Congestion in acute heart failure trials and registries: a systematic review

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Abstract

Introduction

The term “congestion” is used to describe a broad range of clinical presentations. Congestion is a variably understood and assessed entity. Patients develop a mixture of central (pulmonary) and/or peripheral (non-pulmonary) symptoms of congestion. These are likely to have different pathophysiological mechanisms. The presence of subclinical congestion is an independent risk factor for early re-hospitalisation and morbidity. Novel techniques to assess congestion have been developed, but their clinical role is not yet established.

Methods

I performed two systematic reviews of acute heart failure (AHF) trials and registries from Jan 1, 2001 to Dec 31, 2018 on EMBASE and MEDLINE to determine the methods and techniques used to assess and grade congestion. The search terms utilised were “acute heart failure”, “decompensated heart failure” and “hospitalized heart failure”. The minimum enrolment numbers were 180 patients for randomised trials and 2,000 patients for registries.

Results

18 major acute heart failure registries and 21 major trials were analysed. There are no standardised methods for assessing central or peripheral congestion. Acute heart failure trials preferentially recruited patients with pulmonary congestion (manifesting as dyspnoea at rest). In 6 of 8 trials with available data, this was mandatory for 100% of patients. By contrast, for large registry trials this rate ranged from 34 to 73%. Dyspnoea on exertion was a more predominant presentation (61 to 95%). With the exception of a chest X-ray, no trial or registry routinely utilised non-invasive (e.g. lung ultrasound) or invasive (e.g. right heart catheterisation) techniques to objectively and systematically quantify either congestion on recruitment or congestion on discharge.

Conclusion

Congestion is variably assessed and defined. Internationally agreed definitions of the presence and severity of congestion are required. These definitions should include conventional symptoms and signs as well as newer methods of assessing congestion. Trials of treatments for central or peripheral congestion may have different inclusion criteria.

Authors Declaration

I declare that I am the sole author of this thesis. This work has never previously been submitted for a higher degree.

I am grateful for the efforts of Dr Andrew Morrow (AM) and Dr Ninian Nicholas Lang (NNL) for their invaluable assistance with the screening process for both systematic reviews.

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Abbreviations

AC-DHF	Acute-on-chronic decompensated heart failure
ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
ADM	Adrenomedullin
AHA	American Heart Association
AHF	Acute heart failure
ANP	Atrial natriuretic peptide
ARB	Angiotensin receptor blockers
ARNi	Angiotensin receptor-neprilysin inhibitors
AT2	Angiotensin II
ATP	Anti-tachycardia pacing
AV	Atrio-ventricular
BiPPV	Bilevel positive pressure ventilation
BIVA	Bio-electrical vector analysis
BNP	Brain natriuretic peptide
Bpm	Beats per minute
CARBOSE	'Comfortable at rest, breathless on slight exertion'
CHD	Coronary heart disease
CI	Confidence interval
cMRI	Cardiac magnetic resonance imaging
CNP	C-type natriuretic peptide
COPD	Chronic obstructive respiratory disease
CPAP	Continuous positive airways pressure
CRT	Cardiac resynchronisation therapy
CT	Computed tomography
CVP	Central venous pressure
CXR	Chest X-ray
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
DN-AHF	De-novo acute heart failure
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department

ESC	European Society of Cardiology
FGF	Fibroblast growth factor
GRACE	Global Registry of Acute Coronary Events
H-ISDN	Hydralazine-isosorbide dinitrate
HF	Heart failure
HFmrEF	Heart failure with mid-range ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HI	Hydration index
HR	Hazard ratio
IABP	Intra-aortic balloon pump
ICD	Implantable cardiac defibrillators
IVC	Inferior vena cava
JV	Jugular vein
JVP	Jugular venous pressure
LUS	Lung ultrasound
LV	Left ventricle
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MCS	Mechanical circulatory support
MI	Myocardial infarction
MRA	Mineralocorticoid antagonists
NIRS	Near-infrared spectroscopy
NIV	Non-invasive ventilation
NP	Natriuretic peptide
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OMT	Optimal medical therapy
PCWP	Pulmonary capillary wedge pressure
PND	Paroxysmal nocturnal dyspnoea
RAAS	Renin-angiotensin-aldosterone system
RAP	Right atrial pressure
RCT	Randomised control trial
RHC	Right heart catheterisation

RHF	Right heart failure
RR	Relative risk
RV	Right ventricle
SCD	Sudden cardiac death
SOBAR	‘Short of breath at rest’
TTE	Transthoracic echocardiographic
VA	Veno-arterial
VAS	Visual analogue scale
VF	Ventricular fibrillation
VT	Ventricular tachycardia
VV	Veno-venous

1 Introduction to heart failure

1.1 Definition of heart failure

Heart failure (HF) can be defined as complex syndrome comprised of typical symptoms and clinical signs which are the result of structural and/or functional cardiac abnormalities, resulting in reduced cardiac output and elevated intracardiac pressures.[1,2] As a result of failure to produce an adequate cardiac output to meet the metabolic demands of the body, neurohormonal responses are activated to try to restore perfusion.[3] These secondary maladaptive changes produce salt and water retention and eventually recognised features of congestion are manifested clinically. The terms “left ventricular (LV) dysfunction” and “cardiomyopathy” may often be incorrectly used when describing HF, as these are not entirely interchangeable. HF can occur as a result of a wide range of cardiovascular conditions (arrhythmia, coronary artery disease, hypertension etc) which produce the characteristic HF syndrome.

The modes of presentation of HF can vary markedly depending on the underlying aetiology, precipitant trigger and general functional state of the patient. Demonstration of a cardiac abnormality in the setting of classic clinical symptoms are key to concluding a diagnosis of HF.

1.2 Clinical evaluation

As HF becomes symptomatic, a wide constellation of clinical signs and symptoms may appear. These can be classified into features arising from central pulmonary or peripheral (non-pulmonary) congestion, but the distinctions are arbitrary and no formal universal definitions exist.[4,5] In reality, usually a mix of both tend to predominate. The ESC Scientific Statement on Assessing and Grading Congestion (2010) provides a general outline of major symptoms which should be assessed (dyspnoea, orthopnoea, dyspnoea on exertion, pulmonary rales, jugular venous pressure, oedema and body weight) but without mandating any specific

classification system or grading mechanism.[6] Older classifications have historically partitioned features into left and/or right sided congestion.

1.2.1 Central (pulmonary) congestion

Symptoms of central congestion include dyspnoea, orthopnoea and paroxysmal nocturnal dyspnoea (PND). Clinical signs include hypoxia, tachypnoea, and pulmonary rales (on lung auscultation).[7] These can also be regarded as more left sided signs which arise from left heart dysfunction leading to elevated pulmonary pressures and subsequent fluid transudation into the alveolar space.[6]

1.2.2 Peripheral (non-pulmonary) congestion

Symptoms of peripheral (non-pulmonary) congestion include ankle and leg swelling, abdominal discomfort and swelling, nausea, anorexia and weight gain.[8] Clinical signs include elevated jugular venous pressure (JVP), ankle oedema, ascites and hepatomegaly. [9] These signs could be regarded as more right sided which can often arise where there is isolated right ventricular (RV) dysfunction. RV failure can produce elevated peripheral systemic venous pressures which causes fluid to transudate into interstitial space in the lower legs, peritoneal cavity and intestinal capillary bed.[10]

1.2.3 Mixed congestive signs

The distinction between central and peripheral is not absolute.[5] Both central and peripheral congestion can cause breathlessness on exertion – either due to pulmonary oedema or the increased workload of having to move more congested limbs.[11] Fatigue and cachexia are common complaints in both congestive subtypes. Isolated central or peripheral features are rare. Right heart failure (RHF) – secondary to RV infarction or RV cardiomyopathy - can produce a set of exclusively right sided peripheral features. Where left heart disease exists, right

heart dysfunction also eventually arises and mixed central and peripheral congestive signs will normally become apparent.[5]

1.3 Terminology

In 2016, HF was separated into 3 distinct categories based on left ventricular ejection fraction (LVEF): [2,12]

- heart failure with preserved ejection fraction (HFpEF) where the LVEF is ≥50%
- heart failure with reduced ejection fraction (HFrEF) where the LVEF is <40%
- a third "grey zone" in the evidence base for patients with an LVEF between 40 and 49% has also been defined and termed heart failure with mid-range ejection fraction (HFmREF).[1]

Patients with HFrEF had been thought of as having LV systolic (contractile) dysfunction and those with HFpEF as having LV diastolic (relaxational) dysfunction. In reality an overlap of contractile and relaxant abnormalities are found in both cohorts. Though both may also share similar aetiologies and present with similar features of congestion, they have distinct demographic profiles, pathophysiology and prognoses[13]. Medical therapies which have been successful in patients with HFrEF have not produced similar results in HFpEF, therefore being cognisant of a patient's ejection fraction is key to direct evidence based care.[1,2]

1.3.1 HFpEF

Patients with HFpEF tend to exhibit abnormalities of diastolic function; and the term "diastolic heart failure" has previously been used for this syndrome.[14] However, this is not always prevalent and the true mechanism of how congestion manifests is incompletely understood. Instead the term "preserved EF" has been employed (rather than "normal EF") as systolic function in these patients still may have various pathological subtleties which affect contractile function (but

are not significant enough to alter the EF parameter). At present, no gold standard for diagnosing HFpEF exists. The syndrome often been under-recognised so its true incidence, prevalence and prognosis remain more difficult to define.

HFpEF patients characteristically tend to be older, female and with concomitant arterial hypertension, diabetes mellitus, atrial fibrillation and/or obesity.[2] Echocardiographically, LV hypertrophy (and subsequently left atrial enlargement) are frequently noted. Thickening of the myocardial wall causes the heart to "stiffen" and become unable to relax and "suck in" blood from the venous circulation during the diastolic phase of the cardiac cycle.[15] Increased filling pressures subsequently develop and the classical features of congestion then become evident.

1.3.2 HFrEF

The evidence base for proven pharmacological and device therapies came from randomised trials where enrolment was restricted to patients with an LVEF below either 35 or 40%.[16,17] As a consequence, clinical guidelines have historically also employed a similar EF cut off for defining HFrEF [16,17] When compared to patients with HFpEF, patients with HFrEF may more frequently have an ischaemic aetiology and also other echocardiographic abnormalities such as LV dilatation and functional mitral regurgitation. However, the very same diastolic abnormalities found in HFpEF patients are also often present in those with HFrEF.[18] Despite this, both are thought to be separate entities with different pathophysiological mechanisms.[19]

1.3.3 HFmrEF

Between the gap of HFrEF and HFpEF trials lies a 'grey zone' of patients with an LVEF between 40-49%. This intermediate HFmrEF phenotype appears to be composed predominantly of male patients, with substantial hypertensive and diabetic disease but also more coronary heart disease (CHD) compared to HFpEF

equivalents.[20] Similar echocardiographic remodelling involving eccentric LV hypertrophy has also been described. These likely represent a mixture of patients with deteriorating HFpEF and progressive ischaemic coronary disease, and recovering HFrEF post-myocarditis or post-myocardial infarction.[21] Randomised trials are still to detail precisely which therapies are of benefit in this group. This will remain a challenge as HFmrEF patients comprise less that 20% of the HF cohort and despite being labelled as having ‘’mild LV systolic dysfunction and often have no clinical features of HF. [20] Historically, most patients with this intermediate LVEF category have been enrolled into HFpEF trials. As such, treatment guidelines are usually extrapolated from HFpEF rather than HFrEF studies.[1] However, these trials have been re-examined and have demonstrated that guideline based therapies (especially agents producing neurohormonal and sympathetic blockade) do confer benefit in HFmrEF.[22-24]

1.4 Epidemiology

1.4.1 Incidence

The incidence of HF Is believed to range from around 100 to 900 cases per 100,000 person-years (though most of these statistics are derived from developed nations and are difficult to extrapolate on a global scale).[25] Approximately 915,000 new cases of HF are diagnosed in the United States each year and the lifetime risk of HF at age 40 is estimated to be 20%.[26] As a consequence of improved long term management of hypertension and better acute treatments of acute coronary syndromes (ACS), the incidence of HF appears to be falling. Data from the Olmsted County studies suggest that between 2000 and 2010 the age and sex adjusted incidence rates of HF fell by a third from 315.8 to 219.3 per 100,000 residents.[27] However, the prevalence of HF is continuing to rise, driven by an increasingly aging population. The Multi Ethnic Study of Atherosclerosis (MESA) found the highest incident rates of HF amongst African-Americans, followed by white and Hispanic Americans and lowest amongst Chinese-Americans. Various co-morbidities such as diabetes and hypertension may explain some of this variation by ethnicity.[28] Older incidence rates from the Framingham study amongst others are more difficult to verify due

to the lack of objective imaging modalities and biomarkers to confirm the presence of absence of HF.

1.4.2 Prevalence

The prevalence of HF in developed nations is estimated to be around 1-2% of the adult population. [29] Although there are some differences depending on precisely which definition which is utilised, around 37.7 million patients are thought to be living with a diagnosis of HF.[30]

Around 5.7 million (2.2%) adults in the United States were believed to have HF between 2009-12, and this number is expected to increase by 46% to over 8 million by 2030.[31] Unsurprisingly the prevalence is highest in the elderly, rising from under 1% amongst those aged under 40 years to over 10% amongst those above 80.[32] The prevalence of HFpEF – though this population group remains difficult to define and diagnose - is projected to increase and become the numerically largest HF subtype. Data from Olmsted Investigators estimate that the prevalence of HFpEF has already risen by around a fifth from 38% to 57% between 1986 to 2010.[33,34] This is also reflected in results from the Get With the Guidelines Group which described rising rates of hospitalisation for HFpEF from 33% in 2005 to 39% in 2010. [35]

1.4.3 Prognosis

Estimating prognosis for HF patients remains a challenge despite the wealth of observational data available. To date, most prognostic models are only moderately successful in predicting mortality and much less accurate when estimating future morbidity or risk of re-hospitalisation. [36,37] However, it remains a condition with major morbidity and with a mortality comparable to that of cancer.

Mortality from HF has declined over the last 70 years.[27] Between 1950 and 1969, the 5-year mortality rate has fallen steadily amongst both men (70 to 59%) and

women (57 to 45%).[38] An observational study of study of 6,955,461 Medicare patients found that between 1993 and 2006 substantial improvement in in-patient HF related outcomes were observed. Mean length of stay reduced substantially (from 8.8 days to 6.3 days) as did in-patient mortality (from 8.5 to 4.3%) and 30 day mortality from (12.8 to 10.7%).[39] Amongst European patients, significant reductions were also seen in 30-day and one-year mortality. Amongst patients with HFpEF, in hospital mortality and re-hospitalisation rates are also comparable.[40]

In a Swedish review of 156,919 discharges from 1988 to 2000, 1-year mortality fell particularly markedly in younger age groups; by 69% amongst men and 80% among women aged 45–54 years. Among those aged 75-84, these improvements equated to an annual decrease of 4% and 5% in both men and women respectively. Similar improvements were seen a study of HF patients in the United Kingdom; one year survival post-hospitalisation rose from 45% in 1993 to 62% by 2001. In a primary care setting, HF survival rates increased from 2000 to 2016 whether measured for one year (increased by 6.6%), five years (increased by 7.2%) or ten years (increased by 6.4%).[41] However, the event of hospitalisation continues to confer a poorer prognosis, although the causality of influences is not clear.[41]

The introduction of newer medical therapies (particularly beta blockers and angiotensin converting enzyme [ACE] inhibitors), better systems of care, declining rates of smoking, and more rigorous management of co-morbidities are all thought to have contributed to improving outcomes.[42]

1.4.4 Healthcare and economic costs

1-2% of all worldwide hospitalisations are secondary to decompensated HF.[43] Over half of these currently occur in patients aged over 75, with a mean cost per admission of $10,775 under Medicare – a number which is continuing to rise.[44] In 25 years since 1979, HF related admissions tripled in the United States.[45] In the UK, 5% of all casualty admissions arise due to a complication of HF.[46] The 30 day re-hospitalisation rate is also substantial – ranging from 17% to 28% - with little

change in the last decade.[46] The variation between ethnic groups in the United States is also distinctly stark; re-admission rates are 50% higher amongst African-Americans, 20% higher for Hispanic-Americans but 50% lower for Asians-Americans when compared against a reference Caucasian population.[47]
Of the $108 billion spent globally on HF, 86% of this spending was localised to higher income nations. This is projected to increase worldwide, particularly as economic development continues to accelerate in Asia.[42,48] From 2013 to 2030, direct medical costs of HF in the United States will more than double from $21 billion to $53 billion (and when indirect economic costs are also factored, this figure rises to over $70 billion).[31] Similar increases in Europe are expected. Spend on cardiovascular care is projected to increase from €102 billion to €123 billion from 2012 to 2020. Of critical relevance, 80% of these substantive cost increases are expected be incurred from more hospitalisations.

1.5 Aetiology

Ischaemic heart disease and hypertension remain the most common causes of HF. In the Studies of Left Ventricular Dysfunction (SOLVD) trial, almost 80% with left ventricular systolic dysfunction (LVSD) had a history of myocardial infarction, 37% had hypertension and 15% concurrent diabetes mellitus[49]. In the Framingham study, hypertensive cardiovascular disease was the most predominant condition (37% of males) followed by coronary heart disease (14%).[50] A subsequent re-analysis of these datasets found that once more conventional blood pressure thresholds were applied, hypertension was likely present in 90% of patients. It should also be noted that Framingham diagnoses of HF were based on clinical criteria alone and so true LV systolic dysfunction may not have been present. More contemporary reviews have found a similar distribution; 50% of HF cases can be attributed to CHD with fewer due to hypertension – likely a reflection of the increasingly better medical management of the latter in primary care.[51]

However, where multiple associated risk factors for HF are present, discerning the precise primary aetiology remains problematic. These often remain presumed rather than confirmed; more deliberate strategies to uncover

underlying causes (such coronary angiography – with its notable limitations) are often not pursued vigorously.[52]

However, as with other HF studies, most of this research reviews populations in only Western Europe and the United States. In Japan, CHD is a less prevalent aetiology than in other developed Western countries. In Africa, the average age for HF patients is lower (hypertension and dilated cardiomyopathy are the most common causes of HF), and in South America almost half of patients have concomitant valve disease.[53,54]

Changing diagnostic criteria and more definitive investigative strategies mean that published figures will consistently vary from study to study, however CHD and hypertension still continue to appear predominant causes of HF.

1.5.1 Taxonomy of aetiologies

No universally accepted or consistently applied system exists for classifying the aetiology of HF. Most patients will have a number of different potential contributory mechanisms and diagnosis and treatment of all component pathologies is required to optimise outcomes. In general, precipitant causes can be split into three broad categories relating to either disease of the myocardium, abnormal loading conditions or arrhythmias (Table 1-1).[1]

The term 'cardiomyopathy' also has invited much debate. Initially used to describe ischaemic, valvular or hypertensive disease, in 2006 the American Heart Association (AHA) reserved the term primarily for pathologies of the myocardium whilst the European Society of Cardiology (ESC) adopted a more pragmatic approach based on phenotypic characterisation.[55,56]

Within the various aetiologies of cardiomyopathies, there remains a lack of consensus regarding the precise construct of definitions; idiopathic dilated cardiomyopathy (DCM) and diabetic cardiomyopathy notably continue to be difficult to define in an agreed manner.[57,58] For example, in diabetic cardiomyopathy conflicting research groups have continued to differ as to

whether the complete exclusion of potential contributory conditions is required or if it is sufficient that the clinician judges that these were not primarily attributable factors. Disagreement continues to impair evaluations into the true incidence and prevalence of these conditions.

Table 1-1. Aetiologies of heart failure. Adapted from Ponikowski *et al* (2016) [1]

Myocardial disease		
Coronary heart disease		Epicardial coronary artery disease, Coronary microvascular dysfunction
Immune / inflammatory damage	Infective	Bacteria, viruses (HIV), parasites (Chagas disease)
	Non-infective	Myocarditis, auto-immune diseases (connective tissue disorders such as systemic lupus erythematosus),
Infiltration	Malignancy	Direct malignant invasion
	Not related to malignancy	Amyloidosis, sarcoidosis, hemochromatosis (iron), lysosomal storage disease (e.g. Fabry disease).
Metabolic derangement	Hormonal	Thyroid disease, pheochromocytoma
	Nutritional	Thiamine, selenium, iron, calcium deficiency
Toxic damage	Recreational substance abuse	Alcohol, cocaine, amphetamine, anabolic steroid use
	Medications	Cytostatic drugs (e.g. anthracyclines)
	Radiation	
Genetic abnormalities	-	Hypertrophic cardiomyopathy, dilated cardiomyopathy, LV non-compaction
Abnormal Loading conditions		
Hypertension		
Valve and myocardial defects	Acquired	Mitral, aortic, tricuspid and pulmonary valve disease
	Congenital	Atrial and ventricular septal defects
Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis, pericardial effusion
	Endomyocardial	Hypereosinophilic syndrome, endomyocardial fibrosis
High output states		Renal failure, iatrogenic fluid overload
Volume overload		
Arrhythmias	Tachyarrhythmias	Atrial and ventricular arrhythmias
	Bradyarrhythmias	Sinus node dysfunction, conduction block

1.6 Diagnostic testing

A probability assessment must initially be performed for each patient based on clinical history, physical examination and a 12 lead electrocardiogram (ECG)(Figure 1-1).[1] Each patient must be assessed clinically based on their signs and symptoms before deciding whether HF may be a potential diagnosis and what further tests are appropriate. A history can elicit if various risk factors are present for HF, such as the presence of CHD, hypertension, or if other a familial hereditary pattern may be present (which can point a young patient with inherited DCM towards further genetic testing).

Clinical assessment is insufficient on its own and clinical signs are limited by inter-observer variability, poor sensitivity and often poor predictive value. However they remain key to triage further investigations and to assess if other alternative diagnoses are present, such as respiratory pathology.[59]

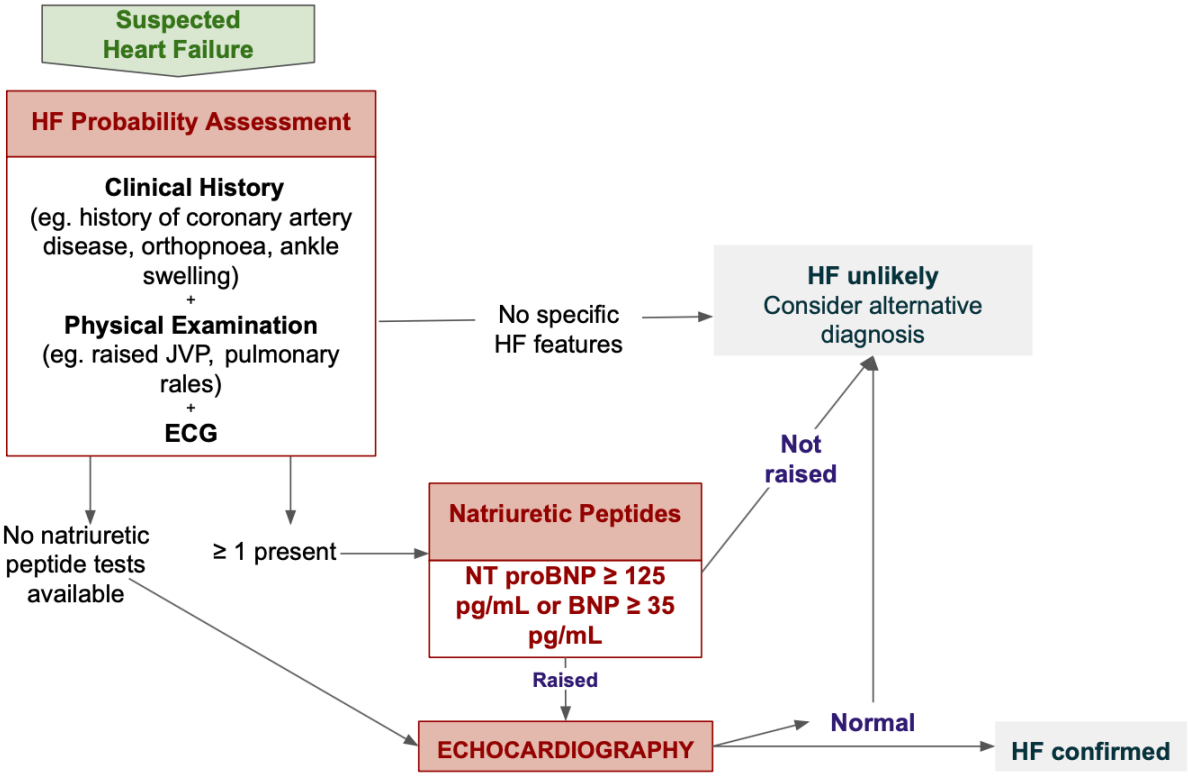

Figure 1-1. Clinical pathway for the diagnosis of heart failure. Adapted from Ponikowski *et al* (2016)[1]. An integrated diagnostic strategy based on clinical history, physical examination and ECG should utilised to guide further testing and the final diagnosis. HF: heart failure; JVP: jugular venous pressure; ECG: electrocardiogram; NT-proBNP: N-terminal-prohormone brain natriuretic peptide; BNP: brain natriuretic peptide.

Following this, a standard 12-lead electrocardiogram (ECG) is recommended by the ESC as part of each routine evaluation.[1] If all assessments are normal then a diagnosis of HF is unlikely. However, if one of either clinical history, physical examination or the ECG is abnormal then natriuretic peptides should be checked (and further HF investigation can be stopped if these are subsequently normal). If natriuretic peptides are elevated (or these are not available) then echocardiography should be performed.

Once testing confirms HF, more detailed investigations can be employed to determine HF aetiology. This may include coronary angiography to look for CHD or specific genetic testing to assess for various inherited cardiomyopathies.

1.6.1 12-lead ECG

An abnormal resting ECG has a high sensitivity in chronic HF of 89%.[60] Risk factors that indicate structural and functional cardiac abnormalities may also be present. Hypertension may produce changes of LV hypertrophy, a previous myocardial infarction can leave residual Q-waves and arrhythmias such as atrial fibrillation will be readily apparent on the trace. The specificity of the ECG is poorer however -around 56% - so whilst an ECG cannot diagnose left ventricular systolic dysfunction (LVSD), the presence of a normal trace is useful for excluding H.[61]

1.6.2 Biomarkers

1.6.2.1 Natriuretic peptides

Natriuretic peptides are the most useful diagnostic plasma test to establish a diagnosis of HF. They are released by cardiomyocytes as a result of myocardial wall stretch - in HF this is secondary to increased end-diastolic pressures arising from congestion. The two most commonly measured peptides are brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP). The normal upper limits depend on whether the patient is in a non-acute or acute setting. The nominal upper limits for non-acute patients are 35 pg/mL for BNP and 125

pg/mL for NTpro-BNP, and in acute patients 100 pg/mL for BNP and 300 pg/mL for NT-proBNP.[62]

The negative predictive values are extremely high (0.94-0.98); a normal circulating level of natriuretic peptides suggests HF is not likely and therefore further investigations are not required.[63] However, false positives are possible. Cardiac stressors (atrial fibrillation, myocarditis, acute coronary syndromes) and non-cardiac co-morbidities (advanced age, anaemia, renal failure) can all raise plasma levels of natriuretic peptides. False negatives are uncommon but arise in those already treated with a diuretic and in obese patients. It Is through that the reduction in circulating concentrations of natriuretic peptides found in obese individuals is the result of adipocyte surface cellular receptors binding natriuretic peptides, but this mechanism is not well understood.[64]

1.6.2.2 Cardiac troponin

Cardiac troponin is often raised in HF during acute episodes of congestion, and may indicate myocardial injury secondary to congestion.[65] Elevated levels usually reflect more severe haemodynamic upset and deleterious LV remodelling, and are associated with a poorer prognosis.[66,67] In acutely hospitalised patients, troponin may also be raised by a precipitating ACS, and so clinicians should consider whether troponin testing may provide additional information in a decompensated HF patient.[2] However, whilst troponin can rise and fall with congestion and treatment, it cannot be used to diagnose HF or direct de-congestive strategies.

1.6.2.3 Novel biomarkers

A number of novel biomarkers have shown early potential in the assessment of congestion in both acute and chronic HF states. Galectin-3 - a marker of fibrosis and inflammation - and has been implicated in HF remodelling. Though elevated levels are predictive of death and recurrent HF in AHF patients, interpretation of these assays are confounded where concurrent renal fibrosis arises from acute kidney injury.[68] ST2 is an inflammatory cytokine which mediates fibrosis and

vascular remodelling and has also demonstrated prognostic value in HF. However, its utility in the diagnosis of stable HF patients is limited.[68]

In the BIOlogy Study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF), fibroblast growth factor 23 (FGF23) and adrenomedullin (ADM) both showed particular promise in this prospective multi-centre European trial of 2179 patients with new-onset or worsening HF.[69] FGF23 has been implicated in maintaining sodium homeostasis and in the development LVH. Adrenomedullin (ADM) is an known endothelial biomarker which helps maintain the integrity of the endothelial barrier. In states of congestion (both pulmonary and systemic), capillary leakage has been associated with elevated plasma ADM.[70] In BIOSTAT-CHF, higher levels of FGF23 and ADM were both shown to correlate with more severe congestive clinical signs, elevated NPs and residual congestion. Both biomarkers could predict subsets of patients at higher risk of poorer clinical outcomes (re-hospitalisation, mortality).

However, in the absence of a gold standard, it remains difficult to determine how accurately novel and existing biomarkers can track congestion in a manner which can inform clinicians on how to modify the therapeutic strategy of an individual patient.[71]

1.6.3 Echocardiography

Transthoracic echocardiographic (TTE) remains the preferred first option to image the heart and complement clinical assessment in the diagnosis of HF.[1] It is a readily available, quick and a cost-effective tool, with no associated radiation exposure. However, this is tempered the interobserver variation rate of 2-dimensional LVEF measurement which can be as high as 10%.[72–74]

Two primary objectives can be achieved with TTE. The first is the quantification of the ejection fraction. This allows the clinician to ascertain which category of HF is present (HFrEF, HFmrEF or HFpEF). Secondly, other structural and functional anomalies which cause HF can be discerned. Doppler tissue velocities can examine myocardial wall motion to determine if ventricular stiffness is

increased and if diastolic dysfunction could be contributing to a HFpEF phenotype.[14] Wall motion abnormalities produced by previous infarction or inflammation can be seen, as can valvular problems which may either be a cause or consequence of HF.

1.6.4 Other imaging modalities.

Other imaging modalities may be utilised to confirm the presence of HF, evaluate alternative causes or determine the underlying aetiology. Routine Chest-x ray (CXR) is not very sensitive or specific and can vary depending on the patients congestive state.[75] In most cases, the non-specific finding of cardiomegaly may be seen.[76] However, imaging of the lung fields may be useful to determine if concurrent lung pathologies are responsible for the patient's symptoms (such as chronic lung disease, neoplasm or infection). Cardiac magnetic resonance imaging (cMRI) is the gold standard for the assessment of cardiac pump function and can also evaluate tissue scarring and can help distinguish if the underlying aetiology is ischaemic, infiltrative or inflammatory.[77] However, it is a time and cost intensive investigation and limited in patients with irregular and elevated heart rates and in those with claustrophobia. Where a history of ischaemic cardiac disease is suspected, non-invasive cardiac computed tomography (cardiac CT) or invasive coronary angiography could be considered. Both carry additional risk from exposure to ionising radiation and are not considered first line investigations.[1]

2 Congestion in heart failure

2.1 Neurohormonal axis and congestion

The pathophysiology of HF is characterised by distal tissue hypoperfusion secondary to low cardiac output (or an inability to provide adequate output while maintaining normal ventricular filling pressures) which triggers compensatory sympathetic and neurohormonal reflexes.[78] These result in sodium and water retention at a renal level which causes expansion in the intravascular and interstitial compartments.[7] Over time, these compensatory mechanisms become deleterious and exert negative effects on the myocardium resulting in further decompensation and feeding downward cycles of maladaptive counter-responses (Figure 2-1). Natriuretic peptides are produced in response to congestion to try and ameliorate these haemodynamic changes, but eventually pathologic mechanisms pre-dominate and the patient develops the well-recognised clinical phenotypes of congestion. Myocardial hypertrophy and dilation serve to remodel the heart in response to increased wall stress, but these changes eventually compromise cardiac function further and compound the mileu of dysfunction.[79]

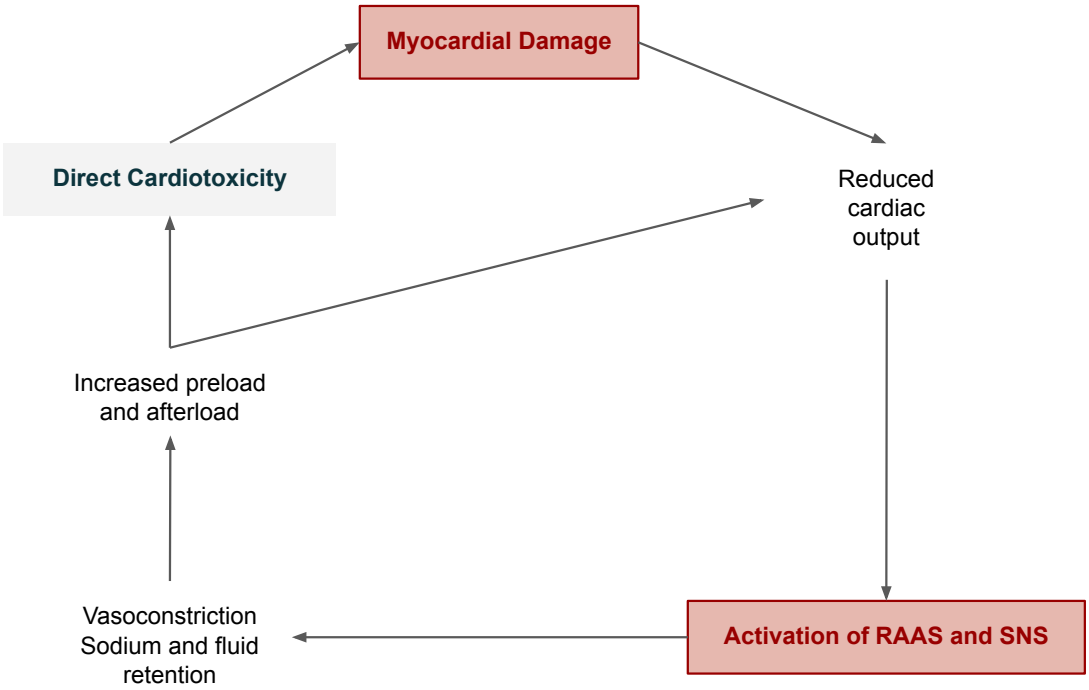

Figure 2-1: Maladaptive neurohormonal responses in heart failure. Progressive neurohormonal activation and further direct cardiotoxicity triggers a cycle of progressive haemodynamic decline in chronic heart failure.

RAAS: renin angiotensin aldosterone system; SNS: sympathetic nervous system

2.1.1 Sympathetic activation

Arterial baroreceptors are triggered in response to low arterial perfusion and produce reflex sympathetic vasoconstriction and increased sympathetic outflow.[80] In normal circumstances, this increases venous return and pre-load which subsequently increases stroke volume via the Frank-Starling mechanism. As myocyte fibres stretch, the strength of each following ventricular contraction is potentiated.[81] However, an optimal zone of contractility exists and once this sarcomere-length reserve is depleted, cardiac output begins to become impaired. In HF, chronic wall stress increases myocardial wall hypertrophy and reduces wall distensibility, depressing the curve downwards and further impairing the mechanism from remaining effective in response to increasing pre-load (Figure 2-2).

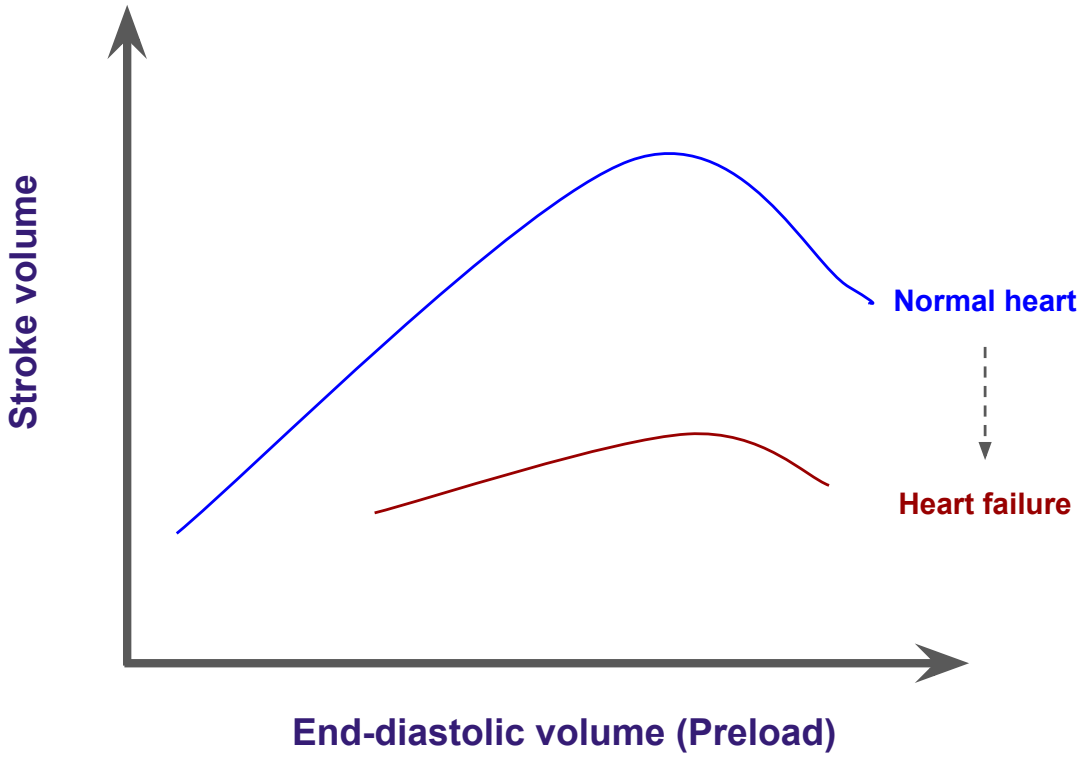

Figure 2-2. Frank-Starling curves in heart failure. The normal length-tension relationship of striated muscle is depressed downwards in heart failure; further increases in pre-load arising from congestion instead can act to compromise stroke volume.

Ventricular hypertrophy further increases tissue oxygen demand and can precipitate ischaemia. Eventually, chronically raised plasma noradrenaline concentrations trigger direct toxic effects on cardiac myocytes. Beta-receptor downregulation at the level of the myocardium also ensues, blunting the effectiveness of this cycle and triggering greater sympathetic activation.

2.1.2 Renin-angiotensin-aldosterone system

At the renal level, the renin-angiotensin-aldosterone system (RAAS) is concurrently activated and drives fluid retention and increases in intravascular plasma volume (Figure 2-3).[82] Renin is released in response to hypoperfusion and mediates the conversion of liver angiotensinogen to angiotensin I. This is then converted by ACE – mostly found in pulmonary vascular endothelial cells – into angiotensin II (AT2). AT2 exerts a number of direct effects. It is a potent vasoconstrictor of the systemic arterial circulation, directly enhances sympathetic activity and promotes aldosterone release.[80] Aldosterone directly acts on cells within the renal collecting duct to promote sodium and water retention.[83]

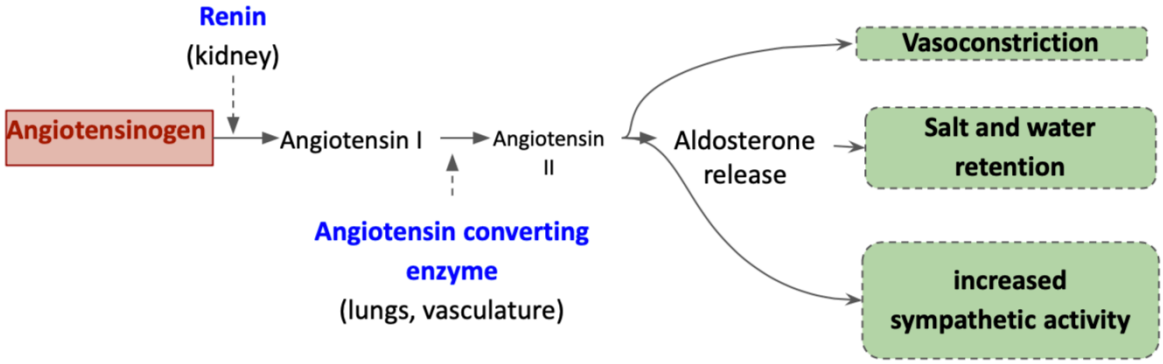

Figure 2-3: Renin-angiotensin-aldosterone system in heart failure. Adapted from Jackson *et al* (2000).[80] Increased renal renin production catalyses a hormonal cascade which eventually triggers further maladaptive haemodynamic and renal effects which all worsen congestion.

2.1.3 Natriuretic peptides

The natriuretic peptide (NP) family consists of three recognised classes of peptides with comparable molecular structure and hormonal effects: atrial natriuretic peptides (ANP), brain natriuretic peptides (BNP) and C-type natriuretic peptide (CNP).[84] ANP and BNP are released by the myocardial wall in response to elevated intra-cardiac pressures and wall stretch.[85,86] CNP is produced by endothelial cells in response to vascular volume overload.

All three act as counter-mechanisms at the levels of the renal, cardiac and central nervous systems to the pathological responses which have been initiated from an impaired cardiac output.[84] Natriuretic peptides can inhibit cardiac remodelling, suppress the renal-aldosterone axis and induce vasodilation to help reduce the preload and afterload on the heart.[84,87] Within the renal system, NP's provoke natriuresis by increasing glomerular filtration via induction of vasodilation of the afferent arterioles and supress sodium retention by inactivating exchange pumps in the proximal renal tubules.[88] However, over the course of time the potency of natriuretic peptides on the reno-cardiovascular system becomes blunted in HF.[89]

2.2 Haemodynamic mechanism of congestion

Congestion is thought to arise through either a process of fluid accumulation or fluid redistribution.[90] Increased fluid alters the balance of oncotic and hydrostatic pressures in capillary networks resulting in systemic and/or pulmonary transudation of fluid and subsequent oedema. These two different pathophysiological processes can lead to the development of congestion requiring hospitalisation.

2.2.1 Fluid accumulation

Compensatory cardiovascular mechanisms which attempt to increase plasma volume also cause a corresponding expansion of the interstitial space as oncotic

and hydrostatic forces ensure that the two compartments are kept in relative equilibrium.[10] In HF, capillary beds become more permeable, partly due to protein and albumin loss (from renal losses and cachexia) which reduces the transcapillary oncotic pressure gradient.[7] There is net fluid movement from the intravascular compartment into the interstitium and this haemodynamic congestion is eventually recognised as symptomatic clinical congestion. If this occurs centrally in the lungs, alveolar pulmonary oedema develops.[7] In the peripheral circulation, this can be visually assessed and palpated as peripheral limb oedema.[7]

In HF, the interstitial space is transformed from a low-compliance to a high-compliance compartment. A study of untreated patients with severe LVSD demonstrated that during periods of congestion the interstitium can increase its retentive capacity by around one-third in conjunction with increases in the intravascular compartment.[91] However, reversal of this process is difficult – even when volumes in the intravascular space have been normalised, such as therapeutically with diuretics. After pulmonary and peripheral congestion has clinically resolved, volumes in this space can remain elevated resulting in refractory subclinical fluid overload.[91]

Volume overload itself may produce a continuous pro-oxidant state mediated by endothelial signalling and encourage further vasoconstriction during episodes of decompensation.[92] Direct wall stress may also precipitate subendocardial ischaemia and myocardial necrosis.[93] Increased venous congestion can also worsen renal function, resulting in diuretic resistance and a vicious cycle of greater congestion and progressive cardio-renal dysfunction.[94]

2.2.2 Fluid redistribution

Studies have demonstrated that a large proportion of patients with HF have no substantive weight gain before hospitalisation, providing an insight into how congestion can arise by fluid redistribution.[95,96]

A nested case-control study observing 134 HF patients from the United States demonstrated that 54% did not gain more than one kilogram prior to hospitalisation.[95] One third of patients in the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) study had a similar 'weight-neutral' prodrome before admission.[96]

The venous system - like the arterial system - is heavily innervated. However it is over 30 times more compliant than the arterial network, holds 70% of the total blood volume and is responsible for mediating rapid fluid shifts.[97] In normal states it can buffer changes in volume to prevent sudden fluctuations in cardiac preload. More dense adrenergic innervation of the media also means that these vessels are able to respond more markedly to sympathetic stimuli, such as to counter drops in blood pressure during orthostatic changes.[98]

In certain instances, fluid can move suddenly from the peripheral venous system into the main circulatory volume in response to peripheral insults. Splanchnic venoconstriction can induce a rapid redistribution of fluid from the latent abdominal reservoir resulting in a marked increase in the circulating intravascular compartment.[98] Venous pressures subsequently increase rapidly, as do central filling pressures. As a consequence, fluid quickly transudates into the alveolar space producing pulmonary oedema.

In these scenarios, the rapidity of increases in pressures would cause pulmonary oedema to develop before worsening of peripheral oedema. This is thought to explain part of the mechanism behind the acute presentations of hypertensive HF.[99] Vasodilators are preferred over diuretics in this scenario, as the pathological process is primarily load-mediated rather than volume mediated.[1]

2.3 Clinical course of decompensation

2.3.1 Time course

The time course of presentation from congestion to hospitalisation has not been charted extensively but remains variable and dependent on multiple factors

including: the precipitants, the balance between fluid accumulation or fluid distribution as the pathological driver of deterioration, the patient's pre-morbid state and cardiovascular reserve. In a study utilising implantable RV haemodynamic monitors in 32 HF patients who ended up with a hospitalisation episode, data could demonstrate that congestive changes would start 4 ± 2 days beforehand with systolic pressures increasing by 25 ± 4% ($p < 0.05$) before clinical symptoms peaked.[100] Another similar study using implantable intrathoracic impedance sensors clearly detailed how increases in extrapulmonary water can develop 18 days before true clinical dyspnoea is apparent.[101] Case control studies charting observed weight changes in HF patients have shown that increases in body weight can begin around one week before admission.[95] The greater the weight gain the greater the risk of hospitalisation, the probability of which increases at gains of greater than one kilogram. However weight gain is non-specific and as some hospitalised patients do not experience an increase before admission, fluid accumulation cannot be the only mechanism leading to congestion. Symptoms also do not correlate exactly with the onset of congestion.

2.3.2 Patterns of presentation

A retrospective case review of hospitalised acute heart failure (AHF) patients by Shoaib and colleagues confirmed the theory that different mechanisms of congestion can produce various phenotypic sub-types of AHF.[11] They sub-categorised patients into those who were 'short of breath at rest' (SOBAR) or who were 'comfortable at rest but breathless on slight exertion' (CARBOSE). This review of 311 patients showed that these groups differed both in baseline characteristics and prognosis. SOBAR patients had greater central pulmonary congestion than those who were CARBOSE (61 vs 41%) but less peripheral oedema (42 vs 48%).[11] They also had features of increased sympathetic drive reflected in statistically higher median heart rates (101 vs 82 bpm) and higher median systolic blood pressure (141 vs 122 mmHg). The findings could be confirmation of a more vasoconstricted phenotype where rapid fluid redistribution (rather than slow fluid accumulation) precipitates pulmonary rather than peripheral oedema.[102] These were also a subgroup of patients more likely to present with

de-novo AHF (33 vs 19%). Divergent prognoses between the groups was also a critical point of note; SOBAR patients did significantly better than CARBOSE patients (19 vs 34%, death at 180 days).[11]

AHF is therefore not a homogenous entity but composed of a spectrum of congestion from predominantly central to peripheral, reflecting different pathophysiological mechanisms and varying degrees of sympathetic activation, fluid retention and fluid re-distribution.[102,103]

2.4 Reliability of clinical assessment of congestion

Clinical assessment is primarily aimed at assessing the presence and severity of congestion.[1,2] The gold standard of investigation remains invasive right heart catheterisation with assessment of right heart pressures and pulmonary capillary wedge pressures (PCWP)[6]. The ESC Scientific Statement on Assessing and Grading Congestion demonstrated the variations in statistical strengths of each of the most commonly reported clinical features (Table 2-1).[6] These analyses are comprised from prospective study data from the clinical assessment and right heart catheterisation (RHC) findings of patients referred for cardiac transplantation. In 50 pre-transplant cardiac patients undergoing invasive catheterisation, even where elevated PCWP was present, in 42% of cases no signs (such as elevated JVP, pulmonary rales or oedema) could be detected clinically.[104] However, these findings are from HF patients with severe but stable HF. The incidence rate and predictive values of these may vary depending on the severity of LV dysfunction, aetiology of LVSD, the precipitant factor and the time course of clinical decompensation.

Table 2-1. Diagnostic value of clinical features of congestion. Adapted from Gheorghiade *et al* (2010).[6]

Clinical feature	Sensitivity	Specificity	PPV	NPV
Dyspnoea on exertion	66	52	45	27
Orthopnoea	66	47	61	37
Peripheral oedema	46	73	79	46
Elevated JVP	70	42	66	44
Third heart sound	73	42	66	44

JVP: jugular venous pressure; PPV: positive predictive value; NPV: negative predictive value.

Five of the most commonly utilised clinical features are reviewed: dyspnoea, orthopnoea, pulmonary rales, elevated JVP and peripheral oedema are all central to assessing congestion. An understanding of the predictive values, pathophysiological origins and limitations of each is essential for evaluating the methods of AHF studies.

2.4.1 Dyspnoea

Dyspnoea remains a common presenting complaint in AHF patients, either at rest or on exertion. However, it is not pathognomonic of HF. It remains a symptom with multiple aetiologies and difficult to assess objectively, and doubts remains about whether congestion is fully represented by breathlessness.

2.4.1.1 Heterogeneric aetiologies of dyspnoea

In patients with HF, there may be multiple underlying causes for breathlessness, from both cardiac and non-cardiac origins and this may not reflect pulmonary congestion.[105] Additionally, the symptoms of dyspnoea and fatigue may be reported inter-changeably by patients with HF.[106]

Chronic lung disease is a common co-morbidity and has been described in up to 30% of patients with AHF.[107,108] Bronchospasm and well as pneumonic processes may produce respiratory symptoms.

Obesity is a common co-morbidity in HF and can also produce breathlessness on exertion.[109] These patients may also have restricted lung function and breathlessness as a result of body weight. Coronary ischaemia may occasionally present as dyspnoea.

2.4.1.2 Pathophysiology of dyspnoea

The pathophysiology of dyspnoea is complex construct which arises from an interplay of afferent, efferent and higher cognitive inputs processed centrally within the respiratory centres of the medulla.[110] When pulmonary ventilation is not able to meet metabolic demands, the sensation of dyspnoea is experienced.

Central chemoreceptors in medulla and peripheral carotid bodies monitor oxygen and carbon dioxide tensions and hydrogen ion concentrations in the bloodstream.[111] In the lungs, pulmonary C-fibre receptors located within the alveolar walls are activated by hypoxia caused by pulmonary oedema. Deviations from normal parameters will trigger increased afferent signalling which is integrated in the central respiratory centres to increase outputs to the ventilatory apparatus of the chest. Both these central inputs and increased firing to respiratory muscles are relayed to higher brain centres to give rise to the conscious feeling of breathlessness.[111] Chest wall mechanoreceptors monitor ventilatory status and modify the intensity of dyspnoea if breathing is not adequate.

The sensation of dyspnoea in HF patients is also exacerbated by multiple physiological factors. Reduced exercise capacity arising from reduced muscle mass, malnutrition, chronotropic incompetence (from beta blocker therapy), and general physiological deconditioning can all impair muscle functioning and produce faster elevations in lactic acid levels, thus triggering dyspnoea more readily on exertion.[112] Limbs made heavier by fluid retention also require more

energy to sustain movement. Higher brain centre experiences (such as anxiety and depression – both prevalent in HF) can produce experiences of dyspnoea disproportionate to the degree of ventilatory impairment.[113]

2.4.1.3 Variable reliability of assessments

The two most common tools to assess breathlessness remain the 7-point Likert scale and the visual analogue scale (VAS). The Likert scale is often more easy to interpret by patients and both Likert and VAS are thought to have a high degree of correlation for determining baseline levels of dyspnoea.[114] However, subtle intermediate changes remain difficult to pinpoint on the more compressed Likert tool as patient recall can often be variable.[115] In the Preliminary study of RELAXin in Acute Heart Failure (Pre-RELAX-AHF) study, VAS was found to detect more subtle changes in symptomatology at an earlier timepoint, but these findings have not yet shown clinical relevance.[116] Other more global assessments of well-being can provide indicators of overall improvement, but these determinations also risk being confounded by other subjective factors which are unrelated to the patient's cardiac status.[117]

2.4.1.4 Dyspnoea may not reflect congestion

Data from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial sub-study demonstrated that whilst a composite score for congestion (including dyspnoea) may normalise towards the end of a hospital admission, natriuretic peptide levels remain elevated well above baseline and this is associated with increased mortality.[118] Patients who had improved symptoms were not left with a benign longer term prognosis. This strongly suggests a disconnect exists between clinical congestion and haemodynamic congestion, regardless of the improvements that are verbalised by the patient, thereby making it unwise to assume that dyspnoea is the absolute metric of haemodynamic congestion.

2.4.2 Orthopnoea

Orthopnoea is defined as breathlessness when lying recumbent.[119] It correlates strongly with invasive haemodynamics and has been demonstrated to have reasonable predictive value in reaching a correct diagnosis of HF.

2.4.2.1 Physiology of orthopnoea

As a clinical symptom, orthopnoea unmasks congestion when dependent fluid is redistributed from the abdominal reservoirs and into the venous circulation when lying recumbent.[119] Up to 500 millilitres (mL) may load into the already congested central venous system further elevating filling pressures.[6] This loading of the right ventricle, will correspondingly increase left sided and pulmonary venous pressures. Reduced pulmonary compliance and pulmonary oedema subsequently develop giving rise to the symptoms of breathlessness when lying down. In many instances, orthopnoea is also denoted alongside the degree of recline (traditionally assessed by asking the patient how many pillows they use during sleep) which is required to alleviate the symptom.

2.4.2.2 Haemodynamic correlation

Orthopnoea correlates closely with PCWP measurement. In pre-transplant cardiac patients, orthopnoea was found to be a positive predictor of an elevated PCWP of ≥ 22mmHg in 91% of patients.[104] In a more contemporary study, clinical examination was reviewed against the invasive haemodynamic assessments of 388 patients enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) study.[120] Right atrial pressures and PCWP were recorded and assessed against various clinical parameters. Only the presence of raised JVP (of ≥ 12 cm) and orthopnoea (specifically of ≥ 2 pillows) were found to be associated with a PCWP of ≥ 30 mmHg. Importantly, a lower 'pillow grade' of orthopnoea was not found to bear as close a correlation. It should be noted that this patient group unlike earlier studies consisted of hospitalised not stable patients and with severe disease (an LVEF ≤30%).[120]

2.4.2.3 Predictive value and confounders

Orthopnoea holds a positive predictive value of 61%, sensitivity of 66 % and specificity of 47% for congestive HF against the gold standard of RHC.[6] In these respects, the predictive values of orthopnoea may be better than that of dyspnoea at rest and on exertion (which have been reported and utilised more extensively in AHF studies). However, as with dyspnoea, it can arise due to non-cardiac causes. In most instances, any condition restricting the ability of the patient to lie supine - such as spinal disease or gastro-oesophageal reflux disease - may impede assessment. Additionally, pulmonary disease (such as chronic obstructive pulmonary disease) and obesity can also produce orthopnoea unrelated to HF.[121]

2.4.3 Pulmonary rales

As pulmonary congestion develops, fluid initially builds up in dependent areas of the alveolar space beginning with the basal lung segments. On auscultation, this can be heard in the form of crepitations.[8] In the acute setting these findings can be clinically valuable. A review of AHF patients presenting with dyspnoea to the emergency department found that the presence of pulmonary rales increased the likelihood of a correct diagnosis of HF when supplemented with the patient's clinical history (likelihood ratio, 2.6; 95% confidence interval, 2.1-3.3).[122]

2.4.3.1 Inter-observer variability of pulmonary rales

Substantial variability exists between clinicians reporting chest examination findings. Auscultation between examiners may not produce consistent results, and clinical seniority is often a mitigating factor against increased interobserver variability.[123] In a blinded study of respiratory patients involving medical students and respiratory physicians, it was noted that there could be a high level of consistency in the detection of pulmonary abnormalities (between 74–89% of the examinations).[123] However, this was only so long as the targets of auscultation were dichotomous lung sounds (such as rales or wheeze) (kappa = 0.30-0.70). In a more recent multicentre study in 2017, a median kappa agreement of 0.49 was observed for crackles[124], though this contrasts with an

older systematic review of chest examination findings which noted that examiner variability was indeed much higher (kappa 0.32 – 0.67).[125] However, studies from these patients involved examiners of varying seniority and the patients enrolled possessed a mix of cardio-respiratory illnesses beyond HF. As agreement for dichotomous sounds are better than for softer adventitious sounds, it also remains to be seen if there is less observer variation for more "severe" signs of congestion, such as when rales at the bases extend completely to the apices and involve the majority of the lung field.[126]

2.4.4 Jugular venous pressure

Blood flows into the right heart at pressure into the cardiac chambers. This pressure is transmitted back through the venous system and produces a detectable column of blood visible as distension of the internal jugular vein.[127] Elevation or depression of this venous manometer can provide insights into right atrial pressure.

2.4.4.1 Assessment and limitations

To review the JVP, the patient is positioned at 45 degrees with neck rotation to allow the window between the clavicle and mandible to become apparent within which the internal jugular vein can be visualised. However, there remains debate amongst clinicians as to the precise reference point above which the JVP should be assessed. Variation remains between the right atrium and sternal angle - the more available reference point.[127] The actual additional difference between these two points – usually quoted as 5 cm - has also been debated and is dependent on the angle of recline.[128] Hepatojugular reflux, defined as the sustained rise of JVP by more than 3 cm for 10 seconds after hepatic pressure, may also be of use to visualise the vein.[129]

In patients with right sided regurgitant valve disease, particularly tricuspid regurgitation, the column of blood in the internal venous system will be raised and not reflective of the true haemodynamic state of the patient.[127] Similarly in pulmonary hypertension, there will be continuous venous distention not

reflective of congestion. Visualisation of the internal jugular vein may also be impeded in patients with increased adiposity or respiratory pathology.[127]

2.4.4.2 Haemodynamic correlation

In a review assessing the efficacy of clinical examination in identifying abnormal haemodynamic findings in pre-transplant patients, JVP distension at rest was found to have a high sensitivity, specificity and positive predictive value (81%, 10% and 81% respectively) of predicting a PCWP of ≥ 18 mmHg.[130] Of note, the threshold for elevation was placed at greater than 7 cm H_20 above standard reference plane, furthering the observation that measurement standards can vary from study to study. An elevated JVP also appears to be associated with increased risk of clinical events. In a retrospective review of SOLVD, elevated JVP was associated with increased re-hospitalization (relative risk [RR], 1.32; 95 percent confidence interval, 1.08 to 1.62; P<0.01) and death from pump failure (RR, 1.37; 95 percent confidence interval, 1.07 to 1.75; P<0.05).[131] However, more recent post-hoc analyses from the Diuretic Optimization Strategies Evaluation (DOSE) trial and Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial found neither JVP elevation on admission nor discharge could predict adverse outcome.[132]

However, other studies are also conflicting[104], and accuracy may wane in more critically ill patients[133], thus it may be only at the more extremes of measurements that these correlations are evident.[120] There is also evidence that the external jugular vein may instead be easier to visualise than the internal jugular vein, and can safely predict central venous pressures at ends of the haemodynamic range.[134] As such, JVP assessment continues to be recommended by the American Heart Association (AHA) guidelines on the management of HF. They suggest its role in assessing LV filling pressure may be more assured in advanced HF, perhaps where signs are most prominent [2].

2.4.5 Peripheral oedema

Peripheral oedema remains one of primary signs of non-pulmonary congestion.[8] It has been noted to have a sensitivity of 46%, specificity of 73% and positive predictive value of 79% in HF.[6] However, peripheral congestion can also develop from non-cardiac causes. Falls in plasma oncotic pressure or damage to the body lymphatic system can also result in fluid transudation to the interstitium in the setting of a normal haemodynamic state. Liver cirrhosis, sepsis and malnutrition can all contribute to a hypalbuminaemic state and must be considered in the assessment of limb swelling.

2.4.5.1 Inter-observer variability

In formal comparisons, the traditional clinical assessment of peripheral oedema has been found to possess poor inter-observer agreement.[135] The precise location of where the clinician examines for oedema on the leg is often not consistently described, leading to the absence of a standardised assessment method. It is also notable that clinician assessment does not always correlate well to pit depth or pit recovery time on a swollen leg. Other methods such as "oedema tester" plates have been developed which consist of a plastic sheet with holes of varying size that can be held at pressure and the indentation observed.[136] There is no consensus on a standard approach to utilising the tool or the threshold which should demarcate mild from severe disease.[136]

2.4.5.2 Alternative assessment methods

Water displacement volumetery remains a reliable method to determine sequential changes in leg volume, but requires recurrent measurements and use of a foot volumeter – which is impractical in a hospitalised patient.[135] Blood volume can be measured with radioisotope techniques and correlate with invasive haemodynamic cardiac assessments. However, beyond research purposes they cannot be readily utilised in a clinical environment.[137]

2.5 Classification of acute HF

HF requiring hospitalisation can be grouped under a wide variety of terms: ‘acute heart failure’, ‘decompensated heart failure’ and ‘hospitalised heart failure’. At present, no single term or classification system has been adopted, though ‘acute heart failure’ remains widespread in its use.[2] These categorisations also do not distinguish between chronic worsening HF and acute de-novo presentations and do not indicate the timespan over which symptoms may have been progressively deteriorating before hospitalisation.

A variety of different overlapping classifications systems have been proposed for the assessment of stable and acute HF. These vary from focusing on quality of life determinations to those based on clinical and haemodynamic review, though no single codification has been universally adopted for use. Current ESC and AHA guidelines on AHF recommend these at the discretion of the clinician and provide only general recommendations as to how they should be utilised.[1,2]

2.5.1 ESC classification of acute heart failure

The ESC has produced a classification system for AHF in a number of guideline publications. The presentations are grouped based on the underlying aetiology and presenting clinical features of the patient:[12,138]

1. Decompensated HF: patients with a history of congestive HF who develop evidence of congestion necessitating admission.
2. Pulmonary oedema: patients presenting with acute pulmonary congestion in the form of tachypnoea, clearly audible pulmonary rales and arterial desaturation to <90%.
3. Hypertensive HF: heart failure precipitated by an acute vasoconstricted state leading to hypertension and rapid fluid redistribution into mostly the pulmonary interstitium
4. Cardiogenic shock: HF characterised by acute tissue hypoperfusion (blood pressure < 90 mmHg or a drop of mean arterial pressure of > 30 mmHg).

5. Isolated right HF: a syndrome of mostly right heart signs such as increased JVP and peripheral oedema but little pulmonary congestion
6. Acute coronary syndrome (ACS) HF: congestion precipitated by ACS

There are two major criticisms of this classification. Firstly, definition for each sub-group remains imprecise and to some extent still rely on a degree of discretion by the individual clinician. Secondly, there is significant overlap between the different entities. A single patient with ACS can develop cardiogenic shock, and signs of right HF as well as a degree of pulmonary oedema thereby making them eligible for multiple classifications. In such an instance, as a result of the lack of clear demarcation between each sub-type, the same phenotype of patient can be classified into several sub-categories leading to dubiety about the validity of results reported under this method.

2.5.2 Forrester classification

The Forrester classification system groups patients into four categories based on an assessment of their level of congestion and level of perfusion.[139] Congested patients are classified as being “wet” (congested) or “dry” (non-congested) and the level of perfusion is denoted by describing the patient as “warm” (well perfused) or “cold” (hypoperfused). This creates the four categories: ‘warm and dry’. ‘warm and wet’, ‘cold and dry’ and ‘cold and wet’ (Figure 2-4).

Current ESC guidelines recommend attempting to perform this assessment to identify those patients at highest risk of morbidity, and provide a general overview of which therapies could be targeted to each subgroup.[1]

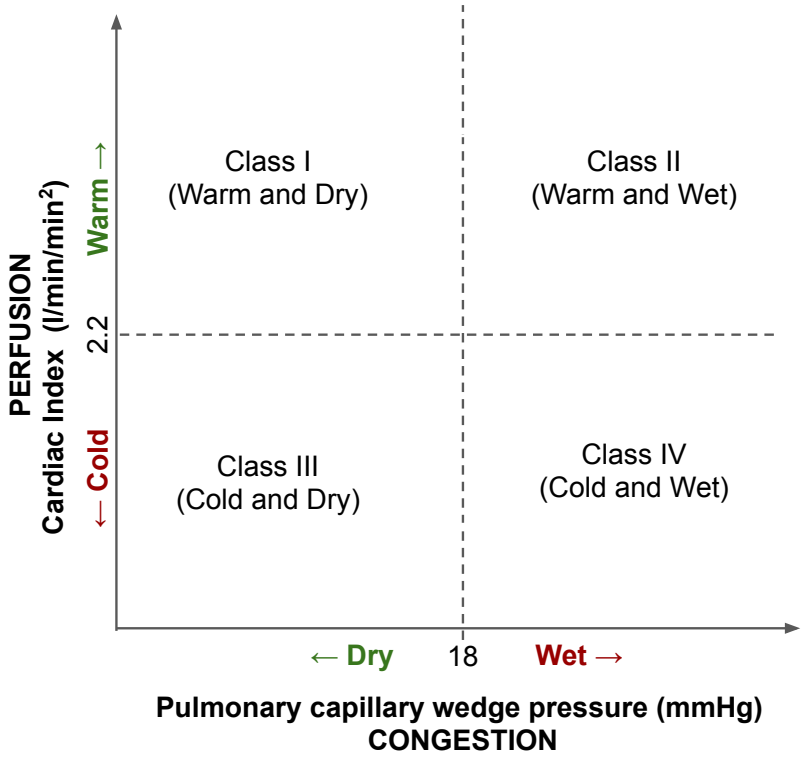

Figure 2-4: Forrester classification system. Adapted from Forrester *et al* (1976) [139]

The Forrester classification system assigns acute heart patients to one of four categories based on levels of congestion and perfusion (as determined by invasive haemodynamics).

The original sub-types were developed based on a clinical, radiographic and invasive haemodynamic evaluation of 200 patients post acute myocardial infarction.[139] To date, there has been limited validation of this system in the AHF population. As has also been demonstrated by Forrester, when correlating clinical and haemodynamic changes, clinical examination is only accurate in 83% of cases. Additionally, when reviewing decongestive changes, clinical assessment does not parallel haemodynamic improvements in 30% of patients. A more modified assessment (using clinical assessment and not invasive catheterisation) has been demonstrated to predict mortality but when validated in an emergency department setting, the system has been shown to have limited inter-rater agreement and remains poorly predictive of a final HF diagnosis. [140,141]

Another substantive criticism of this classification is that the AHF and post-MI populations are two distinct entities with very distinct pathophysiological disturbances. It remains debatable whether a substantial number of true

hospitalised AHF patients are “dry”, or – as is more probable – comprise patients with known LVSD presenting with a heterogenous mileu of non-cardiac pathologies.

Whilst this system appears to reflect a semi-confluent continuum from the stable patient to those in cardiogenic shock, there are further shortcomings in the classification of “dry and cold” patients (i.e. poorly perfused but non-congested patients). Classically a group with acute RV infarction – not AHF - with judicious use of fluids these patients can easily be relocated from “dry and cold” to “dry and warm”, theoretically producing sudden change in Forrester class (and a significant difference in expected but not actual prognosis). Another problematic area is the definition of ‘hypoperfusion’ which is not synonymous with hypotension. Whilst RHC can help clarify normotensive hypoperfused states, the best clinical approach for doing this is still undetermined and inter-observer agreement remains suboptimal.[141]

Unlike other classification systems, determining Forrester class requires the use of an invasive RHC which in some regions limits its application. There is some evidence from hospitalised patients with mixed pathologies in intensive care that the routine use of RHC in acutely compromised patients may be deleterious, however, this is not immediately extrapolatable to patients presenting with AHF.[142] As the availability of RHC in many areas is constrained, physicians are limited to a more abridged clinical assessment.

2.5.3 New York Heart Association classification

The New York Heart Association (NYHA) classification system was originally designed in 1928 and later redeveloped into its current format.[143] Patients are placed into four categories based on a physician assessment of the impact HF on daily activities: NYHA class I patients have no symptoms or limitation to ordinary physical activity, NYHA class II patients have mild symptoms during ordinary activity, NYHA class III patients have marked limitation of even less-than-ordinary activity, NYHA class IV patients have severe limitations and experience symptoms at rest. This classification is primarily applied for chronic stable

rather than decompensated AHF patients requiring hospital admission – a group for which there is no clear consensus on how or when the grading determination should be made.

One shortfall of the NYHA classification system is that it remains highly subjective. There is marked inter-observer variability in distinguishing class II from class III patients. In a study reviewing these differences, 30 cardiologists were asked to determine how they arrived at the marked NYHA score.[144] 70% incorporated the patient's self-reported walking distance into the determination – a factor which is proven to correlate poorly with objective cardio-pulmonary testing. In 46% of cases cardiologists were not able to concur when trying to differentiate whether patients should fall into classes II or III.[144] Specific activity scales have been proposed to improve validity and reproducibility, but these remain un-adopted.[145] Research studies also have failed to provide any standardised approach to determining NYHA class.

Despite its limitations as a valid outcome measure, it is an established predictor of clinical outcomes and correlates with objective determinations of functional status and prognosis.[146] Whilst there is no clear correlation with ejection fraction, it remains evident that those with mild symptoms (i.e. NYHA class II) carry an increased risk of hospitalisation and adverse outcome compared to who are NYHA class I. The Canadian Heart Failure Network demonstrated this risk in a 16,683 patient study of outpatient HF conducted over a twelve year period.[147] Increased hazard ratios were noted for patients who were initially diagnosed as NYHA class II (1.78, CI 1.54-2.06) and NYHA class III (3.51, CI 3.05-4.04) compared to NYHA class I patients.

2.5.4 Killip classification

The Killip classification system was developed in patients post myocardial infarction and is of little relevance to those with decompensated HF.[148] In this method, the severity of clinically determined HF is graded into four classes: class I includes patients with no clinical signs of HF, class II patients have basal crepitations (or a third heart sound or elevated jugular venous pressure), class III

patients are in frank pulmonary oedema and class IV describes those in cardiogenic shock. The scoring system provides important prognostic information. In a large post-hoc analysis of the 41,021 patient Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) study on thrombolysis post-myocardial infarction, Killip class was a strong predictor of 30-day mortality.[149]

However criticism of the scoring system remains. Within class IV, two separate sub-categories clearly exist. Patients may have cardiogenic shock with pulmonary oedema and also be shocked without. This four part classification also does not overlap fully with the Forrester method. For example, within Forrester, there is no equivalent Killip class of patients reflective of patients who are hypo-perfused but not congested ("cold-warm").

In ACS practice, the Killip classification score is more widely reported, particularly due to its ease of application and its robustness in predicting mortality. Risk scores such as the Global Registry of Acute Coronary Events (GRACE) incorporate Killip class to determine cardiovascular outcomes.[150] In registries and trials of AHF, this data does not tend to be reported as the post-infarct cohort is not representative of the broader presenting AHF population.

2.5.5 De-novo, stable and chronic heart failure

The ESC defines a patient with de-novo HF as one with no previous history of HF (or of medical contact with related symptoms) presenting to medical services for the first time.[1] There is no set maximum period between which the patient can have transitioned from an asymptomatic to symptomatic state before presentation. Current ESC AHF guidelines therefore allow the sub-category to include patients who have had an acute severe precipitating insult causing haemodynamic deterioration - such as an acute MI over hours – or those who have gradually deteriorated over a longer period of time as a result of progressive disease – such idiopathic dilated cardiomyopathy lying indolent for months or years. In reality, the majority of patents will have had some symptoms prior to first hospitalisation.[151]

A stable HF patient is defined as one who has had no changes in clinical symptoms over a one month period.[1] This period of time is arbitrary and not derived from any specific evidence base. A definition of transient HF was produced in the 2008 ESC guidelines on HF but not maintained in subsequent documents. It drew attention to a class of patients with "symptomatic HF over a limited time period, [of whom] long-term treatment might be indicated".[12] It was envisaged that this would include patients with myocarditis who can make a full recovery with time or patients with acute myocardial infarction who develop temporarily impaired LV dysfunction which resolves once coronary revascularisation is performed and medical therapy is instituted.

Clinical trials also vary as to what constitutes a de-novo presentation and whether such groups should be excluded from enrolment. However, hospitalisation is a key event in the trajectory of a HF patient's progress. Once this has occurred, being cognisant of this distinction is prognostically relevant as the mortality rate for these cohorts can rise by a factor of three (though the precise reasons for this are multi-factorial).[152]

2.6 Objective assessment of pulmonary congestion

Objective and quantitative assessment of pulmonary congestion continues to be problematic. A CXR is recommended in the initial assessment process of HF, but it remains a modality with limited diagnostic abilities.[1] Lung ultrasound (LUS) is an emerging modality with new applications.

2.6.1 Chest X-ray

On a chest X-ray, cardiomegaly, interstitial oedema and pleural effusions may indicate HF. However, these changes arise in non-sequential manner, and in some cases can pre-date signs of clinical HF.[153] The findings of upper pulmonary venous congestion may occur first at lower pulmonary capillary wedge pressures

(PCWP) of 13-18 mmHg, whilst alveolar oedema may become evident at higher PCWP above 25 mmHg.[75,154]

2.6.1.1 Haemodynamic correlation

The CXR does not always correlate with haemodynamic congestion. In a study of 52 stable patients with severe LVSD who underwent both chest imaging and cardiac catheterisation, X-ray changes were absent in almost a third (39% of patients) with significantly elevated PCWP of ≥ 30 mm Hg.[59] A similar study of end stage cardiac patients awaiting transplantation found that in 68% of cases minimal or no pulmonary congestive changes were seen despite elevations of PCWP.[155] It is speculated that in chronic HF, changes in alveolar membrane permeability or lymphatic drainage may reduce fluid transudation and accumulation in the alveolar space.

2.6.1.2 Inter-observer variability

A shortfall of the CXR is its interobserver variability. Problematic inconsistency exists depending upon whether the images are reviewed on plain film or digital formats, the type and seniority of specialist involved, and if the anomalies observed are cardiac or non-cardiogenic pulmonary changes.[156,157] In some instances, agreement between emergency physicians and radiologists can be under 50%.[158] A systematic review of diagnostic strategies in AHF also found chest films to be only moderately specific (76-83%) with low levels of sensitivity (67-68%) to congestion.[60] Furthermore, this is also dependent on the specific radiographic feature of HF which is being examined on the chest film. The sensitivity and specificity of an X-ray for HF can vary if the feature highlighted is pulmonary venous congestion (54% and 96% respectively) or pleural effusions (26% and 92%). [122]

2.6.2 Lung ultrasound

2.6.2.1 Principles of LUS

Lung ultrasound (LUS) is an emerging semi-quantitative method to detect extravascular lung water and pulmonary congestion.[159] As increased interstitial sub-pleural oedema develops, interlobular septae thicken and at a histological level interfaces form between fluid filled and aerated alveoli. When a cardiac or vascular transducer is applied, the resultant ultrasonographic reflection at these points produces hyperechoic reverberation artefacts which are visualised as "comet tails".[160]

2.6.2.2 Superiority over CXR

The sensitivity and specificity for LUS is high (94.1% and 92.4%) and much better than those reported for most CXR changes of AHF.[161] Unlike clinical examination and CXR assessment, LUS can be performed with a high level of interobserver agreement and with variability consistently below 10%, even between experienced and less experienced personnel.[162-164] The process of skills development and integration into clinical assessment is also easier than most other imaging modalities. In a prospective, cross-sectional study of acutely dyspnoeic patients who presented to an emergency department (ED), a short 30 minute training tutorial was adequate enough to develop a basic competency in LUS assessment.[164]

2.6.2.3 Haemodynamic correlation

Changes in "B-line density" refers to the compactness of visualised 'comet tails' and correlates with changes in pulmonary congestion even within 3 hours of AHF treatment.[165] In a 100 patient study examining HF patients undergoing both catheterisation and LUS, B-line frequency closely matched invasive right atrial pressure, pulmonary artery pressure and pulmonary venous resistance.[166] These findings tie closely with historical data which shows a similar association between LUS findings and natriuretic peptide elevations – all of which predict in-hospital mortality, re-admission and longer term prognosis.[167] Of note, when LUS and dyspnoea assessments were correlated, it was noted that a quarter of patients had no dyspnoea rating on VAS assessments but still possessed evident B-lines on LUS. In a similar study of chronic ambulatory out-patients, 81% of patients with ≥ 3 B-lines had no audible crackles on auscultation.[168] These findings provide valuable insight into the subclinical nature of pulmonary

congestion and emphasise the potential benefits ultrasound technologies could provide in quantifying the congestive characteristics of asymptomatic patients.

2.6.2.4 Clinical utility

LUS is not able to differentiate extravascular lung water arising from pulmonary congestion from that secondary to acute respiratory distress syndrome. [169] Fibrotic lung disease (such as pulmonary fibrosis and systemic sclerosis) can also cause "dry" interlobular thickening of the alveolar structures and produce B-lines on ultrasound.[170] Positional changes of the patient can induce fluid shifts and alter the number of B-lines detected. Although uncommon, adiposity may limit image acquisition and interpretation.[160]

2.7 Objective assessment of peripheral congestion

No established imaging methods are regularly utilised in clinical practice to objectively assess peripheral congestion. Research into ultrasound assessment of the inferior vena cava (IVC) and jugular vein (JV) are bringing new HF applications to existing technologies. Bio-electrical vector analysis (BIVA) is a novel technology for assessing total body water content.

The dilemma of identifying subclinical congestion remains. The optimal hydration point and tolerances for individual patients are variable and single point assessments are inadequate thereby necessitating serial assessments.

2.7.1 Inferior vena cava ultrasound

2.7.1.1 Principles of IVC ultrasound

During cardiac decompensation, either through fluid accumulation or fluid re-distribution, blood enters the venous system and elevates filling pressures as it re-enters the right heart. This creates congestion and leads to distension of the main conduit venous vessels, particularly the IVC.[171] Using ultrasound technology, IVC diameter and its variation with respiration can be used to

estimate intra-cardiac pressures.[171] New generations of pocket devices can provide sufficient 2D resolution to allow basic quantitative evaluation of IVC changes.[172]

2.7.1.2 Haemodynamic correlation

Although the evidence base is still nascent in this area, IVC ultrasound has been demonstrated to be an effective indicator when compared to invasive intra-cardiac pressure measurement by RHC. It also tracks changes in congestion in a faster and more responsive way than cardiac biomarkers. In ESCAPE, patients underwent concurrent echocardiographic and invasive PWCP assessments from baseline to discharge as they decongested with diuretic therapy.[173] IVC diameter and collapsibility corresponded the most to changes in PCWP, with a smaller IVC tracking falling wedge pressures. In a similar study of end-stage renal patients, it was demonstrated that IVC measurements could follow decongestion during fluid removal on dialysis.[174]

2.7.1.3 Predicting prognosis

During hospitalisation, IVC diameter reduces and collapsibility improves over the course of an admission, as would be expected as a result of diuretic therapy. However, residual enlargement and lack of collapsibility predicts hospital re-admission, suggesting that this modality may be able to detect subclinical congestion.[175] IVC enlargement on admission was also shown to be associated with increased 90 day and 36 month mortality, though it is unclear how awareness of this might optimally change therapeutic surveillance.[176,177] In the outpatient setting, similar features of venous engorgement predict the risk of hospitalisation though not mortality.[178]

2.7.1.4 Clinical utility

Acquisition of IVC ultrasound techniques does not require significant additional training for those already skilled in basic echocardiography.[172] A focused study can take as little as 5 minutes.[179] In a study of 304 cardiac outpatients, pocket ultrasound was found to increase the diagnostic yield of cardiac abnormalities from 38% to 70%. Additionally, IVC visualisation has been demonstrated to

reduce time to diagnosis in the emergency department (ED) settings.[180] However, further to clarifying a diagnosis, it is unclear if IVC assessment can be used to direct therapy especially if untreated subclinical congestion is suspected on discharge.

2.7.2 Jugular venous (JV) ultrasound

2.7.2.1 Principles of JV ultrasound

Like the IVC, the jugular vein is a compliant vessel capable of distention in response to increased intravascular pressure and volumes. JV distension can be detected using the same focused ultrasound principles used to detect IVC enlargement.[181]

2.7.2.2 Haemodynamic correlation

Imaging of changes in the JV cross sectional area has been shown to predict increases in invasively assessed central venous pressure (CVP).[182] In patients with a mean CVP of <10 cm H_20, the JV diameter was <7mm whilst for a CVP of >10 cm H_20 this was 12.5 mm.[183] Importantly, a high correlation coefficient was demonstrated amongst operators (0.92; CI 95%).

2.7.2.3 Determining prognosis

Prognostic information about JV distensibility is still being determined, but similar findings have been noted as with those from IVC ultrasound. In a 311 patient study of HF outpatients, JV distension, echocardiographic filling pressures and biomarkers were assessed to determine associations with prognosis. Reduced JV compliance during Valsalva manoeuvres was found to correlate positively with cardiac biomarkers (NT-proBNP, r=-0.39, p<0.001) and echocardiography (E/e' filling pressures, r=-0.33, p=<0.001). Lower levels of JV distensibility could independently identify patients at increased risk of death and HF hospitalisation.[184]

2.7.2.4 JV near infra-red spectroscopy

One shortfall of this imaging method is the lack of a standard set of reference values against which static and dynamic measurements should be referenced. More advanced technologies using near-infrared spectroscopy (NIRS) of the external jugular vein have been utilised to try and provide specific non-invasive quantitative values for the clinician. In the Studies Investigating Co-morbidities Aggravating Heart Failure (SICA-HF) study, NIRS was performed on 243 stable HF patients to non-invasively determine right atrial pressure (RAP).[185] Though these findings have yet to be validated in broader HF populations, higher RAP values were associated with adverse outcomes and matched the prognostic utility of NT-proBNP.

2.7.3 Bio-electrical vector analysis

2.7.3.1 Principles of BIVA

Peripheral oedema will often not develop until after the interstitial fluid volume has expanded to above 30% of normal.[186] BIVA can potentially quantify intravascular volume expansion in AHF and provide the clinician with early data on subclinical congestion.

BIVA functions by utilising the electrical properties of the human body. By determining body resistance (a function of intra- and extracellular fluid volume) alongside body reactance (a function of the dielectric material of tissue cells), the overall total body water of the patient can be calculated and subsequently a quantification made of hydration status.[187]

2.7.3.2 Haemodynamic correlation

Early studies have shown that BIVA can potentially monitor congestion. In study of 57 AHF patients, BIVA was used to assess hydration status in conjunction with their clinical state.[188] BIVA parameter changes matched clinical improvements, and those labelled as having “the most significant congestion” by BIVA on

admission were found to subsequently experience greater improvements in dyspnoea, weight loss and reduction of BNP with diuretic treatment.[188]

2.7.3.3 Determining prognosis

In a study of 292 patients with AHF, the use of BIVA-determined congestion status was combined with BNP to produce a more accurate 90 day predictor of cardiovascular mortality (when compared to BNP alone).[189] A statistically significant improvement in body water status was seen in survivors when compared with non-survivors (hydration index [HI] 85 vs 76, $p<0.001$) and discharge BIVA was an independent marker of an increased risk of cardiovascular death.[189] A follow-up multicentre study by the same research group also demonstrated that patients who showed improvements in BIVA parametrics in response to diuretic therapy had a lower risk of death and rehospitalisation.[190]

2.7.3.4 Clinical utility

To date, no large multicentre studies have attempted to trial a BIVA-directed approach to decongesting HF patients. One single centre Italian study in 2011 attempted a limited non-randomised, non-blinded approach, but focused the algorithmic decongestion strategy heavily on changes in BNP rather than BIVA derived data.[191] The role of BIVA in an acute setting remains uncertain but it may help identify where residual congestion remains (such as in patients with decrementing urine output and persisting mild HF symptoms) and thereby help highlight those who require more intensive diuretic strategies. The identification of patients with subclinical congestion prior to hospital discharge may also be facilitated with the use of BIVA.

2.8 Research questions and study aims

The primary research question is to determine the nature of congestion reporting in the AHF population and the strategies which are undertaken to assess it.

2.8.1 Research aims

Through the process of conducting two systematic reviews – on AHF trials and AHF registries separately - this study aims to ascertain: i) the assessment methods for congestion in AHF trials and in AHF registries, ii) the clinical profiles of congestion in both AHF trials and registries iii) how methods of congestion assessment are structured into enrolment and end point criteria in AHF trials and iv) the congestive profiles of patients with de-novo and acute-on-chronic heart failure enrolled into AHF registries.

3 Treatment of congestive heart failure

3.1 Acute heart failure

AHF is the exacerbation of the clinical symptoms or signs of HF necessitating urgent medical attention. Data from the European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) registry indicate the most common triggers are ACS (30%), arrhythmia (30%) and infection (20%).[192] A clear precipitant is not always identified, though in reality multiple causes often trigger a hospitalisation event. As has been described, congestion can arise slowly over weeks (due to fluid accumulation) or more rapidly over hours (due to fluid redistribution).[90]

3.1.1 Early acute assessment of congestion

The primary aim of an initial assessment is to identify whether congestion is present.[1] Identification of the Forrester haemodynamic profile of the patient can guide therapy – though the majority of patients fall into the "warm and wet" category. The 'ABCDE approach' is utilised to ensure diagnostic and interventional treatments (for HF and precipitants) are performed in parallel.[193]

3.1.2 Clinical and biochemical assessment

No single sign is pathognomonic of AHF, and therefore clinical assessment must be reviewed following comprehensive clinical examination alongside investigatory findings. It is recommended that all patients receive an initial standard CXR to evaluate the presence of pulmonary venous congestion, pleural effusions, and alveolar oedema – though in 20% of cases no anomaly will be readily detected.[59] A standard 12-lead ECG aids the diagnosis of precipitant arrhythmias, ischaemia and shows potential evidence of cardiomyopathy. Echocardiography is recommended for all de-novo patients within 48 hours of presentation and immediately for patients in cardiogenic shock and haemodynamic instability – though guidelines acknowledge the availability of

clinical expertise to be a limiting factor.[1] Assessments can be made of acute mechanical complications (valve or septal rupture), obstructive pathology (RV strain secondary to pulmonary embolus, cardiac tamponade) and overall left ventricular function.

Biochemistry testing will usually be directed by clinical suspicion. Natriuretic peptides are elevated in AHF and have a powerful negative predictive value.[1,2] Positive results must be interpreted within the clinical context of each case. Cardiac causes (such as ACS, pulmonary emboli, myocarditis) and non-cardiac causes (cerebrovascular events, liver disease, severe sepsis) can all elevate BNP and NT-proBNP levels. In AHF, the ceiling reference range is higher than that for chronic stable HF (BNP 100 pg/mL, NT-proBNP 300 pg/mL). Cardiac troponin is not specific for AHF and is often raised secondary to myocardial wall stress or myocyte ischaemia due to hypoxia. Troponin assessment should be performed if a reasonable suspicion of ACS exists. Raised creatinine and blood urea nitrogen can indicate renal venous congestion and should not be taken as indicative of pre-renal compromise. Similarly liver function testing may be deranged arising either from congestion or a shocked cardiogenic state. Routine use of a pulmonary artery catheter is not recommended unless there is significantly impaired perfusion and fluid status is indeterminable by clinical means.[2]

3.1.3 Oxygen therapy

Oxygen therapy should be targeted to those who are hypoxic (due to pulmonary oedema) with an aim to normalise saturations as appropriate for the patient's target range. A range of 88-92% is appropriate for those at risk of hypercapnic respiratory failure (e.g. moderate-severe chronic obstructive respiratory disease [COPD], severe spinal or neuromuscular disease, cystic fibrosis).[194] Otherwise a target of 94-96% should be used. Severely compromised patients with acute pulmonary oedema should initially be treated with oxygen via a reservoir mask at 15 l/min. More stable patients can be managed with nasal cannulae (1-4 l/min) or a simple face mask (7-10 l/min). Those at risk of hypercapnic respiratory failure should be managed instead with controlled oxygen delivery via a Venturi mask to enable titration as required.[194] Care must be taken to

avoid hyperoxygenation which can precipitate vasoconstriction and impair cardiac output.[195]

For patients with refractory hypoxia and persisting acidosis, non-invasive ventilatory (NIV) methods (continuous positive air pressure [CPAP] and bilevel positive pressure ventilation [BiPPV]) can increase alveolar recruitment, reduce alveolar oedema and reduce hypoxia.[196] Both can reduce venous return (thereby reducing preload) and improve cardiac output.[197] BiPPV is also more effective at clearing hypercapnia and reduce the work of breathing. The 3CPO study demonstrated that patients undergoing NIV for cardiogenic pulmonary oedema experience faster symptomatic improvement and normalisation of acidosis and hypercapnia.[198] Whilst no mortality benefit was demonstrated, NIV also reduces progression to intubation.[196]

3.1.4 Identification of haemodynamic profile

ESC guidance advises clinicians attempt to identify the haemodynamic profile of the patient using the Forrester classification.[1,139] However, the method for classifying each sub-category remain subjectively determined and the follow on treatment strategies are still loosely defined.

For patients who are “warm and wet” (well perfused but congested), clinicians must determine whether vasoconstriction or fluid congestion is the predominant pathophysiological disturbance.[1] This is intended to reflect the differing mechanisms of decompensation, namely fluid redistribution and fluid accumulation. In both cases diuretic therapy, usually a loop diuretic such as furosemide, is required to facilitate decongestion. Where vasoconstriction predominates, patients should be treated with a vasodilator and diuretic. Where fluid congestion is the primary feature, patients should be initially managed with diuretics and consideration given to ultrafiltration if this fails.

Patients who are “warm and dry” (appropriately perfused and not congested) should have their oral therapy optimised and no further HF specific interventions

are advised.[1] “Dry and cold” patients who are hypoperfused and underfilled should be considered for cautious fluid challenge followed by inotropic therapy.[1]

“Wet and cold” patients (those congested and poorly perfused) are treated depending on blood pressure.[1] Patients with a systolic blood pressure below 90 mmHg (and in cardiogenic shock) should be given inotropes and diuretic therapy if no alternative cause for hypoperfusion exists. Vasopressors may be utilised with caution with recourse to mechanical support. “Wet and cold” patients with a systolic blood pressure above 90 mmHg (in a non-shocked but poorly perfusing congested state) should be given vasodilators and diuretics with inotropic therapy added in if perfusion does not improve with decongestion.

3.1.5 Congestion scores

Post-hoc analyses from DOSE, EVEREST and PROTECT have attempted to construct congestion scores which revolve around a narrow set of core features of congestion (orthopnoea, elevated JVP, peripheral oedema and pulmonary rales).[118,132,199] Scores which are elevated on admission and fail to improve with therapy have all been demarcated as a risk factors for recurrent re-admission and mortality. EVEREST also demonstrated that patients with low scores can continue to have high levels of circulating NPs – furthering the concern that a dissociation often arises between clinical and haemodynamic congestion. However, how these tools should applied prospectively has yet to be determined.

An integrative assessment has been recommended by Girerd and colleagues comprising not just congestion scores but also biomarkers (particularly NP) and ultrasound imaging (LUS and IVC ultrasound).[71] Pre-discharge targets have also been included as suggested strategies. However, these remain problematic. Clinical assessment is known to remain subjective and variable. In many cases, NYHA or dyspnoea scores will not improve in patients with advanced HF (and concurrent respiratory disease) regardless of how much additional diuretic therapy is deployed. The evidence for instituting pre-discharge thresholds for NPs is also weak - no clear link with lowered readmission rates or mortality has

been identified.[200] NP values can also lag behind true changes in haemodynamic pressures by up to one week.[201] Both congestion scores and biomarker data have not been prospectively trialled within an algorithmic framework and there remains uncertainty of how to approach the "non-responder". The conundrum of subclinical haemodynamic congestion may partially resolved with ultrasound imaging and an integrative strategy provides an initial framework to try and assess this. Providing a 'live snapshot' of the haemodynamic congestive burden could indicate whether a more aggressive diuretic based approach may have value – though what parameters to target remains subject to the discretion of the clinician. A strategy of earlier follow-up for patients with residual congestion (as evidenced though imaging) may reduce rebound admissions – but further RCT evidence is needed.

3.1.6 Pharmacological interventions

In the immediate phase, diuretic, vasodilator and inotropic agents are the primary pharmacological measures utilised for managing AHF. Other medications specific to the precipitant cause can also be administered concurrently. Cautious use of opiates may be considered alongside oxygen therapy to relieve severe dyspnoea, anxiety and ease secondary sympathetic overstimulation.[202] Where pharmacological therapy has failed, ultrafiltration is an option in oliguric patients with hyperkalaemia, acidosis and worsening renal biochemistry.[1]

3.1.6.1 Diuretics

Loop diuretics are the first agent of choice for immediate decongestion, with no evidence of any one agent being more efficacious. Frusemide is most commonly delivered intravenously and possess venodilatory properties when given as bolus injection. DOSE ascertained that no difference exists between bolus and continuous infusion.[203] A strategy of high dose frusemide boluses (defined as 2.5 times the previous oral dose) reduced congestion in patients faster with better dyspnoea improvement but with transient deterioration in renal function and no survival difference. Whilst 80 mg of Frusemide can be delivered rapidly with vasodilatory effect, higher doses must be slowed to 4 mg per minute to avoid

the risk of ototoxicity.[204] In such circumstances, continuous infusions may be preferred. Diuretic naïve patients (such as de-novo patients) are more responsive to diuretics, and so lower doses (e.g. furosemide 40 mg intravenously) are more appropriate.[1] During hospital stay, as diuretic resistance develops, sequential nephron blockade with additional thiazide agents can improve diuresis.[204]

3.1.6.2 Vasodilators

In hypertensive AHF, vasodilators can reduce venous and arterial tone to improve cardiac output and reduce filling pressures. The resultant changes in haemodynamics are rapid and alongside diuretic therapy can quickly lead to resolution of a substantive degree of pulmonary congestion. Nitroglycrine, isosorbide dinitrate, and nitroprusside are the most commonly available agents in European nations.[1] Slow up-titration is required to avoid precipitous drops in systolic blood pressure and they should be avoided in patients with severe obstructive valve disease or hypertrophic obstructive cardiomyopathy.

3.1.6.3 Inotropes

Despite increasing cardiac output, inotropes increase myocardial oxygen demand and can precipitate arrhythmias and vasodilation.[205] No survival advantage has been demonstrated in AHF with either adrenergic or non-adrenergic agents. However current guidance sanctions the cautious use of inotropes in specific scenarios such as where hypoperfusion arises without hypovolaemia, or as a bridge to mechanical support devices.[1]

Dobutamine has direct ß1 and ß 2 adrenergic agonism and produces less tachycardia than adrenaline. Vasodilation does occur and tolerance arises after 72 hours of use.[205] Dopamine induces natriuresis at low doses (3-5 microg/kg/min) and also acts on ß-adrenergic receptors to cause increased inotropy. However blood pressure is augmented mostly by vasoconstriction through actions on α-adrenergic receptors at higher doses (10 to 20 microg/kg/min). Data from ROSE-AHF where patients were randomised to dopamine, nesiritide or placebo suggested that no benefit was achieved with low dose therapy.[206] However in this study, dopamine and nesiritide were both

initiated within 24 hours of hospitalisation and not selectively to patients with worsening renal impairment or diuretic resistance. A trend towards increased urine volume production with dopamine was also observed in HFrEF patients.[206]

Levosimendan and milrinone represent two non-adrenergic agents available in clinical practice. Levosimendan is recommended where shock arises from beta-blockade. In clinical trials, no mortality advantage was demonstrated and adverse effects secondary to pro-arrhythmia occurred.[207,208] Milrinone - a phosphodiesterase inhibitor - produces more pulmonary vasodilation than dobutamine, but when assessed in Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial, hypotension and sustained arrhythmias were more frequently reported with no survival benefit.[209]

3.1.7 Mechanical circulatory support

Mechanical circulatory support (MCS) devices can stabilise cardiac haemodynamics and act as a bridge to transplant, recovery or temporary stabilisation until further evaluation can be undertaken.[1] MCS devices can be short term for days (such as intra-aortic balloon pumps [IABP]) or months-to-years (such as left ventricular assist devices [LVADs]).

IABP are inserted percutaneously into the aorta below the left subclavian. A counter-pulsation mechanism help supports circulatory pressures. During systole rapid deflation of the balloon creates a dead space easing blood flow out from the LV whilst diastolic balloon inflation maintains coronary perfusion. Whilst randomised trials have not shown benefit in cardiogenic shock secondary to MI there have been no trials in AHF. IABPs are used as a bridge to recovery (for example in acute myocarditis), before coronary revascularisation, or prior to repair of mechanical complications (such as acute mitral regurgitation or ventricular septal rupture secondary to myocardial infarction [MI]).[210]

Extracorporeal membrane oxygenation (ECMO) can be veno-venous (VV) or veno-arterial (VA).[211] VV-ECMO is utilised primarily for deficiencies of gas exchanges

due to respiratory failure (such as secondary to severe pneumonia or acute adult respiratory distress syndrome [ARDS]) and not acute HF.[211] VA-ECMO can be used for AHF, difficulty weaning of bypass, or severe RV failure secondary to pulmonary thrombo-embolism (where pulmonary thrombectomy is to be scheduled). ECMO functions as a bridge to LVAD implantation or recovery, but its longer window for use is associated with higher rates of complications.

LVADs consist of a battery operated external mechanical pump with two cannulae surgically implanted into the LV apex and aorta. These devices are used to allow patients to survive until transplantation.[212] Eligibility criteria include an LVEF < 25% (peak VO2 < 12 mL/kg/min), recurrent hospitalisation and inotropic dependence. The absence of severe RV dysfunction is critical to optimise outcomes.[1] Complications from LVAD implantation include bleeding, stroke, pump thrombosis and device infection.

The timing of MCS and specifically LVAD implantation can be guided by classification scores (Table 3-1).[213]

Table 3-1. INTERMACS classification. Adapted from Stevenson *et al* (2009).[214]

INTERMACS Profile	Title	Description
Level 1	Critical cardiogenic shock	Life threatening hypotension refractory to inotropic therapy (“crash and burn”)
Level 2	Progressive decline	Inotrope dependent with worsening end-organ function (“sliding fast” on inotropes”)
Level 3	Inotrope dependent	Stable haemodynamics but dependent on inotropes for stability
Level 4	Resting symptoms	Daily resting symptoms and requiring high dose of oral diuretics
Level 5	Exertion intolerant	Housebound and unable to perform any activities above basic activities of daily living
Level 6	Exertion limited	Rapidly fatigues on performing minor activities (“walking wounded”)
Level 7	Advanced NYHA III	Symptoms on mild exertion

INTERMACS: Interagency Registry for Mechanically Assisted Circulatory Support, NYHA: New York Heart Association.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) scale provides a grading system for risk stratification to aid decision making. Patients are scored from 1 to 7 based on clinical symptoms, inotropic dependency and haemodynamic state. Registry data indicates that survival rates remain better for those implanted at INTERMACS 2 and 3 than INTERMACS 1.[215,216]

3.2 Chronic heart failure: Medical therapy

Medical therapies for chronic HF involve pharmacological antagonism of the adverse neuro-hormonal systems which cause fluid retention and deleterious cardiac remodelling.[1] Oral diuretics are initially utilised to decongest patients. Beta-blockers, ACE inhibitors and mineralocorticoid antagonists [MRA]) are then added to counter the effects of excess sympathetic stimulation and RAAS activation.[1] Angiotensin receptor blockers (ARB) remain an alternative for those who are intolerant of ACE inhibitors. New angiotensin receptor-neprilysin inhibitors (ARNi) have shown positive results in direct comparison against ACE inhibition and may supersede these in future guidelines. For patients who remain tachycardic, ivabradine has a role through heart rate reduction. Hydralazine-isosorbide dinitrate (H-ISDN) has been proven to have beneficial vasodilatory effects in selected patients, particularly those of African-American descent. Although not shown to reduce mortality, digitalis may also provide patients with symptomatic benefit. It should be noted that unless specified the therapies described apply to HFrEF patients. [1]

3.2.1 Diuretics

The primary aim of diuretics is to decongest patients. At present, no large randomised trials have been conducted to demonstrate any mortality benefit of diuretic therapy, though they have been a baseline component of standard care for all major HF studies.[1] A Cochrane review examining diuretics and outcomes concluded that there was some evidence that mortality, worsening HF and exercise tolerance may be improved.[217] Loop diuretics are the first line agents of choice in stable chronic HF and act by inhibiting sodium and potassium

reabsorption in the ascending loop of Henle. They produce a more powerful and shorter acting diuresis when compared to other classes of diuretics. At present, furosemide, torasemide and bumetanide remain the most commonly utilised diuretics in European practice.[1]

Each loop diuretic has a different rate of absorption. During periods of congestion, intestinal oedema can develop as the interstitial space expands significantly, yielding a slower and less pronounced absorption curve.[218] In this setting, clinicians may prioritise agents such as bumetanide with a more lipophilic and bioavailable profile (80% of bumetanide is bioavailable compared to 40% of frusemide). However, the risk of gout remains higher and when equivalent doses are compared the overall effectiveness remains similar.[219]

In cardio-renal syndromes, loop diuretics may not be adequately secreted into the tubular lumen to exert their channel blocking effects. In such cases, increased doses may be required to produce a similar shift in fluid balance. There remains significant variation in maximal doses advised. For furosemide, ESC guidelines recommend a limit of 240 mg per day, the British National Formulary 1,500 mg, whilst small scale individual studies have shown that administrations of up to 4,000 mg day may be possible.[220] However, hypokalaemia, gout and tinnitus occur with increasing frequency at higher doses.[221]

Over time, diuretic resistance can develop necessitating greater doses of loop diuretic or combination therapy with thiazides.[222] The precise prevalence remains unclear, but a retrospective review of the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial found this occurred in 35 % of AHF patients and was independently associated with increased mortality (HR 1.37, $p<0.004$).[223] The mechanism of this “renal brake” involves increased epithelisation of the distal convoluted tubule resulting in greater salt transporting (and therefore water re-absorbing) capacity. By blocking other components of the renal tubule, sequential nephron blockade exerts a synergistic effect to yield a higher volume diuresis. However, these combinations have to be utilised cautiously as over-diuresis and electrolyte

imbalance may occur (specifically hypokalaemia and hyponatraemia). Current evidence suggests different thiazides have broadly equivalent potency.

Critically all these strategies must be in concurrence with the appropriate dietary advice, particularly a restriction of excess fluid and salt intake. After loop diuretic administration, compensatory post-diuretic salt retention can occur, and if excess dietary salt is present the overall fluid balance may be rendered neutral.

3.2.2 Beta-blockers

Beta-blockers act by blocking excess sympathetic activity on the cardiovascular system.[224] They also achieve benefits by reducing arrhythmic risk and assisting with rate control. Current trials have confirmed efficacy in ischaemic and non-ischaemic cardiomyopathy and they produce improvements in symptoms, ejection fraction, hospitalisation rates and mortality. There still remains debate about whether these benefits can be extended to patients with atrial fibrillation and HFmrEF. [225,226]

The transition of beta-blockers from a historically contra-indicated drug to a core therapy for HF has been driven by changing perspectives of the disease process. HF is viewed less as a pure haemodynamic disturbance and more focus has been exerted on correcting the neurohormonal disorder. The Cardiac Insufficiency Bisoprolol (CIBIS II) study was a landmark trial demonstrating a mortality benefit of bisoprolol in NYHA class III-IV patients with severe LVSD.[227] Improvements were seen in all-cause mortality (RR 34%, $p<0.0001$) and hospitalisation (RR 20%, $p<0.0006$). The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial demonstrated similar benefits for carvedilol against placebo in NYHA IV patients with LVEF < 25% (but with ACE inhibitors also comprising standard therapy).[228] Following this, the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT- HF) showed that sustained release metoprolol in HF patients given to a broader NYHA class (II-III) and LVEF < 40% could also produce a survival benefit.[229]

A systematic review and meta-analysis of 21 major beta-blocker trials determined that just three beta blockers demonstrated a clear mortality benefit in HF: bisoprolol, carvedilol and metoprolol.[224] Carvedilol has shown to lower cardiac mortality in various metanalyses but not to a degree that is statistically significant.[224] The mechanisms for this is unclear and may relate to effects on endothelial function, its inherent anti-oxidant properties and superiority in maintaining glycaemic homeostasis in patients with diabetes. In clinical practice, bisoprolol, carvedilol, metoprolol and nebivolol remain the recommended beta blockers of choice. The overall relative mortality benefit in stable HF has been estimated to be 20-35%. [224]

In acute decompensated HF, beta-blockers should only be commenced when patients are stable and preferably euvolaemic (i.e. after the patient is no longer congested).[1] For patients already established on beta-blockers, it should be continued unless cardiogenic shock is evident. Meta-analysis evidence and registry data from OPTIMIZE-HF suggest that acute beta-blocker withdrawal during hospitalisation (where the beta-blocker is not the causative agent of AHF) can trigger increased rebound sympathetic drive and precipitate angina, dysrhythmia and raise mortality. [230,231]

3.2.3 Angiotensin-converting enzyme inhibitors

ACE inhibitors are capable of attenuating LV remodelling to improve mortality.[232] In HF, globular dilatation distorts ventricular shape and compromises contraction. The resultant altered wall stress leads to further cavity dilation and progressively poorer contractile function.[232] In SOLVD, sequential echocardiography demonstrated that ventricular volumes were better stabilised in patients taking enalapril versus placebo.[233] At a cellular level, ACE inhibitors can also temper secondary adverse changes in molecular and gene expression which occur within pathways not associated with haemodynamic overload.[234]

The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and SOLVD trials were the first to establish the beneficial effects of ACE inhibition in

large scale randomised controlled trials (RCTs) using enalapril in symptomatic and asymptomatic patients with severe LVSD.[235,236] Further randomised studies have demonstrated a consistent class effect with other ACE inhibitors.[237] A review by the Collaborative Group on Ace Inhibitor Trials of 32 RCTs demonstrated that patients with the poorest LVEF benefited most, with gains seen more prominently within the first 3 months. Mortality and hospitalisation were all improved (odds ratio [OR], 0.65; 95% CI, 0.57 to 0.74; P < 0.001).[237] Patients post-MI without and without symptoms have also been shown to benefit from ACE inhibition.[238,239]

3.2.4 Mineralocorticoid antagonists

MRAs act on the distal nephron to reduce aldosterone mediated expression of proteins and ion channels involved in sodium retention and potassium secretion. Although the production of aldosterone can be inhibited in a more upstream fashion at the adrenal level by ARBs, hypertension studies have demonstrated that these levels can normalise via an 'aldosterone escape' phenomenon within six months.[240] By utilising MRAs to antagonise the action of aldosterone at the receptor sites of the kidney, this bypass can be effectively inhibited.

MRAs have significant multi-organ effects outwith the nephron. Antagonism of MR receptors in the myocardium can attenuate fibrosis, hypertrophy and apoptosis whilst in the vascular endothelium, MR blockade reduces endothelial dysfunction and vascular stiffness.[241] In hypertensive patients, spironolactone has been demonstrated to reverse the development of left ventricular hypertrophy (LVH) over and above the effect of ACE inhibitors.[242]

In the Randomized Aldactone Evaluation Study (RALES), spironolactone decreased all-cause mortality by 30% against placebo in NYHA III and IV patients with an LVEF < 35%.[243] Hospitalisation was also reduced by an equivalent amount. The positive results of the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study extended use of MRAs to patients with milder NYHA II class symptoms.[244] Patients post-MI with LV impairment have also been shown to benefit from early addition of

eplerenone.[245] As such, all symptomatic patients with an LVEF ≤ 35% should be initiated on MRA therapy.[1]

3.2.5 Angiotensin-receptor neprilysin inhibitor

Angiotensin-receptor neprilysin inhibitors are a new class of HF agents which can deliver both RAAS blockade and enhance natriuretic peptide systems. Neprilysin is an endogenous endopeptidase that breaks down vasoactive peptides including bradykinin, adrenomedullin, substance P and natriuretic peptides.[246] In blocking neprilysin, these counter-systems responding to neurohormonal changes in HF can be enhanced to restore their protective effects on vasodilation, sodium excretion and adverse remodelling.

The provisionally titled agent LCZ696 was efficacious against enalapril in the landmark Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial in patients with NYHA II-IV HF and LVEF < 40%.[247] This combination drug was composed of sacubtril and valsartan. Sacubitril functions as the neprilysin inhibitor and valsartan adds ARB functionality to enable RAAS and direct AT2 blockade. Valsartan is preferred over an ACE inhibitor in this combination as direct ACE blockade can result in an excess build-up of vasodilatory mediators which may precipitate life threatening angioedema.[248] PARADIGM-HF was stopped prematurely as the significant benefits of ARNI over enalapril in reducing hospitalisation (22% vs 27%, P < 0.001) and all-cause mortality (HR 0.84; 95% CI, 0.76 to 0.93; P<0.001) became apparent.[247] Hypotension was more prevalent in the sacubitril-valsartan arm (14 vs 9%, p<0.001) but less hyperkalaemia and renal dysfunction was seen. Sacubitril-valsartan is currently recommended as an ACE inhibitor (or ARB) substitute for patients who remain symptomatic after combination therapy with ACE inhibitor (or ARB), beta-blocker and MRA has been attempted.[1]

3.2.6 Angiotensin II receptor blockers

ARBs may be preferred to ACE inhibitors in a number of instances. ACE inhibitors can produce two particular side effects specific to their mechanism of action which require discontinuation of therapy. Cough is a chronic persistent symptom which has been described in 5 to 35% of patients.[249] The precise mechanism involves the accumulation of bradykinin – an agent normally degraded by ACE.[250] This is a class effect and necessitates switching completely to a different therapeutic class of drug. Angioedema may also occur in 0.1 to 0.2% of patients. The onset is variable (between hours to a weeks of starting therapy) and also arises from the vasodilatory effects of bradykinin.[249]

ARBs function by blocking the action of AT2 at multiple organ system levels. They also antagonise the effects of AT2 produced through non-ACE regulated pathways.[251] ARB therapy can block AT2 mediated-vasoconstriction in the vasculature and attenuate sympathetic upregulation, myocyte remodelling and renal natriuresis. AT2 mediated aldosterone secretion is also inhibited in the adrenal cortex.[251] Cough and angioedema are not typically associated with ARB use.

The Losartan Heart Failure Survival Study (ELITE II) compared losartan against captopril in 3152 patients with symptomatic HF and documented LVEF < 40% to assess if ARB agents could supersede ACE therapy.[252] Most patients were NYHA class II or III and 80% were of an ischaemic aetiology. By trial completion, there were no significant differences between the two cohorts with respect to either mortality or hospitalisation. It should be noted that lorsartan was much better tolerated than captopril (discontinuation rate of 9.7 vs 14.7%, losartan against captopril).[252] In the Valsartan in Acute Myocardial Infarction (VALIANT) study, valsartan and captopril were compared against each other in patients post-MI with LVSD and/or HF. Both therapies were proven to be equally efficacious in this setting.[253] However, combination therapy with an ACE and ARB is not synergistically beneficial. In the Candesartan in Heart failure: Assessment of Reduction in Mortality and Morbidity (CHARM-Added) trial, candesartan was added to patients already on standard therapy (including ACE inhibitors).[254] There were trends towards an improvement in cardiovascular mortality and

hospitalisation but significant adverse effects arose with dual RAAS blockade. In the candesartan arm, 24% of patients discontinued therapy due to side-effects including renal dysfunction (rise in creatinine 7.8%, hyperkalaemia 3.4%) and hypotension (4.5%).

As a consequence of the above studies, ARB use is indicated in HFrEF when an ACE inhibitor cannot be tolerated.[1] Dual combination therapy is not recommended unless patients are unable to take an MRA. In such cases closer monitoring of blood pressure, potassium and renal function is advised.

3.2.7 Ivabradine

Ivabradine functions by reducing the rate of sinus node depolarisation via inhibition of the I*f* current in sinus nodal cells (but without effecting other cells of the conducting system). Pharmacologically, ivabradine has no neurohormonal blocking actions. Where beta-blocker induced respiratory symptoms are problematic, ivabradine remains an alternative. Blood pressure is also not impaired, as the therapeutic effect is mediated by prolongation of diastolic perfusion time thereby improving myocardial perfusion without lowering central aortic blood pressure.[255]

In the Systolic Heart Failure Treatment with the I*f* Inhibitor Ivabradine (SHIFT) study, 6558 patients with symptomatic HF and impaired LVEF (of ≤ 35%) already on baseline medical therapy were randomised to ivabradine or placebo.[256] Patients in both groups were in sinus rhythm and on a beta-blocker if tolerated. Whilst no absolute mortality benefit was seen, the primary outcome was positive driven principally by a 23.8% relative reduction in HF hospitalisation. Patients with greater heart rate reduction also reported better symptomatic benefit.[257] In a post-hoc analysis of the SHIFT trial, a clearer survival benefit was seen in those with heart rates of over 75 bpm (HF death: Hazard ratio [HR] 0.61, 95 % confidence interval [CI], 0.46-0.81, P < 0.0006) leading to this rate stipulation in the current ESC HF Guidelines.[258]

3.2.8 Hydralazine and isosorbide dinitrate

Hydralazine and isosorbide dinitrate (H-ISDN) are both vasodilators capable of lowering ventricular filling pressures and vascular resistance.[259] Combination therapy against ACE inhibition has been studied in the V-HeFT II trial and showed no overall mortality benefit (though H-ISDN was associated with better improvement in LVEF and exercise tolerance).[260] Results from the African-American Heart Failure (A-HeFT) trial which specifically focused on the African-American population suggested that H-ISDN added to optimal medical therapy could reduce mortality. It is speculated that African-Americans with HF may have less aggressive RAAS activation and instead a poorer endogenous vasodilatory response to nitric oxide.[261,262]

3.2.9 Digitalis

Digitalis has been utilised as an inotropic and rate control agent for over 200 years in cardiac disease.[263] It belongs to the cardiac glycoside class of drugs and functions by blocking the function of sodium-potassium exchange pumps in cardiac myocytes.[263] The resultant effect is an increase in intracellular calcium producing a decrease in heart rate and increase in overall contractile function. Blood pressure is also augmented through increases in stroke volume. Due to its narrow therapeutic window and renally mediated method of excretion, caution is advised with elderly patients, females and those with renal dysfunction.[1]

The Digitalis Investigation Group (DIG) trial randomised patients with an LVEF < 45% in sinus rhythm to either digoxin or placebo in addition to standard medical care (diuretics and ACE inhibitors, but not beta blockers). There was no mortality benefit to digoxin use but hospitalisation was reduced.[264] A meta-analysis of 621,845 patients examined the impact of digoxin use on clinical outcomes and similarly concluded that no deleterious effect on mortality were present and hospitalisation was lowered in all trial subtypes.[265] Current recommendations suggest that digoxin only be considered for ventricular rate control when there are no other suitable therapeutic options.[1] The optimal range for rate control is also a subject of ongoing debate for patients in AF.

Evidence from the Rate Control Efficacy in Permanent Atrial Fibrillation (RACE II) study suggests targeting a HR of below <100 beats per minute (bpm) will yield equivalent outcomes to stricter strategies.[266] However the ESC currently still advise targeting a ventricular rate of between 70 to 90 bpm with a caveat that the evidence base is weak in this area.

3.2.10 Contra-indicated drugs

Diltiazem has been shown to increase the risk of worsening HF in patients with HFrEF and AHF.[267] Unlike beta-blockers, this drug produces negative inotropic effects on the heart but without any other protective neurohormonal actions. Other non-dihydropyridine calcium channel blockers such as verapamil are also contra-indicated. Dihydropyridine calcium channel blockers without negative inotropy (amlodipine and felodipine) have a positive safety profile.[1]

Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with an increased risk of HF events and MI. The mechanism of harm is secondary to disruption of cyclo-oxygenase mediated prostaglandin production in renal cells (leading to salt and water retention) and in the endothelium (leading to pro-thromboembolic activation of platelets).[268,269] Thiazolidinediones have also been demonstrated to increase fluid retention and should not be used in HF.[270] RCT evidence for flecainide has proven an increased frequency of fatal ventricular arrhythmias with use in LVSD patients and dronedarone is also associated with increased mortality in HF.[2,271] Corticosteroids may worsen HF through fluid retention, but in select instances the overall risk-benefit ratio may necessitate prescription.

3.2.11 Treatment of heart failure with preserved ejection fraction

All major RCTs assessing the efficacy of beta-blockers, ACE inhibitors, ARB and MRA therapy in HFpEF patients haven demonstrated no survival benefit.[13] The PARAGON-HF trial is due to report on the efficacy of neprilysin inhibition with sacubitril/valsartan in HFpEF, though preliminary results indicate no major

difference will be observed in the rates of cardiovascular death or hospitalisation (ClinicalTrials.gov Identifier: NCT01920711).

At present, symptom relief should be attempted via the use of diuretics to relieve congestion. Concurrent co-morbidities such as hypertension, atrial fibrillation, coronary heart disease and diabetes mellitus must also be managed as directed by standard guidelines.[1,2] The heterogenous nature of the HFpEF population and lack of a single gold standard test to correctly filter trial enrolment may be responsible for some of the neutral outcomes of these studies. Additionally, many HFpEF patients tend to be very elderly with multiple comorbidities making trial recruitment more problematic.[13]

4 Methods

Searches were performed for both AHF trials and AHF registries. PRISMA flow diagrams for both the screening process and results are shown with overviews of the excluded results following full text review.

4.1 Acute heart failure trials and registries

4.1.1 Search strategy

A search strategy was performed on EMBASE and MEDLINE for both AHF trials and AHF registries. The following search terms were utilised: “acute heart failure”, “decompensated heart failure” and “hospitalized heart failure” (Figure 4-1 and Figure 4-2). Each search was limited to consider the above terms in title, subject heading, keyword or abstract. Studies were limited to those enrolling humans and entries which were reported in the English language. Trials were only considered from Jan 1, 2001 to Dec 31, 2018. Patients were included from trials which included either exclusively HFrEF patients or mixed HFrEF and HFpEF populations.

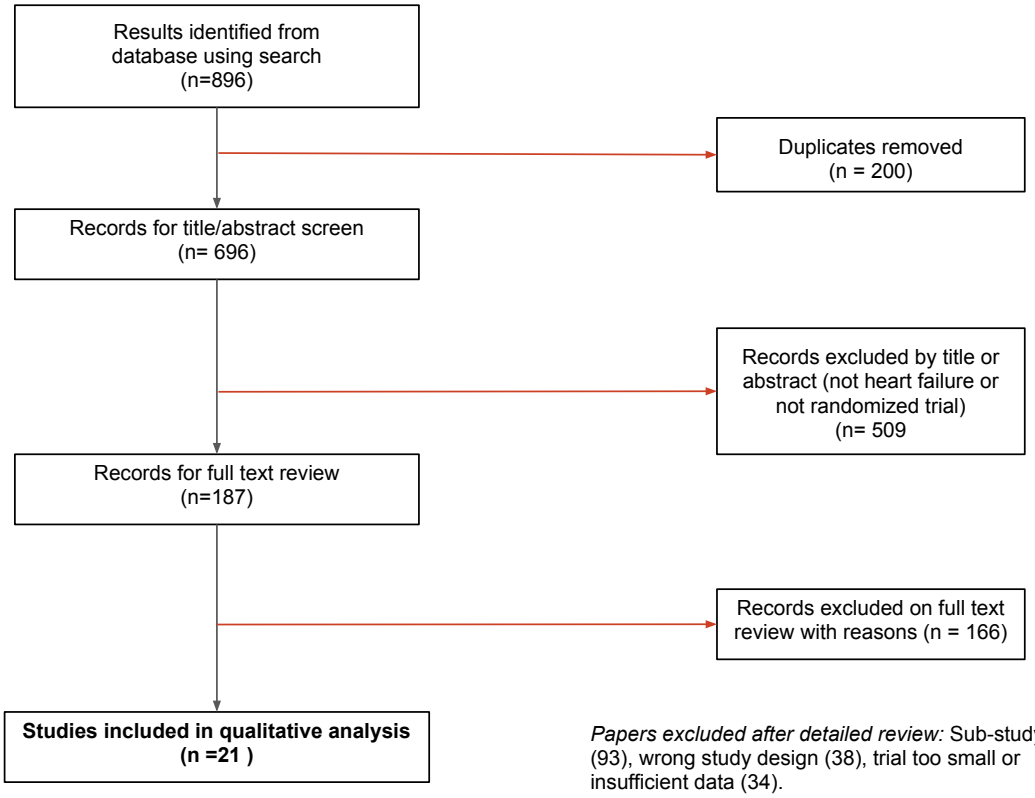

Figure 4-1: Search strategy for acute heart failure trials

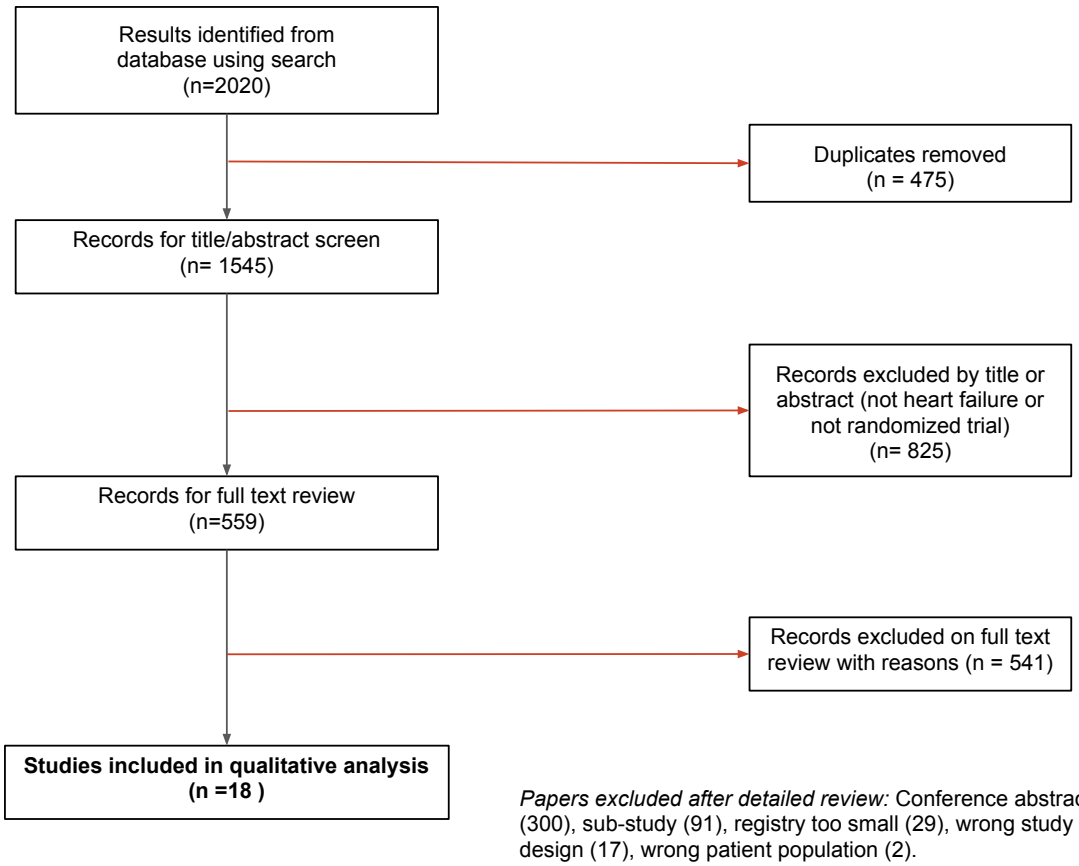

Figure 4-2: Search strategy for acute heart failure registries

4.1.2 Exclusion criteria

Trials were restricted to RCTs which enrolled at least 180 patients. Studies were only considered for oral and intravenous therapies or for existing non pharmacological interventions which may aid decongestion. Registries were restricted to those which were prospective and enrolled a minimum of 2,000 patients. For entry into the systematic review, registries were only considered if they provided some information about the clinical features of the presenting cohort.

4.1.3 Screening and record selection

All titles and abstracts were independently screened buy two reviewers (FA and AM). All identified results then underwent full-text screening followed by data extraction. Conflicts were resolved by FA and AM with NNL acting as a third arbitrating reviewer. Secondary papers published from the same the same original data sets (or primary papers preceding sub-study publications) were also reviewed to determine if they contained data pertinent to the search topic.

4.1.4 Data extraction and analysis

Search results were extracted to a Word document for further review. For each study, data was obtained for the nature of the intervention, duration of intervention, enrolment criteria, primary and secondary endpoints (with a focus on how these relate to congestion). Basic clinical data was also obtained on clinical presentation, NYHA class, radiological assessment, phenotypic classification (as per ESC guidelines on AHF), and haemodynamic profile (as per the Forrester classification method). Further supplementary clinical information was included for demographics, vital signs on presentation, laboratory findings (including baseline cardiac biomarkers [BNP, NT-proBNP], haemoglobin, serum sodium, potassium and creatinine), co-morbidities, aetiology of HF, presenting ECG, precipitating factors for the AHF hospitalisation and therapeutic profile of the patients (including oxygenation on admission, intravenous interventions,

procedural and surgical interventions, pharmacological treatment on admission and discharge). For the registry cohorts, further data on the same were also obtained for at patients presenting with de-novo and acute-on-chronic HF.

5 Systematic review of AHF trials

21 randomised trials were identified comprising a total of 25,841 patients (Table 5-1). [110,190,195-198,280-306,299]

Sixteen of these investigated novel compounds against standard medical therapy, thirteen involved an intravenous agent and three assessed novel oral therapies. Two studies looked at advanced renal interventions (ultrafiltration) compared with pharmacological therapy alone.[300] One trial looked at varying levels of dose and infusion delivery methods of diuretic therapy. One trial investigated the difference between different modalities of oxygen delivery (namely continuous positive airways pressure [CPAP] against both non-invasive BiPPV and standard oxygen treatment).

For the majority of trials, the therapeutic intervention lasted under 72 hours (in 15 out of 21 trials). Only two (EVEREST and PIONEER-HF) investigated long term continuation of therapy. The time to randomisation was specified in thirteen studies. In eleven of these, this was mandated to be within 48 hours of admission or administration of the first dose of diuretic therapy. Only two trials – CARRESS-HF and PIONEER-HF - recruited patients from a longer period out from presentation, namely 10 days.

A mandatory requirement of HFrEF was only present in 7 out of 21 trials (OPTIME-CHF, LIDO, ACTIV-in-CHF, EVEREST, SURVIVE, REVIVE-2 and PIONEER-HF). A mixed combination of either reduced LVEF or another abnormal parameter (wall motion index, elevated biomarkers) was required for VERITAS and ASCEND-HF. The cut off for defining the necessary LVEF varied from < 30% to ≤ 40%. Echocardiography was not always the pre-specified modality of assessment.

Table 5-1: Acute heart failure trial inclusion characteristics

Trial	Year	*n*	Intervention	Duration of intervention	Time to dyspnoea assessment	Time to randomisation	LVEF inclusion criteria	Biomarker cut off	De-novo patients permitted
HFrEF									
OPTIME-CHF [209]	(2002)	951	Milrinone (vs placebo) (1:1)	48 hour infusion	Baseline, Day 3	Within 48 hrs admission	LVEF <40% within 12 months	-	No
LIDO [297]	(2002)	203	Levosimendan (vs placebo) (1:1)	24 hr infusion	Baseline to 24 hrs	-	LVEF < 35% within 1 month	-	Yes
ACTIV-in-CHF [272]	(2004)	319	Tolvaptan (vs placebo) (3:1)	Oral agent for up to 60 days	Day 1 and discharge	-	LVEF < 40% in previous 12 months	-	Yes
EVEREST A and B [276]	(2007)	4133	Tolvaptan (vs placebo) (1:1)	Oral agent (long term; median 9 months)	24 hrs	Within 48 hrs admission	LVEF ≤ 40% in 1 yr	-	No
SURVIVE [208]	(2007)	1327	Levosimendan (vs dobutamine) (1:1)	24 hr infusion	24 hrs	-	LVEF < 30% 12 months	-	Yes
REVIVE-2 [207]	(2013)	600	Levosimendan (vs placebo) (1:1)	24 hr infusion	6, 24, 48 hrs and day 3 and 5.	N/a	LVHEF < 35% at 12 months	-	-
PIONEER HF [277]	(2018)	881	Angiotensin–Neprilysin Inhibition (vs enalapril) (1:1)	Oral agent, long term	-	24 hrs to 10 days	LVEF < 40% in last 6 months	BNP ≥ 400 pg/mL, NT-proBNP ≥ 1,600 pg/mL	Yes
HFrEF and HFpEF									
VMAC [278]	(2002)	489	Nesiritide (vs nitrates vs standard care) (1:1:1)	24 hr infusion	3 hrs, 24 hrs.	-	-	-	Yes
RITZ-2 [294]	(2003)	292	Tezosentan (vs placebo) (1:1)	24 hr infusion	6 hrs, 24 hrs	-	-	-	Yes
UNLOAD [280]	(2007)	200	Ultrafiltration (vs intravenous diuretics) (1:1)	UF within 48 hours	8 hrs, 48 hrs	Within 24 hrs admission	-	-	Yes
VERITAS 1 and 2 [295]	(2007)	1435	Tezosentan (vs placebo) (1:1)	24 to 72 hours	Baseline, 3 hrs, 6hrs, 24 hrs.	Within 24 hours admission	LVEF < 40% in 12 months (or wall motion index ≤ 1.2 within 12 months)	Elevated levels more than 3x upper limit of normal	Yes

Trial	Year	*n*	Intervention	Duration of intervention	Time to dyspnoea assessment	Time to randomisation	LVEF inclusion criteria	Biomarker cut off	De-novo patients permitted
3CPO [281]	(2008)	1069	CPAP (vs NIV vs standard O2 treatment) (1:1:1)	Min 2 hrs (investigator discretion)	1 hr	-	-	-	Yes
Pre-RELAX-AHF [291]	(2009)	234	Relaxin – multiple doses (vs placebo) (8:3)	48 hr infusion	6 h, 12 h, 24 h, 48 h, and days 3, 4, 5, and 14.	Within 16 hrs admission	-	BNP ≥ 350 pg/mL, or NT-proBNP ≥ 1400 pg/mL	Yes
PROTECT [283]	(2010)	2033	Rolofylline (vs placebo) (2:1)	Up to 72 hrs infusion	24 hrs, daily until discharge	Within 24 hrs of presentation	-	-	No
DOSE [203]	(2011)	308	Frusemide (continuous infusion vs bolus and high vs low dose) (1:1:1:1)	Up to 72 hrs infusion	Baseline, 72 hrs.	Within 24 hrs of presentation	-	BNP ≥250 pg/mL, NT-proBNP ≥1000 pg/mL (* exclusion specified)	No
ASCEND-HF [301]	(2011)	7141	Nesiritide (vs placebo) (1:1)	24 hrs to 7 days infusion	6 hrs and 24 hrs	Within 24 hrs of intravenous diuretic	LVEF < 40% within 12 months (or BNP/congestion criteria)	BNP ≥400 pg/mL, NT-proBNP ≥ 1000 pg/mL	Yes
CARRESS-HF [288]	(2012)	188	Ultrafiltration (vs stepped pharmacological therapy) (1:1)	96 hrs infusion	Baseline, 96 hrs, 7 days.	Within 10 days	-	-	Yes
RELAX-AHF [291]	(2013)	1161	Serelaxin (vs placebo) (1:1)	Up to 48 hrs infusion	Baseline, Days 1-5.	Within 16 hours of presentation	-	BNP ≥350 pg/mL, NT-proBNP ≥ 1400 pg/mL	Yes
ROSE [206]	(2013)	360	Nesiritide (vs dopamine)(1:1)	72 hours infusion	24 hrs and 48 hrs	Within 24 hours	-	-	No
TRUE AHF [293]	(2017)	2157	Ularitide (vs placebo) (1:1)	48 hrs infusion	-	-	-	BNP >500 pg/mL or NT-pro BNP >2000 pg/mL.	Yes
ATHENA-HF [299]	(2017)	360	Spironolactone (High dose vs Placebo) (1:1)	96 hours of oral agent	Baseline, , 48 hrs, 92 hrs	Within 24 hours of intravenous diuretic	-	BNP ≥250 pg/ml or NT-proBNP ≥1,000 pg/ml	Yes

- no data available.

HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; LVEF: Left ventricular ejection fraction; BNP: brain natriuretic peptide; NT-proBNP: N-terminal-prohormone brain natriuretic peptide; HF: heart failure; UF: ultrafiltration. OPTIME-CHF: Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure trial; LIDO: Levosimendan Infusion versus Dobutamine study. ACTIV in CHF: Acute and Chronic Therapeutic Impact of a Vasopressin 2 Antagonist (Tolvaptan) in Congestive Heart Failure; EVEREST: Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan; SURVIVE: Survival Of Patients With Acute Heart Failure In Need Of Intravenous Inotropic Support; REVIVE-2: Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy; PIONEER-HF: Comparison of Saocubitril/valsartaN Versus Enalapril on Effect on NTpro-BNP in Patients Stabilized From an Acute Heart Failure Episode; VMAC: Vasodilation in the Management of Acute CHF; RITZ: Randomized Intravenous Tezosentan study; UNLOAD: Ultrafiltration vs. IV Diuretics for Patients Hospital-ized for Acute Decompensated Heart Failure trial; VERITAS: The Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies; 3CPO: Efficacy of non-invasive ventilation in patients with acute cardiogenic pulmonary oedema: Pre-Relax-AHF: The Preliminary study of RELAXin in Acute Heart Failure; PROTECT: Placebo-Controlled Randomized Study of the Selective A_1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function; DOSE: Diuretic Optimization Strategies Evaluation trial; ASCEND-HF: Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure trial; CARRESS-HF: Cardiorenal rescue study in acute decompensated heart failure; RELAX-AHF: Relaxin for the Treatment of Acute Heart Failure; ROSE: Renal Optimization Strategies Evaluation; TRUE-AHF: Trial of Ularitide Efficacy and Safety in Acute Heart Failure; ATHENA-HF: Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure trial.

Nine studies included biomarker inclusion criterion. However, the threshold of BNP or NT-proBNP required to enter the trials were not consistent between those RCTs. Only five studies specifically excluded patients with de-novo acute heart failure. Four required the diagnosis of HF to have been made for a specific duration of time (24 hours prior to hospitalization, such as in ROSE) or the use of diuretic for a set period before unscheduled hospitalisation (at least 1 month of loop diuretic use in DOSE).

5.1 Assessment of congestion in AHF trials

Few trials mandated the presence of measures of congestion (Table 5-2, Appendix Table A-1). There was much variability in: the definitions of pulmonary congestion, the definitions of peripheral congestion and how imaging modalities were used to identify congestion.

5.1.1 Dyspnoea assessment

16 out of 21 trials included some form of dyspnoea assessment within their entry criteria. In 43 % (9 out of 21 trials) there was a mandatory requirement that the patient be hospitalised with either dyspnoea at rest, or dyspnoea on minimal exertion. In all trials the assessment was subjective based on the history of patient. Only two included an objective assessment of respiratory rate. In 3CPO, patients could be eligible if presenting with a respiratory rate of > 20 breaths per minute. In VERITAS, this was ≥ 24 breaths per minute.

5.1.2 Pulmonary congestion assessment

In 18 out of 21 trials the presence of pulmonary congestion (either from clinical examination or radiographic findings) was part of the composite entry criteria to enrol into the study. However, in only four studies was pulmonary congestion a mandatory requirement for inclusion (3CPO, Pre-RELAX-AHF, RELAX-AHF and

TRUE-AHF). For the remainder, a composite score comprising clinical features of congestion had to be met. Clinical examination usually specified rales or crepitations (12 trials), but there was usually no distinction made between basal crepitations and crepitations extending beyond the lower lung field. Five studies required the extent pulmonary rales to be recorded and documented, but only VERITAS, PROTECT and ASCEND-HF required rales of more than one-third of the lung fields to be present to meet the composite entry threshold.

Twelve studies included the use of an imaging modality to aid selection into the study. However, in each case this modality was a CXR. The radiographic features accepted included pulmonary oedema, pleural effusions or non-defined CXR features which the investigator felt could be in keeping with congestive HF, but this was not consistent between each study. No use of either chest or cardiac ultrasound was permitted to affect recruitment. No trials utilised a core lab to validate or standardise CXR findings.

Table 5-2: Summary of congestion requirements for enrolment into acute heart failure trials

Enrolment Criteria	Number of trials		
	Mandatory	Non-mandatory (composite score)	Not included
Dyspnoea	9	8	4
Pulmonary Congestion	5	13	3
Peripheral Congestion	0	11	10
Objective Imaging	47	9	7

Table 5-3: Summary of congestion requirements for end points in acute heart failure trials

End Point Criteria	Number of trials		
	Primary †	Secondary	Not included
Dyspnoea	9	9	3
Pulmonary Congestion	0	7	1
Peripheral Congestion	2	8	10

† Includes primary and co-primary end points

5.1.3 Peripheral congestion assessment

10 out of 21 trials collected clinical confirmation of peripheral congestion as part of their composite entry criteria. However, peripheral congestion was not a sole mandatory inclusion criterion – patients without peripheral findings could still be enrolled if there was sufficient evidence of other features of congestion. Peripheral oedema was the most commonly described clinical sign of peripheral congestion (9 trials), followed by ascites (2 trials) and increased weight gain (only 1 study). As with pulmonary congestion, there was no uniform method to determine varying severities of peripheral oedema. Two studies (PROTECT and CARRESS) made reference to an oedema score (which was rated from 1 to 4 +) but this was not specifically defined within the individual study protocols. EVEREST described oedema in terms of being either absent, slight, moderate or marked. However, again whether this referred to the extent of oedema induration or distribution was not detailed. Only REVIVE-2 made reference to oedema involving sequentially progressive lower limb structures (legs, sacral, lumbar areas) while in PROTECT, either "≥2+" peripheral oedema or pre-sacral oedema could be considered clinical features allowing inclusion into the study.

7 studies included JVP assessment as part of the inclusion criteria. However, there was much heterogeneity with regards to the threshold at which the JVP should be considered suitably elevated. Variations extended from a measurement of > 6 cm above the suprasternal notch to ≥ 10 cm. ACTIV-in-CHF and VMAC, both specified "raised JVP" and "JVP distension" but did not lay down any set elevation point, allowing the clinician to determine what constituted suitable elevation at their own discretion.

Of note, no study incorporated imaging assessments - such as IVC ultrasound - into the eligibility assessment of peripheral congestion.

Just two studies – PIONEER-HF and – left the congestive criteria completely to the discretion of the clinician and specified only the presence of "signs and symptoms of heart failure" or "fluid overload".

5.2 End points and congestion in AHF trials

18 of 21 clinical trials incorporated dyspnoea into either a primary or secondary end point (Table 5-3, Appendix Table A-2). In almost half of these cases (nine trials), dyspnoea was either a primary, primary composite or co-primary end point. The Likert scale was the most common assessment modality (ten studies), followed by a visual assessment scale (VAS) (seven studies) usually with some form of quantification of the area under the curve. RELAX-AHF utilised both scoring systems for dyspnoea evaluation. Only REVIVE-2 utilised a composite end point of "worsening heart failure" as a primary end point which had a dyspnoea measurement integrated into this.

By contrast, measures of pulmonary congestion were not part of any primary end points. In six studies, a variety of different assessments of pulmonary oedema were performed (including orthopnoea and presence of pulmonary rales) and were incorporated as either solitary secondary end points (half of studies) or composite secondary end points. As before, there was no standardised method of recording the degree of congestion on chest examination.

Similarly, a minority of studies incorporated measures of peripheral or non-pulmonary congestion into the primary or secondary end points (eight studies). In the ACTIV-in-CHF, UNLOAD and CARRESS-HF, weight loss was recorded at 24, 48 and 96 hours post-randomisation respectively and formed the primary endpoint. In DOSE and ROSE, weight loss at 72 hours formed the secondary end points. The assessment of peripheral congestion remained variable as before. EVEREST utilised a scoring system dependent on the extent of pitting to grade peripheral congestion, but most other studies merely allowed the investigator to record whether there had been any improvement in limb swelling.

Objective biomarkers were not sampled routinely. Only seven studies utilised either BNP (SURVIVE, REVIVE-2, UNLOAD) or NT proBNP (CARRESS-HF, ROSE, TRUE-AHF and PIONEER HF). With the exception of the Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) and PIONEER-HF trials, these results were not incorporated into the primary end point.

5.3 Presenting features of congestion in patients in AHF trials

A full summary of the clinical features of presentation was not provided by any study (Appendix Table A-3). In eleven of 21 studies, there was no record of either the dyspnoea status of the patient, the clinical findings of pulmonary congestion or the incidence or extent of peripheral oedema.

5.3.1 Presentation with dyspnoea and pulmonary congestion

In six studies (VMAC, VERITAS, 3CPO, Pre-RELAX AHF, ASCEND HF, RELAX AHF) all patients recruited – 100% - presented with dyspnoea at rest. In ACTIV-in-CHF, ATHENA-HF and EVEREST this figure was only marginally lower (89 %, 83 % and 70 % of all patients). Dyspnoea on exertion was not a specifically recorded symptom in any of the clinical trials.

The recording of pulmonary congestion was extremely variable. Only eleven studies provided data on lung assessment, and only two of twelve (REVIVE, PROTECT) detailed any breakdown of the degree of pulmonary rales (i.e. basal, more than one-third of lung fields, more than two thirds of lung fields). In PIONEER-HF – a study which recruited later from the point of admission – the overall incidence of pulmonary oedema was lower than other RCTs (at 33%).Presentation with peripheral congestion

In only half of the trials was there any recording of peripheral oedema. Documentation was inconsistent with no standard grading mechanism. DOSE and PROTECT used an induration scale to determine severity, whereas REVIVE detailed the extent of peripheral swelling in more detail (classifying oedema of the limbs separately from that which extended to the sacral and lumbar regions). Other markers of peripheral congestion (weight gain, hepatomegaly, abdominal swelling, ascites) were not reported at all.

Elevated JVP – a component of the composite entry criteria for most studies – was reported in just under half of studies (ten trials). The cut off again was

variable from 6 cm of H_20 to > 10 cm of H_20. In six of these trials which did report data, over 70% of patients presented with a positive elevated JVP.

5.3.2 Presentation by imaging findings and ESC phenotype

CXR findings were only detailed in four cases (VERITAS, 3CPO, Pre-RELAX-AHF, RELAX-AHF) and a high incidence of positive findings of radiographic pulmonary congestion were noted (83 - 100%).

No AHF trial reported the presenting clinical syndrome in a manner as recommended by successive ESC Heart Failure guidelines.[1,17]

5.4 Baseline clinical characteristics of patients in AHF trials

The median age of all trial patients from the table was 66.5 years (range 59-78). In only five studies was the mean age greater than 70 years. (Appendix Table A-4)

The presence of respiratory rate was recorded only in PROTECT and RELAX-AHF. Baseline natriuretic peptides were fairly varied. BNP measured in six studies ranged from 734 to 7156 pg/ml, NT-proBNP measured in eight studies ranged from 3000 to 7439 pg/mL.

In nine of ten trials that reported data on aetiology, the commonest cause was ischaemia. However, as the majority of trials tended to exclude patients with an ACS, only the 3CPO study reported a significant number of patients presenting with this condition (22%). With the exception of VERITAS, VMAC and RITZ-2, the precise non-ischaemic aetiologies of each patient were not reported in the literature.

The four studies with the highest rates of pulmonary oedema or mandatory clinical or radiological congestion criteria also had the highest average systolic blood pressure (SBP) (132, 142, 148 and 162 mmHg for the VERITAS, RELAX-AHF, Pre-Relax-AHF and 3CPO respectively).

From the reported data, it is difficult to ascertain precisely what number of patients within each cohort were new presentations of acute de-novo HF. For the eight studies that did report data, the percentage of patients with acute-on-chronic decompensated HF ranged from 42 to 88%. The extent of previous HF hospitalisation within 12 months was also extremely variable (ranging from 31 to 95%, from RELAX-AHF and PROTECT respectively).

The initial treatment modalities on admission were also variably described – possibly as most patients received an intravenous intervention very close to the point of randomisation. The majority of patients – where data was available – received some form of intravenous diuretic. These was also variation in the extent of nitrate utilisation in these patient groups. In RELAX-AHF, only 7% of patients received an intravenous vasodilator. In the 3CPO trial, this number was higher at 88%. However, the other five trials which recorded nitrate use, all noted pre-randomization usage rates of 9 to 36%.

RITZ-2 reported a fairly low rate of diuretic use (41 to 56%) but this was only reflective of intravenous administration in the last 24 hours and patients were not recruited immediately on hospitalisation. 3CPO, VERITAS and RELAX-AHF all reported higher rates of diuretic administration (over 89% of patients). Use of inotropic agents appeared low (dobutamine 0.5 to 10%, dopamine 2 to 8%) but as before many studies did not report any final data on these parameters.

5.5 Discussion

In AHF trials, indicators of congestion were incompletely recorded. Few trials mandated the presence of peripheral or central congestion. Measures of congestion played a minor role as primary end points. No studies incorporated imaging modalities other than a CXR and almost used dyspnoea as a key surrogate symptom of congestion. Further examination of the literature does throw into question whether this approach is robust enough for clinical studies.

5.5.1 Limited reporting of congestion

This review of AHF trials demonstrates that there continues to be marked variation in the reporting of congestion. The time at which pulmonary and peripheral congestion were assessed was also not consistent between studies. Whether clinical examination is taken at the point of admission or at the decision to hospitalise (often after diuretic therapy) could affect the extent to which clinical signs – particularly pulmonary congestion – would continue to be present. Symptoms like orthopnoea were reported in a very variable manner with no transparent approach to determining the manner of assessment. In PROTECT, orthopnoea was classified according to whether 1, 2 or 3 pillows were required to alleviate the symptom. In ROSE and DOSE, the prevalence was detailed but without any pre-specified definition.

In most cases, indicators of congestion were reported as part of a composite score which itself may be biased towards different causes of HF (for example, towards right sided heart signs). Additionally, the extent of decongestion after therapy was also not consistently recorded in AHF trials. As different congestive features correlate differently to risk, failure to record these key parameters makes it becomes difficult to assess the varying risk profiles of the cohorts within each trial.[11,302]

5.5.2 Under-utilisation of adjunctive imaging modalities

In clinical trials, a CXR was the only imaging modality utilised to assess pulmonary oedema. In 3CPO, ASCEND-HF, RELAX-AHF and TRUE-AHF, CXR findings of congestion were mandatory elements of the inclusion criteria and in seven other studies they were also a component of the composite scores used to select patients. In none of these trials was a core-lab utilised to validate the diagnosis. Other modalities such as lung and IVC ultrasound were not utilised to determine whether decongestion had been achieved.

As several trials did not exclude de-novo AHF admissions and 11 trials did not require echo assessment of LVEF (and 7 further trials did not require echo nor

natriuretic peptides to qualify for enrolment), there is a probability patients were recruited who did not possess true congestive HF.

The use of better imaging assessments of congestion within inclusion criterion could have helped enrol populations with more to gain from investigative therapies.

5.5.2.1 Variability of CXR congestion requirements

Between clinical trials there remained a variability in the extent of radiological features required to cross the threshold to enter AHF studies. Some trials specified “interstitial oedema” (pre-RELAX AHF) and others “pulmonary oedema or pleural effusions” (CARRESS-HF). It has been established that these CXR changes are not uniform and can occur at different elevations of PCWP.[75,154] To compound this, no core labs were utilised to standardise or validate CXR assessments, which is surprising given the interobserver variability which exists in this reporting method - even amongst specialists. [156,157,158]

5.5.2.2 Radiological congestion and outcomes

As residual clinical congestion has been associated with adverse outcomes, residual radiological congestion could also potentially provide relevant information pertaining to the risk profile of patients and uncover any uncorrected haemodynamic state.[118] However, to date this data remains incomplete. Residual radiological congestion was also not a feature of any clinical trial end point nor noted within any of the major AHF registries. It has been recognised that radiological congestion in the setting of acute MI can be a powerful predictor of mortality.[303] However, the CXR does not completely correlate with haemodynamic congestion, and so more objective imaging such as LUS may be more accurate in identifying residual fluid overload. [59,155]

5.5.3 Imbalanced focus on dyspnoea

This systematic review strongly demonstrates the unbalanced and subjective measurement of dyspnoea. The presumption that changes in breathlessness

closely track congestion and cardiovascular risk may have been a fundamental misconception that has led to persistently neutral outcomes in AHF trials.[102]

5.5.3.1 Dyspnoea is over-utilised in enrolment and end point criteria

AHF trials have shown marked bias towards 'dyspnoea at rest' as the key gatekeeper symptom for entry into clinical studies and for assessing efficacy as a primary end point. In almost half of clinical trials (9 out of 21), breathlessness was incorporated as a mandatory inclusion criterion. In 18 out of 21 it formed a component of the end point (and in 9 of these studies it was either a primary or co-primary end point). Even pulmonary congestion was not as heavily weighted – in only four studies were pulmonary rales mandatory for inclusion and in none were the endpoints primary. Furthermore, in no AHF trial was a symptom of peripheral congestion mandatory for enrolment nor part of the primary end point. In retrospect this may explain neutral trial outcomes as emerging evidence suggests that hospital stay and mortality rates are higher in patients with more severe peripheral oedema.[302] Thus the population characteristics of trials and their assessments of the interventions applied may have been mis-centred around one very limited assessment of congestion.

5.5.3.2 Dyspnoea assessment remains subjective

With the exception of VERITAS and 3CPO, there was no objective measure of dyspnoea – such as respiratory rate or demonstrable proof of oxygen desaturation on pulse oximetry. In these trials, serial measures of dyspnoea comprised subjective patient driven feedback methods, such either Likert scales or VAS.

5.5.4 Criticisms surrounding dyspnoea assessment

Though not captured in this systematic review, various insights from post-hoc analyses and substudies in the literature appear to indicate that dyspnoea assessments are not necessarily robust and that changes do not consistently completely correlate with clinical outcomes.

5.5.4.1 Dyspnoea may resolve rapidly without intervention

The natural progressive history of dyspnoea during an HF admission appears to be one of rapid resolution with standard care. The literature indicates that in many cases, diuretic administration achieves fairly rapid pulmonary decongestion and improvements in overall symptom burden.

In SURIVE, 82% of patients experienced at least a mild improvement in dyspnoea in the placebo group.[208] In RELAX-AHF, 63% of patients reported at least moderate improvement in symptoms as assessed by changes in Likert scores at just 24 hours.[290] A similar pattern was seen in the placebo groups of PROTECT (41% reporting moderate or marked improvement in breathlessness by day 2 and 3) and ACTIV-in-CHF (50% improvement in dyspnoea by day 1).[272, 283] Earlier and more rapid changes in symptoms were also observed at an even earlier timepoints in VMAC.[278,304] 50% of patients who did not receive the active intervention felt that they had symptomatic benefit from standard therapy within just three hours. Though a few studies did report the frequency of resistant symptoms these numbers remained relatively low. In REVIVE-2, the rate of "persistent or unresponsive" dyspnoea in the standard care arm was less remarkable at 18% after just 24 hours.[207]

5.5.4.2 Dyspnoea scores may be unreliable

There also remains no consensus around a reliable method of assessing dyspnoea in AHF trials.[305]

The reported findings can vary depending on factors such as the degree of recumbency of the patient and on the nature of the scoring system used. A patient in a fully supine position may experience a degree of orthopnoea or obesity induced respiratory restriction resulting in a higher baseline score and receive less improvement when compared to one who is sitting upright. As assessments remain non-standardised it is not clear if these factors remain confounders.

Furthermore, in ASCEND-HF, notable geographical differences were observed in dyspnoea relief. The greatest improvement was seen in Latin America (57% of patients) and lowest In Central Europe (36%).[306] It is unclear if the differences are the result of an actual phenotypic variation of the presenting cohort by region, or treatment strategies, or – more problematically in this instance – significant variations in the cultural perceptions of dyspnoea.

In MEASURE-AHF, a multi-centre cohort with hospitalized HF were prospectively assessed with both with patient-reported scores and physician clinical assessments to review their reliability.[117] As expected, dyspnoea improved rapidly in the first 24 hours, but tailed off beyond this point. VAS measures of dyspnoea were more gradual and persistent throughout the course of the hospital stay and correlated better with changes in clinical examination. However, it was noted that clinical signs of HF – notably pulmonary and peripheral oedema – resolved more completely than clinical symptoms. 72% patients were clinically free of oedema by day 7 (or discharge) but only 52% of patients reported improved dyspnoea. This lends suspicion to concern that self-reported breathlessness by patients may be influenced by multi-factorial inputs and once initial symptom relief is achieved, patient perspectives become more dissociated from actual congestion. A retrospective review of symptoms from the ESCAPE trial also speculated that patients may mis-report fatigue as difficulty breathing, as both were pre-dominant symptoms and improved substantially in either arm of the trial.[106]

5.5.4.3 Dyspnoea may not be a robust surrogate for clinical outcomes

Whilst dyspnoea remains a symptom which may trigger medical contact for AHF and symptom relief remains critical to a patients perception of quality of life, it is debatable whether dyspnoea per se is an appropriate therapeutic target.[307] From a pathophysiological standpoint, dyspnoea can induce anxiety and increase sympathetic drive, consequently driving further haemodynamic deterioration if unchecked. However, there is no current evidence to suggest that targeting this consequence of congestion with more than basic diuretic therapy improves overall survival.

5.5.4.4 Dyspnoea relief does not always predict improved mortality

Further analysis of ASCEND-HF suggested that whilst dyspnoea is an important determinant of 30 day mortality, this finding was not sustained at 180 days.[301] This may be a reflection of multiple other serious cardiac and non-cardiac processes which result in cardio-respiratory compromise (such as infection or ischaemia). These might contribute to refractory symptoms and poorer short term outcomes, but are not readily modifiable by investigational HF therapies.

In pre-RELAX-AHF, successful dyspnoea relief at 24 hours did not correlate significantly with reduced mortality at 30 or 60 days.[116] In PROTECT-pilot, whilst a mortality benefit was observed at 30 and 60 days with dyspnoea relief at 72 hours, there was no clear association with the composite 60-day endpoints of mortality and hospitalisation.[308]

5.5.5 Implication for AHF trial outcomes

5.5.5.1 Potential futility of targeting dyspnoea

It remains debatable whether trials should employ such a heavy focus on a symptom which rapidly improves with standard therapy. This emerging oversight may be a large driver towards the neutrality of many AHF studies. To find a beneficial effect of a potential therapy upon a symptom which is already resolving will be difficult. Additionally, the overall clinical benefit for such minor improvements also are yet to be determined. Those patients with refractory respiratory symptoms against whom these treatments are targeted may also be a subgroup that are unlikely to respond to a short infusion of therapy, and as such the majority of interventions which cease after 48 hours will not begin to modify the pathophysiology of this cohort.

It should be noted that in the most recent and positive PIONEER-HF trial, the randomisation period was between 24 hrs to 10 days post-presentation to hospital.[277] This window that was much wider than most other AHF studies. In PIONEER-HF, it is notable that the prevalence of pulmonary oedema was lower than all of the other studies (33% at randomisation). The finding of peripheral

oedema was higher (62%) and is comparable to other trials. Dyspnoea was also less central to enrolment and in the final end point analysis, and may be the correct approach for future AHF trials.

5.5.6 Conclusion

This systematic review has demonstrated how AHF trials have structured their enrolment criteria and end points in an unbalanced fashion to revolve around dyspnoea. Evidence from the broader literature indicates that dyspnoea does not hold a robust correlation with clinical outcomes. Central and peripheral congestive signs should be considered as inclusion criteria to provide greater degree of balance. Resolution of congestion may be a more appropriate target of clinical trials, though this is yet to be proven definitively. The incorporation of adjunctive imaging modalities - such as LUS - into study protocols can provide a route to achieve this.

6 Systematic review of AHF registries

18 registries were identified which investigated AHF presentations and presented data on clinical presentation and patient characteristics (Table 6-1, Appendix Table A-5). [104-105,184, 316-342]

These registries comprised a multi-continent set of 238,651 patients from North America, Europe and Asia. 12 registries were international and only six focused on populations within a single nation state (Beijing AHF – China; Kor-AHF – Korea; IN-HF – Italy; RO-AHFS – Romania; RICA – Spain; KCHF – Korea).

6.1 Assessment of congestion in AHF registries

In every study, the assessment of clinical signs for both pulmonary and non-pulmonary congestion was left to the discretion of the clinician. In particular, clinical signs such as 'raised JVP' did not have a pre-specified definition or method for assessment. 7 registries (EAHFE, AHEAD, ADHERE, HEARTS, RO-AHFS, EHFS-II and RICA) did not report any data on signs or symptoms.

6.1.1 Dyspnoea in AHF registries

With the exception of Gulf CARE (98% of patients) the incidence of dyspnoea at rest varied from as low as 34 to 44% in the larger OPTIMIZE-HF and ADHERE-AP registries, to 73% in ALARM-HF. Most patients also had a degree of accompanying pulmonary oedema, but this was variable (61% to 92%). Dyspnoea on exertion appeared to be more common – though was only recorded in four registries. In OPTIMIZE-HF, 61% of patients presented as such, but in KCHF and the much larger ADHERE and ADHERE-AP studies, this was much higher at 95%. Only ADHERE, OPTIMIZE-HF and ADHERE-AP reported on dyspnoea at rest and dyspnoea on exertion. In all 3, the rate of exertional breathlessness was greater than breathlessness at rest (95% vs 34%, 61% vs 44%, 95% vs 40% for ADHERE, OPTIMIZE-HF and ADHERE-AP respectively).

6.1.2 Pulmonary and peripheral congestion in AHF registries

No study specified any set method for assessing pulmonary rales or peripheral oedema. Unlike AHF trials, no differentiation was made for patients with only basal crepitations versus those with congested lung fields extending up to the apices.

Similarly, for peripheral oedema, swelling that was clinically present only at the ankles or collecting more extensively towards the upper thighs were both recorded as a binary “yes” or “no”. The severity of congestion and oedema were not otherwise documented with any further descriptive detail.

Table 6-1: Summary of clinical presentations of patients in acute heart failure registries

	Summary of Registries	Registries reporting data
Year	2001-16	-
Patients	185,886	-
Clinical Congestion (pulmonary)		**-**
SOB at rest	34 - 98	6
Pulmonary rales	61 - 92	12
Orthopnoea	27 - 80	6
PND	15 – 71	5
Clinical Congestion (Peripheral)		
Peripheral oedema	43 - 82	10
Weight gain	25 - 26	2
Hepatomegaly	25 - 27	2
Ascites	12 - 14	3
Raised JVP	17 - 78	7
Clinical Congestion (Other)		
SOBOE	61 - 95	4
Fatigue	32 - 57	3
Third heart sound	31 - 37	3
Cold extremities	11 - 56	5
Hypoperfusion	9 - 18	3
NYHA Class		
I	2 – 24	3
II	2 - 63	7
III	23 - 44	6
IV	32 - 63	9
Radiological Assessment		
Pulmonary congestion on CXR	9 - 85	5
Pleural effusion on CXR	19 - 46	3
Cardiomegaly on CXR	82 - 89	3

Categorical values are expressed as percentage
† = combined for NYHA class I and II. § = combined for NYHA class III and IV. - = no data available
SOB: shortness of breath; PND: paroxysmal nocturnal dyspnoea; SOBOE: shortness of breath on exertion; JVP: jugular venous pressure; CXR: chest X-ray.

6.1.3 Variability of congestion reporting

The key congestive signs of both pulmonary and peripheral congestion were reported with variable completeness between registries.

6.1.3.1 Pulmonary congestion

Data for “pulmonary rales”, the main clinical sign of pulmonary congestion, was published in only ten registries. There was marked variation in incidence between the registries in which this was recorded (61 to 92%).

Other well recognised and common symptoms of pulmonary congestion were variably described, with little standardisation of data collection. Central pulmonary symptoms of congestion had a wide range of incidence between registries (orthopnoea 27 to 80%; PND 15 to 71%). Registries with the lowest rates of orthopnoea unsurprisingly also had lower reported rates of PND (e.g. OPTIMIZE-HF reported that orthopnoea was present in 15% and PND in 27% of patients, KCHF reported orthopnoea in 80% and PND in 71% of patients).

6.1.3.2 Peripheral congestion

Data for peripheral oedema, the main clinical sign of peripheral congestion, was provided in only 10 registries. The reported rates varied from 43% to 82%. In ALARM-HF and Gulf CARE, 43% and 54% of patients were reported to have presented with peripheral oedema though only 25% and 26% were described as having experienced weight gain. This emphasises the point that hospitalisation arising from pulmonary congestion can occur due to fluid redistribution as well as fluid accumulation.

Other signs of peripheral congestion were not prominently reported either. “Weight gain” was recorded in 3 studies (ALARM-HF, Gulf CARE and a substudy of RO-AHFS) but was not a very common symptom (25% to 26% of patients). It was not clear how much weight gain was required for it to be substantial and

recorded, nor how this was assessed (i.e. patient reported or from objective evidence). In a RO-AHFS sub-study which exclusively looked at patients who presented with pulmonary oedema, only 45% presented with peripheral oedema. This was much lower rate when compared to 6 of the other 7 registries. The presence of hepatomegaly and ascites were also only recorded by three registries.

JVP elevation was recorded in just 7 studies. A positive finding of JVP distention varied greatly between each cohort ranging from 17 to 78%.

6.2 Presenting clinical characteristics of patients in AHF Registries

6.2.1 NYHA and Killip class based classification

The use of NYHA functional classification was also not consistently recorded. It is difficult to identify any specific trends across the AHF registries. In 6 of 9 studies (ATTEND, Beijing AHF, Gulf CARE, Kor-AHF, ADHERE, KCHF), the majority of patients presented with NYHA class III-IV symptoms. In 3 studies, (EAHFE, RICA, KCHF) the majority of patients were NYHA class I-II (63-76% of patients).

It should be noted that registries did not provide data categorising patients with AHF according to the Killip classification system.

6.2.2 Clinical phenotype based classification

Registries utilised two different methods in attempts to classify AHF patients into more discernible groups: phenotypic classification based on either pathophysiology or based on haemodynamic profile (Table 6-2, Appendix Table A-5).

The first type is based on clinical syndromes as defined by the 2008 ESC Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure.[12] These divided patients into 7 sub-categories based on presenting phenotype:

decompensated congestive HF, pulmonary oedema, cardiogenic shock, hypertensive HF, RHF, high output HF and ACS induced HF. The guidelines for each category are laid out in the original reference documents and are discussed previously.[12] The registries did not elaborate further on how this classification may be applied. In each case – as with interpretation of clinical signs – it was left to the discretion of the investigator to decide which phenotypic category each patient should be assigned to.

Eight of 18 registries reported data on phenotypic classification based on ESC recommendations (ALARM-HF, AHEAD, EAHFE, ESC-HF-LT, ESC-HF Pilot, EHFS-II, IN-HF and RO-AHFS). In each study, "decompensated congestive HF" was the most common presentation (ranging from 39 to 77% of cases). "Pulmonary oedema" was the second most common (13% to 37%). However data was not always reported for each sub-type.

6.2.3 Haemodynamic classification

Where haemodynamic profiles were recorded, the Forrester method of classification was used.[139] Within this, patients were placed into four recognised sub-types "warm and dry", "warm and wet", "cold and dry" and "cold and wet", all based on the quality of distal perfusion and the extent of congestion. However, only four registries out of 18 reported data for their cohorts in this manner. The most common presentation was "warm and wet" (70 to 82 % of patients), followed by "cold and wet" (11 to 17%), "warm and dry" (6 to 15%) and "cold and dry" (1 to 3 %). As with the ESC classification system, investigator discretion determined how the patient was classified. No adjunctive invasive methods were utilised to assist this process.

6.2.4 Imaging guided classification

Four registries reported the use of CXR findings from their patient cohorts (Beijing AHF, EAHFE, RO-AHFS and RICA). While most patients appeared to present with cardiomegaly (75% in EAHFE and 89% in RICA) the prevalence of actual pulmonary congestion was very variable (9% in RICA and 85% in Beijing AHF). Of note, no studies incorporated any other imaging modalities – such as lung ultrasound – when trying to determine the nature of congestion.

Table 6-2: Summary of baseline clinical profiles of patients in acute heart failure registries

	Summary of Registries
Clinical Syndromes	
Decompensated congestive HF	44 - 77
Pulmonary oedema	13 - 37
Cardiogenic shock	2 - 14
Hypertensive HF	2 – 18
Right HF	3 – 9
High output HF	1 -3
ACS-HF	2 – 14
Haemodynamic profile	
Warm and dry	6 – 15
Warm and wet	70 – 82
Cold and dry	1 – 3
Cold and wet	11 - 17

All continuous values are given as the mean unless stated otherwise. Categorical values are expressed as percentage
HF: heart failure; ACS: acute coronary syndrome.

6.3 Outcome reporting for patients in AHF registries

Outcome reporting was variable between registries (Table 6-3). The rates of worsening HF were recorded in only two studies, in-patient mortality in 16 studies, re-admission rates in 5 and 1-year all-cause mortality in just eight. It should be noted that the time windows for capturing the rates of re-admission and mortality were also not uniform.

'Worsening HF' was also variably defined between studies and not always clearly consistent with changes in congestion. In KCHF this was described as "additional intravenous drug treatment for HF, haemodialysis, or mechanical circulatory or respiratory support, occurring >24 h after therapy initiation". In OPTIMIZE-HF, the changes in congestive symptoms were instead recorded (as either: "worse", "unchanged", "better, symptomatic" or "better, asymptomatic").

The in-patient mortality rate was found to vary from 5% to 13%, whilst the median length of stay varied from 5 to 21 days.

6.3.1 Outcome by clinical phenotype

Only seven studies published outcomes by presenting clinical syndrome (AHEAD , ESC-HF-LT, ESC-HF Pilot, EHFS-2, IN-HF and RO-AHFS). A comparison between patients presenting with central and peripheral congestion was not possible because the ESC classification method does not contain a separate sub-category for 'peripheral oedema' as it does for 'pulmonary oedema'.

However, a comparison was attempted using data in AHEAD and ESC-HF-LT. Patients presenting with "pulmonary oedema" were classified as such and their outcomes were directly examined. For patients presenting with peripheral oedema, the classification of "right heart failure" was utilised instead (as this most closely matched a predominantly peripherally congested patient). The shortcomings of this should be noted; right heart failure is a classification for congestion arising from isolated RV dysfunction and the overlap with

peripherally congested patients with LV systolic dysfunction is likely to be limited.

In ESC-HF-LT, the rates of adverse outcomes were higher in all categories for patients with peripheral over central pulmonary congestion, including in-hospital mortality (10% vs 6%), re-admission with HF (31% vs 21%) and all cause one year mortality (34% vs 28%). A similar pattern was seen in the AHEAD (in-patient mortality 17% vs 7%).

Table 6-3: Summary of clinical outcomes for patients in acute heart failure registries

	Summary of Registries
In-hospital mortality	4 - 13
Rate with pulmonary oedema	6 – 7
Rate with peripheral oedema	6 – 17
Re-admission rate (1 year)	40 – 47
Rate with pulmonary oedema	21
Rate with peripheral oedema	31
All cause Mortality (1 year)	17 – 32
Rate with pulmonary oedema	28
Rate with peripheral oedema	34
Length of stay (days)	5 – 21
Rate with pulmonary oedema	-
Rate with peripheral oedema	-

All continuous values are given as the mean unless stated otherwise. Categorical values are expressed as percentage
- no data available

6.4 Baseline clinical characteristics of patients in AHF registries

6.4.1 Age, ejection fraction, previous AHF history

The median age of all the registry patients from the table was 71.5 years (range 59-80) (Appendix table A-3). For almost three quarters (11 out of 16) of registries for whom published data was available, the mean or median average for the patient cohort was ≥ 70 years of age.

In the registry population, the average ejection fraction reported in the studies ranged from 35 to 51 %. Half of all registries (eight) reported an average (mean or median) heart rate ≥ 90 beats per minute. By contrast, only 1 AHF trial reported such an elevated level of tachycardia from its enrolled patient cohort.

Only two registries noted the numbers of patients presenting with a previous AHF hospitalisation. In ATTEND and KCHF, these were both at 36%. 9 studies did report the number of patients presenting with a known HF diagnosis, but did not distinguish if this syndrome was HFpEF, HFmrEF or HFrEF. In these cases, the prevalence of previous HF diagnosis varied from 36% to 88%.

6.4.2 Aetiology and precipitating factors

The underlying aetiology of HF was reported in 12 out of 18 studies. However, there was no unifying methodology for arriving at this. In each case, the assessment was left to the discretion of the clinical teams. There was also no published consensus around how the aetiology of each was defined (e.g. idiopathic dilated cardiomyopathy). Ischaemia was the most common cause of HF (27 to 61% of cases). The next most prevalent were hypertension (4 to 44% of cases), cardiomyopathy (15 to 25%) and valvular heart disease (9 to 36 %).

The precipitating factor for AHF was infrequently reported; only nine registries reported any substantive data. ACS appeared to the be most recurrently common cause for hospitalisation. In KOR-AHF, GULF CARE, Beijing AHF, ESC HF

LT, EHFS-2, ALARM HF, HEARTS and IN-HF all reported the incidence of ACS precipitating AHF from 26 to 42%. Other common precipitants included arrhythmia (6 – 30%), infection (16 – 35%), uncontrolled hypertension (3 – 20%) and poor medication adherence (6 – 22%).

Given the heterogeneity of precipitating factors, therapeutic interventions targeting congestion in AHF patients will require a personalised approach incorporating an appreciation of the specific clinical circumstances of each patient. Whilst current approaches dictate broad interventions in terms of oxygen therapy, diuretics and vasodilators, it is clear that trial evidence must help answer the question of how particular causative aetiologies should be managed.

6.5 Acute therapeutic interventions in AHF registries

The most common approach to alleviating congestion in the registry population remains through the use of diuretics and vasodilators, with ultrafiltration, MCS and percutaneous interventional procedures being reserved for a minority of cases. With the exception of KCHF, AHF registries did not provide substantive data on changes in congestive symptoms in response to medical therapy.

Intravenous diuretics were used in the majority of acute admissions for patients with acute decompensated HF (13 registries reported data; administration rate between 70 to 98%). Intravenous vasodilators were also frequently used but variably so (15 studies reported data; administration rate between 14 to 78%) (Appendix Table A-6). Inotropic agents also formed part of the treatment regime for some patients but were less commonly selected (2 to 33%). Of these, dobutamine, dopamine and adrenaline were the most widely utilised.

Invasive respiratory measures such as CPAP or IPPV were not as common. The use of CPAP was noted in a minority of cases (2 to 23%), whilst intubation was performed less frequently (1 to 16% of patients).

Renal replacement or renal supportive measures such as haemodialysis and ultrafiltration were noted in seven studies (1 to 8%). Use of supportive bridging

interventions such as intra-aortic balloon pumps (IABP) were infrequent (0.2 to 5%). LVAD implantation was performed in only a very small minority of patients (0.1 to 0.4 %), but data were only available from 2 registries.

More invasive cardiology procedures were performed in a minority of AHF admissions. Percutaneous coronary intervention was required in 0.1 to 13% of AHF admissions (although the angiography rate without intervention was not accessible). Device implantation (either permanent pacemaker, implantable defibrillator or cardiac resynchronisation therapy) was infrequent, and ranged from 0.01 to 10%. Acute valvular surgery was required in only 0.3 to 4% of patients. However, in common with all the above described interventions, most registries did not supply data.

6.6 Comparing patients with de-novo acute heart failure and acute-on-chronic decompensated heart failure in acute heart failure registries

Six AHF registries provided data comparing patients who presented with de-novo acute heart failure (DN-AHF) against those with a known history of chronic HF who were hospitalised with decompensation (i.e. an acute-on-chronic decompensated heart failure [AC-DHF] cohort)(Table 6-4). These registries were: EHFS-2, ALARM-HF, AHEAD, IN-HF, Gulf CARE and RICA. This comprised a total of 23,096 patients involving hospitalisations from 2006 to 2016. Of these, 9,759 (42%) were new DN-AHF presentations and 13,337 (58 %) were AC-DHF presentations. The precise definition of “de-novo” was taken as per the ESC Guidelines on Acute Heart Failure, namely the episode was required to have been the first presenting event of HF.[1]

Table 6-4: Summary of clinical features of de-novo versus acute-on-chronic decompensated heart failure patients

Subgroup	**DN-AHF**	**AC-DHF**
n	**9759**	**13,337**
Age (years)	57 - 71	70
Male	48 – 63	46 - 64
SBP (mmHg)	130 - 142	129 – 137
HR (beats per minute)	93 - 95	82 – 95
Clinical Presentation (Pulmonary)		
SOB	97	99
Orthopnoea	74	83
PND	56	71
Signs of pleural effusion	16	21
Pulmonary crepitations	81 - 92	76 – 91
Clinical Presentation (Peripheral)		
Peripheral congestion	49	61
Abdo/limb swelling	32	55
Tender liver	22	31
Ascites	7	21
Weight gain	19	32
Clinical Presentation (Other)		
Raised JVP	46	56
Third heard sound	39	36
Cold extremities	10 - 29	11 – 24
Peripheral hypoperfusion	11	12
HF Classification		
Cardiogenic shock	7 - 19	2 – 11
Pulmonary oedema	26 - 40	10 – 35
Hypertensive HF	6 - 11	3 - 11
Right Heart Failure	3	3
NYHA Class		
I	3	3
II	20	20
III	40	46
IV	20	20

All continuous values are given as the mean unless stated otherwise. Categorical values are expressed as percentage

† median, ‡ combined values for NYHA class I and II, § combined values for NYHA class III and IV, - no data available DN-AHF: de-novo acute heart failure; AC-DHF: acute-on-chronic decompensated heart failure; SBP: systolic blood pressure; HR: heart rate; SOB: shortness of breath; PND: paroxysmal nocturnal dyspnoea; JVP: jugular venous pressure; HF: heart failure; NYHA: New York Heart Association.

6.7 Clinical profiles of DN-AHF and AC-DHF patients

6.7.1 Haemodynamic profiles

Patients with DN-AHF and AC-DHF had different clinical profiles, though limited data was published in this area. In Gulf CARE, IN-HF and RICA, the admission blood pressure was higher in each of the registries for DN-AHF compared against AC-DHF. These patients also exhibited higher degrees of tachycardia on presentation in Gulf CARE (98 vs 95 bpm; $p<0.001$), IN-HF (95 vs 82 bpm; $p<0.0001$) and RICA (93 vs 85 bpm; $p<0.001$).

Those with DN-AHF were also more likely to present with a better LVEF. This was observed in ALARM-HF (mean LVEF: 40 vs 37%; $p<0.0001$) Gulf CARE (median LVEF: 38 vs 34% ;$p<0.001$), IN-HF (mean LVEF: 39 vs 37%; $p<0.001$) and RICA (LVEF > 50%: 65 vs 60%; $p<0.007$)

6.7.2 Profiles based on clinical features

Only IN-HF and Gulf CARE provided substantive data on admission characteristics. In IN-HF, DN-AHF patients appeared to present more with symptoms of central congestion, whereas AC-DHF patients presented with more peripheral symptoms. 81% of de-novo patients were noted to have central pulmonary crepitations compared against 76% of patients with chronic HF from IN-HF. However, AC-DHF patients more commonly presented with peripheral congestion such as ankle oedema (61% vs 49%).

Similar data could be observed from Gulf CARE. AC-DHF patients were more likely than their DN-AHF counterparts to present with peripheral congestive symptoms of abdominal or limb swelling (55 vs 32%; $p<0.001$), weight gain (32 vs 19%; $p<0.001$) and other abdominal symptoms of fluid overload such as ascites (21 vs 7%; $p<0.001$).

6.7.3 Profiles based on NYHA class and clinical phenotypes

In RICA there was a more pronounced difference in NYHA symptom classification between the two groups. DN-AHF were often hospitalised with a less severe background of symptoms (75% presenting as NYHA class I-II) when compared to the AC-DHF cohort (57% presenting as NYHA class I-II) ($p<0.001$).

When reviewing HF classification by ESC clinical phenotype, DN-AHF patients from the ALARM study tended to present more often with symptoms of cardiogenic shock (19% vs 8%) and pulmonary oedema (40 vs 35%). A similar pattern was also observed in EHFS-II (cardiogenic shock, 7 vs 2%; pulmonary oedema, 26 vs 10%; $p<0.0001$).

6.7.4 Profiles based on biomarker and laboratory data

Examination of the two presenting HF groups did not reveal any consistent patterns in relation to natriuretic peptide levels (either BNP or NT-proBNP)(Table 6-5). However there were prominent differences in other laboratory findings. In Gulf CARE, IN-HF and RICA patients with AC-DHF were more likely to be anaemic. Comparing ACD-AHF against DN-AHF patients, the average reported haemoglobin results were 122 vs 130 mg/dL ($p<0.001$) in Gulf-CARE, 123 vs 129 mg/dL ($p<0.0001$) in IN-HF and 119 vs 125 mg/dL ($p<0.001$) in RICA. These patients were also more likely to have advanced renal impairment on presentation: average creatinine 1.6 vs 1.4 mg/dL ($p<0.001$) in Gulf CARE, 1.3 vs 1.2 mg/dL ($p<0.0001$) in IN-HF and 1.5 vs 1.2 mg/dL ($p=0.045$) in RICA.

6.8 Clinical background of DN-AHF and AC-DHF patients in AHF registries

Patients with AC-DHF presented with a greater number of pre-existing co-morbidities that those with a new first presentation of DN-AHF (Table 6-6).

6.8.1 Underlying cardiac co-morbidities and congestion

Information detailing differences in co-morbidities and their relationship to congestion remains limited from the registry population. However, notable differences in the rates of co-morbidities were seen between AC-DHF and DN-AHF populations.

In Gulf CARE, almost twice as many patients with AC-DHF presented with underlying CHD than those with DN-AHF (60 vs 30%; p<0.001). In the EHFS-2 registry a similar difference was found (62 vs 39%; p<0.001). Marked differences were also seen with respect to the prevalence of other cardiovascular diseases. In Gulf CARE and EHFS-2, the differences in the rate of atrial fibrillation were very pronounced (17 vs 6 %, 47 vs 25% respectively). Similar patterns were also seen in published data from IN-HF (43 vs 30%; p<0.0001) and RICA (56 vs 52 %; p<0.001). Although only two registries compared underlying valvular heart disease between the AC-DHF and DN-AHF cohorts, in both of these (Gulf CARE and EHFS-2) the prevalence was higher in the hospitalised population with a known background of HF (18 vs 8% in Gulf CARE; 44 vs 19% in EHFS-2).

In all three registries where data on precipitant causes were reported (Gulf CARE, EHFS-2 and RICA), ACS was the first or second most common cause. Furthermore, it was more prevalent in new DN-AHF patients (39 vs 17%, p<0.001; 42 vs 23%, p<0.001; 8 vs 6%, p=0.49). The Gulf CARE registry which supplied data of subsequent follow up interventions noted that the rate of PCI was also higher in the DN-AHF group (10 vs 3%, p<0.001). Data on the use of diuretic and vasodilator therapy was limited and did not appear to show any clear trend.

Though data on underlying aetiologies is mixed between the registries, hypertensive HF was more common in patients with DN-AHF in Gulf CARE (18 vs 14%, p<0.001) and RICA (42 vs 37%, p=0.006). By contrast, cases of dilated (idiopathic) cardiomyopathy were more likely to be found in chronic patients compared to first presentation HF cases in Gulf CARE (20 vs 16%, p<0.001) and EHFS-II (25 vs 10%, p<0.001).

Table 6-5: Echocardiographic and laboratory characteristics of congested de-novo versus acute-on-chronic decompensated heart failure patients

Registry	ALARM-HF [310]		IN-HF [336]		Gulf CARE [337]		RICA [338]	
	DN-AHF	AC-DHF	DN-AHF	AC-DHF	DN-AHF	AC-DHF	DN-AHF	AC-DHF
Echo parameters								
Ejection fraction (%)	40	37	39	37	38 †	34 †	-	-
LVEF < 40%	-	-	-	-	-	-	21	24
Laboratory findings								
BNP (pg/mL)	908 †	1040 †	925 †	1200 †	1605 †	1154 †	-	-
NT-pro BNP (pg/mL)	-	-	5964	4496 †	3236	3127	5678	6706
Elevated Troponin	-	-	-	-	-	-	17	16
Haemoglobin (mg/dL)	-	-	129	123	130 †	122 †	125	119
Na (mmol/)	-	-	-	-	138	138	139	139
K+ (mmol/l)	-	-			4.2	4.2	4.4	4.4
Creatinine (mg/dL)	-	-	1.1 †	1.3 †	1.4	1.6	1.2	1.5

All continuous values are given as the mean unless stated otherwise. Categorical values are expressed as percentage
† median, - no data available
DN-AHF: de-novo acute heart failure; AC-DHF: acute-on-chronic decompensated heart failure; LVEF: left ventricular ejection fraction; BNP; brain natriuretic peptide; ; NT-pro BNP: N-terminal-prohormone brain natriuretic peptide

Table 6-6: Co-morbidities and aetiology of congested de-novo versus acute-on-chronic acute heart failure patients

	EHFS-II [335]		IN-HF [336]		Gulf CARE [337]		RICA [338]	
	DN-AHF	AC-DHF	DN-AHF	AC-DHF	DN-AHF	AC-DHF	DN-AHF	AC-DHF
Co-morbidities								
Chronic lung disease	16	22	27	33	-	-	20	27
Coronary heart disease	39	62	-	-	30	60	-	-
Hypertension	59	64	61	56	54	67	82	88
Hypercholesterolaemia	-	-			27	43	-	-
Diabetes Mellitus	30	34	37	43	44	54	49	59
Chronic kidney disease	11	20	24	39	9	19	-	-
Peripheral vascular disease	-	-	17	22	4	5	-	-
Cerebrovascular disease	11	15	5	5	6	10	-	-
Atrial fibrillation	25	47	30	43	6	17	52	56
Haemodialysis	-	-	-	-	-	-	-	-
Anaemia	11	17	-	-	-	-	-	-
Intra-cardiac device	4.3	12	-	-	-	-	-	-
ICD	-	-	2	15	-	-	-	-
CRT	-	-	1	9	-	-	-	-
BMI (kg/m^2)	-	-	28	28	27 †	27 †	29	29
Smoking	-	-	-	-	30	16	-	-
Valvular heart disease	19	44	-	-	8	18	-	-
Aetiology of LVSD								
Ischaemic	-	-	38	45	55	52	24	29
Hypertensive	-	-	-	-	18	14	42	37
Cardiomyopathy	10	25	-	-	16	20		
Valvular heart disease	-	-	-	-	7	11	12	20

All continuous values are given as the mean unless stated otherwise. Categorical values are expressed as percentage
† median, - no data available DN-AHF: de-novo acute heart failure; AC-DHF: acute-on-chronic decompensated heart failure; ICD: implantable cardiac defibrillator; CRT: cardiac resynchronisation therapy; BMI: body mass index; LVSD; left ventricular systolic dysfunction.

6.8.2 Non-cardiac co-morbidities

Diabetes mellitus was more prevalent in AC-DHF patients across the registries: Gulf CARE (54 vs 44%, p<0.001), IN-HF (43 vs 37%,p=0.008), EHFS-II (34 vs 30%,p<0.01) and RICA (59 vs 49%, p<0.001). Similarly, the incidence of chronic kidney disease was higher for AC-DHF patients in Gulf CARE (19 vs 9%, p<0.001) IN-HF (39 vs 24%,p<0.0001) and EHFS-II (20 vs 11%, p<0.001).

6.9 Outcomes between DN-AHF and AC-DHF patients

Length of stay outcomes and in-hospital mortality did not show a consistent trend between all of the registries when DN-AHF and AC-DHF patients are compared (Table 6-7). However, this was not the case with longer term one year data. Re-hospitalisation at one year was much higher in the AC-DHF population in Gulf CARE 44 vs 34%, p<0.001) and RICA (45 vs 33%, p<0.01). One year mortality was similarly much higher in patients with a known history of decompensated congestive cardiac disease (Gulf CARE: 23 vs 17%, p<0.001; RICA: 27 vs 15%, p<0.01). This may be viewed as unexpected, given that the rates of cardiogenic shock were higher for DN-AHF patients in all registries which reported data, indicating that blood pressure alone does not indicate congestive severity.

6.10 Discussion

This systematic review of AHF registries shines light on two areas: the variations which exist in the reporting of key features of congestion, and the marked differences in patient characteristics between congested patients with de-novo and acute-on-chronic decompensated HF.

6.10.1 Congestion reporting remains limited

Data on congestion in HF registries with respect to clinical presentation, clinical and haemodynamic phenotypes and outcomes are variably (and under-) reported. Collaboration is required between expert groups to agree upon classifications that are reliable, reproducible and relevant. Radiological information regarding congestion remains limited across the registries. As newer technologies – particularly lung and IVC ultrasound are more widely utilised – objective and semi-quantitative assessments should become available for incorporation into registry datasets.

6.10.1.1 Limitations of reporting of presenting clinical features

A retrospective, single-centre review of 311 patients with AHF by Shoaib and colleagues reported how there may be markedly different phenotypic groups of patients with AHF, which can be classified depending on the presenting complaint: dyspnoea at rest, dyspnoea on exertion or predominant ankle oedema.[302,339] Peripheral and central pulmonary decongestion may be associated with different future risks of clinical events. However, only 4 of 18 registries provided complete data on these three key symptoms. Whilst other haemodynamic variables such as blood pressure, heart rate and laboratory data may be well recorded, the presenting clinical features may provide a better indication of the actual nature of the haemodynamic disturbances.

As such, valuable information about prevalence, prognosis, the clinical composition of congestive phenotypes, and how to best structure AHF trials are all limited by the lack of available data. These revealing insights from less selected registry populations have shone light on potential errors within AHF trial recruitment.[102] Current trial inclusion and exclusion criteria result in a population of patients who are predominantly breathless at rest and the proportion of patients with predominant peripheral congestion is limited. This latter group is more prevalent in the 'real world' and have a worse prognosis than their AHF counterparts with predominant 'central/pulmonary congestion'.

Table 6-7: Summary outcomes of de-novo versus acute-on-chronic decompensated heart failure patients

	DN-AHF	AC-DHF
Outcomes		
Length of Stay (days)	6 - 9	7 – 11
In hospital mortality	7 - 14	6 – 14
Re-hospitalisation at 1 yr	33 – 34	44 – 45
Mortality at 1 yr	15 - 17	23 - 27

All continuous values are given as the mean unless stated otherwise. Categorical values are expressed as percentage
DN-AHF: de-novo acute heart failure; AC-DHF: acute-on-chronic decompensated heart failure;

6.10.1.2 Limitations of clinical and haemodynamic classification systems

While the 2008 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic HF suggested a range of clinical phenotypes for categorising AHF patients, just 7 of 18 registries provided data based on this classification.[12] A criticism of these phenotypes remains the significant overlap between categories.

In ESC-HF-LT, the prevalence of each clinical profile exhibited marked geographic variation.[192] Rates of pulmonary oedema varied from 9.9% in Eastern European countries to 35.9% in Western Europe. There may be genuine epidemiological variables driving these differences. However, the distinction between each AHF sub-type remains highly subjective and different cultural perceptions may exist of how these patients were classified. Revealingly, when patients in the registry were stratified by presenting blood pressure, the differences across the European regions were minimal.[192] However whilst there are significant differences in prognosis in each group, there is no defined treatment strategy based on classification, rendering the clinical import of the classification process academic. Therefore it may be unsurprising that in more recent AHF guideline updates, incorporating this system into daily clinical assessment has not been greatly emphasised.[1]

The Killip classification system was not utilised by any registry. Given it is a post-MI assessment score centred mostly around pulmonary congestion and does not direct treatment options, its relevance in an AHF setting is questionable.[148] The Forrester classification also has similar limitations[139] and only four registries noted complete data on patients in this regard. The original gradations were designed for grouping HF in a post-MI setting and involved RHC to determine cardiac index and PCWP.[139] In practice, the assessment of congestion and perfusion is clinical and subjective. In a further assessment of this method, 200 patients post-infarct were evaluated using clinical assessment and haemodynamic tools (primarily right heart catheterisation). Clinical examination was only able to accurately predict the type haemodynamic disturbance in 83% of cases.

A prospective analysis of 452 advanced HF patients from the Brigham and Women's Hospital was performed to group patients into these categories and was able to verify that these clinical profiles predict outcomes.[140] As expected, "wet cold" had the poorest prognosis (HR 1.83, p=0.02) but the classification methodology only utilised clinical judgement when assigning patients to each group. However, it has already been proven in this patient group that the presence of normal clinical signs do not indicate the absence of true congestion.[59]

Data from the 7865 patient ESC-EORP-HFA Heart Failure Long Term registry has confirmed that "cold and wet" patients have the poorest outcome.[340] A large proportion of patients (30.9%) were also discharged with 'residual congestion', but this categorisation was entirely clinical. It raised further questions about interpretations of congestion – particularly ongoing subclinical disturbance - and ascertaining objectively when adequate decongestion has been achieved. Another limitation is the heterogenous nature of the "warm and wet" cohort which comprises around 70% of AHF patients across the registries.[192, 341,342] ESC-EORP-HFA noted that the clinical course for each was diverse – within this group could be found the greatest improvement in natriuretic peptides, the high proportion of in-hospital worsening renal function but also a residual congestion rate of 39%.[340] This suggests the Forrester method - whilst providing prognostic

information - groups too many diverse AHF phenotypes into the broad “warm-wet” category and lacks the discriminatory ability to distinguish the specific haemodynamic interactions and therapeutic requirements of patients in this subgroup.

6.10.2 De-novo and chronic acute heart failure are different entities

This systematic review has collected data from multiple registries (AHEAD, ALARM-HF, EHFS-II, Gulf CARE, IN-HF and RICA) which strongly indicate that patients with de-novo and chronic AHF do not share uniform profiles. The congestive profile of DN-AHF patients tended to be more central and pulmonary rather than peripheral in nature. Haemodynamically, DN-AHF patients present with higher blood pressure, less tachycardia, have more preserved LV systolic function and less concurrent renal dysfunction – all features which are associated with a more favourable prognosis.[109,343] Longer term registry data also confirms the expected findings; reduced hospitalisation and improved survival, which would be expected in a cohort with less advanced disease.

6.10.2.1 Implications for clinical trial design

The current findings are of relevance when considering the inherent heterogeneity of the recruited AHF trial population and persistently neutral results. With the exception of OPTIME-CHF, no recent study from the systematic review of AHF trials excluded de-novo patients. It could be argued this has allowed unintended recruitment of patients without true HF but other co-morbidities – such chronic lung disease – which have been misclassified as HF. Additionally, in the younger de-novo cohort where the aetiology was deemed idiopathic, myocarditis is a typical probable cause.[344] This condition often presents with mild LVSD and recovery is spontaneous within weeks or months. Similar findings have been noted with idiopathic dilated cardiomyopathy.[345] Acute hypertensive episodes, tachyarrhythmias and toxin induced cardiomyopathy (especially alcohol) can produce a rapid recovery of LV function once the precipitant is treated. Contamination of a study population with these

relatively benign subgroups with a different pathological mechanism of HF would influence outcomes.

By focusing trial recruitment on populations with more chronic disease, investigators can ensure that therapies are targeted against a pathophysiological construct which is defined and well established. However the definition of "chronic" and "new" HF and the minimum time window from diagnosis (or diuretic commencement) to hospitalisation remains unclear. A post-hoc analysis from the ATTEND study demonstrated that patients with a diagnosis of up to 1 month duration shared similar characteristics as described.[346] The congestive profile was also more distinct. De-novo patients had more pulmonary rales and less peripheral oedema than those with more chronic disease. Prognosis was equally more favourable; 30 day mortality and hospitalisation was lower (5.9 vs 9.7%, HF duration < 12 months against others) as was the 180 all-cause mortality rate (8.1 vs 12.3%, HF duration < 12 months against others). Thus by enrolling a more consistent phenotype of patient with already poorer outcomes, an evidence of therapeutic benefit may be more easily seen.

7 Conclusions and General Discussion

From these systematic reviews it can be seen that congestion as assessed by dyspnoea does not manifest in an identical manner between AHF trials and AHF registries. There is a varying prevalence of patients recruited based whether breathlessness is sub-categorised as being as either ‘at rest’ or ‘on exertion’. AHF trial design has also been shown to be narrowly focused on dyspnoea over other broader non-pulmonary manifestations of congestion when enrolling patients and for triggering end points.

This systematic review also has shown how the assessment of congestion is inconsistently performed from study to study, both in terms of the lack of formulation of any pre-defined ‘core features’ or in the determination of severity. The use of adjunctive imaging technologies has also not been incorporated into trials or registries with any regularity.

It should be stated that broader conclusions of the complex nature of congestion cannot be drawn from the raw data extracted from these two systematic reviews – which are primarily restricted to detailing the methods and balance of congestion assessments. However, there is a large reservoir of literature derived from substudy analyses and other clinical studies which discuss further the multifaceted nature of congestion. Numerous key aspects of this include: accepting that dyspnoea cannot be considered a uniform entity, congestion does not manifest as a homogenous phenotype, the extensiveness of congestion can be used to predict risk, and that adjunctive imaging may be essential to detect residual subclinical congestion – a feature in itself associated with prognostic hazard. [103]

7.1 Limitations of the systematic reviews

As with any systematic review, a risk remains that the studies included are of significant variability in quality. To attempt to minimise this clinical trials were required to be randomised and registries required to be prospective. The search criteria were broad to ensure a representative population was caught. Eligible RCTs had a low recruitment threshold of 180 patients, and registries a similarly low ceiling of 2000 patients. The cut offs employed had a degree of arbitrariness, but the number of studies enrolled in each group (21 RCTs and 18 registries) suggest that reasonable capture was achieved. Most major reported and recognised studies were included in the literature review. This systematic review did not assess the variability of congestion assessment methods or clinical features by the geographical jurisdiction of each study. This could be a valid shortcoming as regional variations are known to occur.[306,347] However, data availability restricted the ability to review this.

The comparisons made between data from each set of trials and registries was also limited. Access to full data sets may have enabled more statistically rigorous comparisons of clinical profiles to be performed. It could be argued that trials selection should have been based on a requirement for an adequate sample size based on the study questions postulated for each trial. Selecting based on statistical power would have been appropriate for a systematic review examining the efficacy of a common intervention across a cohort of studies, but as this was a general assessment of methods, such a strategy may not have provided much further validity. It remains possible that smaller RCTs may have incorporated more novel or holistic assessment methods for congestion. Publication bias may also have meant that such studies were also not reported. Additionally had the review not excluded RCTs that examined imaging interventions, a different picture may have emerged of more sophisticated assessment methods. However, the broader aim of this review was to be capable critiquing AHF trial design in the context of repeated negative outcome studies in the field of AHF. Therefore the review would have had to primarily incorporate studies from this group.

As has been detailed, these systematic reviews were limited to a focused set of questions and broader discussions on the nature of congestion and adjunctive imaging modalities are obtained from a more general examination of the literature.

7.2 Dyspnoea is not uniform

7.2.1 Marked difference of dyspnoea prevalence between AHF trials and registries

The stringent use of dyspnoea as the main surrogate marker for congestion has resulted in the recruitment of an AHF population into clinical trials which is markedly distinct from the registry and possibly real world populations. Overly tight enrolment criteria permitting only those with dyspnoea to participate has produced a selected cohort which is unrepresentative.

In VERITAS, 3CPO, Pre-RELAX-AHF, ASCEND-AHF and RELAX-AHF, 100% of the enrolled subjects had dyspnoea at rest. Even in ACTIV-in-CHF, ATHENA-HF and EVEREST - which had less rigorous criteria - the proportion of patients with dyspnoea at rest was relatively high at 70% to 89%. The registry group is markedly dis-similar. In ADHERE, ADHERE-AP, ALARM-HF and OPTIMIZE-HF and rate of dyspnoea at rest ranged from 44 to 73% (Figure 7-1). These are substantial registries comprising large numbers of recruits (over 170,000 patients) from multiple continents (North America, Europe and the Asia-Pacific region), lending significant weight to the generalisability of this finding. Furthermore, the rate of dyspnoea on exertion was much higher than dyspnoea at rest: 65% in OPTIMIZE-HF, 95% in ADHERE, 95% in ADHERE AP and 95% in KCHF. In keeping with the analyses from a retrospective review which subdivided patients into SOBAR and CARBOSE categories based on presenting symptoms, it supports the proposition that dyspnoea on exertion is the predominant presenting phenotype of AHF and is under-represented in randomised trials.[11]

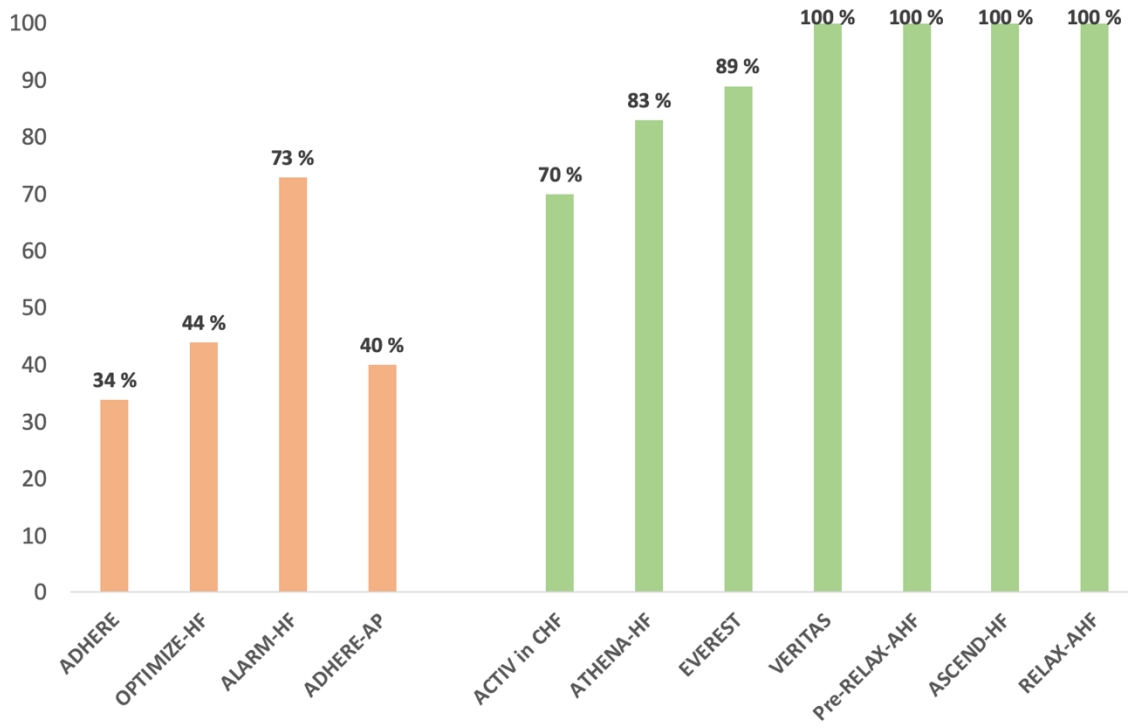

Figure 7-1: Comparison of enrolled patients with dyspnoea at rest in acute heart failure registries and trials. Dyspnoea at rest is present in a far higher proportion of patients enrolled in AHF trials compared to AHF registries suggesting that both are not recruiting patients with the same baseline congestive profile. AHF: acute heart failure.

7.2.2 Implications for AHF trial design

HF induced fluid retention can potentially begin up to 30 days before presentation and congestion accelerates in the week preceding admission.[95] This may explain why registry data has shown dyspnoea at rest is not the primary presenting complaint. The pathological process most likely involves gradual fluid accumulation. By contrast, patients breathless at rest (or minimal exertion) may have sudden fluid redistribution leading to rapid pulmonary oedema. As would be expected, dyspnoea in this latter cohort will improve rapidly and the longer term outcomes should be more favourable.[11] Considering this, peripheral congestion may represent a more appropriate pathophysiological target against which AHF therapies must be trialled.

Another issue that requires consideration is whether congestive processes beginning weeks before presentation can be undone by a short therapeutic intervention lasting just a few days. Of all AHF trials, 15 out of 21 therapeutic

interventions lasted under 72 hours. These intravenous peptides were vasoactive or inotropic compounds with no longer term effects on neurohormonal function. Additionally, randomisation was performed early – usually within 48 hours of medical contact or diuretic administration. A more delayed intervention may instead pick up more diuretic-resistant patients with poorer baseline outcomes against which smaller incremental benefits are seen.

7.2.3 Orthopnoea and risk

The outcome of patients with orthopnoea in clinical trials has not been extensively documented and remains an area for more research. In a pooled analysis of 496 patients enrolled into DOSE and CARRESS-HF, patients with orthopnoea at baseline had a much higher event rate (of a combined endpoint of death and re-hospitalisation) than those who were orthopnoea free (62 vs 41%).[132] This effect was sustained for patients with residual orthopnoea at discharge (70 vs 57%). Critically it should be noted that this finding was specific for ≥2 pillow orthopnoea. In the out-patient setting, orthopnoea post-discharge also remains an adverse prognostic clinical symptom. In a study of 146 patients post-hospital admission with NYHA class IV symptoms of HF, the ongoing presence of orthopnoea at 4 to 6 weeks after hospital discharge predicted a drop in 2-year survival from 77 to 38%.[348] Whilst the study did not determine whether this increased hazard was a result of left-sided central congestion or potential secondary respiratory effects arising from compromised ventilation, the prognostic change was still evident.

7.3 Pulmonary congestion

7.3.1 Extensiveness of pulmonary rales predicts risk

Only REVIVE and PROTECT sought to provide any detailed clinical information on the extent of pulmonary congestion.[207,283] A post hoc analysis of PROTECT demonstrated that not all pulmonary congestion is alike. The study characterised congestion as being either “none”, or noted the different involved

proportions of the lung field ("<1/3", "1/3 to 2/3" or ">2/3"). Multivariable analysis of the cohort demonstrated that when comparing ">2/3 vs none", this increase in pulmonary congestion was a major predictor of all-cause mortality at 180 days (HR 1.650 [95% CI 1.07-2.54]. However this was not included in the final predictive model due to concerns about potential high levels of interobserver variability.

7.3.2 Pulmonary decongestion does not negate ongoing risk

EVEREST demonstrated that patients with the highest composite congestion scores had paradoxically lower levels of pulmonary rales (76 vs 85% for highest against lowest scores).[118] This may be evidence of bias within the scoring system but also suggests that congestive features may not develop in tandem and that pulmonary oedema may not be a precise marker of fluid status. Most of the cohort with higher scores had more severe peripheral oedema, and this was associated with poorer long term outcomes. Importantly, worse than expected outcomes were seen in recovering patients with virtually no pulmonary oedema and a low composite score.[118] This lends credence to the idea that risk does not completely normalise with clinical improvement and a degree of prognostically relevant subclinical haemodynamic disturbance may lie untreated. Unsurprisingly, a clear correlation was also seen between incomplete decongestion and poorer outcomes. Thus the persistence of pulmonary rales on discharge clearly remains a feature which must be reported carefully in AHF studies.

7.4 Peripheral congestion

As with quantifying pulmonary rales, a more nuanced methodology to approaching peripheral oedema is required as peripheral congestion is not a binary entity.

7.4.1 Severe peripheral oedema and risk in AHF trials

In a subgroup analysis of RELAX-AHF, patients graded with moderate or severe (2+ or 3+) peripheral oedema had poorer outcomes than those graded as having no or mild oedema (1+).[349] Similarly. a review of PROTECT found that whilst dyspnoea relief may yield short term benefits, more severe peripheral congestion was associated with longer inpatient stays and higher inpatient mortality.[350] A post-hoc analysis of DOSE and CARRESS-HF found similar confirmatory findings. Persistent refractory peripheral oedema resulted in a higher frequency of adverse post-discharge outcomes when compared with those without oedema (71 vs 51%, rate of death or recurrent hospital contact).[132]

7.4.2 Severe peripheral oedema and risk in registry studies

In the previously described analysis examining presenting HF phenotypes, patients with marked peripheral oedema were dyspnoeic on exertion (possibly due to the exertion of moving their heavier congested limbs).[11] In these 'CARBOSE' groups, the presence of peripheral oedema itself was a remarkable independent risk factor for mortality (52 vs 33%, for patients with peripheral oedema against those without).

To more robustly assess the effect of peripheral oedema on AHF outcomes, Shoaib and colleagues reviewed 121,214 patients from the National Heart Failure Audit for England & Wales.[302] Peripheral oedema was classified as "none", "mild", "moderate" and "severe" in the database. Compared to patients with no leg congestion, more severe oedema was markedly associated with increased length of stay (12 vs 6 days, $p<0.001$), in-patient mortality (16 vs 7%, $p<0.0001$) and mortality at around one year (59 vs 39%).[302] Patients with more severe oedema were also more likely to be older, female, have hypertension, more renal dysfunction and less HFrEF.

A subset of these patients may have concurrent RV dysfunction or increased pulmonary hypertension – both of which are associated with a poorer prognosis. Peripheral congestion may have more deleterious renal affects, produce greater

diuretic resistance or disruption of nutritional absorption as a consequence of an oedematous gut. In the AHF population these patients represent the 'less dramatic' presentations with more indolently deteriorating symptoms, but clearer objective assessment of this group remains critical.

7.5 Future directions

7.5.1 Standardisation of congestion assessment

It is clear that congestive symptoms must be classified and reported in a more objective and complete manner. The severity of both pulmonary and peripheral congestion correlate with various adverse outcomes during and after hospitalisation. Key haemodynamic variables and co-morbidities are routinely documented with a high level of rigour and completeness, and the same must be done with congestion. Achieving standardisation will enable the structuring of more appropriate trial enrolment criteria, allow better comparison across study populations, and aid in the assessment of confounders on outcomes.

7.5.1.1 Objective methods to assess dyspnoea

The methodology of assessing dyspnoea currently remains the subject of ongoing investigation. As has been demonstrated, it becomes clear that dyspnoea at rest and dyspnoea on exertion must be considered as reflective of two different congestive entities with divergent prognoses.[339] Dyspnoea with provocation manoeuvres may be a more effective method to elicit subtle changes in global congestion. The Renal Optimization Strategies Evaluation in Acute Heart Failure and Reliable Evaluation of Dyspnea in the Heart Failure Network (RED-ROSE) study will further investigate provocative dyspnoea assessment against VAS to determine whether it may be a more sensitive tool.[351]

In ASCEND-HF study, peak expiratory flow rate (PEFR) assessment was performed on patients at time points during the first 24 hours of intervention. Increases in PEFR correlated with moderated or marked dyspnoea improvement scores on the Likert scale. Further validation studies with other patient-reported tools may

help researchers arrive at more objective and reproducible methods for documenting the symptom of breathlessness and integrating these into future clinical studies.

7.5.1.2 Orthopnoea

When categorising the presence of orthopnoea, it should be noted that invasive assessment from ESCAPE showed that it was only ≥ 2 pillow orthopnoea that indicated a PCWP of pressure ≥ 30 mmHg (odds ratio, 3.6; P<0.05).[120] Additionally, post-hoc analysis from the DOSE and CARRESS-HF cohorts suggested it was ≥ 2 pillow orthopnoea at baseline that was associated with a greater event rate.[132] Whilst these are based on limited patient numbers, they may form a basis on which to standardise the threshold at which orthopnoea is defined.

7.5.1.3 Systematic quantification of pulmonary congestion

Given then heterogeneity of outcomes dependent on the degree of pulmonary congestion, developing a structured method of grading pulmonary oedema can provide additional value. Platz and colleagues recommended a reporting schema along the following framework by dividing the lung field into thirds:[352]

- No crackles or rales
- Crackles/rales ≤1/3 from bases
- Crackles/rales 1/3 to 2/3 from bases
- Crackles/rales >2/3 from bases

In this manner, the patient can be assessed as having one of four categories of pulmonary rales: no crepitations, crepitations at less than one-third of the lung field, crepitations from one-third to two-thirds of the lung field and crepitations beyond two thirds of the lung field. This may direct AHF inclusion criteria for clinical studies to enable enrichment of trial populations with patients of appropriate risk.

7.5.1.4 Systematic quantification of peripheral congestion

An outcome with significant prognostic import like peripheral oedema must be reported in a meaningful manner. From this review of trials, oedema was not reported consistently (if it all). In REVIVE, the degree of limb oedema was recorded based on how extensive it was ("no oedema", "leg oedema" or "sacral oedema"). In PROTECT and DOSE, a more historical scoring system was utilised based on the extent of pit depth and recovery. In ROSE, oedema was only noted to be present if it met a "≥2+ " threshold. Six studies gave absolute numbers presenting with peripheral limb swelling but no breakdown of severity. Similarly registries allowed the clinician to note whether oedema was present but only in a binary fashion. Whilst trials did not always expressly state their grading methodology, it was assumed that it is based on the universally recognised 4-point scale (Table 7-1).[353]

Grade	Physical Characteristics
1+	Slight pitting, no visible change in the shape of the extremity; depth of indentation 0-1/4" (<6 mm); disappears rapidly.
2+	No marked change in the shape of the extremity; depth of indentation 1/4 -1/2" (6- 12 mm); disappears in 10 to 15 seconds.
3+	Noticeably deep pitting, swollen extremity; depth of pitting1/2-1" (1-2.5 cm); duration 1 to 2 minutes.
4+	Very swollen, distorted extremity; depth of pitting > 1" (>2.5 cm); duration 2 to 5 minutes.

Table 7-1: Standard grading scale for ankle oedema. Adapted from Bates *et al* (1992) [353]

In the absence of a true gold standard for assessing oedema, no substitute technique or technology is validly apparent. However, it would seem reasonable to consider whether a score of 1-4 may be better represented by quantifying the extent of limb swelling (which be of closer resemblance to the severity of fluid accumulation, and by proxy congestion). Such a method would also be easier to apply in a consistent fashion (Table 7-2).

Grade	Physical Characteristics
1+	Pitting oedema at the ankle position
2+	Pitting oedema at the mid-skin
3+	Pitting oedema over the mid-thigh
4+	Sacral oedema

Table 7-2: Proposed alternative grading scale for ankle oedema

7.5.2 Use of adjunctive imaging modalities

The nature of congestion and the perennial dilemma of subclinical congestion suggests that profiling on clinical grounds alone is not adequate and other imaging modalities must be employed to help assess two critical areas: to quantify if congestion is present and to quantify if decongestion has been achieved. New technological modalities may aid to prevent misjudgements of fluid status and better unmask the true treatment effects of therapies investigated.

7.5.2.1 Assessing subclinical congestion.

Clinical assessment has been demonstrated to be variable and not always in synchrony with invasive measurements.[120] ESCAPE has shown that even when congestion appears to have resolved clinically, there may be a detachment from ongoing haemodynamic parameters which have not normalised and still confer risk.[118] This is in keeping with data from the ESC-EORP-HFA HF-LT registry and PROTECT which demonstrate that resistant congestion during therapy or residual congestion on discharge risk both increase mortality. [340,199]

The key questions of congestion remain difficult to assess. Determining the baseline level of congestion and ascertaining what constitutes adequate de-congestion remain unanswered in an objective or quantitative manner. It also invites speculation as to whether patients in AHF trials may have been discharged prematurely. In ESC-HF-LT, 5% of patients were noted to have an increase in body weight on discharge.[192,354] One may query if excess residual

congestion had remained uncleared (or re-accumulated) thus putting the patient at risk of early re-admission and adverse outcome.

Achieving a return to true euvolaemia remains difficult in practice. Hesitation remains amongst clinicians treating AHF that worsening renal failure may be incurred by prolonged diuresis strategies – though the evidence suggests that this does not necessarily result in permanent damage or adverse outcomes.[355,356] Conversely, excess diuresis may induce orthostatic effects such as syncope which will limit re-institution of ACE inhibitors and other critical HF medications. Cultural variations in clinical assessment may also drive early discharge before haemodynamic normalisation has been achieved.

New imaging techniques suggest that ancillary information may potentially be provided to help to tailor patient specific therapies to haemodynamic profiles. However, the application of these during a complete patient journey - from AHF diagnosis, to monitoring de-congestion, tailoring diuretic therapy, and deciding on hospital discharge - is still subject of ongoing evaluation.

7.5.2.2 Pulmonary congestion

LUS is the most developed technology to assist in the quantification of congestion, though it remains unused in AHF trials and registries. In some respects it still remains an emerging technology; a consensus statement on the role of lung ultrasound was only recently published in 2017 by the Acute Heart Failure Study Group of ESC Acute Cardiovascular Care Association.[357] Operator familiarity may also have been another consideration precluding its inclusion in clinical trials. However as LUS represents a closer approximation to a semi-quantitative gold standard for evaluating central pulmonary congestion it should progressively be adopted in a more standardised manner in both AHF trials and AHF registries.

LUS-implemented approaches allow better diagnostic determination of true cardiac congestion and enable a quantification of congestion, determination of subclinical congestion and assessment of risk. In a multi-centre Italian study of 1,005 patients presenting to the emergency department, LUS augmented the

diagnostic process to help more accurately differentiate cardiac from non-cardiogenic dyspnoea, resulting in re-classification of 19% of cases.[358] In clinical trials, such an approach could enrich trial populations by filtering through only truly congested candidates. B-line quantification has been shown to correctly risk stratify patients at higher risk of rehospitalisation and death in both AHF and ambulatory CHF states, and correlates with elevated levels of natriuretic peptides.[159,168,359] Critically when trying to identify subclinical congestion, B-line scores are elevated even when pulmonary auscultation is clear, underlining its value in uncovering residual haemodynamic disturbances.[168]

Integrating LUS into AHF trials is potentially more straightforward than other echocardiographic techniques. A basic degree of proficiency can be delivered with just 30 minutes of training and a focused study requires only 5 minutes.[164,357] A standard curvilinear scanning probe is also sufficient for this purpose. Unlike in the critical care setting, LUS protocols have yet to be developed for congestion assessment in AHF, though Platz and colleagues have suggested a concise method based on scanning pre-specified lung zones.[159] The accelerated incorporation of LUS into clinical studies will provide necessary the impetus for a uniform standard.

7.5.2.3 Peripheral congestion

At present, no imaging modality is yet capable of acting as a gold standard for the evaluation of peripheral congestion. IVC ultrasound has yielded promising data: there is fairly robust haemodynamic correlation between imaging and invasive assessments, it can indicate prognosis, remains easy to perform with low variability and can integrate readily into a clinical assessment.[174–177] However, unlike LUS it does not provide semi-quantitative information about the extent of congestion. Some patients will always have IVC dilation (either due to persistently poor ventricular function or co-morbid cardio-respiratory disease), though a collapsed IVC may steer the clinician away from a misjudged intensification of diuretic therapy. It remains able to track congestion so serial assessments are of value relative to changes in a patient's condition.

BIVA remains a technology that could provide an absolute metric of hydration status, but most studies are still exploratory and single centre.[187] It also is not clear how diuretic strategies would be tailored to BIVA assessments as trials have not been robust in this examining this area.

JV ultrasound - like IVC ultrasound - can track congestion and predict prognosis, but an agreed standard method of assessment and data evaluation remains elusive.[183,184] Near-infrared spectroscopy of the jugular vein may provide more concrete numerical assessments of estimated venous and right pressures to guide therapy and assess therapeutic effectiveness, but trials are ongoing.[185]

8 Future directions

AHF trials of the future have to be more representative of the real world hospitalised population. Whilst dyspnoea at rest is a common symptom, it is not present in all patients admitted with AHF and should not be a sole mandatory requirement for enrolment. As dyspnoea tends to improve rapidly with standard medical therapy, so less focus should be given to this measure as a sole primary end point. Instead, trials must reflect the more balanced picture of patients attending with more chronically accumulated peripheral oedema rather than more acute pulmonary signs.

Congestion also needs to be more clearly defined in a standardised manner. Clinical assessment should be modified to assess and document the severity of central pulmonary and peripheral congestion - as it is clear the degree of both correlate with prognosis. However, as clinical examination is not completely robust in this regard, more objective measurements are also required. Ultrasound technology provides techniques to rapidly assess both pulmonary and peripheral congestion in a semi-quantitative manner. These adjunctive imaging measures should be incorporated into clinical trials to help enrich trial populations by ensuring recruited patients have genuine decompensated AHF.

More robust end points using objective imaging methods can provide a reliable indicator of whether - and to what extent - decongestion has actually been achieved by trial therapies. These tools can also address the dilemma of identifying patients with subclinical congestion – a subgroup at high risk of rehospitalisation and adverse outcome – and ensure adequate strategies are employed to bring patients to a euvolaemic state prior to discharge into the community.

9 Appendix A: Supplementary Tables

Table A-1: Congestion requirements for enrolment into acute heart failure trials

	Inclusion Criteria (Dyspnoea)		Inclusion Criteria (Pulmonary congestion)		Inclusion Criteria (Peripheral congestion features)		Inclusion Criteria (Other non-specific)		Inclusion Criteria (Use of objective imaging)	
Trial	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**
HF-REF										
OPTIME-CHF [209]	No (Part of composite 'HF score')	Dyspnoea (exertional , nocturnal, orthpnoea or at rest)	No (Part of composite 'HF score')	Rales (bases only, or > bases)	No (Part of composite 'HF score')	"JVP > 6 cm with oedema or hepatomegaly"	No (Part of composite 'HF score')	"JVP > 6 cm"	-	-
LIDO [297]	-	-	-	-	-	-	-	-		-
ACTIV-in-CHF [272]	-		No	Rales CXR signs of pulmonary congestion	No	Pedel oedema Increased abdominal girth, Weight gain of > 10 pounds above baseline	No	Raised JVP	No	CXR (signs of pulmonary congestion)
EVEREST A and B [276]	No	Dyspnoea at rest (or minimal exertion)	No	SOB (none, seldom, frequent, continuous. Orthopnoea (none, seldom, frequent, continuous)	No	Pitting oedema (Absent, slight, moderate, marked)	No	JVP (≤ 6 cm, 6-9 cm, 10-15 cm, ≥ 15 cm) Fatigue (none, seldom, frequent, continuous)	-	-

	Inclusion Criteria (Dyspnoea)		Inclusion Criteria (Pulmonary congestion)		Inclusion Criteria (Peripheral congestion features)		Inclusion Criteria (Other non-specific)		Inclusion Criteria (Use of objective imaging)	
Trial	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**
SURVIVE [208]	No	Dyspnoea at rest	No	-	No	-	-	-	-	-
REVIVE-2 [207]	Yes	Dyspnoea at rest	No	Pulmonary rales (basal, >1/3 lungs, > 2/3 lung fields)	No	Peripheral oedema (legs, sacral and/or lumbar)	-	-	-	-
PIONEER HF [277]	No	"Signs and symptoms of fluid overload"	No	"signs and symptoms of heart failure"	No	"signs and symptoms of heart failure"	**No**	"signs and symptoms of heart failure"	-	-
HF-REF and HF-PEF										
VMAC [278]	Yes	Dyspnoea at rest	No	PND Orthopnoea (2 pillow) CXR consistent with heart failure	No	Abdominal discomfort due to mesenteric congestion	No	JVP distension	No	CXR (features consistent with decompensated heart failure)
RITZ-2 [294]	-	-	-	-	-	-	-	-	-	-
UNLOAD [280]	-	-	No	PND Orthopnoea. Pulmonary rales CXR (pulmonary oedema or pleural effusion)	-	-	No	JVP ≥ 7 cm	No	CXR (pulmonary oedema or pleural effusion)

	Inclusion Criteria (Dyspnoea)		Inclusion Criteria (Pulmonary congestion)		Inclusion Criteria (Peripheral congestion features)		Inclusion Criteria (Other non-specific)		Inclusion Criteria (Use of objective imaging)	
Trial	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**
VERITAS 1 and 2 [295]	Yes	Dyspnoea at rest (with RR ≥ 24 breaths per minute)	No	Pulmonary oedema (rales >1/3 chest), CXR (pulmonary congestion or oedema)	-	-	-	-	No	CXR (pulmonary congestion or oedema)
3CPO [281]	Yes	Dyspnoea at rest (with RR > 20 breaths per minute)	Yes	Bilateral crackles CXR (showing interstitial oedema)	-	-	-	-	Yes	CXR (showing interstitial oedema)
Pre-RELAX-AHF [291]	Yes	Dyspnoea at rest (or min exertion)	Yes	CXR showing pulmonary congestion	-	-	-	-	No	CXR (showing pulmonary congestion)
PROTECT [283]	Yes	Dyspnoea at rest (or min exertion)	No	Pulmonary rales ≥ 1/3 not clearing with cough	No	≥2+ peripheral oedema or pre-sacral oedema)	No	JVP >8	-	-
DOSE [203]	No	Dyspnoea at rest	No	Pulmonary rales	No	Peripheral oedema Ascites	-	-	No	CXR (pulmonary vascular congestion)
ASCEND-HF [301]	Yes	Dyspnoea at rest (or min exertion)	Yes	Tachypnoea (RR ≥ 20) or pulmonary congestion (rales ≥1/3 of chest) CXR features of "congestion or oedema"	-	-			Yes	CXR(features of "congestion or oedema")
CARRESS-HF [288]	No	-	No	CXR signs (pulmonary edema, pleural effusions)	No	≥2+ peripheral oedema	No	JVP ≥10 cm	No	CXR (pulmonary edema, pleural effusions)

	Inclusion Criteria (Dyspnoea)		Inclusion Criteria (Pulmonary congestion)		Inclusion Criteria (Peripheral congestion features)		Inclusion Criteria (Other non-specific)		Inclusion Criteria (Use of objective imaging)	
Trial	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**	**Mandatory?**	**Description**
RELAX-AHF [291]	Yes	Dyspnoea at rest (or min exertion)	Yes	Pulmonary congestion on CXR	-	-	-	-	Yes	CXR "pulmonary congestion" (mandatory)
ROSE [206]	No	Dyspnoea at rest	No	Orthopnoea Pulmonary rales Pulmonary vascular congestion on CXR	No	Oedema Ascites	-	-	No	CXR "pulmonary vascular congestion"
TRUE AHF [293]	Yes	Dyspnoea at rest	Yes	CXR (radiological evidence of heart failure)	No	-	-	-	Yes	CXR (radiological evidence of heart failure)
ATHENA-HF [299]	No	Dyspnoea (unspecified)	No	Orthopnoea Pulmonary rales	No	Peripheral oedema Ascites	-	-	No	CXR "pulmonary vascular congestion"

- no data available

HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; CXR: chest X-ray; RR: respiratory rate; JVP: jugular venous pressure; PND; paroxysmal nocturnal dyspnoea.

Table A-2: End points and congestion assessment in acute heart failure trials

		ENDPOINT:	Dyspnoea	ENDPOINT:	Pulmonary Congestion	ENDPOINT:	Peripheral congestion
Trial	**Primary Endpoint**	**Primary or Secondary?**	***(Description)***	**Primary or Secondary ?**	***(Description)***	**Primary or Secondary?**	***(Description)***
HF-REF							
OPTIME-CHF [209]	Days of hospitalization for CV events within 60 days	Secondary *(composite)*	Composite HF score	Secondary *(composite)*	Pulmonary rales (bases, > bases) – part of composite HF score	Secondary (composite)	"JVP > 6 cm", "JVP > 6 cm with oedema or hepatomegaly" – part of composite HF score
LIDO [297]	Proportion of patients achieving haemodynamic improvement at 24 h	-	-	-	-	-	-
ACTIV-in-CHF [272]	2 Co-primary: change in body weight at 24 h; worsening HF at 7 weeks (unscheduled hospitalization or visit for HF, death)	Secondary	VAS	Secondary	Rales	Primary and Secondary	Change in body weight in 24 hrs (primary) Oedema, hepatomegaly, Jugular venous distension (secondary)
EVEREST A and B [276]	2 Co-primary: time to all-cause mortality; time to CV mortality or HF hospitalization	Secondary	7-point Likert scale	Secondary	Rales (4 point-scale: none, base, to <50% base, > 50% base)	Secondary	Change baseline body weight day 1, oedema score (4 point scale: trace, slight, moderate, marked)
SURVIVE [208]	All-cause mortality (180 days)	Secondary	7-point Likert scale	-	-	-	-
REVIVE-2 [207]	Composite: patient-reported clinical improvement, death or worsening clinical status (day 5)	Primary *(composite)*	VAS (quantified by AUC) – as part of "worsening clinical status" composite	-	-	-	-
PIONEER HF [277]	Time averaged proportional change in NT-proBNP from baseline	-	-	-	-	-	-

		ENDPOINT:	Dyspnoea	ENDPOINT:	Pulmonary Congestion	ENDPOINT:	Peripheral congestion
Trial	**Primary Endpoint**	**Primary or Secondary?**	***(Description)***	**Primary or Secondary ?**	***(Description)***	**Primary or Secondary?**	***(Description)***
HF-REF and HF-PEF	-			-		-	
VMAC [278]	Co-primary: change in PCWP; self-reported dyspnoea	Primary	7 point Likert scare	-	-	-	-
RITZ-2 [294]	Mean change in cardiac index from baseline to 6 h	Secondary	7 point Likert scale	-	-	-	-
UNLOAD [280]	Weight loss and patient-reported dyspnoea	Primary	7 point Likert scale		-	Primary	Weight loss (48 hrs post randomization)
VERITAS 1 and 2 [295]	2 co-primary end-points: death or worsening heart failure (7 days): dyspnoea	Co-Primary	VAS (quantified by AUC)	-	-	-	-
3CPO [281]	7 day mortality (and intubation)	Secondary	VAS	-	-	-	-
Pre-RELAX-AHF [291]	Nil (dose finding study)	-	-	-	-	-	-
PROTECT [283]	Composite: dyspnoea, death/HF readmission day 7, worsening HF signs and symptoms	Primary	7-point Likert scale	-	-	-	-
DOSE [203]	2 Co-primary: patient-assessed symptom improvement (72 h); change in serum creatinine (72 h)	Co-Primary	VAS (quantified by AUC)	Secondary (composite)	No orthopnoea; as part of "patients free of congestion" composite end-point at	Secondary	Weight change (at 72 hours) "JVP < 8cm" and "trace peripheral oedema or less"; as part of "patients free of congestion" composite end point
ASCEND-HF [301]	2 Co-primary: change in self-reported dyspnoea (6 and 24 h); composite: HF rehospitalization or death (30 days)	Co-primary	7-point Likert scale	-	-	-	-

		ENDPOINT:	Dyspnoea	ENDPOINT:	Pulmonary Congestion	ENDPOINT:	Peripheral congestion
Trial	**Primary Endpoint**	**Primary or Secondary?**	***(Description)***	**Primary or Secondary ?**	***(Description)***	**Primary or Secondary?**	***(Description)***
CARRESS-HF [288]	Bivariate end-point (change in serum creatinine and weight) assessed at 96 hours	Secondary	VAS (quantified by AUC)	Secondary	Clinical decongestion (including absence of orthopnoea) at 96 hrs, 7 days, 30 and 60 days,	Bivariate and Secondary	Weight change at 96 hours (Bivariate primary end point). Clinical decongestion (including no more trace peripheral oedema, JVP < 8 cm) at 96 hrs, 7 days, 30 and 60 days Weight loss ≥ 3 kg.
RELAX-AHF [291]	2 Co-primary: change in self-reported dyspnoea (day 5); dyspnoea improvement from baseline	Primary	VAS (quantified by AUC), 7 point Likert scale	-	-	-	-
ROSE [206]	2 co-primary end-points: 72 hr cumulative urine volume; change in cystatin C	Secondary	VAS (quantified by AUC)	-	-	Secondary	Change in weight after 72 hours
TRUE AHF [293]	All-cause mortality and cardiovascular rehospitalization at 30 days (co-primary endpoint)	Primary (hierarchical composite)	Clinical composite including 7-point Likert scale of global self-assessment	Secondary (hierarchical composite)	"Worsening signs/symptoms of heart failure"	Secondary (hierarchical composite)	"Worsening signs/symptoms of heart failure"
ATHENA-HF [299]	Proportional change in NT-pro-BNP from randomization to 96 h	Secondary	VAS (quantified by AUC), Likert scale	Secondary	Congestion score (including orthopnoea)	Secondary	Congestion score (including pedel oedema, weight change)

HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; CV: cardiovascular; PCWP: pulmonary capillary wedge pressure; VAS: visual analogue scale; AUC: area under curve; RR: respiratory rate; JVP: jugular venous pressure; PND; paroxysmal nocturnal dyspnoea; BNP: brain natriuretic peptide; NT-proBNP: N-terminal-prohormone brain natriuretic peptide.

Table A-3: Presenting features of congestion in acute heart failure trials [110,190,195-198,280-306]

	OPTIME-CHF	LIDO	ACTIV in CHF	EVEREST	SURVIVE	REVIVE	PIONEER HF	VMAC	RITZ-2	UNLOAD	VERITAS	3CPO	Pre-RELAX-AHF	PROTECT	DOSE	ASCEND-HF	CARRESS HF	RELAX-AHF	ROSE	TRUE-AHF	ATHENA-HF
Clinical Presentation (Pulmonary)																					
SOB at rest	-	-	70	89	-	-	-	100 †	-		100 †	100 †	100 †	-	-	100 †	-	100 †	-	-	83
Pulmonary rales	81	-	77	80	-	76	33	73	-	59	90	100	-	90	-	-	-	-	60	-	62
Orthopnoea	-	-	-	52	-	-	-	-	-	-	-	-	-	96	90	-	-	-	89	-	85
Clinical Presentation (Peripheral)																					
Peripheral oedema	-	-	45	78	-	68	62	73	-	81	-	-	-	86	79	-	89	-	69	-	77
Weight gain	-	-	-	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	-	-
Clinical Presentation (Other)																					
SOBOE	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Third heart sound	59	-	-	-	-	-	-	-	-	44	-	-	-	-	-	-	-	-	-	-	-
Raised JVP	73		80	26	-	-	-	89	-	68	-	-	-	89	92	-	97	-	99	-	-
NYHA Class																					
I	-	-	-	-	-	-	1	-	-	-	-	-	3	-	-	-	-	3	-	5	-
II	8	-	-	-	-	-	23	6	-	-	-	-	26	-	-	-	-	38	-	33	-
III	56	-	72	58	-	-	64	44	-	52	-	-	38	48	-	-	-	44	-	49	-
IV	58	-	55	39	86	-	9	42	-	45	-	-	20	30	-	-	-	14	-	14	-
Radiological Assessment																					
Pulmonary congestion on CXR	-	-	-	-	-	-	-	-	-	-	83	100 †	100 †	-	-	-	-	100 †	-	-	-

All continuous values are given as the mean unless stated otherwise. Categorical values are expressed as percentage
† = mandatory inclusion criteria
- = not recorded
SOB: shortness of breath; PND: paroxysmal nocturnal dyspnoea; SOBOE: shortness of breath on exertion; CXR: chest X-ray; HF: heart failure; ACS: acute coronary syndrome; JVP: jugular venous pressure; PND; paroxysmal nocturnal dyspnoea.

Table A-4: Baseline clinical characteristics of patients in acute heart failure trials [110,190,195-198,280-306]

	OPTIME-CHF	LIDO	ACTIV in CHF	EVEREST	SURVIVE	REVIVE	PIONEER HF	VMAC	RITZ-2	UNLOAD	VERITAS	3CPO	Pre-RELAX-AHF	PROTECT	DOSE	ASCEND-HF	CARRESS	RELAX-AHF	ROSE	TRUE-AHF	ATHENA-HF
Baseline features (& vital signs)																					
Age	65	59	62	66	67	64	61 †	62	62	62	70	78	69	70	66	67	69 †	72	71	69	65
Male	71	88	79	74	74	73	74	73	82	70	60	43	66	67.3	73	67	78		69	66	64
Ejection fraction (%)	24	20	24	28	24	23	24 †	27	24	-	29	-	-	32	35	-	30 †	-	35	-	34
SBP (mmHg)	120	115	119	120	116	116	118 †	121	-	126	132	162	148	124	121	123 †	-	142	114 †	134	120 †
Heart rate (Beats/min)	85	82	84	80	84	81	81 †	-	-	81	81	113	82	80	80	82 †	-	79		86	78 †
RR (breaths/min)	-	-	-	-	-	-	-	-	-	-	-	32	-	21	-	-	-	22	-	-	-
Co-morbidities																					
Hypertension	67.6	-	84	70	61		87	70	54	74	79	55	82	80		72	85	85	80	-	87
Myocardial infarction	48.2	-	53	50	68	55	6	47	64	-	52	-	-	51	-	-	-	-	-	-	28
Atrial fibrillation	31.8	-	52	43	49	-	33	37	24	-	35	-	43	54	51	37	57	51	64	-	50
Chronic lung disease	23.1	-	17	10	-	-		-	-	27	-	15		20				16		-	21
Diabetes Mellitus	44	-	59	38	31	-	18	43	38	50	45	30	49	45	51		65	48	58	38	40
Hypercholesterolaemia	43	-	56	49			36					33	-	-	-	-	-	52	-	-	-
Chronic renal disease	-	-	-	27	-	-	30	-	33	-	39		-	-	-	-	-	-	-	-	24
Valvular heart disease	-	-	-	32	-	-	-	-	-	-	-	11	-	-	-	-	-	-	-	-	-
Coronary heart disease	-	-	-	70	47	-	-	66	-	56	23	64	67	71		60		51	-	51	-
Peripheral Vascular disease	-	-	-	21	-	-	-	-	-	-	-	11	-	-	-	-	-	13	-	-	-
Cerebrovascular disease	-	-	-	11	-	-	10	-	-	-	17	17	-	-	-	-	-	13	-	-	16
Permanent pacemaker	-	-	-	15	-	-	-	27 §	_	_	_	_	_	-	-			11	-	-	-
ICD	-	-	-	-	-	-	18	-	-	-	-	-	-	16	37	_	_	14	43	-	-
CRT	-	-	-	-	-	-	10	-	-	-	-	-	-	11	-	-	-	10	-	-	-
Smoker / Ex-smoker	63	-	75.8	-	-	-	21	-	-	-	-	19	-	-	-	-	-	12	-	-	17
Laboratory findings																					
Serum Na (mmol/L)	138	-	-	-	-	-	-	-	-	139	139	-	141	140 †	138	139 †	-	-	-	-	140 †
Serum K+ (mmolL)	4.2	-	-	-	-	-	4.2 †	-	-	4.0	-	-	-	4.2 †		-	-	-	-	-	3.9 †
Serum Creatinine (mg/dL)	1.4	-	1.9	1.4	-	-	1.3 †	-	1.4	1.5	1.4	-	1.4	1.4 †	1.5	-	1.9 †	-	1.6 †	1.2	1.2 †
Haemoglobin (mg/dL)	-	-	-	-	-	-	-	-	-		130	-	131	126 †	-	-	-	-	-	131 †	-
BNP (pg/mL)	-	-	-	734	1581	-	-	-	-	1256	-	-	-	1290 †	-	994 †	-	-	-	7156 †	1131 †
NT Pto-BNP (pg/mL)	-	-	-	4857	-	-	4821 †	-	-	-	-	-	-	3000 †	7439	4508 †	5013 †	5125 †	5760 †		4028 †
Aetiology of LVSD	-	-	-																		
Ischaemic	51	47		65	76			53	68		73				56			70	60		60
Idiopathic	-	-	-	-	-	-	-	24	20		12	-	-	-	-	-	-	-	-	-	-
Hypertensive	-	-	-	-	-	-	-	9			26	-	-	-	-	-	-	-	-	-	-
Valvular	-	-	-	-	-	-	-				4	-	-	-	-	-	-	-	-	-	-
Precipitating factors																					
ACS	-	-	-	-	-	-	-	-	-	-	-	22	-	-	-	-	-	-	-	-	-
Treatment performed																					
NIV	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPPV	2.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Inotropes	-	-	16	4	-	10	-	29	-	-	-	-	-	-	-	-	-	-	-	-	-
Dobutamine	10	-	-	-	-	-	-	16	-	-	2	-	-	-	-	-	-	-	-	0.5	-
Dopamine	-	-	-	-	8	-	-	7	-	-	2 *	-	-	-	-	-	-	-	-	-	-
Nitrates	-	-	-	-	36	13	-	-	-	-	15 *	88	-	-	-	16	-	7	-	9	-
Cardiac Catheterisation	7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Right heart catheter	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
DC Cardioversion	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IV diuretics	-	-	-	-	**79**	-	-	-	41	-	99	89	-	-	-	-	-	99	-	-	-

	OPTIME-CHF	LIDO	ACTIV in CHF	EVEREST	SURVIVE	REVIVE	PIONEER HF	VMAC	RITZ-2	UNLOAD	VERITAS	3CPO	Pre-RELAX-AHF	PROTECT	DOSE	ASCEND-HF	CARRESS	RELAX-AHF	ROSE	TRUE-AHF	ATHENA-HF
Medication use (pre-admission)																					
ACEi or ARB	-	-	-	42	70	76	47		88	-	63	-	69	76	61	60	55		43		58
ACE inhibitor	70	89	83	-	-	-	-	63	-	49	-	-	-	-	-	-	-	54	-	-	-
Angiotensin receptor blocker	13	-	-	-	-	-	-	9	-	14	-	-	-	-	-	-	-	15	-	-	-
Beta-blocker	22	38	42	70	51	68	60	35	57	65	47	-	59	77	81	57	79	67	80	-	74
Diuretic	90	93	98	97	-		60	87	97	72	33	-	-	-	-	95	91	-	-	-	97
Digoxin	73	75	68	44	-	82	10	60	63		21	-	18	27	-	27	-	21	21	-	8
Calcium channel blocker	14	4	9	11	-	-	-	15	-	8	16	-	11	-	-	-	-	-	-	-	20
Aspirin	46	-	-	-	-	-	-	46	-	-	64	-	-	-	-	-	-	-	-	-	-
Amiodarone / anti-arrhythmic	16	-	-	-	-	-	-	-	22	-	12	-	-	-	-	-	-	-	-	-	-
Nitrates	-	41	-	28	-	-	10	37	69	-	-	-	23	27	-	24	-		27	-	19
Anticoagulants	-	43	-	-	-	-	-	34	-	-	-	-	-	-	-	-	-	-	-	-	-
Anti-platelets	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Mineralocorticoid antagonist	-	-	40	54	51	37	11	-	33	21	19	-	34	45	28	28	22	33	28	-	11
Lipid lowering	-	-	-				-	26	-	-	46	-	-	-	-	-	-	-	-	-	57

All continuous variables are given as the mean unless stated otherwise. Categorical values are expressed as percentage
§ = ICD and PPM, † = median, - = no data available

SBP: systolic blood pressure; RR: respiratory rate; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; ICD: implantable cardiac defibrillator; CRT: cardiac resynchronisation therapy; BNP: brain natriuretic peptide; NT-proBNP: N-terminal-prohormone brain natriuretic peptide; LVSD: left ventricular systolic dysfunction; ACS: acute coronary syndrome; NIV: non-invasive ventilation; IPPV: invasive-positive pressure ventilation; ACEi: angiotensin-converting enzyme inhibitor; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker.

Table A-5: Baseline characteristics of patients in acute heart failure registries [105,184, 316-342]

	ADHERE	OPTIMIZE-HF	EHFS-II	ALARM HF	ADHERE-AP	AHEAD	IN-HF	RO-AHFS	ESC-HF Pilot	HEARTS	ATTEND	Beijing AHF	GULF-CARE	Kor-AHF	ESC HF LT	RICA	EAHFE	KCHF
Age (yrs)	72	73	70	-	66	74 †	72	69	70	61	73	71	59	69	-	79	80	80 †
Male sex	-	48	61	62	57	58	64	56	63	71	58	53	63	53	63	47	45	55
Ejection fraction (%)	34	39	38	-	-	37 †	38	38	38	-	-	44 †	35 †	38	39		51	-
LVEF < 40%	-	49	-	-	-	-	-	-	-	73	53	-	-	-	53	23	22	-
Vital Signs																		
RR	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-	23	-
Pulse oximetery	-	-	-	-	-	-	-	-	-	-	93	-	-	-	-	-	92	-
Systolic blood pressure	144	143	135 †	130	-	134 †	134	143	133	128	146	130	137	131	130 †	139	131	147
SBP >140 mmHg	-	-	-	-	-	-	-	-	-	-	50	43	-	-	-	-	-	54
SBP 100-140 mmHg	-	-	-	-	-	-	-	-	-	-	43	53 †	-	-	-	-	-	39
SBP < 100 mmHg mmHg	-	-	-	21	-	16	-	-	-	-	8	-	-	-	-	-	-	7
DBP (mmHg)	-	-	-	-	-	80 †		-	-	74	83	80 †	81	79	-	-	-	-
HR (bpm)	-	87	95 †	-	-	90 †	93	99	88	88	99	-	97	93	88 †	88	89	96
Laboratory findings																		
BNP	840 †	1273	-	-	-	767 †	1112 †	-	870 †	-	707 †	1280	1300 †	1335	765 †	-	658	721 †
NT-pro BNP	-	-	-	-	-	5,294 †	5168 †	-	4007 †	5738 †	-	4920	3209 †	9240	3825 †	6382	3892	5,830 †
Haemoglobin (mg/dL)	-	121	-	-	-	132 †	125	131	-	124	120	126 †	126 †	124	127 †	121	120	115
Na (mean, mmol/)	-	137	-	-	-	139 †	-	138	-	135.1	139	138 †	138	138	139 †	139	138	139
K+ (mean, mmol/l)	-	-	-	-	-	4.1 †	-	4.4		-	-	-	4.2 †	4		4.4	4.4	-
Glucose (mg/dL)	-	-	-	-	-	144	-	147	110 †	149 †	-	-	-	155	-		-	-
Creatinine (mg/dL)	1.8	1.8	-	-	-	1.2 †	1.5	1.3	-	-	1.4	1.0 †	1.5	1.5	1.2 †	1.4	1.3	1.1
Co-morbidities																		
Chronic lung disease	-	-	19	-	-	16	30	-	15	19	10	15	-	11	19	25	24	8
Myocardial infarction	31	-		-	-	32	-	17	-	-	-	-	-		54			22
Coronary heart disease	57	-	54	31	50	65	-	-	-	53	31	-	47	43	20		30	33
Hypertension	73	71	63	70	64	73	58	67	62	71	70	42	61	62	-	86	84	72
Hypercholesterolaemia	-	-	-	-		-	-	40	-	36	37	-	36	-	-	-	43	38
Diabetes Mellitus	44	42	33	45	45	43	40	33	35	64	34	30	50	40	40	56	42	37
Chronic kidney disease	30	-	17	21	22	-	33	-	26	30	-	17	15	14	26	-	26	45
Peripheral vascular disease	-	-	-	-	-	-	20	-	10	4	-	-	5	-	14	-	9	-
Cerebro-vascular disease	31	-	13	-	13	17	5	-	10	10	14	20	8	15	-	-	13	16
Atrial fibrillation	-	31	39	24	24	27	38	44	44	16	40	28	12	29	-	55	49	41
Haemodialysis	-	-	-	-	-	-	-	-	-		2	-	-	-	-	-	-	-
Anaemia	-	-	15	14	-	35	-	-	42	21	-	-	-	-	16	-	-	67
Pacemaker (PPM, CRT, ICD)	-	-	9	6	-	12	-	-	-	-	-	-	-	-	6	-	9	6
ICD	-	-	-	-	-	-	10	-	6	9	3	-	-	-	-	-	-	2
CRT	-	-	-	-		-	6	-	3	3	-	-	-	-	-	-	-	2
BMI (kg/m^2)	-	-	27 †	-	-	-	28	27	-	29	-	24 †	27 †	23	-	29	28	22

	ADHERE	OPTIMIZE-HF	EHFS-II	ALARM HF	ADHERE-AP	AHEAD	IN-HF	RO-AHFS	ESC-HF Pilot	HEARTS	ATTEND	Beijing AHF	GULF-CARE	Kor-AHF	ESC HF LT	RICA	EAHFE	KCHF
Smoking	-	-	-	-	47	-	-	25	-	33	43	22	22	-	-	-	-	12
Prev HF hospitalization	-	-	-	-	-	-	-	-	-		36	-		-	-	-	-	36
Prev HF diagnosis	75	88	63	36	-	42	57	81	-	64	-	50	-	48	71	-	-	-
Valvular heart disease	-	-	34	-	-	-	-	-	-	-	-	-	13	-	-	-	26	-
Aetiology of LVSD																		
Ischaemic	-	46	-	-	-	-	-	61	51	-	31	43	53	38	57	27	-	33
Hypertensive	-	23	-	-	-	-	-	44	-	-	18	17	16	4	8	39	-	24
Cardiomyopathy	-	-	19	-	-	-	-	25	-	-	13	10	18	21	14		-	15
Valvular heart disease	-	-	-	-	-	-	-	36	-	-	19	10	9	14	12	18	-	20
ECG																		
Atrial Fibrillation	-	-	-	-	-	-	32	44	35	17	-	-	14	-	43	-	49	36
LVH	-	-	-	-	-	-	-	25	16	-	-	-	30	-		-	4	-
LBBB	-	-	22	-	-	-	-	17	-	12	-	-	13	5	15	-	9	-
Paced rhythm	-	-	-	-	-	-	-	4	-	-	-	-	2	-	-	-	9	-
QRS (> 120 ms)	-	-	-	-	-	-	-	4	-	15	-	-	21	-	-	-	-	-
Precipitating Factors																		
ACS	-	-	30	37	-	36	42	11	-	38	-	30	27	26	30	7	2	-
HTN	-	-	-	-	-	-	-	-	-	20	-	-	8	3	17	7	6	-
Arrhythmia	-	-	32	27	-	-	-	-	-	11	-	19	6	20	30	23	15	-
Infection	-	-	18	16	-	-	-	-	-	21	-	26	15	20	20	31	35	-
Medication adherence	-	-	22	13	-	-	-	-	-	21	-	-	19	8	6	-	-	-
Anaemia	-	-	-	-	-	-	-	-	-	-	-	-	3	3	16	-	7	-
Valvular cause	-	-	27	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

All continuous values are given as the mean unless stated otherwise. Categorical values are expressed as percentage

† = median

LVEF: left ventricular ejection fraction; RR: respiratory rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; BNP: brain natriuretic peptide; NT-proBNP: N-terminal-prohormone brain natriuretic peptide; PPM: permanent pacemaker; ICD: implantable cardiac defibrillator; CRT: cardiac resynchronisation therapy; BMI: body mass index; HF: heart failure; LVH: left ventricular hypertrophy; LBBB: left bundle branch block; ACS: acute coronary syndrome; HTN: hypertension.

Table A-6: Therapeutic profiles of patients in acute heart failure registries [105,184, 316-342]

	ADHERE	OPTIMIZE-HF	EHFS-II	ALARM HF	ADHERE-AP	AHEAD	IN-HF	RO-AHFS	ESC-HF Pilot	HEARTS	ATTEND	Beijing AHF	GULF-CARE	Kor-AHF	ESC HF LT	RICA	EAHFE	KCHF
CPAP	-	-	14	10	-	9	-	-	-	-	15	2	10	-	-	-	3	23
IPPV	5	-	5	16	9	14	-	4	-	11	8	2	9	-	-	-	1	4
Intravenous Therapy																		
IV Diuretic	92		84	90	85	-	98	80	85	-	76	79	91	75	82	-	87	84
IV Vasodilator	9	14	38	41	14	-	30	33	19	-	78	75	21	41	21	-	16	68
IV Inotrope	15	7	30		15	-	19	18	11	-	19	33	16	31	12	-	2	16
• *Adrenaline*	-	-	2	4	-	9	-	4	-	-	-	-	-	-	-	-	-	-
• *Dobutamine*	-	-	10	22	-	10	8	10	-	-	11	0.2	-	23	-	-	1	12
• *Dopamine*	-	-	11	13	-	9	14	12	-	-	9	14	-	18	-	-	1	2
• *Levosimendan*	-	-	4	6	-	3	4	2	-	-	-	0.1	-	-	-	-	0.4	-
• *Noradrenaline*	-	-	3	4	-	19	-	-	-	-	5	0.1	-		-	-	0.3	3
Oral Therapy																		
Beta blocker	-	-	10	38	-	-	-	-	-	-	-	31	-	58	-	-	-	-
ACE inhibitor or ARB	-	-	-		-	-	-	-	-	-	-	26	-	76	-	-		-
Mineralocorticoid antagonist	-	-		28	-	-	-	-	-	-	-	34	-	56	-	-		-
Amiodarone/anti-arrhythmic	-	-	18	3	-	-	-	-	-	-	-	-	-	-	-	-		-
Digoxin	-	-		-	-	-	-	26	-	-	-	25	-	-	-	-	15	2
Heparin	-	-	19	2	-	-	-	-	-	-	-	-	-	-	-	-	-	27
LMW Heparin	-	-	41	1	-	-	-	-	-	-	-	13	-	-	-	-	-	-
Oral anti-coagulant	-	-		-	-	-	-	-	-	-	-	5	-	-	-	-	-	-
Anti-platelet	-	-		-	-	-	-	-	-	-	-	35	-	-	-	-	-	-
Nitrate	-	-		-	-	-	-	-	-	-	-	26	-	-	-	-	-	-
Calcium channel blocker	-	-		-	-	-	-	-	-	-	-	10	-	-	-	-	-	-
Statin	-	-		-	-	-	-	-	-	-	-	19	-	-	-	-	-	-
Procedural / Surgical Interventions																		
PCI	8	-	8	13	-	-	-	2	-	-	-	0.1	6	11	10 *	-	-	9
Coronary Artery Bypass Graft	-	-	2	3	-	-	-	0.4	-	-	-	0.03	1	2		-	-	1
Intra-aortic balloon pump	-	-	2	5	-	-	-	0.2	-	3	3	0.3	2	4	1	-	-	3
Permanent pacemaker	-	-	3	3	-	-	-	2	-	-	4	0.03				-	-	2
ICD	6	2	1	2	-	-	-	0.3	-	6	3	-	0.01	1	10	-	-	0.3
CRT	3	-	-	-	-	-	-	-	-	3	2	-	0.01	1	9	-	-	1
Valvular Surgery	-	-	-	4	-	-	-	-	-	-	3	0.3	2	3	-	-	-	1
LVAD	-	-	-	-	-	-	-	-	-	-	0.4	-		0.1	-	-	-	
Haemodialysis / Ultrafiltration	5	-	-	-	-	-	-	1	-	5	-	1	3	8	-	-	-	5
Cardioversion	1	-	-	8	-	-	-	-	-	-	-	-	-		-	-	-	-
Pharmacological treatment (admission)																		
ACE inhibitor or ARB		-	-	-	-	-	59	-	-	68	-	-	-	38	-	-	57	46
ACE inhibitor	41	40	63	-	36	48	-	45	60	_	-	-	43	11	-	-	-	12
ARB	12	12	-		-	12	-	8	-	-	25	_	13	28	-		_	35
Beta-blocker	48	53	43	-	37	51	41	45	62	79	-	-	44	28	-	-	40	38
Mineralocorticoid antagonist	-	7	28	-	21	23	-	34	53	29	-	-	17	18.8	-	-	-	18
Diuretic	70	61	71	-	57	55	64	69	68	53	-	-	58	-	-	-	76	49
Digoxin	28	23	27	-	26	17	16	35	21	-	-	-	17	-	-	-	16	7
Amiodarone (or other anti-arrhythmic)	11	10	13	-		12	-	9	-	-	-	-	3	-	-	-	6	4
Oral anti-coagulant	-	-	24	-	14	18	-	-	-	16	-	-	12	-	-	-	41	31

	ADHERE	OPTIMIZE-HF	EHFS-II	ALARM HF	ADHERE-AP	AHEAD	IN-HF	RO-AHFS	ESC-HF Pilot	HEARTS	ATTEND	Beijing AHF	GULF-CARE	Kor-AHF	ESC HF LT	RICA	EAHFE	KCHF
Anti-platelet	-	40	43	-	42	45	-	41	-	64	-	-	62	-	-	-	-	33
Nitrate	26	22	28	-	32	19	-	-	-	22	-	-	26	-	-	-	18	13
Calcium channel blocker	-	8	18	-		23	-	-	-	-	-	-	-	-	-	-	26	37
Statin	-	39	28	-	40	32	-	21		55	-	-	51	-	-	-	42	-
Pharmacological treatment (discharge)																		
ACE inhibitor or ARB	-	-	-	-	64	-	-	-	-	75	-	29	-	-	-	7	-	57
ACE inhibitor	-	-	80	-	50	69	-	55	-	75	-	-	61	66	-	71	-	25
AT2 blocker	-	-	-	-	-	10	-	11	-	-	46	-	17		-		-	33
Beta-blocker	-	-	61	-	41	77	-	56	-	84	67	40	71	50	-	60	-	66
Mineralocorticoid antagonist	-	-	48	-	31	57	-	54	-	38	-	33	43	45	-	30	-	45
Diuretic	-	-	90	-	81	84	-	81	-	83	-	49	94	71	-	=	-	81
Digoxin	-	-	31	-	34	20	-	40	-	-	-	25	25	8	-	21	-	6
Amiodarone or anti-arrhythmic	-	-	18	-	-	17	-	10	-	-	-	25	5	8	-	-	-	7
Oral anticoagulant	-	-	33	-	18	29	-	10	-	19	-	9	19	28	-	50	-	-
Anti-platelet	-	-	49	-	51	67	-	59	-	76	-	38	81	54	-	36	-	-
Nitrate	-	-	33	-	41	13	-	-	-	34	-	36	38	22	-	-	-	-
Calcium channel blocker	-	-	15	-		18	-	-	-	-	-	15	-	-	-	-	-	34
Anti-lipid agent	-	-	42	-	47	58	-	31	-	70	-	24	72	41	-	45	-	-

* value for PCI and CABG

Categorical values are expressed as percentage

CPAP: continuous positive airways pressure; IPPV: invasive positive pressure ventilation: ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; LMW: low molecular weight; PCI: percutaneous coronary intervention; ICD: implantable cardiac defibrillator; CRT: cardiac re-synchronisation therapy; LVAD: left ventricular assist device.

Table A-7: Summary of precipitating factors and underlying ECG of de-novo versus acute-on-chronic decompensated heart failure patients

	EHFS-II [334]		IN-HF [336]		Gulf CARE [337]		RICA [338]	
	DN-AHF	AC-DHF	DN-AHF	AC-DHF	DN-AHF	AC-DHF	DN-AHF	AC-DHF
Precipitating Factors								
ACS	42	23	-	-	39	17	8	6
HTN	-	-	-	-	10	7	6	7
Arrhythmia	32	33	-	-	5	7	31	19
Infection	15	19	-	-	11	18	26	33
Medication adherence	7	32	-	-	9	28	-	-
Anaemia	-	-	-	-	3	3	-	-
Valvular cause	21	30	-	-	-	-	-	-
ECG								
Atrial fibrillation	-	-	-	-	10	16	-	-
LVH	-	-	-	-	29	32	-	-
LBBB	-	-	7	11	9	16	-	-
Paced rhythm	-	-	-	-	-	-	-	-
QRS duration > 120 ms	-	-	-	-	15	25	-	-

All continuous values are given in mean unless stated otherwise. Categorical values are expressed as percentage
† median, - no data available
DN-AHF: de-novo acute heart failure; AC-DHF: acute-on-chronic decompensated heart failure; ACS: acute coronary syndrome; HTN: hypertension; LVH: left ventricular hypertrophy; LBBB: left bundle branch block.

Table A-8: Summary of therapeutic interventions of de-novo versus acute-on-chronic decompensated heart failure patients

	IN-HF [336]		Gulf CARE [337]	
	DN-AHF	**AC-DHF**	**DN-AHF**	**AC-DHF**
Oxygen Therapy				
CPAP	-	-	11	9
IPPV	-	-	9	8
Intravenous Therapy				
IV Diuretic	98	98	90	92
IV Vasodilator	26	35	24	17
IV Inotrope	21	17	16	16
Adrenaline	-	-	-	-
Dobutamine	10	5	-	-
Dopamine	15	13	-	-
Levosimendan	4	4	-	-
Procedural / Surgical Interventions				
PCI	-	-	10	3
CABG	-	-	2	1
IABP	-	-	2	1
ICD	-	-	0.5	1.5
CRT	-	-	0.1	1
Valvular Surgery	-	-	2	2
HD / UF	-	-	2	3

All continuous values are given as the mean unless stated otherwise. Categorical values are expressed as percentage

- no data available

DN-AHF: de-novo acute heart failure; AC-DHF: acute-on-chronic decompensated heart failure; CPAP: continuous positive airways pressure; IPPV: invasive positive pressure ventilation; PCI; percutaneous coronary intervention; CABG: coronary artery bypass graft; IABP: intra-aortic balloon pump; PPM: permanent pacemaker; ICD: implantable cardiac defibrillator; CRT: cardiac-resynchronisation therapy; LVAD: left ventricular assist device; HD: haemodialysis; UF: ultra-filtration.

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