THE NORTHERN HOSPITAL

HEART FAILURE

"The Dropsical Woman", oil on wood, Gerrit Dou, 1663, Musée du Louvre.

"…Mr. Harrison took four draughts of the foxglove, vomited a little and then purged twenty times with great debility; had next day but one a violent inflammation of the liver with much Pain…

…Mrs. -----, was asthmatic and dropsical, but did not appear near her end. She took four drafts of the decoction of foxglove. She vomited two or three times and then purged twice and died…"

Medical Case notes of Dr Erasmus Darwin, 1776.

The symptoms of heart failure had been well recognized by the medical profession for centuries as demonstrated by the Seventeenth century Dutch painter Gerrit Dou's "The Dropsical Woman". The exact cause, let alone how to treat the condition, remained a complete mystery however until the brilliant discovery by Dr. William Withering in the late Eighteenth century, of digitalis. He was able to deduce that it was "foxglove" that was the beneficial agent of a secret local herbal remedy that appeared to be beneficial in certain types of "dropsy". Withering was a close friend of Dr Erasmus Darwin, (the grandfather of Charles) and both men were children of the "Enlightenment" anxious to embrace the new scientific revolutions of their time. He discussed his findings with Darwin of the beneficial effects of foxglove in patients suffering from "the dropsy". Darwin was so impressed by Withering's results that he enthusiastically took up the new treatment. His initial results however were somewhat disheartening to say the least as can be judged from some of his medical case reports from that time. Withering maintained that Darwin and others with similar disheartening results were not properly experienced in the use of the new drug and were using incorrect dosages and that it was not appropriate for all types of dropsy. As he recognised that the concoction acted on the heart, he deduced that it would only be of benefit in dropsy that was a result of heart disease. Experimental medicines, he cautioned his colleagues could kill as well as cure if not used in an appropriate manner.

Little further advancement was made in the treatment of heart failure over the ensuing two centuries until late in the 20th century when the understanding of the pathophysiology of cardiac failure had progressed to the point that enabled the development new classes of drugs such diuretics and agents capable of reversing the basic pathophysiologic processes of cardiac failure, such as the ACE inhibitors and beta-blockers. In the 21st century we now add agents that manipulate the natriuretic peptide system.

With wondrous advances in technology we stand poised to take the next new steps in the treatment of dropsy, (of the cardiac variety). Unlike in Withering's or Darwin's day we now have an impressive array of investigative modalities that allow us for the first time in history to a make precise diagnoses of the cause and to objectively assess the severity of our patient's dropsy. New technologies include devices that optimize the efficient functioning of the heart while new drugs that would have astounded even the most enlightened men of the Seventeenth century such as Withering and Darwin continue to emerge.

HEART FAILURE

Introduction

Heart failure is a complex clinical syndrome with typical symptoms and signs that generally occur on exertion, but can also occur at rest (particularly when recumbent).

It is secondary to an abnormality of cardiac structure or function that impairs the ability of the heart to fill with blood at normal pressure or eject blood sufficient to fulfil the needs of the metabolising organs.

Chronic Heart Failure is a major public health problem, most frequently seen in older persons and a very common cause of Emergency Department presentations.

Therapies that have been shown to improve survival in patients with heart failure with **reduced ejection fractions** include:

- Angiotensin converting enzyme inhibitors (ACEI) / angiotensin II receptor blockers (ARB)
- Beta blockers
- Mineralocorticoid antagonists (MRAs) (i.e aldosterone antagonists).

More recently the **angiotensin receptor neprilysin inhibitors** (or **ARNIs**) have been introduced and promise a further significant improvement in the treatment of chronic heart failure.

In the past a diagnosis of heart failure meant limited options and poor prognosis, with median survival following a diagnosis of heart failure being quoted at around 3 - 4 years, worse than many cancers.

But in recent years high quality evidence based medicine and interventions has significantly improved the outlook for patients with heart failure.

Heart failure is now becoming a more **preventable** as well as a more **treatable** disease.

Modern diagnosis of heart failure is based on a combination of:

1. **Clinical signs and symptoms**
2. **Echocardiography**
3. **Natriuretic peptide levels**

A major goal of management of heart failure is to identify underlying causes and/or precipitating factors that may be reversed by specific therapies.

However, in the **majority** of patients, there is **irreversible myocardial damage**, and the clinician's only real option is pharmacological and other therapies to control symptoms and signs of heart failure.

See also separate documents on:

- **Acute Cardiogenic Pulmonary Edema (in CVS folder)**
- **Cardiogenic Shock (in CVS folder)**

Terminology

Ejection Fraction:

Ejection fraction is the percentage of ventricular volume that is ejected per heartbeat. The lower limit of normal for the LVEF is **50 - 55%.**

EF = (EDV - ESV)/ EDV

Here EF = ejection fraction; EDV = end diastolic volume; ESV = end systolic volume.

EF therefore is a measure of the cardiac ejection of blood and therefore of systolic function. This haemodynamic parameter is central to the modern classification of heart failure syndromes.

In the past the terms "**right sided**" and "**left sided**" heart failure were used in an attempt to classify heart failure.

Later on the terms "**systolic**" and "**diastolic**" heart failure become popular.

Current terminology does not distinguish right and left or systolic or diastolic as the most important features - rather 2 forms (in **Australia**) are now recognized, **heart failure with reduced ejection fraction**, (or **HRrEF**), and **heart failure with preserved ejection fraction**, (or **HFpEF**) - (**see below for a more detailed description**).

HRrEF corresponds to the older terminology of **systolic heart failure** - or a failure of contractility.

HFpEF corresponds to the older terminology of **diastolic heart failure.** Diastolic function incorporates two components: **LV compliance** (the inverse of stiffness) and **active ventricular relaxation**. Reduced ventricular compliance and abnormal ventricular relaxation may both result in **increased left-sided intra-cavity filling pressure**.

Stable heart failure:

A treated patient with symptoms and signs that have remained generally unchanged for at least **1 month** is said to be "stable" with respect to their heart failure.

Asymptomatic left ventricular dysfunction:

Asymptomatic left ventricular dysfunction refers to reduced LVEF (i.e. EF <50 %) with no current or prior clinical evidence of heart failure.

Its importance lies in being a strong risk factor for the development of clinical heart failure.

New onset heart failure:

New onset or de novo heart failure refers to the first presentation and diagnosis of heart failure in a patient.

The history of symptoms may be short (hours to days) or long (weeks to months).

It follows that these patients

Congestive cardiac failure:

This term is commonly used, despite it having no widely agreed definition.

In general terms it simply means heart failure with **clinical evidence** of **fluid overload**.

Chronic heart failure:

Patients who have had HF for some time are often said to have "chronic HF", although there is no generally accepted definition for what constitutes "chronic" - **3 months** has been arbitrarily assigned according to some literature.

Acute heart failure:

This unhelpful term causes confusion and is not well defined.

The source of confusion mainly lies in what Emergency **Physicians** and **Intensivists** distinguish as "**APO**" and what most cardiologists think of as "**acute exacerbation of chronic heart failure**"

Emergency physicians and **Intensivists** recognize the **immediately life - threatening** condition of what in Australia is commonly referred to as "**Acute Pulmonary Edema**" or in North America as "**Flash Pulmonary Edema**" This is a different entity compared to "**acute exacerbation of heart failure**"

Whilst acute cardiogenic pulmonary edema is primarily a problem of fluid maldistribution, exacerbation of congestive cardiac failure is primarily one of fluid overload.

Acute pulmonary edema usually presents with an elevated blood pressure. When the blood pressure is below 90 mmHg, this represents another life - threatening condition altogether - **acute cardiogenic shock**.

What most cardiologists call "acute heart failure" is really a rapid onset or worsening of a background chronic heart failure, in other words an "**acute exacerbation of chronic heart failure**"

Acute exacerbation of heart failure, **acute pulmonary edema**, and **cardiogenic shock** are not simply the same entities on a spectrum of severity, but usually represent totally different pathologies, and hence require different treatments.

There are **4 variants** that generally come under the (unhelpful) umbrella term of "**acute heart failure**" - even though these entities have *completely different* pathophysiologies and *completely different* treatment approaches.

They include: [1]

1. Acute Cardiogenic Pulmonary Oedema (or "APO" or in North American parlance, "Flash" pulmonary edema):

    - This a life-threatening medical emergency.

      It is characterised by the acute (often within minutes or hours) development of pulmonary oedema as the dominant clinical feature of left heart failure with **redistribution** of fluid into the pulmonary interstitium and then alveolar flooding.

      APO results in the rapid development of respiratory failure and potentially respiratory arrest and death without immediate intervention with NIV and IV nitrates.

2. Cardiogenic shock:

    - This a life-threatening medical emergency, with an especially poor prognosis.

      Cardiogenic shock is typically characterised by the acute development of reduced cardiac output (cardiac index < 2.2 L/min/m^2) and hypotension (systolic blood pressure < 90 mm Hg) in the setting of heart failure (PCWP > 18 mm Hg) to the point where end organ perfusion is compromised.

      Without intervention, multiorgan failure and death ensues.

      Cardiogenic shock most commonly results from a large acute myocardial functional insult (e.g., acute myocardial infarction (MI) or acute fulminant

myocarditis) or a catastrophic cardiac structural insult (e.g., acute torrential valvular regurgitation).

Cardiogenic shock requires inotropic support by drugs or mechanical assist devices, and frequently intubation and ventilation.

3. Acute decompensated heart failure:

- This is the entity most commonly referred to as "acute heart failure".

  It is essentially a relatively acute decompensation in a previously stable patient, due to a precipitating event.

  Treatment involves diuresis and attention to the underlying precipitant.

4. Right heart failure:

- This refers to solitary (or at least predominant) failure of the **right** heart.

  Rare causes are right ventricular (RV) infarction or isolated tricuspid valve pathology; however, the most common cause of right heart failure is right heart pressure overload.

  The right heart is a low-pressure system, and consequently it is particularly sensitive to high afterload (pulmonary hypertension).

  Pulmonary hypertension is a consequence of many prevalent chronic diseases

Epidemiology

The prevalence of chronic HF *depends on the definition* applied:

- Approximately 1 - 2 % of the *general* adult population in *developed countries*
- This figure rises with age however and is ≥10 % among people **> 70** years of age.

Among people > 65 years of age presenting to primary care with **breathlessness on exertion**, **1 in 6** will have unrecognized HF (mainly HFpEF).

The **lifetime** risk of HF at age 55 years is 33% for men and 28% for women.

The proportion of patients with HFpEF ranges from 22 - 73%, depending on the definition applied, the clinical setting (primary care, hospital clinic, hospital admission), age and sex of the studied population, previous myocardial infarction and the year of publication!

Whatever the definitions, two things are quite clear, heart failure is a **very common** disease and its incidence **increases with age.**

Classification

Current *European* (2016) classification of chronic heart failure describes 3 types:

1. **Heart Failure with Reduced Ejection Fraction** (LVEF < 40 %) **(HFrEF)**
2. **Heart Failure with Mid Range Ejection Fraction** (LVEF 40-49 %) **(HFmrEF)**
3. **Heart Failure with Preserved Ejection Fraction** (LVEF LVEF ≥ 50%) **(HFpEF)**

Current *Australian* classification of chronic heart failure describes just 2 types:

1. **Heart Failure with Reduced Ejection Fraction (LVEF < 50 %) (HFrEF)**
2. **Heart Failure with Preserved Ejection Fraction** (LVEF ≥ 50%) **(HFpEF)**

Because heart failure mediation therapy is guided by the 3 European groups, it is possibly more useful, even though slightly more complex.

Note that HFrEF where the EF has **improved** to > 50% **with treatment** (so-called "**recovered HFrEF**") should generally be considered and treated like HFrEF because the underlying pathophysiology is *not believed to have changed* in most cases.

Diagnostic Criteria

Australian Heart failure diagnostic criteria is:

HFrEF	**HFpEF**
• Symptoms +/- clinical signs of heart failure *AND:* • LVEF < 50 %	• Symptoms +/- clinical signs of heart failure *AND:* • LVEF ≥ 50 % *AND:* • Structural heart disease (i.e. LV hypertrophy or LA enlargement

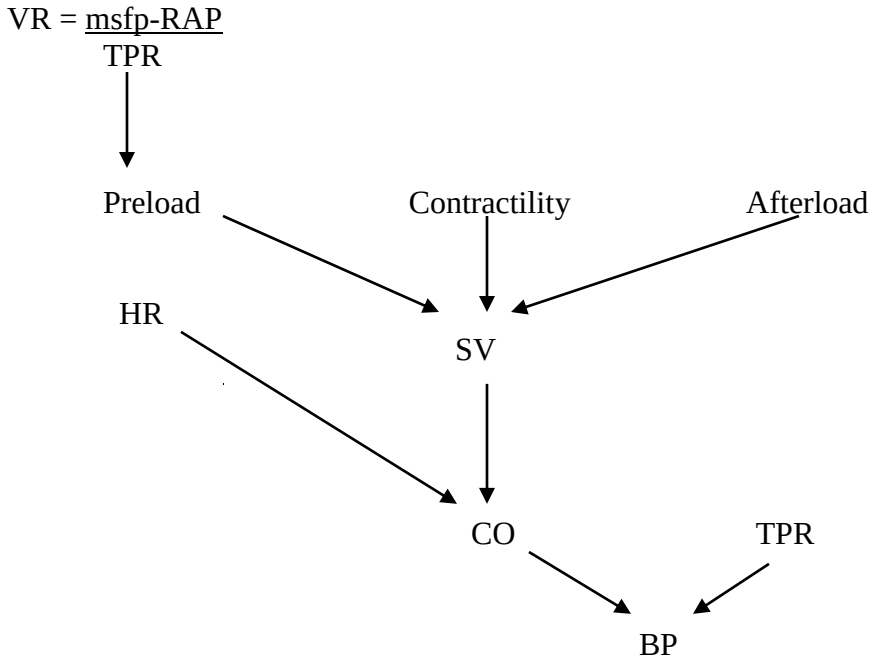
	AND / OR: Diastolic dysfunction, with high filling pressure demonstrated by any of the following: ♥ Invasive means (cardiac catheterisation) ♥ Echocardiography ♥ BNP or NT proBNP elevation ♥ Exercise (invasive or echocardiography)

Physiology

The normal physiological determinants of the cardiac output are determined by

- **Preload**
- **Contractility**
- **Afterload**

The relationships between these 3 entities can be summarised as below:



VR= venous return, RAP= right atrial pressure, msfp= mean systemic filling pressure, HR= heart rate, SV=stroke volume, CO = cardiac output, TPR= total peripheral resistance, BP= blood pressure.

Pathophysiology

Heart Failure is a syndrome characterized by the activation of 3 neurohumeral responses:

1. Sympathetic nervous system (SNS)

2. Renin - Angiotensin - Aldosterone system (RAAS)

3. The natriuretic peptide system (NPS).

Excessive activation of the **SNS** and the **RASS** can lead to **detrimental** results in heart failure.

Pharmacological interventions have therefore been developed to counteract the neuroendocrine overregulation of:

- The SNS (with **β-blockers**).

- The RAAS (with **ACE inhibitors, ARBs** and **mineralcorticoid antagonists** or **MRAs**)

It is now known that the natriuretic peptide system *counter regulates* the *detrimental* effects of the upregulation of the SNS and the RAAS

More recently a novel class of **neprilysin inhibitors** have been developed to enhance the NP system - the **angiotensin receptor neprilysin inhibitors** or **ARNIs**.

The first of this new class is **sacubitril - valsartan**

Sustained activation of the renin angiotensin aldosterone system results in vasoconstriction, renal sodium and fluid retention, activation of cellular growth and proliferation, and subsequent maladaptive cardiovascular remodelling.

Valsartan inhibits detrimental cardiovascular and renal effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II dependent aldosterone release.

Causes:

The general term **cardiomyopathy** is often applied to the failing heart.

The term **primary cardiomyopathy** is generally applied when the aetiology is unknown and **secondary cardiomyopathy** when the aetiology is known.

Dilated cardiomyopathy refers to a primarily dilated failing heart.

Hypertrophic cardiomyopathy refers to a primarily hypertrophied failing heart.

The principle known causes of heart failure include the following:

The commonest causes (by far) include:

1. **Ischemic heart disease**:
    - IHD due to coronary artery disease is the most common cause of heart failure
        - ♥ It can take to form of:
        - ♥ Ischemia / infarction
        - ♥ Microvascular disease
        - ♥ Myocardial stunning
2. **Hypertensive cardiac disease**.
3. Arrhythmias:
    - Tachyarrhythmia (AF) or bradyarrhythmia (sinus node, AV node, conduction dysfunction).

Less common causes include:

4. Structural heart disease:

    Examples include:

    - Valvular heart disease.
    - Chronic constrictive pericarditis
    - Atrial and ventricular septum defects
5. Post infectious / immunological;
    - Viral:
        - ♥ This is usually manifests as a post-viral **dilated cardiomyopathy**.
    - Chagas disease (caused by the parasite Trypanosoma cruzi).

6. Cor pulmonale:

   This is right heart failure secondary to:

   - Severe chronic lung disease.
   - Primary pulmonary hypertension
   - Recurrent pulmonary embolism

7. Physiological heart failure:

   - Anemia
   - Thyroid disease

8. Toxic cardiomyopathies:

   - Alcoholic cardiomyopathy:
     - ♥ Excess alcohol use can cause heart failure that may show some response to supplementation with thiamine
     - ♥ In patients with alcoholic cardiomyopathy, low ejection fraction may improve with abstinence
   - Cardiotoxic drugs:

     Medicinal:

     - ♥ Some cytotoxic agents

     Illicit:

     - ♥ Cocaine / amphetamines / anabolic steroids.
   - Chemical poisons
     - ♥ Heavy metals: Copper, iron, lead, cobalt.
   - Radiation

Uncommon causes include:

9. Genetic disease:

   Examples include:

- Hypertrophic cardiomyopathy (HCM)
- Muscular dystrophies

10. Metabolic / endocrine heart failure:
    - Thiamine deficiency
    - Thyroid toxicity or failure
11. Infiltrative:
    - Amyloidosis / sarcoidosis / haemochromatosis

Causes of exacerbation of heart failure

Regardless of the specific underlying cause, heart failure may have precipitating or aggravating factors requiring specific therapies.

Precipitating factors may include:

1. Acute coronary syndrome (of any type).
2. Arrhythmias:
    - Tachyarrhythmias such as atrial fibrillation, atrial flutter, atrial or ventricular tachycardia.
    - Bradyarrhythmias such as sinus bradycardia or heart block
3. Infection
    - From *any* source
4. Medication related:

    Non-compliance with medication

    Or

    Inadequate medical treatment

    Or

    Drug therapy exacerbating heart failure, including:

    - Negatively inotropic drugs:

- ♥ e.g. **verapamil, diltiazem, in particular**

- Salt-retaining drugs:

  - ♥ e.g. corticosteroids, non-steroidal anti-inflammatory drugs, including COX-2 inhibitors)

5. Fluid overload:

   This may be from:

   - Non-compliance with fluid daily restrictions
   - Severe renal failure

6. Anaemia:

   - Anaemia and iron deficiency are relatively common in patients with heart failure.

     Iron deficiency should be looked for and corrected in patients with heart failure.

7. Pulmonary emboli, (worsening right heart failure).

8. Thyroid disease:

   - Hyperthyroidism or hypothyroidism

9. Acute valvular dysfunction

10. Obstructive sleep apnoea:

    - This may present with isolated right ventricular failure, or even biventricular failure with a pattern of cardiac involvement simulating dilated cardiomyopathy.

      Specific treatment (e.g. continuous positive airway pressure) may reverse the cardiac abnormalities.

11. Increased sympathetic drive:

    - Sympathetic drug abuse
    - Acute hypertension including phaeochromocytoma
    - Takotsubo cardiomyopathy

Clinical features

Clinically signs of heart failure can manifest as left ventricular, with pulmonary congestion and dyspnoea, or right ventricular, with elevated jugular venous pressure, peripheral oedema and liver congestion.

Usually both coexist in the classical syndrome of "congestive", or "biventricular", heart failure.

Pure right ventricular failure can be a consequence of pulmonary hypertension secondary to chronic lung disease.

Important points of history:

The "classical" features of heart failure on history include:

More typical symptoms include:

1. Exertional dyspnea:
    - This is the first sign of heart failure, (though a very non-specific sign).
    - As the severity of heart failure increases, dyspnea occurs at decreasing levels of activity
2. Orthopnea:
    - Dyspnea that develops as soon as the patient assumes a recumbent position.
    - It is usually relived promptly once the patient sits upright
3. Paroxysmal nocturnal dyspnea:
    - Here there is sudden awakening from sleep with breathlessness.
    - In contrast to orthopnea, which may be relieved immediately by sitting up in bed, attacks of paroxysmal nocturnal dyspnea may require 30 minutes or longer in this position for relief.

      This is in distinction to acute cardiogenic pulmonary edema, where the patient develops life threatening symptoms that do not resolve spontaneously, and requires timely medical intervention for survival.
4. Fatigue.

Less typical symptoms include:

5. Nocturnal cough (not otherwise explained).

6. Wheeze

7. Anorexia

8. Dizziness/ syncope.

9. Bendopnoea (dyspnea on leaning forward).

Important points of examination:

The classical sings of heart failure on examination include:

1. Vital signs:

   The following may be seen:

   - Reduced SaO_2 on pulse oximetry
   - Resting tachycardia.
   - Resting tachypnea
   - Pulsus alternans

2. Heart sounds: S_3 "gallop":

   - Despite its apparent textbook importance, this is a subtle, non-specific and subjective sign that held more relevance in the pre-echocardiography era.

3. Evidence of cardiomegaly:

   - Laterally displaced apical impulse

4. Weight changes:

   - Weight gain **(>2 kg/week**) reflects excessive salt and water retention.
   - Weight **loss** however may occur in **advanced** HF ("**cardiac cachexia**")

Heart failure may be left ventricular or right ventricular, however usually both coexist in the syndrome of congestive, or biventricular, heart failure.

5. Evidence of LVF:

   - Basal lung crepitations.

6. Evidence of RVF:

- Elevated JVP / hepatojugular reflux.
- Hepatomegaly.
- Ascites.
- Pitting sacral/ leg edema.

Clinical severity:

The New York Heart Association's Heart Failure classification is a useful measure of the clinical severity of a patient's heart failure.

See Appendix 1 below.

Investigations

Blood tests, (including **natriuretic peptides** where indicated) **ECG**, and **CXR** are routinely done in the ED for patients with HF or suspected HF.

Echocardiography is frequently organized from the ED for patients presenting with possible first presentation of HF or for those with an established diagnosis of HF, but who have an exacerbation of their symptoms.

Other modalities used to assess HF are not routinely organized from the ED.

Investigations for patients with suspected heart failure include the following:

Blood tests:

1. FBE
2. CRP
3. U&Es / glucose
4. LFTs
5. Lipid profile
6. TFTs
7. Iron studies
8. **Natriuretic peptide levels**:

These now play a pivotal role in the diagnosis and treatment of heart failure.

They add **critical supportive** evidence in conjunction with echocardiography and may be used to **exclude** heart failure.

The plasma concentration of natriuretic peptides (NPs) can be used as an initial diagnostic test, especially in the non-acute setting when **echocardiography is not immediately available.**

Elevated NPs help establish:

- An initial working diagnosis
- Identify those who require further cardiac investigation
    - ♥ Patients with values below the cut-point for the exclusion of important cardiac dysfunction do not require echocardiography.

Patients with **normal** plasma NP concentrations are unlikely to have HF.

In general terms:

The upper limit of "normal" in the **non-acute** setting for:

- B-type natriuretic peptide (BNP) is **35 pg/mL**
- N-terminal pro-BNP (NT-proBNP) it is **125 pg/mL**

In the **acute** setting, higher values should be used:

- BNP: 100 pg/mL
- NT-proBNP: 300 pg/mL

With respect to "ruling out" heart failure, current Australian guidelines say:

- BNP < 100 ng/L
- NT proBNP < 300 ng/L

With respect to "ruling in" heart failure, current Australian guidelines say:

- BNP > 400 ng/L
- NT proBNP > 450 ng/L (for age < 50 years).

  > 900 ng/L (for age 50-75 years).

> 1800 ng/L (for age > 75 years).

ECG

A 12 lead ECG is recommended in all patients with HF in order to determine:

- Heart rate
- Heart rhythm
- QRS morphology, and QRS duration,
- Any other relevant abnormalities.

An abnormal (ECG) increases the *likelihood* of the diagnosis of HF, but this has *low* specificity.

HF is *unlikely* in patients presenting with a **completely normal** ECG with moderate sensitivity (89%).

CXR

A CXR should be done, in particular looking for:

1. Confirmatory signs of left heart failure:

   Note that the radiographic signs of heart failure may lag behind the clinical picture, and may be relatively slower to resolve with respect to the clinical picture.

   Radiographic signs of heart failure include:

   - Upper lobe blood diversion is usually the first radiographic sign of heart failure.
   - Interstitial edema, this is represented as fine linear opacities; (peripherally placed basal ones are termed Kerly B lines, whilst more central ones are termed Kerly A lines).

     The **acute onset** of bilateral or unilateral "fluffy" alveolar edema (commonly termed "bats wings") is characteristic of acute cardiogenic pulmonary edema.
   - Cardiomegaly, (a subjective and variable sign however).
   - Pleural effusions

2. Helping to exclude an alternate diagnosis (e.g. infection, fibrosis, COPD).

Echocardiography:

Echocardiography is the most useful imaging modality in patients with suspected HF to establish the diagnosis.

It provides immediate information on:

- Ejection fractions
- Chamber volumes
- Ventricular systolic and diastolic function
- Wall thickness
- Valve function
- The presence (or absence) of pulmonary hypertension.

This information is crucial part in establishing the diagnosis, the degree, and the type of heart failure, as well as assisting in determining the most appropriate treatment.

Stress Echocardiography:

Exercise (or pharmacological) stress echocardiography may be used for the assessment of:

1. Inducible ischaemia
2. Myocardium viability
3. Patients with valve disease in some clinical scenarios (e.g. dynamic mitral regurgitation, low-flow–low-gradient aortic stenosis).
4. The detection of diastolic dysfunction related to exercise in patients with exertional dyspnoea, preserved LVEF and inconclusive diastolic parameters at rest.

Coronary Angiography:

Coronary angiography is recommended in patients with:

1. HF who suffer from angina pectoris recalcitrant to medical therapy provided the patient is otherwise suitable for coronary revascularization.
2. A history of symptomatic ventricular arrhythmia or survival after cardiac arrest.

3. HF and intermediate to high pre-test probability of CAD and the presence of ischaemia in non-invasive stress tests in order to establish the ischaemic aetiology and CAD severity.

Cardiac computed tomography is as a *non-invasive* means to visualize the coronary anatomy in patients with:

1. HF with low - intermediate pre-test probability of CAD

2. Equivocal non-invasive stress tests in order to exclude the diagnosis of CAD

Cardiac CT is only required when its results might affect a therapeutic decision.

Cardiac Magnetic Resonance:

Cardiac magnetic resonance is the *gold standard* for the measurements of cardiac volumes, mass and EF of both the left and right ventricles.

It is the best *alternative* cardiac imaging modality for patients with non-diagnostic echocardiographic studies (particularly for imaging of the right heart) and is the method of choice in patients with complex congenital heart diseases.

It is the preferred imaging method to assess myocardial fibrosis using late gadolinium enhancement (LGE) along with T1 mapping and can be useful for establishing HF aetiology. For example, CMR with LGE allows differentiation between ischaemic and non-ischaemic origins of HF and myocardial fibrosis/scars can be visualized.

CMR allows the *characterization* of myocardial tissue in a range of conditions including:

- Myocarditis
- Amyloidosis
- Sarcoidosis
- Chagas disease
- Haemochromatosis.

CMR may also be used for the assessment of myocardial ischaemia and viability in patients with HF and CAD (considered suitable for coronary revascularization).

Clinical limitations of CMR include local expertise, lower availability and higher costs compared with echocardiography, uncertainty about safety in patients with metallic implants (including cardiac devices) and less reliable measurements in patients with tachyarrhythmias.

Linear gadolinium based contrast agents are contraindicated in individuals with a glomerular filtration rate (GFR) < 30 mL/min/1.73m^2, because they may trigger nephrogenic systemic fibrosis (this may be less of a concern with newer cyclic gadolinium-based contrast agents).

Management

Important aspects of management in exacerbation of **chronic heart** failure in the ED include:

- An assessment of the **degree of disability** of the patient and how this differs from their usual functioning.
- Treatment of patient's immediate symptoms
- Excluding or treating any underlying causative pathology and/ or precipitating event.

Management of HF involves the following modalities:

1. General measures
2. Treating aggravating / precipitating factors
3. Pharmacotherapy
4. Devices based therapies
5. Surgery

General measures:

1. Fluids:
    - In general terms fluid intake is restricted to **1.5 litres per day** in patients with severe or symptomatic HF to relieve *symptoms* due to fluid retention.

      Fluid intake however, may need to be increased during periods of high heat and humidity or nausea/vomiting.

      Body weight monitoring is useful as an indicator of fluid retention.
2. Salt intake:
    - Excessive salt intake (i.e. > 6 grams /day) should be avoided.
3. Weight reduction.

4. Avoidance of excess alcohol.

Treating aggravating / precipitating factors:

These should be looked for and treated as required:

Examples include:

1. **Anaemia**
2. **Iron deficiency**
3. Infection
4. ACS
5. Thyroid dysfunction
6. Arrhythmias
7. Medication compliance/ optimization:
    - **See also Appendix 3 below for drugs to avoid in heart failure.**

Pharmacotherapy:

The Pharmacotherapy of **chronic heart failure** involves 4 principle **classes** of drugs:

1. Diuretics:
2. Sympathetic nervous system (**SNS**) antagonists:
    - Beta blockers
    - Ivabradine
3. Renin - Angiotensin - Aldosterone system (**RAAS**) antagonists:
    - Angiotensin converting enzyme inhibitors (**ACEIs**)
    - Angiotensin receptor blockers (**ARBs**)
    - Mineralcorticoid antagonists (**MRAs**)
4. Natriuretic peptide agonists (in combination with **valsartan**):
    - Neprilysin antagonists with ARBs *or* angiotensin receptor - neprilysin inhibitors (**ARNIs**)

Additional drugs that may be considered include:

5. Hydralazine and isosorbide dinitrate

6. Digoxin

When to use these agents

Use of these agents in chronic heart failure - all else being equal - is guided by the Ejection Fraction - so *not* simply by the "reduced" versus "preserved" heart failure classification.

The following table summarises - in board terms - the current recommendations:

TYPE	**TREATMENTS**	
HFrEF (i.e EF < 50%)	**EF < 40 %**	**EF 41 - 49 %**
	Recommended (as tolerated): 1. ACEI **or** ARB **or** ARNI -Valsartan 2. Beta - blocker &/**or** Ivabradine 3. MRA **Consider:** 1. Diuretics 2. Hydralazine *and* isosorbide dinitrate (as alternative to ACEI or ARB) 3. Digoxin, may be considered in symptomatic patients in sinus rhythm or rapid AF despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA	**Consider** (*depending on exact value - all else being equal*): 1. ACEI **or** ARB **or** ARNI -Valsartan 2. Beta - blocker &/or Ivabradine 3. MRA 4. Diuretics 5. Hydralazine and isosorbide dinitrate (as alternative to ACEI or ARB) 6. Digoxin, may be considered in symptomatic patients in sinus rhythm or rapid AF despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA

HFpEF (i.e EF ≥ 50 %)	**EF ≥ 50 %**
	No treatment has yet been shown, convincingly, to reduce morbidity or mortality in patients with HFpEF Therapy may however be given for symptoms and/or for comorbidities Low dose spironolactone may be *considered* to decrease HF hospitalization.

ACEI = ACE Inhibitor

ARB = Angiotensin receptor blocker,

ARNI = Angiotensin receptor neprilysin inhibitor

MRA = Mineralocorticoid receptor antagonist

ACEIs:

Treatment is **commenced** with **ACEIs *and* beta blockers.**

ACEIs have been shown to reduce mortality and morbidity in patients with **HFrEF** and are recommended (unless contraindicated or not tolerated) in **all symptomatic patients**.

ACEIs should be up-titrated to the **maximum *tolerated* dose** in order to achieve adequate inhibition of the renin - angiotensin - aldosterone system (RAAS).

There is evidence that in clinical practice the majority of patients receive *suboptimal* doses of ACEI.

Beta blockers:

Beta-blockers reduce mortality and morbidity in symptomatic patients with HFrEF, despite treatment with an ACEI and, in most cases, a diuretic.

There is consensus that **beta-blockers and ACEIs** are **complementary**, and can be started together as soon as the diagnosis of HFrEF is made.

There is no evidence favouring the initiation of treatment with a beta-blocker before an ACEI has been started.

Beta-blockers should be initiated in clinically stable patients at a low dose and gradually up-titrated to the maximum tolerated dose.

In patients admitted due to acute HF (AHF) beta-blockers should be cautiously initiated in hospital, once the patient is stabilized.

The **specific** beta blockers which are recommended for adjunctive treatment in **heart failure** are:

- Carvedilol
- Bisoprolol
- Metoprolol succinate
- Nebivolol.

ARBs:

An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients **unable to tolerate an ACE-I** (patients should also receive a beta-blocker and an MRA).

An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.

MRAs:

Spironolactone or eplerenone are recommended in all patients who remain symptomatic, despite treatment with an ACEI and a beta-blocker, with HFrEF and LVEF $\leq$ 35%, to reduce mortality and HF hospitalization.

Caution should be exercised when MRAs are used in patients with impaired renal function and in those with serum potassium levels .5.0 mmol/L. Regular checks of serum potassium levels and renal function should be performed according to clinical status.

Diuretics:

Diuretics are recommended to reduce the **signs and symptoms** of congestion in patients with HFrEF, but their effects on mortality and morbidity have **not** been studied in RCTs

Diuretics appear to improve symptoms including exercise capacity.

Loop diuretics produce a more intense and shorter diuresis than thiazides, although they act synergistically and the combination may be used to treat resistant oedema.

However, adverse effects are more likely and these combinations should only be used with care.

The aim of diuretic therapy is to achieve and maintain euvolaemia with the lowest achievable dose.

Ivabradine:

Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤ 35%, in **sinus rhythm** and a **resting heart rate ≥ 70 bpm** who are **unable to tolerate** or have **contra-indications** for a **beta-blocker**. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).

Ivabradine should also be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤ 35%, in sinus rhythm and a resting heart rate ≥70 bpm **despite** treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB)

ARNIs:

Sacubitril-valsartan is recommended as a ***replacement*** for an **ACE-I** (or **ARB**) to *further* reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA

Hydralazine and isosorbide dinitrate:

Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.

Digoxin:

Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).

In patients with symptomatic HF and AF, digoxin may be useful to slow a rapid ventricular rate, but it is only recommended for the treatment of patients with HFrEF and AF with rapid ventricular rate when other therapeutic options cannot be pursued.

Of note, the optimal ventricular rate for patients with HF and AF has not been well established, but the prevailing evidence suggests that strict rate control might be deleterious.

A resting ventricular rate in the range of 70 - 110 bpm is acceptable.

Note on calcium channel blockers:

Non-dihydropyridine calcium-channel blockers (**CCBs**) are **not** indicated for the treatment of patients with HFrEF.

Diltiazem and **verapamil** have been shown to be **unsafe** in patients with HFrEF

With regard to **dihydropyridine** CCBs; some are known to increase sympathetic tone and they may have a negative safety profile in HFrEF.

There is only evidence on safety for **amlodipine** and **felodipine** in patients with HFrEF, and they can be used only if there is a **compelling** indication in patients with HFrEF.

Note on statins:

Statins have not been shown to be beneficial when prescribed **solely** for HF.

Treatment with statins is recommended in patients **with or at high-risk of CAD** *whether or not* they have LV systolic dysfunction, in order to prevent or delay the onset of HF (caused by CAD) and prolong life.

Note on SGLT2 inhibitors:

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are recommended in patients with type 2 diabetes mellitus associated with cardiovascular disease and insufficient glycaemic control despite metformin, to decrease the risk of cardiovascular events and decrease the risk of hospitalisation for heart failure.

Options include:

- Empagliflozin
- Canagliflozin

Patients with AF and Heart Failure:

Pharmacological therapy aiming for a resting ventricular rate of 60-100 bpm should be considered in patients with HF associated with AF and a rapid ventricular response

Beta-Blockers and/or digoxin are generally favoured for ventricular rate control.

Consider **non-dihydropyridine** calcium entry blockers in patients with HFpEF to control the ventricular rate of AF; however, these drugs should be avoided in patients with HFrEF.

Catheter ablation for AF (either paroxysmal or persistent) should be considered in patients with HFrEF associated with an LVEF $\leq$ 35%, who present with recurrent symptomatic AF, to decrease mortality and hospitalisation for HF.

Consider oral amiodarone in patients with HF associated with AF, to facilitate attainment and maintenance of sinus rhythm (with or without electrical cardioversion), improve

symptoms, or guide decisions regarding the need for more invasive approaches (e.g., AF catheter ablation or atrioventricular node ablation).

Devices based therapies:

There are two main device-based therapies used in patients with heart failure:

Cardiac resynchronization therapy (CRT):

Resynchronisation of ventricular contraction is achieved by pacing both the left and the right ventricles simultaneously. The benefit is greater in patients with a broader QRS duration, and in some studies for left bundle branch block morphology and prolonged PR interval.

Cardiac resynchronization therapy (CRT) is **recommended** in patients with:

- HFrEF associated with sinus rhythm

And:

- An LVEF ≤ 35%

And:

- A QRS duration ≥ 150 ms,

despite optimal medical therapy, to decrease mortality, decrease hospitalisation for HF, and improve symptoms.

CRT should be **considered** in patients with:

- HFrEF associated with sinus rhythm

And

- An LVEF ≤ 35%

And

- A QRS duration of 130-149 ms

despite optimal medical therapy, to decrease mortality, decrease hospitalisation for HF, and improve symptoms.

CRT should be **considered** in patients with:

- HFrEF associated with an LVEF of ≤ 50% accompanied by high grade atrioventricular block requiring pacing, to decrease hospitalisation for HF

CRT is **contraindicated** in patients with:

- QRS duration < 130 ms, because of lack of efficacy and possible harm.

Implantable cardioverter defibrillator (ICD):

An implantable cardioverter defibrillator (ICD) should be considered as a primary prevention indication in patients with:

- HFrEF associated with ischaemic heart disease

And

- An LVEF ≤ 35%,

to decrease mortality.

An ICD may be also considered as a primary prevention indication in patients with HFrEF associated with **dilated cardiomyopathy** and an LVEF ≤ 35%,

Surgery:

Coronary artery bypass graft surgery:

Coronary artery bypass graft surgery should be **considered** in patients with:

- HFrEF associated with ischaemic heart disease

And

- An LVEF ≤ 35%

if they have **surgically correctable** coronary artery disease,

This is to:

- Improve symptoms (e.g. relief of angina and HF symptoms)
- Decrease morbidity and long term mortality.

The benefits of surgery must be balanced against the short term morbidity and mortality risk related to coronary artery bypass graft surgery.

Factors unrelated to the severity of HF - including age, frailty and comorbidities - are important contributors to the surgical risk.

Surgical aortic valve replacement:

Surgical **aortic valve replacement** is recommended in patients with **severe aortic stenosis** or **severe aortic regurgitation** and **HF** in the *absence* of major comorbidities or frailty, to improve symptoms and decrease mortality.

Transcatheter aortic valve implantation (**TAVI**) should be considered in patients with **severe aortic stenosis** and **HF** at **intermediate to high operative mortality risk**, or considered inoperable for surgical aortic valve replacement, and who are deemed suitable for transcatheter aortic valve implantation following assessment by a heart team, to improve symptoms and decrease mortality.

Left ventricular assist devices:

Left ventricular assist devices may be appropriate for patients who are resistant to medical therapies.

Heart transplantation:

Heart transplantation is an ultimate option for patients with end-stage heart failure who meet specific criteria.

Disposition

The modern treatment of HF is complex and referral to a Specialist Heart Failure Physician should be strongly considered, especially in younger patients

Patients will also benefit from specific education services. These services have been found to significantly reduce the relative risk of hospital readmission and of death.

Appendix 1

The New York Heart Association Heart Failure Classification:

CLASS	Features
Class I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 2

Optimal dosing:

	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril[a]	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	10–20 *b.i.d.*
Lisinopril[b]	2.5–5.0 *o.d.*	20–35 *o.d.*
Ramipril	2.5 *o.d.*	10 *o.d.*
Trandolapril[a]	0.5 *o.d.*	4 *o.d.*
Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*[d]
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 *o.d.*
Nebivolol[c]	1.25 *o.d.*	10 *o.d.*
ARBs		
Candesartan	4–8 *o.d.*	32 *o.d.*
Valsartan	40 *b.i.d.*	160 *b.i.d.*
Losartan[b,c]	50 *o.d.*	150 *o.d.*
MRAs		
Eplerenone	25 *o.d.*	50 *o.d.*
Spironolactone	25 *o.d.*	50 *o.d.*
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*
I_f-channel blocker		
Ivabradine	5 *b.i.d.*	7.5 *b.i.d.*

Diuretics	Initial dose (mg)		Usual daily dose (mg)	
Loop diuretics[a]				
Furosemide	20–40		40–240	
Bumetanide	0.5–1.0		1–5	
Torasemide	5–10		10–20	
Thiazides[b]				
Bendroflumethiazide	2.5		2.5–10	
Hydrochlorothiazide	25		12.5–100	
Metolazone	2.5		2.5–10	
Indapamide[c]	2.5		2.5–5	
Potassium-sparing diuretics[d]				
	+ACE-I/ ARB	-ACE-I/ ARB	+ACE-I/ ARB	-ACE-I/ ARB
Spironolactone/ eplerenone	12.5–25	50	50	100–200
Amiloride	2.5	5	5–10	10–20
Triamterene	25	50	100	200

Appendix 3

Drugs that should be avoided in heart failure:

These include:

1. Some anti-arrhythmic agents:

    - Flecainide:

        - ♥ Flecainide may increase the risk of ventricular arrhythmias in impaired left ventricular function and may worsen heart failure.

    - Dronedarone

        - ♥ Dronedarone has been associated with an increased mortality in patients with heart failure

    Amiodarone is **safe**

2. **Non - dihydropyridine** calcium channel blockers:

    - Verapamil / Diltiazem

    These have significant negative inotropic effects.

    The risk is verapamil > diltiazem > dihydropyridines (these last may be used but with caution)

3. NSAIDs:

    May cause:

    - Sodium & water retention

    - May increase the risk of myocardial infarction (COX 2) in patients with higher CVS risk factors.

4. Tricyclic antidepressants:

    - May cause prolonged QT, arrhythmias, and hypotension from alpha-blocking effects.

5. Thiazolidinediones:

    - Rosiglitazone / pioglitazone

    May cause sodium and fluid retention.

6. Directly cardiotoxic drugs:

    - Clozapine
    - Some immunosuppressants used in oncology including TNF antagonists

7. Corticosteroids:

    - Sodium and water retention via their mineralot effects

8. Moxonidine:

    - This drug has been associated with increased mortality in patients with heart failure and is contraindicated in such patients.

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