# Presentation of Acute Heart Failure and its Consequences

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# Abstract

**Background:** Acute heart failure (AHF) is a heterogeneous in aetiology, pathophysiology and presentation and very difficult to classify. Despite this diversity, clinical trials in AHF deal with this syndrome as a single entity, which may be one reason for repeated failures. It is generally believed that patients with AHF present with severe breathlessness at rest but epidemiological data suggest otherwise.

**Methods:** Different data sets were used to assess the presentation of AHF and its consequences. I conducted a detailed case note review to determine what proportions of patients were Short Of Breath At Rest (SOBAR) and Comfortable At Rest but Breathless On Slight Exertion (CARBOSE). Euro Heart Failure Survey 1 (EHFS1) screened consecutive deaths and discharges during 2000-2001 in 24 countries, to ascertain patients with known or suspected Heart Failure (HF). Information on presenting symptoms and signs were gathered. Mortality was assessed during hospital admission and then 3 months after discharge.

**Results:** Of 697 patients, those with SOBAR (45%) had higher median heart rate blood pressure and respiratory rate and these changed quickly in first 24 hours after presentation as compare to CARBOSE (55%) but had better long term prognosis. Of all 10,701 patients admitted with suspected HF in EHFS1, Heart failure was considered to be the primary reason for admission in 4,234 (40%), secondary reason for admission if complicated or prolonged stay in further 1,772 (17%), and in 4,695 (43%) it was uncertain that HF is actively contributing in index admission. Mortality was highest in the secondary heart failure group and lowest in the uncertain group. Heart failure with cardiac arrest/ventricle arrhythmia had worst mortality followed by HF with ACS but considerable number of patients died in uncertain group.

**Conclusion:** AHF is complex, with diverse presentations that are associated with very different subsequent prognosis. Attempts to investigate the effect of agents in all patients with a diagnosis of AHF may be futile. A more coherent approach of focused and tighter patient selection for drug therapy targeted by clinical presentation is more likely to succeed.

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# Author's Declaration

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# Chapter 1 **Why are patients with Heart Failure admitted to hospital?**

## 1.1 **Background**

Heart failure (HF) is common and getting more common. Many patients are hospitalised: indeed, the diagnosis is most often made during a hospitalisation,[1] and more than half of patients with acute heart failure (AHF) are readmitted within 6 months of discharge.[2] Hospitalisation matters because it is associated with a high mortality,[1, 3] is expensive,[4] and associated with a high risk of readmission.[2, 5] However, in contrast to the situation for patients with chronic heart failure (CHF), there is very little evidence to guide therapy for acute heart failure. Partly, this is because patients often present at inconvenient hours of the night when it is least likely they will encounter people with the time or inclination to do research (funding nocturnal research can be expensive). Protocol procedures often cause delays which allow standard therapies to be effective before a new intervention can be started. But, remarkably, very little is known about what precipitates an admission to hospital, and very little is known about the patients' symptoms at admission. It is thus difficult even to know what the target for treatment might be.

Acute heart failure is heterogeneous in nature and varies in clinical presentation, aetiology and pathophysiology. AHF is not a distinct diagnosis but a collection of different clinical syndromes under one umbrella term which requires urgent clinical intervention.[6] European Society of Cardiology (ESC) 2008 guidelines classify AHF into six different clinical presentations which have considerable overlap.[7] Congestion is a prominent feature of patients presenting with AHF and can be present either in

pulmonary, peripheral or affect both regions.[8] Due to its heterogeneity, it is extremely difficult to classify AHF in an absolute sense and each classification has its limitations. This lack of knowledge is problematic in AHF trials where the targeted population is usually not clear. This may be one important reason of repeated failures or neutral results of clinical trials in the field.

## 1.2 How patients with AHF present to hospital

"Acute heart failure is defined as a rapid onset or change in the signs and symptoms of HF, resulting in the need for urgent therapy".[7] AHF may be either of new onset (de novo) or represent a deterioration of preceding chronic HF. Patients may present as a medical emergency with acute pulmonary oedema which needs urgent medical attention or with slowly worsening peripheral oedema over weeks and months. Cardiac ischaemia, dysrhythmias, valvular dysfunction, increased afterload due to systemic or pulmonary hypertension may contribute to cardiac dysfunction and precipitate admissions to hospital.[7]

The ESC 2008 classification of AHF is shown in Table 1. The different clinical presentations are not mutually exclusive and there is overlap among different conditions. A large proportion of AHF patients have worsening or decompensating chronic HF; and after initial therapy and achieving stabilization, they become patients with chronic HF.[7, 9] There are some limitations of the classification which make it unreliable and not helpful for AHF clinical trials. It has never been scientifically validated in clinical settings. It was partly tested in the Euro-Observartional Research program which further highlights its weaknesses (Figure 1).[10] In this study Maggioni and colleagues found 75% of AHF patients presented with "Decompensated CHF". Is this Decompensated HF a homogenous group or a

further mixture of different presentations of AHF which have different underlying aetiologies, pathophysiology and different precipitating factors? In everyday clinical practice a substantial proportion of the patients hospitalized with AHF present with slowly worsening peripheral oedema and may have no significant breathlessness at rest. The classification glosses over this extremely important subset. The classification does not take account of the underlying cardiac dysfunction, particularly in regard to left ventricular systolic function: such an omission may be important when the therapy for heart failure with reduced ejection fraction (HeFREF) and heart failure with preserved ejection fraction (HeFPEF) are quite different in CHF. The classification gives only limited support to AHF clinical trials for establishing new drugs and needs major revision with more robust scientific evidence.

**Table 1 Clinical classification of Acute Heart Failure patients**[7, 11]

| *Table 1: Clinical classification of Acute Heart Failure patients* | | |
|---|---|---|
| *Clinical Presentation* | *Characteristics* | *Targets and Therapies* |
| Worsening or Decompensated Chronic HF | • Usually patients with pre-existing chronic HF on treatment<br>• Develops in days or weeks<br>• Radiographic pulmonary congestion may be minimal<br>• Low BP on admissions is linked to poor outcome<br>• ? Peripheral oedema/congestion | Target: Volume management<br><br>Therapy:<br>• loop diuretics<br>• vasodilators<br>• thiazide diuretics in loop diuretic resistant patients<br>• higher doses of diuretics in renal dysfunction or with chronic diuretic use<br>• Inotropic agents in hypotension and organ hypoperfusion<br>• Ultrafiltration may be effective in less severely ill patients and reduce length of hospital stay |
| Pulmonary oedema | • Abrupt onset<br>• Presented with severe respiratory distress, tachypnoea, orthopnoea and rales over lung fields<br>• Arterial oxygen saturation is usually <90% on room air | Target: BP, volume management<br><br>Therapy:<br>• Morphine, especially when dyspnoea is complemented by pain and anxiety<br>• Supplemental oxygen in patients with hypoxia<br>• Vasodilators when BP is normal or high<br>• Diuretics in patients with volume |

| *Table 1: Clinical classification of Acute Heart Failure patients* | | |
|---|---|---|
| *Clinical Presentation* | *Characteristics* | *Targets and Therapies* |
| | | overload<br>• Inotropic agents in hypotension and organ hypoperfusion<br>• NIPPV and ventilator support |
| Hypertensive HF | • Signs & symptoms of HF with high BP<br>• Usually patients with HFPEF<br>• Patients may be euvolaemic or only mildly hypervolaemic<br>• May be with signs of pulmonary congestion without signs of systemic congestion<br>• Usually rapid response to therapy and hospital mortality is low | Target: BP and volume management<br><br>Therapy:<br>• Vasodilators with close monitoring<br>• Low dose diuretics in patients with volume overload or pulmonary oedema |
| Cardiogenic Shock | • Defined as evidence of tissue hypoperfusion prompted by HF after suitable correction of preload and major arrhythmia[7]<br>• Rapid onset, mainly complicating acute MI, fulminant myocarditis, acute valvular disease | Target: Recovery of cardiac pumping function<br><br>Therapy:<br>• Fluid challenge if clinically indicated (250 ml/10min) followed by inotrope if SBP remains <90mmHg<br>• Vasoactive medications<br>• Mechanical assist devices<br>• Corrective surgery |
| Isolated right HF | • Rapid or gradual onset due to primary or secondary pulmonary arterial hypertension or right ventricle pathology<br>• Characterized by low output syndrome in absence of pulmonary congestion with elevated JVP | Target: Pulmonary artery pressure<br><br>Therapy: |

| *Table 1: Clinical classification of Acute Heart Failure patients* | | |
|---|---|---|
| *Clinical Presentation* | *Characteristics* | *Targets and Therapies* |
| | • With or without hepatomegaly<br>• Low LV filling pressures<br>• Not well characterized due to little epidemiological data | • Nitrates<br>• epoprostenol,<br>• phosphodiesterase inhibitors<br>• endothelin-blocking agents<br>• coronary reperfusion for RV infarcts,<br>• valve surgery |
| AHF & ACS | • 15-25 of ACS patients may have signs/symptoms of HF<br>• Rapid or steady onset<br>• Signs/symptoms of HF may resolve after resolution of ischaemia<br>• All patients with ACS with signs/symptoms of HF should undergo an echocardiography study | Target: coronary thrombosis, plaque stabilization<br><br>Therapy:<br><br>Correction of ischemia |

Abbreviations: HF; heart failure, BP; blood pressure, HFPEF; heart failure with preserved ejection fraction, MI; Myocardial Infarction, SBP; systolic blood pressure, JVP; jugular venous pressure, LV; left ventricle, RV; right ventricle; AHF; acute heart failure, ACS; acute coronary syndrome.

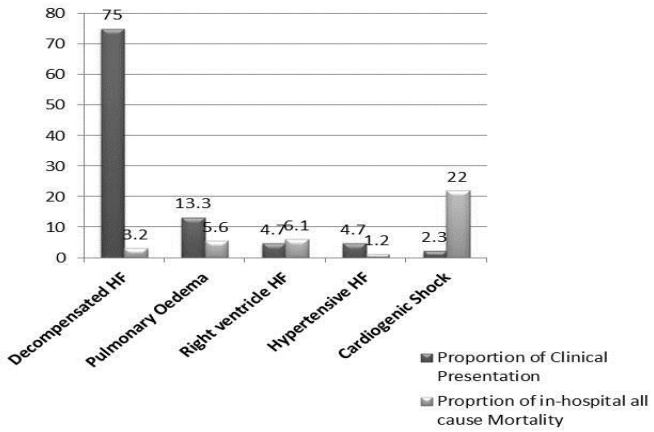



**Figure 1 Clinical Presentations of Acute Heart Failure (AHF) and mortality in Euro-Observational Research Program - Proportions out of 1892 patients admitted with AHF[10]**

## 1.3 Phenotypes of AHF patients

AHF patients can be classified according to their phenotypic appearance (Figure 2).

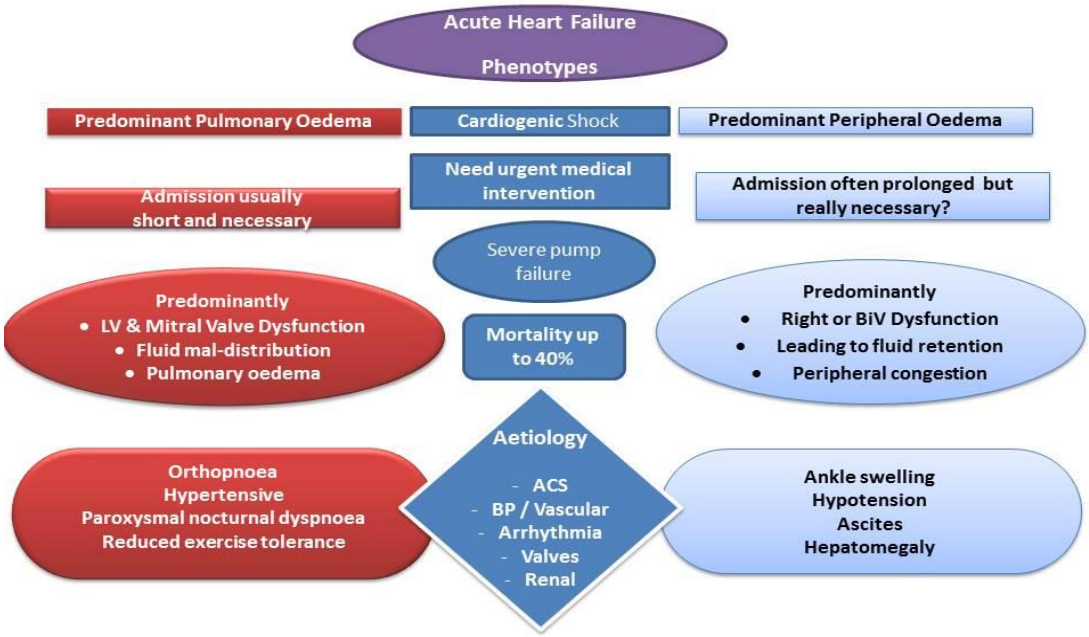



**Figure 2 : Possible causes and presentation of three distinct phenotypes of Acute Heart Failure patients**

ACS; Acute coronary syndrome, BP; Blood pressure, LV; Left ventricle

### 1.3.1 Pulmonary Oedema

These patients typically presents with severe shortness of breath that has developed very rapidly within minutes to hours. The patients prefer to sit upright and may not be able to speak or only gasp a few words. They may have high blood pressure and fast heart rate and respond very well to treatment with relatively rapid resolution of symptoms within the first few hours of presentation. According to ESC guidelines these patients need investigations and treatment simultaneously.[8, 12]

### 1.3.2 Peripheral Oedema

Patients typically give a history of gradual weight gain, spread over weeks to months, often in setting of previous coronary artery disease (CAD), hypertension, atrial fibrillation (AF) and chronic kidney disease. They may have low blood pressure, may sit comfortably on chair or bed, but mild exertion like changing clothes or going to toilet can provoke breathlessness. The patients typically respond very slowly to medical therapy due to the large amount of extra fluid present in dependent parts of body.[8, 13, 14]

### 1.3.3 Distinction between Right ventricle (RV) dysfunction and fluid overload due to secondary hyperaldosteronism in heart failure

It is now well established that as renal perfusion drops, the kidneys retain sodium and heart failure develops. This process is regulated by the secretion of renin in the juxtaglomerular apparatus of the kidneys. As mean arterial pressure (MAP) falls in Heart Failure, more renin is secreted and it leads to increased production of angiotensin I and II and finally aldosterone. This secondary hyperaldosteronism leads to sodium and water retention in the distal convoluted tubule (DCT) of the

nephron. In addition to this, production of antidiuretic hormone (ADH) by the anterior pituitary gland is also increased in HF. Increased ADH production acts on the collecting duct of the nephron, which enhances the movement of water from the lumen of the nephron to the medulla of the kidneys.

Right sided heart failure usually occurs as a natural consequence of left sided heart failure. As the left ventricle fails, increased fluid pressure effect is transmitted back through the lungs and ultimately damages the right heart. Other causes might be tricuspid regurgitation, right ventricle infarction, pulmonary hypertension and right sided cardiomyopathies. However, whatever the underlying reason, when the right ventricle loses ejection power blood accumulates in the body's veins. This usually causes lower limb oedema and oedema in internal viscera like the GI tract and liver which leads to ascites.

### 1.3.4 Cardiogenic shock

The third phenotypic appearance is cardiogenic shock due to severe pump failure. Patients with shock present with tissue hypo-perfusion despite adequate ventricular filing. Acute myocardial infarction is the most common underlying cause but patients with acute presentation of cardiomyopathy can also present in this fashion. Mortality is as high as 40% in this very high risk subgroup.[1]

It's important to recognise that peripheral and pulmonary oedema are two ends of spectrum and many of patients presenting with worsening HF falls somewhere along this range. The situation is similar to that in chronic obstructive pulmonary disease, where we see some typical patients with either emphysema or chronic bronchitis, but many having overlapping features. The overlap means that it may be difficult to

differentiate between the two groups clearly, a potential weakness of this relatively simple classification. This simple classification is again not very much helpful for clinical trials if we ignore underlying aetiology, cardiac phenotype and pathophysiology. For instance, a patient with pulmonary oedema, de novo heart failure, cardiogenic shock with systolic dysfunction due to acute myocardial infarction (AMI) is quite different from those with pulmonary oedema due to uncontrolled hypertension.[6]

## 1.4 What precipitates an admission to hospital?

There are many possible precipitants of a heart failure admission. Some of them are potentially preventable and early diagnosis, prompt treatment, appropriate counselling and patient education can avoid hospitalization.

### 1.4.1 Acute myocardial ischaemia

Acute coronary syndrome (ACS) is an important contributory factor in worsening or new-onset HF. No doubt, acute ST segment elevation myocardial infarction (STEMI) can be easily diagnosed on ECG but other ACS may be harder to diagnose. Chronic elevation of troponin in HF patients, with or without CAD, may further complicate the picture. In newly diagnosed HF patients, clinicians should always consider the underlying possibility of CAD causing HF.[15]

### 1.4.2 Non adherence with medications and excessing sodium/fluid intake

Excessive sodium and fluid intake may precipitate AHF. Non adherence with treatment either due to financial or other reasons may be cause of hospital admission in some patients.[15]

### 1.4.3 Uncontrolled Hypertension

High blood pressure may contribute to AHF, especially among people of African descent, women and those with HeFPEF. Abrupt cessation of antihypertensive drugs may cause decompensation in a previously stable chronic HF patient.[15]

### 1.4.4 Dysrhythmias

Registries and trials data indicate the 20-35% acute heart failure patients suffered from AF at presentation.[16] The combination of AF and acute HF is dangerous: the adverse effects of AF may include loss of atrial transport, fast and irregular ventricular response and the deleterious effects of antiarrhythmic drugs.[17]

### 1.4.5 Drugs

Recent introduction of negative inotropic agents like verapamil, nifidipine, diltiazem and beta blockers can decompensate previously stable HF patients. Drugs like NSAIDs, anti-arrhythmic agents, COX-2 inhibitors, glucocorticoids, thiazolidinedione and over the counter medications like pseudoephedrine may be other culprits.[15]

### 1.4.6 Concomitant infections

Respiratory tract infections are common precipitants of admission in patients with HF, may worsen hypoxia due to increased metabolic demand and are associated with worse prognosis.[15]

### 1.4.7 Pulmonary embolism (PE)

HF is a hypercoagulable condition and PE as a cause of acute decompensation should always be considered.[15]

### 1.4.8 Chronic kidney disease (CKD) & Anaemia

There is plenty of evidence that CKD itself is a major contributor to severe cardiac damage and conversely chronic HF is a major source of progressive chronic kidney disease. Decompensating HF, worsening renal functions and anaemia produce a vicious cycle and each condition causes or aggravates the others. Rapid diagnosis and aggressive management of HF, CKD and associated anaemia may considerably slow the development of both diseases.[18]

### 1.4.9 Endocrine abnormalities

In patients who have hypothyroidism or hyperthyroidism, restoration of normal thyroid function may reverse abnormal cardiovascular status.[15] However, tight glucose control may increase mortality in patients with HF who have diabetes. Aguilar & colleagues found that modest glucose control with a haemoglobin A1c (HbA1c) between 7.1% and 7.8% showed 27% lower mortality risk than tight glycaemic control with a HbA1c of 6.4% or lower (p-value=0.001).[19]

### 1.4.10 Excessive alcohol or illicit drug use

Excessive alcohol consumption and usage of illicit drugs like cocaine and methamphetamine may contribute to decompensation of HF and need to be considered in some patients.[15]

### 1.4.11 Other acute cardiovascular disorders

Native and prosthetic valve endocarditis, aortic dissection and myopericarditis may need to be considered in selected patients as potential causes of HF decompensation.

## 1.5 What Registries tell us about AHF

Clinical trial populations often differ from "real world" patients due to strict inclusion and exclusions criteria. Large clinical registries may provide more rich and real world information regarding presentation, baseline clinical characteristics, quality of service and therapies before and during admission and at the time of discharge. The registries provide very valuable information for clinicians, researchers and policy makers about clinical features and outcome of HF patients during hospital admission, but follow up data is either not available or only for a limited period of time. [20]

In large HF surveys & registries (Table 2), the average age of AHF patient varies from 70-73 years, the proportion of women from 37-52%, 32-44% patients presented with acute breathlessness and approximately two thirds had peripheral oedema at time of admission. The prevalence of hypertension is quite high in all registries and varies from 53-73%, diabetes mellitus (DM) from 25-35%, AF from 23-44%, COPD from 19-32% in European and US registries but only 9% in Japan. In the majority of registries, approximately half of HF patients had a past history of coronary artery disease (CAD), but the proportion is much lower in Japan (31%).[3, 21] The prevalence of chronic kidney disease is exceptionally high in Japan (70%) but varies from 17-30% in European and US registries. The average length of stay during an index hospital admission is around 8-11 days in Europe, less in the US (4.3-6.4 days) but remarkably longer in Japan (21 days). According to the Euro HF survey II (EHFSII), acute ischaemic events (30%), atrial arrhythmias (32%), infections (18%) and heart valvular problems (27%) are common precipitating factors leading to hospital admission.[1] In-hospital mortality is consistently lower in the US (4%) as compared

to Europe (7-9%). However, it is very interesting to note that even though the in-hospital mortality is lower in US registries, it is much the same as other registries at 30 days and one year after index admission Table 3.

The registries suggest that in contrast to the general perception, the majority of patients with AHF don't present with acute or severe breathlessness at the time of is more than 50%.Thirdly, at least two-thirds of AHF patients have a prior history of heart failure and one third has de novo HF. These observations highlight many important questions which are still unanswered. How does the large proportion of AHF patients present to emergency department if they are not short of breath at rest? Is peripheral oedema a more common presentation of AHF patients than acute pulmonary oedema? If most patients are not short of breath at rest, then can we hypothesize that these AHF patients are comfortable at rest but slight exertion makes them breathlessness? For those who present with breathlessness at rest, how quickly do their signs and symptoms change in response to standard treatment? How do measures such as blood pressure, respiratory rate and heart rate in these different presentations respond to standard treatments? Do the different presentations of AHF have different associated short and long term mortality? How can we approach these different clinical presentations of AHF in clinical trials for more targeted and focused drug therapy?

**Table 2 Large Heart Failure surveys and registries**

| *Table 2: Large Heart Failure surveys & registries* | *EHFS 1*[3, 22] | *EHFS II*[1] | *EHF Pilot*[10, 23] | *ADHERE*[21] | *E&W NHFA*[24] | *OPTIMIZE-HF*[16, 25-27] | *Attend Registry*[28] | *Urgent Dyspnoea study*[29] |
|---|---|---|---|---|---|---|---|---|
| Year of data Collection | 2000-2001 | 2004-05 | 2009-10 | 2001-04 | 2012-13 | 2003-04 | 2007-11 | 2007 |
| Year of Study First Published | 2003 | 2006 | 2010 | 2005 | 2013 | 2006 | 2013 | 2010 |
| Number of Institutions/Hospitals | 115 | 133 | 136 | 282 | 145 | 259 | 53 | 35 |
| Number of Patients recruited | 10701 | 3580 | 1892 | 107362 | 43894 | 48612 | 4842 | 524 |
| Age (Years) | 71 | 70 | 70 | 72 | 72 | 73 | 73 | 68 |
| Females (%) | 47 | 38.7 | 37.3 | 52 | 52 | 52 | 42 | 43 |
| Acute or Severe Breathlessness/NYHA class | 40 | . | . | 32 | 35 | 44 | 44 | 36 |

*Table 2: Large Heart Failure surveys & registries*

| | *EHFS 1*[3, 22] | *EHFS II*[1] | *EHF Pilot*[10, 23] | *ADHERE*[21] | *E&W NHFA*[24] | *OPTIMIZE-HF*[16, 25-27] | *Attend Registry*[28] | *Urgent Dyspnoea study*[29] |
|---|---|---|---|---|---|---|---|---|
| IV (%) | | | | | | | | |
| Peripheral Oedema (%) | . | 54 | 65 | 66 | 50 | 65 | 70 | . |
| Hypertension (%) | 53 | 62.5 | 61.8 | 73 | 55 | 71 | 69.4 | 75 |
| DM(%) | 27 | 32.8 | 35.1 | 44 | 31 | 25 | 33.8 | 37 |
| AF/Af(%) | 23 | 38.7 | 43.7 | 31 | 42 | 31 | 39.6 | . |
| COPD (%) | 32 | 19.3 | | 31 | 17 | 28 | 9.5 | 17 |
| CAD(%) | 68 | 53.6 | 50.7 | 57 | 47 | 50 | 31.1 | 43 |
| CKD(%) | 17 | 16.8 | 26 | 30 | 24 | 20 | 69.5 | 26 |
| Anaemia(%) | . | 14.7 | 31.4 | . | . | 18 | | 14 |

*Table 2: Large Heart Failure surveys & registries*

| | *EHFS 1*[3, 22] | *EHFS II*[1] | *EHF Pilot*[10, 23] | *ADHERE*[21] | *E&W NHFA*[24] | *OPTIMIZE-HF*[16, 25-27] | *Attend Registry*[28] | *Urgent Dyspnoea study*[29] |
|---|---|---|---|---|---|---|---|---|
| HR (beat / minute) | 75 | 95 | 88 | . | . | 87 | 99 | 90 |
| SBP (mmHg) | 133 | 135 | 133 | 144 | . | 143 | 146 | 140 |
| RR(Per minute) | . | 20 | . | . | . | . | . | 22 |
| Prior HF(%) | 65 | 63 | | 75 | | 88 | 36.2 | 62 |
| Therapy Prior to Admission | | | | | | | | |
| Diuretics (%) | 56 | 71.2 | 65 | 70 | . | 61 | 46 | 65 |
| ACEi (%) | . | 55 | . | 41 | . | 40 | 14 | 47 |
| ARB (%) | . | 9.3 | . | 12 | . | 12 | 35 | 12 |
| ACI/ARB (%) | . | . | 60 | . | . | . | 44 | 59 |
| BB (%) | . | 43.2 | 63 | 48 | . | 53 | 34 | 51 |

*Table 2: Large Heart Failure surveys & registries*

| | *EHFS 1*[3, 22] | *EHFS II*[1] | *EHF Pilot*[10, 23] | *ADHERE*[21] | *E&W NHFA*[24] | *OPTIMIZE-HF*[16, 25-27] | *Attend Registry*[28] | *Urgent Dyspnoea study*[29] |
|---|---|---|---|---|---|---|---|---|
| MRA (%) | . | 28.1 | 33 | | . | 7 | 18 | 11 |
| Digoxin (%) | . | 26.6 | 22 | 28 | . | 23 | 7 | 19 |
| Therapy at discharge | | | | | | | | |
| Diuretics (%) | 86.9 | 90.1 | 87 | . | 91* | . | 82 | . |
| ACEi (%) | 61.8 | 71.1 | . | 66 | 73 | . | 31 | . |
| ARB (%) | 4.5 | 10.4 | . | . | 18 | . | 46 | . |
| ACi/ARB (%) | . | . | 77 | . | 85 | . | 75 | . |
| BB (%) | 36.9 | 61.4 | 81 | . | 82 | . | 67 | . |
| MRA (%) | 20.5 | 47.5 | 53 | . | 49 | . | 43 | . |
| Digoxin (%) | 35.7 | 31 | 18 | . | 22 | . | 15 | . |

*Table 2: Large Heart Failure surveys & registries*

| | *EHFS 1*[3, 22] | *EHFS II*[1] | *EHF Pilot*[10, 23] | *ADHERE*[21] | *E&W NHFA*[24] | *OPTIMIZE-HF*[16, 25-27] | *Attend Registry*[28] | *Urgent Dyspnoea study*[29] |
|---|---|---|---|---|---|---|---|---|
| Duration of Index admission in days | 11 | 9(IQR6-14) | 8 (IQR 5-11) | 4.3 | 8 | 6.4 | 21 | . |
| In Hospital Mortality (%) | 6.9 | 6.7 | 3.75 | 4 | 9.4 | 3.8 | 6.4 | . |
| Duration of Follow up | 12 Weeks | 3 Months & 1 year | 1 year | . | 30 days | 60-90 Days | . | . |
| Readmission during follow up (%) | 24.2 | . | 43.9 | . | . | 30 | . | . |
| Mortality during follow up (%) | 13.5 | 8.1 (3 months)<br>20.5 (12 Months) | 17.4 | . | 14.9 | 9 | . | . |

Abbreviations: HF; Heart Failure, EHFS1; Euro heart failure survey 1, EHFSII; Euro heart failure survey II; EHF Pilot; Euro Heart Failure Pilot survey, E&W NHFA; England & Wales National heart failure audit; NYHA; New York heart association, DM; Diabetes Mellitus; AF; Atrial fibrillation, Af; Atrial flutter, COPD; Chronic obstructive pulmonary disease; CAD; Coronary artery disease, CKD; Chronic kidney disease, HR; Heart Rate, SBP: Systolic blood pressure, RR; Respiratory rate, HF; Heart Failure, ACEi; Angiotensin converting enzyme inhibitor, ARB; Angiotensin receptor blocker, BB; Beta blocker, MRA; Mineralocorticoid receptor antagonist, *Only for those patients who have LVSD on discharge, ≠ Haemoglobin < 12 g / dl

**Table 3 Mortality after hospital admission**

| *Table 3: Mortality after hospital admission* | | | | | |
|---|---|---|---|---|---|
| *%* | *E & W national audit*[24] | *Scotland 2008*[30] | *ESC HF pilot survey*[10, 23] | *Ontario 2007*[31] | *USA*[32, 33] |
| In-Patient | 9.4 | 13.8 | 3.75 | 10.4 | 4.3 |
| 30 Days | 14.9 | 14.3 | . | 16.3 | 10.7 |
| I year | 30 | 36.6 | 17.4 | 34.6 | 32 |

## 1.6 What Clinical trials tell us about AHF

Despite the remarkable success of treatment for chronic HF in the last 2-3 decades, there is a disappointing lack of progress in AHF. Table 4 is showing a list of AHF trials where the results were either neutral or hazardous.[34-38] Trying to investigate a single new agent which might benefit all these different presentations of AHF is likely to be futile. Some presentations of AHF, especially acute pulmonary oedema, are very difficult to study in clinical trials. Firstly, it is difficult to establish the underlying diagnosis in the early hours of an admission. Secondly, clinical and haemodynamic instability make recruitment to clinical trials problematic. Thirdly, technically it is hard to take consent for very sick patients such as those with pulmonary oedema. Fourthly, it is difficult to set in place a research establishment geared to recruit patients presenting unpredictably (and often out of office hours). For these reasons, AHF clinical trials have usually recruited patients with "acutely decompensated chronic heart failure". However, as it is discussed earlier, this presentation is not homogenous, has a variety of underlying aetiologies and pathophysiology, and is inadequate as a descriptor to provide a focused target for new drugs (Table 4).[6]

Timely recruitment to clinical trials is highly essential for success. For instance, if treatment of pulmonary congestion is the aim of the study, then very early recruitment is vital. But in reality, clinical trials in acute heart failure have mostly failed to recruit patients within 8 hours of presentation to hospital – by which time, many patients have been actively treated and have recovered.[39] In contrast, patients presented predominately with peripheral oedema, treatment for new novel therapies could be started after 24 hours of hospital admission.

**Table 4 Major Acute Heart Failure Clinical Trials**

| *Table 4: Acute Heart Failure Clinical trials* | | | | | |
|---|---|---|---|---|---|
| *Trial Name* | *Patients Enrolled* | *End Point* | *Treatment* | *Patients Characteristics* | *Results* |
| DOSE[40, 41] | 308 | Co-primary end points were patients' global assessment of symptoms, quantified as the area under the curve (AUC) of the score on a visual-analogue scale over the course of 72 hours, and the change in the serum creatinine level from baseline to 72 hours. | Low versus high dose Furosemide<br><br>Continuous versus intermittent IV bolus | • Decompensated chronic heart failure patients presented within 24 hours<br>• Signs and symptoms suggestive of HF<br>• History of CHF treated with 80-240 mg/day furosemide at least for one month | No significant difference either in symptoms or change in creatinine level in both arms |
| ASCEND-HF[40, 42] | 7,141 | Co-primary end points were the change in dyspnoea at 6 and 24 hours, as measured on a 7-point Likert scale, and the composite end point of rehospitalisation for heart failure or death within 30 days | Nesiritide versus standard medical therapy | • Decompensated chronic heart failure patients<br>• Dyspnoea at rest or on minimal exertion<br>• Signs and symptoms suggestive of decompensated HF<br>• Randomization within 24 hours for first IV therapy | No significant difference between placebo and nesiritide |
| DAD-HF[40, 43] | 60 | Primary end point was the incidence of worsening renal function(WRF) | Dopamine + low dose furosemide (LDF) | • Decompensated chronic heart failure patients<br>• Signs of fluid overload<br>• eGFR $\geq$ 30 ml/min | There was a significantly higher incidence of WRF in serum creatinine from baseline to 24 hours, |

*Table 4: Acute Heart Failure Clinical trials*

| *Trial Name* | *Patients Enrolled* | *End Point* | *Treatment* | *Patients Characteristics* | *Results* |
|---|---|---|---|---|---|
| | | during the first 24 hours from randomization | versus high dose furosemide (LDF) | | observed in the HDF group compared with the LDF group |
| PROTECT[40, 44] | 2033 | • Improvement in dyspnoea<br>• Deaths or readmissions for HF<br>• Persistent renal impairment | Rolofylline versus placebo | • Decompensated chronic heart failure patients<br>• Persistent Dyspnoea at rest or on minimal exertion<br>• Estimated creatinine clearance 20-80 ml/min<br>• BNP ≥ 500 pg/ml or NT-proBNP ≥ 2000 pg/ml<br>• Intra venous loop diuretic therapy<br>• Randomization within 24 hours | Rolofylline did not improve primary outcomes or improve renal function or 60-day outcomes<br>Rolofylline was also associated with a higher incidence of seizures and stroke |
| CARRESS[40, 45] | 188 | The primary end point was the bivariate change from baseline in the serum creatinine level and body weight, as assessed 96 hours after random assignment. Patients were followed for 60 days. | Ultrafiltration versus stepped pharmacologic therapy | • Decompensated chronic heart failure patients who develop cardiorenal syndrome<br>• Randomization within 7 days from admission after implantation of IV diuretics | Ultrafiltration was inferior to pharmacologic therapy with respect to the bivariate end point of the change in the serum creatinine level and body weight 96 hours after enrolment (P=0.003) |
| RELAX-AHF[40, 46] | 1,161 | Improvements in signs and symptoms<br>Improve 180 days mortality | Seralaxin versus placebo for 48 hours | • Patients with breathlessness at rest or on slight exertion<br>• Pulmonary congestion on X-Ray, BNP ≥ 350 ng/L (NT-proBNP ≥ 1400 ng/L) | Improvement in the initial signs and symptoms of heart failure, as well as reduced mortality |

*Table 4: Acute Heart Failure Clinical trials*

| *Trial Name* | *Patients Enrolled* | *End Point* | *Treatment* | *Patients Characteristics* | *Results* |
|---|---|---|---|---|---|
| | | | | • eGFR 30-75 ml/min and Systolic Blood pressure 125 mmHg | |
| ASTRONAUT[40, 47] | 1,615 | Reduction of rate of cardiovascular (CV) death or HF rehospitalisation among Hospitalized HF patients | Aliskiren versus placebo | • Hospitalized heart failure patients with stable haemodynamic<br>• Median time of randomization is 5 days after admission<br>• Clinical features suggestive volume overload | Among patients hospitalized for HF with reduced LV EF, initiation of Aliskiren in addition to standard therapy did not reduce CV death or HF rehospitalisation at 6 months or 12 months after discharge. |
| VMAC[6, 48] | 489 | Change in pulmonary capillary wedge pressure (PCWP) among catheterized patients and patient self-evaluation of dyspnoea at 3 hours after initiation of study drug among all patients | IV Nesiritide versus IV Nitroglycerine or Placebo | • Decompensated chronic heart failure patients with dyspnoea at rest<br>• No left ventricle ejection fraction cut off point | Nesiritide improves hemodynamic function and some self-reported symptoms more effectively than intravenous Nitroglycerine or placebo. |
| OPTIME[6, 49] | 949 | To assess the interaction between heart failure (HF) etiology and response to milrinone in decompensated HF in terms of death and readmission | IV Milrinone versus Placebo | • Decompensated systolic heart failure patients who are not requiring Inotropes<br>• 48-72 Hours of IV Milrinone or placebo<br>• Mean LV ejection fraction 23% | Milrinone may have a bidirectional effect based on etiology in decompensated HF. Milrinone may be deleterious in ischemic HF, but neutral to beneficial in nonischemic cardiomyopathy. |
| VERITAS[6, 36] | 1,435 | The co-primary end points were change in dyspnoea (measured at 3, 6, and 24 | IV Tezosentan versus | • Acute Heart failure admitted within previous 24 hours with persistent dyspnoea and | Tezosentan did not improve symptoms or clinical outcomes in patients with acute heart failure. |

*Table 4: Acute Heart Failure Clinical trials*

| *Trial Name* | *Patients Enrolled* | *End Point* | *Treatment* | *Patients Characteristics* | *Results* |
|---|---|---|---|---|---|
| | | hours using a visual analog scale from 0-100) over 24 hours (as area under the curve) and incidence of death or worsening heart failure at 7 days | placebo | respiratory rate ≥ 24/min were eligible provided they met Inclusion criteria's; two out of four- elevated BNP, pulmonary oedema, chest x-ray congestion, LV ejection fraction (EF) <40%<br>• Mean EF 20% in VERITAS I & 28% in VERITAS II | |
| SURVIVE[6, 38] | 1,327 | Primary endpoint was reduction in mortality by 25% at six months | IV Levosimendan versus IV dobutamine | • Acutely decompensated HF patients requiring inotropes<br>• Left ventricle EF < 30% for inclusion<br>• Mean Left ventricle EF < 24% | Did not meet primary end point |
| REVIVE -2[6, 50] | 600 | Improvements in clinical symptoms at 6, 24 hours and five days | IV Levosimendan or Placebo | • Acutely decompensated HF patients<br>• Already received IV diuretics & other standard treatment within 24 hours but still symptomatic<br>• Left ventricle EF <35% | Increased mortality in Levosimendan arm |
| EVEREST[6, 35] | 4,133 | Dual primary end points were all-cause mortality (superiority and noninferiority) and cardiovascular death or hospitalization for heart failure (superiority only). Secondary end points | Oral Tolvaptan or Placebo | • Decompensated chronic heart failure patients require hospitalization<br>• Left ventricle EF ≤ 40%<br>• Within 48 hours of admission, randomly assign for oral Tolvaptan or placebo<br>• Mean left ventricle EF 28% | Tolvaptan initiated for acute treatment of patients hospitalized with heart failure had no effect on long-term mortality or heart failure-related morbidity |

*Table 4: Acute Heart Failure Clinical trials*

| *Trial Name* | *Patients Enrolled* | *End Point* | *Treatment* | *Patients Characteristics* | *Results* |
|---|---|---|---|---|---|
| | | included changes in dyspnoea, body weight, and oedema. | | | |

HF; Heart Failure, IV; Intra venous, CHF; Chronic Heart Failure, LV; Left ventricle, EF; Ejection fraction, eGFR; Estimated glomerular filtration rate

## 1.7 Conclusion & Rationale for thesis

Acute heart failure is a heterogeneous clinical condition and can present in different manners. These different presentations of AHF have distinct underlying aetiology and pathophysiology. Due to its large diversity, it is very difficult to classify acute heart failure and each classification has limitations. Despite of its complexity, clinical trials in AHF deal this syndrome as a single entity, which may be one reason of repeated failures. We can get more meaningful results in clinical trials, if we adopt a more coherent approach of focused and tighter patient selection for more targeted therapy with well thought clinical trials designs.[6] Current classification of AHF needs review for better characterization of different presentations of this syndrome. Contrary to general perception, many large registries and surveys have showed that majority of AHF patients are not breathlessness at rest at the time of presentation to hospital. I sought to verify this finding more vigorously in different clinical research studies and large data sets in more depth and detail. Main rationale behind this thesis is that how the patients of AHF present to hospital and what are effects of these different presentations to mortality?

# Chapter 2 Acute Heart Failure (Suspected or Confirmed): Initial Diagnosis and Subsequent Evaluation with Traditional and Novel Technologies

## 2.1 Introduction

Heart failure (HF) is common and as longevity increases its incidence and prevalence will rise.[12] Most cases of heart failure are first diagnosed during an episode of hospital care and heart failure is one of the most common reasons for emergency admission. [51] The diagnosis may often be initially unclear, requiring further investigation, the passage of time or both to make the diagnosis with some certainty. Even so, controversy surrounds the definition of acute heart failure (AHF). Admissions for heart failure are often prolonged and recurrent, leading to high rates of hospital bed occupancy. In the USA, where length of stay is short, hospital mortality is around 5% and the rate of readmission within 30 days is high (25%).[52] In Europe, where length of stay is two or three times as long, hospital mortality is between 10-20% but 30-day readmission rates are lower at around 10-15%, 30-50% of which will be due to worsening HF.[1, 53] More than 50% of patients will either die or be readmitted in the year subsequent to discharge.[54]

Surprisingly, epidemiological data on the precise mode of presentation of acute heart failure is remarkably difficult to come by. Most authorities assume that breathlessness is the main presenting symptom and that most patients are acutely distressed by it at rest. Recent data from a National Audit of England & Wales have called this assumption into question. Many patients present with worsening exertional breathlessness and peripheral oedema but are comfortable at rest. [53] [14] Also, recent reports suggest that many patients have worsening symptoms and

evidence of congestion for several days prior to presentation suggesting that technologies, such as home tele-monitoring, might be deployed for early detection and that redesign of services might prevent a large proportion of admissions.[55-57]

There is often also great initial uncertainty about whether HF is the cause of symptoms. Many patients are treated with diuretics without the clinician making a conscious diagnosis of HF, leading to deficiencies in investigation and treatment. Unfortunately, such patients, who may be far more common than those labelled as CHF, will not be picked up by most audits of Heart Failure.[58] Therefore, many cases of heart failure may be epidemiologically 'silent'; they are just treated with diuretics but never given the diagnostic 'label' of heart failure. [59]

Early assessment and prompt diagnosis or exclusion of HF will improve the quality and efficiency of care, shorten hospital stay, reduce readmission and improve prognosis.[60] Accordingly, there is great interest in finding new tools for early and precise diagnosis. [54]

## 2.2 Clinical Evaluation of Acute Heart Failure (AHF)

### 2.2.1 Purpose

Patients with breathlessness or oedema or those treated with loop diuretics for uncertain cause should be assessed to identify

a) whether they have heart failure and whether it is the cause of their symptoms and signs,

b) Other medical conditions that may contribute to worsening of symptoms (eg:- atrial fibrillation, acute coronary syndrome, infection, anaemia or chronic kidney disease).
c) their dominant acute symptom (breathlessness or peripheral oedema)
d) their cardiac phenotype (such as heart failure due to left ventricular systolic function, or heart failure due to valvular heart disease)) that will determine what treatment they should receive
e) their heart rate and rhythm and blood pressure which will also guide treatment.

Patients with the acute onset of severe dyspnoea often present in the early morning hours. In many healthcare systems, this is when the most junior and least experienced staff will be available. Although experts may be able to manage patients without the reassurance of technical support, less experienced staff may welcome investigations that provide them with the confidence they might otherwise lack. However, experienced staff also needs to review their practice critically. The outcome of acute heart failure both in hospital and after discharge is often poor which may be due, in part, to the persistence of outmoded concepts and practice in the care of these patients.

### 2.2.2 Clinical Features

Exacerbations of heart failure cover a wide spectrum of presentations with two distinctly different clinical phenotypes. Patients may present with **S**hortness **O**f **B**reath **A**t **R**est (SOBAR) which is due to a high left atrial pressure and pulmonary congestion; these patients might be termed ‘puffers. SOBAR usually reflects left

ventricular failure due to rapid atrial fibrillation, a high systemic vascular resistance or acute ventricular damage due to ischaemia or infarction but can be due to mitral regurgitation or other reasons. These patients generally have neither a raised venous pressure nor peripheral oedema. Their problem is fluid in the wrong place (the lungs). Other relatively specific symptoms of heart failure are orthopnoea, and paroxysmal nocturnal dyspnoea.

Patients may present with increasing peripheral oedema which may developed over many weeks or months, due predominantly to right or bi-ventricular failure; these patients may be termed 'bloaters'. They are often **C**omfortable **A**t **R**est but **B**reathless **O**n **S**light **E**xertion (CARBOSE).

There are many other nonspecific features that may be due to heart failure, such as fatigue, disturbed sleep pattern, skeletal muscle wasting and depression, which are generally unhelpful for its diagnosis. These patients developed symptoms over longer period of times and their pattern of presentation is closer to CARBOSE.

## 2.3 Physical examination

Raised jugular venous pressure is one of the most specific signs of heart failure but often difficult to elicit, especially in a patient who is acutely breathless and using their accessory muscles of respiration. It reflects right atrial pressure and therefore will only be increased if there is a problem on the right side of the heart, which is a late manifestation of left sided heart disease.[61] Peripheral oedema is often present in patients with AHF but is usually a sign of late-stage disease and may be due to many other causes.[60]

A third heart sound may be normal in young people but indicates left ventricular dysfunction in people aged >40 years. The pulmonary component of the second heart sound (P2) will be increased in pulmonary hypertension, which may be secondary to left atrial hypertension. However, detection of these signs by auscultation has poor inter-observer reproducibility and is usually only obvious in patients with severe decompensation who are in sinus rhythm.

Examination of the lungs may reveal fine crepitations indicating pulmonary oedema. Crepitations are not an accurate guide to left ventricular filling pressure in patients with chronic heart failure, but may be clinically useful in the setting of acute pulmonary oedema. The Killip classification is a powerful prognostic tool in this clinical setting .[62] Most patients with chronic heart failure do not have lung crepitations even if left atrial pressure is increased, perhaps because of reduced permeability of the alveolar-capillary membrane or to increased pulmonary lymphatic clearance of fluid.[8 63, 64] However, many patients have coarse crepitations due to pulmonary disease, some have fine crepitations due to pulmonary fibrosis and most patients who have rested in bed for a few hours will have some fine crepitations due to alveolar collapse that will resolve with a few coughs. Pulmonary crepitations in a patient who is not breathless at rest or on minimal exertion are unlikely to be due to heart failure.

## 2.4 Traditional investigations

The initial investigations performed in the acute setting are useful to assist in diagnosis, to identify precipitating factors and to help in risk stratification and triage

for escalation to a high-dependency unit or transfer to a general ward or to an observation unit and same-day discharge (Figure 3).

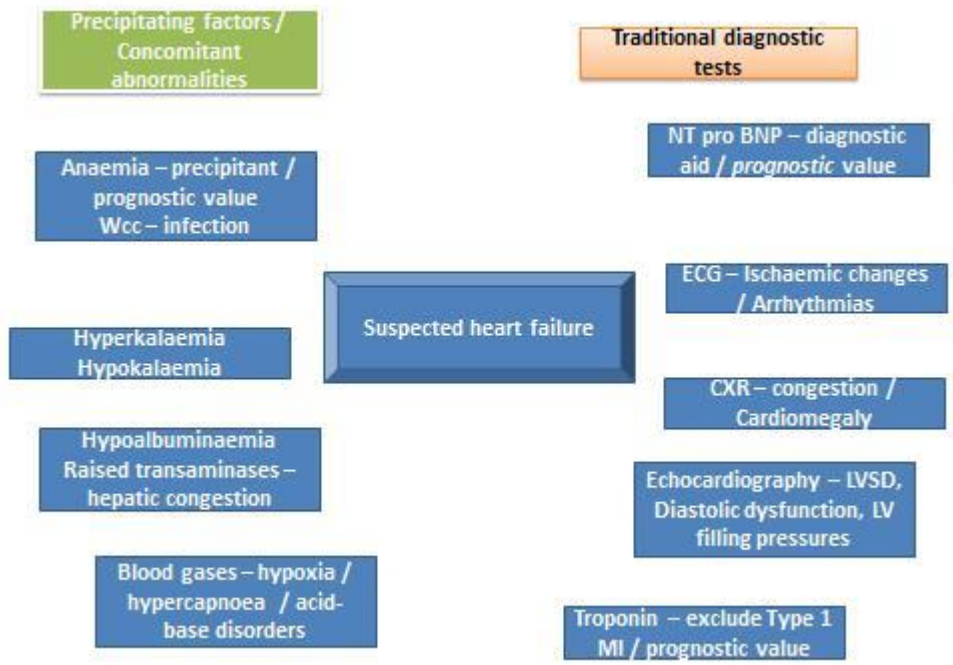



**Figure 3 Standard diagnostic tests and possible abnormalities in acute heart failure**

The ESC guidelines strongly recommend an ECG, transthoracic echocardiography, measurement of blood chemistry and haematology and, less strongly, a chest X-ray and measurement of natriuretic peptides (BNP, NT-proBNP or MR-proANP). [12] However, these recommendations are often not implemented in the acute setting, even in expert units. Respiratory rate is probably the best method by which to quantify dyspnoea and yet it is often overlooked. Many authorities would consider it medical negligence not to order a chest X-ray for a patient with severe breathlessness to exclude pulmonary disease. Taking arterial gases is often painful for patients and entirely unnecessary. Transcutaneous oxygen saturations combined with venous gases provide all the necessary information. On the other hand, internationally, rather

few acute medical receiving units have echocardiography available 24 hours a day, seven days per week.

### 2.4.1 Natriuretic Peptides

Natriuretic peptides can be considered cardiac stress hormones. Increases in natriuretic peptides are non-specific with respect to the nature of the stress but when normal are reassuring that the patient's cardiovascular system is not under great threat and when elevated that the patient has a problem requiring clarification. In the acute setting, measurement of natriuretic peptides may improve diagnostic accuracy by ruling out heart failure (NT-proBNP <300ng/L or BNP <100ng/L) or by increasing the certainty of a clinical diagnosis (NT-proBNP >2000ng/L or BNP >500ng/L). However, accurate interpretation requires experience and many patients will have a value in the diagnostic grey-zone.[65, 66] The two main reasons for a substantial elevation in natriuretic peptides other than ventricular dysfunction are atrial fibrillation and renal dysfunction. In addition, sex (women have higher levels) and body mass index (fat people have lower levels) have a modest effect. Older people have higher levels but this reflects the decline in renal function and diastolic left ventricular function that occur with age. It is inappropriate to correct natriuretic peptides for age.[67]

Natriuretic peptides do not discriminate between left ventricular systolic and diastolic dysfunction after correction for their impact on left atrial pressure, nor between right (eg:- primary or secondary pulmonary hypertension) and left sided heart disease and cannot determine whether failure is due to intrinsic myocardial disease or due to excessive load on fairly normal myocardium (eg:- valve disease,

malignant hypertension). In a very large registry of 48,629 patients, hospital mortality was more than three times higher in patients with BNP levels >1730ng/L (fourth quartile) as compared to those with levels <430ng/L (first quartile).[68]

Whether natriuretic peptides can be used to guide therapy in the setting of acute or chronic heart failure remains controversial.[69, 70]

### 2.4.2 Adrenomedullin, Copeptin & Procalcitonin

In the BACH study, MR-proANP (>120 pmol/ml) was not inferior to BNP (>100 pg/ml) for identifying patients with heart failure and MR-pro ADM was superior to BNP and NT-proBNP for predicting 90-day mortality.[71] Copeptin and MR-proADM are probably relatively non-specific markers of metabolic stress.[72] Their value may be in identifying patients who are likely to deteriorate and who require careful observation. Procalcitonin is a marker of infection, although also increased in heart failure, where it indicates an adverse prognosis. If it is elevated disproportionately to plasma concentrations of natriuretic peptides, it suggests that infection is an important component of the illness.[73] Thus, a panel of biomarkers combined with standard haematology and biochemistry profiles can build a patient profile that identifies diagnosis, precipitating factors and risk.

### 2.4.3 Troponin

Most patients with heart failure will have coronary artery disease as a cause or co-morbidity of heart failure. Acute coronary syndromes (ACS) may often be a precipitating factor for exacerbations of heart failure. However, even patients with chronic stable heart failure commonly have raised troponin levels and the great

majority have measurable levels with the latest generation of assays. The diagnosis of ACS requires demonstration of a typical rise of troponin above the 99$^{th}$ centile and, preferably, a subsequent fall. Patients with heart failure may be subject to what is termed Type II myocardial infarction (supply-demand mismatch rather than acute coronary obstruction), reflecting reduced subendocardial perfusion due to high left ventricular filling pressure, hypoxaemia, increases in afterload and/or hypotension. This may lead to myocardial damage and accelerated cardiac myocyte apoptosis.[74]

Troponin appears to be higher in patients with AHF (57%) compared to patients with other causes of dyspnoea.[74] In the Acute Decompensated Heart Failure National Registry (ADHERE), 75% of patients with AHF had detectable troponin levels using an older generation assay although only 6.2% had values above the upper level of reference limit. This latter group of patients had, on average, lower ejection fractions and systolic blood pressure and a higher hospital mortality (8.0% vs 2.7%).[75] Since the introduction of high sensitivity assays, it is possible to detect troponin in a large proportion of the healthy population.[76] Two recent clinical studies show that almost all patients with AHF had increases in high sensitivity troponin I or T and that higher levels predict poor in-patient and post-discharge prognosis.[77, 78] In PROTECT (*P*lacebo-controlled *R*andomized study of the selective A(1) adenosine receptor antagonist rolofylline for patients hospitalized with acute heart failure and volume *O*verload to assess *T*reatment *E*ffect on *C*ongestion and renal funcTion) , 21% of patients of AHF had no detectable [or "had normal"] troponin at baseline but had detectable levels by day 7: these patients had higher mortality by 60 days.[79] Recently, the RELAX-AHF study showed that administration of the pregnancy-related vasodilator hormone serelaxin could reduce both plasma concentrations of

natriuretic peptides and troponin and the effect appeared to be associated with an improvement in outcome.[80]

### 2.4.4 Echocardiography

Clinical guidelines recommend early echocardiography in acutely dyspnoeic patients who are suspected of having heart failure. This is a mostly unrealised ideal situation that rarely happens in clinical practice. Indeed, international research protocols in AHF have learnt to avoid requiring an immediate echocardiogram because that would preclude getting substantial numbers of patients into studies. There are too few adequately trained staff and too little access to equipment to provide 24 hour cover seven days per week in most hospitals where these patients are seen.

Ideally, prompt echocardiography should be part of the diagnostic work-up of all patients with suspected heart failure in the emergency setting, especially if a structural cause is suspected that might be amenable to intervention (such as aortic stenosis or ruptured mitral chordae). Echocardiography will identify patients with heart failure and a reduced ejection fraction (HeFREF), although the severity of ventricular dysfunction is prone to substantial observer error. Ultrasound may also be used to assess lung oedema.[81 82] However, echocardiography is not very helpful in diagnosing heart failure with a preserved left ventricular ejection fraction (HeFPEF) with the single most helpful echocardiographic measure being the left atrial volume or size. Doppler echocardiography is complex to interpret, subject to many measurement errors and has failed the multi-centre clinical study test on many occasions. Regional wall motion abnormalities or thinning may indicate myocardial ischaemia or infarction but is usually unable to distinguish between acute and

chronic ventricular dysfunction. Echocardiography is very useful for diagnosing valve problems and assessing RV function (particularly using tricuspid annular plane systolic excursion or TAPSE), pulmonary artery systolic pressure, inferior vena cava dilation (indicating increased right atrial pressure), pericardial effusion and, with less confidence, constrictive pericarditis.

## 2.5 Novel technologies

### 2.5.1 Bio impedance

"From Ohm's law, when an electrical current is passed through human tissue, the voltage difference between two points on the body is proportional to impedance".[83] Blood and solid organs that are fluid-rich offer lower impedance compared to bone and aerated lung and these principles can be used to assess hydration and haemodynamics by measuring fluctuations in signals that are proportional to the stroke volume and indices of myocardial contractility and relaxation.[83]

Bio-impedance can be measured using external electrodes placed on wrists and ankles rather like a standard ECG or by electrode configurations that seek to measure thoracic impedance only. A major problem with non-invasive bio-impedance is the high impedance offered by skin. More recently, bio-impedance has been incorporated into implantable pacemakers and defibrillators which can then measure the impedance across the lung, bypassing the problem of skin impedance.

Using an implanted system, the MIDHeFT study reported that impedance monitoring could detect volume overload and predict the risk of hospitalisation with some success in a small single centre experience.[84] The larger, multi-centre FAST study,

showed that impedance monitoring was more sensitive than weight gain in predicting future heart failure events (76 vs 23%).[85] However, the DOT-HF study showed that providing patients with alerts increased the risk of hospitalisation.[86] Too many false positive alerts were observed for the technology to be viable.[53]

There are too few data on the use of non-invasive bio-impedance to evaluate its diagnostic value in the emergency setting or its usefulness for subsequent monitoring during the recovery phase. [83] However, it is a simple, low-cost technology that offers many advantages. It can be used to monitor heart rate and rhythm and respiratory rate. Studies have shown that the technology can track a reduction in lung fluid during diuresis, [87] [88] monitor changes in cardiac output ,[89] predict decompensation in outpatients,[90] and may give independent prognostic information .[91] However, there is a great range of bio impedance equipment and in some studies it has performed poorly.[92] More experience is required to understand its value. [93]

### 2.5.2 Remote Dielectric Sensing (ReDS)

This technology uses either a wearable patch or implantable device that emits low-power electromagnetic signals into the chest. [94] [95] Tissues reflect the signal according to their fluid content and this can be used to measure lung water. This might be used to predict deterioration or monitor resolution of lung oedema to identify the patient's optimal 'dry' weight and timing of discharge.

### 2.5.3 Pulse Wave Analysis (PWA)

Pulse wave reflections can affect LV afterload and coronary perfusion[96] and may be important in the genesis of heart failure and its exacerbations. PWA, using non-

invasive techniques such as applanation tonometry, may be used to assess systemic arterial stiffness and endothelial dysfunction . In the general population, abnormal arterial wave reflections predict incident cardiovascular events including the development of heart failure. [96] Sung and others recently conducted pulse wave analysis shortly after admission for AHF and observed that abnormal wave reflections on admission predicted adverse events over the following 18 months, even after adjusting for other risk factors including NT-proBNP.[97] Whether PWA can be used as a therapeutic target for existing and novel therapeutic interventions should be explored.[98]

### 2.5.4 Acoustic Cardiography (AC)

Although the third heart sound (S3) may be specific for increased left ventricular filling pressure in adults and can predict outcome, it is often clinically difficult to detect in acute settings due to ambient noise, body habitus and tachypnoea. Expertise in auscultation will also vary greatly. Modern technological innovations now make it possible to capture information about S3 at the same time as the ECG recording.[99] In the HEARD-IT trial, acoustic cardiography appeared helpful in risk stratification and diagnosis for patients with 'grey zone' plasma concentrations of BNP. Patients with a 'grey zone' BNP and an S3 by AC were more likely to have a diagnosis of AHF confirmed subsequently and were more than twice as likely to have adverse events. AC is more sensitive in detecting an S3 than clinician auscultation whatever the body habitus [100] but may not provide clinically useful prognostic information independent of other readily available clinical variables.[99]

### 2.5.5 Finger Photoplethysmography (FPP)

FPP can be used to measure the blood pressure (and heart rate) continuously, beat-to-beat. This feature alone may be useful for assessing patients with acute heart failure who are potential candidates for powerful old and new vasodilator agents that may cause profound hypotension.[80] Hypotensive episodes may not only cause distressing symptoms for the patient and an emergency situation for clinical staff, but may cause renal dysfunction and further myocardial damage that have an adverse impact on longer term morbidity and mortality. However, FPP can also provide information on pulse volume (which is a measure of stroke volume).[101] If heart rate, blood pressure and stroke volume are known, cardiac output and vascular resistance can be calculated, allowing haemodynamic therapies to be tailored to the individual patient's situation. Clinical assessment of LVEDP is not accurate in patients with AHF. [102, 103] A good correlation between pulse amplitude ratio (PAR) measured by FPP during a Valsalva manoeuvre and invasively measured left ventricular end diastolic Pressure has been reported.[101] Whether therapy guided to reduce LVEDP in patients with acute HF can reduce recurrent hospitalization is controversial.[103] [92] Further studies with new technologies are needed.

### 2.5.6 Swan-Ganz Catheter and Implantable Pressure Monitoring Devices

The Swan Ganz catheter was the classic instrument for assessing and monitoring acute heart failure in the latter part of the 20$^{th}$ Century. Many people doubted its utility. A large randomized trial demonstrated no advantage to direct measurement of pressures with treatment tailored to haemodynamic targets .[104] This may reflect the fact that haemodynamic decompensation depends not only on the absolute atrial pressure but also the rate of rise. Thus, a patient with chronic severe ventricular

dysfunction may be relatively asymptomatic with a pulmonary capillary wedge pressure of 20mmHg and a patient with new onset cardiac dysfunction may be in pulmonary oedema with a wedge pressure of 15mmHg. Invasive haemodynamic monitoring might be of value in complex cases (for instance patients who have significant lung disease or those with severe right ventricular dysfunction), or when arterial pressure is low, to ensure that the ventricular filling pressure is not reduced excessively resulting in a fall in cardiac output and the development of hypotension and shock.

More recently, chronically implantable pulmonary artery pressure monitors have been developed.[56] Preliminary evidence suggests that increases in pulmonary artery pressure predict the risk of decompensation and that treating pulmonary artery pressure reduces the risk of decompensation. Pressure monitors that screw into the atrial septum and can monitor left atrial pressure are also being developed.[105]

### 2.5.7 Coronary Angiography

In acute HF**,** current US guidelines recommend urgent cardiac catheterization followed by attempted revascularization when prolonged meaningful survival is expected in patients with known or suspected myocardial ischaemia, especially when there are clinical features of hypoperfusion.[106] Neither the safety nor efficacy of this recommendation has been established, nor is it currently practically feasible in most clinical settings where patients with acute heart failure are managed. European guidelines are less dogmatic on the issue, which may reflect the publication of two substantial randomised trials of revascularisation in patients with chronic heart failure, neither of which showed a benefit on mortality. [107, 108]

## 2.6 Conclusion

Despite limitations, clinical evaluation remains the primary tool for initial assessment and monitoring the response to therapy. A single measurement of plasma concentrations of a natriuretic peptide provides reassurance that a clinical diagnosis of AHF is correct; normal concentrations alert the clinician to rare diagnoses, such as constrictive pericarditis, or alternative diagnoses mimicking heart failure. However, natriuretic peptides are not diagnostic when used alone, nor has it been established that serial measurement of natriuretic peptides adds value to clinical monitoring.

Further studies are required to assess the practical clinical value of applying novel technologies to the management of AHF to monitor the response to treatment, discharge readiness and the risk of readmission. However, monitoring will not help patients unless it changes management. Ultimately, novel technologies need to show that they change decisions about care made by clinicians and/or patients, leading to more favourable outcomes including better symptom control, less disability and a longer life. If, as a by-product, they can also reduce the frequency or shorten the duration of hospitalisation, a surrogate measure of patient well-being and health-service costs, then so much the better.

# Chapter 3 **Methodology**

The aims of the studies in this thesis are: to describe the different clinical presentations of patients with acute heart failure; and to assess the effects of those presentations on outcomes. I have used many sources of data for the purpose, and whilst details of the design of each study and its execution will be discussed in each chapter separately, in this chapter I will describe the outlines of the general methodology of the different research studies.

## 3.1 OPERA-HF: the Rationale behind my thesis

OPERA-HF (Observational study to Predict ReAdmission for HF patients) is an ongoing observational study on patients admitted with heart failure in Hull and East Yorkshire Hospitals NHS trust. I am part of the study as a co-investigator.[109] The primary aim of the study is to design a model that can characterise patients admitted with heart failure in order to predict those at risk of early re-admission and death. Detailed demographic, clinical and psychological information is gathered during hospital admission.

As part of the study, I collected information on the clinical presentation of patients with acute heart failure. I had initially assumed that the dominant mode of presentation was with acute pulmonary oedema – that is, I expected that most patients would present with acute shortness of breath at rest. However, it rapidly became apparent to me that most patients had a far more chronic illness prior to admission than I had anticipated, and were most often comfortable at rest at presentation. Their major symptom was of oedema with breathlessness only on exertion: the majority were *not* breathless at rest.

I thus formed the hypothesis that the presenting symptoms of patients with chronic heart failure were not well understood and described; and decided to explore patients' symptoms at presentation using available datasets relating to acute heart failure admissions. Understanding the symptoms of patients at presentation has clear implications for the design of clinical trials of interventions designed for patients with acute heart failure.

## 3.2 Breathlessness in AHF: Chapter 4

The Hull and East Yorkshire Hospitals NHS trust regularly participates in the National Heart Failure Audit (NHFA) and consistently makes returns on approximately 700 admissions per year.[24] For the study described in Chapter 4, over a 24 month period between 2011-2013, I identified the first 13 patients reported to the NHFA in each month, to provide a cohort of 311 patients. I spread patient selection over a long period to avoid potential selection and seasonal bias.

Detailed clinical information data was gathered through retrospective review of case notes and electronic databases. Length of stay, in-patient mortality and deaths up to 180 days after presentation were recorded. Patients were categorized according to the severity of breathlessness based on their clinical record and respiratory rate (RR). Patients were classified as having SOBAR (Shortness of Breath at Rest) if they fulfilled all three of the following criteria: i) described in the notes as being breathless at rest, with ii) >20 breaths per minute; and iii) given intravenous therapy or opiates within 24 hours of presentation. Patients who did not fulfil all three criteria were reviewed and classified using clinical judgement as SOBAR, CARBOSE (Comfortable At Rest Breathless On Slight Exertion) or, if no

breathlessness was reported, as "Not SOB"(short of breath) .[110] More detailed methodology and results are discussed in Chapter 4.

## 3.3 Breathlessness in AHF; Chapter 5

Kings College Hospital NHS Foundation Trust and The Whittington Hospital NHS Trust are two large tertiary care hospitals in London which also participate in National Heart Failure Audit. Results of my study in Chapter 4 are validated in Chapter 5. I explored similar datasets using the same technique as in Chapter 4 with help of Dr Susan Piper, a clinical research fellow from Kings College Hospital London. Baseline clinical characteristics of patients from Hull and London are first compared and contrasted and then combined.

## 3.4 Diagnostic position and Modes of presentations of AHF; Chapter 6 & 7

The Euro Heart Failure Survey 1 (EHFS1) screened consecutive deaths and discharges during 2000-2001 primarily from medical wards in 115 hospitals from 24 countries in Europe, to identify patients with known or suspected HF. The design and implementation of the survey have been already published in detail.[111] Information was gathered from patients' case notes to identify if the patient fulfilled one or more of the following inclusion criteria:[3]

1. A diagnosis of heart failure on the index admission, irrespective of the primary reason for admission.
2. A diagnosis of heart failure recorded in the hospital records at any time during the previous three years.

3. Loop diuretics given in the 24 hours prior to death or at discharge, unless for renal failure.
4. Administration of treatment for heart failure or major ventricular dysfunction within the 24 hours prior to death or discharge. [3]

Surgical, gynaecology, ophthalmology and renal wards are excluded. Detailed information regarding events contributing to the current admission, clinical investigations, cardiovascular and comorbid illnesses and therapy at discharge or 24 hours prior to death were gathered. Mortality was measured during index hospital admission as well as death and readmission within 12 weeks of discharge.

Admissions were then classified by investigators, according to their personal opinion, as follows:-

- Heart failure as the primary diagnosis
- Heart failure as a secondary diagnosis, complicating or prolonging admission
- Heart failure as an incidental finding or diagnostically uncertain

Patients were also sorted into seven mutually exclusive classes according to modes presentation. Class 1: HF with cardiac arrest/ ventricular arrhythmia; class 2: HF & ACS; class 3: HF and AF with rapid ventricular response; class 4: HF & acute breathlessness; class 5: stable HF; class 6: presenting with other symptoms of HF such as worsening pulmonary oedema; and class 7: no HF.

Through Professor John Cleland, I got access to dataset of this survey. I analysed the data to assess the relation between diagnostic positions (primary, secondary and uncertain) and outcome (chapter 6); and the relation between different modes of presentation and outcome (chapter 7).

## 3.5 Statistical Analysis

Continuous data are presented as means (standard deviation) if normally distributed and median ($25^{th}/75^{th}$ centiles) if not normally distributed. Categorical data are presented as percentages. I used Quantile- Quantile plots (QQ plots) and normal distribution curves to assess the normality of continuous variables.[112]

Independent sample t-tests were used to compare two means if following assumptions were met

- The observations came from normal distributions
- Variances were equal

When the above assumptions did not stand I used Man Whitney or Wilcoxon Rank sign tests.

I used paired t-tests to assess two dependent group mean if distribution was normal and Wilcoxon signed rank test in not normally distributed variables.[112]

For comparing more than two means, I used one-way analysis of variances (ANOVA) if the distribution was normal and variances were uniform and Kruskal-Wallis test if these assumptions did not stand.[112]

To assess the association between categorical variables, I used Pearson's Chi-squared if at least 80% of the expected frequencies exceeded 5 and all the expected frequencies exceeded 1 and used Fisher's exact test otherwise. I used the odds ratio (OR) or hazard ratio to quantify how strongly the presence or absence of one quality was associated with the presence or absence of the other quality in given data set. I

used logistic regression analysis to assess the relationship between a categorical dependent variable and other independent variables.[112]

Prognostic models for all-cause mortality were developed using Cox regression together with k-fold cross-validation.[113] This procedure splits the data randomly into k partitions. For each partition, it fits the specified model using the other k-1 groups, and uses the resulting parameters to predict the dependent variable in the unused group. I arbitrarily choose k as 25 (hence 25-fold cross-validation). The proportionality of hazards assumption (PH) was verified for all covariates using tests based on Schoenfeld residuals.[113, 114] There was no departure from the PH assumption for any covariate. Cox metrics include the hazard ratio (HR), 95% confidence intervals (CIs) and pseudo $r^2$ (the square of the correlation coefficient of the actual and predicted values of the dependent variable). Kaplan-Meier curves constructed using the log-rank test were used to compare outcomes in groups. An arbitrary level of 5% statistical significance (two-tailed) was assumed.

The Stata statistical computer package 13 was used to analyse the data.

In the following chapters, I will describe study designs, methodologies and statistical methods used to analyse the data sets in greater detail.

# Chapter 4 **Breathlessness at Rest is Not the Dominant Presentation of Patients Admitted with Heart Failure.**

## 4.1 Introduction

Approximately 4.5% of all adult medical and surgical admissions in the UK are caused by, or complicated by, heart failure.[115] Many assume that most patients with heart failure are admitted because they are severely breathless at rest,[116] but a review of baseline data from trials of acute heart failure suggests that many patients enrolled were comfortable at rest with little increase in heart or respiratory rate to indicate cardio-respiratory distress.[8, 14, 117] Furthermore, National Audit data from England and Wales suggest that only about 30% of patients with a death or discharge diagnosis of heart failure have breathlessness at rest at the time of admission and that moderate or severe peripheral oedema was a more prevalent problem.[8, 115]

There are several possible explanations why many patients enrolled in trials or audits of acute heart failure do not appear to be acutely breathless. Clinical trials generally require patients to have received initial therapy before inclusion and patients may already have had a partial response. Surveys suggest that symptoms improve in most patients with the use of intravenous diuretics (with or without vasodilators) within 3-6 hours;[29] but the median time to recruitment in clinical trials is rarely less than 6 hours. Patients in trials are required to give consent which may exclude many sicker patients. On the other hand, audit and survey data are collected across many centres and by a range of staff that may select patients and interpret questions about symptoms differently from one another, which could lead to anomalous results.

We sought to verify or refute the findings of the National Audit for England & Wales on presenting symptoms by conducting a retrospective case-note review in a representative sample of patients admitted with a primary diagnosis of heart failure in a single centre.

## 4.2 Methods

### 4.2.1 Patients Cohort

The Hull and East Yorkshire NHS Hospital Trust is the sole provider of emergency care to residents of the city of Kingston-upon-Hull and the surrounding area (population about 550,000). Patients may refer themselves to the emergency department directly or through community services. The Trust participates in the National Heart Failure Audit (NHFA) and consistently reports about 700 admissions with heart failure per year.[115] Over a 24 month period between 2011-2013, the first 13 patients reported to the NHFA in each month were identified, to provide a cohort of approximately 300 patients. Sampling in this way reduces potential selection and seasonal bias from the data.

The clinical variables extracted from the case-note review are shown in Table 5. Plasma concentrations of N-terminal pro B-type natriuretic peptide (NT-proBNP) were requested during admission for 195 patients, generally 3-5 days after admission. Length of stay, in-patient mortality and deaths up to 180 days after presentation were recorded. Patients were categorized according to the severity of breathlessness based on their clinical record and respiratory rate. Patients who were reported to be i) breathless at rest, with ii) >20 breaths per minute and iii) given intravenous therapy or opiates soon after presentation were classified as SOBAR if they fulfilled all three criteria. Patients who did not fulfil all three criteria were

reviewed and classified using clinical judgement as SOBAR, CARBOSE or, if no breathlessness was reported, as "Not SOB" (short of breath).[110, 118]

### 4.2.2 Statistical Analysis

Continuous data are summarized by the median ($25^{th}$/$75^{th}$ centiles); categorical data by percentages. Prognostic models for all-cause mortality were developed using Cox regression. The proportionality of hazards assumption (PH) was verified for all covariates using tests based on Schoenfeld residuals. [113, 114] There was no departure from the PH assumption for any covariate. Cox metrics include the hazard ratio (HR), 95% confidence intervals (CIs) and pseudo $r^2$ (the square of the correlation coefficient of the actual and predicted values of the dependent variable).

## 4.3 Results

Of 311 patients, 42% were classified as SOBAR and 56% as CARBOSE (Figure 4).

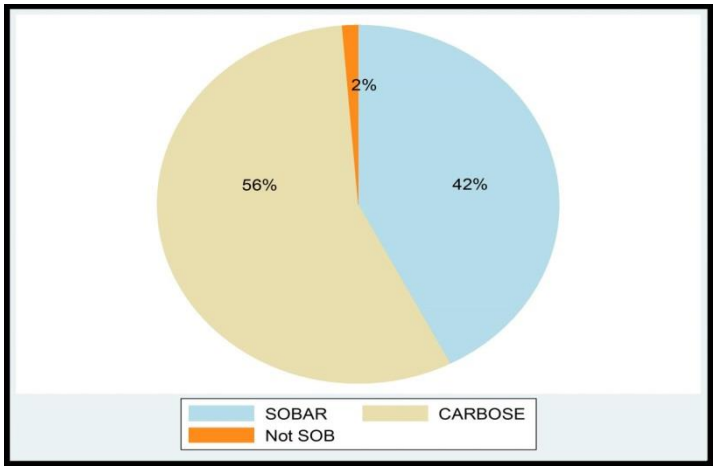



**Figure 4 Pie Chart of proportion of patients presenting with SOBAR, CARBOSE or who were not short of breath (SOB) – n=311**

**Table 5 Clinical Characteristics at Presentation**

| *Table 5* | *Missing Data* | *Overall (n=307)* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* |
|---|---|---|---|---|---|
| Age | 0 | 77 (IQR 71-84) | 76 (IQR 71-83) | 78 (IQR 69 – 84) | 0.9 |
| Women | 0 | 107 (34%) | 55 (46%) | 51 (29%) | 0.03 |
| Prior IHD | 0 | 169 (54%) | 73 (55%) | 94 (54%) | 0.81 |
| Prior CVA/TIA | 0 | 31 (10%) | 12 (9%) | 19 (11%) | 0.7 |
| Prior DM | 0 | 105(34%) | 52 (39%) | 52 (30%) | 0.08 |
| Prior COPD/Asthma | 0 | 74 (24%) | 38 (29%) | 35 (20%) | 0.08 |
| Prior CKD (eGFR <60) | 0 | 180 (58%) | 73 (55%) | 104 (59%) | 0.48 |
| Prior Hypertension | 0 | 176 (57%) | 78 (59 %) | 95 (54%) | 0.41 |
| Prior AF | 2 | 138 (45%) | 67 (51%) | 71 (41%) | 0.08 |
| AF (Presentation ECG) | 4 | 156 (51%) | 71 (54%) | 85 (49%) | 0.34 |
| Prior HF | 4 | 227 (75%) | 87 (67%) | 140 (81%) | 0.005 |
| Weight at admission (Kg) | 46 | 80 (69-92) | 80 (68-94) | 80 (70-91) | 0.40 |
| Paired mean weight loss (Kg) during admission | | 4.1 P-Value <0.001 | 4.1 P-Value <0.001 | 4.1 P- Value <0.001 | |
| QRS Duration | 22 | 108 (92-138) | 104 (90-130) | 111 (96-140) | 0.03 |
| Heart Rate (HR) | 1 | 89 (IQR 74-108) | 100 (IQR 78-120) | 85 (IQR 72-100) | <0.001 |
| Heart Rate if in SR | 0 | 85 (IQR 75-105) | 101 (IQR 80-120) | 82 (IQR 71-90) | <0.001 |
| Heart Rate if in AF | 1 | 91 (IQR 74-110) | 98 (IQR 76-120) | 88 (IQR 72-100) | 0.02 |
| Systolic BP (SBP) | 0 | 132 (IQR110-150) | 141 (IQR120-160) | 122 (IQR 108-141) | <0.001 |

*Table 5*

| | *Missing Data* | *Overall (n=307)* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* |
|---|---|---|---|---|---|
| Systolic BP >125mmHg | 0 | 179 (58%) | 96 (73%) | 80 (46%) | <0.001 |
| Respiratory Rate | 2 | 20 (IQR 18-24) | 24 (IQR 22-29) | 18 (IQR 17-20) | <0.001 |
| Moderate-Severe oedema | 1 | 141 (46%) | 56 (42%) | 84 (48%) | 0.44 |
| Mild oedema | 1 | 79 (26%) | 40 (30%) | 39 (25%) | 0.35 |
| Oxygen Saturation | 7 | 97% (IQR 94-99 %) | 95% (IQR 93-98%) | 97% (IQR 95-98%) | 0.008 |
| Echocardiogram | 22 | | | | |
| Moderate-Severe LVSD | | 195 (68%) | 79 (66%) | 116 (70%) | 0.44 |
| No / Mild LVSD | | 90 (32%) | 41 (34%) | 49 (30%) | 0.42 |
| Left Atrium dilatation | 119 | 128 (67%) | 63 (77%) | 65 (61%) | 0.03 |
| Pulmonary Congestion (X-Ray) | 16 | 140 (49%) | 75 (61%) | 65 (41%) | 0.001 |
| Severe Valve Disease | 124 | 72 (39%) | 31 (39%) | 41 (39%) | 1 |
| Haemoglobin (g/dl) | 1 | 12.3 (IQR 11-13.8) | 12.4 (IQR 10.95 – 13.8) | 12.3 (IQR 11 -13.6) | 0.85 |
| WBC ($x10^9$/L) | 79 | 9.1 (IQR 6.8-11.9) | 10.0 (IQR 7.4-13.1) | 8.4 (IQR 6.6 -10.7) | 0.003 |
| hsCRP (mg/L) | 64 | 16 (IQR 5.8-46) | 17.5 (IQR 7.1-51.0) | 15.0 (IQR 4.8-43.0) | 0.24 |
| Sodium (mmol/L) | 0 | 138 (IQR 135-140) | 138 (IQR 134 - 140) | 137 (IQR 135-140) | 0.92 |
| Potassium (mmol/L) | 10 | 4.4 (4.0 -4.8) | 4.4 (3.9 -4.9) | 4.4 (4.0-4.8) | 0.90 |
| Urea (mmol/l) | 1 | 8 (5.7 -13.1) | 8 (5.6 -11.5) | 9 (5.8 -14.6) | 0.13 |
| Creatinine (µmol/L) | 0 | 111 (85-152) | 109 (83 -143) | 117 (86 -161) | 0.87 |
| eGFR (ml/min/1.73$m^2$) | 0 | 53 (37 -73) | 55 (39 – 74) | 52 (37-72) | 0.41 |

*Table 5*

| | *Missing Data* | *Overall (n=307)* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* |
|---|---|---|---|---|---|
| hsTnT (ng/L) | 168 | 79 (35 -497) | 100 (46-497) | 74 (24-341) | 0.13 |
| NT-proBNP (pg/ml) | 112 | 4082 (1895-10279) | 4076 (2320-9244) | 4160 (1483-11229) | 0.99 |

IHD,Ischaemic Heart disease; CVA, Cerebrovascular accident; TIA, Transient Ischaemic attack; DM, Diabetes Mellitus; COPD, Chronic Obstructive Pulmonary Disease; eGFR, Estimated glomerular filtration rate; SBP, Systolic Blood Pressure; HR, Heart Rate; RR, Respiratory Rate; LVSD, Left Ventricle Systolic dysfunction; WBC, White Blood count; hsCRP, high sensitivity C-Reactive protein; hsTnT, High sensitivity Troponin T. KG, Kilo gram.

Only four patients were classified as not SOB and are not considered in subsequent analyses. For the remaining 307 patients, the median age was 77 years [interquartile range (IQR 71-84)]. Just over half had a prior diagnosis of ischaemic heart disease (54%) and most patients had one or more co-morbid condition (chronic kidney disease (58%), atrial fibrillation (45%), hypertension (57%), and diabetes (34%)). Patients in the two groups were of similar age but patients with SOBAR were more often women (46% versus 29%). Aetiology, comorbidity, the proportion with left ventricular systolic dysfunction (LVSD), and plasma concentrations of both NT-proBNP and high-sensitivity cardiac troponin T (hsTnT) were similar between the groups (Table 5).

Prior to decompensation, there were slightly more patients on ACEI/ARB (angiotensin converting enzyme inhibitor/ angiotensin receptor blockers) (61% v 56%) but fewer on beta adrenergic receptor blockers (44% v 53%), MRA (mineralocorticoid receptor antagonist) (15% v 22%) or loop diuretics (52% v 60%) in those with SOBAR as compared to CARBOSE, whereas in each group 20% of patients were on digoxin. Patients with SOBAR were treated more aggressively

during hospital admission, with a higher proportion receiving oxygen therapy, ventilatory support and intravenous therapy (Table6)

Patients with SOBAR had a higher systolic blood pressure (BP) at presentation, which declined substantially over the first 24 hours of admission as did diastolic BP, heart rate and respiratory rate. In contrast, patients who were CARBOSE had clinically non-significant (though statistically significant) change in systolic or diastolic BP, heart rate or respiratory rate in the first 24 hours. (Figure 5, **Figure 6** & **Figure 7**).

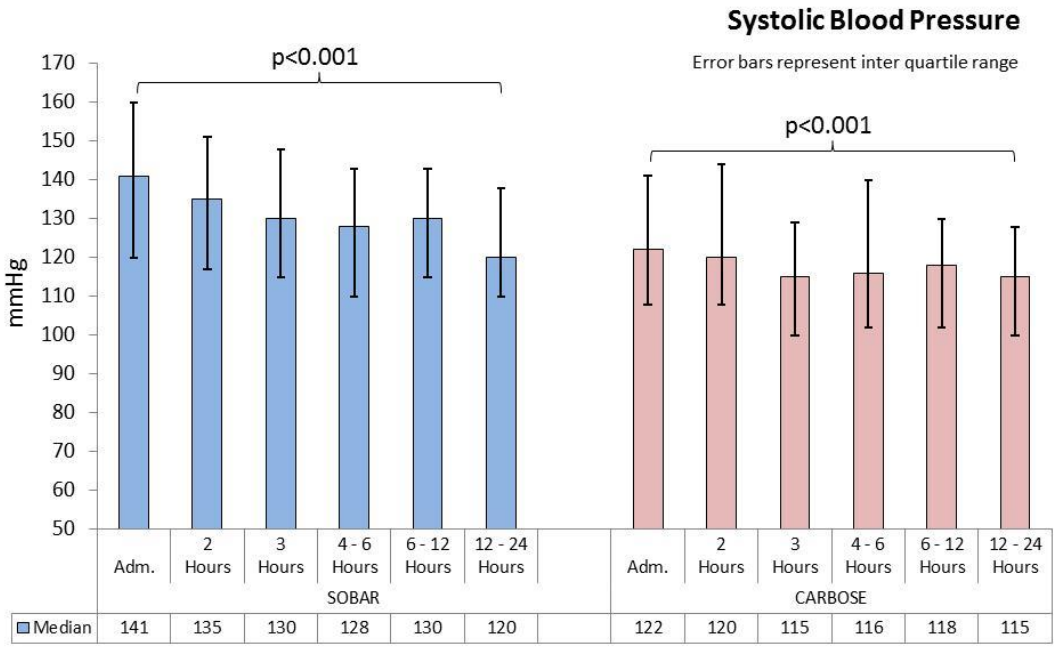



**Figure 5 Changes in systolic blood pressure over the first 24 hours after presentation**

**Table 6 : Therapy prior to decompensation and during index admission**

| Table 6 | | | | | |
|---|---|---|---|---|---|
| Therapy | Missing Data | Overall (n=307) | SOBAR (n=132) | CARBOSE (n=175) | SOBAR vs CARBOSE P-Value |
| Prior to Decompensation | 6 | | | | |
| ACEi | | 131 (43%) | 62 (48%) | 69 (40%) | 0.20 |
| ARB | | 44 (14%) | 17 (13%) | 27 (16%) | 0.62 |
| ACEi or ARB | | 175 (57%) | 79 (61%) | 96 (56%) | 0.42 |
| BB | | 147 (49%) | 57 (44%) | 90 (53%) | 0.12 |
| MRA | | 58 (19%) | 20 (15%) | 38 (22%) | 0.18 |
| Loop Diuretic | | 172 (56%) | 68 (52%) | 104 (60%) | 0.14 |
| Thiazide Diuretic | | 14 (5%) | 8 (6%) | 6 (3%) | 0.40 |
| Nitrates | | 48 (16%) | 19 (15%) | 29 (17%) | 0.75 |
| CCB | | 36 (12%) | 19 (15%) | 17 (10%) | 0.21 |
| Digoxin | | 56 (20%) | 24 (20%) | 32 (20%) | 1 |
| During admission | 5 | | | | |
| Oxygen at presentation | | 78 (26%) | 48 (37%) | 30 (17%) | <0.001 |
| IV Diuretic in First 24 Hours | | 187 (61%) | 116 (88%) | 71 (41%) | <0.001 |
| IV Nitrate | | 31 (10%) | 19 (15%) | 12 (7%) | 0.03 |
| IV Opiate | | 28 (9%) | 19 (14%) | 9 (5%) | 0.008 |
| IV Inotropic Agent | | 8 (3%) | 4 (3%) | 4 (2%) | 0.73 |
| C-PAP | | 9 (3%) | 8 (6%) | 1 (<1%) | 0.006 |
| Intubation & Ventilation | | 5 (2%) | 5 (4%) | 0 (0%) | 0.01 |

| Table 6 | | | | | |
|---|---|---|---|---|---|
| Therapy | Missing Data | Overall (n=307) | SOBAR (n=132) | CARBOSE (n=175) | SOBAR vs CARBOSE P-Value |
| At Discharge (survivors; n= 276) | 0 | | | | |
| ACEi | | 197 (71%) | 83 (69%) | 114 (73%) | 0.46 |
| ARB | | 29 (10%) | 11 (9%) | 18 (11%) | 0.52 |
| ACEi or ARB | | 226 (81) | 94 (78%) | 132 (84%) | 0.17 |
| BB | | 219 (79%) | 90 (74%) | 129 (83%) | 0.09 |
| MRA | | 142 (51%) | 56 (46%) | 86 (55%) | 0.16 |
| Loop Diuretic | | 239 (86%) | 103 (85%) | 136 (87%) | 0.72 |
| Thiazide diuretic | | 23 (8%) | 8 (7%) | 15 (10%) | 0.15 |
| Nitrates | | 42 (15%) | 20 (17%) | 22 (14%) | 0.56 |
| CCB | | 18 (6%) | 9 (7%) | 9 (6%) | 0.57 |
| Digoxin | | 80 (29%) | 40 (33%) | 40 (26%) | 0.21 |

ACEi, Angiotensin converting enzyme inhibitor; ARB, Angiotensin Receptor Blocker; BB, Beta adrenergic receptor Blocker; MRA, Mineralocorticoid Receptor antagonist; CCB, Calcium Channel blocker; C-PAP, Continuous positive airway pressure.

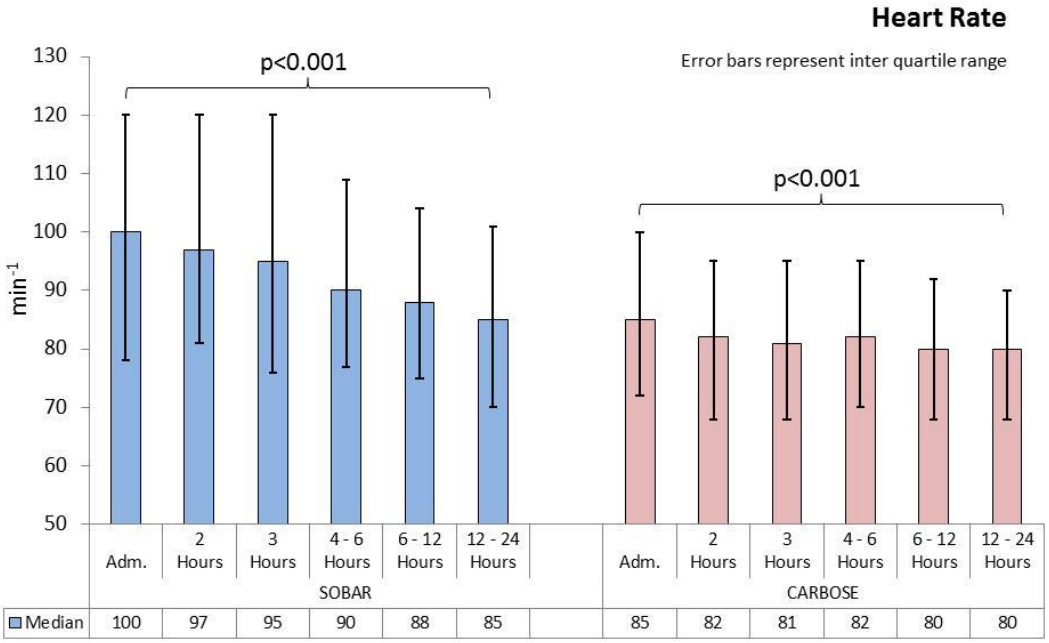



**Figure 6 : Changes in heart rate in first 24 hours**

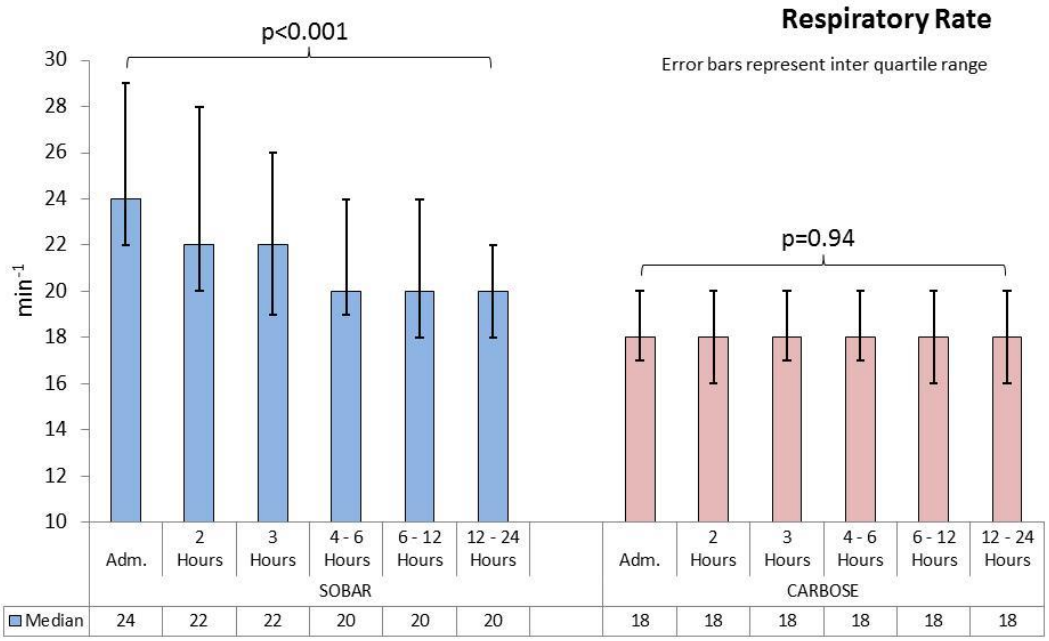



**Figure 7 : Changes in respiratory rate in first 24 hours**

The RELAXin in Acute Heart Failure clinical trial (RELAX-AHF) entry criterion of a systolic BP >125mmHg was met by 73% of patients at presentation, 58% within one hour of presentation, but only 44% at 4-6 hour and 34% at 12-24 hours.[46, 80] However, the proportion was much higher in those with SOBAR compared with CARBOSE (73% vs 46% at presentation, 63% v 30% at 4-6 hours and 44% v 26% at 12-24 hours)(Table 7). Peripheral oedema was reported slightly more often in patients with CARBOSE than SOBAR.

Although the in-hospital mortality tended to be higher in patients who were CARBOSE (11%) than those who were SOBAR (8%) with an odds ratio (OR) of 1.41, the difference was not statistically significant (p=0.38, CI 0.66-3.08). During the first 3 months after presentation, 26% of those who were CARBOSE died compared to 13% who were SOBAR, with an OR of 2.34 (CI 1.27-4.31; P=0.006). At 6 months, 34% of those who were CARBOSE had died compared to 19% who were SOBAR (OR 2.29;CI 1.29-4.06; P=0.005). At the final censorship date, August 2013, 47% of those who were CARBOSE and 31% who were SOBAR had died (**Figure 8**: hazard ratio 1.58; CI 1.09-2.29; P=0.016). Mortality was higher amongst patients with peripheral oedema at presentation (Table 8).

**Table 7 : Changes in vital signs in first 24 hours**

| Table 7 | Admission | 2 Hours | 3 Hours | 4-6 Hours | 6-12 Hour | 12-24 Hour |
|---|---|---|---|---|---|---|
| Oxygen Therapy (%) | 79 (26%) | 58 (31%) | 94 (42%) | 102 (38%) | 110 (38%) | 101 (34%) |
| SOBAR | 48 (37%) | 41 (46%) | 65 (62%) | 64 (52%) | 68 (54%) | 58 (45%) |
| CARBOSE | 30 (17%) | 17 (18%) | 28 (24%) | 37 (25%) | 40 (25%) | 41 (24%) |
| $O_2$ Sat if not on $O_2$ therapy (%), median (IQR) | 97 (95-98) | 96 (95-98) | 96 (95-97) | 96 (95-98) | 96 (94-98) | 96 (95-98) |
| SOBAR | 95 (92-97) | 96 (94-98) | 96 (95-97%) | 96 (94-97) | 96 (94-98) | 96 (94-97) |
| CARBOSE | 97 (95-98) | 96 (95-98) | 96 (95-98) | 96 (95-98) | 96 (95-98) | 96 (95-98) |
| Systolic BP (mmHg), median (IQR) | 132 (110-150) | 130 (110-148) | 121 (105-140) | 120 (105-140) | 121 (105-138) | 118 (103-131) |
| SOBAR | 141 (120-160) | 135 (117-151) | 130 (115-148) | 128 (110-143) | 130 (115-143) | 120 (110-138) |
| CARBOSE | 122 (108-141) | 120 (108-144) | 115 (100-129) | 116 (102-140) | 118 (102-130) | 115 (100-128) |
| Diastolic BP (mmHg), median (IQR) | 77 (63-91) | 75 (62-88) | 70 (60-85) | 70 (60-82) | 70 (60-80) | 69 (60-80) |
| SOBAR | 82 (68-99) | 78 (66-90) | 74 (65-90) | 70 (60-84) | 70 (60-80) | 69 (60-80) |
| CARBOSE | 74 (62-85) | 71 (61-83) | 69 (60-78) | 70 (60-80) | 68 (60-76) | 68 (60-75) |
| HR ($min^{-1}$), median (IQR) | 89 (74-108) | 87 (70-109) | 86 (71-105) | 86 (73-100) | 83 (70-96) | 82 (68-95) |
| SOBAR | 100 (78-120) | 97 (81-120) | 95 (76-120) | 90 (77-109) | 88 (75-104) | 85 (70-101) |
| CARBOSE | 85 (72-100) | 82 (68-95) | 81 (68-95) | 82 (70-95) | 80 (68-92) | 80 (68-90) |
| RR ($min^{-1}$), median (IQR) | 20 (18-24) | 20 (18-22) | 20 (18-23) | 20 (17-22) | 19 (17-22) | 18 (17-20) |
| SOBAR | 24 (22-29) | 22 (20-28) | 22 (19-26) | 20 (19-24) | 20 (18-24) | 20 (18-22) |
| CARBOSE | 18 (17-20) | 18 (16-20) | 18 (17-20) | 18 (17-20) | 18 (16-20) | 18 (16-20) |
| Systolic BP >125 mmHg, % | 58% | 54% | 46% | 44% | 43% | 34% |
| SOBAR | 73% | 64% | 63% | 52% | 57% | 44% |
| CARBOSE | 46% | 44% | 30% | 37% | 33% | 26% |

BP, Blood Pressure; IQR, Inter quartile range; HR, Heart Rate; RR, Respiratory Rate

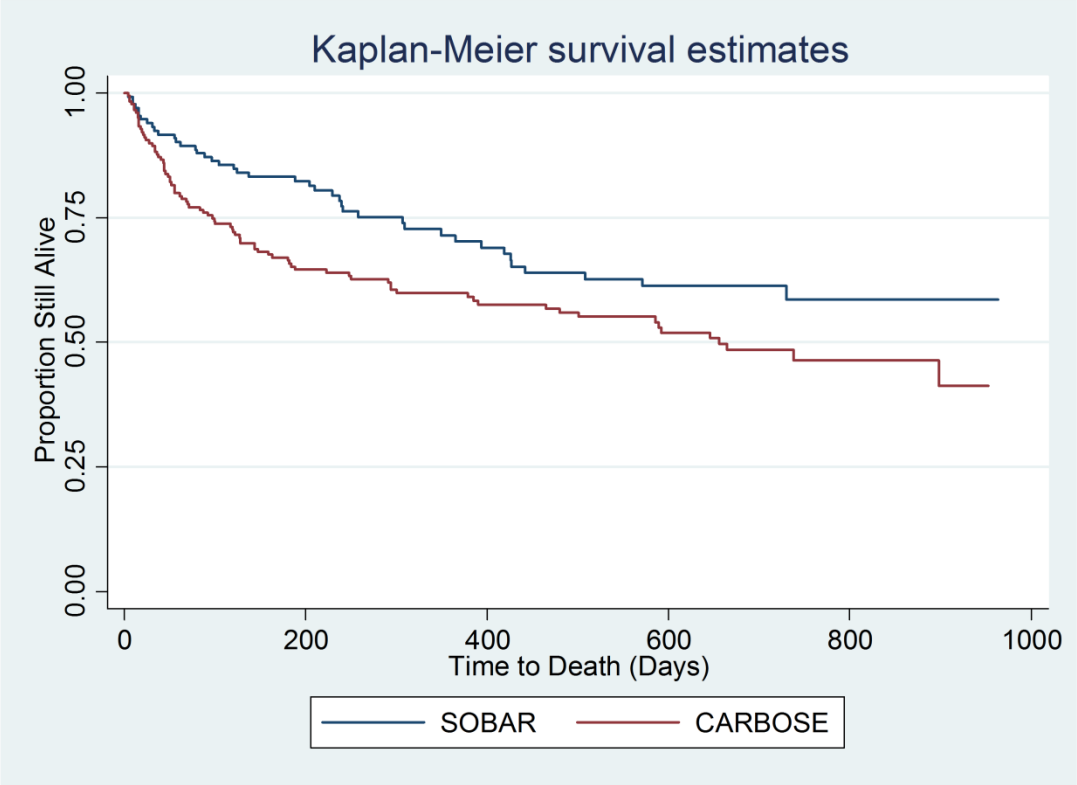



**Figure 8 : Survival Comparison of SOBAR & CARBOSE**

Kaplan Meir Survival Estimates: Hazard Ratio 1.58 (P-value 0.016, CI 1.09-2.29) Log Rank test p-value 0.0152.

Using 25-way cross-validation, CARBOSE was associated with a higher all-cause mortality compared with SOBAR in all 25 Cox-regression models when adjusted for age and sex, with a hazard ratio ranging from 1.5 to 1.9. When the covariates were extended to include SBP, RR, creatinine, HR, and severity of LVSD, CARBOSE was again significant in all of the models, with a hazard ratio ranging from 2.0 to 2.6.

**Table 8 : Duration of Hospital Stay and Mortality**

| Table 8 | *Missing Data* | *Overall (n=307)* | *SOBAR (n=132)* | *CARBOSE (n=175)* |
|---|---|---|---|---|
| Length of stay, median days (IQR) | 0 | 11 (6-18) | 11 (7-17) | 11 (6-18) |
| Deaths in Hospital, n (%) | 0 | 31 (10%) | 11 (8%) | 20 (11%) |
| Length of stay for survivors of index admission, median days (IQR) | 0 | 11 (6-17) | 11 (7-17) | 11 (5-18) |
| Length of Stay for deaths during index admission, median days (IQR) | 0 | 16 (11-33) | 16 (9-33) | 15 (10-23) |
| Deaths 30 days after presentation, n (%) | 0 | 26 (8%) | 8 (6%) | 18 (10%) |
| Deaths 90 days after presentation, n (%) | 0 | 63 (20%) | 17 (13%) | 45 (26%) |
| Deaths 180 days after presentation, n (%) | 0 | 78 (28%) | 21 (19%) | 56 (34%) |
| All deaths up to August 2013, n (%) | 0 | 124 (40%) | 42 (31%) | 82 (47%) |
| Deaths in absence of peripheral oedema at presentation | 1 | 27 of 87 (31%) | 10 of 36 (28%) | 17 of 51 (33%) |
| Deaths in presence of peripheral oedema at presentation | 1 | 97 of 220 (44%) | 32 of 96 (33%) | 65of 123 (52%) |

IQR; Interquartile range

Of the covariates, lower SBP (appearing in all 25 models), higher RR (appearing in 20 models), older age (appearing in all 25) and higher creatinine (only 1 model) were associated with greater all-cause mortality. Sex, HR and LVSD did not appear in any of the cross-validation models. When log[NT-proBNP], measured in the post-acute phase, was added as a covariate, only older age and higher NT-proBNP predicted outcome and did so in every cross-validation model. No other variable appeared in any cross-validation model. However, due to the limited availability of routine natriuretic peptide testing in patients recruited early in the study, a measurement was only available in 63% of patients, which reduced the cohort size for the model.

## 4.4 Discussion

I found that in patients hospitalized with a primary diagnosis of heart failure, slightly fewer than half of patients were breathless at rest. These results are similar to those reported, but not highlighted, by others. The IMPACT-HF registry reported that only 47% of patients with decompensated heart failure presented with dyspnoea at rest.[117] The first EuroHeart Failure survey reported that only 40% of 11,701 patients with suspected or confirmed HF reported severe breathlessness.[3] The National Heart Failure Audit for England & Wales data also reported that only one third of patients with a primary death or discharge diagnosis of heart failure presented with breathlessness at rest.[115] In the USA, the OPTIMIZE-HF registry reported that only 44% of patients hospitalized with heart failure patients had dyspnoea at rest.[26, 119] However, none of these studies was conducted, analysed or interpreted with a primary focus on the severity of breathlessness.

The severity of breathlessness is of fundamental importance in patient management. Patients who are breathless at rest need urgent symptomatic treatment and close

observation, usually in hospital. For patients with less severe symptoms, especially if it is peripheral oedema, admission to hospital may be a matter of medical convenience rather than necessity. For some patients with less severe symptoms, intermediate levels of care, which might include a day-care facility or rapid access to specialist services in the community or out-patient clinic, may be preferable.

Patients with SOBAR had a higher heart rate and blood pressure at presentation consistent with greater activation of the sympathetic nervous system. Higher respiratory rate and lower oxygen saturation are consistent with greater respiratory stress. Higher white cell count might also be a sign of greater stress rather than infection; however, plasma concentrations of high sensitivity C-reactive protein were similar between groups.

The signs of cardiovascular stress settled more rapidly in patients with SOBAR, perhaps due to greater medical sensitivity to (and intense therapy for) their symptoms.[120] This is problematic for clinical trials of acute heart failure which generally recruit patients with more than a 6 hour delay after presentation to hospital.[46, 80] Researchers may not be alerted to a patient's admission for several hours, time is required to obtain consent and to get the results of tests required to confirm eligibility. Administrative delays may be incurred by the randomisation process and preparing the investigational treatment. Many protocols require patients to have received intravenous diuretics some hours before randomisation, which cause symptoms to abate. Compassionate clinicians, or those who wish to avoid the extra work incurred, may avoid recruiting sicker patients. This makes clinical trials in patients with SOBAR extremely difficult. Very early intervention will enrol patients who are very likely to respond rapidly to conventional therapy, leading to a

neutral outcome. Substantial delay will mean that a mixture of patients including those recalcitrant to treatment , who may respond poorly to many therapies, those who have received insufficient initial treatment and those whose symptoms are on the verge of resolution, are enrolled, again leading to a neutral outcome. A finding that appears surprising at first sight was that patients presenting with CARBOSE had a worse prognosis than those with SOBAR. Why might that be? Patients who are CARBOSE may have more peripheral congestion reflecting more severe right ventricular (RV) dysfunction, which is an important determinant of prognosis.[121] Statistical modelling suggested that the worse prognosis amongst patients with CARBOSE could be accounted for by differences in plasma concentrations of NT-proBNP, a marker reflecting the severity of congestion. Indeed, the presence of peripheral oedema indicated a worse prognosis regardless of the severity of breathlessness. Peripheral oedema was also an in useful predictor of higher mortality in the National Heart Failure Audit although not in landmark clinical trials.[24] This observation needs to be confirmed in other data-sets. Patients who were CARBOSE also had a lower systolic blood pressure, which has consistently been associated with a poor prognosis in studies of heart failure.[122, 123]

Although patients with peripheral oedema may look less unwell than those with acute breathlessness, they have a higher mortality, suggesting that more attention should be paid to their management. A prior history of heart failure was more common in the CARBOSE than the SOBAR group (Table 5), suggesting that many patients in this group have long standing heart failure and may now have late-stage disease

The RELAX-HF study reported that use of serelaxin might improve prognosis of patients hospitalized with worsening heart failure and breathlessness at rest or slight exertion despite initial treatment with intravenous diuretics provided they had a systolic blood pressure >125mmHg. The median time from presentation to randomization was 8 hours.[46] Whilst I found that 73% of patients with SOBAR met the trial's blood pressure entry criterion at presentation, only 46% of those with CARBOSE would have met this criterion. The proportion of patients meeting the blood pressure entry criterion fell rapidly after admission, presumably in response to haemodynamically active treatment and lower sympathetic drive as symptoms and anxiety decreased.

There are many reasons why trials of new therapies in acute heart failure might fail, but lack of involvement of emergency department (ED) staff may be a common factor. This may reflect the view that an ED is not a suitable place to start investigational therapy for patients with acute heart failure. Historically, ED physicians have a track record of recruiting patients in complex conditions such as ACS (acute coronary syndrome), acute ischaemic stroke and major trauma. Close collaboration of ED physicians and cardiologists may be helpful in identifying appropriate patients. The partnership needs to start at a local level and spread to national and international trial design.[11]

## 4.5 Limitations

The study was conducted in a single centre with a modest number of patients. I collected data retrospectively from the review of case notes of patients assigned a primary diagnosis of heart failure by the hospital coding department. This might cause some selection bias but the same bias would also then apply to the National

Audit for England & Wales. I divided patients into two groups but in reality there will be a spectrum extending from patients with extreme breathlessness and impending respiratory failure through to patients whose major functional limitation and breathlessness is due to the severity and sheer weight of peripheral oedema. Many patients with CARBOSE did not have marked peripheral oedema and may well have been a heterogeneous group, some with milder degrees of heart failure that neither caused breathlessness at rest nor peripheral oedema and others with severe congestion. This may explain why NT-proBNP eliminated CARBOSE from the prognostic model. This also suggests that there may be a very high risk subgroup amongst those with CARBOSE. Further exploration of the natural history and outcome of these extreme cases is required.

Models including NTproBNP may have been over fitted due to the smaller number of patients included. Concato and colleagues suggest a minimum of 10 events for every candidate predictive variable.[124] Models including NTproBNP had only 7-8 events per variable. My results should be verified in other data-sets. Natriuretic peptides measured at admission may add little prognostic information to standard variables but other analysis suggest that they may provide powerful prognostic information when measured later in the hospital course,[125, 126] as in the current report.

## 4.6 Conclusion

Most patients admitted with a primary diagnosis of heart failure are not breathless at rest but do have breathlessness on slight exertion. Patients with SOBAR often respond quickly to treatment with rapid improvement in symptoms and signs. It is possible that control of acute breathlessness is a need that is generally met by existing conventional therapy. New agents targeting breathlessness either need to be

initiated very early with the intent of accelerating resolution or later, when patients who are recalcitrant to conventional therapy become obvious, or very late, targeting exertional breathlessness in the peri-discharge period. Muddling these targets is problematic and may have contributed to the neutrality of many trials of acute heart failure. However, contrary to the assumptions of many physicians, patients who present with less severe symptoms appear to have a worse prognosis, perhaps reflecting more severe right ventricular dysfunction, as evidenced by peripheral congestion. The timing and approach to treatment of peripheral congestion may be different from acute breathlessness.

# Chapter 5 **Breathlessness at Rest is Not the Dominant Presentation of Patients Admitted with Heart Failure-Validation with London data**

## 5.1 Introduction

Acute heart failure (AHF) is an unstable and heterogeneous condition and a primary or contributory reason for 3.5 million NHS bed-days annually in the UK.[115] It is generally believed that majority of patients admitted with AHF have severe shortness of breath at rest but some baseline data from large registries and surveys suggests that many patients were comfortable at rest with some signs of cardio-respiratory distress and I have already confirmed it in my dataset in chapter 4.[3, 14, 16, 115, 117]

In clinical practice, treatment for acute breathlessness is usually implemented within minutes of presentation but in clinical trials, there is usually a delay of 6-12 hours before the research intervention due to study related administrative procedures. Changes in heart rhythm & blood pressure (BP) may precipitate AHF. The distress of AHF causes an increase in heart (HR) and respiratory rate (RR) and an increase in systemic vascular resistance (SVR) that may lead to a rise in BP. Treatment directly or indirectly will improve each of these problems.

The primary aim of this study is to show how patients hospitalised with heart failure present in terms of severity of breathlessness and their initial course in terms of blood pressure, heart rate and respiratory rate during first 24 hours after hospital admission by conducting a multi-centre, retrospective case-note review.

## 5.2 Methods

### 5.2.1 Patient Cohort

The Hull and East Yorkshire Hospitals NHS trust, Kings College Hospital NHS foundation trust London and The Whittington Hospital NHS trusts London are three large tertiary care hospitals in the UK that provide emergency care to approximately 500,000 people. All three trusts participate in the England and Wales National Heart Failure Audit (NHFA). Over a 36 months period between 2010-13, the first 20 patients reported to the NHFA in each month were identified, providing a cohort of approximately 701 patients (311 from Hull and 390 from London). Patient sampling in this manner was done to remove possible selection and seasonal bias in the data. The clinical variables extracted from the case-note reviews are shown in Table 9 and Table 10. Plasma concentrations of N-terminal pro B-type natriuretic peptide (NT-proBNP) were requested during admission for 195 patients, generally 3-5 days after admission. However pro-BNP data was only available from Hull, as Natriuretic peptides are not routinely checked in London for AHF admissions. Data collection was carried out by me (AS) in Hull and the Dr Sue Piper (SP) in London. Patients were categorized according to the severity of breathlessness based on their clinical record and respiratory rate (RR). Patients who were reported to be i) breathless at rest, with ii) >20 breaths per minute and iii) given intravenous therapy (IV) or opiates soon after presentation were classified as SOBAR (Shortness of Breath At Rest) if they fulfilled all three criteria. Patients who did not fulfil all three of these criteria were reviewed and classified using clinical judgement as SOBAR, CARBOSE (Comfortable at Rest Breathless on Slight Exertion) or, if no breathlessness was reported, as ”Not SOB”(short of breath).

Patients' clinical characteristics and a detailed comparison of presentations and survival analysis from Hull is already reported in chapter 4 and published elsewhere.[127] Here, we sought to validate our results first by comparing and contrasting the baseline clinical characteristics from both sites (Table 9 &Table 11 ) and then by combining all patients' data with a relatively larger sample (Table 10 & Table 12). Similar statistical methods and techniques were applied as described in chapter 4

## 5.3 Results

Of all the 701 patients, 315 (45%) were classified as SOBAR, 382 (54%) as CARBOSE. Four patients were classified as 'not SOB', and were not considered in subsequent analysis. In the remaining 697 patients, 307 patients' data was collected from Hull and 390 from London. Patients from Hull were older (77 v 74 years), there were more men (64% v 59%), had they a higher prevalence of prior Ischaemic heart disease (IHD) (54% v 39%), Chronic kidney disease (CKD) (58% v 48%) and Atrial fibrillation (AF) (45% v 37%) as compared to patients in London (Table 9).

However, patients in London had more moderate to severe peripheral oedema at presentation (85% v 46%), lost more weight during index admission (5.2 v 4.1 Kg) and more received intravenous (IV) diuretics (71% v 61%) during first 24 hours of presentation compared to Hull ( Table 9& Table 11). The rest of the base line clinical characteristics are quite similar among patients belonging to both sites (Table 9 & Table 11). In the remaining 697 patients who were considered for final analysis, the median age was 76 years, just over half had a prior history of hypertension (57%), CKD (52%) and two thirds had moderate to severe peripheral oedema (67%) (Table 10).

**Table 9 : Comparison of Base line Clinical characteristics of two sites**

| Table 9 | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| Age (IQR) | 0 | 77 ( 71-84) | 76 ( 71-83) | 78 ( 69 – 84) | 0.9 | 0 | 74 (62-82) | 74 (64-83) | 73 (59-81) | 0.2 | <0.001 |
| Women | 0 | 107 (34%) | 55 (46%) | 51 (29%) | 0.03 | 0 | 159 (41%) | 82 (45%) | 77 (37%) | 0.08 | 0.09 |
| Prior IHD | 0 | 169 (54%) | 73 (55%) | 94 (54%) | 0.81 | 0 | 153 (39%) | 79 (43%) | 74 (36%) | 0.13 | <0.001 |
| Prior CVA/TIA | 0 | 31 (10%) | 12 (9%) | 19 (11%) | 0.7 | 0 | 38 (10%) | 8 (9%) | 11 (10%) | 0.51 | 0.8 |
| Prior DM | 0 | 105(34%) | 52 (39%) | 52 (30%) | 0.08 | 1 | 123 (32%) | 63 (35%) | 60 (29%) | 0.14 | 0.53 |
| Prior COPD/Asthma | 0 | 74 (24%) | 38 (29%) | 35 (20%) | 0.08 | 0 | 99 (25%) | 49 (27%) | 50 (24%) | 0.55 | 0.63 |

| Table 9 | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| Prior CKD (eGFR <60) | 0 | 180 (58%) | 73 (55%) | 104 (59%) | 0.48 | 0 | 187 (48%) | 83 (45%) | 104 (50%) | 0.34 | 0.01 |
| Prior Hypertension | 0 | 176 (57%) | 78 (59 %) | 95 (54%) | 0.41 | 1 | 227 (58%) | 103 (57%) | 124 (60%) | 0.50 | 0.64 |
| Prior AF | 2 | 138 (45%) | 67 (51%) | 71 (41%) | 0.08 | 0 | 144 (37%) | 68 (37%) | 76 (37%) | 0.93 | 0.03 |
| AF at presentation | 4 | 156 (51%) | 71 (54%) | 85 (49%) | 0.34 | 1 | 164 (42%) | 81 (44%) | 83 (40%) | 0.43 | <0.001 |
| QRS Duration (IQR) | 22 | 108 (92-138) | 104 (90-130) | 111 (96-140) | 0.03 | 0 | 110 (91-138) | 108 (90-138) | 111 (92-142) | 0.91 | 0.77 |

| Table 9 | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| Prior HF | 4 | 227 (75%) | 87 (67%) | 140 (81%) | 0.005 | 390 | - | - | - | - | - |
| Weight at admission (Kg) | 46 | 80 (69-92) | 80 (68-94) | 80 (70-91) | 0.40 | 1 | 80 (67-94) | 79 (66-90) | 81 (67-97) | 0.93 | 0.97 |
| Paired mean weight loss (Kg) | | 4.1 P-Value <0.001 | 4.1 P-Value <0.001 | 4.1 P- Value <0.001 | | 1 | 5.18 P-Value <0.001 | 4.95 P-Value <0.001 | 5.38 P-Value <0.001 | | |
| HR (IQR) | 1 | 89 (74-108) | 100 (78-120) | 85 (72-100) | <0.001 | 0 | 90 (73-110) | 100 (82-120) | 82 (70-103) | <0.001 | 0.83 |
| HR if in SR (IQR) | 3 | 85 ( 75-105) | 101 (80-120) | 82 (I71-90) | <0.001 | 1 | 91 (75-108) | 100 (85-116) | 83(70-101) | <0.001 | 0.29 |

| Table 9 | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| Heart Rate if in AF | 1 | 91 (74-110) | 98 (76-120) | 88 (72-100) | 0.02 | 0 | 89 (70-117) | 97 (79-126) | 82 (68-104) | 0.003 | 0.91 |
| Systolic BP (IQR) | 0 | 132 (110-150) | 141 (120-160) | 122 (108-141) | <0.001 | 0 | 133 (115-153) | 142 (124-166) | 129 (110-144) | <0.001 | 0.09 |
| Systolic BP >125mmHg | 0 | 179 (58%) | 96 (73%) | 80 (46%) | <0.001 | 0 | 239 (61%) | 129 (70%) | 110 (53%) | <0.001 | 0.29 |
| RR (IQR) | 2 | 20 (18-24) | 24 (22-29) | 18 (17-20) | <0.001 | 0 | 22 (19-28) | 28 (24-33) | 20 (18-21) | <0.001 | <0.001 |
| Moderate - Severe oedema | 1 | 141 (46%) | 56 (42%) | 84 (48%) | 0.44 | 14 | 318 (85%) | 139 (78%) | 179 (89%) | 0.003 | <0.001 |

| Table 9 | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| Mild oedema | | 79 (26%) | 40 (30%) | 39 (25%) | 0.35 | | 41 (11%) | 20 (11%) | 21 (11%) | 0.90 | <0.001 |
| Echo | 22 | | | | | 75 | | | | | |
| Moderate-Severe LVSD | | 195 (68%) | 79 (66%) | 116 (70%) | 0.44 | | 250 (79%) | 122 (83%) | 128 (76%) | 0.14 | 0.002 |
| No / Mild LVSD | | 90 (32%) | 41 (34%) | 49 (30%) | 0.42 | | 65 (21%) | 25 (17%) | 40 (24%) | 0.13 | 0.003 |
| Left Atrium dilatation | 119 | 128 (67%) | 63 (77%) | 65 (61%) | 0.03 | 390 | - | - | - | - | - |
| Severe Valve | 124 | 72 (39%) | 31 (39%) | 41 (39%) | 0.98 | 390 | - | - | - | - | - |

| Table 9 | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| Disease | | | | | | | | | | | |
| Haemoglobin (g/dl) (IQR) | 1 | 12.3 (11-13.8) | 12.4 (10.95 – 13.8) | 12.3 (11 -13.6) | 0.85 | 390 | - | - | - | - | - |
| WBC ($x10^9$/L) (IQR) | 79 | 9.1 (6.8-11.9) | 10.0 (7.4-13.1) | 8.4 (6.6 - 10.7) | 0.003 | 390 | - | - | - | - | - |
| hsCRP (mg/L) (IQR) | 63 | 16 (5.8-46) | 17.5 (7.1-51.0) | 15.0 (4.8-43.0) | 0.24 | 101 | 14 (5-31) | 12 (5-29)) | 11 (5-27) | 0.74 | 0.01 |
| Sodium (mmol/L) (IQR) | 0 | 138 (135-140) | 138 (134 - 140) | 137 (135-140) | 0.92 | 0 | 139 (136-141) | 139 (136-142) | 138 (136-141) | 0.40 | 0.007 |

| Table 9 | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| Potassium (mmol/L) (IQR) | 10 | 4.4 (4.0 - 4.8) | 4.4 (3.9 - 4.9) | 4.4 (4.0-4.8) | 0.90 | 1 | 4.4 (4.1-4.9) | 4.4 (4.1-4.9) | 4.4 (4.1-4.8) | 0.33 | 0.79 |
| Urea (mmol/l) (IQR) | 1 | 8 (5.7 - 13.1) | 8 (5.6 - 11.5) | 9 (5.8 - 14.6) | 0.13 | 372 | 11 (7-16) | 10 (5-16) | 13 (8-15) | 0.65 | 0.22 |
| Creatinine (µmol/L) (IQR) | 0 | 111 (85-152) | 109 (83 - 143) | 117 (86 - 161) | 0.87 | 371 | 114 (76-163) | 111 (70-171) | 115 (93-153) | 0.64 | 0.79 |
| eGFR (ml/min/1.73m$^2$) (IQR) | 0 | 53 (37 -73) | 55 (39 – 74) | 52 (37-72) | 0.41 | 1 | 52 (35-75) | 51 (35-73) | 55 (35-78) | 0.52 | 0.87 |
| hsTnT (ng/L)(IQR) | 168 | 79 (35 - 497) | 100 (46-497) | 74 (24-341) | 0.13 | 390 | - | - | - | - | - |

| Table 9 | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| NT-proBNP (pg/ml) (IQR) | 112 | 4082 (1895-10279) | 4076 (2320-9244) | 4160 (1483-11229) | 0.99 | 390 | - | - | - | - | |

IHD; Ischaemic Heart disease, CVA; Cerebrovascular accident, TIA; Transient Ischaemic attack, DM; Diabetes Mellitus, COPD; Chronic Obstructive Pulmonary Disease, eGFR; Estimated glomerular filtration rate, SBP; Systolic Blood Pressure, HR; Heart Rate, RR; Respiratory Rate, Echo; Echocardiography, LVSD; Left Ventricle Systolic dysfunction, WBC; White Blood count, hsCRP; high sensitivity C-Reactive protein, hsTnT; High sensitivity Troponin T, KG; Kilo gram.

**Table 10 : Over all Base line clinical characteristics (Combined London & Hull)**

| Table 10 | *Missing Data* | *Overall (N=697)* | *SOBAR N-315(45%)* | *CARBOSE N-382 (55%)* | *SOBAR vs CARBOSE (P-Value)* |
|---|---|---|---|---|---|
| Age (IQR) | 0 | 76 (65-73) | 76 (66-83) | 76 (64-82) | 0.35 |
| Women | 0 | 265 (38%) | 137 (43%) | 128 (34%) | 0.007 |
| Prior IHD | 0 | 320 (46%) | 152 (48%) | 168 (44%) | 0.26 |
| Prior CVA/TIA | 0 | 69 (10%) | 33 (11%) | 36 (10%) | 0.38 |
| Prior DM | 1 | 227 (33%) | 115 (37%) | 112 (29%) | 0.04 |
| Prior COPD/Asthma | 0 | 172 (25%) | 87 (28%) | 85 (22%) | 0.06 |
| Prior CKD (eGFR <60) | 0 | 364 (52%) | 156 (50%) | 208 (54%) | 0.20 |
| Prior Hypertension | 1 | 400 (57%) | 181 (58%) | 219 (57%) | 0.93 |
| Prior AF | 2 | 282 (41%) | 135 (43%) | 147 (39%) | 0.25 |
| AF (Presentation ECG) | 5 | 320 (46%) | 152 (48%) | 168 (44%) | 0.21 |
| QRS Duration (IQR) | 22 | 108 (92-138) | 106 (90-134) | 111 (94-140) | 0.99 |
| Prior HF | 394 | 227 (75%) | 87 (67%) | 140 (81%) | 0.005 |

| Table 10 | *Missing Data* | *Overall (N=697)* | *SOBAR N-315(45%)* | *CARBOSE N-382 (55%)* | *SOBAR vs CARBOSE (P-Value)* |
|---|---|---|---|---|---|
| Weight at admission (Kg) (IQR) | 49 | 80 (68-93) | 79 (67-92) | 80 (68-94) | 0.82 |
| Paired mean weight loss (Kg) | 120 | 4.8<br>P-Value <0.001 | 4.6<br>P-Value <0.001 | 4.9<br>P-Value <0.001 | |
| Heart Rate (HR) (IQR) | 1 | 90 (74-109) | 100 (80-120) | 84 (70-100) | <0.001 |
| Heart Rate if in SR | 5 | 89 (75-106) | 100 (83-117) | 83 (70-98) | <0.001 |
| Heart Rate if in AF | | 90 (72-114) | 98 (78-125) | 85 (69-102) | <0.001 |
| Systolic BP (SBP)(IQR) | 0 | 133 (113-152) | 142 (124-164) | 125 (110-143) | <0.001 |
| Systolic BP >125mmHg | 0 | 415 (60%) | 225 (71%) | 190 (50%) | <0.001 |
| Respiratory Rate | 2 | 22 (18-26) | 26 (24-32) | 19 (18-20) | <0.001 |
| Moderate - Severe oedema | 14 | 458 (67%) | 195 (63%) | 263 (70%) | 0.06 |
| Mild Oedema | 14 | 128 (19%) | 63 (20%) | 65(18%) | 0.80 |
| Echo | | | | | |

| Table 10 | *Missing Data* | *Overall (N=697)* | *SOBAR N-315(45%)* | *CARBOSE N-382 (55%)* | *SOBAR vs CARBOSE (P-Value)* |
|---|---|---|---|---|---|
| Moderate-Severe LVSD | 97 | 445 (74%) | 201 (75%) | 244 (73%) | 0.57 |
| No / Mild LVSD | 97 | 155(26%) | 66 (25%) | 89 (27%) | 0.56 |
| Left Atrium dilatation | 509 | 128 (67%) | 63 (77%) | 65 (61%) | 0.03 |
| Pulmonary Congestion (X-Ray) | 24 | 395 (59%) | 218 (71%) | 177 (48%) | <0.001 |
| Severe Valve Disease | 513 | 72 (39%) | 31 (39%) | 41 (39%) | 0.98 |
| Haemoglobin (g/dl) (IQR) | 391 | 12.3 ( 11-13.8) | 12.4 (10.95 – 13.8) | 12.3 (11 - 13.6) | 0.85 |
| WBC ($x10^9$/L)(IQR) | 468 | 9.1 (6.8-11.9) | 10.0 (7.4-13.1) | 8.4 (6.6 - 10.7) | 0.003 |
| hsCRP (mg/L) (IQR) | 164 | 14 (5-33) | 15 (5-35) | 14 (5-31) | 0.26 |
| Sodium (mmol/L) (IQR) | 0 | 138 (135-141) | 138 (135-141) | 138 (135-141) | 0.54 |
| Potassium (mmol/L) (IQR) | 11 | 4.4 (4-4.9) | 4.4 (4-4.9) | 4 (4.4-4.8) | 0.67 |
| Urea (mmol/l)(IQR) | 373 | 9 (6-13) | 8 (5-12) | 9 (6-15) | 0.12 |

| Table 10 | *Missing Data* | *Overall (N=697)* | *SOBAR N-315(45%)* | *CARBOSE N-382 (55%)* | *SOBAR vs CARBOSE (P-Value)* |
|---|---|---|---|---|---|
| Creatinine (µmol/L) (IQR) | 371 | 111 (85-153) | 109 (83-143) | 117 (86-159) | 0.59 |
| eGFR (ml/min/1.73 $m^2$) (IQR) | 1 | 53 (36-74) | 52 (36-74) | 53 (36-74) | 0.93 |
| hsTnT (ng/L) (IQR) | 558 | 77 (35-490) | 100 (46-497) | 74(24-341) | 0.14 |
| NT-proBNP (pg/ml) (IQR) | 502 | 4082 (1895-10279) | 4076 (2320-9244) | 4160 (1483-11229) | 0.99 |

IHD; Ischaemic Heart disease, CVA; Cerebrovascular accident, TIA; Transient Ischaemic attack, DM; Diabetes Mellitus, COPD; Chronic Obstructive Pulmonary Disease, eGFR; Estimated glomerular filtration rate, SBP; Systolic Blood Pressure, HR; Heart Rate, RR; Respiratory Rate, Echo; Echocardiography, LVSD; Left Ventricle Systolic dysfunction, WBC; White Blood count, hsCRP; high sensitivity C-Reactive protein, hsTnT; High sensitivity Troponin T, KG; Kilo gram.

**Table 11 : Therapy prior to decompensation, during index admission and at discharge (Comparisons of two sites)**

| Table 11 *Therapy* | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| Prior to Decompensation | | | | | | | | | | | |
| ACEi | 6 | 131 (43%) | 62 (48%) | 69 (40%) | 0.20 | 0 | 174 (45%) | 78 (43%) | 96 (46%) | 0.46 | 0.77 |
| ARB | | 44 (14%) | 17 (13%) | 27 (16%) | 0.62 | 0 | 54 (14%) | 24 (13%) | 30 (14%) | 0.69 | 0.81 |
| ACEi/ARB | | 175 (57%) | 79 (61%) | 96 (56%) | 0.42 | 0 | 228 (59%) | 102 (56%) | 126 (60%) | 0.55 | 0.75 |
| BB | | 147 (49%) | 57 (44%) | 90 (53%) | 0.12 | 0 | 177(45%) | 79 (43%) | 98 (47%) | 0.41 | 0.35 |
| MRA | | 58 (19%) | 20 (15%) | 38 (22%) | 0.18 | 0 | 68 (17%) | 23 (13%) | 45 (22%) | 0.02 | 0.56 |
| Loop Diuretic | | 172 (56%) | 68 (52%) | 104 (60%) | 0.14 | 0 | 237 (61%) | 105 (57%) | 132 (64%) | 0.20 | 0.29 |
| Thiazide Diuretic | | 14 (5%) | 8 (6%) | 6 (3%) | 0.40 | 0 | 34 (9%) | 10 (5%) | 24 (12%) | 0.04 | 0.04 |

| Table 11 *Therapy* | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| Nitrates | | 48 (16%) | 19 (15%) | 29 (17%) | 0.75 | 0 | 36 (9%) | 22 (12%) | 14 (7%) | 0.08 | 0.007 |
| CCB | | 36 (12%) | 19 (15%) | 17 (10%) | 0.21 | 0 | 70 (18%) | 31 (17%) | 39 (18%) | 0.36 | 0.03 |
| Digoxin | | 56 (20%) | 24 (20%) | 32 (20%) | 1 | 0 | 49 (13%) | 29 (16%) | 20 (10%) | 0.05 | 0.01 |
| During admission | | | | | | | | | | | |
| IV Diuretic in First 24 Hours | | 187 (61%) | 116 (88%) | 71 (41%) | <0.001 | 0 | 277 (71%) | 164 (90%) | 113 (55%) | <0.001 | 0.005 |
| IV Nitrate | | 31 (10%) | 19 (15%) | 12 (7%) | 0.03 | 0 | 95 (24%) | 74 (40%) | 21 (10%) | <0.001 | <0.001 |
| IV Opiate | | 28 (9%) | 19 (14%) | 9 (5%) | 0.008 | 390 | - | - | - | - | |
| IV Inotropic Agent | | 8 (3%) | 4 (3%) | 4 (2%) | 0.73 | 0 | 11 (3%) | 8 (4%) | 3 (1%) | 0.08 | 1 |

| Table 11<br>*Therapy* | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| C-PAP | | 9 (3%) | 8 (6%) | 1 (<1%) | 0.006 | 0 | 12 (3%) | 11 (6%) | 1 (0.5%) | 0.001 | 1 |
| Intubation & Ventilation | | 5 (2%) | 5 (4%) | 0 (0%) | 0.01 | 0 | 4 (1%) | 4 (2%) | 0 | 0.04 | 0.52 |
| At Discharge | | | | | | | | | | | |
| ACEi | | 197 (71%) | 83 (69%) | 114 (73%) | 0.46 | | 281 (78%) | 135 (80%) | 146 (76%) | 0.44 | 0.03 |
| ARB | | 29 (10%) | 11 (9%) | 18 (11%) | 0.52 | | 41 (11%) | 19 (11%) | 22 (11%) | 1 | 0.78 |
| ACEi /ARB | | 226 (81) | 94 (78%) | 132 (84%) | 0.17 | | 322 (89%) | 154 (91%) | 168 (87%) | 0.55 | 0.02 |
| BB | | 219 (79%) | 90 (74%) | 129 (83%) | 0.09 | | 278 (77%) | 135 (78%) | 143 (75%) | 0.27 | 0.50 |
| MRA | | 142 (51%) | 56 (46%) | 86 (55%) | 0.16 | | 191 (52%) | 92 (53%) | 99 (51%) | 0.68 | 0.87 |

Table 11

| *Therapy* | *Data Collection from Hull* | | | | | *Data Collection from London* | | | | | *P-Value Hull v London* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Missing data* | *Overall N=307* | *SOBAR N=132 (43%)* | *CARBOSE N=175 (57%)* | *SOBAR vs CARBOSE P-Value* | *Missing data* | *Overall N=390* | *SOBAR N= 183 (47%)* | *CARBOSE N=207 (53%)* | *SOBAR vs CARBOSE P-Value* | |
| Loop Diuretic | | 239 (86%) | 103 (85%) | 136 (87%) | 0.72 | | 344 (92%) | 162 (92%) | 182 (92%) | 1 | 0.02 |
| Thiazide diuretic | | 23 (8%) | 8 (7%) | 15 (10%) | 0.15 | | 19 (5%) | 6 (3%) | 13 (7%) | 0.17 | 0.07 |
| Nitrates | | 42 (15%) | 20 (17%) | 22 (14%) | 0.56 | | 23 (14%) | 14 (17%) | 9 (11%) | 0.27 | 0.89 |
| CCB | | 18 (6%) | 9 (7%) | 9 (6%) | 0.57 | | 26 (14%) | 10 (12%) | 16 (16%) | 0.53 | 0.009 |
| Digoxin | | 80 (29%) | 40 (33%) | 40 (26%) | 0.21 | | 60 (16%) | 31 (17%) | 29 (15%) | 0.57 | <0.001 |

ACEi, Angiotensin converting enzyme inhibitor; ARB, Angiotensin Receptor Blocker; BB, Beta adrenergic receptor Blocker; MRA, Mineralocorticoid Receptor antagonist; CCB, Calcium Channel blocker; C-PAP, Continuous positive airway pressure.

**Table 12 : Therapy prior to decompensation, during index admission and discharge (Combined Hull and London)**

| *Table 12 Therapy* | *Missing Data* | *Overall (N=697)* | *SOBAR N=315(45%)* | *CARBOSE N=382 (55%)* | *SOBAR vs CARBOSE (P-Value)* |
|---|---|---|---|---|---|
| Prior to Decompensation | | | | | |
| ACEi | 6 | 305 (44% | 140 (45%) | 165 (44%) | 0.78 |
| ARB | 3 | 44 (14%) | 41 (13%) | 57 (15%) | 0.47 |
| ACEi or ARB | | 349 (58%) | 181 (58%) | 222 (59%) | 0.72 |
| BB | 7 | 324 (47%) | 136 (43%) | 188 (50%) | 0.09 |
| MRA | 4 | 126 (18%) | 43 (14%) | 83 (22%) | 0.006 |
| Loop Diuretic | 4 | 409 (59%) | 173 (55%) | 236 (62%) | 0.05 |
| Thiazide Diuretic | 6 | 48 (7%) | 18 (6%) | 30 (8%) | 0.25 |
| Nitrates | 7 | 84 (12%) | 41 (13%) | 43 (11%) | 0.48 |
| CCB | 4 | 106 (15%) | 50 (16%) | 56 (15%) | 0.36 |
| Digoxin | 22 | 105 (16%) | 53 (17%) | 52 (14%) | 0.24 |
| During admission | | | | | |
| IV Diuretic in First 24 Hours | 0 | 464 (67%) | 280 (89%) | 184 (48%) | <0.001 |
| IV Nitrate | 3 | 126 (18%) | 93 (30%) | 33 (9%) | <0.001 |
| IV Opiate | | 28 (9%) | 19 (14%) | 9 (5%) | 0.008 |
| IV Inotropic Agent | 3 | 19 (3%) | 12 (4%) | 7 (2%) | 0.16 |
| C-PAP | 4 | 21 (3%) | 19 (6%) | 2 (0.5%) | <0.001 |
| Intubation & | 4 | 9 (1%) | 9 (3%) | 0 | 0.001 |

| *Table 12 Therapy* | *Missing Data* | *Overall (N=697)* | *SOBAR N=315(45%)* | *CARBOSE N=382 (55%)* | *SOBAR vs CARBOSE (P-Value)* |
|---|---|---|---|---|---|
| Ventilation | | | | | |
| At Discharge | | | | | |
| ACEi | | 478 (75%) | 218 (75%) | 260 (75%) | 0.45 |
| ARB | | 70 (11%) | 30 (10%) | 40 (11%) | 0.61 |
| ACEi or ARB | | 488 (86%) | 248 (85%) | 300 (86%) | 0.60 |
| BB | | 498 (78%) | 226 (77%) | 272 (79%) | 0.63 |
| MRA | | 334 (52%) | 149 (51%) | 185 (53%) | 0.64 |
| Loop Diuretic | | 584 (89%) | 266 (89%) | 318 (90%) | 0.90 |
| Thiazide diuretic | | 42 (6%) | 14 (5%) | 28 (8%) | 0.11 |
| Nitrates | | 65 (15%) | 34 (17%) | 31 (13%) | 0.28 |
| CCB | | 44 (9%) | 19 (9%) | 25 (10%) | 0.88 |
| Digoxin | | 147 (22%) | 74 (24%) | 73 (20%) | 0.22 |

ACEi, Angiotensin converting enzyme inhibitor; ARB, Angiotensin Receptor Blocker; BB, Beta adrenergic receptor Blocker; MRA, Mineralocorticoid Receptor antagonist; CCB, Calcium Channel blocker; C-PAP, Continuous positive airway pressure.

There was no significant difference in left ventricle systolic dysfunction (LVSD) between the groups. Prior to decompensation, more patients in CARBOSE were on Mineralocorticoid receptor antagonists (MRA) (22% v 14%), loop diuretics (62% v 55%) and beta blockers (BB) (50% v 43%) (Table 12). Patient with SOBAR were treated more aggressively during index admission. A higher proportion in this group received IV diuretics during first 24 hours of presentation (89% v 48%), IV Nitrates (30% v 9%), IV Opiates (14% v 5%) and Continuous positive airway pressure (C-

PAP) (6% v 0.5%). There was no significant difference in treatment on discharge between two groups (Table 12).

Patients with SOBAR had a higher systolic blood pressure (BP) at presentation (142 v 125), which declined steeply over the first 24 hours of admission (Figure 9) as did diastolic BP (82 v 75), heart rate (100 v 84) and respiratory rate (26 v 19) (Figure 10 & Figure 11). In contrast, patients who were CARBOSE had clinically non-significant change in systolic or diastolic BP, heart rate or respiratory rate in the first 24 hours (Figure 9, Figure 10 & Figure 11).

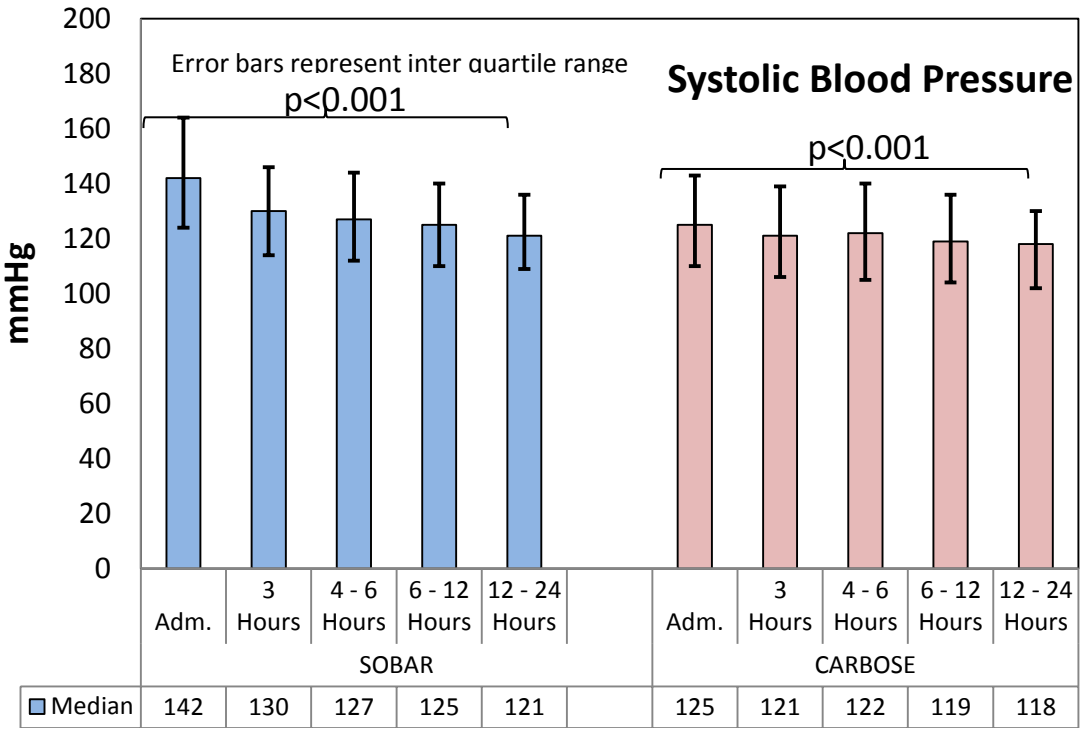



**Figure 9: Changes in Systolic Blood Pressure**

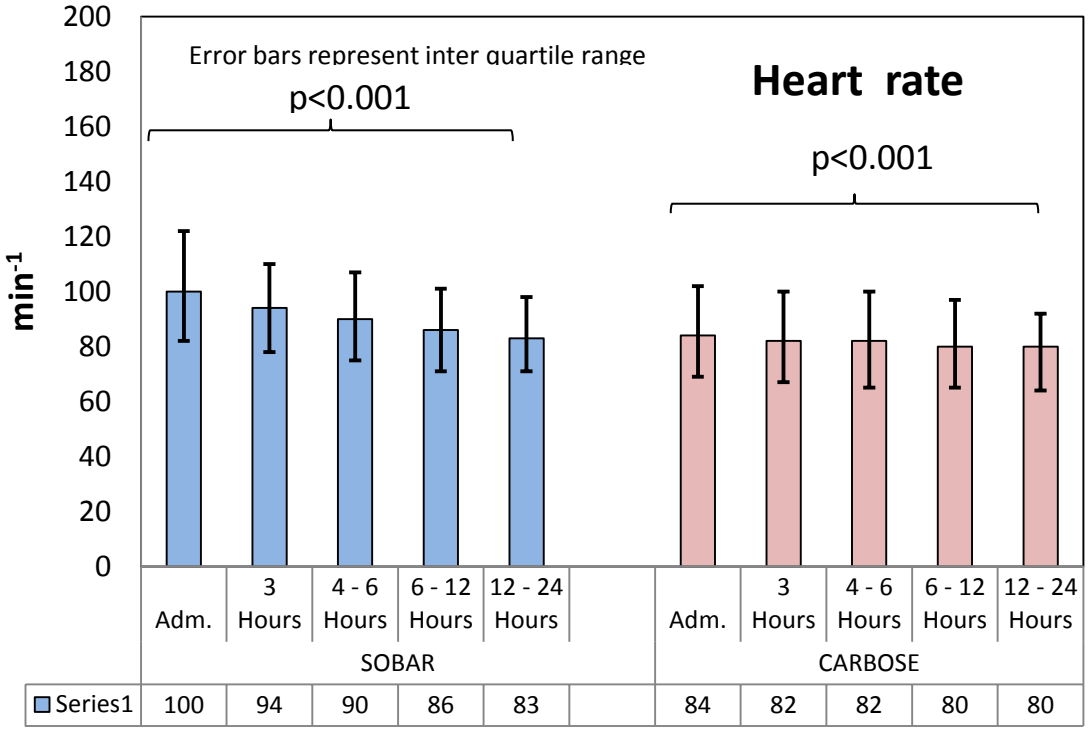



**Figure 10 : Changes in Heart Rate**

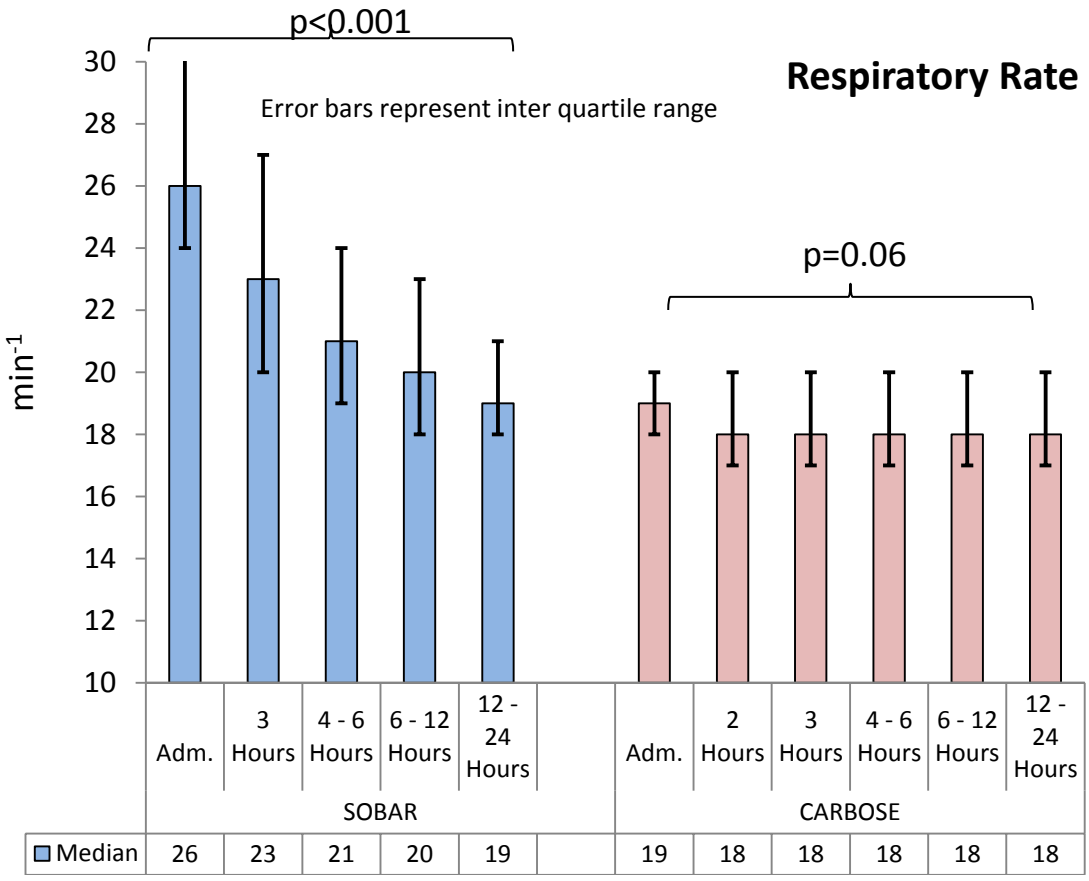



**Figure 11 : Changes in Respiratory Rate**

In RELAX-AHF, one important inclusion criterion was systolic BP >125 mmHg which was met by 60 % at presentation and 49 % within three hours of presentation, falling to only 47% at 4-6 hour and 37% at 12-24 hours.[46] However, the proportion was much higher in those with SOBAR compared with CARBOSE (71% vs 50% at presentation, 52% v 43% at 4-6 hours and 44% v 31% in 12-24 hours).

The median length of stay in days during index admission was 11 in CARBOSE and 10 in SOBAR (P- 0.20). Although the 30-day mortality tended to be higher in patients who were CARBOSE (8%) than SOBAR (6%) with an odds ratio (OR) of 1.36, the difference was not statistically significant (p=0.32, CI 0.74-2.5). During the first 3 months after presentation, 17% of those who were CARBOSE died compared to 10% who were SOBAR, with an OR of 1.73 (p=0.02, CI 1.1-2.7). At 6 months, 25% of those who were CARBOSE had died compared to 15% who were SOBAR (OR 1.92; p=0.001, CI 1.30-2.84). At the final censorship date, August 2013, 45% of those who were CARBOSE and 31% who were SOBAR had died (Figure 12 : Survival Comparison of SOBAR & CARBOSE Hazard ratio 1.54; p=0.001; CI 1.20-1.98: hazard ratio 1.54; p=0.001; CI 1.20-1.98). Mortality was higher amongst patients with peripheral oedema at presentation in the CARBOSE group (Table 14).

**Table 13 : Changes in Vital Signs in first 24 hours**

| Table 13 | *Admission* | *3 Hours* | *4-6 Hours* | *6-12 Hour* | *12-24 Hour* |
|---|---|---|---|---|---|
| Systolic BP (mmHg), median (IQR) | 133 (113-152) | 125 (110-143) | 124 (108-143) | 121 (107-138) | 119 (105-133) |
| SOBAR | 142 (124-164) | 130 (114-146) | 127 (112-144) | 125 (110-140) | 121 (109-136) |
| CARBOSE | 125 (110-143) | 121 (106-139) | 122 (105-140) | 119 (104-136) | 118 (102-130) |
| Diastolic BP (mmHg), median (IQR) | 78 (65-91) | 72 (63-85) | 70 (61-84) | 70 (60-80) | 69 (60-79) |
| SOBAR | 82 (69-96) | 74 (65-86) | 72 (60-85) | 70 (61-80) | 68 (60-80) |
| CARBOSE | 75 (63-87) | 71 (60-83) | 70 (62-84) | 69 (60-80) | 69 (60-78) |
| HR ($min^{-1}$), median (IQR) | 90 (73-109) | 86 (70-105) | 85 (72-101) | 83 (69-97) | 82 (68-95) |
| SOBAR | 100 (80-120) | 94 (75-115) | 90 (75-105) | 86 (72-103) | 83 (70-96) |
| CARBOSE | 84 (70-100) | 82 (68-98) | 82 (70-97) | 80 (68-93) | 80(68-94) |
| RR ($min^{-1}$), median (IQR) | 22 (18-26) | 20 (18-24) | 20 (18-22) | 19 (18-22) | 18 (17-20) |
| SOBAR | 26 (24-32) | 23 (20-27) | 21 (19-24) | 20 (18-23) | 19 (18-21) |
| CARBOSE | 19 (18-20) | 18 (17-20) | 18 (17-20) | 18 (17-20) | 18 (17-20) |
| Systolic BP >125 mmHg, % | 415 (60%) | 301 (49%) | 313 (47%) | 292 (43%) | 256 (37%) |
| SOBAR | 225 (71%) | 164 (57%) | 160 (52%) | 153 (49%) | 138 (44%) |
| CARBOSE | 190 (50%) | 137 (42%) | 153 (43%) | 139 (38%) | 118 (31%) |

BP, Blood Pressure; IQR, Inter quartile range; HR, Heart Rate; RR, Respiratory Rate

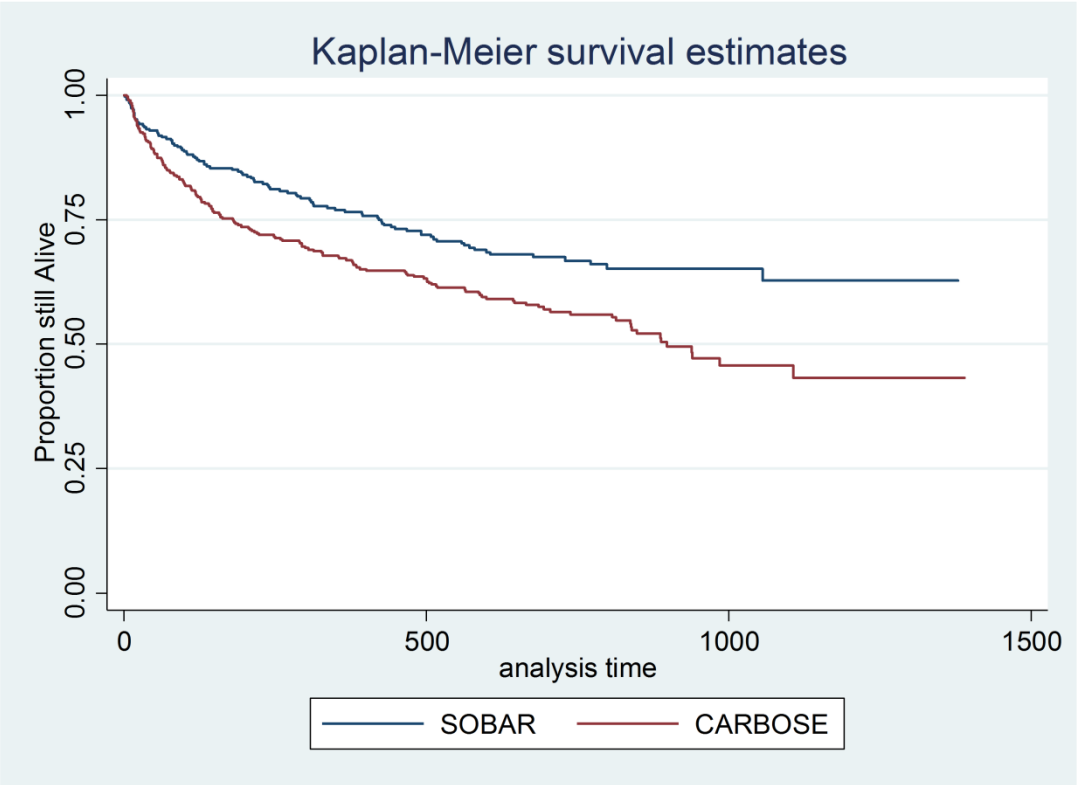



**Figure 12 : Survival Comparison of SOBAR & CARBOSE Hazard ratio 1.54; p=0.001; CI 1.20-1.98**

In multi variable analysis with 25 Cross-validation, I started with 15 clinically relevant covariates (Table 15). CARBOSE, increasing age, prior history of IHD and lower systolic BP were associated with all-cause mortality and remained statistically significant in all 25 cross-validations and prior history of CKD and CVA in 22 each. I did not include NT-proBNP as this is only available for 195 patients out of 697. In our final Cox model after inclusion of all these six covariates, CARBOSE remain significantly associated with higher mortality with Hazard ratio (HR) of 1.41 (P 0.01, CI 1.08-1.83) as compared to SOBAR (Table 16). Harrell's C-statistic for this model was 0.71 which showed moderate discrimination.

**Table 14 : Duration of Hospital Stay and Mortality**

| Table 14 | | *Overall (n=697)* | *SOBAR (n=315)* | *CARBOSE (n=382)* | *P-Value/ OR/HR- (CARBOSE as compare to SOBAR)* |
|---|---|---|---|---|---|
| Length of stay, median days (IQR) | 1 | 11 (6-17) | 10 (7-17) | 11 (6-19) | 0.20 |
| Deaths 30 days after presentation, n (%) | 15 | 47 (7%) | 18 (6%) | 29 (8%) | OR;1.36 (P 0.32, CI 0.74-2.5) |
| Deaths 90 days after presentation, n (%) | 15 | 94 (14%) | 32 (10%) | 62 (17%) | OR; 1.73 (0.02, CI 1.1 – 2.72) |
| Deaths 180 days after presentation, n (%) | 15 | 140 (21%) | 46 (15%) | 94 (25%) | OR; 1.92 (P 0.001, CI 1.30 -2.84) |
| Total deaths | 15 | 261 (38%) | 95 (31%) | 166 (45%) | HR; 1.54 (P-0.001, CI 1.20-1.98) |
| Total Deaths in absence of peripheral oedema* at presentation | 15 | 73/224 (32%) | 35/113 (31%) | 47/111 (34%) | HR 1.12 (P 0.64, CI 0.71-1.77) |
| Total Deaths in presence of peripheral oedema* at presentation | 15 | 184/458 (41%) | 57/195 (29%) | 127/263(48%) | HR 1.85 (P <0.001, CI 1.35-2.53) |

*Moderate to Severe Peripheral Oedema

**Table 15 : Variables used in 25 Cross validation**

| Table 15 | |
|---|---|
| Variables in 25 Cross-Validation | In number of models, variables remained significant |
| CARBOSE/SOBAR presentation | 25 |
| Age at Presentation | 25 |
| Gender | 1 |
| Prior h/o DM | 1 |
| Prior h/o Asthma | 2 |
| AF rhythm at presentation | 5 |
| Prior H/O Hypertension | 1 |
| Prior H/O CKD | 22 |
| Prior H/O CVA | 22 |
| Prior H/O IHD | 25 |
| SYS BP at presentation | 25 |
| RR at presentation | 1 |
| HR at presentation | 0 |

| Table 15 | |
|---|---|
| Moderate/Severe LVSD at presentation | 0 |
| Moderate/Severe Oedema at presentation | 0 |

h/o, History of ; DM, Diabetes Mellitus; CKD, Chronic kidney disease; CVA, Cerebrovascular accident ; IHD,Ischaemic Heart disease; Sys BP, Systolic Blood pressure; LVSD, Left Ventricle Systolic dysfunction

## 5.4 Discussion

This study has shown that in patients admitted with a primary diagnosis of Acute Heart Failure; more than half of patients are not short of breath at rest, but instead are relatively comfortable at rest, becoming breathless with minimal exertion. This study validates my previous single centre research study (chapter 4) findings now in a multi-centre setting with more robust evidence.[14, 118, 120, 127] Although, some large scale surveys and registries reported similar findings, none of these studies were primarily designed, conducted, analysed or interpreted to assess severity of breathlessness in AHF patients. For instance, in first Euro heart failure survey only 40% patients with suspected or confirmed diagnosis of HF had severe breathlessness at presentation.[3] Moreover, for those patients who were hospitalized for HF, 44% in OPTIMIZE-HF, 47% in IMPACT HF and one third in National Heart Failure audit for England & Wales had dyspnoea at rest.[16, 26, 115, 117] However, none of these studies described serial changes in vital signs of AHF patients during first 24 hours in relation to presentation. The severity of breathlessness drives the patients' management in acute settings. Urgent symptomatic treatment and close observation in hospital is necessary for those who present with severe breathlessness at rest.

**Table 16 : Cox-Model to assess mortality**

| Table 16 | *Hazard Ratio* | *P-Value* | *Lower bound 95% CI* | *Upper bound 95% CI* |
|---|---|---|---|---|
| CARBOSE | 1.41 | 0.01 | 1.08 | 1.83 |
| Age | 1.05* | <.001 | 1.04 | 1.07 |
| Systolic BP at presentation | 0.99# | <0.001 | 0.98 | 0.99 |
| Prior H/O IHD | 1.52≠ | 0.001 | 1.18 | 1.96 |
| Prior H/O CKD | 1.29≠ | 0.07 | 0.98 | 1.69 |
| Prior H/O CVA | 1.39≠ | 0.07 | 0.97 | 1.99 |

h/o, History of ; BP, Blood pressure; IHD, Ischaemic Heart disease; CKD, Chronic kidney disease; CVA, Cerebrovascular accident, *; Per one year change, #; Per one degree Blood pressure change, ≠; Compare to not having prior disease history

Patients with SOBAR had higher blood pressure, heart and respiratory rates at presentation, which are signs of a highly activated sympathetic nervous system drive. However, either due to more intense treatment or greater sensitivity, these signs of cardiovascular stress settled rapidly in patients with SOBAR. This observation is highlighting a potential problem in trials of AHF which usually need more than six hours for patient's recruitment.[46, 80] This delay may be due to either study related administrative procedures, randomisation processes or preparation of investigational medical products. Moreover, the majority of patients receive treatments like IV diuretics, opiates or Nitrates before randomization, which subside important clinical symptoms and signs. Furthermore, many patients who present with SOBAR had no prior history of HF, which makes it difficult to make a firm diagnosis in acute settings. For these reasons, it is very difficult to design and conduct clinical trials in this subset group.

Patients who were CARBOSE had a less dramatic presentation, apparently looked less sick but have a worse long-term outcome. They had more peripheral congestion, which may be caused by more severe underlying right ventricle (RV) dysfunction, an important prognostic indicator.[121] Lower systolic blood pressure at admission in the CARBOSE patients may be another explanation for their higher mortality. Lower systolic blood pressure at presentation in acute heart failure patients is strongly associated with increasing mortality in many clinical studies.[122, 123] A Prior history of heart failure was more common in the CARBOSE than the SOBAR group (Table 9 & Table 10), suggesting that many patients in this group have long standing heart failure and may now have late-stage disease. Worse long term prognosis in CARBOSE suggests that more attention should be paid to their management. Interestingly, a difference in mortality between the two groups becomes more obvious in presence of peripheral oedema (Table 14), which suggests that there is some interaction between the SOBAR/CARBOSE presentations and moderate to severe peripheral oedema

In RELAX-AHF, treatment of acute heart failure patients with Serelaxin was associated with dyspnoea relief and improvement in prognosis despite early treatment with IV diuretics provided they had systolic blood pressure >125mmHg.[46] The median time from presentation to randomization was of 8 hours. I observed that overall 60% patient met this trial entry criterion at admission and it declined to 43% after 6-12 hours of presentation. However, this proportion was much higher in patients who were SOBAR than CARBOSE at presentation (71% v 50%) and after 6-12 hours (49% v 38%) of hospital admission. More active treatment results in lower sympathetic drive and relief in anxiety which translates into reduced

proportion of patients meeting the blood pressure entry criterion fell rapidly after admission.

## 5.5 Limitations

Although this study was conducted in three centres, some missing data, especially for NTproBNP is a concern. However, natriuretic peptides measured at admission may add little prognostic information to standard variables but other analysis suggest that they may provide powerful prognostic information when measured later in the hospital course.[125, 126] Moreover, data regarding prior history of heart failure is only available for patients belonging to one centre, though there is still a difference between the two groups that is statistically significant. Patients' selection through retrospective case notes review studies can introduce some selection bias, but we tried to avoid it by spreading the data collection over a period of three years, taking the first 20 patients each month. We also divided the patients into two groups, but in reality the presentation of acute heart failure may fall on a spectrum where patients with severe shortness of breath and pulmonary congestion lying on one end, and patients who have major functional limitation and breathlessness due to gross peripheral oedema on the other end, and in the centre of this spectrum there may be a third group where this differentiation is very difficult to make. Many patients with CARBOSE did not have significant peripheral oedema and this may reflect the heterogeneous nature of this group, where some with a milder degree of heart failure that neither caused breathlessness at rest nor peripheral oedema and others with more severe congestion. This suggests that there may be a very high risk subgroup amongst those with CARBOSE. Further exploration of the natural history and outcome of these extreme cases is required.

## 5.6 Conclusion

Contrary to general belief, most patients admitted with a primary diagnosis of heart failure don't have dyspnoea at rest but are breathlessness on slight exertion. Patients presenting with SOBAR had higher heart rates, respiratory rates and systolic blood pressures and often respond very quickly to conventional treatments with rapid improvement in clinical signs. Although patients with SOBAR have more alarming initial symptoms and signs, patients with CARBOSE have a worse prognosis, perhaps reflecting more severe cardiac dysfunction.

# Chapter 6 Is The Diagnostic Position of Acute Heart Failure (AHF) Related to Mortality? - A report from the Euro Heart Failure Survey-1(EHFS-1)

## 6.1 Introduction

Heart failure (HF) is a common reason for hospitalization and also commonly complicates hospitalization for other reasons.[24] Indeed, about 80% of hospitalisations caused or complicated by heart failure will have another diagnosis in the primary position. Most patients with heart failure will have other medical problem many of which cause, contribute to, complicate or are complicated by heart failure.[115, 128] Heart failure as a secondary diagnosis is important for several reasons.[3]

- The diagnosis of heart failure is usually first made during a hospital admission and this will often be due to a precipitating cause such as an acute coronary syndrome, arrhythmia or infection.[129]
- An acute medical problem that is complicated by heart failure might be more likely to lead to admission.
- Although heart failure might not cause admission it might be the key illness that dictates the length of hospital stay and prognosis.
- When heart failure is due to LVSD, it should usually be treated with disease modifying agents whether it is a primary or secondary diagnosis.

  Hospitalisation offers an opportunity to review and improve management,

> although sadly the reverse is often the case on general medical wards, although this may be improving with the introduction of heart failure 'out-reach'.

Most previous audits, registries and publications reporting on deaths and discharges for heart failure focussed only on patients with heart failure as a primary discharge diagnosis; a small minority of all hospitalisations complicated by heart failure. [16, 21, 24, 26] Little is known about the outcome of patients admitted for another reasons but in whom heart failure is either a secondary or incidental diagnosis. Moreover, it is likely that the diagnosis of heart failure is often overlooked during a hospital admission. Many patients are treated with and discharged on loop diuretics for no obvious reason other than symptoms and signs of congestion. Even if these patients do not have heart failure, it should be suspected and investigated, although this is often not the case.[59] Failure to consider all admissions with suspected heart failure will lead to a serious under-estimate of the health economic impact of heart failure and under-provision of resources for its care.

The Euro Heart Failure Survey 1 (EHFS-1) enrolled patients either discharged on loop diuretics or with a diagnosis of heart failure preceding, causing or complicating hospitalisation.[3] I explored the nature and importance of heart failure as a secondary or incidental diagnosis in this data-set.

## 6.2 Methods

In the EHFS-1 consecutive deaths and discharges primarily from medical wards were screened over a 6 week period during 2000-2001 from 115 hospitals in 24 countries belonging to the European Society of Cardiology, to identify patients with

known or suspected HF.[3 22] The design and implementation of the survey have been published in detail previously.[111] Information was gathered from patients' case notes to identify if the patient fulfilled one or more of the following inclusion criteria; the criteria were deliberately set wide in order to capture as much relevant diagnostic and therapeutic activity as possible:[3]

5. A diagnosis of heart failure on the index admission, irrespective of the primary reason for admission.
6. A diagnosis of heart failure recorded in the hospital records at any time during the previous three years.
7. Loop diuretics given in the 24 hours prior to death or at discharge, unless for renal failure.
8. Administration of treatment for heart failure or major ventricular dysfunction within the 24 hours prior to death or discharge. Investigators especially reviewed the use of angiotensin converting enzyme inhibitors (ACE-I), beta blockers, mineralo-corticoid receptor antagonists (MRA), diuretics and digitalis compounds during this period to ascertain the reason for administration.

Admissions were then classified by investigators, according to their personal opinion, as follows:-

- Heart failure as the primary diagnosis
- Heart failure as a secondary diagnosis, complicating or prolonging admission
- Heart failure as an incidental finding or diagnostically uncertain

Presentation, events contributing to this admission, cardiovascular investigations, comorbid illnesses and therapy were recorded. Deaths occurring during the index hospital admission and deaths and readmissions up to 3 months after discharge were reported.

Continuous data are summarized by the median (25th/75th centiles); categorical data by percentages. Prognostic models for all-cause mortality were developed using Cox regression. The proportionality of hazards (PH) assumption was verified for all covariates using tests based on Schoenfeld residuals. [114, 130] There was no departure from the proportional hazard assumption for any covariate. Cox metrics include the hazard ratio (HR), 95% confidence intervals (CIs) and pseudo r2 (the square of the correlation coefficient of the actual and predicted values of the dependent variable). This is a measure of goodness-of-fit.[130] Prognostic models were developed using k-fold cross-validation.[113] This procedure splits the data randomly into k partitions. For each partition, it fits the specified model using the other k-1 groups, and uses the resulting parameters to predict the dependent variable in the unused group. We arbitrarily chose k as 25 (hence 25-fold cross-validation). [131] We started with 50 variables and then selected nine variables that were significant in at least 70% of cross-validations for the final model to assess mortality during the index hospital admission.

Kaplan-Meier curves constructed using the log-rank test was used to compare outcomes in groups during index admission. I used logistic regression to assess mortality and readmission within 12 weeks after discharge from index admission. An arbitrary level of 5% statistical significance (two-tailed) was assumed. The Stata statistical computer package 13 was used to analyse the data.

## 6.3 Results

Of 10,701 patients admitted with suspected HF, heart failure was considered to be the primary reason for admission in 4,234 (40%), the secondary (if HF complicated or prolonged hospital stay) in a further 1,772 (17%), and in 4,695 (43%) it was uncertain whether HF was actively contributing to the admission. The clinical characteristics of each group are shown in Table 17. Although there were statistical differences in age and sex amongst the three groups, these were small and of dubious clinical relevance. More patients with a primary diagnosis of HF were prescribed loop diuretics at admission and discharge (71% & 84%) but this was only slightly greater than amongst patients with an incidental or uncertain finding of HF (58% & 74% respectively) (Table 17). Indeed, there were remarkably few substantial differences amongst the three groups of patients. More patients with a secondary diagnosis of heart failure had a primary diagnosis of ACS. More patients with a primary diagnosis of heart failure had a dilated cardiomyopathy. Chest pain, arrhythmias, respiratory infection and cardiac procedures were the most common primary reasons for admission when HF was a secondary or incidental diagnosis. However, this fails to highlight the importance of infection as a secondary problem precipitating or complicating admission; this is shown in Table 18. Although statistical differences were observed, there was no substantial difference in smoking or alcohol consumption amongst the three groups. The reliability of patient reporting and clinical documentation of alcohol consumption is open to question (Table 18). Although factors such as worsening heart failure, atrial fibrillation or ACS may be important precipitants for admission these may be triggered or complicated by non-cardiovascular problems. Some of these are shown in Table 18. This picture is

**Table 17 : Clinical Characteristics**

| Table 17 | *Primary* | *Secondary* | *Uncertain* | *P--Value* |
|---|---|---|---|---|
| N = (%) | 4,234 (40%) | 1,772 (17%) | 4,695 (44%) | |
| Age in Years (IQR) | 72 (63-80) | 74 (65-80) | 73 (64-80) | <0.001 |
| Women | 1,890 (45%) | 837 (47%) | 2,293 (49%) | <0.001 |
| BMI ($kg/m^2$) | 26 (24-29) | 26 (24-30) | 27 (24-30) | 0.1 |
| Loop diuretics prior to admission | 2,782 (71%) | 859 (52%) | 2,395 (58%) | <0.001 |
| Loop diuretics at discharge | 3,532 (84%) | 1,359 (77%) | 3,455 (74%) | <0.001 |
| MI during this admission | 215 (5%) | 456 (26%) | 413 (9%) | <0.001 |
| MI (anytime) | 1,421 (34%) | 844 (48%) | 1,746 (37%) | <0.001 |
| UA this admission | 417 (10%) | 331 (19%) | 724 (16%) | <0.001 |
| UA (anytime) | 902 (21%) | 523 (30%) | 1,199 (26%) | <0.001 |
| h/o Angina (anytime) | 1,785 (43%) | 961 (55%) | 2,362 (51%) | <0.001 |
| PCI this admission | 82 (2%) | 79 (4%) | 203 (4%) | <0.001 |
| PCI (anytime) | 277 (7%) | 147 (8%) | 455 (10%) | <0.001 |
| CABG during this admission | 55 (1%) | 68 (4%) | 199 (4%) | <0.001 |
| CABG (anytime) | 400 (9%) | 199 (11%) | 613 (13%) | <0.001 |
| Heart transplant this admission | 9 (<1%) | 1 (<1%) | 18 (<1%) | 0.05 |
| Heart Transplant | 13 (<1%) | 2 (<1%) | 36 (<1%) | <0.001 |

| Table 17 | | | | |
|---|---|---|---|---|
| | *Primary* | *Secondary* | *Uncertain* | *P--Value* |
| (anytime) | | | | |
| LVAD implanted this admission | 12 (<1%) | 4 (<1%) | 3 (<1%) | 0.03 |
| LVAD implanted (anytime) | 23 (<1%) | 8 (<1%) | 9 (<1%) | 0.02 |
| Evidence for DCM this admission | 722 (17%) | 101 (6%) | 277 (6%) | <0.001 |
| Evidence for DCM (anytime) | 755 (18%) | 115 (7%) | 336 (7%) | <0.001 |
| Valve replacement this admission | 104 (2%) | 32 (2%) | 159 (3%) | <0.001 |
| Valve replacement (anytime) | 278 (7%) | 70 (4%) | 290 (6%) | <0.001 |
| Valve repair this admission | 33 (1%) | 7 (0.4%) | 49 (1%) | 0.03 |
| Valve repair (anytime) | 93 (2%) | 28 (2%) | 99 (2%) | 0.28 |
| New onset or paroxysmal AF/SVT | 1,018 (24%) | 482 (27%) | 1,046 (22%) | <0.001 |
| Chronic AF/SVT | 1,228 (29%) | 351 (20%) | 903 (19%) | <0.001 |
| VT/VF this admission | 239 (6%) | 156 (9%) | 143 (3%) | <0.001 |
| VT/VF (anytime) | 382 (9%) | 196 (11%) | 296 (6%) | <0.001 |
| Brady-arrhythmia this admission | 210 (5%) | 168 (10%) | 261 (6%) | <0.001 |
| Brady-arrhythmia | 424 (10%) | 236 (13%) | 476 (10%) | <0.001 |

Table 17

| | *Primary* | *Secondary* | *Uncertain* | *P--Value* |
|---|---|---|---|---|
| (anytime) | | | | |
| PPM this admission | 137 (3%) | 61 (3%) | 165 (4%) | 0.76 |
| PPM (anytime) | 393 (9%) | 139 (8%) | 347 (7%) | 0.004 |
| ICD implanted this admission | 32 (1%) | 11 (1%) | 27 (1%) | 0.56 |
| ICD implanted (anytime) | 70 (2%) | 23 (1%) | 60 (1%) | 0.29 |
| h/o Hypertension (anytime) | 2,245 (53%) | 982 (56%) | 2,452 (53%) | 0.06 |
| Disabling stroke this admission | 43 (1%) | 67 (4%) | 128 (3%) | <0.001 |
| Disabling stroke (anytime) | 303 (7%) | 198 (11%) | 438 (9%) | <0.001 |
| Non disabling stroke/TIA this admission | 42 (1%) | 54 (3%) | 128 (3%) | <0.001 |
| Non disabling stroke/TIA (anytime) | 348 (8%) | 196 (11%) | 539 (12%) | <0.001 |
| Syncope or blackouts this admission | 182 (4%) | 190 (11%) | 417 (9%) | <0.001 |
| Syncope or blackouts (anytime) | 501 (12%) | 347 (20%) | 783 (17%) | <0.001 |
| Dementia or confusion this admission | 383 (9%) | 281 (16%) | 478 (10%) | <0.001 |

Table 17

| | *Primary* | *Secondary* | *Uncertain* | *P--Value* |
|---|---|---|---|---|
| Dementia or mental confusion (anytime) | 422 (10%) | 301 (17%) | 544 (12%) | <0.001 |
| Renal failure this admission | 815 (19%) | 328 (19%) | 512 (11%) | <0.001 |
| Renal failure (anytime) | 882 (21%) | 358 (20%) | 593 (13%) | <0.001 |
| Respiratory disease (anytime) | 1,332 (32%) | 653 (37%) | 1,392 (24%) | <0.001 |
| Gout this admission | 192 (5%) | 54 (3%) | 154 (3%) | 0.002 |
| Gout (anytime) | 256 (6%) | 77 (4%) | 223 (5%) | 0.005 |
| Arthritis (anytime) | 358 (9%) | 242 (14%) | 499 (11%) | <0.001 |
| DM (anytime) | 1,193 (28%) | 494 (28%) | 1,220 (26%) | 0.05 |
| Pulmonary embolism this admission | 47 (1%) | 31 (2%) | 58 (1%) | 0.13 |
| Pulmonary embolism (anytime) | 129 (3%) | 78 (4%) | 145 (3%) | 0.02 |

HF; Heart failure, BMI; Body mass index, MI; Myocardial infarction, UA; Unstable angina, PCI; Percutaneous coronary intervention, CABG; Coronary artery bypass grafting, DCMP; Dilated cardiomyopathy, AF; Atrial fibrillation, SVT; Supraventricular tachycardia, VT; Ventricle tachycardia, VF; Ventricle fibrillation, TIA; Transient Ischaemic attack, DM; Diabetes Mellitus.

**Table 18 Non-Cardiovascular Factors that may have precipitated this admission**

| *Table 18* | *Primary* | *Secondary* | *Uncertain* | *P--Value* |
|---|---|---|---|---|
| N = (%) | 4,234 (40%) | 1,772 (17%) | 4,695 (44%) | |
| Infection at admission | 868 (21%) | 569 (33%) | 1,108 (24%) | <0.001 |
| Infection developed after admission | 461 (11%) | 146 (8%) | 363 (8%) | <0.001 |
| Non-compliance with medication at admission | 239 (6%) | 90 (5%) | 155 (4%) | <0.001 |
| Side effects of treatment at admission | 158 (4%) | 84 (5%) | 192 (4%) | 0.12 |
| Side effects of treatment (anytime) | 236 (6%) | 122 (7%) | 280 (6%) | 0.16 |
| Dietary salt excess | 110 (3%) | 30 (2%) | 26 (1%) | <0.001 |

HF; Heart Failure

dominated by infection. However, non-compliance and dietary salt excess may have been poorly documented in case notes and, consequently, their importance underestimated. Patients with a primary or secondary diagnosis of HF exhibited broadly similar echocardiographic features although the prevalence and severity of abnormalities tended to be greater in those with a primary diagnosis. Patients with an incidental or uncertain diagnosis were much less likely to have had an echocardiogram. This highlights an important point; surveys that include only patients with a confirmed diagnosis of heart failure are an unreliable source of data on the quality of diagnostic investigation.

**Table 19 : Life Style choices**

| Table 19 | *Primary* | *Secondary* | *Uncertain* | *P--Value* |
|---|---|---|---|---|
| N = (%) | 4,234 (40%) | 1,772 (17%) | 4,695 (44%) | |
| Smoker - Previous | 1,485 (43%) | 689 (47%) | 1,781 (49%) | <0.001 |
| Smoker - Current | 462 (13%) | 263 (17%) | 569 (14%) | <0.001 |
| Heavy Alcohol Consumption - Previous | 287 (8%) | 103 (7%) | 259 (7%) | 0.12 |
| Heavy Alcohol Consumption - Current | 130 (4%) | 52 (3%) | 134 (3%) | 0.93 |

HF, Heart Failure

It is likely that a diagnosis of HF would have been confirmed in a large proportion of patients had adequate diagnostic investigation been conducted. There was no substantial difference in laboratory investigations, although patients with an incidental or uncertain diagnosis of HF had, statistically, better renal function. Most patients in all three groups had either cardiomegaly or signs of pulmonary congestion or both on their chest X-ray although the proportion was substantially greater in those with a primary or secondary diagnosis of heart failure (Table 21)

**Table 20 : Cardiac dysfunction**

| *Table 20* | *Primary* | *Secondary* | *Uncertain* | *P--Value* |
|---|---|---|---|---|
| N = (%) | 4,234 (40%) | 1,772 (17%) | 4,695 (44%) | |
| Number with echo data | 2,854 | 945 | 2,339 | |
| Mild LVSD | 451 (16%) | 187 (20%) | 469 (20%) | <0.001 |
| Moderate / Severe LVSD | 1,652 (58%) | 489 (52%) | 951 (41%) | <0.001 |
| Most recent median LVEF (IQR) | 40% (28-50) | 40% (30-53) | 45% (35-58) | <0.001 |
| Moderate / Severe LV diastolic dysfunction | 415 (15%) | 139 (15%) | 266 (11%) | <0.001 |
| Moderate / Severe LV dilatation | 1,026 (36%) | 222 (23%) | 462 (20%) | <0.001 |
| Moderate / Severe LA dilatation | 1,139 (40%) | 265 (28%) | 574 (25%) | <0.001 |
| Moderate / Severe Mitral Stenosis | 111 (4%) | 22 (2%) | 73 (3%) | 0.06 |
| Moderate / Severe Mitral Regurgitation | 1,080 (38%) | 271 (29%) | 574 (25%) | <0.001 |
| Moderate / Severe Aortic stenosis | 275 (10%) | 59 (6%) | 163 (7%) | <0.001 |
| Moderate / Severe Aortic regurgitation | 268 (9%) | 64 (7%) | 169 (9%) | 0.004 |
| Moderate / Severe Right ventricle dysfunction | 262 (9%) | 62 (7%) | 93 (4%) | <0.001 |
| Moderate / Severe Pulmonary hypertension | 674 (24%) | 131 (14%) | 266 (11%) | <0.001 |

HF; Heart Failure, LVSD; Left ventricle systolic dysfunction, IQR; Interquartile Range, LVEDD; Left ventricle end diastolic diameter, LVESD; Left Ventricle end systolic diameter, LV; Left ventricle, LA; Left atrium.

**Table 21 : Investigations during index admission**

| Table 21 | *Primary* | *Secondary* | *Uncertain* | *P--Value* |
|---|---|---|---|---|
| N = (%) | 4,234 (40%) | 1,772 (17%) | 4,695 (44%) | |
| Haemoglobin (g/dl) | 12.9 (11.4-14.2) | 12.7 (11.3-14.2) | 12.9 (11.3-14.2) | 0.15 |
| Sodium (mmol/l) | 139 (136-142) | 139 (136-142) | 139 (136-142) | 0.06 |
| Potassium | 4.3 (3.9- 4.7) | 4.3 (3.9-4.7) | 4.2 (3.9-4.6) | 0.01 |
| Urea mmol/l | 10.71 (7-17.6) | 11.02 (7-17.85) | 8.9 (6.2-14.5)` | <0.001 |
| Creatinine (umol/l) | 106 (88.4-135) | 106 (88.4-141) | 101 (83-126) | <0.001 |
| Cholesterol most recent (mmol/l) | 4.89 (3.9-5.8) | 5.1 (4.1-5.93) | 5.1 (4.3-5.92) | <0.001 |
| Chest X-Ray: Cardiomegaly/Pulmonary congestion | 3,218 (86%) | 1,205 (78%) | 2,281 (61%) | <0.001 |

*****Median and Interquartile range (IQR) are shown in continuous variables.

During the index admission, 16% (290) of those with a secondary diagnosis of HF, 7% (301) of those with a primary diagnosis of HF and 4% (189) of those in whom the diagnosis was uncertain died. The unadjusted Hazard ratios (HR) were 3.26 for secondary HF group and 1.73 for primary HF as compared to the group with an uncertain diagnosis)(Figure 13). Worsening HF was the main factor contributing death in those with a primary or secondary diagnosis of HF and for 18% of those in the uncertain group. Myocardial infarction contributed to death in 34% of deaths where HF was a secondary diagnosis but only 18% where HF was a primary diagnosis and 16% when the diagnosis of HF was uncertain (Table 22). Stroke was an important contributor to death amongst patients with an incidental diagnosis of HF.

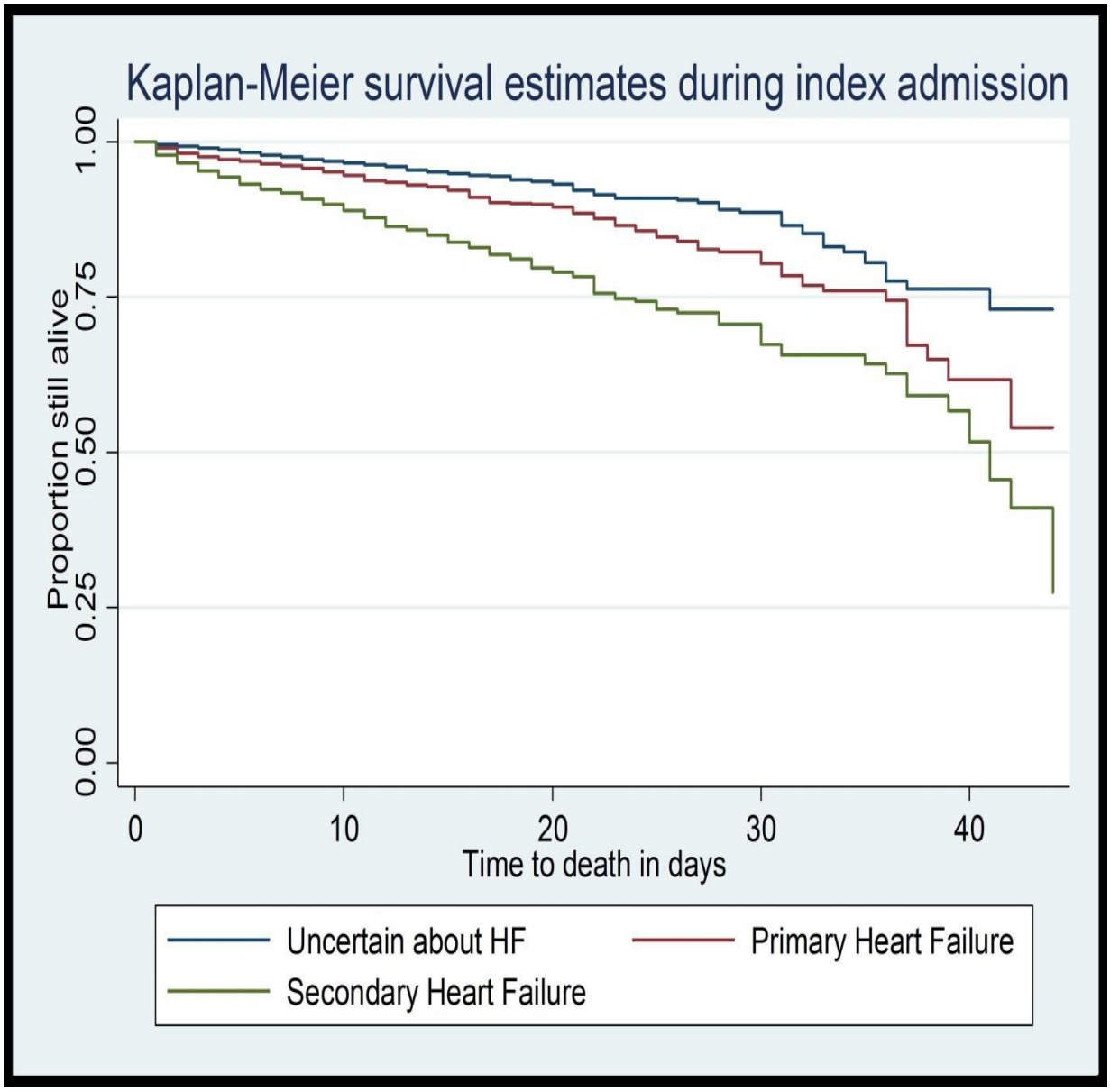



**Figure 13 : Kaplan- Meier survival estimates during index admission**

**Table 22 : Mortality & Length of stay (LOS) during index admission**

| Table 22 | *Primary* | *Secondary* | *Uncertain* | *P--Value* |
|---|---|---|---|---|
| N = (%) | 4,234 (40%) | 1,772 (17%) | 4,695 (44%) | |
| Deaths | 301 (7%) | 290 (16%) | 189 (4%) | <0.001 |
| Unadjusted HR (95% CI) | 1.73 (1.43-2.08) | 3.26 (2.70-3.93) | | |
| Events Contributing to death (proportion deaths) | | | | |
| MI | 53 (18%) | 100 (34%) | 31 (16%) | <0.001 |
| Worsening HF | 239 (79%) | 203 (70%) | 35 (18%) | <0.001 |
| Renal Failure | 79 (26%) | 76 (26%) | 21 (11%) | <0.001 |
| Ventricular Arrhythmia | 42 (14%) | 35 (12%) | 13 (7%) | <0.001 |
| Atrial Arrhythmia | 35 (12%) | 39 (13%) | 8 (4%) | <0.001 |
| Infection | 87 (29%) | 93 (32%) | 57 (30%) | <0.001 |
| Stroke | 6 (2%) | 31 (11%) | 32 (17%) | <0.001 |
| Cancer | 10 (3%) | 22 (8%) | 30 (16%) | <0.001 |
| Other | 43 (14%) | 76 (26%) | 72 (38%) | <0.001 |
| Median LOS during index admission in days (IQR) | 8 (4-14) | 11 (8-17) | 8 (4-13) | <0.001 |

HF; Heart Failure, HR; Hazard ration, CI; Confidence interval, MI; Myocardial Infarction, IQR; Interquartile range, LOS; Length of stay

Length of stay was on average three days longer in patients who had a secondary diagnosis of HF compared to the other two groups.

Table 23 is describing mode of death during index admission. After adjusting for prognostic variables male sex, MI during index admission, unstable angina during index admission, evidence of dilated cardiomyopathy, history of ventricular

tachycardia or fibrillation, history of stroke and moderate to severe left ventricle dilatation present in our final model, the HR for death during the index admission was 3.45 (CI 2.29-5.22) for those with a secondary diagnosis of HF and 2.55 (CI 1.73 – 3.77) for those with a primary diagnosis of HF (Table 24). Harrell's C statistic was 0.72 for the overall model suggesting moderate discrimination

Drugs at discharge or within 24 hours before death are shown in Table 25.

There were few substantial differences in prescription rates; only for digoxin was there a >20% difference in prescribing rates with those assigned a primary diagnosis prescribed 48% versus 26% in those with an incidental diagnosis. The absolute difference in prescribing rate of loop diuretics, ACE inhibitors and MRA were 10-20% higher in patients with an incidental compared to a primary diagnosis of HF. However, the proportion of patients prescribed beta blockers was similar in all three groups, although statistically lower in those with a primary diagnosis of HF

In the 12 weeks following discharge, 287 (7%) patients with a primary, 117 (8%) with a secondary and 238 (5%) with an incidental or uncertain diagnosis of HF died. The odds ratio (OR) for death was 1.30 (CI 1.01-1.55) for a primary and 1.47 (CI 1.16-1.85) for a secondary diagnosis compared to those with an incidental or uncertain diagnosis (Table 26). However, no significant difference was observed in multi-variable analysis. The area under receiver operator characteristics (ROC) curve was 0.55 for the final model.

**Table 23: Mode of death during index admission**

| Table 23<br>N = (%) | *Primary*<br>4,234 (40%) | *Secondary*<br>1,772 (17%) | *Uncertain*<br>4,695 (44%) | *P--Value* |
|---|---|---|---|---|
| Deaths | 301 (7%) | 290 (16%) | 189 (4%) | <0.001 |
| Mode of death (proportion deaths) | | | | |
| Cardiogenic shock | 120 (40%) | 109 (38%) | 26 (14%) | <0.001 |
| Pulmonary oedema | 98 (33%) | 80 (28%) | 14 (7%) | <0.001 |
| Stroke | 5 (2%) | 23 (8%) | 25 (13%) | <0.001 |
| Other cardiovascular disease | 50 (17%) | 60 (21%) | 31 ((16%) | <0.001 |
| Cancer | 10 (3%) | 22 (8%) | 30 (16%) | <0.001 |
| Accident or violence | 0 | 0 | 2 | |
| Other Non-cardiovascular cause | 28 (9%) | 64(22%) | 45 (24%) | <0.001 |
| Sudden death | 24 (8%) | 23 (8%) | 18 (10%) | <0.001 |
| Cardiac cachexia | 14 (5%) | 4 (1%) | 3 (2%) | 0.01 |
| | | | | |

**Table 24 : Multi variable Cox Model Showing Variables Associated with Death during the Index Admission**

| Table 24 | *Hazard Ratio* | *Standard error* | *Z Statistics* | *P Value* | *95% Confidence interval* |
|---|---|---|---|---|---|
| Primary HF | 2.55 | 0.50 | 4.74 | <0.001 | 1.73 - 3.76 |
| Secondary HF | 3.45 | 0.72 | 5.90 | <0.001 | 2.28 – 5.22 |
| Male | 0.81 | 0.11 | -1.55 | 0.12 | 0.62 – 1.05 |
| MI during index admission | 1.79 | 0.30 | 3.45 | 0.001 | 1.29 – 2.50 |
| Admission for UA during this admission | 0.96 | 0.20 | -0.22 | 0.83 | 0.64 – 1.42 |
| Evidence for DCMP (anytime) | 1.19 | 0.23 | 0.91 | 0.36 | 0.82 – 1.73 |
| VT/VF diagnosed (anytime) | 1.78 | 0.29 | 3.54 | <0.001 | 1.29 – 2.45 |
| Disabling stroke (anytime) | 1.47 | 0.29 | 1.89 | 0.06 | 0.98 – 2.19 |
| Moderate / Severe LV dilatation | 0.94 | 0.15 | -0.37 | 0.71 | 0.69 – 1.28 |
| Creatinine (umol/l) | 1.07 | 0.001 | 4.70 | <0.001 | 1.04 – 1.09 |

HF; Heart failure, MI; Myocardial Infarction, UA; Unstable angina, DCMP; Dilated cardiomyopathy, VT; Ventricle tachycardia, VF; Ventricle fibrillation, LV; Left ventricle, umol/l; Micro mole / per liter

**Table 25 : Drugs at discharge**

| Table 25 | *Primary* | *Secondary* | *Uncertain* | *P—Value* |
|---|---|---|---|---|
| | 4,234 (40%) | 1,772 (17%) | 4,695 (43%) | |
| Spironolactone | 1,357 (32%) | 300 (17%) | 540 (12%) | <0.001 |
| Furosemide | 3,489 (82%) | 1,335 (75%) | 3,327 (71%) | <0.001 |
| Bumetanide | 126 (3%) | 4 (2%) | 110 (2%) | 0.16 |
| Torasemide | 163 (4%) | 64 (4%) | 140 (3%) | 0.07 |
| Metolazone | 77 (2%) | 19 (1%) | 21 (<1%) | <0.001 |
| Thiazide diuretic | 508 (12%) | 163 (9%) | 397 (8%) | <0.001 |
| ACEI | 2,964 (70%) | 1,069 (60%) | 2,577 (55%) | <0.001 |
| ARB | 218 (5%) | 50 (3%) | 213 (5%) | <0.001 |
| Nitrate | 1,872 (44%) | 817 (46%) | 2,005 (43%) | 0.04 |
| Calcium channel blockers | 773 (18%) | 361 (20%) | 1,131 (24%) | <0.001 |
| Beta blockers | 1,459 (34%) | 695 (39%) | 1,790 (38%) | <0.001 |
| Digoxin | 2,036 (48%) | 562 (32%) | 1,227 (26%) | <0.001 |
| Antiarrhythmic drugs | 703 (17%) | 272 (15%) | 599 (13%) | <0.001 |
| Lipid lowering drugs | 747 (18%) | 343 (19%) | 1,097 (23%) | <0.001 |

HF; Heart Failure, ACI; Angiotensin converting enzyme inhibitor, ARB; Angiotensin receptor blockers

Table 27 is describing pattern of modes of death after discharge. Re-admissions, all-cause, due to cardiovascular reasons or due to heart failure within 12 weeks after discharge were more common in patients with a primary, compared to a secondary or incidental/uncertain HF diagnosis (Table 26). For the composite outcome of cardiovascular re-admissions or cause or death within 12 weeks after discharge, the OR was 1.48 for those with a primary diagnosis and 1.30 for those with a secondary diagnosis, compared to those with an incidental/uncertain diagnosis of HF. However, again these differences were not statistically significant in multi variable analysis.

The area under ROC curve for the final model was 0.58 suggesting poor discrimination.

## 6.4 Discussion

Despite limitations, research survey and registries are a rich source of information which is closer to real-life patients as compare to those enrolled in clinical trials. Although some substantial differences were observed amongst patients with a primary, secondary or incidental/uncertain diagnosis of heart failure they were few; the three populations had greater similarities than differences. Importantly, the outcome after discharge for each group was similar in terms of mortality and re-admission, although the causes of readmission and death did appear to differ amongst groups. Most readmissions were for CV reasons amongst patients with a primary or secondary diagnosis of HF but only two-thirds of those with an incidental/uncertain diagnosis.

The characteristics of patients admitted to cardiology wards with a primary diagnosis of HF have been well described in many surveys. However, many patients with a primary diagnosis of HF are admitted under the care of general physicians or geriatricians and these are less well represented. One exception is the National Heart Failure audit for England & Wales which focuses on patients with a primary diagnosis of heart failure but includes a large proportion of patients managed on medical wards.[24]

**Table 26 : Mortality & Readmission within 12 Weeks after discharge**

| Table 26 | *Primary* | *Secondary* | *Uncertain* | ***P--Value*** |
|---|---|---|---|---|
| Deaths | 287 (7%) | 117 (8%) | 229 (7%) | 0.001 |
| Unadjusted OR (95% CI) | 1.30 (1.01-1.55) | 1.47 (1.16-1.85) | | |
| Events contributing to death (proportion deaths) | | | | |
| MI | 27 (9%) | 10 (9%) | 25 (11%) | 0.88 |
| Worsening HF | 114 (40%) | 29 (25%) | 50 (22%) | <0.001 |
| Renal Failure | 23 (8%) | 12 (10%) | 12 (6%) | 0.02 |
| Ventricular Arrhythmia | 22 (8%) | 2 (2%) | 7 (3%) | 0.002 |
| Atrial Arrhythmia | 8 (3%) | 4 (3%) | 8 (3%) | 0.87 |
| Infection | 24 (8%) | 17 (15%) | 40 (17%) | 0.16 |
| Stroke | 19 (7%) | 9 (8%) | 19 (8%) | 0.87 |
| Death caused by cancer | 16 (6%) | 9 (8%) | 28 (12%) | 0.27 |
| Other events contributing to death | 43 (15%) | 30 (26%) | 63 (28%) | 0.07 |
| Readmission within 12 weeks | | | | |

| Table 26 | *Primary* | *Secondary* | *Uncertain* | ***P--Value*** |
|---|---|---|---|---|
| after discharge | | | | |
| All cause | 961 (23%) | 344 (19%) | 980 (21%) | 0.01 |
| | OR 1.12 (CI 1.01-1.22) | OR 0.91 (CI 0.80 – 1.04) | | |
| Due to cardiovascular cause | 772 (18%) | 240 (14%) | 580 (13%) | <0.001 |
| | OR 2.92 (CI 2.38-3.58) | OR 1.61 (CI 1.24-2.09) | | |
| Due to Heart Failure | 517 (12%) | 134 (8%) | 240 (5%) | <0.001 |
| | OR 3.8 (CI 3.03-4.46) | OR 1.99 (CI 1.53-2.59) | | |

HF; heart failure, MI; Myocardial infarction, OR; Odd ratio, CI; Confidence interval

Table 27: Mode of death after discharge

| Table 27 | *Primary* | *Secondary* | *Uncertain* | *P--Value* |
|---|---|---|---|---|
| Deaths | 287 (7%) | 117 (8%) | 229 (7%) | 0.001 |
| Mode of death after discharge (proportion deaths) | | | | |
| Cardiogenic shock | 52 (18%) | 8 (7%) | 20 (9%) | <0.001 |
| Pulmonary oedema | 60 (21%) | 10 (9%) | 18 (8%) | <0.001 |
| Stroke | 17 (6%) | 7 (6%) | 16 (7%) | 0.88 |
| Other cardiovascular disease | 27 (9%) | 7 (6%) | 24 (10%) | 0.46 |
| Cancer | 16 (6%) | 9 (8%) | 29 (13%) | 0.27 |
| Accident or violence | 1 | 1 | | |
| Other Non-cardiovascular cause | 26 (9%) | 11 (9%) | 41 (31%) | 0.30 |
| Sudden death | 21 (7%) | 7 (6%) | 22 (10%) | 0.86 |
| Cardiac cachexia | 5 (2%) | 4 (3%) | 2 (1%) | 0.12 |

It is difficult to avoid selection bias in surveys of heart failure and this may have accounted for the relative youth in some countries, such as Germany, in this survey. However, in the UK and many Scandinavian countries, EHFS-1 appeared to be successful in recruiting older patients with much co-morbidity. It is likely that the EHFS-1 underestimated the full burden of this third large group of patients.

The management and outcome of heart failure as a secondary diagnosis has been less well-described. This survey shows that ACS is most often the primary diagnosis when HF is considered an important secondary diagnosis and that these patients have a poor in-hospital prognosis, although no worse than for patients with a primary diagnosis of HF if the patients survives to discharge.

However, the characteristics and outcome of the large number of patients in whom the diagnosis of HF is an incidental finding or diagnostically uncertain has rarely been described. Cleland et al described the outcome of patients discharged on loop diuretics with or without a diagnosis of heart failure in a prospective survey over 18 months from a single large hospital.[59] Only a small proportion (~15%) of patients taking loop diuretics had a primary diagnosis of HF and less than half had a diagnosis of HF in any diagnostic position. However, patients receiving loop diuretics who had not been diagnostically labelled as HF had only a slightly lower mortality at two years compared to those who bore a diagnosis of HF. The study showed that few of these patients underwent diagnostic tests for HF. This diagnostic short-fall was also observed in EHFS-1. It is likely that this population contains a large proportion of patients with HF who have the characteristics and poor prognosis of other patients with HF but diluted by patients treated inappropriately with diuretics with a range of disease, some malign (eg:- stroke and cancer) and others relatively benign (eg:- COPD). Ignoring the diagnostic and therapeutic needs of this group of patients is likely to be detrimental to their well-being and prognosis and seriously underestimates the resources required to manage HF and the economic burden it imposes.

The diagnostic uncertainty of HF is a dilemma.[110] Diagnostic tests such as echocardiography often require referral to the cardiology team which can be a barrier and rate-limiting step in many hospitals. Conventionally, this is considered part of the gold-standard for diagnosis although problems with reproducibility and interpretation skills have led to its central role being questioned. Natriuretic peptides can be measured in routine blood samples regardless of who is caring for the patient. This greatly democratizes access to the diagnostic pathway in HF. However,

although natriuretic peptides are useful to rule out HF they are considered prone to many false-positive results causing confusion for the inexperienced.[110] Symptoms of HF are often mimicked by other conditions especially respiratory tract problems like chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) and chest infections which may often co-exist with HF. Peripheral oedema in many older patients may be due to conditions other than HF. In the presence of many comorbid illnesses, treating clinicians may be uncertain whether HF is contributing to the admission or not, even if these patients have a prior history of heart failure. These patients often receive therapy, such as diuretics, to relieve symptoms. However, hospitalisation provides an opportunity to correct diagnosis and rationalise and improve therapy even if HF is not the primary reason for admission.

## 6.5 Limitations

EHFS1 was conducted at the turn of the century before the roles of beta blockers and cardiac resynchronization of therapy were well established. This will have influenced choice of therapy but should not have affected diagnosis. Natriuretic peptides were not recorded during admission. However, NT-proBNP was <125ng/L in only 47 of 2,368 patients in whom it was measured at the 12 week follow-up and 75% had values >400ng/L.[7] Median serum creatinine was 130umol/L indicating a substantial contribution of moderate renal dysfunction to increases in natriuretic peptides. About 25% were in atrial fibrillation, another cause for elevated plasma natriuretic peptide concentrations. However, even after controlling for renal dysfunction and atrial fibrillation, the increase in natriuretic peptides suggests that the great majority of patients had important cardiac dysfunction. Although, in surveys there are always chances of selection bias, EHFS1 was designed to avoid

this confounding factor as much as possible.[111] In particular, the short but intense collection period, the attempt to recruit from medical wards and the high proportion of non-University hospitals should have reduced bias. However, without 100% ascertainment of suspected cases from a prospectively defined sampling frame it is impossible to be sure that no bias occurred. Indeed, it is likely that there was a bias towards sampling patients from cardiology wards and against patients in whom the diagnosis was in doubt.

## 6.6 Conclusion

Mortality is high even if heart failure is not main reason of admission but complicates another primary diagnosis. The high mortality may reflect the prognosis of the primary disease or other patient characteristics that impair the delivery of effective care, including the place of care. Mortality amongst patients with an equivocal diagnosis of HF is also substantial and there appears to be a large diagnostic short-fall. Registries and surveys that do not include patients with HF as a contributory diagnosis may provide an over-optimistic view of prognosis and underestimate the resources required for diagnosis and effective management.

# Chapter 7 **Does the mode of presentation affect the mortality of patients presenting with acute heart failure? A report from Euro Heart Failure Survey-1(EHFS-1)**

## 7.1 Introduction

Acute Heart Failure is heterogeneous in nature; patients vary in clinical presentation, underlying aetiology and pathophysiology. European Society of Cardiology (ESC) 2008 guidelines classify AHF into six different clinical presentations, amongst which there is considerable overlap. Most events are classified as decompensated chronic HF and the rest as acute pulmonary oedema, cardiogenic shock, right HF or associated with severe hypertension or acute coronary syndrome.[7] It is clear that AHF is not a discrete diagnosis but a collection of different clinical syndromes that require urgent clinical intervention.[6] If the purpose and target of therapy is diverse then trials that treat AHF syndromes as a single entity are likely to fail. Better characterization of the heterogeneous clinical presentation of AHF might help inform the design of future clinical trials that target the unmet needs of specific presentations of AHF. Accordingly, we obtained information from the EuroHeart Failure -1 Survey that enrolled more than 10,000 patients from 115 hospitals over a 6 week period in order to describe the outcome of patients with different presentations of AHF.[3]

## 7.2 Methods

Euro heart failure survey-1 (EHFS1) screened consecutive deaths and discharges during 2000-2001 primarily from medical wards over a 6 week period in 115 hospitals from 24 countries in Europe, to identify patients with known or suspected

HF. The design and implementation of the survey have been published in detail previously and described in chapter 6 as well.[111]

Patients, who fulfilled one or more inclusion criteria, as described earlier in chapter 6, were further classified according to clinical presentation, aetiology, final diagnosis and whether HF was the primary diagnosis, a secondary diagnosis complicating hospital admission or an incidental finding.

Classification of Presentation

Presentation at hospital admission was classified hierarchically (patients belonging to a preceding class could not belong to any subsequent class) as follows:-

1. Cardiac arrest, ventricular tachycardia or ventricle fibrillation or cardiogenic shock.
2. Acute myocardial infarction (AMI) or unstable angina
3. AF with rapid ventricular response (>120/minute)
4. Acute shortness of breath
5. Asymptomatic cardiac dysfunction
6. Other symptoms of HF, such as worsening peripheral oedema
7. Contribution of HF to admission uncertain

Detailed information regarding events contributing to the current admission, cardiovascular and non-cardiovascular comorbid illnesses, and clinical investigations during admission and therapy at discharge or 24 hours prior to death were gathered.

Deaths during the index hospital admission and deaths and readmissions within 12 weeks after discharge were recorded.

As time to event data were not recorded after discharge, prognostic models for all-cause mortality were developed using Logistic regression. Prognostic models were developed using k-fold cross-validation as described in chapter 3.[113] We started with 50 clinical relevant variables and then selected those variables in the final model that remain significant at least in 70% of cross-validations. The significance level to remain in model was first set 0.05 and then 0.1 for each model. From the logistic regression models, Receiver Operating Characteristic (ROC) curves were plotted as sensitivity versus 1-specificity. An area under the ROC curve was calculated using methods outlined in Hanley and McMeil.[132] The area under the ROC represents the probability of classifying an individual as dead/alive. An area under the ROC curve of 1.0 means perfect classification, while an area of 0.5 means classification is no better than chance. The Stata 13 statistical computer package was used to analyse the data.

## 7.3 Results

Heart failure was the primary diagnosis in 4,234 (40%) patients, a secondary diagnosis in 1,772 (17%) patients and was considered not to have caused or complicated and admission in 4,695 patients. The most common presentations were HF as an uncertain or incidental finding (44%), acute breathlessness (24%), other (10% - presumed mostly to be admissions for the management of peripheral oedema) and rapid atrial fibrillation (8%). Some patients had no symptoms of heart failure at the time of admission (7%) or had acute coronary syndromes (5%) or cardiac arrest or cardiogenic shock (2%) (Figure14).

Data are presented in following tables

Table 28: Clinical Characteristics

Table 29: Factors that may have precipitated this admission

Table 30: Life Style choices

Table 31: Cardiac dysfunction

Table 32: Investigations during index admission

Table 33: Mortality & Length of stay during index admission

Table 34: Drugs at discharge or 24 Hours prior to death

Table 35: Mortality & Readmission within 12 Weeks after discharge

Table 36: Mode of death during index admission

Table 37: Mode of death after discharge

Table 38: Logistic regression model for mortality during index admission

Patients' baseline clinical characteristics are shown in Table 29. Of the 10,701 patients, HF was not thought to have made an important contribution to the admission in 4,695 (44%) patients. The median age of these patients and the proportion that were women was similar to that observed in most other classes of presentation. Of these patients, 58% were receiving loop diuretics on admission which increased to 74% at discharge; a similar proportion of patients were discharged on ACE inhibitors and beta-blockers to most other classes; about half had some history of ischaemic heart disease, 37% were in atrial fibrillation and 61% had

cardiomegaly or pulmonary congestion on their X-ray. About half of these patients had an assessment of cardiac function showing mild LVSD in 20% and moderate to severe LVSD in 41%, 30% were reported to have left atrial dilatation and 25% moderate to severe mitral regurgitation. Mortality during the index admission was lower than in other groups, although investigators stated that worsening heart failure contributed to 18% of deaths in this group despite not listing heart failure as an important reason for admission (Figure 15). Length of stay was slightly shorter than for most other groups. However, mortality in the 12 weeks after discharge was only slightly lower than in other groups, although fewer of these deaths appeared cardiovascular in nature. The rate of all-cause readmission was also slightly lower than in most other groups but these were less likely to be due to heart failure or CV reasons. In summary, this group had many features of heart failure and a substantial morbidity and mortality although cardiovascular problems appeared to drive outcome less frequently than in other groups.

Of the remaining 6,006 patients in whom HF was thought to cause or complicate admission, the most common presentation was breathlessness (n = 2,749; 46% of such patients). This group of patients was more likely to have had a prior admission with heart failure, be treated with loop diuretics and to have renal dysfunction and respiratory disease. Mortality during and after the index hospitalization and readmissions were only slightly greater than for patients in whom HF was not thought to make an important contribution to admission but events were more often attributed to worsening HF.

Patients in the groups classified as ‘other’, rapid AF or not having HF symptoms at presentation were similar in most respects to those presenting with breathlessness

both in terms of patient characteristics and outcome. Patients whose presentation was ACS, a ventricular arrhythmia, cardiac arrest or shock were less likely to have a prior history of HF but had a mortality exceeding 20% during the index admission. However, rates for readmission and death were similar in the 12 weeks after discharge to those presenting with breathlessness (Figure 16).

Table 29 shows factors that precipitated or complicated the index admission. Infection was the main factor identified. A substantial minority of patients were current smokers or admitted to heavy alcohol consumption (Table 30)

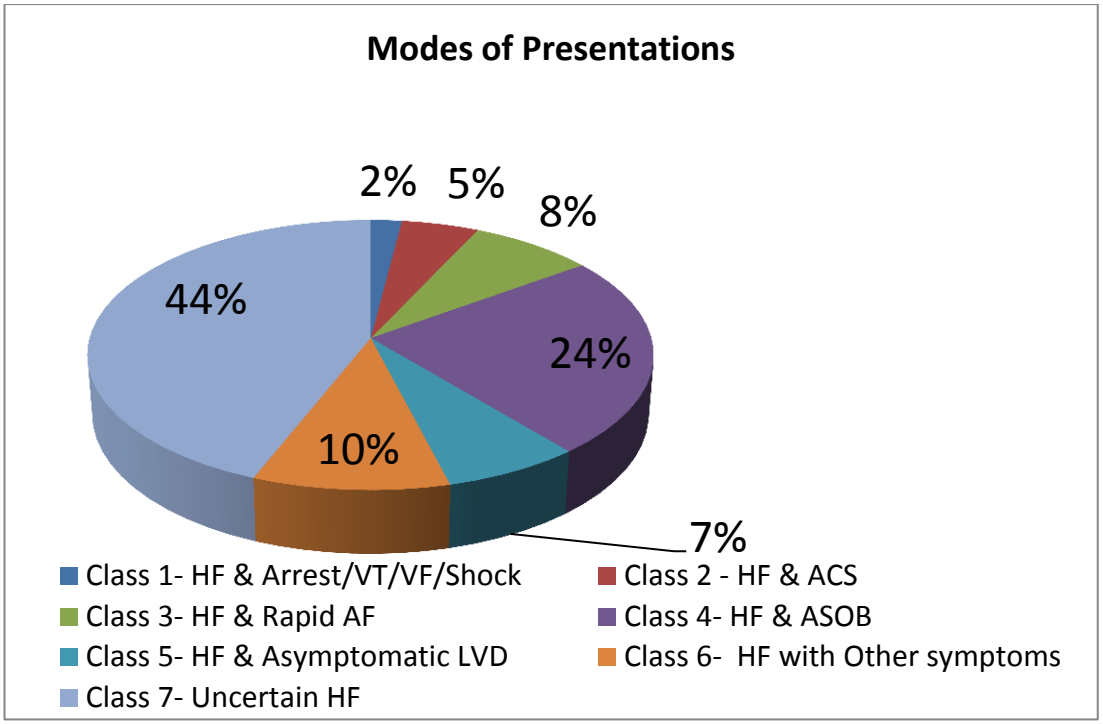



**Figure 14: Modes of Presentations**

HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath, VT; Ventricular tachycardia, Asymp LVD; asymptomatic Left ventricular systolic dysfunction

**Table 28: Clinical Characteristics**

| Table 28 | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
|---|---|---|---|---|---|---|---|
| Presentation | Arrest/VT / Shock | ACS | Rapid AF | ASOB | Asymp. LVD | Other | Uncertain |
| Numbers (%) | 260 (2%) | 560 (5%) | 799 (8%) | 2,479 (24%) | 703 (7%) | 1,040 (10%) | 4,695 (44%) |
| Age in years (IQR) | 69 (61-76) | 73 (66-81) | 75 (66-82) | 74 (66-80) | 66 (56-76) | 72 (62-79) | 73 (64-80) |
| Women (%) | 90 (35%) | 240 (43%) | 424 (53%) | 1,185 (48%) | 258 (37%) | 457 (44%) | 2,293 (49%) |
| BMI ($KG/M^2$) (IQR) | 26 (24-29) | 26 (24-29) | 26 (23-30) | 26 (23-29) | 26 (24-30) | 26 (24-30) | 27 (24-30) |
| Prior HF admission (%) | 89 (38%) | 92 (35%) | 322 (40%) | 1,136 (46%) | 320 (46%) | 429 (41%) | 708 (15%) |
| Loop diuretics prior to admission (%) | 131 (59%) | 184 (36%) | 408 (55%) | 1,651 (71%) | 530 (79%) | 665 (70%) | 2,395 (58%) |
| Loop diuretics prior to death or discharge (%) | 211 (82%) | 428 (77%) | 667 (84%) | 2,177 (88%) | 539 (77%) | 748 (72%) | 3,455 (74%) |
| MI - this admission | 87 (34%) | 493 (89%) | 13 (2%) | 43 (2%) | 10 (1%) | 9 (1%) | 413 (9%) |
| MI (anytime) | 146 (56%) | 530 (95%) | 183 (23%) | 782 (32%) | 213 (31%) | 335 (32%) | 1,746 (37%) |
| Admission for UA - this admission | 29 (11%) | 139 (25%) | 76 (10%) | 283 (11%) | 43 (6%) | 103 (10%) | 724 (16%) |
| Admission for UA (anytime) | 65 (25%) | 212 (38%) | 144 (18%) | 584 (24%) | 124 (18%) | 214 (21%) | 1,199 (26%) |

| Table 28 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
| H/O Angina - this admission | 99 (39%) | 280 (51%) | 196 (25%) | 790 (33%) | 211 (30%) | 448 (43%) | 1,788 (39%) |
| H/O Angina (anytime) | 126 (49%) | 323 (59%) | 281 (35%) | 1,105 (46%) | 293 (42%) | 522 (51%) | 2,362 (51%) |
| PCI - this admission | 18 (7%) | 51 (9%) | 8 (1%) | 30 (1%) | 20 (3%) | 20 (2%) | 203 (4%) |
| PCI (anytime) | 33 (13%) | 76 (14%) | 24 (3%) | 133 (5%) | 57 (8%) | 71 (7%) | 455 (10%) |
| CABG - this admission | 7 (3%) | 33 (6%) | 21 (3%) | 21 (1%) | 16 (2%) | 8 (1%) | 199 (4%) |
| CABG (anytime) | 31 (12%) | 66 (12%) | 53 (7%) | 244 (10%) | 78 (11%) | 95 (9%) | 613 (13%) |
| Heart transplant - this admission | 2 (1%) | 3 (1%) | 0 | 2 (0.1%) | 3 (0.5%) | 0 | 18 (0.4%) |
| Heart Transplant (anytime) | 2 (1%) | 3 (1%) | 1 (0.1%) | 3 (0.1%) | 4 (1%) | 1 (0.1%) | 36 (1%) |
| LVAD - this admission | 7 (3%) | 3 (1%) | 1 (0.1%) | 0 | 0 | 5 (0.5%) | 3 (0.1%) |
| LVAD (anytime) | 7 (3%) | 5 (1%) | 1 (0.1%) | 8 (0.3%) | 3 (0.4%) | 6 (1%) | 9 (0.2%) |
| Evidence for DCMP (anytime) | 48 (19%) | 32 (6%) | 88 (11%) | 380 (15%) | 181 (26%) | 128 (12%) | 336 (7%) |
| Valve replacement - this admission | 3 (1%) | 9 (2%) | 33 (4%) | 38 (2%) | 29 (4%) | 22 (2%) | 159 (3%) |
| Valve replacement (anytime) | 12 (5%) | 14 (3%) | 62 (8%) | 130 (5%) | 59 (8%) | 67 (6%) | 290 (6%) |
| Valve repair - this | 1 | 4 | 9 | 15 | 3 | 6 | 49 |

| Table 28 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
| admission | (0.5%) | (1%) | (1%) | (1%) | (0.5%) | (1%) | (1%) |
| Valve repair (anytime) | 8 (3%) | 5 (1%) | 19 (2%) | 52 (2%) | 13 (2%) | 21 (2%) | 99 (2%) |
| AF (%) | 111 (43%) | 188 (34%) | 765 (96%) | 1,006 (41%) | 239 (34%) | 415 (40%) | 1,738 (37%) |
| VT/VF - this admission | 144 (56%) | 69 (13%) | 47 (6%) | 57 (2%) | 31 (4%) | 40 (4%) | 143 (3%) |
| VT/VF diagnosed (anytime) | 148 (58%) | 77 (14%) | 62 (8%) | 134 (5%) | 74 (11%) | 72 (7%) | 296 (6%) |
| Brady-arrhythmia - this admission | 44 (17%) | 63 (11%) | 51 (6%) | 95 (4%) | 41 (6%) | 79 (8%) | 261 (6%) |
| Brady-arrhythmia (anytime) | 54 (21%) | 77 (14%) | 86 (11%) | 255 (9%) | 76 (11%) | 130 (13%) | 476 (10%) |
| Pacemaker - this admission | 23 (9%) | 16 (3%) | 19 (2%) | 56 (2%) | 33 (5%) | 46 (4%) | 165 (4%) |
| Pacemaker (anytime) | 41 (16%) | 31 (6%) | 51 (6%) | 219 (9%) | 81 (12%) | 96 (9%) | 347 (7%) |
| ICD - this admission | 17 (7%) | 4 (1%) | 0 | 7 (0.3%) | 1 (1%) | 8 (1%) | 27 (1%) |
| ICD (anytime) | 29 (11%) | 4 (1%) | 1 (0.1%) | 22 (1%) | 17 (2%) | 17 (2%) | 60 (1%) |
| h/o Hypertension - this admission | 109 (43%) | 282 (51%) | 342 (43%) | 1,176 (48%) | 311 (45%) | 498 (48%) | 2,138 (46%) |
| h/o Hypertension (anytime) | 132 (52%) | 329 (60%) | 398 (50%) | 1,377 (56%) | 347 (50%) | 550 (53%) | 2,452 (53%) |
| Disabling stroke - this admission | 4 (2%) | 17 (3%) | 8 (1%) | 28 (1%) | 17 (2%) | 29 (3%) | 128 (3%) |

| Table 28 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
| Disabling stroke (anytime) | 17 (7%) | 53 (10%) | 45 (6%) | 199 (8%) | 64 (9%) | 111 (11%) | 438 (9%) |
| Minor stroke/TIA - this admission | 6 (2%) | 12 (2%) | 12 (2%) | 26 (1%) | 15 (2%) | 19 (2%) | 128 (3%) |
| Minor stroke/TIA (anytime) | 26 (10%) | 50 (9%) | 70 (9%) | 230 (9%) | 65 (9%) | 87 (8%) | 539 (12%) |
| Syncope - this admission | 62 (24%) | 33 (6%) | 45 (6%) | 98 (4%) | 37 (5%) | 83 (8%) | 417 (9%) |
| Syncope (anytime) | 84 (32%) | 65 (12%) | 116 (15%) | 299 (12%) | 90 (13%) | 169 (16%) | 783 (17%) |
| Dementia/ Confusion - this admission | 26 (10%) | 66 (12%) | 99 (12%) | 260 (11%) | 68 (10%) | 133 (13%) | 478 (10%) |
| Dementia or confusion (anytime) | 29 (11%) | 72 (13%) | 108 (14%) | 288 (12%) | 71 (10%) | 141 (14%) | 544 (12%) |
| Renal Dysf - this admission | 68 (26%) | 117 (21%) | 128 (16%) | 502 (20%) | 128 (18%) | 181 (17%) | 512 (11%) |
| Renal Dysf. (anytime) | 72 (28%) | 124 (22%) | 145 (18%) | 554 (22%) | 131 (19%) | 193 (19%) | 593 (13%) |
| Resp. Disease - this admission | 53 (21%) | 119 (22%) | 234 (29%) | 846 (34%) | 136 (19%) | 250 (24%) | 1,118 (24%) |
| Resp. Disease (anytime) | 63 (25%) | 147 (27%) | 289 (36%) | 985 (40%) | 166 (24%) | 297 (29%) | 1,392 (30%) |
| Gout - this admission | 3 (1%) | 22 (4%) | 20 (3%) | 130 (5%) | 30 (4%) | 34 (3%) | 154 (3%) |
| Gout (anytime) | 6 (2%) | 29 (5%) | 30 (4%) | 171 (7%) | 42 (6%) | 47 (5%) | 223 (5%) |

Table 28

| | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
|---|---|---|---|---|---|---|---|
| Arthritis - this admission | 10 (4%) | 49 (9%) | 68 (9%) | 201 (8%) | 48 (7%) | 69 (7%) | 409 (9%) |
| Arthritis (anytime) | 13 (5%) | 56 (10%) | 86 (11%) | 271 (11%) | 72 (10%) | 88 (9%) | 499 (11%) |
| DM - this admission | 56 (22%) | 147 (26%) | 171 (22%) | 749 (30%) | 197 (28%) | 279 (27%) | 1,178 (25%) |
| DM (anytime) | 59 (23%) | 148 (26%) | 176 (22%) | 773 (31%) | 202 (29%) | 282 (27%) | 1,220 (26%) |
| PTE - this admission | 2 (1%) | 8 (1%) | 16 (2%) | 36 (1%) | 7 (1%) | 7 (1%) | 58 (1%) |
| PTE (anytime) | 11 (4%) | 15 (3%) | 29 (4%) | 92 (4%) | 17 (2%) | 37 (4%) | 145 (3%) |

HF; Heart failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath Asymp. LVD; Asymptomatic left ventricle dysfunction, BMI; Body mass index, MI; Myocardial infarction, USA; Unstable angina, PCI; Percutaneous coronary intervention, CABG; Coronary artery bypass grafting, DCMP; Dilated cardiomyopathy, SVT; Supraventricular tachycardia, VT; Ventricle tachycardia, VF; Ventricle fibrillation, TIA; Transient Ischaemic attack, DM; Diabetes Mellitus

**Table 29 : Factors that may have precipitated this admission**

| Table 29 | Class 1 | Class 2 | Class 3 | Class 4 | Class 5 | Class 6 | Class 7 |
|---|---|---|---|---|---|---|---|
| Presentation | Arrest/VT/ Shock | ACS | Rapid AF | ASOB | Asymp. LVD | Other | Uncertain |
| Numbers (%) | 260 (2%) | 560 (5%) | 799 (8%) | 2479 (24%) | 703 (7%) | 1,040 (10%) | 4,695 (44%) |
| Infection at presentation | 61 (24%) | 107 (19%) | 213 (27%) | 712 (29%) | 116 (17%) | 185 (18%) | 1,108 (24%) |
| Infection complicating admission | 79 (31%) | 157 (28%) | 290 (36%) | 974 (40%) | 174 (25%) | 316 (31%) | 1,471 (32%) |
| Non-compliance with meds at presentation | 3 (3%) | 20 (4%) | 51 (7%) | 176 (8%) | 31 (5%) | 43 (4%) | 155 (4%) |
| Side effects of treatment at presentation | 15 (6%) | 19 (4%) | 28 (4%) | 104 (4%) | 38 (6%) | 34 (3%) | 192 (4%) |
| Side effects of treatment complicating | 22 (9%) | 24 (4%) | 43 (6%) | 154 (7%) | 44 (6%) | 62 (6%) | 280 (6%) |

| Table 29 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Class 1 | Class 2 | Class 3 | Class 4 | Class 5 | Class 6 | Class 7 |
| admission | | | | | | | |
| Dietary salt excess at presentation | 5 (3%) | 10 (2%) | 20 (3%) | 71 (4%) | 16 (3%) | 16 (2%) | 26 (1%) |

HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath, VT; Ventricular tachycardia, Asymp LVD; asymptomatic Left ventricular systolic dysfunction

**Table 30 : Life Style choices**

| Table 30 | Class 1 | Class 2 | Class 3 | Class 4 | Class 5 | Class 6 | Class 7 |
|---|---|---|---|---|---|---|---|
| Presentation | Arrest/VT/ Shock | ACS | Rapid AF | ASOB | Asymp. LVD | Other | Uncertain |
| Numbers (%) | 260 (2%) | 560 (5%) | 799 (8%) | 2479 (24%) | 703 (7%) | 1,040 (10%) | 4,695 (44%) |
| Smoker previously | 85 (44%) | 218 (48%) | 257 (39%) | 905 (45%) | 311 (51%) | 335 (40%) | 1,781 (49%) |
| Current smoker | 40 (19%) | 108 (23%) | 76 (11%) | 273 (13%) | 69 (11%) | 134 (15%) | 569 (14%) |
| Heavy alcohol consumption previously | 18 (9%) | 22 (5%) | 59 (8%) | 167 (8%) | 42 (7%) | 77 (9%) | 259 (7%) |
| Current heavy alcohol consumption | 5 (2%) | 12 (3%) | 34 (5%) | 74 (3%) | 18 (3%) | 37 (4%) | 134 (3%) |

HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath, VT; Ventricular tachycardia, Asymp LVD; asymptomatic Left ventricular systolic dysfunction

**Table 31 : Cardiac dysfunction**

| Table 31 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Class 1** | **Class 2** | **Class 3** | **Class 4** | **Class 5** | **Class 6** | **Class 7** |
| Presentation | Arrest/VT/ Shock | ACS | Rapid AF | ASOB | Asymp. LVD | Other | Uncertain |
| Echo data available | 177 | 376 | 513 | 1,562 | 498 | 591 | 2,339 |
| | | | | | | | |
| Mild LVSD | 33 (19%) | 72 (19%) | 106 (21%) | 272 (17%) | 64 (13%) | 67 (11%) | 469 (20%) |
| Moderate / Severe LVSD | 122 (69%) | 240 (64%) | 245 (48%) | 840 (54%) | 317 (64%) | 346 (59%) | 951 (41%) |
| Most recent median LVEF (IQR) | 35 (26-46) | 39 (30-48) | 45 (33-55) | 40 (30-53) | 35 (25-50) | 40 (30-52) | 45 (35-58) |
| Moderate / Severe LV diastolic dysfunction | 31 (18%) | 60 (16%) | 71 (14%) | 217 (14%) | 66 (13%) | 97 (16%) | 266 (11%) |
| LVEDD (cm) | 5.7 (5.1-6.5) | 5.4 (5-6) | 5.6 (4.9-6.1) | 5.7 (5-6.4) | 6.1 (5.2-7) | 5.8 (5-6.7) | 5.3 (4.8-6) |

Table 31

| | **Class 1** | **Class 2** | **Class 3** | **Class 4** | **Class 5** | **Class 6** | **Class 7** |
|---|---|---|---|---|---|---|---|
| LVESD (cm) | 4.5 (3.8-5.6) | 4.2 (3.5-4.9) | 4.1 (3.5-5) | 4.3 (3.5-5.3) | 4.6 (3.6-5.7) | 4.5 (3.4-5.6) | 3.9 (3.2-4.8) |
| Moderate / Severe LV dilatation | 72 (41%) | 78 (21%) | 129 (25%) | 514 (33%) | 202 (41%) | 236 (40%) | 462 (20%) |
| Moderate / Severe LA dilatation | 59 (33%) | 82 (22%) | 194 (38%) | 605 (39%) | 195 (39%) | 247 (42%) | 574 (25%) |
| Moderate / Severe Mitral Stenosis | 5 (3%) | 10 (3%) | 24 (5%) | 56 (4%) | 10 (2%) | 26 (4%) | 73 (3%) |
| Moderate / Severe Mitral Regurgitation | 53 (30%) | 100 (27%) | 192 (37%) | 559 (36%) | 180 (36%) | 247 (42%) | 574 (25%) |
| Moderate / Severe Aortic stenosis | 7 (4%) | 20 (5%) | 39 (8%) | 157 (10%) | 43 (9%) | 62 (10%) | 163 (7%) |
| Moderate / Severe Aortic | 8 | 19 | 52 | 147 | 40 | 61 | 169 |

Table 31

| | **Class 1** | **Class 2** | **Class 3** | **Class 4** | **Class 5** | **Class 6** | **Class 7** |
|---|---|---|---|---|---|---|---|
| regurgitation | (5%) | (5%) | (10%) | (9%) | (8%) | (10%) | (7%) |
| Moderate / Severe Right ventricle dysfunction | 16 (9%) | 8 (2%) | 52 (10%) | 136 (9%) | 34 (7%) | 75 (13%) | 93 (4%) |
| Moderate / Severe Pulmonary hypertension | 21 (12%) | 38 (10%) | 107 (21%) | 379 (24%) | 110 (22%) | 142 (24%) | 266 (11%) |

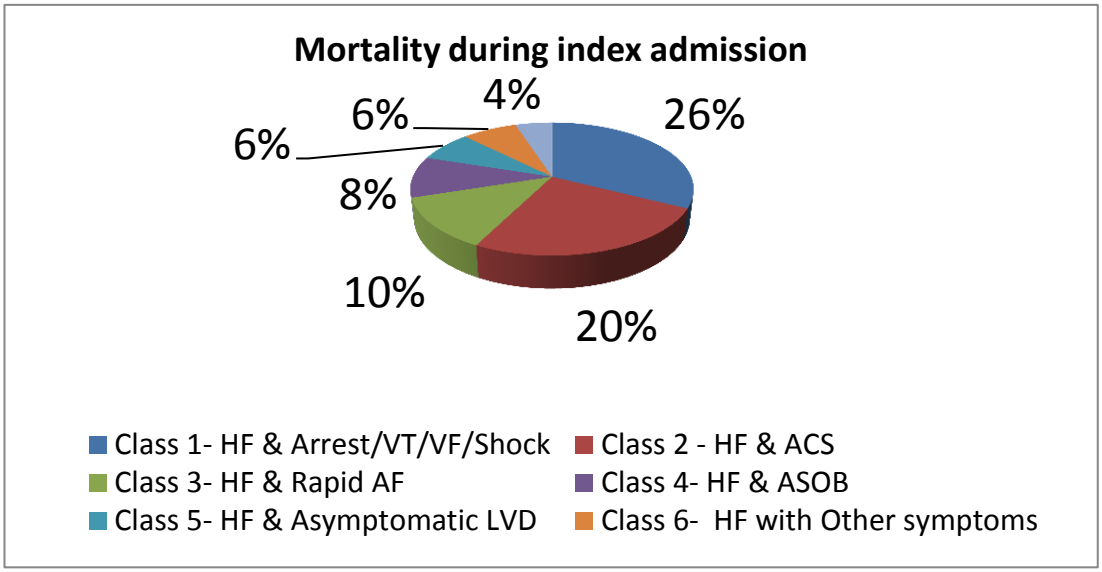
HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath, LVSD; Left ventricle systolic dysfunction, IQR; Interquartile Range, LVEDD; Left ventricle end diastolic diameter, LVESD; Left Ventricle end systolic diameter, LV; Left ventricle, LA; Left atrium. VT; Ventricular tachycardia, Asymp LVD; asymptomatic Left ventricular systolic dysfunction

**Table 32 : Investigations during index admission**

| Table 32 | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
|---|---|---|---|---|---|---|---|
| Presentation | Arrest/VT/ Shock | ACS | Rapid AF | ASOB | Asymp. LVD | Other | Uncertain |
| Numbers (%) | 260 (2%) | 560 (5%) | 799 (8%) | 2479 (24%) | 703 (7%) | 1,040 (10%) | 4,695 (44%) |
| Median (IQR) | | | | | | | |
| Haemoglobin (g/dl) | 12.5 (11-14.2) | 12.7 (11.2-13.9) | 12.7 (1.1-14.2) | 12.7 (11.3-14) | 13.1 (1.5-14.7) | 13.3 (11.8-14.5) | 12.9 (11.3-14.2) |
| Sodium (mmol/l) | 139 (135-142) | 139 (136-142) | 139 (136-142) | 139 (136-142) | 139 (136-142) | 140 (137-142) | 139 (136-142) |
| Potassium (mmol/l) | 4.2 (3.8-4.6) | 4.2 (3.8-4.6) | 4.2 (3.9-4.6) | 4.2 (3.9-4.6) | 4.3 (4-4.7) | 4.4 (4-4.8) | 4.2 (3.9-4.6) |
| Urea mmol/l | 12.9 (6.9-20.7) | 10.7 (6.8-17) | 10.4 (7.1-17.5) | 11.8 (7.5-18.6) | 10.5 (6.9-17.1) | 9.4 (6.6-15) | 8.9 (6.2-14.5) |
| Creatinine | 124 | 106 | 106 | 106 | 106 | 106 | 101 |

| Table 32 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
| (umol/l) | (99-168) | (88-137) | (85-133) | (88-138) | (88-135) | (88-134) | (83-126) |
| Cholesterol most recent (mmol/l) | 5.1 (4-5.8) | 5.1 (4.3-6) | 4.7 (3.8-5.6) | 4.9 (4-5.8) | 5.1 (4.1-5.9) | 4.9 (3.9-5.9) | 5.1 (4.3-5.9) |
| Chest X-Ray: Cardiomegaly /Pulmonary congestion | 205 (94%) | 392 (79%) | 618 (86%) | 1,938 (88%) | 457 (76%) | 717 (79%) | 2,281 (61%) |

HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath, IQR; Interquartile range, VT; Ventricular tachycardia, Asymp LVD; asymptomatic Left ventricular systolic dysfunction,




HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath, VT; Ventricular tachycardia, Asymp LVD; asymptomatic Left ventricular systolic dysfunction

**Figure 15 Mortality during index admission**

**Table 33 : Mortality & Length of stay during index admission**

| Table 33 | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
|---|---|---|---|---|---|---|---|
| Presentation | Arrest/VT/ Shock | ACS | Rapid AF | ASOB | Asymp. LVD | Other | Uncertain |
| Numbers (%) | 260 (2%) | 560 (5%) | 799 (8%) | 2479 (24%) | 703 (7%) | 1,040 (10%) | 4,695 (44%) |
| Deaths | 67 (26%) | 114 (20%) | 80 (10%) | 201 (8%) | 41 (6%) | 65 (6%) | 189 (4%) |
| HR compared to class 7 (uni-variable analysis) | 4.86 (P=<0.001, CI 3.57-6.6) | 3.95 (P=<0.001 CI 3.1-5) | 2.22 (P=<0.001 CI 1.7-2.9) | 2.09 (P=<0.001 CI 1.70-2.56) | 1.44 (P=0.04 CI 1.02-2.02) | 1.36 (P=0.04 CI 1.02-1.81) | |
| MI (%) | 32 (47%) | 98 (86%) | 5 (6%) | 11 (5%) | 3 (7%) | 4 (6%) | 31 (16%) |
| Worsening HF | 45 (67%) | 81 (71%) | 60 (75%) | 167 (83%) | 21 (51%) | 52 (80%) | 35 (18%) |
| Renal Dysfunction | 20 (30%) | 33 (29%) | 18 (23%) | 54 (27%) | 10 (24%) | 19 (29%) | 21 (11%) |
| Ventricular | 18 | 21 | 14 | 18 | 3 | 3 | 13 |

Table 33

| | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
|---|---|---|---|---|---|---|---|
| Arrhythmia | (27%) | (18%) | (18%) | (9%) | (7%) | (5%) | (7%) |
| Atrial Arrhythmia | 5 (7%) | 15 (13%) | 30 (38%) | 14 (7%) | 4 (10%) | 5 (8%) | 8 (4%) |
| Infection | 13 (5%) | 18 (16%) | 26 (33%) | 65 (32%) | 14 (34%) | 31 (48%) | 57 (30%) |
| Stroke | 3 (5%) | 5 (4%) | 2 (3%) | 10 (5%) | 6 (15%) | 10 (15%) | 32 (1%) |
| Cancer | 0 | 2 (2%) | 5 (6%) | 16 (8%) | 2 (5%) | 2 (3%) | 30 (16%) |
| Other | 11 (16%) | 13 (11%) | 22 (28%) | 45 (22%) | 10 (24%) | 12 (18%) | 72 (38%) |
| | | | | | | | |
| LoS - index admission (days) (Median / IQR) | 9 (4-16) | 11 (7-18) | 10 (6-15) | 8 (5-13) | 8 (3-14) | 10 (5-17) | 8 (4-13) |

HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath, HR; Hazard ratio, CI; Confidence interval, MI; Myocardial Infarction, IQR; Interquartile range, VT; Ventricular tachycardia, Asymp LVD; asymptomatic Left ventricular systolic dysfunction, LoS; length of stay

**Table 34 : Drugs at discharge or 24 Hours prior to death**

| Table 34 | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
|---|---|---|---|---|---|---|---|
| Presentation | Arrest/VT/ Shock | ACS | Rapid AF | ASOB | Asymp. LVD | Other | Uncertain |
| Numbers (%) | 260 (2%) | 560 (5%) | 799 (8%) | 2479 (24%) | 703 (7%) | 1,040 (10%) | 4,695 (44%) |
| Spironolactone | 61 (23%) | 94 (17%) | 203 (25%) | 693 (28%) | 230 (33%) | 351 (34%) | 540 (12%) |
| Furosemide | 202 (78%) | 436 (78%) | 663 (83%) | 2,121 (86%) | 511 (73%) | 774 (74%) | 3,327 (71%) |
| Bumetanide | 7 (3%) | 7 (1%) | 26 (3%) | 97 (4%) | 12 (2%) | 19 (2%) | 110 (2%) |
| Torasemide | 14 (5%) | 19 (3%) | 38 (5%) | 93 (4%) | 31 (4%) | 30 (3%) | 140 (3%) |
| Metolazone | 0 | 2 (0.4%) | 11 (1%) | 61 (2%) | 4 (1%) | 16 (2%) | 21 (0.5%) |
| Thiazide diuretic | 33 (13%) | 41 (7%) | 69 (9%) | 219 (9%) | 96 (14%) | 198 (19%) | 397 (8%) |

Table 34

| | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
|---|---|---|---|---|---|---|---|
| ACEI | 158 (61%) | 399 (71%) | 494 (62%) | 1,655 (67%) | 496 (71%) | 735 (71%) | 2,577 (55%) |
| ARB | 7 (3%) | 18 (3%) | 28 (4%) | 114 (5%) | 51 (7%) | 47 (5%) | 213 (5%) |
| Nitrate | 106 (41%) | 316 (56%) | 269 (34%) | 1,137 (46%) | 258 (37%) | 525 (50%) | 2,005 (43%) |
| CCB | 30 (12%) | 119 (21%) | 178 (22%) | 483 (19%) | 107 (15%) | 184 (18%) | 1,131 (24%) |
| Beta blockers | 115 (44%) | 309 (55%) | 256 (32%) | 676 (27%) | 288 (41%) | 433 (42%) | 1,790 (38%) |
| Digoxin | 87 (33%) | 140 (25%) | 501 (63%) | 1,059 (43%) | 296 (42%) | 469 (45%) | 1,227 (26%) |
| Antiarrhythmic drugs | 85 (33%) | 96 (17%) | 244 (31%) | 300 (12%) | 127 (18%) | 104 (10%) | 599 (13%) |
| Lipid lowering drugs | 38 (15%) | 147 (26%) | 83 (10%) | 420 (17%) | 159 (23%) | 192 (18%) | 1,097 (23%) |

HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath, ACI; Angiotensin converting enzyme inhibitor, ARB; Angiotensin receptor blockers

**Table 35 : Mortality & Readmission within 12 Weeks after discharge**

| **Table** 35 | ***Class 1*** | ***Class 2*** | ***Class 3*** | ***Class 4*** | ***Class 5*** | ***Class 6*** | ***Class 7*** | ***Chi2 statistic (P-Value)*** |
|---|---|---|---|---|---|---|---|---|
| Presentation | Arrest/ VT/ Shock | ACS | Rapid AF | ASOB | Asymp. LVD | Other | Uncertain | |
| Number at Risk | 193 | 446 | 719 | 2,278 | 662 | 975 | 4,506 | |
| Deaths after Discharge | 12 (6%) | 36 (8%) | 47 (7%) | 175 (8%) | 41 (6%) | 63 (6%) | 229 (5%) | 15 (0.02) |
| Unadjusted OR compared to class 7 | 1.18 (P=0.58, CI 0.64-2.15) | 1.56 (p=0.02, 1.08-2.25) | 1.26 (P=0.17, CI 0.91-1.75) | 1.46 (P=<0.001, CI 1.19-1.79) | 1.18 (P=0.35, CI 0.84-1.68) | 1.14 (P=0.37, CI 0.86-1.53) | | |
| Events contributing to death (proportion deaths) | | | | | | | | |
| MI (%) | 1 (8%) | 10 (28%) | 4 (9%) | 12 (7%) | 2 (5%) | 5 (8%) | 25 (11%) | 21 0.002 |
| Worsening HF (%) | 3 (25%) | 9 (26%) | 10 (21%) | 68 (39%) | 17 (41%) | 25 (40%) | 50 (22%) | 35 (0.001) |
| Renal Dysf. (%) | 0 | 2 (6%) | 3 (6%) | 19 (11%) | 6 (15%) | 3 (5%) | 12 (6%) | 15 (0.02) |
| Ventricular Arrhythmia | 1 (8%) | 3 (9%) | 2 (4%) | 7 (4%) | 3 (7%) | 3 (5%) | 7 (3%) | 6 (0.38) |

**Table** 35

| | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* | *Chi2 statistic (P-Value)* |
|---|---|---|---|---|---|---|---|---|
| (%) | | | | | | | | |
| Atrial Arrhythmia (%) | 0 | 0 | 1 (2%) | 6 (3%) | 2 (5%) | 0 | 8 (3%) | 5 (0.60) |
| Infection (%) | 0 | 3 (9%) | 6 (13%) | 14 (8%) | 4 (10%) | 8 (12%) | 40 (17%) | 3 (0.75) |
| Stroke | 0 | 1 (3%) | 8 (17%) | 10 (6%) | 3 (7%) | 4 (6%) | 19 (8%) | 8 (0.22) |
| Cancer | 0 | 1 (3%) | 3 (6%) | 11 (6%) | 3 (7%) | 6 (9%) | 28 (12%) | 3 (0.81) |
| Other | 1 (8%) | 7 (23%) | 16 (34%) | 32 (18%) | 5 (12%) | 7 (11%) | 63 (28%) | 10 (0.11) |
| Readmission within 12 weeks after discharge | | | | | | | | |
| Number at Risk | 193 | 446 | 719 | 2,278 | 662 | 975 | 4,506 | |
| All cause | 43 (22%) | 109 (24%) | 166 (23%) | 557 (24%) | 192 (29%) | 189 (19%) | 980 (22%) | 28 (<0.001) |
| Due to CV cause | 33 (17%) | 85 (19%) | 131 (18%) | 421 (18%) | 150 (23%) | 155 (16%) | 580 (13%) | 97 (<0.001) |
| Due to Heart Failure | 20 (10%) | 45 (10%) | 73 (10%) | 298 (13%) | 98 (15%) | 98 (10%) | 240 (5%) | 170 (<0.001) |

HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath OR; Odds ratio VT; Ventricular tachycardia, Asymp LVD; asymptomatic Left ventricular systolic dysfunction

**Table 36: Mode of death during index admission**

| Table 36 | | | | | | | |
|---|---|---|---|---|---|---|---|
| | ***Class 1*** | ***Class 2*** | ***Class 3*** | ***Class 4*** | ***Class 5*** | ***Class 6*** | ***Class 7*** |
| Presentation | Arrest/VT/ Shock | ACS | Rapid AF | ASOB | Asymp. LVD | Other | Uncertain |
| Numbers | 260 (2%) | 560 (5%) | 799 (8%) | 2479 (24%) | 703 (7%) | 1,040 (10%) | 4,695 (44%) |
| Deaths | 67 (26%) | 114 (20%) | 80 (10%) | 201 (8%) | 41 (6%) | 65 (6%) | 189 (4%) |
| | | | | | | | |
| Mode of death (proportion deaths) | | | | | | | |
| Cardiogenic shock | 45 (67%) | 65 (57%) | 24 (30%) | 55 (27%) | 12 (29%) | 22 (34%) | 26 (14%) |
| Pulmonary oedema | 19 (28%) | 32 (28%) | 24 (30%) | 74 (37%) | 8 (20%) | 14 (25%) | 14 (7%) |
| Stroke | 2 (3%) | 1 (1%) | 3 (4%) | 5 (2%) | 5 (12%) | 11 (17%) | 25 (13%) |
| Other Cardiovascular cause | 7 (12%) | 30 (26%) | 16 (20%) | 47 (23%) | 2 (5%) | 7 (11%) | 31 (16%) |
| Cancer | 0 | 2 (2%) | 5 (6%) | 16 (8%) | 2 (5%) | 2 (3%) | 30 (16%) |
| Accident or violence | 0 | 0 | 0 | 0 | 0 | 0 | 2 (1%) |
| Other non-Cardiovascular cause | 3 (4%) | 10 (9%) | 20 (25%) | 33 (16%) | 9 (22%) | 10 (15%) | 45 (24%) |
| Sudden death | 2 (3%) | 14 (12%) | 6 (8%) | 9 (4%) | 6 (15%) | 6 (9%) | 18 (10%) |
| Cardiac cachexia | 2 (3%) | 1 (1%) | 3 (4%) | 7 (3%) | 1 (2%) | 4 (6%) | 3 (2%) |

HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath, HR; MI; Myocardial Infarction, IQR, VT; Ventricular tachycardia, Asymp LVD; asymptomatic Left ventricular systolic dysfunction

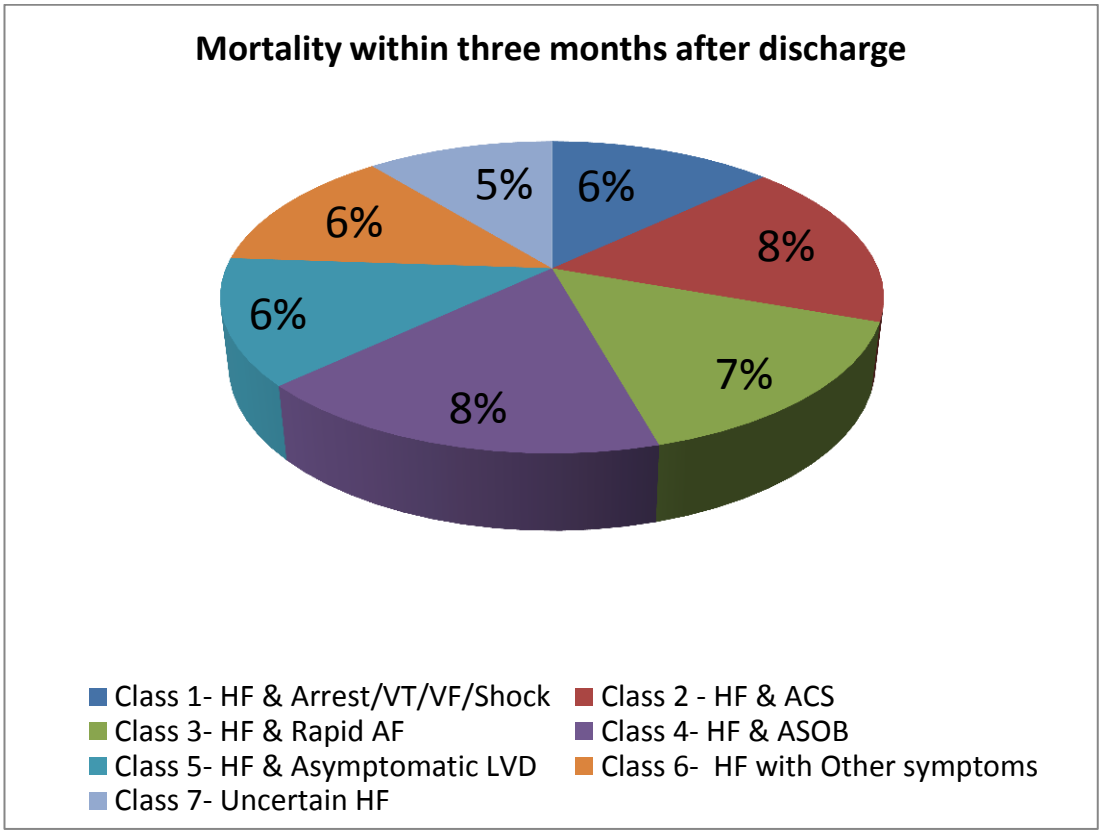



**Figure 16 Mortality within three months after discharge**

HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath, VT; Ventricular tachycardia, Asymp LVD; Asymptomatic Left ventricular systolic dysfunction

**Table 37: Mode of death after discharge**

| **Table 37** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | ***Class 1*** | ***Class 2*** | ***Class 3*** | ***Class 4*** | ***Class 5*** | ***Class 6*** | ***Class 7*** |
| Presentation | Arrest/VT/ Shock | ACS | Rapid AF | ASOB | Asymp. LVD | Other | Uncertain |
| Number at Risk | 193 | 446 | 719 | 2,278 | 662 | 975 | 4,506 |
| Deaths after Discharge | 12 (6%) | 36 (8%) | 47 (7%) | 175 (8%) | 41 (6%) | 63 (6%) | 229 (5%) |
| | | | | | | | |
| Mode of death (proportion deaths) | | | | | | | |
| Cardiogenic shock | 2 (17%) | 6 (17%) | 5 (11%) | 24 (14%) | 7 (17%) | 15 (24%) | 20 (9%) |
| Pulmonary oedema | 0 | 6 (17%) | 9 (19%) | 37 (21%) | 8 (20%) | 10 (16%) | 18 (8%) |
| Stroke | 0 | 2 (6%) | 7 (15%) | 9 (5%) | 3 (7%) | 3 (5%) | 16 (7%) |
| Other Cardiovascular cause | 1 (8%) | 2 (6%) | 3 (6%) | 19 (11%) | 6 (15%) | 2 (3%) | 24 (10%) |

**Table 37**

| | *Class 1* | *Class 2* | *Class 3* | *Class 4* | *Class 5* | *Class 6* | *Class 7* |
|---|---|---|---|---|---|---|---|
| Cancer | 0 | 1 (3%) | 3 (6%) | 11 (6%) | 3 (7%) | 6 (10%) | 29 (13%) |
| Accident or violence | 0 | 1 (3%) | 0 | 1 (1%) | 0 | 0 | 0 |
| Other non-Cardiovascular cause | 2 (17%) | 2 (6%) | 7 (15%) | 18 (10%) | 3 (7%) | 5 (8%) | 41 (18%) |
| Sudden death | 3 (25%) | 5 (42%) | 5 (11%) | 8 (5%) | 2 (5%) | 5 (8%) | 22 (10%) |
| Cardiac cachexia | 0 | 1 (3%) | 1 (2%) | 2 (1%) | 3 (7%) | 2 (2%) | 2 (1%) |

HF; Heart Failure, ACS; Acute Coronary Syndrome, AF; Atrial fibrillation, ASOB; Acute Shortness of Breath, HR; MI; Myocardial Infarction, IQR, VT; Ventricular tachycardia, Asymp LVD; asymptomatic Left ventricular systolic dysfunction

Multivariable analysis identified the following variables, selected using a p-value of <0.05, were associated with in-patient mortality; MI or UA during the index admission, history of VT/VF, history of stroke, left ventricle dilatation and serum creatinine concentrations. The area under Receiver Operating Characteristics (ROC) curve was 0.74. In a second model we used a p-value 0.1 for selection which identified four more variables; age, gender, medical history of hypertension and

infection. Area under ROC curve in the second model was 0.78 (Figure 17). We used Akaike's information criterion (AIC) and Bayesian information criterion (BIC) to compare the two models. Smaller AIC/BIC ratio in model 2 (0.96 in model 1 and 0.95 in model 2) and large difference of BIC between models (67) indicated that model 2 is better than model 1 and we used it for our further interpretation (Table 38)

In our final logistic regression model after adjusting all relevant covariates, mortality remained higher in class 1-6 as compare to class 7 (Table 38)

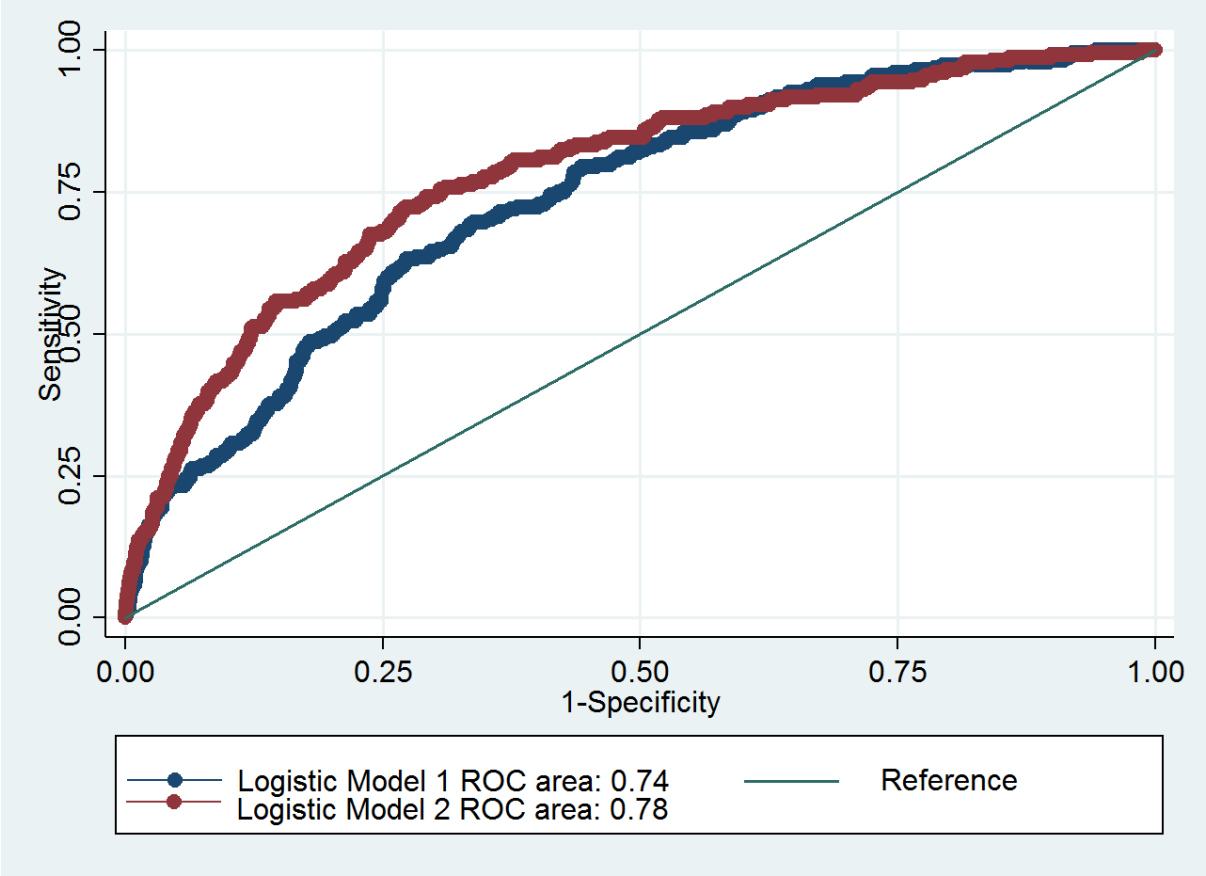



**Figure 17: Comparison of two logistic Regression Models to assess mortality during index admission by ROC curves**

ROC; Receiver Operator Characteristics

**Table 38 : Logistic regression model for mortality during index admission**

| *Table 38* | | | | |
|---|---|---|---|---|
| | *Odds Ratio As compare to class 7* | *P-value* | *Lower Bound 95% Confidence Interval* | *Upper Bound 95% Confidence Interval* |
| Class 1 | 4.18 | <0.001 | 2.2 | 8.1 |
| Class 2 | 4.08 | <0.001 | 2.14 | 7.79 |
| Class 3 | 4.09 | <0.001 | 2.39 | 7.05 |
| Class 4 | 3.27 | <0.001 | 2.10 | 5.09 |
| Class 5 | 2.90 | 0.001 | 1.54 | 5.48 |
| Class 6 | 3.39 | <0.001 | 1.94 | 5.95 |
| Age | 1.03 | <0.001 | 1.01 | 1.04 |
| Gender | 0.86 | 0.36 | 0.64 | 1.17 |
| MI this admission | 2.52 | 0.001 | 1.47 | 4.35 |
| USA this admission | 0.92 | 0.72 | 0.60 | 1.43 |
| | | | | |
| VT/VF (anytime) | 3.10 | <0.001 | 2.15 | 4.49 |
| h/o Hypertension | 0.93 | 0.62 | 0.70 | 1.24 |
| Stroke (anytime) | 1.62 | 0.03 | 1.04 | 2.52 |
| h/o Infection | 3.37 | <0.001 | 2.52 | 4.50 |
| LV dilatation | 1.06 | 0.74 | 0.79 | 1.48 |
| Creatinine | 1.01 | 0.04 | 1.001 | 1.02 |

Class 1; Heart failure (HF) + Shock/arrest/ Ventricular arrhythmia
Class 2; HF + Acute coronary syndrome (unless part of class 1)
Class 3; HF+ Rapid Atrial fibrillation (Unless part of class ½
Class 4; HF+ Acute shortness of breath (Unless part of class 1/2/3)
Class 5; HF + asymptomatic /stable (unless part of class 1/2/3/
Class 6; HF + other deterioration of HF and none from first five classes
Class 7; Heart Failure not present or uncertain
MI; Myocardial Infarction, USA; Unstable Angina, VT; Ventricle Tachycardia, VF; Ventricle fibrillation, H/O; History of, LV; Left ventricle

For assessment of mortality in the 12 week period after discharge, history of valve repair was the only variable which was significant using P <0.05 for model selection in 25 cross validations and the model discrimination was poor (ROC 0.55). If P<0.01 was used, history of DM, left ventricle systolic dysfunction (LVSD), left ventricle dilatation and history of angina during index admission provided additional information but this improved the ROC only to 0.57. In the logistic regression model, only Class 2 (OR 1.73, P 0.03, CI 1.07-2.95) and Class 4 (OR 1.61, P 0.002, CI 1.18-2.18) added to model prediction (OR compared to Class 7).

In a multivariable analysis investigating variables associated with all-cause readmission during the 12 week follow up period, medical history of hypertension, LVSD and aortic stenosis were identified in 25 cross-validations when we consider P < 0.05 as a selection criterion. In the logistic regression, only Class 5 added to the model with OR of 1.69 (P <0.001, CI 1.34 – 2.12) compared to Class 7. However, the area under the ROC curve was only 0.55. When P <0.1 was used to select variables from 25 Cross-validations, three further variables, history of infection or of valve replacement and mitral regurgitation, were identified that improved the ROC to 0.57 and again, only Class 5 added to logistic regression model (OR of 1.77 (P <0.001, CI 1.40-2.24).

## 7.4 Discussion

The Euro Heart Failure survey was designed to investigate overall heart failure-related activity in hospitals and not just a narrowly defined group of patients admitted with heart failure as a primary diagnosis and managed by cardiologists. The survey emphasizes the heterogeneity of presentation. Most patients hospitalized with a diagnosis or features suspicious of heart failure are admitted primarily for another

reason. This group of patients has lower in-patient mortality but similar rates of death and readmission subsequent to discharge, although such events were less likely to be related to worsening heart failure.

Not unsurprisingly, patients presenting with cardiogenic shock, VT/VF and ACS had a much worse in-hospital prognosis but subsequent to discharge the prognosis, both in terms of readmissions and death was rather similar regardless of presentation. Clearly, these patients require urgent measures to correct the haemodynamic disturbance and to limit myocardial damage.

It is now fashionable to highlight the lack of progress in the treatment of AHF, as opposed to the huge progress made in the last 25 years for CHF.[6, 133-135] Unfortunately, the only Class 1, level of evidence A recommendation for the management of AHF in the ESC guidelines of 2012 is thrombo-embolism prophylaxis.[12] There are many possible reasons for lack of progress in AHF. The interventions studied may be truly ineffective or study design may have been inadequate. However, the heterogeneity of the patient population probably plays a major role. More precise patient selection, timing of intervention and targeting of therapy in clinical trials could reap large dividends. More precise targeting does not necessarily mean more restrictive inclusion criteria. For instance, if congestion and peripheral oedema is the primary treatment target then there is little point in trying to enrol patients in the first 24 hours after admission, which is logistically difficult from a research perspective and greatly reduces recruitment. Patients who have long standing CHF present with slowly developing peripheral oedema and renal dysfunction are quite different from those with acute pulmonary oedema.[6] The latter group often respond symptomatically with a few hours whereas the latter may

require days or even weeks of treatment to control congestion. Historically, spectacular success in management of Acute Myocardial Infarction (AMI) was not possible until segregation of patients into ST elevation MI (STEMI) and Non-ST elevation MI (NSTEMI). The same may or may not be true for the segregation of CHF into Heart Failure with Reduced Ejection Fraction (HFREF) and Heart Failure with Preserved Ejection Fraction (HeFPEF), since the primary reason for this segregation was the inability to discriminate reliably between HeFPEF and normal cardiac function; patients who genuinely do have heart failure may respond similarly to treatment regardless of LVEF.[6]

Most trials of AHF have enrolled a mixture of patients presenting with severe acute-onset breathlessness at rest (pulmonary oedema) and others with sub-acute worsening of peripheral congestion who are not breathless sitting upright at rest but have orthopnoea and are breathless on minor exertion. The median time to enrolment in trials of AHF, with one exception, has never been less than six hours, by which time most patients with acute pulmonary oedema have responded to a combination of diuretics and oxygen and have only residual symptoms.[6, 29] The one exception is the 3CPO study that enrolled patients with acute pulmonary oedema with heart and respiratory rates of 114 and 33 respectively less than 6 hours of hours of presentation.[136] In our study Class 4 (acutely breathless patients) had a slightly higher mortality on the index hospitalization as Classes 5 and 6, which probably included patients with more peripheral congestion. However, the late outcome of patients in these three groups of patients was similar. .

## 7.5 Limitations

EHFS1 was conducted in 2000-01 but, until now, there have been few innovations in therapy for chronic and none for acute HF. Recent trials suggest that the 12 week mortality of AHF has changed little in the past 15 years. We developed mutually exclusive categories of patients but of course, in reality, some patients will belong to more than one class. However in most such clinical situations one presentation dominates. We relied on investigators from many countries providing accurate data, but case reports forms were in English and some questions may have been unclear, especially when translated locally. Attempting to avoid falling into the trap of capturing data on only narrowly defined 'cardiological' heart failure may have caused some confusion and inconsistent answers, especially for patients who were taking loop diuretics but who had not been diagnosed with heart failure. However, it is impossible to assess the quality of care with respect to investigation if only patients who already have a diagnosis of heart failure are included. Most patients in whom the contribution of heart failure to admission was in doubt had features to suggest that they did have heart failure and these patients had a high morbidity and mortality subsequent to discharge.

A major limitation of this survey was the failure to specifically ask about peripheral oedema. We assume that when peripheral oedema was the major presentation, these will have been classified as 'other'. However, many of these patients will have had breathlessness on mild exertion or even at rest and may have been classified as acutely short of breath rather than with peripheral oedema. .

## 7.6 Conclusion

AHF is a complex clinical condition and is a collection of different syndromes with different clinical presentations, underlying aetiology and pathophysiology with quite variable clinical course and prognosis. It is still an area of great unmet clinical need. Attempts to investigate the effect of a single agent in all AHF patients may be futile. A more coherent approach with tighter patient selection for more targeted drug therapy by clinical presentation is more likely to succeed.

# Chapter 8 **Summary**

Acute heart failure (AHF) is an unstable and complex condition and a common reason for admission to hospital, especially in the elderly population.[1, 10, 117] It is generally believed that majority of patients admitted with AHF have severe shortness of breath at rest but some baseline data from large registries and surveys suggests that many patients are comfortable at rest with some signs of cardio-respiratory distress.[3, 26, 117, 119] However, the data from registries and surveys were collected across a number of centres and by a variety of staff who might have selected patients and interpreted questions about symptoms differently, leading to inconsistent results.[115] Secondly, none of these studies was conducted, analysed or interpreted with a primary focus on the severity of breathlessness. Understanding symptoms at presentation has important repercussions for both service and clinical trial design. In clinical practice, treatment for acutely breathless patients is usually implemented within minutes of presentation, but novel therapies studied in trials are not usually implemented until 6-18 hours after initial presentation by which time patients may have already had a partial response.

Acute heart failure is often assumed to be more-or-less synonymous with acute pulmonary oedema. However, when I began a project to examine the time course of treatment and outcomes of patients admitted with acute heart failure, I realised that this assumption was false. My starting point for the present thesis was the realisation that most patients presenting with acute heart failure are not, in fact, breathless at rest, but only on some exertion. The realisation has important implications for understanding the pathophysiology of acute heart failure, and has clear implications for the development of new therapeutic agents for treating heart failure.

I thus embarked on the present project with the aim of trying to describe more closely what symptoms patients have when they present with acute heart failure; to describe what happens to their vital signs during admission; and to investigate what impact the symptoms at presentation had on outcome. In addition, using large European datasets, I was able to explore in more detail the impact of a heart failure diagnosis on outcome, and the relation between mode of presentation and outcome.

In chapter *4*, I described how I conducted a detailed case note review of 311 patients with heart failure, and developed the concept that there were two distinct patterns of symptomatic presentation: patients who were breathless at rest, whom I have described as being "SOBAR", and patients who were comfortable at rest, but became breathless on exertion, whom I have described as being "CARBOSE". I found that 42% were SOBAR on admission and that they tended to have higher heart rate, blood pressure and respiratory rate than those who were CARBOSE (56%). Their vital signs responded more rapidly to treatment that did those who were CARBOSE and they had a better prognosis.

I then sought to validate these findings in chapter *5* where I extended my data collection to include 390 patients from London in order to validate my model. Apart from few minor differences, the patients' baseline clinical characteristics were similar in both sites. Joint analysis of both datasets reconfirmed my earlier findings that CARBOSE is a common presentation of acute heart failure patients leading to admission. Although patients with SOBAR have more alarming initial symptoms and signs, patients with CARBOSE have a worse prognosis, perhaps reflecting more severe cardiac dysfunction. The difference in mortality remained significant even in multivariable analysis after adjusting for relevant covariates. The rapid resolution of

symptoms in the SOBAR group highlighted that at the time of recruitment into clinical trials of novel therapy, patients' symptoms might already partially responded due to routine treatment. Relatively small numbers, retrospective data collection and incomplete data of some important variables like natriuretic peptides are the main limitations of my analysis. However, the study is hypothesis generating and more detailed exploration of how patients with heart failure present are now needed.

Most previous publications reporting deaths and discharges with heart failure focussed only on patients with heart failure as a primary discharge diagnosis, which is a minority of all admissions of patients with heart failure admitted to hospitals. The National Heart Failure audit in England and Wales also focuses solely on patients with a primary diagnosis of heart failure. Failure to measure the magnitude of the problem is likely to lead to an under-estimate of the health economic influence of heart failure and under-provision of resources for its care. Euro Heart Failure Survey 1 (EHFS1) screened consecutive deaths and discharges during 2000-2001 primarily from medical wards over a 6 week period in 115 hospitals from 24 countries in Europe, to identify patients with known or suspected HF. Information on presenting symptoms and signs were gathered. Mortality was assessed during hospital admission and then 12 weeks after discharge. In chapter 6, I conducted post hoc analysis of the data in order to characterize patients admitted with known or suspected heart HF according to diagnostic position and then to assess the relation between mode of presentation and mortality. Of all 10,701 patients admitted with suspected HF, heart failure was considered to be the primary reason for admission in 4,234 (40%), a secondary reason for admission (if it complicated or prolonged stay) in further 1,772 (17%), and in 4,695 (43%), it was uncertain whether HF was actively contributing to the index admission. Mortality was highest in the secondary

heart failure group and lowest in the uncertain group, with the primary group being intermediate. Significant number of patients was died from that group where diagnosis of HF was uncertain. Importantly, the mortality and re-admission following discharge was similar in each of the three groups, although the causes of readmission and death did appear to differ between groups.

Despite the diversity of modes of presentation, the majority of clinical trials in AHF deal with the syndrome as if it were a single entity, which may be one reason for repeated failures or neutral results. In chapter 7, I carried out a further post hoc analysis of EHFS1 data to assess the relation between different modes of presentation of AHF and mortality. Patients were sorted into seven mutually exclusive classes according to presentation. Class 1: HF with cardiac arrest/ ventricular arrhythmia; class 2: HF & acute coronary syndrome (ACS); class 3: HF and atrial fibrillation (AF) with rapid ventricular response; class 4: HF & acute breathlessness; class 5: stable HF; class 6: presenting with other symptoms of HF such as worsening peripheral oedema; and class 7: no HF. Patients presenting with cardiogenic shock, VT/VF and ACS had a much worse in-hospital prognosis; however, after discharge, the prognosis, in terms of readmissions and death, was similar regardless of presentation.

In summary, the studies presented in this thesis extend our understanding of the modes of presentation of patients with AHF. Acute heart failure is not a discrete diagnosis but is a collection of different clinical syndromes under one umbrella term which need urgent clinical intervention. Attempting to treat the different AHF syndromes as a single entity in new clinical trials is likely to be futile. Better characterization of the different clinical presentations of AHF at the time of

recruitment into clinical trials is essential to target therapeutic appropriately. Mortality is high for patients with an admission for AHF and even higher when heart failure is not main reason of admission. Registries and surveys that do not include patients with HF as a contributory diagnosis may provide an over-optimistic view of the prognosis of AHF and underestimate the resources required for its diagnosis and effective management.

# References


1. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, Hochadel M, Komajda M, Lassus J, Lopez-Sendon JL, Ponikowski P, Tavazzi L. EuroHeart Failure Survey II (EHFS II): a survey on hospitalized acute heart failure patients: description of population. Eur Heart J. 2006 Nov;27(22):2725-36.
2. Desai AS, Stevenson LW. Rehospitalization for heart failure: predict or prevent? Circulation. 2012 Jul 24;126(4):501-6.
3. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J. The EuroHeart Failure survey programme-- a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J. 2003 Mar;24(5):442-63.
4. Storrow AB, Jenkins CA, Self WH, Alexander PT, Barrett TW, Han JH, McNaughton CD, Heavrin BS, Gheorghiade M, Collins SP. The Burden of Acute Heart Failure on U.S. Emergency Departments. JACC: Heart Failure. 2014 6//;2(3):269-77.
5. Bottle A, Aylin P, Bell D. Effect of the readmission primary diagnosis and time interval in heart failure patients: analysis of English administrative data. Eur J Heart Fail. 2014 Jul 8.
6. McDonagh TA, Komajda M, Maggioni AP, Zannad F, Gheorghiade M, Metra M, Dargie HJ. Clinical trials in acute heart failure: simpler solutions to complex problems. Consensus document arising from a European Society of Cardiology cardiovascular round-table think tank on acute heart failure, 12 May 2009. Eur J Heart Fail. 2011 Dec;13(12):1253-60.
7. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008 Oct;10(10):933-89.
8. Clark AL, Cleland JG. Causes and treatment of oedema in patients with heart failure. Nat Rev Cardiol. 2013 Mar;10(3):156-70.
9. Gheorghiade M, Pang PS. Acute heart failure syndromes. J Am Coll Cardiol. 2009 Feb 17;53(7):557-73.
10. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Leiro MC, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F, Tavazzi L. EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail. 2010 Oct;12(10):1076-84.
11. Weintraub NL, Collins SP, Pang PS, Levy PD, Anderson AS, Arslanian-Engoren C, Gibler WB, McCord JK, Parshall MB, Francis GS, Gheorghiade M. Acute heart failure syndromes: emergency department presentation, treatment, and disposition: current approaches and future aims: a scientific statement from the American Heart Association. Circulation. 2010 Nov 9;122(19):1975-96.
12. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip

GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Guidelines ESCCfP. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012 Jul;33(14):1787-847.

13. Shoaib A, Raza A, Waleed M, Djahit A, Kassianides X, J Z, Mabote T, Torabi A, Clark A, JG C. Presenting symptoms and changes in heart and respiratory rate and blood pressure in the first 24 hours after admission in patients admitted with heart failure. ESC Heart Failure; 25-28 May 2013; Lisbon, Portugal2013.

14. Shoaib A DB, Mabote T, Pellicori P, Torabi A, Clark A, Wong K, Cleland JG. Checking-up on the National Audit on Heart Failure: are only a minority of patients admitted with heart failure truly breathless at rest and how many are suitable for Serelaxin? BCS Annual conference 2013; London2013.

15. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239.

16. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. JAMA. 2006 Nov 8;296(18):2217-26.

17. DiMarco JP. Atrial fibrillation and acute decompensated heart failure. Circ Heart Fail. 2009 Jan;2(1):72-3.

18. Silverberg D, Wexler D, Blum M, Schwartz D, Iaina A. The association between congestive heart failure and chronic renal disease. Curr Opin Nephrol Hypertens. 2004 Mar;13(2):163-70.

19. Aguilar D, Bozkurt B, Ramasubbu K, Deswal A. Relationship of Hemoglobin A1C and Mortality in Heart Failure Patients With Diabetes. Journal of the American College of Cardiology. 2009;54(5):422-8.

20. Kociol RD, Hammill BG, Fonarow GC, Klaskala W, Mills RM, Hernandez AF, Curtis LH. Generalizability and longitudinal outcomes of a national heart failure clinical registry: Comparison of Acute Decompensated Heart Failure National Registry (ADHERE) and non-ADHERE Medicare beneficiaries. Am Heart J. 2010 Nov;160(5):885-92.

21. Adams KF, Jr., Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005 Feb;149(2):209-16.

22. Komajda M, Follath F, Swedberg K, Cleland J, Aguilar JC, Cohen-Solal A, Dietz R, Gavazzi A, Van Gilst WH, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, Widimsky J, Freemantle N, Eastaugh J, Mason J. The EuroHeart Failure Survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J. 2003 Mar;24(5):464-74.

23. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Fabbri G, Urso R, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors AA, Nielsen OW, Zannad F, Tavazzi L. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail. 2013 Jul;15(7):808-17.
24. Cleland J, Dargie H, Hardman S, Mcdonagh T, Mitchell P. National Heart Failure Audit April2012-March 20132013. Available from: http://www.ucl.ac.uk/nicor/audits/heartfailure/additionalfiles/pdfs/annualreports/NHFA13medium.pdf.
25. Young JB, Abraham WT, Albert NM, Gattis Stough W, Gheorghiade M, Greenberg BH, O'Connor CM, She L, Sun JL, Yancy CW, Fonarow GC. Relation of low hemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF registry). Am J Cardiol. 2008 Jan 15;101(2):223-30.
26. Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007 Aug 21;50(8):768-77.
27. Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. J Am Coll Cardiol. 2009 Jan 13;53(2):184-92.
28. Sato N, Kajimoto K, Keida T, Mizuno M, Minami Y, Yumino D, Asai K, Murai K, Muanakata R, Aokage T, Sakata Y, Mizuno K, Takano T. Clinical features and outcome in hospitalized heart failure in Japan (from the ATTEND Registry). Circ J. 2013;77(4):944-51.
29. Mebazaa A, Pang PS, Tavares M, Collins SP, Storrow AB, Laribi S, Andre S, Mark Courtney D, Hasa J, Spinar J, Masip J, Frank Peacock W, Sliwa K, Gayat E, Filippatos G, Cleland JG, Gheorghiade M. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. Eur Heart J. 2010 Apr;31(7):832-41.
30. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, Chalmers JW, Capewell S, McMurray JJ. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation. 2009 Feb 3;119(4):515-23.
31. Yeung DF, Boom NK, Guo H, Lee DS, Schultz SE, Tu JV. Trends in the incidence and outcomes of heart failure in Ontario, Canada: 1997 to 2007. CMAJ. 2012 Oct 2;184(14):E765-73.
32. Bueno H, Ross JS, Wang Y, Chen J, Vidan MT, Normand SL, Curtis JP, Drye EE, Lichtman JH, Keenan PS, Kosiborod M, Krumholz HM. Trends in length of stay and short-term outcomes among Medicare patients hospitalized for heart failure, 1993-2006. JAMA. 2010 Jun 2;303(21):2141-7.
33. Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. JAMA. 2011 Oct 19;306(15):1669-78.
34. Cleland JG, Coletta AP, Clark AL, Cullington D. Clinical trials update from the American College of Cardiology 2009: ADMIRE-HF, PRIMA, STICH,

REVERSE, IRIS, partial ventricular support, FIX-HF-5, vagal stimulation, REVIVAL-3, pre-RELAX-AHF, ACTIVE-A, HF-ACTION, JUPITER, AURORA, and OMEGA. Eur J Heart Fail. 2009 Jun;11(6):622-30.
35. Konstam MA, Gheorghiade M, Burnett JC, Jr., Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. 2007 Mar 28;297(12):1319-31.
36. McMurray JJ, Teerlink JR, Cotter G, Bourge RC, Cleland JG, Jondeau G, Krum H, Metra M, O'Connor CM, Parker JD, Torre-Amione G, van Veldhuisen DJ, Lewsey J, Frey A, Rainisio M, Kobrin I. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. JAMA. 2007 Nov 7;298(17):2009-19.
37. Silver MA, Horton DP, Ghali JK, Elkayam U. Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure. J Am Coll Cardiol. 2002 Mar 6;39(5):798-803.
38. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, Thakkar R, Padley RJ, Poder P, Kivikko M. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA. 2007 May 2;297(17):1883-91.
39. Mentz RJ, Felker GM, Ahmad T, Peacock WF, Pitt B, Fiuzat M, Maggioni AP, Gheorghiade M, Ando Y, Pocock SJ, Zannad F, O'Connor CM. Learning from recent trials and shaping the future of acute heart failure trials. Am Heart J. 2013 Oct;166(4):629-35.
40. Givertz MM, Teerlink JR, Albert NM, Westlake Canary CA, Collins SP, Colvin-Adams M, Ezekowitz JA, Fang JC, Hernandez AF, Katz SD, Krishnamani R, Stough WG, Walsh MN, Butler J, Carson PE, Dimarco JP, Hershberger RE, Rogers JG, Spertus JA, Stevenson WG, Sweitzer NK, Wilson Tang WH, Starling RC. Acute Decompensated Heart Failure: Update on New and Emerging Evidence and Directions for Future Research. Journal of Cardiac Failure. 2013 6//;19(6):371-89.
41. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM. Diuretic Strategies in Patients with Acute Decompensated Heart Failure. New England Journal of Medicine. 2011;364(9):797-805.
42. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJV, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalán R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Méndez GF, Metra M, Mittal S, Oh B-H, Pereira NL, Ponikowski P, Tang WHW, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of Nesiritide in Patients with Acute Decompensated Heart Failure. New England Journal of Medicine. 2011;365(1):32-43.
43. Giamouzis G, Butler J, Starling RC, Karayannis G, Nastas J, Parisis C, Rovithis D, Economou D, Savvatis K, Kirlidis T, Tsaknakis T, Skoularigis J, Westermann D, Tschöpe C, Triposkiadis F. Impact of dopamine infusion on renal function in hospitalized heart failure patients: Results of the dopamine in acute

decompensated heart failure (DAD-HF) trial. Journal of Cardiac Failure. 2010;16(12):922-30.
44. Massie BM, O'Connor CM, Metra M, Ponikowski P, Teerlink JR, Cotter G, Weatherley BD, Cleland JG, Givertz MM, Voors A, DeLucca P, Mansoor GA, Salerno CM, Bloomfield DM, Dittrich HC. Rolofylline, an adenosine A1-receptor antagonist, in acute heart failure. N Engl J Med. 2010 Oct 7;363(15):1419-28.
45. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, Redfield MM, Deswal A, Rouleau JL, LeWinter MM, Ofili EO, Stevenson LW, Semigran MJ, Felker GM, Chen HH, Hernandez AF, Anstrom KJ, McNulty SE, Velazquez EJ, Ibarra JC, Mascette AM, Braunwald E. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med. 2012 Dec 13;367(24):2296-304.
46. Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF, Jr., Dorobantu MI, Grinfeld LR, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin TM, Metra M. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. Lancet. 2013 Jan 5;381(9860):29-39.
47. Gheorghiade M, Bohm M, Greene SJ, Fonarow GC, Lewis EF, Zannad F, Solomon SD, Baschiera F, Botha J, Hua TA, Gimpelewicz CR, Jaumont X, Lesogor A, Maggioni AP. Effect of aliskiren on postdischarge mortality and heart failure readmissions among patients hospitalized for heart failure: the ASTRONAUT randomized trial. JAMA. 2013 Mar 20;309(11):1125-35.
48. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA. 2002 Mar 27;287(12):1531-40.
49. Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, Gheorghiade M, O'Connor CM. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. J Am Coll Cardiol. 2003 Mar 19;41(6):997-1003.
50. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, Padley RJ, Thakkar R, Delgado-Herrera L, Salon J, Garratt C, Huang B, Sarapohja T. Effect of levosimendan on the short-term clinical course of patients with acutely decompensated heart failure. JACC Heart Fail. 2013 Apr;1(2):103-11.
51. Johansson S, Wallander MA, Ruigomez A, Garcia Rodriguez LA. Incidence of newly diagnosed heart failure in UK general practice. Eur J Heart Fail. 2001 Mar;3(2):225-31.
52. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, Barreto-Filho JA, Kim N, Bernheim SM, Suter LG, Drye EE, Krumholz HM. Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia. JAMA. 2013 Jan 23;309(4):355-63.
53. Cleland JG, Antony R. It makes SENSE to take a safer road. Eur Heart J. 2011 Sep;32(18):2225-7.
54. Howlett JG. Acute heart failure: lessons learned so far. Can J Cardiol. 2011 May-Jun;27(3):284-95.
55. Inglis SC, Clark RA, McAlister FA, Stewart S, Cleland JG. Which components of heart failure programmes are effective? A systematic review and meta-analysis of the outcomes of structured telephone support or telemonitoring as the primary component of chronic heart failure management in 8323 patients: Abridged Cochrane Review. Eur J Heart Fail. 2011 Sep;13(9):1028-40.

56. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. Lancet. 2011 Feb 19;377(9766):658-66.
57. Adamson PB. Ambulatory hemodynamics in patients with chronic heart failure: implications for volume management in elderly patients. Am J Geriatr Cardiol. 2005 Sep-Oct;14(5):236-41.
58. Cleland JG, Coletta AP, Yassin A, Buga L, Torabi A, Clark AL. Clinical trials update from the European Society of Cardiology Meeting 2009: AAA, RELY, PROTECT, ACTIVE-I, European CRT survey, German pre-SCD II registry, and MADIT-CRT. Eur J Heart Fail. 2009 Dec;11(12):1214-9.
59. Cleland J, Yassin A, Arrow Y, Taylor J, Britchford G, Goode K, Clark AL. Outcome of patients discharged on loop diuretic therapy with or without diagnosis of Heart Failure. Europeon Heart Failure 2009; Nice, France2009.
60. Nohria A, Mielniczuk LM, Stevenson LW. Evaluation and monitoring of patients with acute heart failure syndromes. Am J Cardiol. 2005 Sep 19;96(6A):32G-40G.
61. Drazner MH, Brown RN, Kaiser PA, Cabuay B, Lewis NP, Semigran MJ, Torre-Amione G, Naftel DC, Kirklin JK. Relationship of right- and left-sided filling pressures in patients with advanced heart failure: a 14-year multi-institutional analysis. J Heart Lung Transplant. 2012 Jan;31(1):67-72.
62. Parakh K, Thombs BD, Bhat U, Fauerbach JA, Bush DE, Ziegelstein RC. Long-term significance of Killip class and left ventricular systolic dysfunction. Am J Med. 2008 Nov;121(11):1015-8.
63. Smith AA, Cowburn PJ, Parker ME, Denvir M, Puri S, Patel KR, Cleland JG. Impaired pulmonary diffusion during exercise in patients with chronic heart failure. Circulation. 1999 Sep 28;100(13):1406-10.
64. Puri S, Baker BL, Dutka DP, Oakley CM, Hughes JM, Cleland JG. Reduced alveolar-capillary membrane diffusing capacity in chronic heart failure. Its pathophysiological relevance and relationship to exercise performance. Circulation. 1995 Jun 1;91(11):2769-74.
65. Maisel A, Mueller C, Adams K, Jr., Anker SD, Aspromonte N, Cleland JG, Cohen-Solal A, Dahlstrom U, DeMaria A, Di Somma S, Filippatos GS, Fonarow GC, Jourdain P, Komajda M, Liu PP, McDonagh T, McDonald K, Mebazaa A, Nieminen MS, Peacock WF, Tubaro M, Valle R, Vanderhyden M, Yancy CW, Zannad F, Braunwald E. State of the art: using natriuretic peptide levels in clinical practice. Eur J Heart Fail. 2008 Sep;10(9):824-39.
66. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalo-Bel M, Pinto YM, Richards M. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J. 2006 Feb;27(3):330-7.
67. Frankenstein L, Clark AL, Goode K, Ingle L, Remppis A, Schellberg D, Grabs F, Nelles M, Cleland JG, Katus HA, Zugck C. The prognostic value of individual NT-proBNP values in chronic heart failure does not change with advancing age. Heart. 2009 May;95(10):825-9.
68. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M, Committee ASA, Investigators. Admission B-type natriuretic peptide levels and in-

hospital mortality in acute decompensated heart failure. J Am Coll Cardiol. 2007 May 15;49(19):1943-50.
69. Felker GM, Hasselblad V, Hernandez AF, O'Connor CM. Biomarker-guided therapy in chronic heart failure: a meta-analysis of randomized controlled trials. Am Heart J. 2009 Sep;158(3):422-30.
70. Singer AJ, Birkhahn RH, Guss D, Chandra A, Miller CD, Tiffany B, Levy P, Dunne R, Bastani A, Thode HC, Jr., Hollander JE. Rapid Emergency Department Heart Failure Outpatients Trial (REDHOT II): a randomized controlled trial of the effect of serial B-type natriuretic peptide testing on patient management. Circ Heart Fail. 2009 Jul;2(4):287-93.
71. Maisel A, Mueller C, Nowak R, Peacock WF, Landsberg JW, Ponikowski P, Mockel M, Hogan C, Wu AH, Richards M, Clopton P, Filippatos GS, Di Somma S, Anand I, Ng L, Daniels LB, Neath SX, Christenson R, Potocki M, McCord J, Terracciano G, Kremastinos D, Hartmann O, von Haehling S, Bergmann A, Morgenthaler NG, Anker SD. Mid-region pro-hormone markers for diagnosis and prognosis in acute dyspnea: results from the BACH (Biomarkers in Acute Heart Failure) trial. J Am Coll Cardiol. 2010 May 11;55(19):2062-76.
72. Peacock WF, Nowak R, Christenson R, DiSomma S, Neath SX, Hartmann O, Mueller C, Ponikowski P, Mockel M, Hogan C, Wu AH, Richards M, Filippatos GS, Anand I, Ng LL, Daniels LB, Morgenthaler N, Anker SD, Maisel AS. Short-term mortality risk in emergency department acute heart failure. Acad Emerg Med. 2011 Sep;18(9):947-58.
73. Maisel A, Neath SX, Landsberg J, Mueller C, Nowak RM, Peacock WF, Ponikowski P, Mockel M, Hogan C, Wu AH, Richards M, Clopton P, Filippatos GS, Di Somma S, Anand I, Ng LL, Daniels LB, Christenson RH, Potocki M, McCord J, Terracciano G, Hartmann O, Bergmann A, Morgenthaler NG, Anker SD. Use of procalcitonin for the diagnosis of pneumonia in patients presenting with a chief complaint of dyspnoea: results from the BACH (Biomarkers in Acute Heart Failure) trial. Eur J Heart Fail. 2012 Mar;14(3):278-86.
74. Januzzi JL, Jr., Filippatos G, Nieminen M, Gheorghiade M. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. Eur Heart J. 2012 Sep;33(18):2265-71.
75. Peacock WFt, De Marco T, Fonarow GC, Diercks D, Wynne J, Apple FS, Wu AH, Investigators A. Cardiac troponin and outcome in acute heart failure. N Engl J Med. 2008 May 15;358(20):2117-26.
76. Twerenbold R, Jaffe A, Reichlin T, Reiter M, Mueller C. High-sensitive troponin T measurements: what do we gain and what are the challenges? Eur Heart J. 2012 Mar;33(5):579-86.
77. Xue Y, Clopton P, Peacock WF, Maisel AS. Serial changes in high-sensitive troponin I predict outcome in patients with decompensated heart failure. Eur J Heart Fail. 2011 Jan;13(1):37-42.
78. Pascual-Figal DA, Manzano-Fernandez S, Boronat M, Casas T, Garrido IP, Bonaque JC, Pastor-Perez F, Valdes M, Januzzi JL. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. Eur J Heart Fail. 2011 Jul;13(7):718-25.
79. O'Connor CM, Fiuzat M, Lombardi C, Fujita K, Jia G, Davison BA, Cleland J, Bloomfield D, Dittrich HC, Delucca P, Givertz MM, Mansoor G, Ponikowski P, Teerlink JR, Voors AA, Massie BM, Cotter G, Metra M. Impact of serial troponin

release on outcomes in patients with acute heart failure: analysis from the PROTECT pilot study. Circ Heart Fail. 2011 Nov;4(6):724-32.
80. Metra M, Cotter G, Davison BA, Felker GM, Filippatos G, Greenberg BH, Ponikowski P, Unemori E, Voors AA, Adams KF, Jr., Dorobantu MI, Grinfeld L, Jondeau G, Marmor A, Masip J, Pang PS, Werdan K, Prescott MF, Edwards C, Teichman SL, Trapani A, Bush CA, Saini R, Schumacher C, Severin T, Teerlink JR. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. J Am Coll Cardiol. 2013 Jan 15;61(2):196-206.
81. Platz E, Lattanzi A, Agbo C, Takeuchi M, Resnic FS, Solomon SD, Desai AS. Utility of lung ultrasound in predicting pulmonary and cardiac pressures. Eur J Heart Fail. 2012 Nov;14(11):1276-84.
82. Picano E, Gargani L. Ultrasound lung comets: the shape of lung water. Eur J Heart Fail. 2012 Nov;14(11):1194-6.
83. Tang WH, Tong W. Measuring impedance in congestive heart failure: current options and clinical applications. Am Heart J. 2009 Mar;157(3):402-11.
84. Yu CM, Wang L, Chau E, Chan RH, Kong SL, Tang MO, Christensen J, Stadler RW, Lau CP. Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. Circulation. 2005 Aug 9;112(6):841-8.
85. Abraham WT, Compton S, Haas G, Foreman B, Canby RC, Fishel R, McRae S, Toledo GB, Sarkar S, Hettrick DA, Investigators FS. Intrathoracic impedance vs daily weight monitoring for predicting worsening heart failure events: results of the Fluid Accumulation Status Trial (FAST). Congest Heart Fail. 2011 Mar-Apr;17(2):51-5.
86. van Veldhuisen DJ, Braunschweig F, Conraads V, Ford I, Cowie MR, Jondeau G, Kautzner J, Aguilera RM, Lunati M, Yu CM, Gerritse B, Borggrefe M. Intrathoracic impedance monitoring, audible patient alerts, and outcome in patients with heart failure. Circulation. 2011 Oct 18;124(16):1719-26.
87. Freimark D, Arad M, Sokolover R, Zlochiver S, Abboud S. Monitoring lung fluid content in CHF patients under intravenous diuretics treatment using bio-impedance measurements. Physiol Meas. 2007 Jul;28(7):S269-77.
88. Arad M, Zlochiver S, Davidson T, Shovman O, Shoenfeld Y, Adunsky A, Abboud S. Estimating pulmonary congestion in elderly patients using bio-impedance technique: correlation with clinical examination and X-ray results. Med Eng Phys. 2009 Oct;31(8):959-63.
89. Northridge DB, Findlay IN, Wilson J, Henderson E, Dargie HJ. Non-invasive determination of cardiac output by Doppler echocardiography and electrical bioimpedance. Br Heart J. 1990 Feb;63(2):93-7.
90. Packer M, Abraham WT, Mehra MR, Yancy CW, Lawless CE, Mitchell JE, Smart FW, Bijou R, O'Connor CM, Massie BM, Pina IL, Greenberg BH, Young JB, Fishbein DP, Hauptman PJ, Bourge RC, Strobeck JE, Murali S, Schocken D, Teerlink JR, Levy WC, Trupp RJ, Silver MA. Utility of impedance cardiography for the identification of short-term risk of clinical decompensation in stable patients with chronic heart failure. J Am Coll Cardiol. 2006 Jun 6;47(11):2245-52.
91. Malfatto G, Corticelli A, Villani A, Giglio A, Della Rosa F, Branzi G, Facchini M, Parati G. Transthoracic bioimpedance and brain natriuretic Peptide assessment for prognostic stratification of outpatients with chronic systolic heart failure. Clin Cardiol. 2013 Feb;36(2):103-9.

92. Kamath SA, Drazner MH, Tasissa G, Rogers JG, Stevenson LW, Yancy CW. Correlation of impedance cardiography with invasive hemodynamic measurements in patients with advanced heart failure: the BioImpedance CardioGraphy (BIG) substudy of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) Trial. Am Heart J. 2009 Aug;158(2):217-23.
93. Di Somma S, Navarin S, Giordano S, Spadini F, Lippi G, Cervellin G, Dieffenbach BV, Maisel AS. The emerging role of biomarkers and bio-impedance in evaluating hydration status in patients with acute heart failure. Clin Chem Lab Med. 2012 Dec;50(12):2093-105.
94. Amir O, Rappaport D, Zafrir B, Abraham WT. A Novel Approach to Monitoring Pulmonary Congestion in Heart Failure: Initial Animal and Clinical Experiences Using Remote Dielectric Sensing Technology. Congest Heart Fail. 2013 Jan 25.
95. Gal T Ben AO, Rappaport D, Rekant K, Adamson P. B, Anker S, Cleland JG, Jaarsma T, Abraham WT. A pilot study on the feasibility of heart failure medical management based on daily monitoring of pulmonary subclinical congestion with ReDS technology in outpatient set up. ESC Heart Failure 2013; Lisbon2013.
96. Chirinos JA, Kips JG, Jacobs DR, Jr., Brumback L, Duprez DA, Kronmal R, Bluemke DA, Townsend RR, Vermeersch S, Segers P. Arterial Wave Reflections and Incident Cardiovascular Events and Heart Failure: MESA (Multiethnic Study of Atherosclerosis). J Am Coll Cardiol. 2012 Nov 20;60(21):2170-7.
97. Sung SH, Yu WC, Cheng HM, Lee CW, Lin MM, Chuang SY, Chen CH. Excessive wave reflections on admission predict post-discharge events in patients hospitalized due to acute heart failure. Eur J Heart Fail. 2012 Dec;14(12):1348-55.
98. Shah SJ, Wasserstrom JA. Increased arterial wave reflection magnitude: a novel form of stage B heart failure? J Am Coll Cardiol. 2012 Nov 20;60(21):2178-81.
99. Collins SP, Peacock WF, Lindsell CJ, Clopton P, Diercks DB, Hiestand B, Hogan C, Kontos MC, Mueller C, Nowak R, Chen WJ, Huang CH, Abraham WT, Amsterdam E, Breidthardt T, Daniels L, Hasan A, Hudson M, McCord J, Naz T, Wagoner LE, Maisel A. S3 detection as a diagnostic and prognostic aid in emergency department patients with acute dyspnea. Ann Emerg Med. 2009 Jun;53(6):748-57.
100. Maisel AS, Peacock WF, Shah KS, Clopton P, Diercks D, Hiestand B, Kontos MC, Mueller C, Nowak R, Chen WJ, Collins SP. Acoustic cardiography S3 detection use in problematic subgroups and B-type natriuretic peptide "gray zone": secondary results from the Heart failure and Audicor technology for Rapid Diagnosis and Initial Treatment Multinational Investigation. Am J Emerg Med. 2011 Oct;29(8):924-31.
101. Silber HA, Trost JC, Johnston PV, Maughan WL, Wang NY, Kasper EK, Aversano TR, Bush DE. Finger photoplethysmography during the Valsalva maneuver reflects left ventricular filling pressure. Am J Physiol Heart Circ Physiol. 2012 May 15;302(10):H2043-7.
102. Gheorghiade M, Konstam MA, Burnett JC, Jr., Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C, Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan I. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA. 2007 Mar 28;297(12):1332-43.

103. Sharma GV, Woods PA, Lindsey N, O'Connell C, Connolly L, Joseph J, McIntyre KM. Noninvasive monitoring of left ventricular end-diastolic pressure reduces rehospitalization rates in patients hospitalized for heart failure: a randomized controlled trial. J Card Fail. 2011 Sep;17(9):718-25.
104. Yamokoski LM, Hasselblad V, Moser DK, Binanay C, Conway GA, Glotzer JM, Hartman KA, Stevenson LW, Leier CV. Prediction of rehospitalization and death in severe heart failure by physicians and nurses of the ESCAPE trial. J Card Fail. 2007 Feb;13(1):8-13.
105. Ritzema JL, Richards AM, Crozier IG, Frampton CF, Melton IC, Doughty RN, Stewart JT, Eigler N, Whiting J, Abraham WT, Troughton RW. Serial Doppler echocardiography and tissue Doppler imaging in the detection of elevated directly measured left atrial pressure in ambulant subjects with chronic heart failure. JACC Cardiovasc Imaging. 2011 Sep;4(9):927-34.
106. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, American College of Cardiology F, American Heart A. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol. 2009 Apr 14;53(15):e1-e90.
107. Doenst T, Cleland JG, Rouleau JL, She L, Wos S, Ohman EM, Krzeminska-Pakula M, Airan B, Jones RH, Siepe M, Sopko G, Velazquez EJ, Racine N, Gullestad L, Filgueira JL, Lee KL. Influence of Crossover on Mortality in a Randomized Study of Revascularization in Patients with Systolic Heart Failure and Coronary Artery Disease. Circ Heart Fail. 2013 Mar 20.
108. Cleland JG, Calvert M, Freemantle N, Arrow Y, Ball SG, Bonser RS, Chattopadhyay S, Norell MS, Pennell DJ, Senior R. The Heart Failure Revascularisation Trial (HEART). Eur J Heart Fail. 2011 Feb;13(2):227-33.
109. Crundall-Goode A, Goode K, Shoaib A, Geliijnse G, Vries JGd, Robson E, Dobbs K, Wong K, Clark A, Cleland J. OPeRA-HF study design (Risk Arm): an Observational study to assess and Predict the in-patient course, risk of Re-Admission and mortality for patients hospitalised for or with Heart Failure. Heart Failure 2013; Lisbon Portugal 2013.
110. Shoaib A, Mabote T, Zuhair M, Kassianides X, Cleland J. Acute heart failure (suspected or confirmed): Initial diagnosis and subsequent evaluation with traditional and novel technologies. World Journal of Cardiovascular Diseases. 2013 June 2013;3 No.3(2013):290-300.
111. Cleland JG, Swedberg K, Cohen-Solal A, Cosin-Aguilar J, Dietz R, Follath F, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Preda I, van Gilst WH, Widimsky J, Mareev V, Mason J, Freemantle N, Eastaugh J. The Euro Heart Failure Survey of the EUROHEART survey programme. A survey on the quality of care among patients with heart failure in Europe. The Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The Medicines Evaluation Group Centre for Health Economics University of York. Eur J Heart Fail. 2000 Jun;2(2):123-32.
112. Bland M. An introduction to medical statistics. Oxford [u.a.]: Oxford Univ. Press; 2008.

113. Sauerbrei W. The Use of Resampling Methods to Simplify Regression Models in Medical Statistics. Journal of the Royal Statistical Society: Series C (Applied Statistics). 1999;48(3):313-29.
114. Cain KC, Lange NT. Approximate Case Influence for the Proportional Hazards Regression Model with Censored Data. Biometrics. 1984;40(2):493-9.
115. McDonagh T, Cleland J, Dargie HJ, Whittaker T, Standing M, Mitchell M, Cunningham D. Ntional Heart Failure Audit April 2010-March 2011. National Institute For Cardiovascular Outcomes Research (NICOR), 2011 2012. Report No.
116. Butler J, Fonarow GC, Gheorghiade M. Strategies and opportunities for drug development in heart failure. JAMA. 2013 Apr 17;309(15):1593-4.
117. O'Connor CM, Stough WG, Gallup DS, Hasselblad V, Gheorghiade M. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. J Card Fail. 2005 Apr;11(3):200-5.
118. Shoaib A, Kassianides X, Zuhair M, Waleed M, Goode K, Wong K, Cleland J, Clark A. SEVERE BREATHLESSNESS AT REST IS NOT THE MOST IMPORTANT PRESENTATION OF ACUTE HEART FAILURE. Journal of the American College of Cardiology. 2014;63(12_S).
119. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. J Am Coll Cardiol. 2013 Jan 29;61(4):391-403.
120. Shoaib A, Shahid M, Zohair M, Waleed M, Djahit A, Kassianides X, Wong K, Rigby A, Cleland J, Clark A. 59 Is presentation of acute heart failure patients linked to mortality? Heart. 2014 Jun;100 Suppl 3:A34.
121. Pellicori P, Carubelli V, Zhang J, Castiello T, Sherwi N, Clark AL, Cleland JGF. IVC Diameter in Patients With Chronic Heart Failure: Relationships and Prognostic Significance. JACC: Cardiovascular Imaging. 2013 1//;6(1):16-28.
122. Siirila-Waris K, Lassus J, Melin J, Peuhkurinen K, Nieminen MS, Harjola VP. Characteristics, outcomes, and predictors of 1-year mortality in patients hospitalized for acute heart failure. Eur Heart J. 2006 Dec;27(24):3011-7.
123. Fonarow GC. Epidemiology and risk stratification in acute heart failure. Am Heart J. 2008 Feb;155(2):200-7.
124. J C, P P, TH H, AR F. Importance of events per independent variable in proportional hazards analysis. I. Background, goals and general strategy. Journal of Clinical Epidemiology. 1996;48:1503-10.
125. Nunez J, Nunez E, Robles R, Bodi V, Sanchis J, Carratala A, Aparici M, Llacer A. Prognostic value of brain natriuretic peptide in acute heart failure: mortality and hospital readmission. Rev Esp Cardiol. 2008 Dec;61(12):1332-7.
126. Cowie MR, Collinson PO, Darige H, Hobbs FR, McDonagh TA, McDonald K, Rowell N. Recommendations on the clinical use of B-type natriuretic peptide testing (BNP or NTproBNP) in the UK and Ireland. The British Journal of Cardiology. 2010 March 2010;17(2):Br J Cardiol 2010;17:76–80.
127. Shoaib A, Waleed M, Khan S, Raza A, Zuhair M, Kassianides X, Djahit A, Goode K, Wong K, Rigby A, Clark A, Cleland J. Breathlessness at Rest is Not the Dominant Presentation of Patients Admitted with Heart Failure. . European journal of Heart Failure. 2014.
128. Mehra MR, Butler J. Comorbid conditions in heart failure: an unhappy marriage. Heart Fail Clin. 2014 Apr;10(2):ix.
129. Cleland JG, Khand A, Clark A. The heart failure epidemic: exactly how big is it? Eur Heart J. 2001 Apr;22(8):623-6.

130. Verweij PJM, Van Houwelingen HC. Cross-validation in survival analysis. Statistics in Medicine. 1993;12(24):2305-14.
131. Ingle L, Rigby AS, Carroll S, Butterly R, King RF, Cooke CB, Cleland JG, Clark AL. Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure. Eur Heart J. 2007 Mar;28(5):560-8.
132. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology. 1983 Sep;148(3):839-43.
133. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med. 2005 Apr 14;352(15):1539-49.
134. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med. 1987 Jun 4;316(23):1429-35.
135. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999 Sep 2;341(10):709-17.
136. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J. Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med. 2008 Jul 10;359(2):142-51.

## Definitions

ACEi; Angiotensin converting enzyme inhibitor

ACS; acute coronary syndrome

AF; Atrial fibrillation

Af; Atrial flutter

AHF; acute heart failure

ARB; Angiotensin receptor blocker

ASOB; Acute Shortness of Breath

Asymp. LVD; Asymptomatic left ventricle dysfunction

BB; Beta blocker

BMI; Body mass index

BP; blood pressure

CABG; Coronary artery bypass grafting

CAD; Coronary artery disease

CARBOSE; Comfortable at rest breathless on slight exertion

CCB, Calcium Channel blocker

CHF; Chronic Heart Failure

CI; Confidence interval

CKD; Chronic kidney disease

COPD; Chronic obstructive pulmonary disease

C-PAP; Continuous positive airway pressure

CVA, Cerebrovascular accident

DCMP; Dilated cardiomyopathy

DM; Diabetes Mellitus

Echo; Echocardiography

ED; Emergency department

EF; Ejection fraction

eGFR; Estimated glomerular filtration rate

EHFS-1; Euro heart failure survey 1

EHFS-II; Euro heart failure survey II

EHF Pilot; Euro Heart Failure Pilot survey

ESC; European society of cardiology

E&W NHFA; England & Wales National heart failure audit

E & W national audit; England & Wales national audit,

HF; heart failure

HFPEF; heart failure with preserved ejection fraction

HR; Heart Rate

HR; Hazard ration

hsCRP, high sensitivity C-Reactive protein

hsTnT, High sensitivity Troponin T

IHD,Ischaemic Heart disease

IQR, Inter quartile range

IV; Intra venous

JVP; jugular venous pressure

KG, Kilo gram

LA; Left atrium.

LOS: Length of stay

LV; left ventricle

LVEDD; Left ventricle end diastolic diameter

LVESD; Left Ventricle end systolic diameter

LVSD, Left Ventricle Systolic dysfunction

MI; Myocardial Infarction

MRA; Mineralocorticoid receptor antagonist

NT-proBNP; N-terminal pro B-type natriuretic peptide

NYHA; New York heart association

OR; Odd ratio

PCI; Percutaneous coronary intervention

QRST

RR; Respiratory rate

RV; right ventricle

SBP; systolic blood pressure

SOBAR; Shortness of breath at rest

SVT; Supraventricular tachycardia

TIA, Transient Ischaemic attack

UA; Unstable angina

USA: United States of America

VF; Ventricle fibrillation

VT; Ventricle tachycardia

WBC, White Blood count