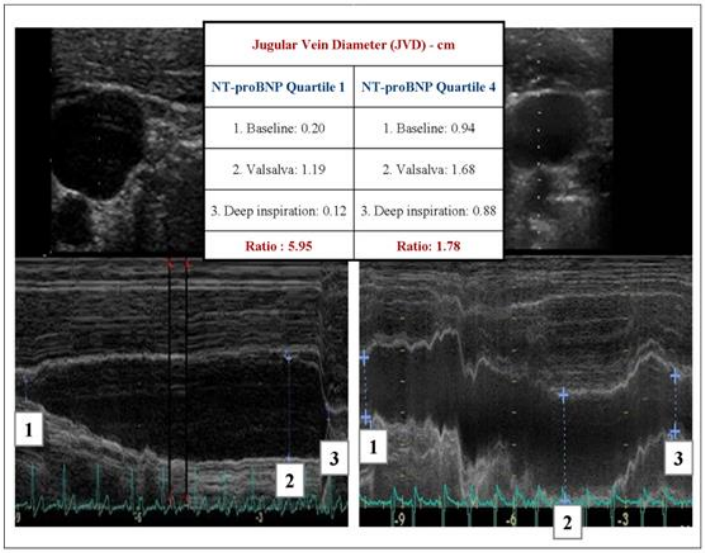

Figure 2: Jugular Vein Measurements*. With the patient reclining and head and neck elevated at 45°, the internal jugular vein (JV) is identified and JV diameter (JVD) and its changes are measured continuously by M-mode ultrasound at rest in the expiratory phase (1), then during a Valsalva manoeuvre (2) and, finally, during deep inspiration (3). The ratio between maximum JV diameter during Valsalva and diameter at rest is calculated (JVD ratio). JVD changes and JVD ratio in different patients with HF are shown (on the left side, for a patient in the lowest NTproBNP quartile and on the right side for a patient in the highest NTproBNP quartile). The scale used is different in each panel.*

2.6.3 Statistical methods

Twenty JV measurements were randomly selected and measured separately by the applicant and another operator blind to each other's results. The intra- and inter-

operators reproducibility of the JVD measurements were tested using the Bland-Altman method.

The relations between JVD and other variables were assessed by scatter plots and using Pearson, Spearman and point-biserial correlation coefficients depending on distribution of the data. One-way ANOVA and Kruskal-Wallis tests were used to compare continuous variables between groups depending on the normality of the distribution, and the chi-squared test for categorical variables.

Simple and multiple linear regression models were used to identify variables associated with JVD ratio. Only variables that were significantly associated with JVD ratio in univariable analysis ($p<0.1$) were entered into the multivariable analysis. A ROC curve for the relationship between JVD ratio and prognosis at one year was constructed to identify the Youden index.

2.6.3.1 Analysis 1

Two different multivariable Cox proportional hazard regression models were used to investigate the relationship of JVD and prognosis using a limited number of variables to prevent statistical overfitting. In Model A, we chose, prospectively, five candidate variables of interest (age, NYHA class, urea, haemoglobin and log [NTproBNP]) in addition to ultrasound JVD measurements; and for Model B, we selected the three echocardiographic variables that were most strongly associated with prognosis in univariable analysis, in addition to age, log (NTproBNP) and JVD measurements.

2.6.3.2 Analysis 2

In order to estimate the predictive value of the different variables of interest, I constructed a basic model, and then tested the additive value of each potential variable (and combinations of variables) in turn. The basic model included age, sex and four variables strongly associated with prognosis in univariable analysis: NYHA (III v II/I), creatinine, haemoglobin and LVEF. The variables of interest to be added to the basic model were: log (NTproBNP), clinical (JVP assessment 2/1 vs 0) and ultrasound measurements or right atrial pressure (either IVC diameter or JVD measurements). The incremental value of the variables (the model's cumulative discrimination) was measured using Harrell's C statistic. Kaplan-Meier curves with the log-rank statistic were used to illustrate outcome.

CHAPTER III. Results

3.1 Associations of IVC with outcome in ambulatory patients with heart failure (part 1; paper 1)

3.1.1 Inferior vena cava measurements

Internal consistency (Cronbach's alpha = 0.993 with 95% CI (0.989, 0.996)) and reproducibility (Bland Altman plot: Mean difference = -0.040, 95% limits of agreement: -2.480, 2.400 mm) of measurements of IVC diameter were good. The distribution of IVC diameter for patients with and without HF is shown in figure 3.

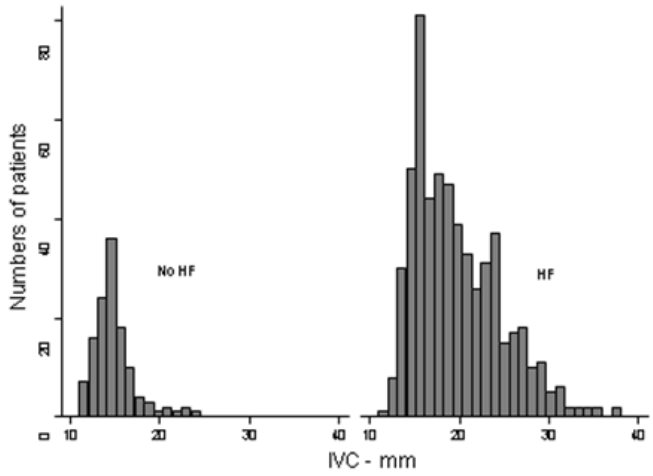

***Figure 3**: The distribution of IVC diameter in patients without (left panel) or with (right panel) heart failure (HF).*

3.1.2 Patient characteristics

Of the 721 patients enrolled, 4 were excluded because NTproBNP results were not available and 24 because IVC was poorly visualised. A total of 693 patients were

studied: 372 patients (53%) had an LVEF ≤45%, 196 (29%) had LVEF>45%, with both a dilated LA and raised NTproBNP, and 125 (18%) were considered not to have HF (supplementary table 1).

Patients with HF in the highest tertile of IVC diameter were older, were more likely to have AF and to be treated with diuretics. They had more severe symptoms, more signs of congestion and higher NTproBNP plasma levels. They also had larger LA volumes, more mitral and tricuspid regurgitation, more severe RV dysfunction and higher pulmonary pressures. LVEF and blood pressure were similar across tertiles (supplementary table 1).

3.1.3 Correlates of Inferior Vena Cava Diameter

In patients with HF, IVC diameter correlated with log (NTproBNP) ($r=0.55$; $p<0.001$), with congestion index and with the individual signs used to derive that score (peripheral oedema: $r= 0.30$; $p<0.001$; lung crepitations: $r=0.17$; $p <0.001$; JVP: $r=0.31$; $p <0.001$; hepatomegaly: $r=0.22$; $p<0.001$).

There was no relation between IVC diameter and measures of LV volumes or systolic function but there was a weak correlation between IVC diameter and GLS.

Increasing age, Log (NTproBNP), LAVI and estimated systolic pulmonary artery pressure, AF and tricuspid regurgitation were independently associated with increasing IVC diameter (Table 1; overall $R^2=0.53$).

Variables associated with IVC diameter	Univariable analysis		Multivariable analysis	
	Correlation Coefficient	p- value	Unstandardized Coefficients (with 95% CI)	t-stat (p-value)
Clinical data				
Age	0.18	<0.01	-0.53 (-0.87,-0.20)	-3.17 (<0.01)
Men	0.01	0.92		
NYHA class	0.25	<0.01		
IHD	-0.07	0.10		
DM	-0.10	0.80		
HTN (or SBP > 140 mmHg)	-0.03	0.55		
Smoker	-0.08	0.05		
Atrial fibrillation	0.42	<0.01	1.52 (0.67,2.38)	3.51 (<0.01)
COPD	0.02	0.65		
SBP – mmHg	-0.06	0.13		
Heart rate - bpm	0.07	0.12		
BMI - kg/m^2	-0.10	0.02		
Congestion ≥3	0.34	<0.01		
Blood Test				
Creatinine – umol/l	0.15	<0.01		
Urea* – mmol/l	0.19	<0.01		
eGFR – ml/min/1.73m^2	-0.14	<0.01		
Haemoglobin - g/dl	-0.21	<0.01		
Albumin – g/l	-0.20	<0.01		
Bilirubin – umol/l	0.32	<0.01		
Cholesterol - mmol/L	-0.19	<0.01		
NT-proBNP* – ng/l	0.55	<0.01	2.55 (1.69,3.40)	5.87 (<0.01)
hsCRP* – mg/l	0.04	0.36		
Echocardiographic data				
LVEDD - mm	0.05	0.27		
LVEDV – ml	0.06	0.15		
LVEF (%)	0.02	0.61		
GLS (%)	0.10	0.02		
LA diameter – mm	0.38	<0.01		
LA area – mm^2	0.47	<0.01		
LAVI - ml/m^2	0.44	<0.01	0.02 (0.08,0.40)	2.99 (<0.01)
TAPSE – mm	-0.34	<0.01		
TR gradient - mmHg	0.54	<0.01	0.09 (0.05,0.12)	4.95 (<0.01)
Mitral regurgitation	0.33	<0.01		
Tricuspid regurgitation	0.48	<0.01	1.24 (0.63,1.86)	3.98 (<0.01)

***Table 1**: Variables associated with inferior vena cava (IVC) diameter in patients with heart failure (n.568). A log transformation was also done for variables labelled with * before conducting the analysis to satisfy the model assumptions. The columns for the multivariable analysis (right) show the coefficients for slope of the linear relation between all the variables independently associated with IVC diameter (R^2= 0.53)). List of abbreviation used: NYHA – New York Heart Association; IHD - Ischemic Heart Disease; DM – Diabetes Mellitus; HTN – Hypertension; COPD - Chronic Obstructive Pulmonary Disease; SBP - Systolic Blood Pressure; BMI - Body Mass Index; eGFR - estimated Glomerular Filtration Rate; NTproBNP - N-terminal B-type natriuretic peptide; hsCRP - high sensitivity C-reactive protein; LVEDD - Left Ventricle End-Diastolic Diameter; LVEDV - Left Ventricle End Diastolic Volume; LVEF – Left Ventricular Ejection Fraction; GLS - Global Longitudinal Strain; LA – Left Atrium; LAVI - Left Atrial Volume Index; TAPSE - Tricuspid Annular Plane Systolic Excursion; TR gradient- Trans-Tricuspid systolic gradient.*

3.1.4 IVC, worsening heart failure or cardiovascular death

Patients with HF were followed up for a median of 567 (IQR: 413 – 736) days. The minimum follow up in survivors was 365 days. There were 158 events (78 patients were admitted to hospital with HF and 80 died due to CV causes, of which 48 were attributed to HF, 26 to out of hospital sudden death and five to a

myocardial infarction and one to a stroke). Neither LVEF nor GLS predicted events (table 2).

Variables	Univariable analysis			Multivariable analysis			Multivariable analysis NT-proBNP excluded IVC excluded		
	HR (95% CI)	Wald χ^2	p-value	HR (95% CI)	Wald χ^2	p-value	HR (95% CI)	Wald χ^2	p-value
Age -years	1.03 (1.01,1.05)	15.90	<0.01						
Men	1.00 (0.71,1.41)	0.01	0.99						
NYHA class III vs. I/II	2.40 (1.75, 3.33)	30.08	<0.01	1.65 (1.15,2.37)	7.34	<0.01	1.66 (1.16,2.40) 1.58 (1.09,2.28)	7.56 5.96	<0.01 0.02
IHD	0.88 (0.63,1.19)	0.77	0.38						
DM	1.01 (0.71,1.41)	0.01	0.97						
Hypertension or SBP >140mmHg	0.61 (0.45,0.84)	7.47	<0.01	0.67 (0.45,0.98)	4.12	0.02	0.67 (0.45,0.98) -	4.20 -	0.04 -
Atrial fibrillation	1.75 (1.28,2.40)	12.44	<0.01						
COPD	1.05 (0.65,1.70)	0.04	0.84						
SBP – mmHg	0.99 (0.98,1.00)	7.60	<0.01						
Heart rate - bpm	1.01 (0.99,1.02)	1.29	0.25						
BMI - kg/m^2	0.96 (0.93,0.99)	7.73	<0.01						
Congestion ≥3 signs	2.77 (1.94,3.93)	31.80	<0.01						
JVP	2.29 (1.86,2.81)	62.44	<0.01						
Creatinine – umol/l	1.01 (1.00,1.01)	39.28	<0.01						
Urea – mmol/l	1.10 (1.07,1.12)	50.68	<0.01	1.06 (1.02,1.09)	11.27	<0.01	1.06 (1.03,1.09) 1.05 (1.02,1.08)	13.14 8.21	<0.01 <0.01
eGFR – ml/min/1.73m^2	0.98 (0.97,0.99)	21.45	<0.01						
Haemoglobin - g/dl	0.77 (0.71,0.84)	35.47	<0.01						
Albumin – g/l	0.89 (0.86,0.93)	29.98	<0.01						
Bilirubin – umol/l	1.04 (1.01,1.06)	10.30	<0.01						
Cholesterol - mmol/L	0.72 (0.62,0.85)	15.08	<0.01						
Log (NT-proBNP)	4.36 (3.14,6.06)	77.31	<0.01				- 1.76 (1.05,2.94)	- 4.67	- 0.03
hsCRP – mg/l	1.01 (1.00,1.02)	6.88	<0.01						
IVC - mm	1.17 (1.13,1.20)	112.14	<0.01	1.12 (1.07,1.17)	21.51	<0.001	1.13 (1.08,1.18) -	25.48 -	<0.01 -
LVEDV - ml	1.00 (0.99,1.00)	1.58	0.21						
LVEDD - mm	1.01 (0.99,1.03)	0.83	0.36						
LVEF (%)	0.99 (0.98,1.01)	0.38	0.54						
GLS (%)	1.04 (0.99,1.08)	2.93	0.09						
LA diameter - mm	1.04 (1.02-1.06)	16.36	<0.01						
LAVI - ml/m^2	1.02 (1.01,1.02)	44.98	<0.01						
TAPSE – mm	0.90 (0.87,0.93)	30.26	<0.01						
TR gradient - mmHg	1.05 (1.04,1.06)	84.92	<0.01				- 1.02 (1.01,1.04)	- 7.76	- <0.01
Mitral regurgitation	1.82 (1.50,2.21)	36.79	<0.01						
MR: Moderate vs. Mild	2.79 (2.00,3.89)	36.71	<0.01						
Tricuspid regurgitation	2.29 (1.87,2.82)	62.59	<0.01						
TR: Moderate vs. Mild	4.89 (2.60,5.81)	43.98	<0.01						

Table 2: *Univariable and multivariable Cox regression models for the composite endpoint CV death or HF hospitalization in patients with HF (n = 568 patients with heart failure who had 158 events). In the first column the univariable analysis is shown, the second column shows a multivariable model based on a more robust data set, which includes both LogNTproBNP and Inferior Vena Cava (IVC) diameter. In the last column two different multivariable models have been tested: one excluding logNTproBNP and one excluding IVC diameter. List of abbreviation used: NYHA – New York Heart Association; IHD - Ischemic Heart Disease; DM – Diabetes Mellitus; COPD - Chronic Obstructive Pulmonary Disease; SBP - Systolic Blood Pressure; BMI - Body Mass Index; JVP - Jugular Venous Pressure ; eGFR - estimated Glomerular Filtration Rate; NTproBNP - N-terminal B-type natriuretic peptide; hsCRP - high sensitivity C-reactive protein; LVEDD - Left Ventricle End-Diastolic Diameter; LVEDV - Left Ventricle End Diastolic Volume; LVEF – Left Ventricular Ejection Fraction; GLS - Global Longitudinal Strain; LA – left atrium; LAVI - Left Atrial Volume Index; TAPSE - Tricuspid Annular Plane Systolic Excursion; TR gradient- Trans-Tricuspid systolic gradient, MR: mitral regurgitation; TR: tricuspid regurgitation.*

IVC diameter was the strongest predictor of adverse prognosis in the univariable analysis. In multivariable analysis, the "parsimonious" model (table 3) identified decreasing systolic blood pressure, and increasing NYHA class, urea, IVC diameter and the trans-tricuspid systolic gradient as independent predictors of poor outcome.

When IVC diameter was excluded, Log (NTproBNP) and LAVI entered the model. When a more extensive data set was used (Table 2) and both log (NTproBNP) and IVC diameter were included, IVC diameter but not log (NTproBNP) was independently associated with a poor outcome.

Variables	Multivariable analysis			Multivariable analysis IVC excluded		
	HR (95% CI)	Wald χ^2	p-value	HR (95% CI)	Wald χ^2	p-value
Age - years	1.01 (0.99,1.03)	1.05	0.31	1.01 (0.99,1.02)	0.31	0.57
NYHA class III vs. I/II	1.51 (1.08,2.11)	5.83	0.02	1.49 (1.06,2.09)	5.22	0.02
SBP - mmHg	0.99 (0.98,1.00)	6.26	0.01	0.99 (0.98,1.00)	7.70	<0.01
Urea - mmol/l	1.05 (1.01,1.08)	9.19	<0.01	1.05 (1.01,1.08)	8.45	<0.01
Haemoglobin - g/dl	0.92 (0.83,1.02)	2.31	0.13	0.93 (0.84,1.03)	1.99	0.16
Log [NT-proBNP]- pg/ml	1.36 (0.85,2.11)	1.67	0.20	1.85 (1.18,2.89)	7.13	<0.01
IVC - mm	1.10 (1.06,1.14)	26.28	<0.01	-	-	-
LVEF - %	1.00 (0.99,1.02)	0.05	0.82	1.00 (0.99,1.01)	0.09	0.76
LAVI - ml/m^2	1.00 (0.99,1.01)	1.48	0.22	1.01 (1.00,1.01)	4.64	0.03
TR gradient - mmHg	1.02 (1.00,1.03)	4.09	0.04	1.03 (1.01,1.04)	13.77	<0.01

***Table 3**: A "parsimonious" multivariable Cox regression model for the composite endpoint of CV death or HF hospitalization in patients with HF. To avoid over-fitting, eight candidate variables of interest in addition to inferior vena cava (IVC) diameter and N-terminal B-type natriuretic peptide (NT-proBNP) were chosen. On the left, the model includes IVC. On the right, IVC was excluded. List of abbreviation used: NYHA – New York Heart Association; SBP - systolic blood pressure; LVEF – left ventricular ejection fraction; LAVI - left atrial volume index; TR gradient - Trans-Tricuspid systolic gradient.*

Patients in the highest tertile of IVC diameter had about a 40% risk of an adverse event within the first year; patients with HF in the lowest tertile of IVC diameter had a similar outcome to subjects who did not have HF (Figure 4).

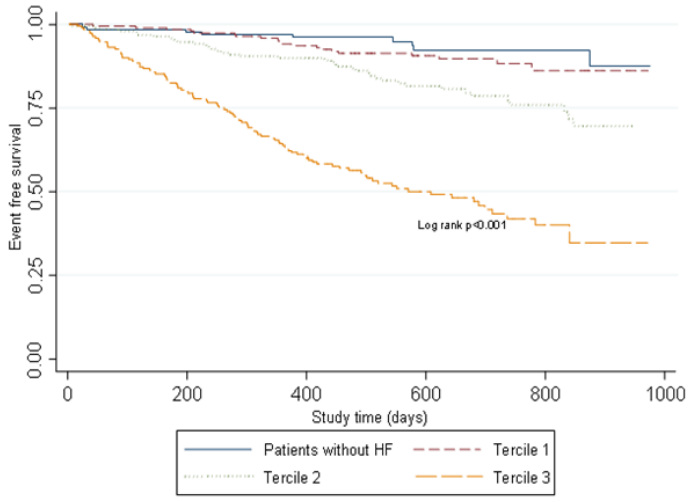

***Figure 4**: Kaplan-Meier (KM) curves for the primary composite endpoint (HF hospitalization or CV death) in patients without heart failure (solid blue line) and by tertiles of IVC diameter in patients with heart failure (red is lowest tertile, green is mid-tertile and orange is highest tertile). Patients in the lowest tertile of IVC diameter had a similar rate of events to those considered not to have heart failure. For patients with HF, the hazard ratio for this outcome was 7.02 (95% CI: 4.34 -11.37; p<0.001) in the highest versus lowest tertile.*

ROC curves for outcome at one year (Figure 5) showed no difference between IVC diameter and log (NTproBNP) (p= 0.20).

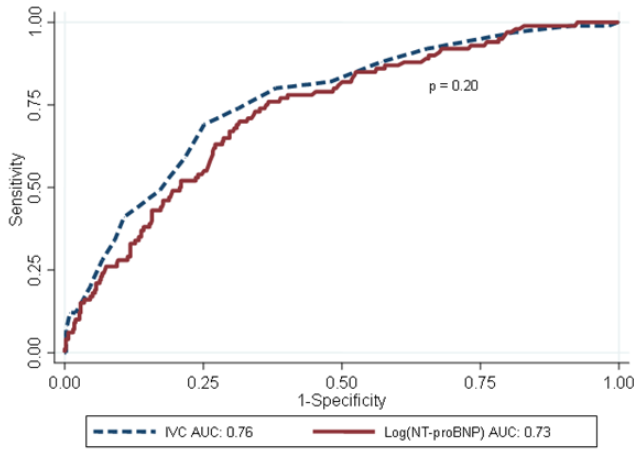

Figure 5: *ROC curves for IVC diameter and Log [NT-proBNP] in predicting event-free survival to one year (HF admissions and CV death): IVC had a slightly greater area under the curve (AUC, 0.76 with a 95% CI: 0.71-0.81) than Log [NT-proBNP] (AUC: 0.73, 95% CI: 0.68-0.78); but the difference was not statistically significant (p= 0.20).*

Amongst other echocardiographic measures, IVC diameter had the greatest area under the curve in predicting survival to one year (figure 6).

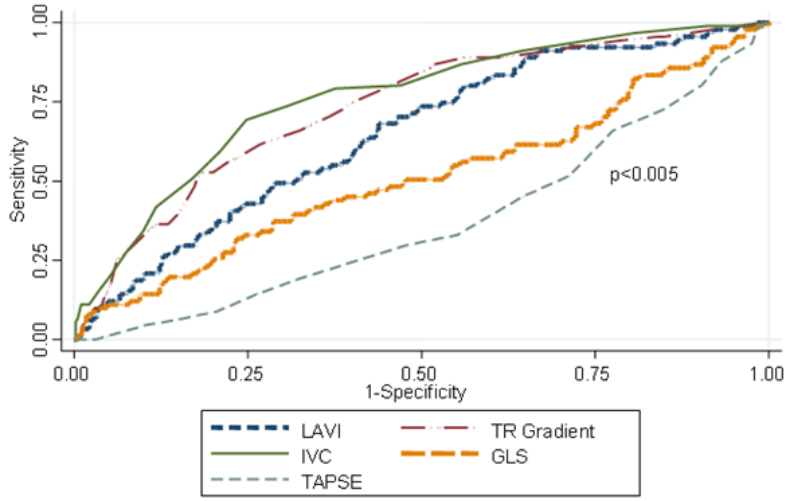

Figure 6: *ROC curves for IVC diameter and other echocardiographic measures (LAVI, TAPSE, TR gradient and GLS) in predicting the combined endpoint of HF admissions and CV death. IVC diameter had a greater AUC (0.76 with a 95% CI: 0.70-0.81) than TR gradient (AUC: 0.73, 95% CI: 0.67-0.78), LAVI (AUC: 0.64, 95% CI: 0.59-0.71), GLS (AUC: 0.51, 95% CI: 0.44-0.58) or TAPSE (AUC: 0.37, 95% CI: 0.31-0.43). The difference was statistically significant (χ^2 = 78.44; p<0.001).*

3.1.5 Inferior vena cava diameter and total mortality

During a median follow-up of 600 (IQR: 449-756) days, 98 patients (17%) with HF died. The "parsimonious" model (Table 4) identified decreasing haemoglobin and systolic blood pressure, and increasing age, urea and IVC diameter as independent predictors of mortality. When IVC diameter was excluded, increasing Log (NTproBNP) entered the model.

Variables	Multivariable analysis			Multivariable analysis IVC excluded		
	HR (95% CI)	Wald χ^2	p-value	HR (95% CI)	Wald χ^2	p-value
Age - years	1.03 (1.01,1.06)	6.25	0.01	1.03 (1.00,1.06)	4.75	0.03
NYHA class I/II vs. III	1.21 (0.80,1.84)	0.81	0.37	1.21 (0.79,1.85)	0.78	0.38
SBP - mmHg	0.98 (0.97,0.99)	11.10	<0.01	0.98 (0.97,0.99)	10.66	<0.01
Urea - mmol/l	1.04 (1.01,1.08)	5.33	0.02	1.05 (1.01,1.09)	6.89	<0.01
Haemoglobin - g/dl	0.82 (0.72,0.93)	9.13	<0.01	0.83 (0.74,0.94)	8.46	<0.01
Log [NT-proBNP)] pg/ml	1.48 (0.82,2.65)	1.69	0.19	1.92 (1.10,3.36)	5.24	0.02
IVC - mm	1.09 (1.04,1.14)	11.76	<0.01	-	-	-
LVEF - %	1.01 (0.99,1.02)	0.40	0.53	1.01 (0.99,1.02)	0.75	0.38
LAVI - ml/m^2	1.00 (0.99,1.01)	0.84	0.36	1.01 (0.99,1.01)	2.06	0.15
TR gradient - mmHg	1.00 (0.98,1.02)	0.10	0.75	1.01 (0.99,1.03)	1.65	0.20

***Table 4**: A "parsimonious" multivariable Cox regression model for the secondary endpoint of death for all causes in patients with HF. To avoid over-fitting, eight candidate variables of interest in addition to inferior vena cava (IVC) diameter and N-terminal B-type natriuretic peptide (NT-proBNP) were chosen. On the left, the model includes IVC. On the right, IVC was excluded. List of abbreviation used: SBP - systolic blood pressure; LVEF – left ventricular ejection fraction; LAVI - left atrial volume index; TR gradient- Trans-Tricuspid systolic gradient.*

The relation between both IVC diameter and Log (NTproBNP) and one year mortality was similar on ROC curve analysis (Figure 7).

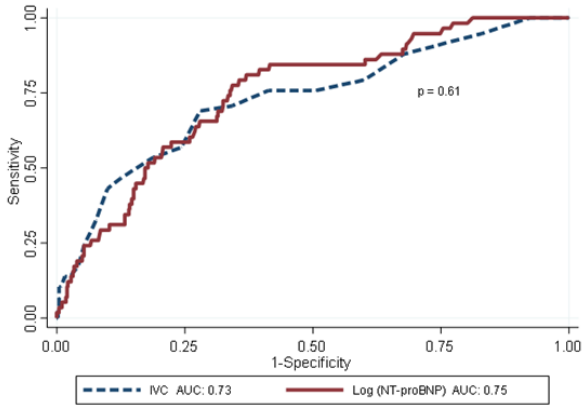

***Figure 7:** ROC curves for IVC diameter (AUC 0.73 with 95% CI: 0.66-0.80) and log [NT-proBNP] (AUC 0.75 with 95% CI: 0.69-0.81) in predicting all-cause mortality at one year (p=0.61 for the difference).*

3.2 Associations of GLS with outcome in ambulatory patients with HFNEF (part 1, paper 2)

3.2.1 Patient characteristics

In the 20 control subjects, the mean age (SD) was 65±11 years, 55% were women and their echocardiograms were normal: mean (± standard deviation) LVEF was 60±5%, mean GLS by speckle tracking was -19.1±2.1% and median plasma NTproBNP was 107 pg/ml (IQR: 46 – 147).

Of the 780 consecutive patients assessed in clinic, 313 (40%) had symptoms or signs suspicious of HF and an LVEF ≥50%, thus fulfilling the study criteria (Table 2 supplementary).

Of the 313 patients with LVEF ≥50%, 76 were considered not to have HFNEF, 99 to have possible HFNEF and 138 to have definite HFNEF. Compared to the control group, patients with definite HFNEF were older, were more likely to have AF, had more symptoms and more signs of fluid retention, and were more likely to be treated with diuretics. The proportion of patients with a history of IHD, diabetes, hypertension and COPD were similar in all three groups of patients, but fewer patients in Group A (no substantial cardiac dysfunction) had AF.

When the analysis was restricted to patients in sinus rhythm, patients with definite HFNEF still were older, had more symptoms, worse renal function and higher systolic blood pressure and NTproBNP levels than the other two subgroups.

3.2.2 Echocardiographic findings

LVEF was similar in all three sub-groups of patients and in control subjects. GLS was impaired in both groups of patients compared to control subjects but most severely impaired in patients who fulfilled our criteria for definite HFNEF (Group A:-15.9 (2.4)%, Group B: - 15.2 (3.1)%, Group C (HFNEF): - 13.6 (3.0)%; p<0.001). Patients with definite HFNEF had greater LV volumes, more RV dysfunction (as estimated by TAPSE) and more substantial mitral and tricuspid regurgitation than the other two groups. They also had higher pulmonary pressure and IVC diameter (Table 2 supplementary). Similar results were seen when the analysis was restricted to patients in sinus rhythm.

For 14 patients (3 with no heart disease, 4 with possible HFNEF and 7 with definite HFNEF) analysis of GLS was not possible due to poor quality images. For other patients, 85% of LV segments could be analyzed. Internal consistency and reproducibility of measurements of GLS (mean difference = 0.12 %; 95% Limits of agreement: -0.75, 0.99) and individual segments (mean difference = 0.12%; 95% Limits of agreement: -4.16, 4.40) were good.

Amongst the patient group as a whole, GLS was more negative (better function) in women v men [-15.8 (3.0) % v -13.8 (2.8) %, p<0.001] and in those with no history of IHD [-15.2 (3.0) % v -14.0 (2.9) %, p=0.001]. GLS was higher (more impaired) in patients who were taking loop diuretics (-14.4 (3.0) % v -15.4 (3.0) %, p=0.007). There was no relation between GLS and either NYHA class or congestion score. There was no relation between GLS and age (r: -0.06, p=0.31) but there was a relation between GLS and log (NTproBNP) (worsening long axis

function associated with increasing NTproBNP, r: 0.32, p<0.001 figure 8)) and renal function (creatinine: r: 0.20, p= 0.001, urea: r: 0.16, p= 0.009).

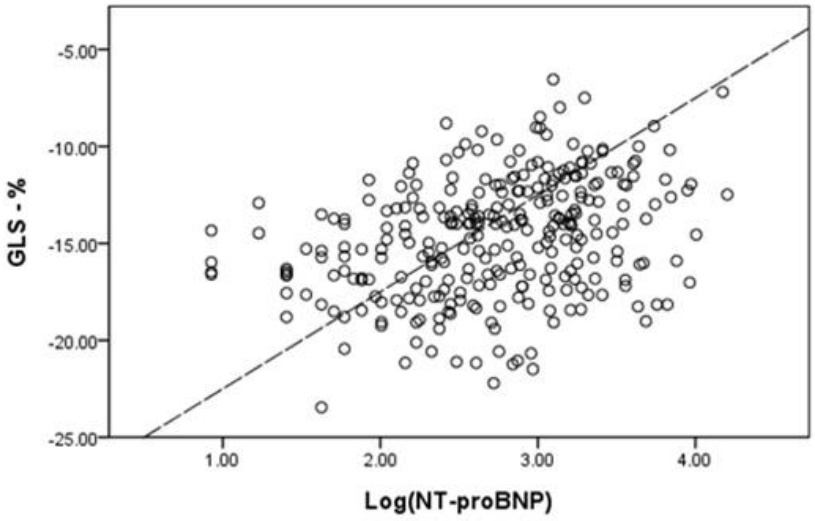

Figure 8: *Relation between GLS and log (NT-proBNP): LV long axis function worsens with higher plasma concentrations of NT-proBNP.*

3.2.3 Outcome

All patients were followed for at least one year. There were 62 primary outcome events during the median follow up of 572 (IQ range: 440 - 736) days. The first qualifying event was hospitalisation due to worsening HF in 30 patients and CV death in 32 patients.

In univariable Cox regression analysis (Table 5), GLS, but not LVEF, predicted events. Left atrial diameter, TAPSE, TR systolic gradient as well as moderate mitral regurgitation or tricuspid regurgitation were also associated with a worse outcome.

Variables	Univariable analysis		
	HR (95% CI)	χ^2	p-value
Age - years	1.06 (1.03-1.09)	15.60	<0.001
Men	1.03 (0.62-1.71)	0.02	0.902
NYHA class II	3.52 (1.06-11.61)	3.52	0.039
NYHA class III	6.70 (2.05-21.90)	6.70	0.002
Definite HFNEF	4.32 (2.44-7.64)	25.32	<0.001
IHD	1.14 (0.69-1.89)	0.26	0.611
DM	0.75 (0.44-1.27)	1.13	0.287
Atrial fibrillation	2.55 (1.52-4.26)	12.74	<0.001
COPD	2.35 (0.94-5.88)	3.34	0.068
SBP – mmHg	0.99 (0.98-1.01)	0.70	0.401
Heart rate - bpm	0.99 (0.98-1.01)	0.06	0.809
BMI - kg/m²	0.99 (0.96-1.04)	0.04	0.846
Congestion score >3	3.88 (2.31-6.51)	26.38	<0.001
Creatinine – umol/l	1.01 (1.01-1.01)	20.26	<0.001
Urea – mmol/l	1.10 (1.07-1.14)	36.86	<0.001
eGFR – ml/min/1.73m²	0.98 (0.97-0.99)	8.79	0.003
Haemoglobin - g/dl	0.67 (0.58-0.77)	32.59	<0.001
Albumin – g/l	0.87 (0.82-0.93)	16.82	<0.001
Bilirubin – umol/l	1.02 (0.98-1.06)	0.69	0.405
Log (NT-proBNP)	6.09 (3.73-9.96)	51.93	<0.001
Log (hsCRP)	2.13 (1.38-3.28)	11.72	0.001
Echocardiographic data			
LVEDV - ml	1.00 (0.99-1.01)	1.36	0.243
LVEF - %	1.00 (0.96-1.04)	0.00	0.991
GLS - %	1.09 (1.00-1.19)	3.98	0.046
LA Diameter - mm	1.07 (1.04-1.09)	22.46	<0.001
LAVI - ml/m²	1.02 (1.01-1.03)	30.23	<0.001
TAPSE – mm	0.87 (0.82-0.93)	19.65	<0.001
TR gradient - mmHg	1.04 (1.03-1.06)	33.55	<0.001
IVC - mm	1.21 (1.15-1.26)	72.94	<0.001
Mitral regurgitation			
Mild	1.35 (0.69-2.65)	0.75	0.385
Moderate/Severe	4.67 (2.66-8.21)	28.68	<0.001
Tricuspid regurgitation			
Mild	2.15 (1.17-3.95)	6.18	0.013
Moderate/Severe	5.48 (2.89-10.38)	27.23	<0.001

***Table 5**: Univariable Cox regression models for the composite endpoint CV death or HF hospitalization (313 patients, 62 events). List of abbreviation used: IHD - ischemic heart disease; DM – diabetes mellitus; COPD - chronic obstructive pulmonary disease; SBP - systolic blood pressure; BMI - body mass index; eGFR - estimated Glomerular Filtration Rate; NTproBNP - N-terminal B-type natriuretic peptide; hsCRP - high sensitivity C-reactive protein; LVEDV - left ventricle end diastolic volume; LVEF – left ventricular ejection fraction; GLS - global longitudinal strain; LA – Left atrium; LAVI - left atrial volume index; TAPSE - Tricuspid Annular Plane Systolic Excursion.*

In multivariable analysis, increasing urea and log (NTproBNP) were the only variables independently related to an adverse outcome in Model A (Table 6).

Variables	Multivariable analysis		
	HR (95% CI)	Wald χ^2	p-value
Age	1.01 (0.97,1.04)	0.16	0.68
Definite HFNEF	1.74 (0.97- 3.67)	2.15	0.14
NYHA class IIIvsII	1.49 (0.82,2.65)	1.69	0.19
SBP – mmHg	0.99 (0.98,1.00)	2.17	0.14
Urea – mmol/l	1.11 (1.05,1.17)	17.30	<0.01
Atrial fibrillation	1.33 (0.68,2.61)	0.69	0.40
Log (NT-proBNP)	3.57 (1.61,7.89)	9.91	<0.01
GLS - %	0.99 (0.90,1.11)	0.06	0.80
Congestion score ≥ 3	1.63 (0.86,3.10)	2.21	0.14
TR gradient - mmHg	1.00 (0.98,1.02)	0.11	0.74

***Table 6**. A multivariable Cox regression for the primary endpoint of CV death and admission with heart failure. Model A: eight candidate variables of clinical interest in addition to Global longitudinal strain (GLS) and the diagnostic category (Definite HFNEF vs. others) were chosen. List of abbreviation used: SBP - systolic blood pressure; NTproBNP - N-terminal B-type natriuretic peptide; TR gradient- Trans-Tricuspid systolic gradient.*

In Model B (Table 7), increasing urea and logNTproBNP, as well as increasing LAVI, IVC diameter and the presence of AF were independently related to outcome.

Variables	Multivariable analysis CV death and admission with heart failure			Multivariable analysis Death from all causes		
	HR (95% CI)	Wald χ^2	p-value	HR (95% CI)	Wald χ^2	p-value
Age	1.02 (0.97, 1.04)	0.14	0.91	1.02 (0.98, 1.06)	0.98	0.32
AF	2.51 (1.23, 5,12)	6.45	0.01	2.27 (1.03, 4.98)	4.17	0.04
Congestion score > 3	1.64 (0.93, 2.98)	3.09	0.08	1.75 (0.91, 3.48)	2.85	0.09
Urea – mmol/l	1.10 (1.05,1.16)	16.19	<0.01	1.03 (0.98,1.09)	1.61	0.20
Log (NT-proBNP)	2.52 (1.25, 5.07)	6.72	<0.01	3.74 (1.71, 8.21)	10.83	<0.01
Definite HFNEF	1.01 (0.47, 2.19)	0.01	0.98	2.41 (1.07, 5.43)	4.47	0.03
LAVI - ml/m^2	1.01 (1.00, 1.02)	4.01	0.04	1.01 (1.00, 1.03)	4.00	0.04
IVC - mm	1.15 (1.09, 1.23)	21.71	<0.01	1.05 (0.97, 1.13)	1.49	0.22

***Table 7**. A multivariable Cox regression for the primary endpoint of CV death and admission with heart failure (left) and for the secondary endpoint of death for all causes (right). Model B: The eight variables which were the strongest independent predictors of adverse outcome in the univariable analysis. List of abbreviation used: AF: atrial fibrillation; NTproBNP - N-terminal B-type natriuretic peptide; IVC: inferior vena cava diameter; LAVI: left atrial volume index.*

Patients with a definite diagnosis of HFNEF had the highest rate of adverse events; 25% at 1 year (Figure 9).

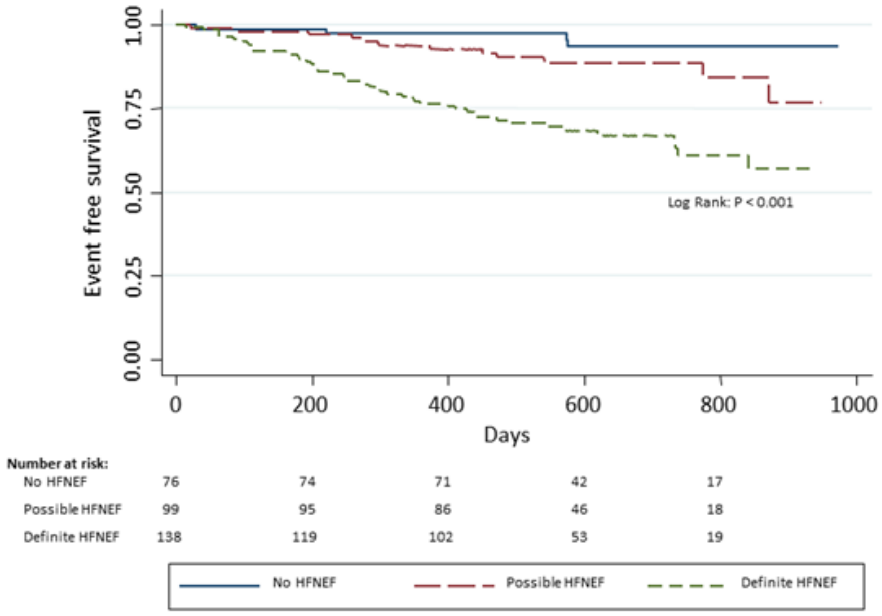

***Figure 9**: Kaplan-Meier (KM) curves for the composite endpoint (HF hospitalization or CV death) in patients considered to have no evidence of significant cardiac disease (solid blue line, Group A), in patients with "possible HFNEF" (red line, Group B) and patients with definite HFNEF (green line, Group C). For patients with definite HFNEF, the hazard ratio for this outcome was 7.86 (95% CI: 2.82 - 21.87; p<0.001) compared to those considered not to have evidence of significant cardiac disease.*

There were 48 deaths during the median follow of 598 (IQ range: 471 - 756) days for all patients: AF, a greater LAVI and higher plasma NTproBNP were independent predictors of all-cause mortality (Table 7). Thus, a definite diagnosis of HFNEF was associated with increased all-cause mortality.

3.3 Associations of left atrial function and outcome in ambulatory patients with heart failure (Part 2, paper 3)

3.3.1 Reproducibility of measurements of left atrial volumes and ejection fraction

Twenty five LA measurements (volumes and LAEF in two- and four-chamber views) were randomly selected and measured separately by myself and another experienced operator. The reproducibility of LA measurements was tested using the Bland-Altman method. Reproducibility of LAEF was good (mean difference for two- versus four-chamber (±SD) for operator 1: -1.44±3.96%; for operator 2: -4.43±7.4%; inter-observer variability: mean difference (±SD) for LAEF for two-chamber view: 0.43±4.06%, mean difference for four-chamber view: -0.65±9.25%).

A strong linear relation was found between LAEF measured in the two- and four-chamber views, overall ($r=0.89$; $p<0.001$), for controls ($r=0.75$, $p<0.001$) and for patients with HF ($r=0.90$, $p<0.001$). The four-chamber view was used in subsequent analyses.

3.3.2 Patient characteristics

Of 982 patients enrolled, 664 were in sinus rhythm and were considered to have HF. For patients with HF, median (IQR) age was 69 (61-75) years, median LVEF was 37 (29-46) % and median plasma NTproBNP was 864 (388–1978) ng/l. Of patients with HF, most were men (79%), had IHD (71%) and 82% had an LVEF <50% (Table 3 supplementary).

3.3.3 LA function: measurements and correlates

LA volumes were larger and LAEF lower in patients with confirmed HF compared to those in whom the criteria for HF were not met. Amongst patients with HF, those in the lowest quartile (worst function) of LAEF had worse kidney and liver function, lower body mass index (BMI), higher plasma concentrations of NTproBNP and were taking more loop diuretics.

They also had lower LVEF, larger LV, LA and RV volumes, higher LV and RV mass and more mitral and tricuspid regurgitation when compared to those in the highest quartile. LA emptying volume decreased as LAEF declined (Table 3 supplementary).

In patients with HF, Log (LAEF) was correlated inversely with log (NTproBNP) and positively with LVEF (Table 8).

Variables associated with LAEF*	Univariable analysis		Multivariable analysis Upper line - RV included Lower line - RV excluded	
	Correlation Coefficient	p- value	Unstandardized Coefficients (with 95% CI)	t-stat (p-value)
Clinical data				
Age - years	-0.025	0.524		
SBP – mmHg	0.111	0.004		
Heart rate - bpm	-0.110	0.005		
BMI - kg/m^2	0.111	0.004		
BSA – m^2	0.063	0.107		
Blood Test				
Creatinine –µmol/l	-0.100	0.010		
Urea* – mmol/l	-0.135	<0.001		
Haemoglobin - g/dl	0.058	0.137		
Albumin – g/l	0.030	0.446		
Bilirubin – µmol/l	-0.228	<0.001	-0.004 (-0.006,-0.001) -0.005 (-0.008,-0.003)	-2.986 (0.003) -4.812 (<0.001)
NT-proBNP* – ng/l	-0.410	<0.001	-0.096 (-0.130,-0.062) -0.100 (-0.130,-0.069)	-5.583 (<0.001) -6.440 (<0.001)
MRI Data				
LVEDV – ml	-0.383	<0.001		
LVEF - %	0.437	<0.001	0.004 (0.002, 0.006) 0.004 (0.003, 0.006)	4.598 (<0.001) 6.918 (<0.001)
LV mass –g	-0.232	<0.001	- 0.000 (-0.001,0.000)	- -2.144 (0.032)
LA Max – 4ch – ml	-0.393	<0.001		
LA Max – 2ch - ml	-0.339	<0.001		
LA total emptying volume -ml	0.434	<0.001		
LA conduit volume - ml	-0.240	<0.001		
RVEDV - ml	-0.246	<0.001		
RVEF - %	0.470	<0.001	0.004 (0.003,0.005) -	6.370 (<0.001) -
RV mass - g	-0.210	<0.001		
Mitral regurgitation (≥mild)	-0.248	<0.001	-0.036 (-0.068,-0.005) -0.050 (-0.079,-0.022)	-2.293 (0.022) -3.458 (0.001)

Table 8: *Variables associated with Log (LAEF) in patients with heart failure. List of abbreviation used: LAEF : Left Atrial Ejection Fraction; SBP - Systolic Blood Pressure; BMI - Body Mass Index; BSA: Body surface Area; NTproBNP - N-terminal B-type natriuretic peptide; LVEDV - Left Ventricle End Diastolic Volume; LVEF – Left Ventricular Ejection Fraction; LV: Left Ventricle; RVEDV - Right Ventricle End Diastolic Volume; RVEF – Right Ventricular Ejection Fraction; RV: Right Ventricle. Two models were tested. In the first RV measurements were included, in the second RV measurements were excluded (Variables entered in Model 1 (RV measurements included): NTproBNP*, Bilirubin, Heart rate, LV mass, Urea*, BMI, RVEF, Age, LVEF, RVEDV, SBP, Mitral regurgitation. R=0.62, R²=0.39, Adjusted R²=0.37. Variables entered in model 2 (RV measurements excluded): NTproBNP*, Bilirubin, Heart rate, LV mass, Urea*, BMI, Age, LVEF, SBP, Mitral regurgitation; R=0.56, R²=0.32, Adjusted R²=0.31). * Log transformation has been used for correlations.*

LAEF was similar in men and women (Table 9). LAEF was only weakly related to the severity of symptoms or congestion but this dissociation may be because patients with lower LAEF were prescribed higher doses of diuretics.

Group	LA EF (median and IQR)		
	0	1	P value
Sex (0=Women,1=Men)	42 (30-50)	42 (31-51)	0.238
NYHA class (I/II=0, III=1)	42 (31-51)	41 (29-50)	0.675
DM (0=no,1=yes)	41 (31-51)	44 (30-53)	0.235
BMI (< 30=0, >30=1)	40 (29-50)	45 (33-52)	0.011
COPD (0=no,1=yes)	41 (31-51)	43 (35-53)	0.183
IHD (0=no,1=yes)	45 (34-53)	41 (29-50)	0.009
LVEF (≤40%=0, > 40%=1)	37 (27-46)	49 (40-55)	<0.001
Congested (<3 signs=0,≥3 signs=1)	42 (31-51)	40 (26-48)	0.122
Loop Diuretics (0=no,1=yes)	47 (36-53)	40 (29-50)	<0.001

Table 9: *Left Atrial emptying function (LAEF) in patients with heart failure, divided by clinical or demographic characteristics. List of abbreviations used: NYHA – New York Heart Association; DM – Diabetes Mellitus; BMI – Body Mass Index; COPD – Chronic Obstructive Pulmonary Disease; IHD – Ischaemic Heart Disease; LVEF – Left Ventricular Ejection Fraction.*

3.3.4 Hospitalisation for heart failure or all-cause mortality

During a median follow-up of 883 (IQR 469-1626) days (censored at time of first event), 394 (59%) patients with, and 28 (29%) patients considered not to have, HF were either admitted for heart failure or died.

For patients with HF, increasing LAEF measured in a 4-chamber view predicted a better prognosis in univariable analyses, overall and in patients either with LVEF ≤40% (HR per 10% increase: 0.82 (95%CI: 0.74, 0.87), χ^2 =20.51) or > 40% (HR per 10% increase: 0.83 (95%CI: 0.72, 0.89), χ^2 =8.44) (Table 10).

Variables	Univariable analysis			Multivariable analysis			Multivariable analysis Upper Line - NT-proBNP excluded Lower Line - LAEF excluded		
	HR (95% CI)	χ^2	p-value	HR (95% CI)	χ^2	p-value	HR (95% CI)	χ^2	p-value
Clinical data									
Age - 10 years increase	1.28 (1.16-1.42)	22.34	<0.001	1.13 (1.01-1.27)	4.37	0.037	1.16 (1.03-1.29) 1.15 (1.02-1.28)	6.14 5.07	0.013 0.024
Sex (Men)	1.02 (0.80-1.31)	0.03	0.854						
NYHA class III vs. I/II	1.27 (1.04-1.62)	5.33	0.021						
IHD	1.23 (0.98-1.55)	3.23	0.072						
DM	1.26 (0.99-1.60)	3.55	0.060						
COPD	1.34 (0.97-1.85)	3.12	0.077						
SBP – mmHg	1.00 (0.99-1.01)	0.50	0.478						
Heart rate - bpm	1.00 (0.99-1.01)	0.04	0.837						
BMI - kg/m^2	1.00 (0.99-1.02)	0.17	0.683						
BSA - m^2	0.75 (0.47-1.19)	1.47	0.226						
Congestion≥3	1.57 (1.12-2.19)	6.89	0.009						
Diagnostic category (HFREF vs. HFNEF)	0.84 (0.69-1.03)	2.79	0.095						
Blood Test									
Creatinine –10µmol/L	1.01 (1.00-1.01)	18.53	<0.001						
Urea – mmol/l	1.02 (1.01-1.04)	11.61	0.001						
Haemoglobin - g/dl	0.86 (0.80-0.91)	23.55	<0.001						
Albumin – g/l	0.93 (0.91-96)	24.22	<0.001	0.96 (0.93-0.99)	7.75	0.005	0.96 (0.93-0.99) 0.96 (0.93-0.99)	8.75 5.68	0.003 0.017
Bilirubin – µmol/l	1.01 (0.99-1.02)	0.50	0.479						
Log(NT-proBNP)	1.78 (1.48-2.15)	36.66	<0.001				- 1.44 (1.16-1.78)	- 10.87	- 0.001
MRI data									
LVEDV – ml	1.01 (1.00-1.01)	4.32	0.035						
LVEF - %	0.99 (0.99-1.00)	1.85	0.174						
LV mass -g	1.00 (0.99-1.00)	1.55	0.214						
LA Max – 4ch – ml	1.01 (1.00-1.01)	12.52	<0.001						
LA Max – 2ch - ml	1.01 (1.00-1.01)	11.51	0.001						
LAEF – 4ch – 10% increase	0.82 (0.74-0.87)	32.16	<0.001	0.81 (0.73-0.90)	13.35	<0.001	0.81 (0.74-0.89) -	21.57 -	<0.001 -
LA total emptying volume -ml	0.99 (0.98-1.00)	1.67	0.196						
L A conduit volume - ml	1.01 (0.99-1.02)	2.57	0.109						
RVEDV - ml	1.00 (0.99-1.00)	1.88	0.170						
RVEF - %	0.99 (0.98-1.00)	8.94	0.003						
RV mass - g	1.01 (1.00-1.01)	3.51	0.061						

Table 10: *Univariable and multivariable Cox regression models for a combined endpoint of all-cause mortality and admissions for heart failure in patients with HF (n = 664 patients with heart failure who had 394 events during a median FU of 883 (IQ 469-1626) days). In the first column the univariable analysis is shown, the second column shows a multivariable model, which includes both Log (NTproBNP) and LAEF. In the last column two different multivariable models have been tested: one excluding log (NTproBNP) and one excluding LAEF. Measurements of right ventricular size and function were not included in the multivariable analysis because these were available for only 549 patients with HF. Variables entered in multivariable models: Age, Sex, NYHA III vs I/II, IHD, DM, COPD, Congestion≥3, creatinine, haemoglobin, albumin, log (NTproBNP), LVEDV, LAEF.*

In a multivariable model including both log (NTproBNP) and LAEF in a 4-chamber view, only increasing age, decreasing LAEF and albumin were independent predictors of an adverse outcome. When LAEF was excluded, log (NTproBNP) entered the model.

Adding either LAEF or Log (NTproBNP) to the standard set of clinical variables improved model discrimination and fit but adding LAEF was superior to Log (NTproBNP). Adding log (NTproBNP) to LAEF did not improve the model further. (Table 11).

	Discrimination			Model fit		
Model No.	Model	c-statistics	Difference	LogLL	LR statistic	Compared with base model
1	Base model*	0.620		-2226.3	Chi2(9)=60.78	
2	1 + log(NT-proBNP)	0.627	0.007	-2221.2	Chi2(10)=71.14	LRchi2(1)=10.36, p-value=0.001
3	1 + LAEF	0.643	0.023	-2215.8	Chi2(10)=81.79	LRchi2(1)=21.01, p-value<0.001
4	1 + log(NTproBNP)+LAEF	0.645	0.025	-2214.5	Chi2(11)=84.51	LRchi2(1)=23.73, p-value<0.001
5	1 + log(NTproBNP)+LAEF		0.002			Compared with 3: Chi2(1)=2.72, p=0.099

***Table 11**: The model's discrimination and overall model fit. *base model: age, sex, NYHA (III/IV), IHD, congestion≥3, creatinine, albumin, haemoglobin and left ventricular end-diastolic volume (LVEDV).*

LAEF was similar in patients with HF in the top quartile of LAEF and those who did not fulfil the criteria for HF, but patients with HF had a worse outcome (HR 1.65, 95% CI: 1.06-2.57, p=0.027). For patients with HF, those in the lowest quartile of LAEF had the worst outcome (HR: 1.97 (95% CI: 1.45 – 2.65, p<0.001; HR: 1.88 (95% CI: 1.39 -2.54), p<0.001 adjusted for age) (figure 10).

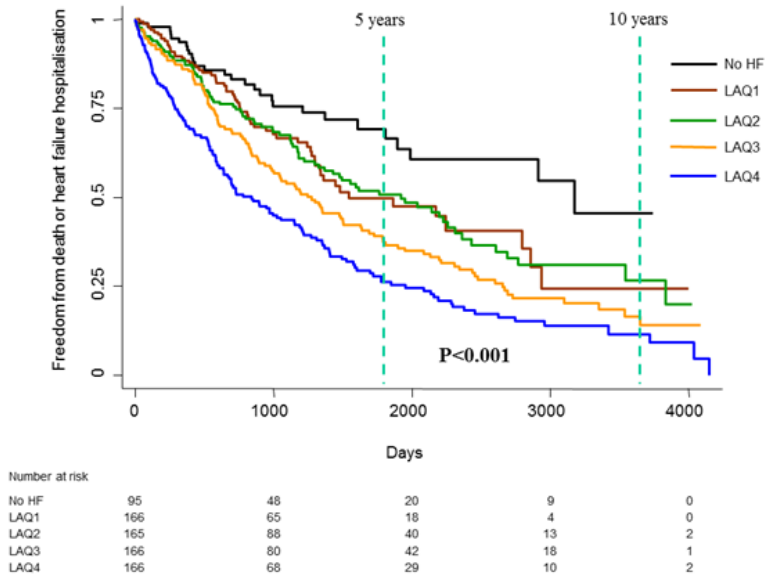

***Figure 10**: Kaplan-Meier (KM) curves for a composite endpoint of admissions for HF or all-cause mortality in patients considered not to have heart failure (black line) and by quartiles of LAEF. For patients with HF, those in the lowest quartile of LAEF had the worst outcome (HR: 1.97 (95% CI: 1.45 – 2.65; p<0.001 compared to highest quartile).*

3.3.5 All-cause mortality

During a median follow up of 1390 days (IQ range 763 – 2342) censored at the time of death, seven patients (7%) without and 202 patients (30%) with HF died. For patients with HF, LAEF and RVEF, but not LVEF, predicted deaths in univariable analysis. Maximum LA volume was not associated with an adverse outcome, even when it was indexed for body surface area (BSA).

In a multivariable model including both log [NTproBNP] and LAEF, increasing age, decreasing LAEF (HR: 2.72 (95% CI: 1.69 – 4.38), p<0.001 for lowest versus highest quartile; HR 2.50 (95% CI: 1.55 - 4.02), p<0.001 adjusted for age; Figure 11) and more severe congestion were independent predictors of mortality. When LAEF was excluded, log [NTproBNP] entered the model (Table 12).

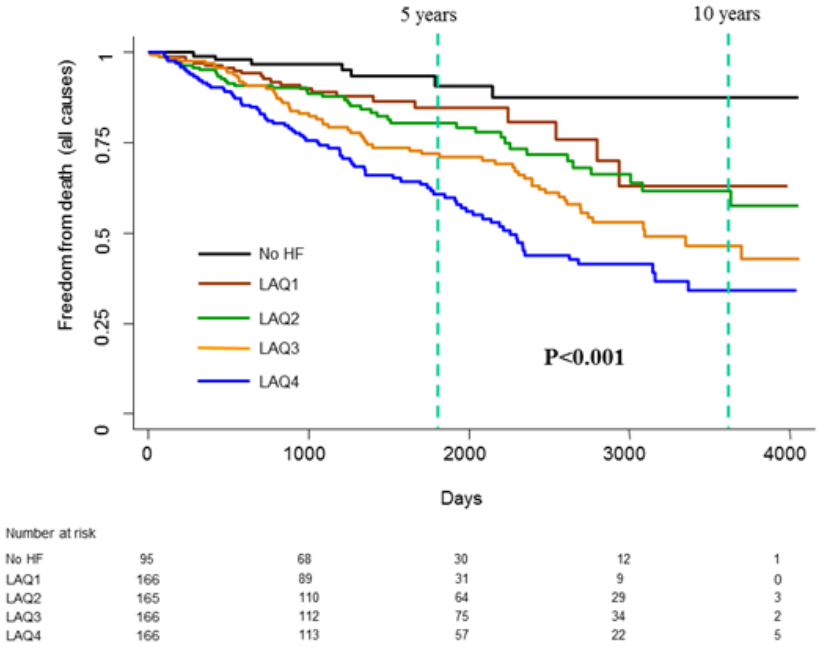

***Figure 11**: Kaplan-Meier (KM) curves for all-cause mortality in patients considered not to have heart failure (black line) and by quartiles of LAEF. For patients with HF, those in the lowest quartile of LAEF had the worst outcome (HR 2.72 (95% CI: 1.69 – 4.38; p<0.001 compared to highest quartile).*

3.3.6 Cardiovascular mortality

There were 110 CV deaths in patients with HF (54% of all deaths); 77 (70%) occurred in those with LVEF <40%. In univariable analysis, decreasing LAEF and LVEF, but not RVEF, were associated with reduced survival.

In a multivariable model including both NTproBNP and LAEF, only increasing age and decreasing LAEF (HR 3.65 (95% CI: 1.90 – 7.01), p<0.001 lowest compared to highest quartile; HR: 3.40 (95% CI: 1.77 – 6.54), p<0.001 adjusted for age) were independent predictors of CV mortality. When LAEF was excluded, log [NTproBNP] entered the model (Table 12).

Variables	Mortality from all causes# First line - Overall Second line - NT-proBNP excluded Third line - LAEF excluded			CV Mortality+ First line - Overall Second line - NT-proBNP excluded Third line - LAEF excluded			Incidence of AF* First line - Overall Second line - NT-proBNP excluded Third line - LAEF excluded		
	HR (95% CI)	χ^2	p-value	HR (95% CI)	χ^2	p-value	HR (95% CI)	χ^2	p-value
Age - 10 years increase	1.48 (1.22-1.79) 1.48 (1.22-1.79) 1.48 (1.22-1.80)	16.74 17.91 17.93	<0.001 <0.001 <0.001	1.34 (1.00-1.63) 1.35 (1.00-1.69) 1.35 (1.00-1.69)	5.81 7.40 6.59	0.016 0.007 0.01	1.71 (1.33-2.20) 1.72 (1.36-2.20) 1.69 (1.32-2.18)	17.83 19.33 17.14	<0.001 <0.001 <0.001
IHD							- - 1.69 (1.01-2.84)	- - 3.99	- - 0.046
Congestion>3	1.66 (1.06-2.61) 1.66 (1.06-2.61) 1.67 (1.05-2.65)	4.87 4.86 4.75	0.027 0.027 0.029						
Creatinine - 10 µmol/L increase	- 1.03 (1.00-1.05) -	- 4.99 -	- 0.026 -						
Haemoglobin - g/dl increase				- 0.087 (0.76-0.99) -	- 4.17 -	- 0.04 -			
Log(NT-proBNP) increase	- - 1.46 (1.06-2.00)	- - 5.44	- - 0.02	- - 1.75 (1.12-2.74)	- - 5.98	- - 0.014			
LAEF – 4ch – 10% increase	0.82 (0.74-0.90) 0.81 (0.73-0.91) -	10.86 10.86 -	0.001 0.001 -	0.74 (0.60-0.90) 0.63 (0.59-0.82) -	12.54 16.96 -	<0.001 <0.001 -	0.81 (0.69-0.95) 0.80 (0.69-0.93) -	6.24 9.21 -	0.012 0.002 -

Table 12. *Multivariable Cox regression models for the secondary endpoints of Mortality from all causes (first column), Cardiovascular (CV) Mortality (second column) and incidence of Atrial Fibrillation (AF) (third column) in patients with Heart Failure (HF). Three models were tested: one including both Log (NTproBNP) and LAEF (top), one excluding log (NTproBNP) (middle) and one excluding LAEF (bottom). Abbreviations used: IHD – Ischaemic Heart Disease; LAEF – Left Atrial Ejection Fraction; NT- proBNP - N-terminal B-type natriuretic peptide.*
*(Variables entered in multivariable models:# Age, sex, NYHA III vs I/II, BSA, Congestion>3, creatinine, albumin, haemoglobin, LVEDV, log (NTproBNP), LAEF; +Age, Sex, NYHA III vs I/II, Congestion>3, creatinine, haemoglobin, albumin, log (NTproBNP), LVEF, LAEF; * Age, Sex, IHD, Creatinine, Bilirubin, Log (NTproBNP), LAEF).*

3.3.7 Incidence of atrial fibrillation

During a median follow up of 1282 days (IQ range 701-2197), 101 patients (15.2%) with and 4 (4.2%) without HF developed AF. Decreasing LAEF was associated with incident AF both in patients with LVEF ≤40% (HR per 10% increase: 0.78 (95%CI: 0.65, 0.94), χ^2 =7.05, p=0.008) or >40% (HR: 0.69 (95%CI: 0.53, 0.89), χ^2 =7.97, p=0.005). Age (HR for 10 years increase: 1.71 (1.33-2.20), p<0.001) and LAEF (HR for 10% increase: 0.81 (0.69-0.95), p=0.012) were the only variables independently associated with incident AF (table 12). Patients in the lowest quartile of LAEF had the highest incidence of AF (HR: 3.06 (95% CI: 1.61 – 5.81, p<0.001 comparing lowest and highest quartiles; HR: 2.78 (95% CI: 1.46 – 5.29), p<0.001 adjusted for age) (Figure 12).

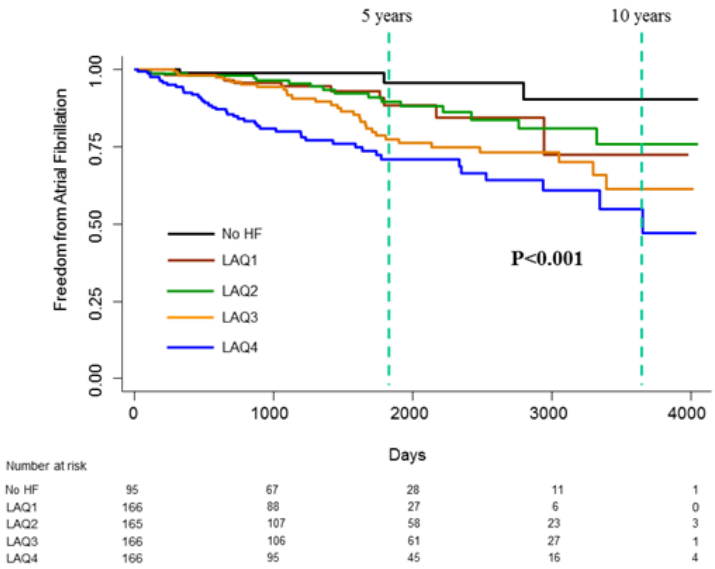

***Figure 12**: Kaplan-Meier (KM) curves for incident Atrial Fibrillation (AF) in patients considered not to have heart failure (black line) and by quartiles of LAEF. Patients with HF were at greater risk of developing AF, with the risk rising progressively with lower values of LAEF (HR: 3.06 (95% CI: 1.61 – 5.81; p<0.001 lowest compared to highest quartile).*

3.4 The relationship of QRS morphology with cardiac structure and function in patients with heart failure (part 2, paper 4)

3.4.1 Patient characteristics

Amongst 940 patients referred, heart failure was confirmed in 877 (93%). Of patients with HF, 320 (36%) had QRS ≥120 msec of whom 201 patients (62%) had LBBB, 65 (20%) had RBBB and 54 (18%) had IVCD. Compared to patients with narrower QRS (<120 ms), those with QRS ≥120 ms were older, had more severe symptoms and higher plasma levels of NTproBNP (Table 4 supplementary). Patients with LBBB had greater QRS duration, were less likely to be in AF and were more likely to have non-ischaemic dilated cardiomyopathy and to receive CRT than patients with either IVCD or RBBB (Table 13).

Compared to patients with LBBB, those with RBBB had more signs of congestion and higher plasma NTproBNP.

	IVCD (54)	LBBB (201)	RBBB (65)	P value across 3 subgroups	P-value Between LBBB and RBBB
Demographic & clinical					
Age - years	71 (65-76)	70 (65-76)	72 (64-78)	0.598	0.657
Sex – male	48 (89)	158 (79)	58 (89)	0.059	0.057
IHD – no. (%)	40 (74)	128 (64)	48 (74)	0.166	0.132
Previous MI – no. (%)	31 (57)	83 (42)	34 (53)	0.057	0.103
DCM – no. (%)	7 (13)	55 (27)	8 (12)	0.008	0.016
Unclassified – no. (%)	7 (13)	18 (9)	9 (14)	0.822	0.685
DM - no. (%)	17 (32)	43 (21)	16 (25)	0.297	0.587
Hypertension - no. (%)	27 (50)	108 (54)	32 (49)	0.770	0.528
NYHA class - no. (%)					
I	10 (19)	35 (18)	10 (15)	0.973	0.826
II	26 (48)	97 (48)	30 (46)		
III	18 (33)	69 (34)	25 (39)		
SBP – mmHg	128 (20)	133 (24)	126 (23)	0.110	0.058
Congestion > 3	5 (9)	22 (11)	16 (25)	0.012	0.006
BMI - kg/m^2	28.3 (5.0)	28.1 (5.3)	27.5 (4.2)	0.686	0.460
BSA – m^2	1.94 (0.21)	1.90 (0.21)	1.90 (0.18)	0.481	0.849
Atrial fibrillation	11 (20)	23 (11)	17 (26)	0.012	0.004
Blood results					
Haemoglobin – g/dl	13.3 (1.4)	13.1 (1.9)	13.1 (1.6)	0.769	0.990
Creatinine – umol/l	112 (93-144)	108 (91-138)	103 (82-143)	0.985	0.918
Albumin - g/l	38 (3)	38 (3)	37 (3)	0.597	0.328
Bilirubin - umol/l	15 (12-21)	14 (12-18)	15 (12-19)	0.052	0.091
NT-proBNP – ng/l	1069 (470-2995)	1159 (589-2207)	2013 (659-3573)	0.026	0.019
ECG					
Heart rate – bpm	69 (13)	68 (13)	70 (13)	0.493	0.225
QRS - msec	126 (122-132)	152 (138-166)	142 (129-155)	<0.001	<0.001
Successful CRT implant during FU – no. (%)	10 (18)	63 (31)#	9 (14)	0.008	0.006
CRT-D implant during FU – no. (%)	5 (10)	24 (12)	4 (6)	0.747	0.715
Medications					
Beta-blockers - no. (%)	43 (79)	160 (79)	51 (79)	0.979	0.844
Ace-Inhibitors or ARB - no. (%)	50 (93)	185 (92)	52 (80)	0.016	0.007
Aldosterone Antagonist -no. (%)	21 (39)	70 (35)	30 (46)	0.258	0.101
Loop diuretics - no. (%)	45 (83)	147 (73)	49 (75)	0.304	0.720
Furosemide > 40 mg/day – no. (%)	24 (44)	69 (34)	25 (39)	0.375	0.545

***Table 13**: Characteristics of patients with wide QRS, divided by QRS morphology. List of abbreviation used: IVCD: indeterminate ventricular conduction delay; LBBB - left bundle branch block, RBBB - right bundle branch block; IHD - Ischemic Heart Disease; DCM - Non-ischaemic dilated cardiomyopathy; DM – Diabetes Mellitus; NYHA – New York Heart Association; SBP - Systolic Blood Pressure; BMI - Body Mass Index; BSA: Body surface Area; NTproBNP - N-terminal B-type natriuretic peptide; ARB - Angiotensin receptor blocker; CRT: cardiac resynchronization therapy; CRT-D – CRT with defibrillator; FU: follow up. # Possible reasons why CRT was not implanted: NYHA I class, LVEF >35%, AF, QRS < 150 ms; also some patients died before 2005 (prior to CRT being guideline-indicated), others were unwilling or had other life-shortening disease and in some it was not done.*

3.4.2 cMRI measurements

Compared to patients who had QRS <120 ms, those with a longer QRS duration had larger LV volumes and greater LV mass, lower LVEF and higher prevalence of substantial mitral regurgitation, but RV size and function were similar (Table 4 supplementary).

Amongst patients with QRS ≥120msec, LV end-diastolic volume and LVEF were similar regardless of QRS morphology. Compared with patients who had LBBB, patients with RBBB had lower LV mass, larger left atrial volumes, greater RV mass and diastolic volume and lower RV ejection fraction (Table 14).

	IVCD (54)	LBBB (201)	RBBB (65)	P value across 3 subgroups	P-value Between LBBB and RBBB
LVEDV – ml	233 (196-265)	230 (184-295)	223 (167-283)	0.735	0.662
LVEF - %	35 (27-42)	33 (27-44)	32 (27-43)	0.983	0.906
LV mass - g	160 (140-201)	178 (144-211)	150 (122-200)	0.014	0.010
LA Max volume - ml	110 (82-132)	92 (63-125)	107 (73-143)	0.027	0.010
RVEDV – ml	148 (117-192)	126 (104-152)	149 (116-192)	<0.001	<0.001
RVEF - %	48 (43-55)	52 (42-61)	46 (37-57)	0.014	0.007
RV mass - g	49 (40-61)	45 (36-56)	53 (42-73)	<0.001	0.002
Mitral regurgitation				0.456	0.404
Mild	19 (35)	79 (39)	31 (48)		
Moderate/Severe	4 (7)	7 (4)	3 (5)		
Tricuspid regurgitation				0.577	0.289
Mild	13 (24)	38 (19)	18 (28)		
Moderate/Severe	1 (2)	2 (1)	1 (2)		

***Table 14**: CMRI characteristics of different QRS morphologies in patients with confirmed HF and QRS≥120 msec. List of abbreviation used: IVCD: indeterminate ventricular conduction delay; LBBB - left bundle branch block, RBBB - right bundle branch block; LV – Left ventricle; LVEDV - Left Ventricle End Diastolic Volume; LVEF – Left Ventricular Ejection Fraction; LA: Left atrium; RV: Right Ventricle; RVEDV - Right Ventricle End Diastolic Volume; RVEF – Right Ventricular Ejection Fraction. Measurements of RV size and function were available only for 47 (87%) patients with indeterminate morphology, 172 (86%) with LBBB and 56 (86%) with RBBB.*

Results were similar when the analysis was restricted to patients who had complete sets of cMRI measurements available, for the overall population and when restricted to those patients who fulfilled criteria for CRT (those with a LVEF≤35%).

3.4.3 QRS morphologies and outcome

During a median follow-up of 1302 days (IQR: 742-2237), 311 patients with HF died (35%). The primary cause of death was attributed to cardiovascular causes (including terminal HF, unexpected out of hospital death, acute myocardial infarction or stroke) in 200 patients (65%); in 41 cases it was attributed to a cancer (13 %); and other causes (including infections and traumatic injuries) were responsible for 69 deaths (22%) ; data were not available for one patient.

There were no differences across the IVCD, LBBB, RBBB and QRS<120 msec groups for each of the causes of deaths considered (CV deaths: 14 (56%), 50 (61%), 23 (70%), 113 (67%) respectively (p=0.522); cancer deaths: 4 (16%), 16 (19%), 6 (18%), 15 (9%), respectively (p=0.098); other causes of death: 7 (28%), 17 (20%), 4 (12%), 41 (24%) respectively, (p=0.395). The mortality rate amongst patients with IHD (227 deaths in 574 patients; 40%) was higher than in patients who did not have IHD (84 deaths in 303 patients; 27%).

CRT devices were more likely to be implanted in those with LBBB (table 13). Reasons for not implanting a CRT device were not recorded but many patients had died before publication of the results of landmark trials and relevant guidelines.

Patients with a QRS duration ≥120msec had a worse prognosis but this was significant only for patients with a non-LBBB pattern (figure 13).

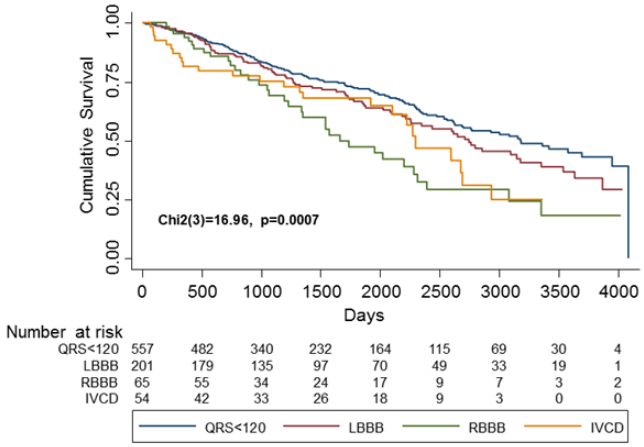

Figure 13: *Kaplan-Meier (KM) curves for all-cause mortality in patients considered to have heart failure. Compared with patients who had QRS <120 msec (blue line), RBBB (green) and IVCD (yellow) morphologies were associated with an adverse outcome, but LBBB (red) was not.*

However, when patients who received CRT during their follow-up were not considered in the analysis, patients with LBBB had a significantly worse prognosis than those with QRS <120 ms ((HR: 1.65 with 95% CI: 1.25-2.19, χ^2 12.32; p<0.001) and a similar prognosis to those with RBBB (HR: 0.79 with 95% CI: 0.52-1.22, χ^2 1.15, p=0.284; Figure 14).

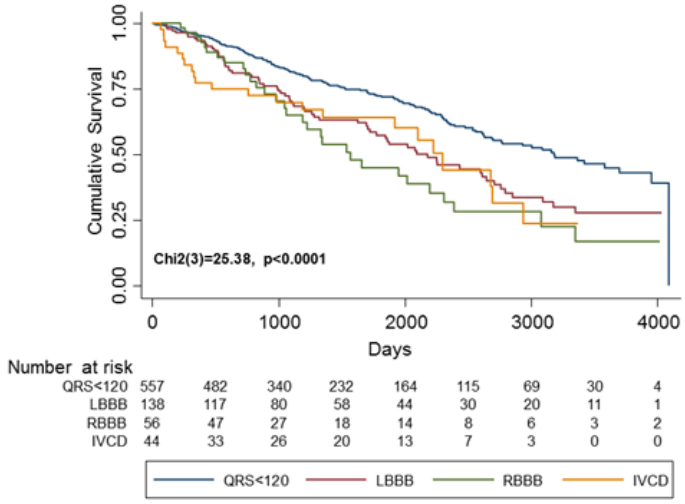

Figure 14: *Kaplan-Meier (KM) curves for all-cause mortality in patients considered to have heart failure. Patients who received a CRT during follow-up were excluded. Compared with patients who had QRS <120 msec (blue line), RBBB (green), IVCD (yellow) and LBBB (red) morphologies were all associated with an adverse outcome. The hazard ratio (HR, with 95% CI) was 1.82 (95% CI: 1.16-2.83, p=0.009) for IVCD, 2.09 (95% CI: 1.42-3.08, p<0.001) for RBBB and 1.65 (95% CI: 1.25 – 2.19, p<0.001) for LBBB.*

Amongst cMRI variables, LA maximum volume and RVEF were the strongest predictors of outcome. In multivariable models, greater age, heart rate and plasma NTproBNP and lower haemoglobin and serum albumin were independently associated with increasing mortality. Neither QRS duration nor morphology was independently associated with mortality. If NTproBNP was included in the model, none of the cMRI measurements was independently associated with outcome (table 15).

Variables	Univariable analysis			Multivariable analysis (QRS duration included) NTproBNP included/ NTproBNP excluded			Multivariable analysis (QRS morphology included) NTproBNP included/ NTproBNP excluded		
	HR (95% CI)	χ^2	p-value	HR (95% CI)	χ^2	p-value	HR (95% CI)	χ^2	p-value
Clinical data									
Age -years	1.07 (1.05-1.08)	88.18	<0.001	1.05 (1.03-1.07) 1.05 (1.04-1.07)	36.25 40.62	<0.001 <0.001	1.05 (1.03-1.07) 1.05 (1.04-1.07)	36.36 40.67	<0.001 <0.001
Sex (Men)	1.06 (0.78-1.42)	0.13	0.721						
NYHA class III vs. I/II	1.61 (1.27-2.06)	15.30	<0.001	- 1.32 (1.02-1.72)	- 4.39	- 0.036	- 1.31 (1.01-1.70)	- 3.99	- 0.046
IHD	1.25 (0.97-1.61)	3.07	0.08						
DM	1.25 (0.95-1.64)	2.56	0.11						
Hypertension or SBP >140mmHg	1.20 (0.96-1.50)	2.62	0.105						
SBP – mmHg	0.99 (0.99-1.00)	0.11	0.74						
Heart rate - bpm	1.01 (0.99-1.01)	2.90	0.088	1.01 (1.00-1.02) 1.01 (1.00-1.02)	3.99 4.93	0.046 0.026	1.01 (1.00-1.02) 1.01 (1.00-1.02)	4.25 5.29	0.039 0.021
Atrial fibrillation	1.42 (1.09-1.85)	6.77	0.009						
BMI - kg/m^2	0.96 (0.94-0.99)	8.48	0.004						
BSA - m^2	0.30 (0.17-0.51)	20.15	<0.001	- 0.43 (0.22-0.83)	- 6.19	- 0.013	- 0.43 (0.22-0.85)	- 5.90	- 0.015
Congestion > 3	2.07 (1.54-2.79)	23.24	<0.001						
QRS duration – per 10 msec increase	1.05 (1.02-1.09)	8.07	0.004						
IVCD vs. QRS <120 msec	1.65 (1.08 -2.51)	5.47	0.019						
LBBB vs. QRS < 120 msec	1.24 (0.96-1.61)	2.60	0.107						
RBBB vs. QRS < 120 msec	1.98 (1.37-2.86)	13.16	<0.001						
QRS 120-150msec vs. < 120 msec	1.48 (1.14-1.93)	8.42	0.004						
QRS >150 msec vs. <120 msec	1.35 (1.01-1.81)	4.08	0.043						
Blood Test									
Creatinine – per 10 umol/l increase	1.06 (1.04-1.07)	41.00	<0.001						
Haemoglobin - g/dl	0.79 (0.74-0.85)	45.03	<0.001	0.91 (0.83-0.99) 0.90 (0.83-0.98)	4.91 5.76	0.027 0.016	0.91 (0.84-0.99) 0.91 (0.83-0.99)	4.54 5.18	0.033 0.023
Albumin – g/l	0.91 (0.89-0.94)	30.99	<0.001				- 0.97 (0.93-1.00)	- 3.91	- 0.048
Log(NT-proBNP)	2.56 (2.09-3.01)	82.61	<0.001	1.48 (1.13-1.94)	8.09	0.004	1.45 (1.11-1.90)	7.28	0.007
MRI data									
LVEDV – per 10 ml increase	1.02 (1.00-1.03)	4.24	0.039	- 1.02 (1.00-1.03)	- 5.42	- 0.021	- 1.02 (1.00-1.03)	- 5.71	- 0.017
LVEF - %	0.99 (0.99-1.00)	2.56	0.11						
LV mass -g	1.00 (0.99-1.00)	0.00	0.98						
LA Max – 4ch – per 10 ml increase	1.03 (1.01-1.05)	8.70	0.003						
RVEDV - ml	1.00 (0.99-1.00)	0.34	0.56						
RVEF – per 10% decrease	0.88 (0.82-0.97)	7.03	0.008						
RV mass - g	1.00 (0.99-1.01)	0.04	0.78						

Table 15: *Univariable and multivariable Cox regression models for the primary endpoint of all-cause mortality in patients with HF (n = 877 patients with heart failure who had 311 events during a median FU of 1302 days (IQR: 742-2237)). In the first column the univariable analysis is shown. In the central and left columns, different multivariable models were constructed, including QRS lengths or morphologies and including/excluding NTproBNP plasma levels. RV measurements were excluded from these MV models as they were not available for 24% of patients.*

3.5 Development of a newer ultrasound method to measure the jugular vein diameter in ambulatory patients with heart failure (part 3, paper 5 and 6)

3.5.1 Patient characteristics

Comparing patients with HF by tertile of JVD ratio, those in the highest tertile (lowest JVD ratio; most congested) were older, were more likely to have AF, were more symptomatic, had more signs of congestion and were more likely to be treated with diuretics. They also had larger LA volumes, higher mitral E/E' ratio,

more mitral and tricuspid regurgitation, more severe RV dysfunction and higher pulmonary pressures.

However, left ventricular dimension, volumes and LVEF were similar across tertiles (supplementary table 5 and 6).

3.5.2 Jugular vein measurements and correlates

Reproducibility of measurements of JVD ratio was good (intra-operator reproducibility: mean difference = 0.42 (95% limits of agreement: −1.26, 2.11); inter-operator reproducibility: mean difference = −0.22 (95% limits of agreement: −1.24, 0.80). The coefficient of variation (CV, with 95% CI) for JVD ratio measured by two operators was 9.9% (6.0% - 12.6%), with an intra-class correlation coefficient of 0.95 (CI: 0.86-0.98). Reproducibility between 2D and M-mode measurements was also tested in 21 randomly selected patients with HF, with a mean difference in JVD ratio of 0.015 between the two methods (95% limits of agreement (-0.890, 0.920), with 5% of measurements outside limits of agreement on Bland-Altman plots). The coefficient of variation (CV, with 95% CI) between M-mode and 2D was 5.3% (2.8% - 6.9%), with an intra-class correlation coefficient of 0.99 (0.98-1.00).

Increasing JVD at rest and during deep inspiration correlated with increasing log plasma [NTproBNP] ($r=0.37$ and $r=0.34$ respectively; $p<0.001$ for both), whilst JVD ratio was inversely related to plasma log [NTproBNP].

There was no relation between JVD ratio and measures of LV dimension or systolic function. There was, however, a correlation between JVD ratio and measurements of diastolic function expressed by E/E' ratio or LA volume. In patients with HF, multiple linear regression models identified decreasing TAPSE and increasing pulmonary artery pressure as independently associated with decreasing JVD ratio (Table 16) (overall R^2=0.27). When the analysis was restricted to patients with low LVEF (≤ 40%), only decreasing TAPSE was an independent predictor of a decreasing JVD ratio (R^2=0.36). When the analysis was restricted to patients with LVEF (>40%) only increasing pulmonary artery pressure was an independent predictor of decreasing JVD ratio (R^2=0.27).

	Univariable analysis		Multivariable analysis Overall population (R^2=0.27, Adjusted R^2=0.24)		Multivariable analysis LVEF ≤ 40% (R^2=0.36, Adjusted R^2 =0.28) LVEF> 40% (R^2=0.27, Adjusted R^2=0.20)	
	Correlation coefficient	p-value	Unstandardized Coefficients with 95% CI	t-stat (p-value)	Unstandardized Coefficients with 95% CI	t-stat (p-value)
Age - years	-0.256	<0.001				
Advanced NYHA class (III)	-0.223	0.001				
SBP – mmHg	0.009	0.895				
Heart rate - bpm	-0.003	0.964				
BMI - kg/m²	0.131	0.057				
Congestion score	-0.387	<0.001				
Urea* – mmol/l	-0.228	0.001				
eGFR – ml/min1.73/m²	0.279	<0.001				
Haemoglobin - g/dl	0.217	0.001				
NT-proBNP* – ng/l	- 0.392	<0.001				
Echocardiographic data						
LVEDV – ml	-0.038	0.580				
LVEF - %	0.122	0.077				
E/E'	-0.335	<0.001				
LAVI - ml/m²	-0.212	0.002				
TAPSE – mm	0.327	<0.001	0.093 (0.024,0.162)	0.009	0.132 (0.020,0.245) - -0.066 (-0.119,-0.013)	0.021 - 0.015
TR gradient - mmHg	-0.399	<0.001	-0.061 (-0.102,-0.021)	0.003		
MR (Mod vs. mild)	-0.253	<0.001				
TR: (Mod vs. mild)	-0.299	<0.001				
IVC - mm	-0.413	<0.001				

***Table 16**: Variables associated with JVD ratio in patients with heart failure (n.211). The first column on the left (Univariable analysis) represents the correlation between JVD ratio and the variables studied. A log transformation was also done for variables labelled with * before conducting the analysis to satisfy the model assumptions. The column for the multivariable analysis (in the middle) shows the coefficients for slope of the linear relation between all the variables independently associated with JVD ratio diameter (R^2=0.27, Adjusted R^2=0.24) for the overall population of patients with heart failure. On the right, two different models were tested, one (top) for patients with LVEF < 40% (R^2=0.36, Adjusted R^2 =0.28), the second one (bottom) for patients with LVEF> 40% (R^2=0.27, Adjusted R^2=0.20). List of abbreviations used: NYHA – New York Heart Association; SBP - Systolic Blood Pressure; BMI - Body Mass Index; eGFR - estimated Glomerular Filtration Rate; NTproBNP - N-terminal B-type natriuretic peptide; LVEDV - Left Ventricle End Diastolic Volume; LVEF – Left Ventricular Ejection Fraction; LAVI - Left Atrial Volume Index; TAPSE - Tricuspid Annular Plane Systolic Excursion; TR gradient- Trans-Tricuspid systolic gradient; MR – Mitral Regurgitation; TR – Tricuspid Regurgitation; IVC – Inferior Vena Cava.*

3.5.3 Jugular vein measurements and outcome

There were 48 primary outcome events during a median follow up of 516 (IQ range: 335 - 622) days. The first qualifying event was hospitalisation due to worsening HF in 17 patients and death in 31 patients.

There were three events (1% of patients) in the first tertile of JVD, 15 (5% of patients) in the mid tertile and 30 events (10% of patients) in the highest tertile (lowest JVD ratio).

3.5.3.1 Analysis 1

In univariable Cox regression analysis, increasing JVD at rest and during deep inspiration, and decreasing JVD ratio (but not JVD during Valsalva), were associated with an increased risk of HF hospitalization or death.

In multivariable analysis, increasing log [NTproBNP] and JVD measurements were the only variables independently related to an adverse outcome in Model A based on clinical variables (Table 17).

Variable	Association with the Composite of First HFH or Death								
	Multivariable analysis								
	HR (95% CI)	χ^2	p-value	HR (95% CI)	χ^2	p-value	HR (95% CI)	χ^2	p-value
Age - year	0.99 (0.97-1.03)	0.03	0.871	0.99 (0.97-1.03)	0.02	0.900	0.99 (0.96-1.02)	0.19	0.664
NYHA class (III vs. I/II)	1.27 (0.69-2.35)	0.58	0.449	1.30 (0.70-2.40)	0.71	0.398	1.44 (0.79-2.64)	1.40	0.237
Urea - mmol/l	1.02 (0.98-1.06)	0.78	0.377	1.01 (0.97-1.05)	0.42	0.515	1.02 (0.98-1.06)	0.69	0.405
Haemoglobin -g/dl	0.82 (0.68-1.00)	3.65	0.056	0.83 (0.68-1.01)	3.49	0.062	0.86 (0.71-1.04)	2.54	0.111
Log [NT-proBNP]	3.89 (1.80-8.39)	11.97	0.001	3.96 (1.84-8.53)	12.32	<0.001	3.72 (1.71-8.09)	10.96	0.001
Ultrasound JVD	Resting (cm) 7.57 (2.65-21.58)	14.34	<0.001	Deep Insp (cm) 7.93 (2.57-24.48)	12.98	<0.001	Ratio (Max/Rest) 0.78 (0.65-0.94)	6.91	0.009

***Table 17**: Model A – Clinical Variables - five candidate variables of interest (age, NYHA class III vs I/II, urea, haemoglobin and log [NTproBNP]) were chosen prospectively in addition to ultrasound JVD measurements. A small number of variables were selected to avoid over-fitting. Three separate analyses are shown to test the independent association of different ultrasound JVD measurements with outcome, including JVD at rest, JVD during deep inspiration and JVD ratio. For continuous variables, the values are the hazard ratios associated with a unit increase in that variable.*

In Model B (Table 18), based predominantly on echocardiographic variables, again only increasing logNTproBNP and JVD measurements were independently associated with an adverse outcome.

Variable	Association with The Composite of First HFH or Death Multivariable analysis								
	HR (95% CI)	χ^2	p-value	HR (95% CI)	χ^2	p-value	HR (95% CI)	χ^2	p-value
Age - year	1.01 (0.97-1.04)	0.20	0.651	1.01 (0.97-1.04)	0.22	0.637	1.00 (0.97-1.03)	0.01	0.982
Log [NT-proBNP]	5.42 (2.47-11.87)	17.84	<0.001	5.25 (2.41-11.43)	17.49	<0.001	4.37 (1.97-9.71)	13.08	<0.001
LVEF - %	0.99 (0.96-1.02)	0.87	0.352	0.98 (0.96-1.02)	0.94	0.332	0.98 (0.96-1.02)	0.95	0.329
E/E'	0.97 (0.91-1.03)	0.98	0.322	0.97 (0.91-1.03)	0.93	0.335	0.97 (0.91-1.03)	0.93	0.334
LAVI – ml/m²	1.01 (0.99-1.03)	0.95	0.331	1.01 (0.99-1.03)	1.25	0.264	1.02 (0.99-1.04)	2.42	0.120
Ultrasound JVD	Resting (cm) 7.54 (2.65-21.45)	14.37	<0.001	Deep Insp (cm) 8.22 (2.73-24.74)	14.05	<0.001	Ratio (Max/Rest) 0.76 (0.62-0.92)	7.66	0.006

***Table 18**: Model B – Echocardiographic Variables - In addition to age and Log [NT-proBNP], the three echocardiographic variables that were most strongly associated with prognosis in univariable analysis were included in addition to ultrasound JVD measurements. A small number of variables were selected to avoid over-fitting. Three separate analyses are shown to test the independent association of different ultrasound JVD measurements with outcome, including JVD at rest, JVD during deep inspiration and JVD ratio. For the continuous variables, the values are the hazard ratios associated with a unit increase in that variable*

3.5.3.2 Analysis 2

Adding either clinical or ultrasound measurements of JV distension or Log (NTproBNP) to the base model improved the model discrimination; adding ultrasound JVD measurements led to a greater increase in the c-statistic than a model that included NTproBNP or IVC diameter (Table 19).

	Model Discrimination				
Model No.	Model	c-statistics	Difference		
			Compared to 1#	Compared to 2#	Compared to 3b#
1	Base model*	0.7559	Compared to 1#	Compared to 2#	Compared to 3b#
2	1 + log(NT-proBNP)	0.7812	0.0253		
3a	1+ clinical JVP (2/1 vs 0)	0.7619	0.0060		
3b	1 + ultrasound IVC	0.7600	0.0041		
4	1 + ultrasound log(JVD rest)	0.7716	0.0157		
5	1 + ultrasound JVD ratio	0.7896	0.0337		
6	1+ ultrasound log(JVD insp)	0.7739	0.0180		
7	2 + ultrasound log (JVD rest)	0.7890	0.0331	0.0078	
8	2+ ultrasound JVD ratio	0.7989	0.0430	0.0177	
9	2 + ultrasound log(JVD insp)	0.7913	0.0354	0.0101	
10	3b + ultrasound log (JVD rest)	0.7703	0.0144		0.0103
11	3b+ ultrasound JVD ratio	0.7882	0.0323		0.0282
12	3b + ultrasound log (JVD insp)	0.7731	0.0172		0.0131

***Table 19**: Summary of model discrimination when variables are added cumulatively. *base model: age, sex, NYHA (III vs II/I), creatinine, haemoglobin and left ventricular ejection fraction (LVEF). Other abbreviations used: JVD – Jugular venous diameter; JVD insp – JVD deep inspiration; JVP – jugular venous pressure; IVC – inferior vena cava. 1 = basic model; 2 = basic model plus log (NT-proBNP); 3b = basic model plus IVC. # = incremental c-statistic – larger values indicate greater incremental value.*

Patients with HF in the first tertile of JVD ratio and control subjects had similar values for JVD ratio and a similar rate of adverse outcomes (HR 1.75, 95% CI: 0.18-16.83, p=0.63).

Patients with HF in the third tertile of JVD ratio had a much worse outcome than those in the first tertile (HR 10.05, 95% CI: 1.45 - 17.31; p<0.001) (figure 15).

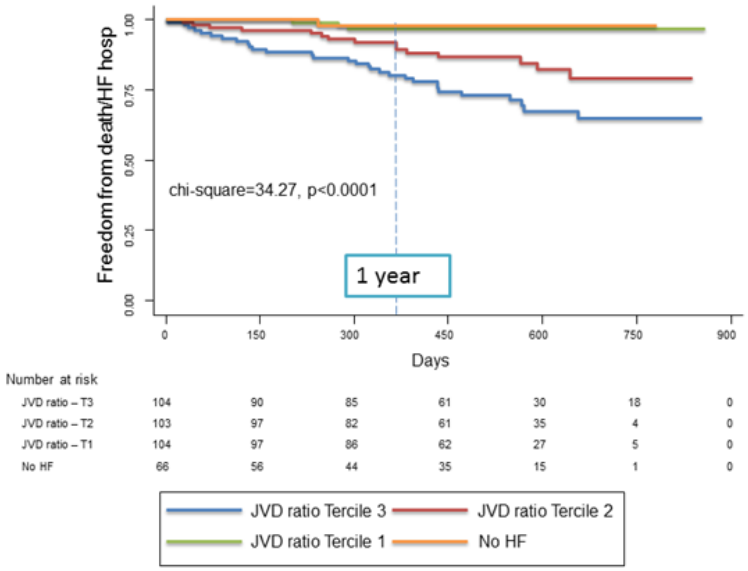

Figure 15. Kaplan Meier curve for the primary outcome of death from all causes and heart failure hospitalizations.

Receiver-operator characteristic (ROC) curves for predicting prognosis at one year (Figure 16) showed an area under curve (AUC) of 0.72 (95%CI: 0.62- 0.81 for JVD ratio.

The optimal cut-off was at 3.95 (Youden index), with sensitivity=0.60 and specificity=0.77.

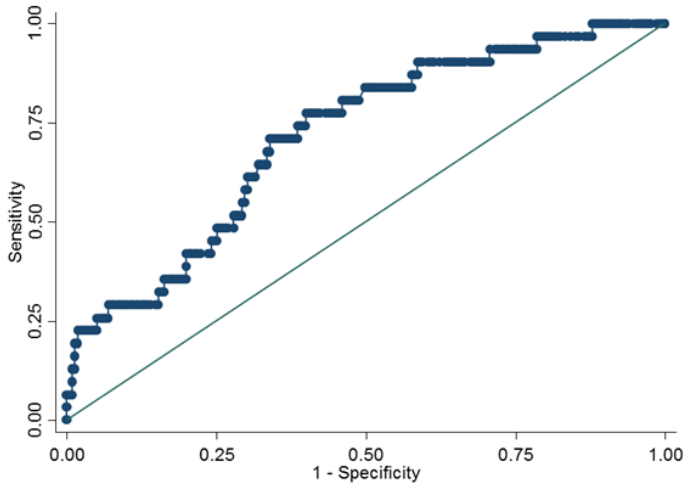

***Figure 16**: Receiver-operator characteristic (ROC) curve for predicting prognosis at one year (246 patients with heart failure, who had 31 events) showed an area under curve (AUC) of 0.715 (95%CI: 0.623- 0.807) for JVD ratio.*

CHAPTER IV. Discussion

The results of my research show that the upstream consequences of a dysfunctional left ventricle in ambulatory patients with HF, such as impaired left atrial function measured by cMRI, and a distended IVC or internal jugular vein measured by ultrasound, are associated with more severe clinical congestion and higher natriuretic peptides; detecting these consequences also provides powerful prognostic information, similar to that obtained by measuring NTproBNP plasma levels (which is commonly thought of as being the best single marker of HF prognosis), regardless of whether the patient has a reduced or normal LVEF.

The clinical diagnosis of heart failure requires the demonstration of objective evidence of cardiac dysfunction in the presence of symptoms, such as breathlessness, and signs, such as peripheral oedema. A routine echocardiographic assessment of the LV function may be misleading in many cases: a substantial number of patients with symptoms and signs of heart failure and elevated NTproBNP have no gross abnormality of LV systolic function and yet these patients often respond symptomatically to diuretics, have recurrent admissions for HF and have a poor prognosis [41, 42].

I found that novel and more sophisticated echocardiographic techniques, such as GLS measured by speckle tracking, are able to detect subtle impairment of LV longitudinal systolic function even in the absence of structural (dilated left atrium) or biochemical (increased NTproBNP) abnormalities. I also found that worsening LV longitudinal systolic dysfunction was related to other indices of abnormal function, similar to previous studies [43, 44]. Thus, deterioration in LV longitudinal

function might be an early manifestation in the developing pathophysiology of HFNEF [45]. However, GLS provided no additional prognostic information to biochemical measures of cardiac dysfunction or echocardiographic measures of congestion.

This suggests that a broader view of what constitutes cardiac dysfunction is still required. Raised NTproBNP plasma levels, as well as LA dysfunction or an increased IVC or JV diameter, might be more useful in characterising and identifying patients with HF at higher risk of adverse outcome. If congestion is the hallmark of cardiac dysfunction (and it does lead to a substantial number HF hospitalizations and deaths[4]), then left atrial dysfunction and distension of the great veins may be the best markers to use during cardiac imaging.

Left ventricular dysfunction will cause an increase in LV filling pressure. Prolonged exposure to high LV filling pressure will increase LA volume and decrease LAEF, which, in turn, are thus markers of a sicker LV which integrate the effects of a decline in both systolic and diastolic performance. With sustained increases in LV and LA pressure, LA contractile reserve becomes exhausted and, in end-stage HF, the LA becomes mainly a passive conduit dictated by ventricular distensibility [46].

The high LV filling pressure is also transmitted back through the pulmonary circulation to cause pulmonary arterial hypertension which, in turn, compounds any pre-existing RV dysfunction and exacerbates tricuspid regurgitation. All of these abnormalities result in an increase in right atrial pressure and distension of

the great veins, both jugular vein and IVC. Neuro-endocrine activation and a decline in renal perfusion may also cause salt and water retention leading to congestion even in the absence of gross elevation in atrial pressures [4, 15].

As with natriuretic peptides, a distended IVC or JV will provide little information about the cause of congestion. However, their assessment might have some advantages over natriuretic peptides. IVC and JV diameters can be measured at the same time as echocardiography and may be more specific for congestion. In addition, the results are immediately available.

On the other hand, in primary care or other clinical settings without easy access to echocardiography, measuring natriuretic peptides is simpler, less expensive, and more efficient in terms of patient and staff time.

A simple ECG might also help in identifying patients with HF with more RV dysfunction, subclinical congestion, and a higher risk of adverse outcome. We have previously reported that patients with HF and a prolonged QRS duration have more severely compromised LV function and a worse prognosis [47]; however, compared to those with LBBB morphology, patients with RBBB have more advanced right heart disease on cardiac MRI and a higher mortality. Patients with LBBB and RBBB might represent two distinct clinical phenotypes, with a potentially different response to CRT; patients with LBBB morphology generally have longer QRS duration [48] than those with non-LBBB, and they are also less likely to have ischaemic heart disease [49] or AF. In studies of CRT, RV dysfunction is, indeed, an indicator of a poor prognosis, but the impact of CRT on outcome is

not diminished [49, 50]. A recent echocardiographic study, broadly consistent with my cMRI findings, suggested that RBBB identified patients who had a higher LVEF, smaller LV volumes and lower mass but more depressed RV function and worse outcome, compared with those who had LBBB [51].

In summary, the results of my research suggest that congestion, assessed either clinically, biochemically, or by imaging, is a powerful marker of an adverse prognosis and is a potentially relevant therapeutic target. In addition, imaging has the potential to quantify congestion more objectively, particularly in those cases where it is not clinically evident.

These results have a potentially important clinical impact, because they allow trials to be designed which can, for the first time, provide evidence about the proper use of diuretics - the decongestive drugs par excellence. Despite their extensive use in patients with HF, there is very little known about the long-term effects of loop diuretics on hard outcomes such as mortality. A more objective measure of congestion (identified biochemically, by raised natriuretic peptides, or by ultrasound, with a dilated vena cava for instance) might allow the identification of higher risk patients who should be enrolled in randomised controlled trials designed to test different decongestive strategies.

Such an approach might be particularly useful in patients with normal left ventricular ejection fraction. In the past few years, we have seen large and expensive trials in patients with HFNEF reporting neutral results. The reason, perhaps, is not so much because a drug was ineffective (in this case

spironolactone), but simply because a substantial number of patients enrolled in the trials (namely ALDO-DHF and TOPCAT [52-54]) had breathlessness or oedema not of cardiac origin, and thus a good prognosis. Moreover, we still do not know how to tailor the use of diuretics to patients with HF with systolic dysfunction; using imaging and biochemical measures of congestion to select specific populations of patients might allow more robust trial design to assess specific responses in those who were, but are no longer *clinically* congested, in those in whom congestion is only detected by imaging, and in those in whom congestion is still present despite intense diuretic treatment.

CHAPTER V. Limitations

I enrolled patients with HF with either reduced LVEF or raised natriuretic peptides (NTproBNP >400 ng/l, or >125 ng/l when treated with loop diuretics), in agreement with ESC-HF guidelines that were contemporary when the studies were conceived [21, 55]. However, there is no universally accepted definition of HF and, in the absence of significant left ventricular systolic dysfunction, many would not accept elevation of NTproBNP alone as diagnostic of HF. Also, thresholds for NTproBNP have been changing over time, and a diagnostic cut-off of 400 ng/l was higher than that suggested for the exclusion of HF in more recent guidelines (<125ng/L) (20, 21) or for the diagnosis of HFNEF in an ESC consensus statement (>220ng/l) [56]. I will therefore have excluded patients with less severe cardiac dysfunction as well as those in whom the disease was perhaps controlled by drugs, including diuretics and ACE-inhibitors [57].

Many of the patients without HF who formed my comparator groups cannot be considered entirely "normal" as they were referred because of diagnostic concerns or complained of exertional breathlessness. It is possible that some of their symptoms reflected reversible myocardial ischaemia or that some of them were simply unfit with high body mass index. As a consequence of the SICA-HF study design, the control group enrolled for that study included many patients with diabetes and/or hypertension who were already on treatment with an ACE-inhibitor and/or beta-blockers. However, most had a plasma concentration of NTproBNP <125ng/L, suggesting that few had occult cardiac dysfunction and that they all had a good cardiovascular prognosis [20, 21].

Echocardiograms obtained more than 5 years before writing (2016) did not include a routine assessment of E/E' ratio, a marker of left atrial pressure advocated by guidelines to diagnose HFNEF. Although E/E' ratio predicts cardiac events in patients with systolic HF [58], it adds little prognostic information to left atrial size and function [59] which was one of the main topics of my studies. Large studies show that E/E' is not an independent predictor of adverse outcome in patients with HFNEF [59, 60]. I did not evaluate LV mass by echocardiography, which is known to be associated with increasing cardiovascular risk in the general population [61].

The indications for referral for cardiac MRI were not recorded and a referral bias for investigation by cMRI is likely; for instance, patients with implanted cardiac resynchronization or defibrillator devices will have been excluded and younger patients may be more likely to be referred for (and agree to have) cMRI compared to frail elderly patients with advanced comorbidities.

I did not routinely correct cMRI measurements for body surface area (BSA) as BSA itself is strongly associated with mortality in a much larger HF data-set [62].

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Appendices – Supplementary tables

Variable	Total (n=693)	Not Heart Failure (n=125)	Heart failure (n=568)	P-value	HF IVC Lowest Tertile (n=190)	HF IVC Mid-Tertile (n=189)	HF IVC Highest Tertile (n=189)	P-value
IVC – mm	18 (16 – 22)	15 (14-16)	19 (16 -23)	<0.01	16 (15-16)	19 (18-20)	24 (23 -27)	Not applicable
Clinical data								
Age - years	73 (12)	68 (15)	73 (11)	0.01	71 (12)	74 (10)	76 (11)	<0.01
Men - no. (%)	468 (67)	66 (53)	402 (71)	<0.01	133 (70)	132 (70)	137 (72)	0.82
NYHA class - no. (%)								
I	125 (18)	34 (27)	91 (16)		41 (22)	31 (16)	19 (10)	
II	328 (47)	55 (44)	273 (48)	0.01	104 (55)	93 (49)	76 (40)	<0.01
III	240 (35)	36 (29)	204 (36)		45 (24)	65 (34)	94 (50)	
IHD - no. (%)	407 (59)	51 (41)	356 (63)	<0.01	123 (65)	129 (68)	104 (55)	0.02
DM - no. (%)	198 (29)	30 (24)	168 (30)	0.12	61 (32)	57 (30)	50 (27)	0.47
Hypertension - no. (%)	409 (59)	85 (68)	324 (57)	0.02	112 (59)	110 (58)	102 (54)	0.57
Smoker - no. (%)	113 (16)	18 (14)	95 (17)	0.31	38 (20)	34 (18)	23 (12)	0.11
Atrial fibrillation – no. (%)	233 (34)	5 (4)	228 (40)	<0.01	34 (18)	71 (38)	123 (65)	<0.01
COPD - no. (%)	94 (14)	27 (21)	67 (12)	<0.01	17 (9)	29 (15)	21 (11)	0.15
SBP – mmHg	130 (24)	135 (21)	128 (24)	<0.01	131 (24)	128 (23)	127 (26)	0.29
Heart rate - bpm	72 (15)	72 (13)	72 (15)	0.94	71 (12)	73 (14)	73 (18)	0.26
BMI - kg/m^2	29 (6)	31 (7)	29 (6)	<0.01	30 (6)	29 (6)	28 (5)	<0.01
Congestion ≥ 3 – no. (%)	95 (14)	13 (10)	82 (14)	0.15	9 (5)	21 (11)	52 (28)	<0.01
Blood results								
Creatinine – umol/l	100 (82 – 131)	86 (73 -108)	104 (84 – 136)	<0.01	99 (82 – 120)	105 (84 – 141)	113 (86 – 146)	<0.01
Urea – mmol/l	7.0 (5.2 -9.8)	5.3 (4.1 – 7.7)	7.2 (5.5 – 10.0)	<0.01	6.6 (5.2 – 9.3)	7.1 (5.5 – 10.0)	8.1 (6.1 -11.9)	<0.01
eGFR – ml/min/1.73m^2	65 (27)	78 (29)	62 (26)	<0.01	66 (22)	63 (28)	58 (26)	0.01
Haemoglobin - g/dl	13.2 (1.8)	13.4 (1.6)	13.1 (1.8)	0.09	13.5 (1.7)	13.2 (1.7)	12.7 (1.9)	<0.01
Albumin – g/l	38 (3)	39 (4)	38 (3)	0.03	38 (3)	38 (3)	37 (4)	<0.01
Bilirubin – umol/l	14 (11-18)	13 (10-15)	14 (12 -19)	<0.01	13 (11-16)	14 (11-18)	17 (13-22)	<0.01
Cholesterol - mmol/l	4.3 (1.1)	4.6 (1.1)	4.2 (1.1)	<0.01	4.4 (1.2)	4.2 (1.1)	4.0 (1.1)	<0.01
NT-proBNP – ng/l	997 (329 – 2291)	160 (59 -274)	1331 (602 – 2883)	<0.01	537 (294 -1101)	1437 (854-2414)	3095 (1627-5547)	<0.01
hsCRP – mg/l	3.6 (1.5 -7.3)	3.6 (1.6 -6.8)	3.4 (1.5 – 7.6)	0.58	2.8 (1.2 – 5.8)	3.3 (1.4 -8.0)	4.8 (2.1 -9.1)	0.15
Medications – no. (%)								

Beta-blocker	499 (72)	61 (49)	438 (77)	<0.01	159 (84)	146 (77)	133 (70)	<0.01
ACE inhibitor or ARB	572 (83)	90 (72)	482 (85)	<0.01	162 (85)	169 (89)	151 (80)	0.03
Aldosterone antagonist	227 (33)	21 (17)	206 (36)	<0.01	68 (36)	69 (37)	69 (37)	0.99
Loop diuretic	526 (76)	80 (64)	446 (79)	<0.01	133 (70)	155 (82)	158 (84)	<0.01
Statin	441 (64)	74 (59)	367 (65)	0.15	132 (70)	129 (68)	106 (56)	0.01
Antiplatelets	361 (52)	66 (53)	295 (52)	0.47	117 (62)	96 (51)	82 (43)	<0.01
Digoxin	148 (21)	3 (2)	145 (26)	<0.01	27 (14)	51 (27)	67 (35)	<0.01
Warfarin	194 (28)	7 (6)	187 (33)	<0.01	38 (20)	64 (34)	85 (45)	<0.01
CRT	34 (5)	0	34 (6)	0.04	8 (4)	11 (6)	15 (8)	0.31
ICD	52 (7)	3 (2)	49(9)	0.02	17 (9)	14 (7)	18 (9)	0.75
Echocardiographic data								
LVEDD - mm	56 (10)	47 (7)	58 (9)	<0.01	57 (9)	59 (10)	59 (10)	0.12
LVEDV - ml	155 (73)	97 (33)	167 (73)	<0.01	156 (67)	170 (76)	176 (74)	0.03
LVEF (%)	45 (14)	59 (6)	42 (13)	<0.01	44 (11)	40 (13)	42 (15)	0.09
GLS (%)	-10.8 (4.6)	-15.9 (2.6)	-9.6 (4.1)	<0.01	- 10.5 (3.7)	-9.2 (4.1)	-9.0 (4.5)	<0.01
LA diameter - mm	43 (8)	37 (6)	45 (7)	<0.01	42 (6)	45 (8)	48 (7)	<0.01
LA area – mm^2	24 (8)	18 (5)	26 (8)	<0.01	22 (5)	25 (8)	30 (7)	<0.01
LAVI - ml/m^2	43 (22)	27 (12)	47 (23)	<0.01	35 (13)	46 (23)	60 (24)	<0.01
TAPSE – mm	18.5 (4.6)	21.5 (4.1)	17.9 (4.5)	<0.01	19.5 (4.1)	18.0 (4.0)	16.2 (4.4)	<0.01
TR gradient - mmHg	27 (11)	21 (9)	28 (11)	<0.01	22 (6)	27 (9)	36 (12)	<0.01
Mitral regurgitation								
Mild	189 (27)	12 (10)	177 (31)	<0.01	45 (24)	67 (35)	65 (34)	<0.01
Moderate/Severe	104 (15)	5 (4)	99 (17)		9 (5)	33 (17)	57 (30)	
Tricuspid regurgitation								
Mild	141 (20)	6 (5)	135 (24)	<0.01	15 (8)	50 (26)	70 (37)	<0.01
Moderate/Severe	52 (7)	2 (1)	50 (9)		2 (1)	6 (3)	42 (22)	

Table 1 Supplementary: Characteristics of patients by diagnosis and by tertiles of inferior vena cava (IVC) diameter. Data are mean and standard deviation if the variable is normally distributed and median and inter-quartile range if not. The statistical difference between variables is given for the comparison between patients with and without heart failure, and between tertiles of IVC diameter in the heart failure population only. List of abbreviation used: IHD - Ischemic Heart Disease; DM – Diabetes Mellitus; COPD - Chronic Obstructive Pulmonary Disease; SBP - Systolic Blood Pressure; BMI - Body Mass Index; eGFR - estimated Glomerular Filtration Rate; NTproBNP - N-terminal B-type natriuretic peptide; hsCRP - high sensitivity C-reactive protein; CRT - Cardiac Resynchronization Therapy; ICD - Implantable Cardioverter Defibrillator; LVEDD - Left Ventricle End-Diastolic Diameter; LVEDV - Left Ventricle End Diastolic Volume; LVEF – Left Ventricular Ejection Fraction; GLS - Global Longitudinal Strain; LA: left atrium; LAVI - Left Atrial Volume Index; TAPSE - Tricuspid Annular Plane Systolic Excursion; TR gradient- Trans-Tricuspid systolic gradient.

	Normal group (20)	All patients (313)	P-value	Group A (76)	Group B (99)	Group C (138)	P-value (between groups)
Clinical & Demographic							
Age - years	65 (11)	74 (13)	0.005	67 (15)	73 (13)	78 (10)	< 0.001
Men - no. (%)	9 (45)	181 (58)	0.261	37 (49)	57 (58)	87 (63)	0.126
NYHA Class							
I	20 (100)	60 (19)		21 (28)	20 (20)	19 (14)	
II	0 (0)	151 (48)	<0.001	28 (37)	56 (57)	67 (49)	0.014
III	0 (0)	102 (32)		27 (35)	23 (23)	52 (37)	
IHD - no. (%)	0 (0)	136 (44)	<0.001	30 (40)	41 (41)	65 (47)	0.495
DM - no. (%)	0 (0)	85 (27)	0.007	20 (26)	27 (27)	38 (27)	0.981
Hypertension or SBP > 140 mmHg- no. (%)	0 (0)	219 (70)	<0.001	51 (67)	69 (70)	99 (72)	0.777
Smoker - no. (%)	1 (5)	40 (13)	0.305	13 (17)	14 (14)	13 (9)	0.242
Atrial fibrillation – no. (%)	0 (0)	126 (40)	<0.001	1 (1)	25 (25)	100 (73)	<0.001
COPD - no. (%)	0 (0)	47 (15)	0.061	13 (17)	20 (20)	14 (10)	0.086
BMI - kg/m^2	27.0 (4)	29.9 (6)	0.054	29.8 (6)	31.1 (8)	29.1 (6)	0.058
SBP – mmHg	136 (13)	136 (24)	0.941	134 (22)	136 (23)	138 (26)	0.581
Heart rate - bpm	64 (8)	72 (14)	0.007	72 (13)	74 (14)	71 (15)	0.235
Congestion score ≥ 3 (%)	0 (0)	49 (16)	0.055	9 (12)	9 (9)	31 (23)	0.012
Blood							
Creatinine – μmol/l	73 (62 -79)	98 (80 – 130)	<0.001	86 (84 -109)	97 (77 – 127)	107 (82 – 141)	<0.001
Urea – mmol/l	4.9 (4.3 – 6.1)	7.0 (4.8 – 10.0)	<0.001	5.3 (3.9 – 7.3)	7.1 (4.8 – 9.1)	7.9 (5.6 – 11.8)	<0.001
eGFR – ml/min/1.73m^2	98 (23)	68 (30)	<0.001	78 (29)	71 (33)	61 (26)	<0.001
Haemoglobin - g/dl	14.4 (1.0)	13.1 (1.9)	<0.001	13.4 (1.5)	13.4 (1.8)	12.8 (2.0)	0.016
Albumin – g/l	39.9 (2.1)	37.8 (3.4)	<0.001	38.6 (3.8)	38.1 (2.9)	37.3 (3.5)	0.022
Bilirubin – umol/l	13.2 (3.8)	15.0 (5.9)	0.196	13.2 (4.8)	14.4 (4.6)	16.4 (6.9)	<0.001
NT-proBNP – ng/l	107 (46 -147)	591 (202– 1636)	<0.001	164 (59-268)	414 (143 -887)	1627 (868-2837)	**
hsCRP – u/l	1.5 (0.77 – 2.4)	4.0 (1.7 – 7.8)	<0.001	3.6 (1.1 -6.8)	3.6 (1.6 – 6.3)	4.8 (2.2 -9.8)	0.104

Medications – no. (%)							
Beta-blocker	0 (0)	188 (60)	<0.001	37 (48)	57 (58)	94 (68)	0.018
ACE inhibitor or ARB	0 (0)	230 (74)	<0.001	56 (74)	72 (73)	102 (74)	0.944
Aldosterone antagonist	0 (0)	67 (21)	0.021	14 (18)	19 (19)	34 (25)	0.461
Loop diuretic	0 (0)	221 (71)	<0.001	43 (56)	73 (74)	105 (76)	0.008
*** Dose of Furosemide**	0 (0)	40 (40)	<0.001	24 (32)	33 (33)	48 (48)	<0.001
Statin	2 (10)	180 (58)	0.001	45 (59)	59 (59)	76 (55)	0.740
Antiplatelets	0 (0)	135 (43)	0.001	40 (53)	48 (49)	47 (34)	0.014
Digoxin	0 (0)	69 (22)	0.018	0 (0)	16 (16)	53 (38)	<0.001
Warfarin	0 (0)	90 (29)	0.005	5 (6)	20 (20)	65 (47)	<0.001
CRT	0 (0)	10 (3)	0.417	1 (1)	3 (3)	6 (4)	0.480
ICD	0 (0)	10 (3)	0.417	2 (3)	3(3)	5 (4)	0.228
Echocardiographic data							
LVEDD - mm	46 (6)	49 (7)	0.026	47 (6)	48 (7)	51 (6)	<0.001
LVEDV - ml	89 (28)	105 (37)	0.056	95 (29)	100 (38)	115 (38)	<0.001
LVEF - %	60 (5)	58 (6)	0.236	59 (6)	59 (6)	58 (6)	0.213
GLS - %	-19.1 (2.1)	-14.7 (3.1)	<0.001	-15.9 (2.4)	- 15.2 (3.1)	- 13.6 (3.0)	<0.001
LA Diameter - mm	31.5 (3.6)	42.5 (7.6)	<0.001	35.1 (4.6)	40.3 (5.5)	48.1 (5.7)	**
LAVI - ml/m^2	20 (6)	40 (23)	<0.001	25 (10)	33 (13)	55 (25)	**
TAPSE – mm	23 (3)	20 (5)	0.001	21 (4)	21 (5)	18 (4)	<0.001
TR gradient - mmHg	20 (4)	27 (12)	<0.001	19 (5)	25 (12)	33 (12)	<0.001
IVC - mm	15 (2)	18 (5)	<0.001	15 (2)	17 (3)	22 (5)	<0.001
Mitral regurgitation							
None/trivial	15 (75)	209 (67)		67 (88)	79 (80)	63 (46)	<0.001
Mild	5 (25)	64 (20)	0.231	7(9)	16 (16)	41 (30)	
Moderate	0	40 (13)		2 (3)	4 (4)	34 (24)	
Tricuspid regurgitation							
None/trivial	20 (100)	233 (74)		74 (97)	80 (81)	79 (57)	<0.001
Mild	0	48 (15)	0.035	2 (3)	12 (12)	34 (25)	
Moderate	0	32 (10)		0 (0)	7 (7)	25 (18)	

Table 2 Supplementary: Characteristics of patients. Data are mean and standard deviation if normally distributed and median and inter-quartile range if not. The statistical difference between patients with suspected heart failure and controls, and the difference between Groups A, B and C is shown. List of abbreviation used: NYHA – New York Heart Association; IHD - ischemic heart disease; DM – diabetes mellitus; COPD - chronic obstructive pulmonary disease; SBP - systolic blood pressure; BMI - body mass

index; eGFR - estimated Glomerular Filtration Rate; NTproBNP - N-terminal B-type natriuretic peptide; hsCRP - high sensitivity C-reactive protein; CRT - cardiac resynchronization therapy; ICD - implantable cardioverter defibrillator; LVEDD - left ventricle end-diastolic diameter; LVEDV - left ventricle end diastolic volume; LVEF - ejection fraction; GLS - global longitudinal strain; LA – Left atrium; LAVI - left atrial volume index; TAPSE - Tricuspid Annular Plane Systolic Excursion; TR gradient- Trans-Tricuspid systolic gradient; IVC : inferior vena cava diameter. *Daily dose of furosemide or equivalent (bumetanide 1 mg = furosemide 40 mg). **The difference between the 3 groups in LA size and NT-proBNP was significant by definition.

	No definite evidence of heart failure (95)	Evidence of Heart failure (664)	P-value	LAEF Quartile 1 (166)	LAEF Quartile 2 (166)	LAEF Quartile 3 (166)	LAEF Quartile 4 (166)	P-value
Main LA measurements - MRI								
LAEF 2 chambers -%	52 (47 – 61)	41 (31 – 50)	<0.001	54 (49 – 59)	46 (43 -50)	37 (34 – 41)	23 (16 – 29)	NA
LAEF 4 chambers - %	55 (48-61)	42 (31 -51)	<0.001	56 (53 – 61)	47 (45 – 49)	37 (34 – 39)	23 (17 – 28)	NA
Max LA volume (4 chambers) - ml	69 (49 -86)	84 (60 – 114)	<0.001	70 (51 – 93)	78 (55 – 102)	80 (64 – 110)	115 (90 – 138)	<0.001
Max LAvolume/BSA (4 chamber)	35 (27 -44)	43 (31 – 60)	<0.001	37 (28 -47)	39 (30 – 52)	42 (32 – 59)	62 (50 -76)	<0.001
Demographic data								
Age - years	65 (56 – 73)	69 (61 – 75)	0.015	68 (61 – 73)	68 (59 -75)	69 (61 – 75)	69 (62 -76)	0.216
Sex – male	61 (64)	525 (79)	0.001	125 (75)	137 (82)	132 (79)	131 (78)	0.451
IHD – no. (%)	34 (36)	469 (71)	<0.001	109 (66)	112 (68)	120 (72)	128 (77)	0.096
Previous MI – no.	27 (28)	345 (53)	<0.001	85 (52)	76 (47)	94 (58)	90 (54)	0.239
DM - no. (%)	17 (18)	145 (22)	0.380	42 (25)	38 (23)	28 (17)	37 (22)	0.297
Hypertension - no. (%)	53 (56)	332 (50)	0.291	88 (53)	91 (55)	78 (47)	75 (45)	0.233
COPD - no. (%)	10 (11)	59 (9)	0.603	15 (9)	17 (10)	16 (10)	11 (7)	0.674
NYHA class - no. (%)								
I	38 (40)	126 (19)	<0.001	38 (23)	34 (21)	31 (19)	23 (14)	0.498
II	38 (40)	357 (54)		84 (51)	89 (54)	91 (55)	93 (56)	
III	19 (20)	181 (27)		44 (26)	43 (25)	44 (26)	50 (30)	
SBP – mmHg	138 (126 – 156)	130 (115 – 149)	0.003	130 (118 – 151)	134 (120 – 150)	129 (114 – 149)	125 (112 – 143)	0.140
Heart rate – bpm	67 (14)	67 (13)	0.680	67 (12)	66 (11)	66 (12)	69 (17)	0.047
Congestion > 3	5 (5)	58 (9)	0.251	10 (6)	15 (9)	14 (8)	19 (11)	0.378
BMI - kg/m^2	31 (6)	28 (5)	<0.001	29 (6)	29 (5)	28 (5)	27 (5)	0.050
BSA – m^2	1.98 (0.24)	1.91 (0.22)	0.023	1.93 (0.21)	1.94 (0.24)	1.92 (0.20)	1.89 (0.21)	0.199
Blood results								
Haemoglobin – g/dl	13.9 (1.4)	13.5 (1.6)	0.001	13.4 (1.7)	13.5 (1.6)	13.4 (1.5)	13.1 (1.6)	0.160
Creatinine –µmol/l	88 (74 – 102)	103 (85 – 132)	<0.001	92 (81 – 110)	102 (84 – 132)	105 (88 – 134)	112 (92 – 142)	0.031
Urea – mmol/l	5.3 (4.3 – 6.9)	6.8 (5.3 – 9.3)	<0.001	6.2 (4.7 – 9.0)	6.8 (4.9 – 9.1)	7.0 (5.7 – 9.6)	7.5 (5.6 – 11.2)	0.085
Albumin - g/l	38 (3)	38 (3)	0.308	38 (4)	38 (3)	38 (3)	38 (4)	0.492
Bilirubin - µmol/l	14 (4)	15 (6)	0.014	14 (4)	15 (6)	16 (7)	17 (7)	<0.001

NT-proBNP – ng/l	131 (64 – 259)	864 (388 – 1978)	<0.001	414 (217 – 907)	803 (386 – 1480)	829 (435 – 2058)	1797 (912 – 3780)	<0.001
Medications								
Beta-blockers - no. (%)	48 (51)	515 (78)	<0.001	133 (80)	129 (78)	128 (77)	125 (75)	0.170
Ace-Inhibitors or ARB - no. (%)	56 (59)	584 (88)	<0.001	151 (91)	144 (87)	146 (88)	143 (86)	0.541
Aldosterone Antagonist -no. (%)	11 (12)	224 (34)	<0.001	56 (34)	59 (36)	49 (30)	60 (36)	0.575
Loop diuretics - no. (%)	15 (16)	480 (72)	<0.001	102 (61)	115 (69)	126 (76)	137 (83)	<0.001
Furosemide – patients ≥40 mg/day (%)	12 (13)	446 (67)	<0.001	95 (57)	108 (65)	113 (68)	130 (78)	<0.001
Furosemide - patients ≥ 80 mg/day (%)	3 (3)	191 (29)	<0.001	34 (20)	43 (26)	49 (30)	65 (39)	<0.001
Antiplatelets – no (%)	40 (42)	439 (66)	<0.001	116 (70)	112 (68)	103 (62)	108 (65)	0.078
Statin – no (%)	53 (56)	412 (62)	0.241	109 (66)	102 (61)	93 (56)	108 (65)	0.247
Other MRI data								
LVEDV – ml	134 (110 – 167)	210 (166 – 266)	<0.001	181 (143 – 216)	203 (161 -240)	217 (175 – 268)	252 (205 – 314)	<0.001
LVEF - %	60 (54 -66)	37 (29 -46)	<0.001	47 (38-53)	39 (32 – 46)	34 (28 – 44)	29 (24 – 37)	<0.001
LV mass - g	121 (102 – 152)	157 (129 – 194)	<0.001	136 (117 -168)	162 (136 – 200)	157 (133 – 192)	176 (142 – 211)	<0.001
MAX LA volume – 2ch	72 (53-97)	89 (65 – 115)	<0.001	79 (60 -99)	85 (58 – 106)	85 (61 – 115)	113 (88 – 137)	<0.001
LA total emptying volume - ml	37 (27 – 48)	31 (22 – 43)	<0.001	39 (30 – 54)	36 (26 – 47)	30 (23 – 39)	23 (15 – 31)	<0.001
LA conduit volume - ml	46 (36 – 58)	44 (32 – 57)	0.327	40 (30 – 52)	42 (31 – 51)	46 (31 – 58)	52 (38 – 65)	<0.001
RVEDV – ml	161 (121 – 171)	127 (102 – 158)	0.025	130 (107 – 159)	125 (102 – 157)	119 (97 – 147)	139 (110 – 184)	<0.001
RVEF - %	59 (56-62)	53 (44 – 60)	0.010	59 (53 – 65)	56 (49 – 62)	53 (45 – 60)	44 (32 – 55)	<0.001
RV mass - g	50 (41 – 54)	45 (37 – 56)	0.456	44 (35 – 52)	45 (37 -56)	43 (35- 53)	49 (40 -63)	<0.001
Mitral regurgitation								
Mild	21 (22)	222 (33)	0.02	44 (27)	46 (28)	49 (30)	83 (50)	<0.001
Moderate/Severe	0 (0)	24 (4)		1 (1)	3 (2)	4 (2)	16 (10)	
Tricuspid regurgitation								
Mild	18 (19)	114 (17)	0.692	31 (19)	20 (12)	18 (11)	45 (27)	0.001
Moderate/Severe	0 (0)	4 (1)		1 (1)	0 (0)	2 (1)	1 (1)	

Table 3 supplementary: Characteristics of patients by diagnosis and, for patients with heart failure by quartiles of left atrial ejection fraction (LAEF). Data are mean and standard deviation if the variable is normally distributed and median and inter-quartile range if not. The statistical difference between variables is given for the comparison between patients with and without heart failure, and between quartiles of LAEF only in patients with heart failure. List of abbreviation used: LAEF : Left Atrial Ejection Fraction; IHD - Ischemic Heart Disease; DM – Diabetes Mellitus; COPD - Chronic Obstructive Pulmonary Disease; NYHA – New York Heart Association; SBP - Systolic Blood Pressure; BMI - Body Mass Index; BSA: Body Surface Area; NT-proBNP - N-terminal B-type natriuretic peptide; ARB - Angiotensin receptor blocker; LVEDV - Left Ventricle End Diastolic Volume; LVEF – Left Ventricular Ejection Fraction; LV: Left Ventricle; RVEDV - Right Ventricle End Diastolic Volume; RVEF – Right Ventricular Ejection Fraction; RV: Right Ventricle. For right ventricular size and function, only 25 measurements were available for patients considered not to have heart failure and 549 for those considered to have heart failure.

	No HF (63)	HF with Narrow QRS (557)	HF with Broad QRS (320)	P value (narrow vs. broad QRS)
Demographic & clinical				
Age - years	64 (56-72)	68 (60-75)	71 (65-77)	<0.001
Sex – male	37 (60)	449 (81)	264 (82)	0.490
IHD – no. (%)	24 (38)	358 (64)	216 (67)	0.333
Previous MI – no. (%)	17 (27)	260 (47)	148 (46)	0.797
DM - no. (%)	9 (14)	113 (20)	76 (24)	0.230
Hypertension - no. (%)	40 (65)	271 (49)	167 (52)	0.314
NYHA				
I	25 (39)	103 (19)	55 (17)	0.009
II	27 (44)	313 (56)	153 (48)	
III	11 (17)	141 (25)	112 (35)	
SBP – mmHg	143 (23)	132 (25)	131 (23)	0.559
Congestion > 3	3 (4)	64 (11)	43 (13)	0.396
BMI - kg/m^2	31.0 (5.8)	28.6 (5.4)	27.9 (5.1)	0.005
BSA – m^2	1.94 (0.24)	1.95 (0.23)	1.91 (0.20)	0.019
Atrial fibrillation	0 (0)	129 (23)	51 (16)	0.011
Blood results				
Haemoglobin – g/dl	14.0 (1.4)	13.7 (1.7)	13.2 (1.6)	<0.001
Creatinine – umol/l	86 (71-96)	102 (85-130)	108 (90-140)	<0.001
Albumin - g/l	39 (3)	38 (3)	38 (3)	0.689
Bilirubin - umol/l	13 (11-16)	15 (12-19)	15 (12-18)	0.997
NT-proBNP – ng/l	146 (68-256)	888 (391-2192)	1238 (588-2619)	0.001
ECG				
Heart rate – bpm	70 (16)	71 (17)	69 (14)	0.009
QRS - msec	94 (83-106)	98 (88-106)	146 (130-162)	<0.001
Medications				
Beta-blockers - no. (%)	31 (49)	424 (76)	254 (79)	0.268
Ace-Inhibitors or ARB - no. (%)	38 (61)	488 (88)	287 (90)	0.356

Aldosterone Antagonist -no. (%)	5 (8)	176 (32)	121 (38)	0.061
Loop diuretics - no. (%)	0 (0)	405 (73)	241 (75)	0.400
Furosemide > 40 mg/day – no. (%)	0 (0)	160 (29)	118 (37)	0.013
MRI DATA				
LVEDV – ml	128 (107-157)	192 (153-238)	230 (180-289)	<0.001
LVEF - %	61 (55-69)	41 (32-51)	34 (27-43)	<0.001
LV mass - g	119 (97-153)	146 (123-181)	170 (138-206)	<0.001
LA Max volume - ml	68 (47-84)	92 (64-129)	97 (69-128)	0.551
RVEDV – ml	155 (115-170)	133 (103-168)	131 (108-160)	0.945
RVEF - %	58 (56-61)	52 (41-59)	50 (40-59)	0.168
RV mass - g	50 (35-56)	46 (38-59)	47 (37-58)	0.867
Mitral regurgitation				
Mild	15 (25)	167 (30)	129 (40)	0.005
Moderate/Severe	0 (0)	20 (4)	14 (4)	
Tricuspid regurgitation				
Mild	11 (17)	98 (18)	69 (22)	0.350
Moderate/Severe	0 (0)	8 (1)	4 (1)	

Table 4 supplementary: Characteristics of patients by diagnostic category. In the first column (left) patients with no HF, in the mid column patients with narrow QRS (< 120 msec), in the third column patients with broad QRS (>120 msec) are shown. List of abbreviation used: IVCD: indeterminate ventricular conduction delay; LBBB - left bundle branch block, RBBB - right bundle branch block; IHD - Ischemic Heart Disease; DM – Diabetes Mellitus; NYHA – New York Heart Association; SBP - Systolic Blood Pressure; BMI - Body Mass Index; BSA: Body surface Area; NTproBNP - N-terminal B-type natriuretic peptide; ARB - Angiotensin receptor blocker; LV – Left ventricle; LVEDV - Left Ventricle End Diastolic Volume; LVEF – Left Ventricular Ejection Fraction; LA: Left atrium; RV: Right Ventricle; RVEDV - Right Ventricle End Diastolic Volume; RVEF – Right Ventricular Ejection Fraction. Measurements of RV size and function were available only for 15 patients no heart failure, 420 for patients with narrow QRS and 275 for patients with wide QRS.

	JVD ratio Tercile 1 (70)	JVD ratio Tercile 2 (71)	JVD ratio Tercile 3 (70)	P-value
JVD – Ratio (Valsalva/Rest)	6.5 (5.7-7.9)	4.4 (3.8-4.7)	2.3 (1.7-2.7)	NA
Demographic data				
Age	67 (11)	69 (10)	74 (9)	0.001
Sex – male	52 (74)	57 (80)	49 (70)	0.368
IHD – no. (%)	45 (64)	41 (58)	43 (61)	0.727
DM - no. (%)	25 (36)	21 (30)	20 (29)	0.614
Hypertension - no. (%)	28 (40)	22 (31)	33 (47)	0.144
COPD - no. (%)	6 (9)	3 (4)	7 (10)	0.402
NYHA class - no. (%)				
I	25 (36)	17 (24)	9 (13)	0.003
II	34 (49)	44 (62)	38 (54)	
III	11 (15)	10 (14)	23 (33)	
Atrial fibrillation – no. (%)	16 (23)	23 (32)	32 (46)	0.016
SBP – mmHg	127 (25)	124 (24)	125 (26)	0.776
Heart rate – bpm	68 (11)	67 (9)	68 (12)	0.819
Congestion > 3	2 (3)	4 (6)	21 (30)	<0.001
BMI - kg/m^2	30 (6)	30 (5)	28 (5)	0.044
Blood results				
Haemoglobin – g/dl	13.8 (1.6)	13.8 (1.4)	12.7 (1.8)	<0.001
eGFR – ml/min/1.73m^2	68 (23)	64 (22)	54 (17)	<0.001
Urea – mmol/l	6.7 (5.4-8.4)	6.8 (5.3-9.5)	8.9 (6.2-11.7)	0.001
NT-proBNP – ng/l	552 (248-1287)	771 (409-1505)	1762 (846-3038)	<0.001
Medications				
Beta-blockers - no. (%)	61 (87)	66 (93)	59 (84)	0.267
Ace-Inhibitors or ARB - no. (%)	62 (89)	65 (91)	65 (93)	0.662
Aldosterone Antagonist -no. (%)	33 (47)	38 (53)	46 (66)	0.080
Loop diuretics - no. (%)	36 (51)	45 (63)	50 (71)	0.049

Furosemide – patients ≥40 mg/day (%)	32 (46)	36 (51)	46 (66)	0.047
Furosemide – patients ≥80 mg/day (%)	16 (23)	13 (18)	20 (29)	0.352
Echocardiographic data				
LVEDV – ml	140 (61)	150 (59)	138 (61)	0.453
LVEF - %	44 (12)	42 (11)	43 (13)	0.573
LAVI - ml/m^2	38 (16)	39 (16)	47 (18)	0.003
Mitral E/E'	10.2 (1.7)	11.1 (3.9)	13.4 (5.2)	<0.001
TAPSE – mm	20 (4)	18 (4)	16 (5)	<0.001
TR gradient - mmHg	23 (6)	27 (6)	31 (10)	<0.001
IVC - mm	17 (3)	18 (3)	22 (4)	<0.001
Mitral regurgitation				
Mild	28 (40)	33 (47)	34 (49)	<0.001
Moderate/Severe	2 (3)	9 (13)	20 (29)	
Tricuspid regurgitation				
Mild	19 (27)	26 (37)	25 (36)	<0.001
Moderate/Severe	2 (3)	5 (7)	21 (30)	

Table 5 supplementary: Characteristics of patients with heart failure by terciles of JVD ratio (paper 5). Data are mean and standard deviation if the variable is normally distributed and median and inter-quartile range if not. List of abbreviation used: JVD: Jugular Vein Diameter; IHD - Ischemic Heart Disease; DM – Diabetes Mellitus; COPD - Chronic Obstructive Pulmonary Disease; NYHA – New York Heart Association; SBP - Systolic Blood Pressure; BMI - Body Mass Index; eGFR - estimated Glomerular Filtration Rate; NTproBNP - N-terminal B-type natriuretic peptide; ARB - Angiotensin receptor blocker; LVEDV - Left Ventricle End Diastolic Volume; LVEF – Left Ventricular Ejection Fraction; LAVI - Left Atrial Volume Index; TAPSE - Tricuspid Annular Plane Systolic Excursion; TR gradient- Trans-Tricuspid systolic gradient; IVC - Inferior Vena Cava; NA – Not Applicable.

Variable	No evidence of Heart Failure (n=66)	Heart failure (n=311)	P-value	HF JVD ratio Tertile 1 (n=104)	HF JVD ratio Tertile 2 (n=103)	HF JVD ratio Tertile 3 (n=104)	P-value
Ultrasound JVD measurements							
JVD Rest – cm	0.16(0.14-0.20)	0.23 (0.17-0.33)	<0.001	0.16 (0.14-0.19)	0.23 (0.20-0.26)	0.41 (0.32-0.66)	<0.001
JVD Deep inspiration – cm	0.10(0.07-0.13)	0.14 (0.09-0.22)	<0.001	0.08(0.07-0.11)	0.14 (0.10-0.16)	0.33 (0.21-0.54)	<0.001
JVD Maximal – cm	1.03(0.90-1.16)	1.08(0.90-1.25)	0.276	1.13 (0.98-1.26)	1.06 (0.89-1.20)	0.99 (0.81-1.28)	0.029
JVD Ratio (Max/Baseline)	6.3 (4.9-7.6)	4.5 (2.9-6.1)	<0.001	6.8 (6.1-7.7)	4.5 (4.2-4.9)	2.3 (1.7-2.9)	NA
Demographics							
Age - years	68 (61-72)	71 (64-77)	0.001	68 (62-75)	71 (62-77)	73 (69-80)	0.001
Men - no. (%)	38 (58)	236 (76)	0.002	80 (77)	83 (81)	73 (70)	0.208
NYHA class - no. (%)							
I	56 (85)	67 (22)		30 (29)	27 (26)	10 (10)	
II	6 (9)	168 (54)	<0.001	58 (56)	56 (54)	54 (51)	<0.001
III	4 (6)	76 (24)		16 (15)	20 (20)	40 (39)	
IHD - no. (%)	11 (17)	196 (63)	<0.001	68 (65)	67 (65)	61 (59)	0.527
DM - no. (%)	37 (56)	104 (33)	0.001	36 (35)	36 (35)	32 (31)	0.777
Hypertension - no. (%)	36 (55)	117 (37)	0.011	37 (36)	37 (36)	43 (41)	0.629
Smoker - no. (%)	5 (9)	34 (12)	0.716	11 (12)	13 (14)	10 (10)	0.740
Atrial fibrillation – no. (%)	1 (1)	103 (33)	<0.001	23 (22)	29 (28)	51 (49)	<0.001
COPD - no. (%)	4 (6)	27 (9)	0.481	10 (10)	6 (6)	11 (11)	0.439
SBP – mmHg	136 (20)	126 (24)	0.001	125 (23)	128 (24)	126 (25)	0.529
Heart rate - bpm	70 (13)	68 (12)	0.220	67 (12)	66 (10)	69 (15)	0.158
BMI - kg/m^2	30.0 (5.9)	29.4 (5.5)	0.005	29.3 (5.6)	29.8 (5.4)	29.1 (5.6)	0.599
BSA – m^2	1.97 (0.24)	1.95 (0.22)	0.661	1.95 (0.22)	1.98 (0.22)	1.93 (0.23)	0.227
Congestion ≥ 3 – no. (%)	1 (1)	46 (15)	0.003	3 (3)	5 (5)	38 (37)	<0.001
Bloods							
Creatinine – umol/l	80 (66-98)	104 (87-137)	<0.001	99 (81-122)	108 (86-137)	110 (91-153)	0.034
Urea – mmol/l	5.4 (4.4-7.0)	7.3 (5.6-10.2)	<0.001	6.7 (5.1-8.7)	7.6 (5.5-10.5)	8.1 (6.0-11.8)	0.002
eGFR – 1.73ml/min/m^2	84 (69-103)	61 (45-76)	<0.001	65 (51-82)	59 (44-79)	56 (38-71)	0.003
Haemoglobin - g/dl	13.8 (1.3)	13.3 (1.6)	0.009	13.6 (1.4)	13.6 (1.6)	12.8 (1.8)	0.001

Albumin – g/l	40 (3)	39 (3)	0.005	39 (3)	40 (3)	38 (3)	0.006
Bilirubin – umol/l	13.4 (4.3)	15.5 (6.7)	0.001	14.3 (5.0)	14.7 (5.8)	17.5 (8.3)	0.001
NT-proBNP – ng/l	110 (38-213)	979 (441-2007)	<0.001	588 (263-1206)	836 (426-1887)	1791 (962-3327)	<0.001
NT-proBNP – ng/l (Patients in SR only)	106 (38 – 198)	622 (337 – 1753)	<0.001	482 (203 – 864)	598 (393 – 1762)	1768 (566 – 4023)	<0.001
Treatment							
Beta-blocker - no. (%)	25 (38)	276 (89)	<0.001	93 (90)	93 (90)	90 (86)	0.670
ACE inhibitor/ARB - no. (%)	41 (62)	281 (90)	<0.001	94 (90)	93 (90)	94 (90)	1.000
Aldosterone antagonist - no. (%)	7 (11)	169 (54)	<0.001	53 (51)	54 (52)	62 (60)	0.407
Loop diuretic - no. (%)	10 (15)	193 (62)	<0.001	53 (51)	66 (64)	74 (71)	0.010
Loop >40 mg Furosemide – no. (%)	5 (8)	77 (25)	0.002	23 (22)	21 (20)	33 (32)	0.145
Statin - no. (%)	39 (59)	223 (72)	0.043	86 (83)	73 (71)	64 (61)	0.003
CRT - no. (%)	0	37 (12)	0.003	10 (10)	13 (13)	14 (14)	0.667
Echocardiography							
LVEDD – mm	49 (6)	57 (9)	<0.001	57 (8)	58 (10)	58 (9)	0.623
LVEDV – ml	93 (31)	147 (62)	<0.001	141 (55)	158 (65)	143 (64)	0.104
LVEF - %	59 (6)	42 (12)	<0.001	43 (11)	41 (12)	42 (12)	0.645
LVEF <40% no. (%)	0 (0)	137 (44)	<0.001	44 (42)	48 (47)	45 (43)	0.808
LAD – mm	35 (5)	42 (7)	<0.001	40 (7)	41 (6)	44 (7)	<0.001
LAVI - ml/m^2	25 (11)	41 (15)	<0.001	38 (16)	40 (15)	47 (15)	<0.001
Mitral E/E'	8 (3)	12 (5)	<0.001	11 (5)	12 (5)	13 (5)	<0.001
TAPSE – mm	22 (4)	18 (4)	<0.001	20 (4)	18 (4)	17 (5)	<0.001
TR gradient – mmHg	20 (6)	28 (10)	<0.001	23 (6)	26 (7)	33 (12)	<0.001
IVC – mm	16 (3)	19 (4)	<0.001	17 (3)	18 (3)	22 (4)	<0.001
Mitral regurgitation							
Mild	6 (9)	156 (50)	<0.001	47 (45)	52 (50)	57 (55)	<0.001
Moderate/Severe	1 (1)	37 (12)		2 (2)	9 (9)	26 (25)	
Tricuspid regurgitation							
Mild	8 (12)	111 (36)	<0.001	27 (26)	36 (35)	48 (46)	<0.001
Moderate/Severe	1 (1)	33 (11)		1 (1)	6 (6)	26 (25)	

Table 6 supplementary: Characteristics of patients by diagnosis and by tertiles of JVP Ratio (paper 6). List of abbreviation used: IHD - ischemic heart disease; DM – diabetes mellitus; COPD - chronic obstructive pulmonary disease; SBP - systolic blood pressure; BMI - body mass index; eGFR - estimated Glomerular Filtration Rate;

NTproBNP - N-terminal B-type natriuretic peptide; hsCRP - high sensitivity C-reactive protein; CRT - cardiac resynchronization therapy; ICD - implantable cardioverter defibrillator; LVEDD - left ventricle end-diastolic diameter; LVEDV - left ventricle end diastolic volume; LVEF – left ventricular ejection fraction; LAVI - left atrial volume index; TAPSE - Tricuspid Annular Plane Systolic Excursion; TR gradient- Trans-Tricuspid systolic gradient; NA – not applicable.