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ESC Guidelines

Guidelines on the diagnosis and treatment of acute heart failure—full text

The Task Force on Acute Heart Failure of the European Society of Cardiology

Endorsed by the European Society of Intensive Care Medicine (ESICM)

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Preamble

Guidelines and Expert Consensus Documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) and by different organizations and other related societies. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they have been developed by an unquestionable decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents.

In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied with in the vast majority of cases. It is therefore of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their implementation programmes must also be well conducted. Attempts have been made to determine whether guidelines improve the quality of clinical practice and the utilization of health resources.

The *ESC Committee for Practice Guidelines* (CPG) supervises and coordinates the preparation of new *Guidelines and Expert Consensus* Documents produced by Task Forces, expert groups, or consensus panels. The chosen experts in these writing panels are asked to provide disclosure statements of all relationships they may have which might be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

The Task Force has classified and ranked the usefulness or efficacy of the recommended procedure and/or treatments and the Level of Evidence as indicated in the tables that follow.

Classes of Recommendations	
Class I	Evidence and/or general agreement that a given diagnostic procedure/treatment is beneficial, useful, and effective
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy
Class IIb	Usefulness/efficacy is less well established by evidence/opinion
Class III*	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful

*Use of Class III is discouraged by the ESC.

Levels of evidence	
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of evidence B	Data derived from a single randomized clinical trials or large non-randomized studies
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies and registries

1. Introduction

The aim of these guidelines is to describe the rationale behind the diagnosis and treatment of acute heart failure (AHF) in the adult population. These guidelines are written for all specialists caring for patients with AHF.

The Committee for Practice Guidelines (CPG) of the European Society of Cardiology (ESC) nominated the Task Force for the AHF guidelines. The Task Force included representatives from the Heart Failure Association of the ESC and members of the European Society of Intensive Care Medicine (ESICM). The Task Force recommendations were circulated among a review board and approved by the CPG, and by the ESICM. Together with the Guidelines for the diagnosis and treatment of chronic heart failure[1] these Guidelines form the recommendations on diagnosis and treatment of heart failure.

The recommendations are also published as a shorter document,[2] and as a pocket guideline. Updated versions will be prepared in due course.

2. Epidemiology, aetiology, and clinical context

The combination of the aging of the population in many countries and improved survival after acute myocardial infarction (AMI) has created a rapid growth in the number of patients currently living with chronic heart failure (CHF), with a concomitant increase in the number of hospitalizations for decompensated heart failure. Heart failure is the leading cause of hospital admissions in the Medicare population in the United States.[3] In Europe, Scottish data show that both the number of' 'first ever' diagnosis, and principal and secondary diagnosis of heart failure, hospitalizations have increased. In a hospital registry survey 4.7% of hospitalizations in women, and 5.1% in men, were due to heart failure (in any diagnostic position), and was highly age-related.[4] While some hospitalizations are due to new onset of AHF, most hospitalizations are caused by decompensation of CHF. The crude incidence of heart failure of all grades of severity varies from 2.3 to 3.7 per thousand per annum.[1,5,6]

Coronary heart disease is the aetiology of AHF in 60–70% of patients,[7,8] particularly in the elderly population. In younger subjects, AHF is frequently caused by dilated cadiomyopathy, arrhythmia, congenital or valvular heart disease, or myocarditis. The causes and complications of AHF are described in *Table 1*.

The large number and long duration of hospitalization associated with AHF or decompensated CHF create a substantial economic burden on the health care system. The management of heart failure in the United States consumes nearly $20 billion annually, 10% of all health care dollars spent on cardiovascular disease.[9] Around 75% of expenditure on heart failure relates to in-patient care. Advanced heart failure and related acute decompensation have become the single most costly medical syndrome in cardiology.[10,11]

AHF or CHF is often a combination of cardiac and other end-organ disease, particularly metabolic disease. In the Euroheart Failure survey[8] of patients hospitalized with heart failure, mitral regurgitation was found in the echo substudy in 29% of patients, aortic regurgitation in 7%, aortic stenosis in 7%, and mitral stenosis in 3%. Furthermore, 44% of the patients gave a history of paroxysmal atrial arrhythmias. Hospitalization due to life threatening arrhythmia was reported in 8%. The heart failure syndrome was accompanied with hypertension or left ventricular hypertrophy (LVH) in 53%, diabetes in 27%, with renal problems in 17%, and respiratory disease in 32%. The prevalence of myocardial dysfunction in acute myocardial infarct patients is up to 30–35%[12] and in unstable angina patients 9%.[13]

Patients with AHF have a very poor prognosis. In the largest randomized trial to date in patients hospitalized with decompensated heart failure, the 60-day mortality rate was 9.6% and the combined rate for mortality or rehospitalization within 60 days was 35.2%.[8,12] Mortality is high particularly in patients with AMI accompanied by severe heart failure, with a 30% 12 month mortality.[14] Likewise, in acute pulmonary oedema a 12% in-hospital and 40% 1-year mortality have been reported.[15] The predictors of mortality are high pulmonary capillary wedge pressure (PCWP $\geq$ 16 mmHg), low serum sodium, increased left ventricular dimension, and low peak oxygen consumption.[16,17]

About 45% of patients hospitalized with AHF will be rehospitalized at least once (and 15% at least twice)

Table 1 Causes and precipitating factors in AHF

(1) Decompensation of pre-existing chronic heart failure (e.g. cardiomyopathy)
(2) Acute coronary syndromes
  (a) myocardial infarction/unstable angina with large extent of ischaemia and ischaemic dysfunction
  (b) mechanical complication of acute myocardial infarction
  (c) right ventricular infarction
(3) Hypertensive crisis
(4) Acute arrhythmia (ventricular tachycardia, ventricular fibrillation, atrial fibrillation or flutter, other supraventricular tachycardia)
(5) Valvular regurgitation/endocarditis/rupture of chordae tendinae, worsening of pre-existing valvular regurgitation
(6) Severe aortic valve stenosis
(7) Acute severe myocarditis
(8) Cardiac tamponade
(9) Aortic dissection
(10) Post-partum cardiomyopathy
(11) Non-cardiovascular precipitating factors
  (a) lack of compliance with medical treatment
  (b) volume overload
  (c) infections, particularly pneumonia or septicaemia
  (d) severe brain insult
  (e) after major surgery
  (f) reduction in renal function
  (g) asthma
  (h) drug abuse
  (i) alcohol abuse
  (j) phaeochromocytoma
(12) High output syndromes
  (a) septicaemia
  (b) thyrotoxicosis crisis
  (c) anaemia
  (d) shunt syndromes

within twelve months.[18,19] Estimates of the risk of death or rehospitalizations within 60 days of admission for this disease vary from 30 to 60%, depending on the population studied.[7,8,20–23]

I. Definitions, diagnostic steps, instrumentation, and monitoring of the patient with AHF

3. Definition and clinical classification of AHF

3.1. Definition

Acute heart failure is defined as the rapid onset of symptoms and signs secondary to abnormal cardiac function. It may occur with or without previous cardiac disease. The cardiac dysfunction can be related to systolic or diastolic dysfunction, to abnormalities in cardiac rhythm, or to preload and afterload mismatch. It is often life threatening and requires urgent treatment.

AHF can present itself as acute *de novo* (new onset of acute heart failure in a patient without previously known cardiac dysfunction) or acute decompensation of CHF.

The patient with AHF may present with one of several distinct clinical conditions (*Table 2*):

(i) Acute decompensated heart failure (*de novo* or as decompensation of CHF) with signs and symptoms of AHF, which are *mild* and do not fulfil criteria for cardiogenic shock, pulmonary oedema, or hypertensive crisis.

(ii) Hypertensive AHF: Signs and symptoms of heart failure are accompanied by high blood pressure and relatively preserved left ventricular function with a chest radiograph compatible with acute pulmonary oedema.

(iii) Pulmonary oedema (verified by chest X-ray) accompanied by severe respiratory distress, with crackles over the lung and orthopnoea, with O_2 saturation usually $<90\%$ on room air prior to treatment.

(iv) Cardiogenic shock: Cardiogenic shock is defined as evidence of tissue hypoperfusion induced by heart failure after correction of preload. There is no clear definition for haemodynamic parameters, which explains the differences in prevalence and outcome reported in studies (*Table 2*), but cardiogenic shock is usually characterized by reduced blood pressure (systolic BP < 90 mmHg or a drop of mean arterial pressure >30 mmHg) and/or low urine output (<0.5 ml/kg/h), with a pulse rate >60 bpm with or without evidence of organ congestion. There is a continuum from low cardiac output syndrome to cardiogenic shock.

(v) High output failure is characterized by high cardiac output, usually with high heart rate (caused by arrhythmias, thyrotoxicosis, anaemia, Paget's disease, iatrogenic or by other mechanisms), with warm peripheries, pulmonary congestion, and sometimes with low BP as in septic shock.

Table 2 Terminology and common clinical and haemodynamic characteristics

Clinical status	Heart rate	SBP mmHg	CI L/min/m^2	PCWP mmHg	Congestion Killip/ Forrester	Diuresis	Hypoperfusion	End organ hypoperfusion
I Acute decompensated congestive heart failure	+/−	Low normal/ High	Low normal/ High	Mild elevation	K II/F II	+	+/−	−
II Acute heart failure with hypertension/hypertensive crisis	Usually increased	High	+/−	>18	K II–IV/FII–III	+/−	+/−	+, with CNS symptoms
III Acute heart failure with pulmonary oedema	+	Low normal	Low	Elevated	KIII/FII	+	+/−	−
IVa Cardiogenic shock*/ low output syndrome	+	Low normal	Low, <2.2	>16	K III–IV/F I–III	Low	+	+
IVb Severe cardiogenic shock	>90	<90	<1.8	>18	K IV/F IV	Very low	++	+
V High output failure	+	+/−	+	+/−	KII/FI–II	+	−	−
VI Right-sided acute heart failure	Usually low	Low	Low	Low	F I	+/−	+/−, acute onset	+/−

The above values in Table 2 are general rules.
*The differentiation from low cardiac output syndrome is subjective and the clinical presentation may overlap these classifications.
SBP = systolic blood pressure; CI = cardiac index; PCWP = pulmonary capillary wedge pressure; CNS = central nervous system.

(vi) Right heart failure is characterized by low output syndrome with increased jugular venous pressure, increased liver size and hypotension.

Various other classifications of the AHF syndrome are utilized in coronary care and intensive care units. The Killip classification is based on clinical signs and chest X-ray findings, and the Forrester classification is based on clinical signs and haemodynamic characteristics. These classifications have been validated in AHF after AMI and thus are best applied to *de novo* AHF. The third 'clinical severity' classification has been validated in a cardiomyopathy service[24] and is based on clinical findings.[25] It is most applicable to chronic decompensated heart failure.[24]

3.1.1. Killip classification. The Killip classification was designed to provide a clinical estimate of the severity of myocardial derangement in the treatment of AMI:[26]

- Stage I—No heart failure. No clinical signs of cardiac decompensation;
- Stage II—Heart failure. Diagnostic criteria include rales, S3 gallop and pulmonary venous hypertension. Pulmonary congestion with wet rales in the lower half of the lung fields;
- Stage III—Severe heart failure. Frank pulmonary oedema with rales throughout the lung fields;
- Stage IV—Cardiogenic shock. Signs include hypotension (SBP $\leq$ 90 mmHg), and evidence of peripheral vasoconstriction such as oliguria, cyanosis, and diaphoresis.

3.1.2. Forrester classification. The Forrester AHF classification was also developed in AMI patients, and describes four groups according to clinical and haemodynamic status (*Figure 1*).[27] Patients are classified clinically on the basis of peripheral hypoperfusion (filliform pulse, cold clammy skin, peripheral cyanosis, hypotension, tachycardia, confusion, oliguria) and pulmonary congestion (rales, abnormal chest X-ray), and haemodynamically on the basis of a depressed cardiac index ($\leq$2.2 L/min/m^2) and elevated pulmonary capillary pressure ($>$18 mmHg). The original paper defined the treatment strategy according to the clinical and haemodynamic status. Mortality was 2.2% in group I, 10.1% in group II, 22.4% in group III, and 55.5% in group IV.

3.1.3. 'Clinical severity' classification. The clinical severity classification is based on observation of the peripheral circulation (perfusion) and on auscultation of the lungs (congestion). The patients can be classified as Class I (Group A) (warm and dry), Class II (Group B) (warm and wet), Class III (Group L) (cold and dry), and Class IV (Group C) (cold and wet). This classification has been validated prognostically in a cardiomyopathy service[28] and is therefore applicable to patients with CHF, whether hospitalized or outpatients.

3.2. The clinical syndrome of AHF

AHF is a clinical syndrome, with reduced cardiac output, tissue hypoperfusion, increase in the pulmonary capillary wedge pressure, and tissue congestion. The underlying mechanism may be cardiac or extra-cardiac, and may be transient and reversible with resolution of the acute syndrome or may induce permanent damage leading to chronic heart failure. The cardiac dysfunction can be related to systolic or diastolic myocardial dysfunction (mainly induced by ischaemia or infection), acute *valvular* dysfunction, pericardial tamponade, abnormalities of cardiac rhythm, or preload/afterload mismatch. Multiple extra-cardiac pathologies may result in AHF by changing the cardiac loading conditions for example (i) increased afterload due to systemic or pulmonary hypertension or massive pulmonary emboli, (ii) increased preload due to

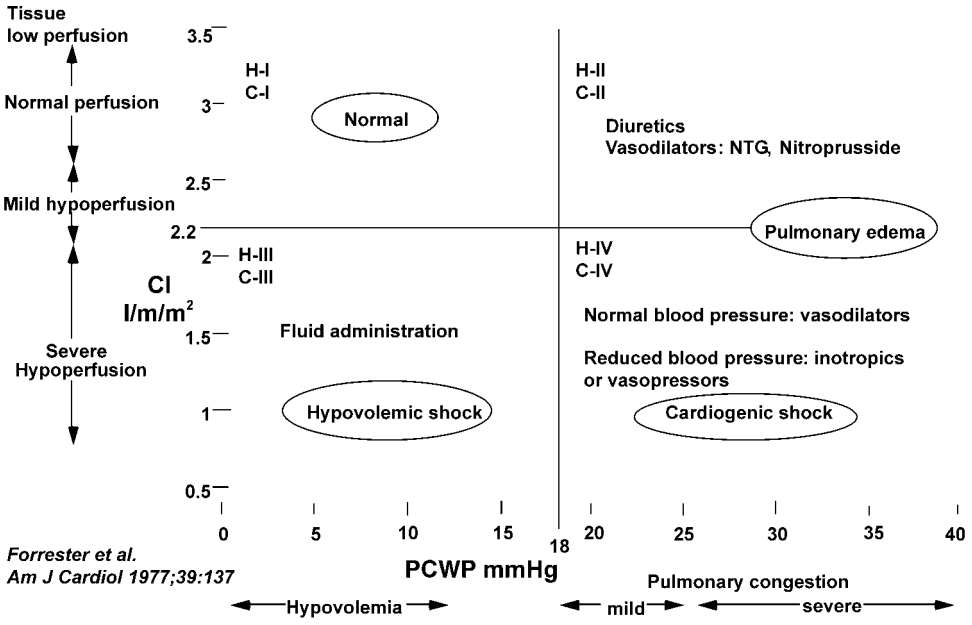

Figure 1 Clinical classification of the mode of heart failure (Forrester classification). H I–IV refers to haemodynamic severity, with reference figures for cardiac index and pulmonary capillary pressures shown on the vertical and horizontal axes, respectively. C I–IV refers to clinical severity.

increased volume intake or reduced excretion due to renal failure or endocrinopathy, or (iii) high output state due to infection, thyrotoxicosis, anaemia, and Paget's disease. Heart failure can be complicated by co-existing end-organ disease. Severe heart failure can also induce multi-organ failure, which may be lethal.

Appropriate long-term medical therapy and, if possible, anatomical correction of the underlying pathology may prevent further AHF syndrome 'attacks' and improve the poor long-term prognosis associated with this syndrome.

The clinical AHF syndrome may be classified as predominantly left or right forward failure, left or right backward failure, or a combination of these.

3.2.1. Forward (left and right) AHF. Forward acute heart failure may be mild-to-moderate with only effort fatigue, up to severe with manifestations of reduced tissue perfusion at rest with weakness, confusion, drowsiness, paleness with peripheral cyanosis, cold clammy skin, low blood pressure, filliform pulse, and oliguria, culminating in the full blown presentation of cardiogenic shock.

This syndrome may be induced by a large variety of pathologies. An adequate history may indicate the main diagnosis for example (i) acute coronary syndrome with the relevant risk factors, past history, and suggestive symptoms; (ii) acute myocarditis with a recent history suggestive of acute viral infection; (iii) acute valvular dysfunction with a history of chronic valve disease or valve surgery, infection with the possibility of bacterial endocarditis, or chest trauma; (iv) pulmonary embolism with a relevant history and suggestive symptoms; or (v) pericardial tamponade.

Physical examination of the cardiovascular system may be indicative of the main diagnosis, for example by distended neck veins and paradoxical pulse (pericardial tamponade), muffled heart sounds related to myocardial systolic dysfunction, or the disappearance of artificial valve sounds or an appropriate murmur indicating a valvular problem.

In forward AHF immediate management should include supportive treatment to improve cardiac output and tissue oxygenation. This can be achieved with vasodilating agents, fluid replacement to achieve an optimal preload, short-term inotropic support and (sometimes) intra aortic balloon counterpulsation.

3.2.2. Left-heart backward failure. Left-heart backward failure may be related to left ventricular dysfunction with varying degrees of severity from mild-to-moderate with only exertional dyspnoea, to pulmonary oedema presenting with shortness of breath (dry cough, sometimes with frothy sputum), pallor or even cyanosis, cold clammy skin, and normal or elevated blood pressure. Fine rales are usually audible over the lung fields. Chest X-ray shows pulmonary congestion/oedema.

Pathology of the left heart may be responsible for this syndrome, including: myocardial dysfunction related to chronic existing conditions; acute insult such as myocardial ischaemia or infarction; aortic and mitral valve dysfunction; cardiac rhythm disturbances; or tumours of the left heart. Extra-cardiac pathologies may include severe hypertension, high output states (anaemia, thyrotoxicosis), and neurogenic states (brain tumours or trauma).

Physical examination of the cardiovascular system, including the apex beat, the quality of the heart sounds, the presence of murmurs, and auscultation of the lungs for fine rales and expiratory wheezing ('cardiac asthma') may be indicative of the main diagnosis.

In left heart backward failure patients should be treated mainly with vasodilation and the addition of diuretics, bronchodilators, and narcotics, as required. Respiratory support may be necessary. This can either be with continuous positive airway pressure (CPAP) or non-invasive positive pressure ventilation, or in some circumstances invasive ventilation may be required following endotracheal intubation.

3.2.3. Right-heart backward failure. The syndrome of acute right heart failure is related to pulmonary and right heart dysfunction, including exacerbations of chronic lung disease with pulmonary hypertension, or acute massive lung disease (e.g. massive pneumonia or pulmonary embolism), acute right ventricular infarction, tricuspid valve malfunction (traumatic or infectious), and acute or subacute pericardial disease. Advanced left heart disease progressing to right sided failure should also be considered, and similarly long standing congenital heart disease with evolving right ventricular failure should be taken into account. Non-cardiopulmonary pathologies include nephritic/nephrotic syndrome and end-stage liver disease. Various vasoactive peptide-secreting tumours should also be considered.

The typical presentation is with fatigue, pitting ankle oedema, tenderness in the upper abdomen (due to liver congestion), shortness of breath (with pleural effusion), and distension of the abdomen (with ascites). The full-blown syndrome includes anasarca with liver dysfunction and oliguria.

History and physical examination should confirm the syndrome of acute right heart failure, indicate the suspected diagnosis and guide further investigation, which is likely to include ECG, blood gases, D-dimer, chest X-ray, cardiac Doppler-echocardiography, pulmonary angiography, or chest CT scan.

In right heart backward failure fluid overload is managed with diuretics, including spironolactone and sometimes with a short course of low dose ('diuretic dose') of dopamine. Concomitant treatment may include antibiotics for pulmonary infection and bacterial endocarditis; Ca^{++} channel blockers, nitric oxide, or prostaglandins for primary pulmonary hypertension; and anticoagulants, thrombolytics, or thrombectomy for acute pulmonary embolism.

4. Pathophysiology of AHF

4.1. The vicious cycle in the acute failing heart

The final common denominator in the syndrome of AHF is a critical inability of the myocardium to maintain a cardiac output sufficient to meet the demands of the peripheral circulation. Irrespective of the underlying

cause of AHF a vicious cycle is activated that, if not appropriately treated, leads to chronic heart failure and death. This is shown in *Figure 2*, and is described in detail elsewhere.[29–34]

In order for patients with AHF to respond to treatment the myocardial dysfunction must be reversible. This is particularly important in AHF due to ischaemia, stunning or hibernation, where a dysfunctional myocardium can return to normal when appropriately treated.

4.2. Myocardial stunning

Myocardial stunning is the myocardial dysfunction that occurs following prolonged ischaemia, which may persist in the short-term even when normal blood flow is restored. This phenomenon has been described experimentally[35] as well as clinically.[36] Mechanisms of dysfunction are excessive oxidative stress,[37] changes in Ca^{++} homeostasis, and Ca^{++} desensitization of contractile proteins,[38] as well as myocardial depressant factors.[39] The intensity and duration of stunning is dependent on the severity and duration of the preceding ischaemic insult.[36]

4.3. Hibernation

Hibernation is defined as an impairment of myocardial function due to severely reduced coronary blood flow although myocardial cells are still intact. By improving blood flow and oxygenation, hibernating myocardium can restore its normal function.[40] Hibernation can be regarded as an adaptive mechanism to reduce oxygen consumption to prevent ischaemia and necrosis following reduced blood flow to the myocardium.[41]

Hibernating myocardium and stunning can co-exist. Hibernation improves in time with reinstitution of blood flow and oxygenation, whilst stunned myocardium retains inotropic reserve and can respond to inotropic stimulation.[36] Since these mechanisms depend on the duration of myocardial damage, a rapid restoration of oxygenation and blood flow is mandatory to reverse these pathophysiological alterations.

5. Diagnosis of AHF

The diagnosis of AHF is based on the symptoms and clinical findings, supported by appropriate investigations such as ECG, chest X-ray, biomarkers, and Doppler-echocardiography (*Figure 3*). The patient should be classified according to previously described criteria for systolic and/or diastolic dysfunction (*Figure 4*), and by the characteristics of forward or backward left or right heart failure.

5.1. Clinical evaluation

Systematic clinical assessment of the peripheral circulation, venous filling, and peripheral temperature are important.

Right ventricular filling in decompensated heart failure may usually be evaluated from the central jugular venous pressure. When the internal jugular veins are

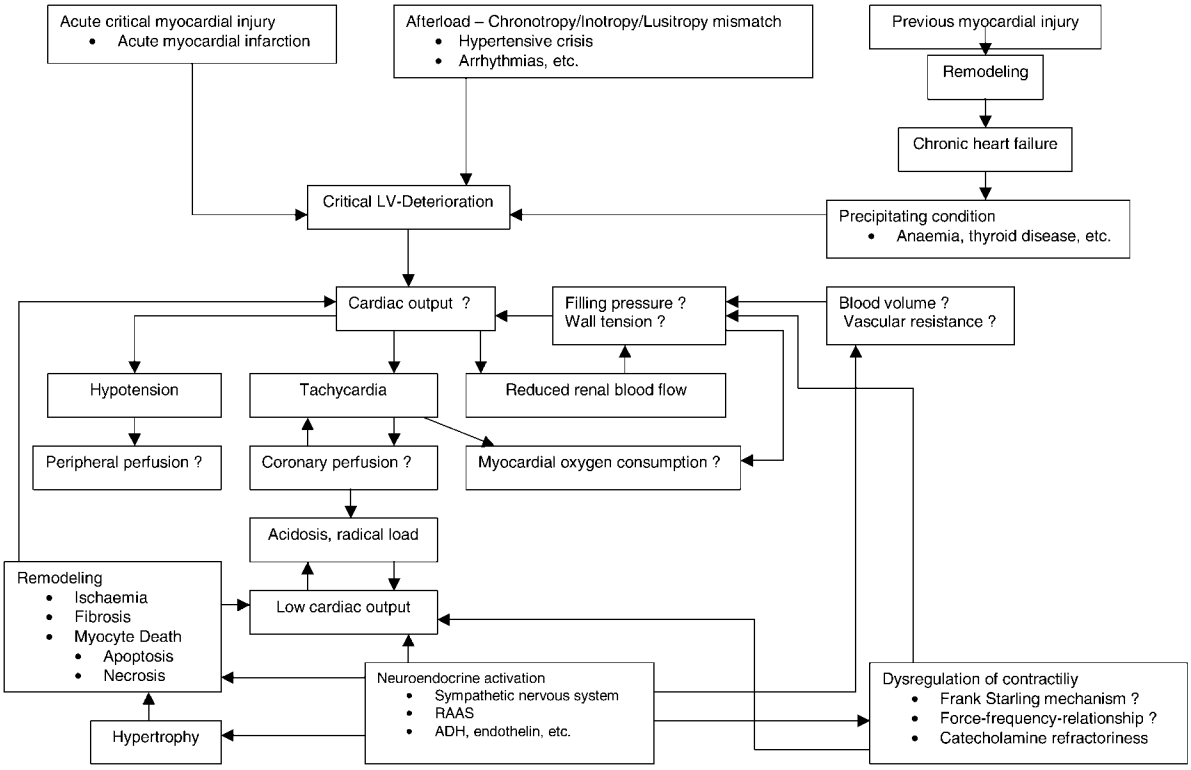

Figure 2 Pathophysiology of the syndrome of AHF. Following acute critical events, LV deterioration occurs rapidly and requires urgent medical treatment. The pathophysiology of the syndrome of heart failure is summarized. Mechanical, haemodynamic, and neurohormonal changes are similar but not identical to those observed in CHF. The time course of development or reversal of these changes varies considerably and strongly depends on the underlying cause of left ventricular deterioration as well as preexisting cardiovascular disease. However, changes develop rapidly and therefore AHF is considerably different to the syndrome of CHF.

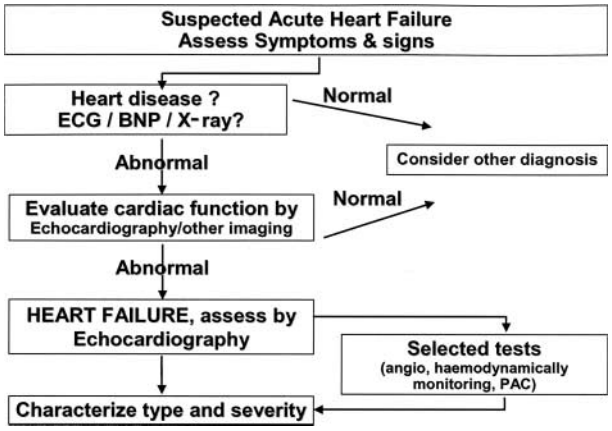

Figure 3 Diagnosis of AHF.

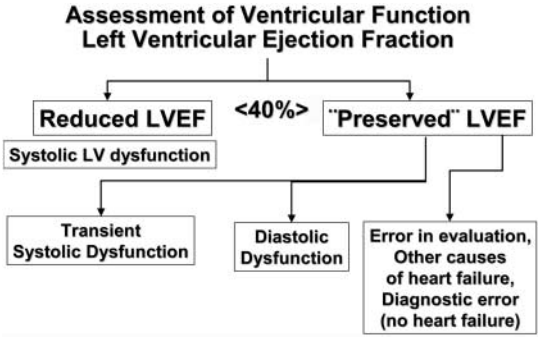

Figure 4 Assessment of LV function in AHF.

impractical for evaluation (e.g. due to venous valves) the external jugular veins can be used. Caution is necessary in the interpretation of high measured central venous pressure (CVP) in AHF, as this may be a reflection of decreased venous compliance together with decreased RV compliance even in the presence of inadequate RV filling.

Left sided filling pressure is assessed by chest auscultation, with the presence of wet rales in the lung fields usually indicating raised pressure. The confirmation, classification of severity, and clinical follow up of pulmonary congestion and pleural effusions should be done using the chest X-ray.

Class I recommendation, level of evidence C

Again, in acute conditions the clinical evaluation of left sided filling pressure may be misleading due to the rapidly evolving clinical situation. Cardiac palpation and auscultation for ventricular and atrial gallop rhythms (S3, S4) should be performed. The quality of the heart sounds, and presence of atrial and ventricular gallops and valvular murmurs are important for diagnosis and clinical assessment. Assessment of the extent of arteriosclerosis by detecting missing pulses and the presence of carotid and abdominal bruits is often important, particularly in elderly subjects.

5.2. Electrocardiogram

A normal electrocardiogram (ECG) is uncommon in AHF. The ECG is able to identify the rhythm, and may help determine the aetiology of AHF and assess the loading conditions of the heart. It is essential in the assessment of acute coronary syndromes.[42–44] The ECG may also indicate acute right or left ventricular or atrial strain, perimyocarditis and pre-existing conditions such as left and right ventricular hypertrophy or dilated cardiomyopathy. Cardiac arrhythmia should be assessed in the 12-lead ECG as well as in continuous ECG monitoring.

5.3. Chest X-ray and imaging techniques

Chest X-ray and other imaging should be performed early for all patients with AHF to evaluate pre-existing chest or cardiac conditions (cardiac size and shape) and to assess pulmonary congestion. It is used both for confirmation of the diagnosis, and for follow-up of improvement or unsatisfactory response to therapy. Chest X-ray allows the differential diagnosis of left heart failure from inflammatory or infectious lung diseases. Chest CT scan with or without contrast angiography and scintigraphy may be used to clarify the pulmonary pathology and diagnose major pulmonary embolism. CT scan, transesophageal echocardiography, or MRI should be used in cases of suspicion of aortic dissection.

5.4. Laboratory tests

A number of laboratory tests should be performed in AHF patients (*Table 3*). Arterial blood gas analysis (Astrup) enables assessment of oxygenation (pO_2), respiratory adequacy (pCO_2), acid–base balance (pH), and base deficit, and should be assessed in all patients with severe heart failure. Non-invasive measurement with pulse oximetry and end-tidal CO_2 can often replace Astrup (**Level of evidence C**) but not in very low output, vasocontricted shock states. Measurement of venous O_2 saturation (i.e. in the jugular vein) may be

Table 3 Laboratory tests in patients hospitalized with AHF

Blood count	Always
Platelet count	Always
INR	If patient anticoagulated or in severe heart failure
CRP	To be considered
D-dimer	To be considered (may be falsely positive if CRP elevated or patient has been hospitalized for prolonged period)
Urea and Electrolytes (Na^+, K^+, urea, creatinine)	Always
Blood Glucose	Always
CKMB, cardiac TnI/TnT	Always
Arterial blood gases	In severe heart failure or in diabetic patients
Transaminases	To be considered
Urinanalysis	To be considered
Plasma BNP or NTproBNP	To be considered

Other specific laboratory tests should be taken for differential diagnostic purposes or in order to identify end-organ dysfunction.

INR = International normalized ratio of thromboplastin time; TnI = troponin I; TnT = troponin T.

useful for an estimation of the total body oxygen supply–demand balance.

Plasma B-type natriuretic peptide (BNP) is released from the cardiac ventricles in response to increased wall stretch and volume overload and has been used to exclude and/or identify congestive heart failure in patients admitted for dyspnoea to the emergency department.[1,45] Decision cut points of 300 pg/mL for NT-proBNP and 100 pg/mL for BNP have been proposed, but the older population has been poorly studied. During' 'flash' pulmonary oedema, BNP levels may remain normal at the time of admission. Otherwise, BNP has a good negative predictive value to exclude heart failure.[46] The data are not consistent on reference values and on the effect of treatment. Various clinical conditions may affect the BNP concentration, including renal failure and septicaemia. If elevated concentrations are present, further diagnostic tests are required. If AHF is confirmed, increased levels of plasma BNP and NT-pro BNP carry important prognostic information. The exact role of BNP remains to be fully clarified.[47]

5.5. Echocardiography

Echocardiography is an essential tool for the evaluation of the functional and structural changes underlying or associated with AHF, as well as in the assessment of acute coronary syndromes

Class I recommendation, level of evidence C

Echocardiography with Doppler imaging should be used to evaluate and monitor regional and global left and right ventricular function, valvular structure and function, possible pericardial pathology, mechanical complications of acute myocardial infarction, and, on rare occasions, space occupying lesions. Cardiac output can be estimated by appropriate Doppler aortic or pulmonary time velocity contour measurements. An appropriate echo-Doppler study can also estimate pulmonary artery pressures (from the tricuspid regurgitation jet) and has been also used for the monitoring of left ventricular preload.[48–50] Echocardiography has not been validated with right heart catheterisation in patients with AHF.[51]

5.6. Other investigations

In cases of coronary artery related complications such as unstable angina or myocardial infarction, angiography is important and angiography-based revascularization therapy has been shown to improve prognosis.[39,42,43]

Class I recommendation, level of evidence B

Coronary arteriography is also often indicated in prolonged AHF, unexplained by other investigations, as recommended in the guidelines for diagnosis of CHF.[1]

Insertion of a pulmonary artery catheter (PAC) may assist the diagnosis of and follow up AHF. See Section 7.2.3 for further details.

6. Goals of the treatment of AHF

The immediate goals are to improve symptoms and to stabilize the haemodynamic condition (*Table 4*, *Figure 5*).

An improvement in the haemodynamic parameters (primarily an increase in cardiac output and stroke volume and a reduction in the pulmonary capillary wedge pressure and right atrial pressure) have traditionally been regarded as beneficial effects of the treatment of AHF.[52–57] An improvement in haemodynamic parameters only may be misleading, and a concomitant improvement in symptoms (dyspnoea and/or fatigue) is generally required.[58] These short-term benefits must also be accompanied by favourable effects on longer-term outcomes. This is likely to be achieved by avoidance, or limitation, of myocardial damage.

Dyspnoea is the dominant symptom in AHF but is subjective. Objective assessment can be made by standardized tools, such as the Borg Rating of perceived exertion,[59] indexes of dyspnoea,[60] and various visual analogue scales.[61] Changes from the initial assessment may be used as measures of improvement or deterioration.

Another objective of treatment is the reduction in the clinical signs of heart failure, although these may often be difficult to quantify. A reduction in body weight and/or an increase in diuresis are beneficial effects of therapy in congestive and oliguric patients with AHF.[56,62] Similarly, an improvement in oxygen saturation and in laboratory tests such as renal and/or hepatic function and/or serum electrolytes are meaningful goals of treatment. Plasma BNP concentration can reflect haemodynamic improvement and decreased levels are beneficial. However, short-term haemodynamic benefits may be dissociated from a favourable effect on prognosis. Thus, a beneficial (or at least a neutral) effect on patient outcome is required in addition to an improvement in symptoms and/or clinical signs.[54,58]

Beneficial effects of therapy on outcome include a reduction in the duration of intravenous vasoactive

Table 4 Goals of treatment of the patient with AHF

Clinical
↓ symptoms (dyspnoea and/or fatigue)
↓ clinical signs
↓ body weight
↑ diuresis
↑ oxygenation
Laboratory
Serum electrolyte normalisation
↓ BUN and/or creatinine
↓ S-bilirubin
↓ plasma BNP
Blood glucose normalisation
Haemodynamic
↓ pulmonary capillary wedge pressure to <18 mmHg
↑ cardiac output and/or stroke volume
Outcome
↓ length of stay in the intensive care unit
↓ duration of hospitalisation
↑ time to hospital re-admission
↓ mortality
Tolerability
Low rate of withdrawal from therapeutic measures
Low incidence of adverse effects

BUN = blood urea nitrogen.

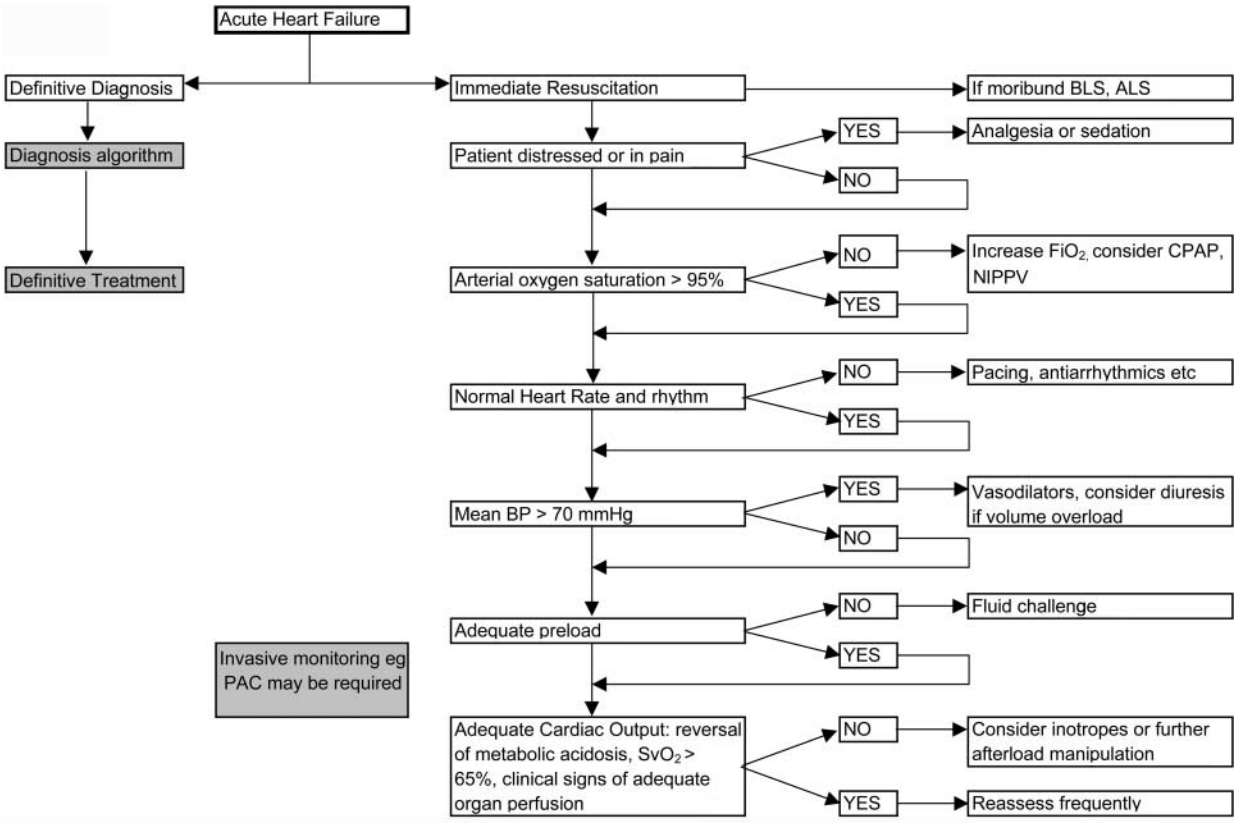

Figure 5 Immediate goals in treatment of the patients with acute heart failure. In coronary patients mean blood pressure (mBP) should be higher to ensure coronary perfusion, mBP >70, or systolic >90 mmHg.

therapy,[63] the length of stay (both in the intensive care unit and in the hospital),[54,58,63,64] and a reduction in the readmission rate with an increase in the time to readmission.[58,63,64] A reduction in both in-hospital and long-term mortality is the major goal of treatment[54,58,63,64] although the effect of short-term treatment may be dissociated from the long-term effects.

Lastly, a favourable safety and tolerability profile is also necessary for any treatment used in patients with AHF. Any agent used in this condition should be associated with a low withdrawal rate with a relatively low incidence of untoward side effects.

6.1. Organization of the treatment of AHF

Best results are achieved if patients with AHF are treated promptly by expert staff in areas reserved for heart failure patients, be it an emergency area, acute coronary care, or surgical or medical intensive care. An experienced cardiologist and/or other suitably trained staff should treat AHF patients. The diagnostic services should provide early access to diagnostic procedures such as echocardiography and coronary angiography, as needed.

Treatment of patients with AHF requires a treatment plan in the hospital system.[16,21]

Class I recommendation, level of evidence B

Comparative studies have shown shorter hospitalization time in patients treated by staff trained in heart failure management. The treatment of AHF should be followed by a subsequent HF clinic programme when applicable and as recommended by ESC guidelines.[1]

The care and information needs of the acutely ill patient and his/her family will usually be addressed by expert nurses.

Heart failure staff nurses and cardiologist/heart failure/intensive care specialists should be given the opportunity for continuing professional education.

Recommendations on the standard structure, nursing staff and equipment requirements in intensive cardiology care units and relevant step-down care units based on the expert opinion of the Working Group of Acute Cardiac Care are under preparation.

7. Instrumentation and monitoring of patients in AHF

Monitoring of the patient with AHF should be initiated as soon as possible after his/her arrival at the emergency unit, concurrently with ongoing diagnostic measures addressed at determining the primary aetiology. The types and level of monitoring required for any individual patient vary widely depending on the severity of the cardiac decompensation and the response to initial therapy. Local logistic issues may also be relevant. There are no prospective randomized controlled outcome-based studies on the use of different monitoring

modalities in AHF. The guidelines discussed here are therefore based on expert opinion.

7.1. Non-invasive monitoring

In all critically ill patients, monitoring the routine basic observations of temperature, respiratory rate, heart rate, the ECG, and blood pressure are mandatory. Some laboratory tests should be done repeatedly, i.e. electrolytes, creatinine and glucose or markers for infection or other metabolic disorders. Hypo- or hyperkalaemia must be controlled. These can all be monitored easily and accurately with modern automated equipment. If the patient becomes more unwell, the frequency of these observations will need to be increased.

ECG monitoring (arrhythmias and ST segment) is necessary during the acute decompensation phase, particularly if ischaemia or arrhythmia is responsible for the acute event.

Class I recommendation, level of evidence C

Blood pressure monitoring is critical during the institution of therapy and should be checked regularly (e.g. every 5 min), until the dosage of vasodilators, diuretics, or inotropes has been stabilized. The reliability of non-invasive, automatic plethysmographic measurement of blood pressure is good in the absence of intense vasoconstriction and very high heart rate.

Class I recommendation, level of evidence C

The pulse oximeter is a simple non-invasive device that estimates the arterial saturation of haemoglobin with oxygen (SaO_2). The estimate of the SaO_2 is usually within 2% of a measured value from a co-oximeter, unless the patient is in cardiogenic shock. The pulse oximeter should be used continuously on any unstable patient who is being treated with a fraction of inspired oxygen (FiO_2) that is greater than air. It should also be used at regular intervals (every hour) in any patient receiving oxygen therapy for an acute decompensation.

Class I recommendation, level of evidence C

Cardiac output and preload can be monitored non-invasively with the use of Doppler techniques (see Section 5.5.). There is little to no evidence to help choose which of these monitors to use and it makes no difference as long as the limitations of an individual device are understood and the data are used appropriately.

Class IIb recommendation, level of evidence C

7.2. Invasive monitoring

7.2.1. Arterial line. The indications for the insertion of an indwelling arterial catheter are the need for either continuous beat-to-beat analysis of arterial blood pressure due to haemodynamic instability especially with IABC or the requirement for multiple arterial blood analyses. The complication rate for the insertion of a 20-gauge 2-inch radial artery catheter is low.

Class IIb recommendation, level of evidence C

7.2.2. Central venous pressure lines. Central venous pressure (CVP) lines provide access to the central venous circulation and are therefore useful for the delivery of fluids and drugs and can also be used to monitor the CVP and venous oxygen saturation (SvO_2) in the superior vena cava (SVC) or right atrium, which provides an estimate of oxygen transport.

Class IIa recommendation, level of evidence C

Caution has to be advised, however, to avoid the over-interpretation of right atrial pressure measurements, as these rarely correlate with left atrial pressures (and therefore LV filling pressures) in patients with AHF. CVP measurements are also affected by the presence of significant tricuspid regurgitation and positive end-expiratory pressure (PEEP) ventilation.

Class I recommendation, level of evidence C

7.2.3. Pulmonary artery catheter. The pulmonary artery catheter (PAC) is a balloon flotation catheter that measures pressures in SVC, right atrium, right ventricle, and pulmonary artery as well as cardiac output. Modern catheters can measure the cardiac output semi-continuously as well as the mixed venous oxygen saturation and right ventricular end-diastolic volume and ejection fraction. The acquisition of these data can allow for a comprehensive evaluation of the cardiovascular haemodynamics.

Although the insertion of a pulmonary artery catheter for the diagnosis of AHF is usually unnecessary, PAC can be used to distinguish between a cardiogenic and a non-cardiogenic mechanism in complex patients with concurrent cardiac and pulmonary disease. PAC is also frequently used to estimate PCWP, CO, and other haemodynamic variables and therefore guide therapy in the presence of severe diffuse pulmonary pathology or ongoing haemodynamic compromise not resolved by initial therapy.[65–67] However, it should be remembered that PCWP is not an accurate reflection of LVEDP in patients with mitral stenosis (MS) or aortic regurgitation (AR), pulmonary and occlusion disease, ventricular interdependence, high airway pressure, and stiff LV (due to, e.g., LVH, diabetes, fibrosis, inotropes, obesity, ischaemia). Severe tricuspid regurgitation, frequently found in patients with AHF, can overestimate or underestimate CO measured by thermodilution.

Several retrospective studies assessing the use of the PAC in AMI demonstrated increased mortality with the PAC. These observations were partially explained by case-mix differences between the groups of the study.[68–70] Similar observational findings have subsequently been reported in other groups of patients.[70–73] A recent prospective randomized study enrolled a mixed group of critically ill patients to either a PAC group or to treatment without the use of data from a PAC. This study did not follow a protocol therapy in either group and failed to demonstrate a difference in outcome. Management with PAC led to increased fluid resuscitation within the first 24 h. The PAC did not cause harm to patients, rather it was the use of the information derived from the catheter (sometimes in an inappropriate fashion) that was detrimental.[74]

The use of a PAC is recommended in haemodynamically unstable patients who are not responding in a predictable

fashion to traditional treatments, and in patients with a combination of congestion and hypoperfusion. In these cases, it is inserted in order to ensure optimal fluid loading of the ventricles and to guide vasoactive therapies and inotropic agents[75] (*Table 5*). Because the complications are increasing with the duration of its utilization, it is critical to insert the catheter when specific data are needed (usually regarding the fluid status of the patient) and to remove it as soon as it is not of further help (i.e. when diuretic and vasodilating therapy have been optimized).

Class IIb recommendation, level of evidence C

In cardiogenic shock and prolonged severe low-output syndrome, it is recommended to measure the mixed venous oxygen saturation from the pulmonary artery as an estimation of oxygen extraction (SpO_2–SvO_2). The aim should be to maintain $SvO_2 > 65\%$ in patients with AHF. Yet, severe MR may be misleading by increasing O_2 saturation measured from PAC.

II. Treatment of AHF

8. General medical issues in the treatment of AHF

Infections: Patients with advanced AHF are prone to infectious complications, commonly respiratory or urinary tract infections, septicaemia, or nosocomial infection with Gram positive bacteria. In elderly patients with heart failure, infection such as pneumonia may be a cause for worsening heart failure and dyspnoea. An increase in C-reactive protein (CRP) and a decrease in general condition may be the only signs of infection—fever may be absent. Meticulous infection control and measures to maintain skin integrity are mandatory. Routine cultures are recommended. Prompt antibiotic therapy should be given when indicated.

Diabetes: AHF is associated with impaired metabolic control. Hyperglycemia occurs commonly. Routine hypoglycemic drugs should be stopped and glycaemic control should be obtained by using short acting insulin titrated according to repeated blood glucose measurements. Normoglycemia improves survival in diabetic patients who are critically ill.[76]

Catabolic state: Negative caloric and nitrogen balance is a problem in ongoing AHF. This is related to reduced caloric intake due to reduced intestinal absorption. Care should be undertaken to maintain calorie and nitrogen balance. Serum albumin concentration, as well as nitrogen balance, may help to monitor metabolic status.

Renal failure: A close interrelationship exists between AHF and renal failure. Both may cause, aggravate, and influence, the outcome of the other. Close monitoring of renal function is mandatory. Preservation of renal function is a major consideration in the selection of the appropriate therapeutic strategy for these patients.

9. Oxygen and ventilatory assistance

9.1. Rationale for using oxygen in AHF

The main priority in treating patients with AHF is the achievement of adequate levels of oxygenation at the cellular level in order to prevent end-organ dysfunction and the onset of multiple organ failure. The maintenance of an SaO_2 within the normal range (95–98%) is thus important in order to maximize oxygen delivery to the tissues and tissue oxygenation.

Class I recommendation, level of evidence C

This is best achieved first by ensuring that there is a patent airway and then by administration of an increased FiO_2. Maintenance of a patent airway is imperative. This can be achieved by using simple manoeuvres or equipment. Endotracheal intubation is indicated if these measures fail to improve tissue oxygenation.

Class IIa recommendation, level of evidence C

Despite this intuitive approach to giving oxygen, there is little to no evidence available that giving increasing doses of oxygen results in an improved outcome. The evidence available is controversial. Studies have demonstrated that hyperoxia can be associated with reduced coronary blood flow, reduced cardiac output, increased blood pressure, and increased systemic vascular resistance. A study that randomized 200 patients with AMI to receive either oxygen via a variable-performance facemask or to breathe room air reported a trend to higher mortality and an increased incidence of ventricular tachycardia.[67]

Table 5 General therapeutic approach in AHF by findings on invasive haemodynamic monitoring

Haemodynamic characteristic	Suggested therapeutic approach				
CI	Decreased	Decreased	Decreased	Decreased	Maintained
PCWP	Low	High or Normal	High	High	High
SBP (mmHg)		>85	<85	>85	
Outline of therapy	Fluid loading	Vasodilator (nitroprusside, NTG) fluid loading may become necessary	Consider inotropic agents (dobutamine, dopamine) and i.v. diuretics	Vasodilators (nitroprusside, NTG) and i.v. diuretics and consider inotrope (dobutamine, levosimendan, PDEI)	i.v. diuretics If SBP is low, vasoconstrictive inotropes

In AHF patients: decreased CI, <2.2 L/min/m^2; PCWP; low if <14 mmHg, high if >18–20 mmHg.

The administration of increased concentrations of oxygen to hypoxaemic patients with acute cardiac failure is unquestionably warranted.

Class IIa recommendation, level of evidence C

The use of increased concentrations of oxygen to patients without evidence of hypoxaemia is more controversial and may cause harm.[77]

9.2. Ventilatory support without endotracheal intubation (non-invasive ventilation)

Two techniques are used for ventilatory support: CPAP or non-invasive positive pressure ventilation (NIPPV). NIPPV is a method of providing mechanical ventilation to patients without the need for endotracheal intubation. There is a strong consensus that one of these two techniques should be used before endotracheal intubation and mechanical ventilation. Utilization of non-invasive techniques dramatically reduce the need for endotracheal intubation and mechanical ventilation.

9.2.1. Rationale. Application of CPAP can cause pulmonary recruitment and is associated with an increase in the functional residual capacity. The improved pulmonary compliance, reduced transdiaphragmatic pressure swings, and decreased diaphragmatic activity can lead to a decrease in the overall work of breathing and therefore a decreased metabolic demand from the body. NIPPV is a more sophisticated technique that requires a ventilator: a certain volume of air (or oxygen/air mix) can be delivered to the patient from the ventilator at a pre-set pressure and through either a nasal- or face-mask. Addition of a PEEP to the inspiratory assistance results in a CPAP mode (also known as bilevel positive pressure support, BiPAP). The physiological benefits of this mode of ventilation are the same as for CPAP but also include the inspiratory assist. This would further increase the mean intrathoracic pressure and therefore potentially increase the benefits of CPAP, but more importantly can further reduce the work of breathing and therefore the overall metabolic demand.

9.2.2. Evidence for the use of CPAP and NIPPV in LV failure. There have been five randomized controlled trials[78–82] and a recent meta-analysis[83] comparing the use of CPAP vs. standard therapy in patients with cardiogenic pulmonary oedema. Consistent endpoints that have been reported in these studies are the need for endotracheal intubation and therefore mechanical ventilation (a surrogate marker of deterioration and severity), and in-hospital mortality. There are very few data regarding longer-term outlook or function.

CPAP in this patient group improves oxygenation, decreases symptoms and signs of AHF, and results in a decreased need for endotracheal intubation. The studies have been relatively small and therefore have not reported a statistically significant reduction in mortality. A systematic review published in 1998[83] following the first three trials suggested that CPAP was associated with a decreased need for intubation [relative risk reduction −26% (95%CI −13 to −38%)] and a trend to a decrease in hospital mortality [relative risk reduction −6.6% (95%CI −16 to +3%)] compared with standard therapy alone. Evidence was lacking, however, on the potential for CPAP to actually cause harm.

There have been three randomized controlled trials of the use of NIPPV in the setting of acute cardiogenic pulmonary oedema. One of the trials compared NIPPV against conventional oxygen therapy,[84] one against high-dose intravenous nitrate therapy,[85] and one against CPAP.[86] NIPPV appears to decrease the need for endotracheal intubation, but this does not translate into a reduction in mortality or improvement in long-term function.

9.2.3. Conclusions. The randomized controlled trials suggest that the use of CPAP and NIPPV in acute cardiogenic pulmonary oedema is associated with a significant reduction in the need for tracheal intubation and mechanical ventilation.

Class IIa recommendation, level of evidence A

There are insufficient data to demonstrate a significant reduction in mortality; however, the data does trend in that direction.

9.3. Mechanical ventilation with endotracheal intubation in AHF

Invasive mechanical ventilation (with endotracheal intubation) should not be used to reverse hypoxemia that could be better restored by oxygen therapy, CPAP, or NIPPV, but rather to reverse AHF-induced respiratory muscle fatigue. The latter is the most frequent reason for endotracheal intubation and mechanical ventilation. AHF-induced respiratory muscle weakness is only rarely related to the worsening of already diseased respiratory muscles. More usually, worsening respiratory muscle contraction is due to the decrease in oxygen delivery related to hypoxaemia (pulmonary oedema) and low cardiac output. Respiratory muscle fatigue may be diagnosed by a decrease in respiratory rate, which is associated with hypercapnia and confusion. Intubation and mechanical ventilation are needed: (i) to relieve respiratory distress (decrease in work of breathing); (ii) to protect airways from gastric regurgitation; (iii) to improve pulmonary gas exchange, mostly to reverse hypercapnia and hypoxaemia and if the patient is unconscious due to prolonged resuscitation and anaesthetic medication; and (iv) to ensure bronchial lavage and prevent bronchial plugging and atelectasis.

Invasive mechanical ventilation should only be used if acute respiratory failure does not respond to vasodilators, oxygen therapy, and/or CPAP or NIPPV. Another consideration should be the need for immediate intervention in a patient with pulmonary oedema secondary to acute coronary syndrome.

10. Medical treatment

10.1. Morphine and its analogues in AHF

Morphine is indicated in the early stage of the treatment of patient admitted with severe AHF especially if they present with restlessness and dyspnoea.

Class IIb recommendation, level of evidence B

Morphine induces venodilatation and mild arterial dilatation and has the ability to reduce heart rate.[87] In most studies, intravenous boluses of morphine 3 mg were administered as soon as the intravenous line was inserted in AHF patients. It acts to relieve breathlessness and other symptoms in patients with CHF and AHF. This dosing can be repeated if required.

10.2. Anticoagulation

Anticoagulation is well established in acute coronary syndrome with or without heart failure.[42] The same is true in atrial fibrillation.[44] There is less evidence for the initiation of unfractionated heparin or low molecular heparin (LMWH) in AHF. A large placebo controlled trial of enoxaparine 40 mg subcutaneoulsy in acutely ill and hospitalised patients including a major group of heart failure patients showed no clinical improvement but less venous thrombosis.[88] There are no large comparative studies comparing LMWH with unfractionated heparin (given as 5000 IU twice or three times daily). Careful monitoring of the coagulation system is mandatory in AHF as there is often concomitant liver dysfunction. LMWH is contraindicated if the creatinine clearance is <30 mL/min or should be used with extreme care with monitoring of the anti-Factor Xa level.

10.3. Vasodilators in the treatment of AHF

Vasodilators are indicated in most patients with AHF as first line therapy, if hypoperfusion is associated with an adequate blood pressure and signs of congestion with low diuresis, to open the peripheral circulation and to lower preload (*Table 6*).

10.3.1. Nitrates. Nitrates relieve pulmonary congestion without compromising stroke volume or increasing myocardial oxygen demand in acute left heart failure, particularly in patients with acute coronary syndrome. At low doses they only induce venodilation, but as the dose is gradually increased they cause the arteries, including the coronary arteries, to dilate. With appropriate doses nitrates exert balanced vasodilation of the venous and arterial side of the circulation, thereby reducing left ventricular preload and afterload, without impairing tissue perfusion. Their effect on cardiac output depends on pre-treatment preload and afterload and the ability of the heart to respond to baroreceptor-induced increases in sympathetic tone.

Initially nitrates may be given orally but intravenous nitrates are also well tolerated in AMI. Two randomized trials in AHF have established the efficacy of intravenous nitrates in combination with furosemide and have demonstrated that dose titration to the highest haemodynamically tolerable dose of nitrates with low dose furosemide is superior to high dose diuretic treatment alone.

Class I recommendation, level of evidence B

In one of these randomized studies, furosemide and isosorbide dinitrate as bolus injections was tested and reported that intravenous high dose nitrate was more effective than furosemide treatment in controlling severe pulmonary oedema.[89]

In practical use, nitrates have a U-shaped curve effect. If given in sub-optimal doses vasodilators may have a limited effect in preventing acute heart failure recurrences. However, administration of high doses may also reduce their effectiveness. One disadvantage of nitrates is the rapid development of tolerance especially when given intravenously in high doses, limiting their effectiveness to 16–24 h only. Nitrates should be given at doses aimed at achieving optimal vasodilation, leading to an increase in cardiac index (CI) and decrease in pulmonary wedge pressure. Inappropriate vasodilation may induce a steep reduction in blood pressure, which may result in haemodynamic instability.

Nitroglycerin can be administered orally or by inhalation [glycerylnitrate (GTN) spray 400 μg (2 puffs) every 5–10 min)] or buccally (isosorbide dinitrate 1 or 3 mg), while monitoring blood pressure. The intravenous administration and dosing of nitrates (GTN 20 μg/min increasing dose up to 200 μg/min, or isosorbide dinitrate 1–10 mg/h) should be done with extreme caution, under careful blood pressure monitoring, titrating the dose administered against blood pressure decrease. One should be particularly cautious when administering nitrates to a patient with aortic stenosis, although this therapy may help in these complex situations. The dose of nitrates should be reduced if systolic blood pressure

Table 6 Indications and dosing of vasodilators in AHF

Vasodilator	Indication	Dosing	Main side effects	Other
Glyceryl trinitrate, 5-mononitrate	Acute heart failure, when blood pressure is adequate	Start 20 μg/min, increase up to 200 μg/min	Hypotension, headache	Tolerance on continuous use
Isosorbide dinitrate	Acute heart failure, when blood pressure is adequate	Start with 1 mg/h, increase up to 10 mg/h	Hypotension, headache	Tolerance on continuous use
Nitroprusside	Hypertensive crisis, cardiogenic shock combined with intoropes	0.3–5 μg/kg/min	Hypotension, isocyanate toxicity	Drug is light sensitive
Nesiritide[a]	Acute decompensated heart failure	Bolus 2 μg/kg + infusion 0.015–0.03 μg/kg/min	Hypotension	

[a]Limited sales approval in ESC countries.

decreases below 90–100 mmHg and discontinued permanently if blood pressure drops further. From a practical point of view a reduction of 10 mmHg in mean arterial pressure should be achieved.

10.3.2. Sodium nitroprusside. Sodium nitroprusside (SNP) (0.3 μg/kg/min uptitrating carefully to 1 μg/kg/min up to 5 μg/kg/min) is recommended in patients with severe heart failure, and in patients with predominantly increased afterload such as hypertensive heart failure or mitral regurgitation.

Class I recommendation, level of evidence C

SNP should be titrated cautiously and usually requires invasive arterial monitoring and close supervision. Prolonged administration may be associated with toxicity from its metabolites, thiocyanide and cyanide, and should be avoided especially in patients with severe renal or hepatic failure. Controlled trials with SNP in AHF are lacking and its administration in AMI has yielded equivocal results.[90] SNP should be tapered down to avoid rebound effects. In AHF caused by acute coronary syndromes, nitrates are favoured over SNP as SNP may cause 'coronary steal syndrome'.[91,92]

10.3.3. Nesiritide. Recently, nesiritide, a new class of vasodilator, has been developed for the treatment of AHF.[52] Nesiritide is a recombinant human brain peptide or BNP which is identical to the endogenous hormone produced by the ventricle in response to increased wall stress, hypertrophy, and volume overload. Nesiritide has venous, arterial, and coronary vasodilatory properties that reduce preload and afterload, and increase cardiac output without direct inotropic effects.

Systemic infusion of nesiritide in patients with congestive heart failure has beneficial haemodynamic actions, results in an enhanced sodium excretion and suppression of the renin–angiotensin–aldosterone and sympathetic nervous system.[93] The drug has been shown to be efficacious in improving subjective dyspnoea score as well as inducing significant vasodilation. Nesiritide was compared with intravenous nitroglycerin and resulted in improvement in haemodynamics more effectively and with fewer adverse effects.[94] Clinical experience with nesiritide is still limited. Nesiritide may cause hypotension and some patients are non-responders. Use of nesiritide has not translated into improvement in clinical outcome.[94]

10.3.4. Calcium antagonists. Calcium antagonists are not recommended in the treatment of AHF. Diltiatzem, and verapamil, and dihydropyridines should be considered contraindicated.

10.4. ACE inhibitors in AHF

10.4.1. Indications. ACE-inhibitors are not indicated in the early stabilisation of patients with AHF.

Class IIb recommendation, level of evidence C

However, as these patients are at high risk, ACE inhibitors have a role in early management of AHF patients and AMI. There is still debate on the selection of patients and the timing of initiation of ACE-inhibitor therapy.

10.4.2. Effects and mechanism of action. The haemodynamic effects of ACE inhibitors result from decreased formation of AII and increased levels of bradykinin, which in turn decreases total peripheral vascular resistances, alternates LV remodelling, and promotes natriuresis. Short-term treatment is accompanied by a decrease in AII and aldosterone and an increase in angiotensin I and plasma renin activity.

ACE inhibitors decrease renal vascular resistance, increase renal blood flow, and promote Na^+ and water excretion. The glomerular filtration rate (GFR) remains unchanged or falls slightly, and thus, filtration fraction is decreased. This is due to the relatively greater effect in dilating the glomerular efferent rather than afferent arterioles, leading to a reduction in glomerular capillary hydrostatic pressure and GFR. Natriuresis is due to the improvement in renal haemodynamics and a decreased release of aldosterone and bradykinin, which exert direct tubular effects, and inhibiton of the direct renal effects of angiotensin II.

There have been no efficacy studies of ACE inhibitors in AHF to date. Studies with ACE inhibitors in heart failure after myocardial infarction have focused on long-term effects.[95,96] A recent meta-analysis found that mortality at 30 days was reduced from 7.6% in the placebo group to 7.1% in the ACE inhibitor group [relative risk reduction 7% (95% CI 2–11%, $P < 0.004$)]. This equates to about five fewer deaths per 1000 patients treated for 4–6 weeks (NNT to prevent 1 death = 200). The trials which selected high risk patients found that ACE inhibitors led to large relative and absolute reductions in mortality.[97]

10.4.3. Practical use. Intravenous ACE-inhibition should be avoided. The initial dose of the ACE-inhibitor should be low and increased progressively after early stabilization within 48 h with monitoring of blood pressure and renal function. The duration of therapy, when initiated, should be at least 6 weeks.

Class I recommendation, level of evidence A

ACE inhibitors should be used with caution in patients with marginal cardiac output as they may significantly reduce glomerular filtration.The risk of intolerance to the ACE-inhibitors is increased by the concomitant administration of non-steroid anti-inflammatory agents and in the presence of bilateral renal artery stenosis.

10.5. Diuretics

10.5.1. Indications. Administration of diuretics is indicated in patients with AHF decompensated heart failure in the presence of symptoms secondary to fluid retention.

Class I recommendation, level of evidence B

The symptomatic benefits and their universal clinical acceptance has precluded a formal evaluation in large scale randomized clinical trials to clearly establish their safety and efficacy profile in patients with congestive heart failure, including their possible impact on

outcomes.[98,99] For the same reasons, the data on the relative efficacy and tolerability of the various types of diuretics are scarce and further clinical research is encouraged.

10.5.2. Effects and mechanisms of action. Diuretics increase the urine volume by enhancing the excretion of water, sodium chloride, and other ions, leading to a decrease in plasma and extracellular fluid volume, total body water and sodium, and a reduction in right and left ventricular filling pressures and a decrease in peripheral congestion and pulmonary oedema.[98,99] Intravenous administration of loop diuretics also exerts a vasodilating effect, manifested by an early (5–30 min) decrease in right atrial and pulmonary wedge pressure as well as pulmonary resistances.[100] With high bolus doses (>1 mg/kg) there is a risk of reflex vasoconstriction. As opposed to chronic use of diuretics, in severe decompensated heart failure, the use of diuretics normalizes loading conditions and may reduce neurohormonal activation in the short term.[101] Especially in acute coronary syndromes diuretics should be used in low doses and preference given to vasodilator therapy.[102]

10.5.3. Practical use. Intravenous administration of loop diuretics (furosemide, bumetanide, torasemide), with a strong and brisk diuretic effect the preferred choice in patients with AHF. Therapy can safely be initiated before hospital admission[89,102–104] and the dose should be titrated according to the diuretic response and relief of congestive symptoms. Administration of a loading dose followed by continued infusion of furosemide or torasemide have been shown to be more effective than bolus alone.[105–110] Thiazides[111–113] and spironolactone[114] can be used in association with loop diuretics, the combination in low doses being more effective and with less secondary effects than the use of higher doses of a single drug.[111–114] Combination of loop diuretics with dobutamine, dopamine[106] or nitrates[102] is also a therapeutic approach that is more effective and produces fewer secondary effects than increasing the dose of the diuretic.[115]

Class IIb recommendation, level of evidence C

Table 7 lists the recommendations for the practical use of diuretics. *Table 8* gives the recommended doses of commonly used diuretics in heart failure.

Table 7 Practical use of diuretics in AHF

Start with individualized dose depending on clinical condition (see *Table 8*).
Titrate according to clinical response.
Reduce dose when fluid retention is controlled.
Monitor serum K^+, $Na,^+$ and renal function at frequent intervals (every 1–2 days), according to diuretic response
Replace K^+ and Mg^+ loss.
In case of diuretic resistance follow suggestions in *Table 10*

Table 8 Diuretic dosing and administration

Severity of fluid retention	Diuretic	Dose (mg)	Comments
Moderate	Furosemide, or	20–40	Oral or intravenous according to clinical symptoms
	Bumetanide, or	0.5–1.0	Titrate dose according to clinical response
	Torasemide	10–20	Monitor Na^+, K^+, creatinine, and blood pressure
Severe	Furosemide, or	40–100	Intravenously
	Furosemide infusion	5–40 mg/h	Better than very high bolus doses
	Bumetanide, or	1–4	Orally or intravenously
	Torasemide	20–100	Orally
Refractory to loop diuretics	Add HCTZ, or	25–50 twice daily	Combination with loop diuretic better than very high dose of loop diuretics alone
	Metolazone, or	2.5–10 once daily	Metolazone more potent if creatinine clearance <30 mL/min
	Spironolactone	25–50 once daily	Spironolactone best choice if patient not in renal failure and normal or low serum K^+
In case of alkalosis	Acetazolamide	0.5	Intravenously
Refractory to loop diuretic and thiazides	Add dopamine for renal vasodilataion, or dobutamine as an inotropic agent		Consider ultrafiltration or haemodialysis if co-existing renal failure

HCTZ = hydrochlorothiazide.

Table 9 Causes of diuretic resistance

Intravascular volume depletion
Neurohormonal activation
Rebound Na^+ uptake after volume loss
Hypertrophy of distal nephron
Reduced tubular secretion (renal failure, NSAIDs)
Decreased renal perfusion (low output)
Impaired gut absorption of an oral diuretic
Non-compliance with drugs or diet (high sodium intake)

10.5.4. Diuretic resistance. Diuretic resistance is defined as the clinical state in which diuretic response is diminished or lost before the therapeutic goal of oedema relief has been achieved.[116] Such resistance is associated with a poor prognosis.[117] It is more frequent in patients with chronic, severe heart failure on long-term diuretic therapy, although it has also been reported with acute volume depletion after intravenous administration of loop diuretics.[118] Diuretic resistance can be attributed to a number of factors (*Table 9*).[116,118] A number of therapeutic approaches to overcome diuretic resistance have been explored (*Table 10*), and in clinical practice different strategies may be of value in a particular patient. Continuous infusion of furosemide is more effective than individual boluses.[119]

10.5.5. Secondary effects, drug interactions. Although diuretics can be used safely in the majority of patients, secondary effects are frequent and may be life-threatening. These include neurohormonal activation, especially of the angiotensin–aldosterone system and the sympathetic nervous system;[112] hypokalemia, hypomagnesemia and hypochloraemic alkalosis which may lead to severe arrhythmias;[106] nephrotoxicity and aggravation of renal failure.[115,120] Excessive diuresis may reduce venous pressure, pulmonary wedge pressure, and diastolic filling excessively, leading to a reduction in stroke volume and cardiac output, particularly in patients with severe heart failure and predominant diastolic failure or ischaemic right ventricular dysfunction. Intravenous administration of acetazolamide (one or two doses) may be helpful for the correction of alkalosis.[121]

10.5.6. New diuretic agents. Some new compounds with diuretic and other effects are under investigation, including vasopressin V2 receptor antagonists, brain natriuretic peptides (see Section 10.3.3), and adenosine receptor antagonists. Vasopressin V2 receptor antagonists inhibit the action of vasopressin on the collecting duct, thereby increasing free water clearance. The diuretic effect is independent of the levels of sodium and these agents could be helpful in the presence of hyponatraemia. Adenosine receptor antagonists exert a diuretic effect reducing proximal tubular Na^+ and water reabsorption without inducing kaliuresis.

Table 10 Managing resistance to diuretics

Restrict Na^+/H_2O intake and follow electrolytes[113]
Volume repletion in cases of hypovolaemia[113]
Increase dose and/or frequency of administration of diuretic[109,116]
Use intravenous administration (more effective than oral)[113] as bolus, or as intravenous infusion (more effective than high dose intravenous bolus)[103–107,116]
Combine diuretic therapy:[108] furosemide + HCTZ,[109] furosemide + spironolactone,[111] metolazone + furosemide (this combination is also active in renal failure)[110,107]
Combine diuretic therapy with dopamine,[112] or dobutamine[117]
Reduce the dose of ACE-inhibitor[118] or use very low doses of ACE-inhibitor[118,119]
Consider ultrafiltration or dialysis if response to above strategies ineffective[120]

10.6. β-Blocking agents

10.6.1. Indications and rationale for β-blocking agents. There has been no study with β-blocker therapy in AHF targeted to acutely improve the condition. On the contrary, AHF has been considered a contraindication for this treatment. Patients with more than basal pulmonary rales, or hypotension, have been excluded from trials early after AMI. In patients with AMI who are not in overt heart failure or hypotensive, β-blockers limit infarct size, reduce life-threatening arrhythmias, and relieve pain.[43,122–124].

Intravenous administration should be considered in patients with ischaemic chest pain resistant to opiates, recurrent ischaemia, hypertension, tachycardia, or arrhythmia. In the Gothenburg Metoprolol Study, intravenous metoprolol or placebo was initiated early after an AMI and followed by oral therapy for 3 months. Fewer patients developing heart failure in the metoprolol group.[125] In patients with signs of pulmonary congestion with basal rales and/or treatment with intravenous furosemide, metoprolol therapy had even greater effects and reduced mortality and morbidity.[126] There is experience with the short-acting beta-blocker esmolol mainly in the setting of cardiac surgery. One small study has compared celiprolol and esmolol in severe heart failure. Celiprolol reduced cardiac index less at similar heart rate reduction, which was claimed to be due to differences in the vasodilation effect.[127] The clinical importance of this difference is unclear. Invasive haemodynamic monitoring was carried out in the MIAMI trial on patients with elevated pulmonary wedge pressures up to 30 mmHg. These patients when treated with metoprolol showed a decrease in filling pressures.[128]

10.6.2. Practical use. In patients with overt AHF and more than basal pulmonary rales, β-blockers should be used cautiously. Among such patients where ongoing ischaemia and tachycardia are present, intravenous metoprolol can be considered.

Class IIb recommendation, level of evidence C

However, in patients with an AMI, who stabilize after developing AHF, β-blockers should be initiated early.

Class IIa recommendation, level of evidence B

In patients with CHF β-blockers should be initiated when the patient has stabilized after the acute episode (usually after 4 days).

Class I recommendation, level of evidence A

The initial oral dose of bisoprolol, carvedilol, or metoprolol should be small and increased slowly and progressively to the target dose used in the large clinical trials. Up-titration should be adapted to individual response. β-Blockers may reduce blood pressure and heart rate excessively. As a general rule, patients on β-blockers admitted to hospital due to worsening heart failure should be continued on this therapy unless inotropic support is needed but the dose could be reduced if signs of excessive dosages are suspected (i.e. bradycardia and hypotension).

10.7. Inotropic agents

10.7.1. Clinical indications. Inotropic agents are indicated in the presence of peripheral hypoperfusion (hypotension, decreased renal function) with or without congestion or pulmonary oedema refractory to volume replacement diuretics and vasodilators at optimal doses (*Figure 6*).

Class IIa recommendation, level of evidence C

Their use is potentially harmful as they increase oxygen demand and calcium loading and they should be used with caution.[129]

In patients with decompensated CHF the symptoms, clinical course, and prognosis of the disease may become critically dependent on the haemodynamics. Thus, improvements in the haemodynamic parameters may become a goal of treatment and inotropic agents may be useful and life saving in this setting. The beneficial effects of an improvement in the haemodynamic parameters is, however, partially counteracted by the risks of arrhythmias and, in some cases, myocardial ischaemia and by the possible long-term progression of myocardial dysfunction caused by an excessive increase in energy expenditure.[129,130] The risk–benefit ratio may not, however, be the same for all the inotropic agents. Those acting through the stimulation of the β_1-adrenergic receptors which increase cytoplasmic myocardial cell Ca^{++} concentration may be associated with the greatest risk.[131,132] Lastly, only a few controlled trials with inotropic agents in patients with AHF have been performed, and very few have assessed their effects on the symptoms and signs of heart failure and their long-term effects on prognosis.[132]

10.7.2. Dopamine. Dopamine is an endogenous catecholamine, and a precursor of norepinpephrine. Its effects are dose-dependent and they involve three different receptor populations: dopaminergic, β-adrenergic, and α-adrenergic receptors.[133]

At low doses (<2 μg/kg/min i.v.) it acts only on peripheral dopaminergic receptors and lowers peripheral resistance both directly and indirectly. Vasodilation occurs predominantly in the renal, splanchnic, coronary, and cerebral vascular beds. At this dosage, its action may cause an improvement in the renal blood flow, glomerular filtration rate, diuresis and sodium excretion rate, with an increased response to the diuretic agents, in patients with renal hypoperfusion and failure.[133–136]

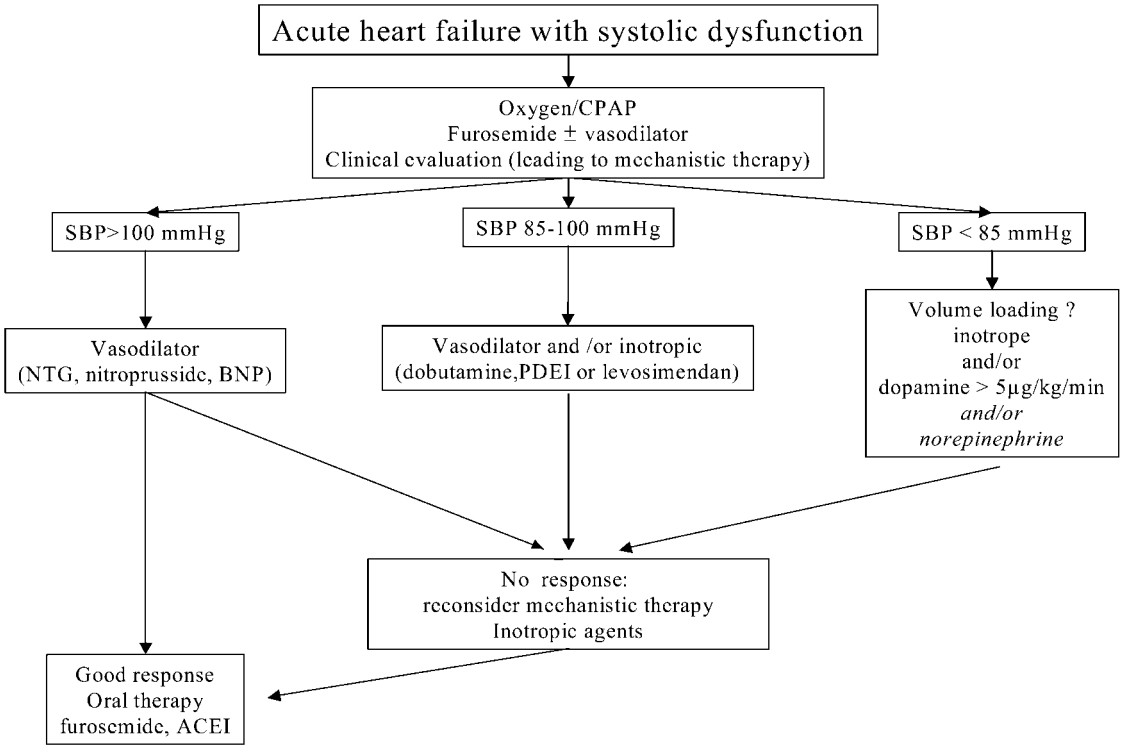

Figure 6 Rationale for inotropic drugs in AHF.

At higher doses (>2 μg/kg/min i.v.) dopamine stimulates the β-adrenergic receptors both directly and indirectly with a consequent increase in myocardial contractility and cardiac output. At doses >5 μg/kg/min dopamine acts on α-adrenergic receptors with an increase in the peripheral vascular resistance which, though potentially useful in the hypotensive patients, may be deleterious in the patients with heart failure as it may augment the left ventricular afterload, pulmonary artery pressure, and resistance.[137]

The effects of dopamine in patients with AHF have been studied only in small study groups[133,135,136] and no controlled trials regarding its long-term effects on renal function and survival have been performed. In addition, concerns regarding its potential untoward effects on pituitary function, T-cell responsiveness, gastrointestinal perfusion, chemoreceptor sensitivity, and ventilation have been raised.[138,139]

10.7.3. Dobutamine. Dobutamine is a positive inotropic agent acting mainly through stimulation of β_1-receptors and β_2-receptors in a 3:1 ratio.[133,137] Its clinical action is the result of direct dose-dependent positive inotropic and chronotropic effects[140,141] and secondary adaptation to increased cardiac output, such as a decrease in sympathetic tone in heart failure patients, leading to a decrease in vascular resistance.[17] The resultant benefit may therefore differ from patient to patient. At low doses, dobutamine induces mild arterial vasodilatation, which augments stroke volume by reductions in afterload. At higher doses dobutamine causes vasoconstriction.[91]

Heart rate is generally increased in a dose-dependent manner to a lesser extent than with other catecholamines. However, in patients with atrial fibrillation, heart rate may be increased to undesirable rates, due to facilitation of atrio-ventricular conduction. Systemic arterial pressure usually increases slightly, but may remain stable, or decrease. Similarly pulmonary arterial pressure and capillary wedge pressure usually decrease, but may remain stable or even increase in some patients with heart failure.[133,137,142]

The improved diuresis observed during dobutamine infusion in patients with CHF is the result of improved haemodynamics with an increased renal blood flow in response to improved cardiac output.

10.7.4. Practical use. Dopamine may be used as an inotrope (>2 μg/kg/min i.v.) in AHF with hypotension. Infusion of low doses of dopamine (≤2–3 μg/kg/min i.v.) may be used to improve renal blood flow and diuresis in decompensated heart failure with hypotension and low urine output. However if no response is seen, the therapy should be terminated (*Table 11*).[143]

Class of recommendation IIb, level of evidence C

Dobutamine is used to increase the cardiac output. It is usually initiated with a 2–3 μg/kg/min infusion rate without a loading dose. The infusion rate may then be progressively modified according to symptoms, diuretic response or haemodynamic monitoring. Its haemodynamic actions are proportional to its dosage, which can be increased to 20 μg/kg/min. The elimination of the drug is rapid after cessation of infusion, making it a very convenient inotropic agent.

In patients receiving β-blocker therapy with metoprolol, dobutamine doses have to be increased as high as 15–20 μg/kg/min to restore its inotropic effect.[144] The effect of dobutamine differs in patients receiving carvedilol: It can lead to an increase in pulmonary vascular resistance during the infusion of increasing doses of dobutamine (5–20 μg/kg/min).[145]

On the basis of haemodynamic data alone, the inotropic effect of dobutamine is additive to that of phosphodieasterase inhibitors (PDEI), the combination of PDEI and dobutamine produces a positive inotropic effect greater than each drug alone.[145,146]

Prolonged infusion of dobutamine (>24–48 h) is associated with tolerance and partial loss of haemodynamic effects.[137] Weaning from dobutamine may be difficult because of recurrence of hypotension, congestion, or renal insufficiency. This can sometimes be solved by very progressive tapering of dobutamine (i.e. decrease

Table 11 Administration of positive inotropic agents

	Bolus	Infusion rate i.v.
Dobutamine	No	2–20 μg/kg/min (β+)
Dopamine	No	<3 μg/kg/min: renal effect (δ+) 3–5 μg/kg/min: inotropic (β+) >5 μg/kg/min: (β+), vasopressor (α+)
Milrinone	25–75 μg/kg over 10–20 min	0.375–0.75 μg/kg/min
Enoximone	0.25–0.75 mg/kg	1.25–7.5 μg/kg/min
Levosimendan	12–24 μg/kg[a] over 10 min	0.1 μg/kg/min which can be decreased to 0.05 or increased to 0.2 μg/kg/min
Norepinephrine	No bolus	0.2–1.0 μg/kg/min
Epinephrine	Bolus: 1 mg can be given i.v. at resuscitation, may be repeated after 3–5 min, endotracheal route is not favoured	0.05–0.5 μg/kg/min

[a]Current recommended dosing. In patients with hypotension, therapy should be started without a bolus.

in dosage by steps of 2 μg/kg/min every other day) and optimization of oral vasodilator therapy such as with hydralazine and/or an ACE-inhibitor[147] It is sometimes necessary to tolerate some renal insufficiency or hypotension during this phase.

Infusion of dobutamine is accompanied by an increased incidence of arrhythmia originating from both ventricles and atria. This effect is dose-related and may be more prominent than with PDEI[148,149] and should prompt strict potassium compensation during intravenous diuretic use. Tachycardia may also be a limiting parameter, and dobutamine infusion may trigger chest pain in patients with coronary artery disease. In patients with hibernating myocardium, dobutamine appears to increase contractility in the short term at the expense of myocyte necorosis and loss in myocardial recovery.[150] There are no controlled trials on dobutamine in AHF patients and some trials show unfavourable effects with increased untoward cardiovascular events.[54,131]

Dobutamine is currently indicated when there is evidence of peripheral hypoperfusion (hypotension, decreased renal function) with or without congestion or pulmonary oedema refractory to volume replacement diuretics and vasodilators at optimal doses (*Table 11*).

Class IIa recommendation, level of evidence C

10.7.5. Phosphodiesterase inhibitors. The Type III PDEIs block the breakdown of cyclic-AMP (cAMP) into AMP. Milrinone and enoximone are the two PDEIs used in clinical practice. When administered to patients with advanced heart failure, these agents are associated with a significant inotropic, lusitropic, and peripheral vasodilating effects, with an increase in cardiac output and stroke volume and a concomitant decline in pulmonary artery pressure, pulmonary wedge pressure, and systemic and pulmonary vascular resistance.[137,151] Their haemodynamic profile is intermediate between that of a pure vasodilator, like nitroprusside, and that of a predominant inotropic agent, like dobutamine.[142] As their site of action is distal to the β-adrenergic receptors, PDE-Is maintain their effects even during concomitant β-blocker therapy.[136,144,152]

Type III PDEI are indicated when there is evidence of peripheral hypoperfusion with or without congestion refractory to diuretics and vasodilators at optimal doses, and preserved systemic blood pressure.

Class of recommendation IIb, level of evidence C

These agents may be preferred to dobutamine in patients on concomitant β-blocker therapy and/or with an inadequate response to dobutamine.

Class of recommendation IIa, level of evidence C

In practical use milrinone is administered as a 25 μg/kg bolus over 10–20 min followed by a continuous infusion at 0.375–0.75 μg/kg/min. Similarly, enoximone is administered as a bolus of 0.25–0.75 mg/kg followed by a continuous infusion at 1.25–7.5 μg/kg/min[148] (*Table 11*). Hypotension caused by excessive peripheral venodilation is an untoward effect observed mainly in the patients with low filling pressures. It may be avoided by starting the infusion without any bolus. Distinctly from amrinone, the incidence of thrombocytopenia is relatively rare with milrinone (0.4%) and enoximone.

Milrinone or enoximone are used for the treatment of AHF on the basis of their favourable haemodynamic effects. No information is available regarding their effects on heart failure symptoms and signs. The data regarding the effects of PDEI administration on the outcome of the patients with AHF are insufficient, but raise concerns about safety, particularly in patients with ischaemic heart failure.[63,132,153]

10.7.6. Levosimendan. Levosimendan has two main mechanisms of action: Ca^{++} sensitization of the contractile proteins responsible for a positive inotropic action, and smooth muscle K^{+} channel opening responsible for peripheral vasodilation. Some data suggest levosimendan may also have PDEI effect. Levosimendan has a potent acetylated metabolite that is also a Ca^{++}-concentration dependent Ca^{++} sensitizer. Its half-life is ~80 h, which probably explains the prolonged haemodynamic effects of a 24 h levosimendan infusion.[154,155]

Levosimendan is indicated in patients with symptomatic low cardiac output heart failure secondary to cardiac systolic dysfunction without severe hypotension (*Table 11*).

Class of recommendation of IIa, level of evidence B

Levosimendan is generally administered as a continuous intravenous infusion at a dose of 0.05–0.1 μg/kg/min preceded by a loading dose of 12–24 μg/kg, administered over 10 min.[54,156–158] Its haemodynamic effects are dose-dependent and the infusion rate may be uptitrated to a maximal rate of 0.2 μg/kg/min.[155,157–159] Most of the clinical data have been obtained with intravenous infusions lasting from 6 h[158] to 24 h,[54,157] but the haemodynamic effects persist for >48 h after the end of the infusion.[154,159]

Levosimendan infusion in patients with acutely decompensated HF caused by LV systolic dysfunction has been associated with a dose-dependent increase in the cardiac output and stroke volume; a decline in the pulmonary wedge pressure, systemic vascular resistance, and pulmonary vascular resistance; and a slight increase in the heart rate and decrease in the blood pressure.[54,159] An improvement in symptoms of dyspnoea and fatigue and a favourable outcome has been shown in randomized trials comparing levosimendan with dobutamine.[54] Differently from dobutamine, the haemodynamic response to levosimendan is maintained, or even of greater magnitude, in patients on concomitant β-blocker therapy.[54]

Tachycardia and hypotension are described with high-dose levosimendan infusion[54] and it is not currently recommended in patients with systolic blood pressure <85 mmHg.[159] Levosimendan has not been associated with an increased frequency of malignant arrhythmias in comparative trials with either placebo[157,158] or dobutamine.[54] A reduction in the haematocrit, haemoglobin, and plasma potassium, likely secondary to vasodilation

and secondary neurohumoral activation, have been described[54,159] and seem to be dose dependent.[159]

10.7.7. Vasopressor therapy in cardiogenic shock. When the combination of inotropic agent and fluid challenge fails to restore adequate arterial and organ perfusion despite an improvement in cardiac output, therapy with vasopressors may be required. Vasopressors may also be used, in emergencies, to sustain life and maintain perfusion in the face of life-threatening hypotension. Since cardiogenic shock is associated with high vascular resistances, any vasopressor should be used with caution and only transiently, because it may increase the afterload of a failing heart and further decrease end-organ blood flow.

10.7.7.1. Epinephrine. Epinephrine is a catecholamine with high affinity for β_1-, β_2-, and α-receptors. Epinephrine is used generally as an infusion at doses of 0.05–0.5 μg/kg/min when dobutamine refractoriness is present and the blood pressure remains low. The use of epinephrine requires direct arterial pressure monitoring, and monitoring of haemodynamic response by PAC is recommended (*Table 11*).

10.7.7.2. Norepinephrine. Norepinehrine is a catecholamine with high affinity for α-receptors and is generally used to increase systemic vascular resistance. Norepinephrine-induced increases in heart rate are less than with epinephrine. The dosing is similar to epinephrine. The choice between epinephrines depends on clinical situation. Norepinephrine (0.2–1 μg/kg/min) is favoured in situations with low blood pressure related to reduced systemic vascular resistances such as septic shock. Norepinephrine is often combined with dobutamine to improve haemodynamics.[160] Norepinehrine may reduce end-organ perfusion. Other new modes of treatments in septic shock are out of the scope of this report.

10.7.8. Cardiac glycosides. Cardiac glycosides inhibit myocardial Na^+/K^+ ATPase, thereby increasing Ca^{++}/Na^+ exchange mechanisms, producing a positive inotropic effect. In heart failure, the positive inotropic effect following β-adrenergic stimulation is attenuated and the positive force–frequency relationship is impaired. In contrast to β-adrenoceptor agonists, the positive inotropic effect of cardiac glycosides is unchanged in failing hearts[160] and the force–frequency relationship is partially restored.[161] In CHF, cardiac glycosides reduce symptoms and improve clinical status, thereby decreasing the risk of hospitalization for heart failure without effects on survival (The Digitalis Investigation Group).[162] In the AHF syndrome, cardiac glycosides produce a small increase in cardiac output[163] and a reduction of filling pressures.[164] In patients with severe heart failure following episodes of acute decompensation, cardiac glycosides have shown to be efficacious in reducing the re-occurrence of acute decompensation.[165] Predictors for these beneficial effects are a third heart sound, extensive LV dilatation, and distended jugular veins during the AHF episode.

However, in patients following myocardial infarction with heart failure, a substudy of the AIRE Investigation has shown adverse effects on the outcome after AMI accompanied by heart failure.[166] Furthermore, following AMI, an increase of creatine kinase was more pronounced in patients receiving cardiac glycosides.[167] In addition, for patients with myocardial infarction and AHF, digitalis was a predictor for life-threatening pro-arrhythmic events.[168]. Therefore, inotropic support with cardiac glycosides cannot be recommended in AHF, in particular following myocardial infarction.

Indication for cardiac glycosides in AHF may be tachycardia-induced heart failure, e.g. in atrial fibrillation with insufficient rate control by other agents such as β-blockers. Rigorous control of heart rate in tachyarrhythmia during the course of AHF can control heart failure symptoms.[169] Contraindications to the use of cardiac glycosides include bradycardia, second and third degree AV-block, sick sinus syndrome, carotid sinus syndrome, Wolff–Parkinson–White syndrome, hypertrophic obstructive cardiomyopathy, hypokalaemia, and hypercalcaemia.

11. Underlying diseases and co-morbidities in AHF

There are several acute morbidities which can cause *de novo* AHF or trigger decompensation in CHF. Coronary heart disease and acute coronary syndromes are the most frequent causes for AHF. Non-cardiac comorbidities may also significantly complicate the therapy of AHF.

11.1. Coronary artery disease

AHF induced or complicated by coronary artery disease may present with forward failure (including cardiogenic shock),[170] left-heart failure (including pulmonary oedema), or right-heart failure. The diagnosis is indicated by appropriate history (with background risk factors and suggestive chest pain), and a typical ECG with evidence of AMI or dynamic ST/T changes suggestive of myocardial ischaemia.

In acute coronary syndromes (unstable angina or myocardial infarction) complicated by AHF, coronary angiography is indicated (*Figure 7*). In AMI, reperfusion may significantly improve or prevent AHF.[33,34,42,43] Emergency balloon angioplasty (PCI), or on occasion surgery, should be considered at an early stage and performed as indicated. Such procedures can be life saving. If neither PCI or surgery is readily available or can only be provided after a long delay, early fibrinolytic therapy is recommended.[42,43]

For further diagnostic purposes, an echocardiogram is helpful for the assessment of regional and global ventricular function, associated valve dysfunction (mainly mitral regurgitation) and ruling out other disease states (e.g. perimyocarditis, cardiomyopathy, and pulmonary embolism). All patients with AMI and signs and symptoms of heart failure should undergo an echocardiographic study.

Class I recommendation, level of evidence C

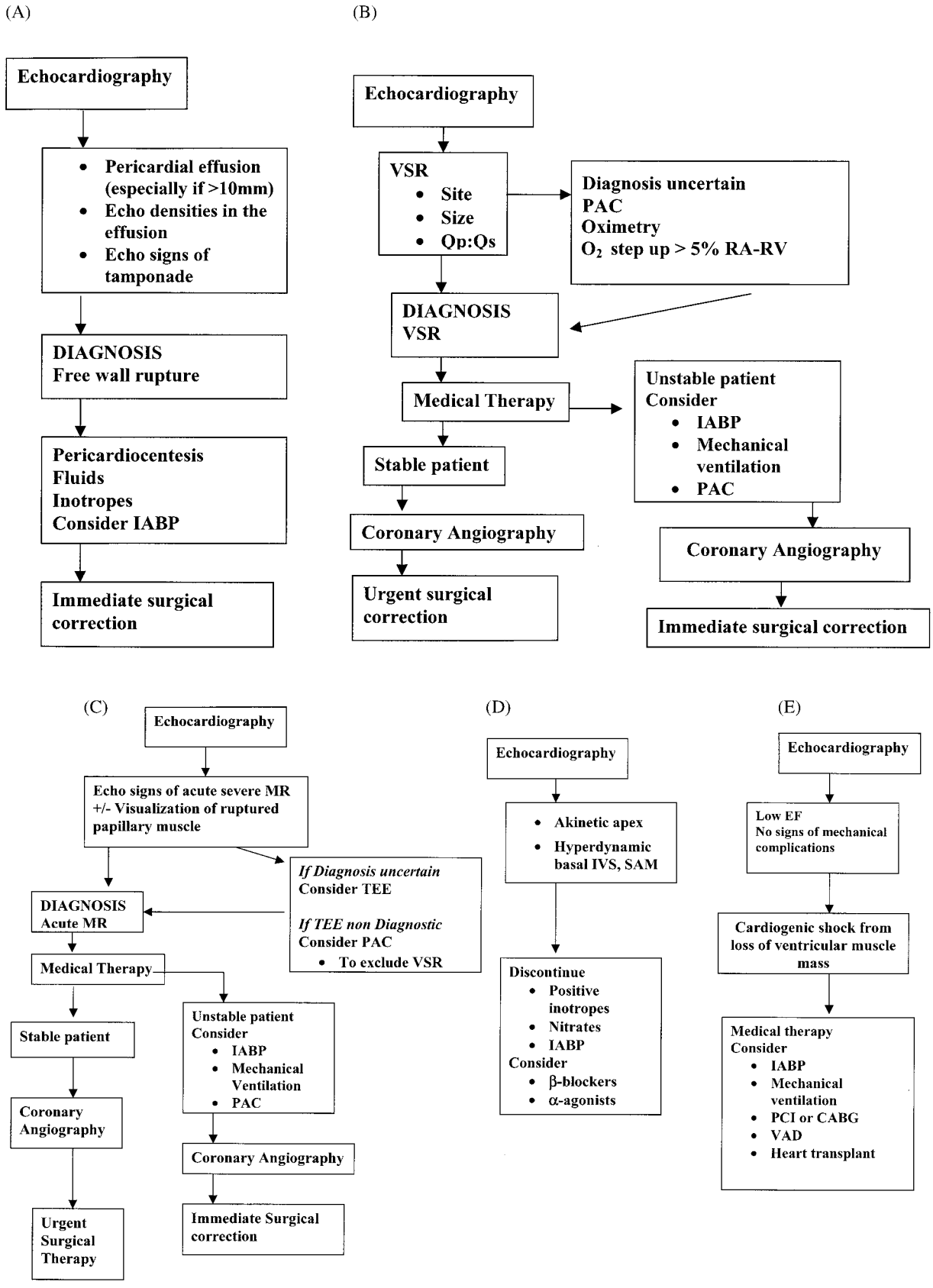

Figure 7 Algorithm: AHF in AMI. IABP = intra-aortic balloon pump; VSR = ventricular septal rupture; PAC = pulmonary artery catheterization; TEE = trans-esophageal echocardiography; EF = ejection fraction; MR = mitral regurgitation; IVS = intraventricular septum; SAM = systolic anterior movement; RA = right atrium; RV = right ventricle; PCI = percutaneous coronary intervention; Qp:Qs = pulmonary circulation volume:systemic circulation volume.

Special tests to provide evidence of reversible myocardial ischaemia are sometimes necessary.

In cardiogenic shock caused by acute coronary syndromes, coronary angiography and revascularization should be performed as soon as possible.[171]

Class I recommendation, level of evidence A

Temporary stabilization of the patient can be achieved by adequate fluid replacement, intra-aortic balloon counter-pulsation, pharmacological inotropic support, nitrates, and artificial ventilation. Repeated blood samples for monitoring of electrolytes, glucose, renal function, and arterial blood gases should be taken, particularly in diabetic patients.

Metabolic support with high-dose glucose, insulin, and potassium cannot be recommended (except in diabetic patients) until the results from larger scale studies in AMI become available.[172]

Class II recommendation, level of evidence A

When the haemodynamic state continues to be unstable for several hours, the introduction of an indwelling PAC may be considered. Repeated measurements of mixed venous blood oxygen saturation from the PAC can be helpful.

Class II recommendation, level of evidence B

When all these measures fail to achieve stabilization of the haemodynamic status, mechanical support with a left ventricular assist device should be considered, particularly if heart transplantation is contemplated.

In left-heart failure/pulmonary oedema, the acute management is similar to other causes of pulmonary oedema. Inotropic agents may be deleterious. Intra-aortic balloon counter-pulsation should be considered.[171,173,174]

The long-term management strategy should include adequate coronary revascularization and where there is evidence of reduced LV function long-term treatment with RAAS-inhibition and β-blockade should follow.

Acute right-heart failure is usually related to acute right ventricular ischaemia in acute coronary syndromes, particularly right ventricular infarction with a characeristic ECG and echocardiogram. Early revascularization of the right coronary artery and its ventricular branches is recommended. Supportive treatment should focus on fluid-loading and inotropic support.

11.2. Valvular disease

AHF can be caused by valvular conditions unrelated to acute coronary syndromes such as acute mitral or aortic valve incompetence (i.e. from endocarditis or trauma), aortic or mitral stenosis, thrombosis of a prosthetic valve, or aortic dissection.

In patients with endocarditis, treatment is initially conservative with antibiotics and other medical means of treatment of AHF. Cardiac dyfunction may be aggravated by myocarditis. However, acute valve incompetence is the most common cause of AHF in patients with infective endocarditis. Heart failure should be promptly treated. Rapid diagnosis and therapeutic decisions require expert consultation. Surgical consultations are warranted. Surgical intervention should be performed early in severe acute aortic or mitral regurgitation.

If there is a prolonged period of acute mitral regurgitation and the cardiac index has decreased to <1.5 L/min/m^2 and the ejection fraction is $<35\%$, urgent surgical intervention usually will not improve the prognosis. Stabilization of the patient with intra-aortic balloon counterpulsation can be of great value.

Urgent surgery is indicated in patients with endocarditis and severe acute aortic regurgitation.[175–179]

11.3. Management of AHF due to prosthetic valve thrombosis

AHF from prosthetic valve thrombosis (PVT) is associated with a high mortality.[180–183] All patients with heart failure symptoms and suspected prosthetic valve thrombosis should undergo chest fluoroscopy and an echocardiographic study (transthoracic and/or transesophageal if visualization of the prosthetic valve area is inadequate).

Class I recommendation, level of evidence B

The management remains controversial. Thrombolysis is used for right-sided prosthetic valves, and for high-risk surgical candidates. Surgery is preferred for left sided prosthetic valve thrombosis.

Class IIa recommendation, level of evidence B

Surgical mortality is high for emergency operations in critically ill patients with haemodynamic instability (NYHA Class III/IV, pulmonary oedema, hypotension). However, thrombolysis takes several hours to be effective and this delay may lead to further deterioration of the patient, dramatically increasing the risk of re-operation if thrombolytic treatment fails.

For patients who are in NYHA I/II or with non-obstructive thrombus, surgical mortality is lower. Recent data from non-randomized studies suggest that long term antithrombotic and/or thrombolytic therapy may be equally effective in these patients.[180,184]

Thrombolytic therapy is not effective when fibrous tissue ingrowth (pannus) is implicated in the obstruction with minor secondary thrombosis.

In patients with very large and/or mobile thrombi, thrombolytic therapy is associated with a much higher risk for major embolism and stroke. In all these patients surgical intervention should be considered as an alternative. Before deciding therapy, pannus formation or structural defects of the prosthetic valve should be ruled out by transesophageal echocardiography.[185]

Echocardiography should be performed in all patients after thrombolytic therapy. Surgical intervention should be considered in all cases if thrombolysis fails to resolve the obstruction although repeated infusions of thrombolytic therapy is an alternative.[182,184]

The thrombolytics used are: rtPA 10 mg intravenous bolus followed by 90 mg infused over 90 min; streptokinase 250–500 000 IU over 20 min followed by 1–1.5

million IU infused over 10 h. After thrombolysis, unfractionated heparin should be administered by intravenous infusion in all patients (activated partial thromboplastin time 1.5–2.0 times control). Urokinase is also an alternative in a dose of 4400 IU/kg/h for 12 h without heparin or 2000 IU/kg/h with heparin for 24 h.

11.4. Aortic dissection

Acute aortic dissection (particularly Type 1) may present with symptoms of heart failure with or without pain.[186] Following a period of pain, heart failure may become the main symptom.[186] The AHF is usually related to a hypertensive crisis (see Section 11.6), acute aortic valve incompetence, or myocardial ischaemia. Immediate diagnosis and surgical consultation are warranted. Transoesophageal echocardiography is the best technique to assess the morphology and function of the valve.[186] Speed in surgical intervention is usually vital.

11.5. AHF and hypertension

AHF is one of the well-known complications of hypertensive emergencies. The latter are defined as situations that require immediate blood pressure reduction (not necessarily to the normal values) to prevent or limit organ damage including encephalopathy, aortic dissection, or acute pulmonary oedema. The pathophysiology of hypertensive crisis is multifactorial and well described elsewhere.[187] The epidemiology of hypertension-induced pulmonary oedema shows that it usually appears in older patients (particularly in women >65 years of age) with a long-lasting history of hypertension, LV hypertrophy (present in more than half of patients), and inadequate treatment of their hypertension.[188,189] The clinical signs of AHF associated with a hypertensive crisis are almost exclusively the signs of pulmonary congestion. The latter can be mild or very severe with an acute pulmonary oedema throughout both lungs. It is called 'flash pulmonary oedema' because of its rapid onset. Rapid treatment with specific interventions is required.

Systolic function is often preserved in patients hospitalized with pulmonary oedema and hypertension (more than half of patients have an LVEF > 45%). In contrast, diastolic abnormalities with decreased LV compliance are often present.[190,191]

The goals of the treatment of acute pulmonary oedema with hypertension are reduction in LV preload and afterload, reduction of cardiac ischaemia, and maintenance of adequate ventilation with clearing of the oedema. Treatment should be started immediately and in the following order: O_2 therapy, CPAP or non-invasive ventilation, and if necessary, invasive mechanical ventilation, for usually a very short period, and administration of intravenous antihypertensive agent(s).

Antihypertensive therapy should aim for an initial rapid (within a couple of minutes) reduction of SBP or DBP of 30 mmHg, followed by a more progressive decrease of BP to the values measured before the hypertensive crisis: this may take several hours. No attempt should be made to restore normal values of BP as this may cause a deterioration in organ perfusion. The initial rapid reduction of BP may be achieved by the following medications given alone or combined if hypertension persists: (i) intravenous loop diuretics, particularly if the patient is clearly fluid overloaded with a long history of CHF; (ii) intravenous nitroglycerin or nitroprusside to decrease venous preload and arterial afterload and increase coronary blood flow; (iii) a calcium-channel blocker (such as nicardipine) may be considered as these patients usually have diastolic dysfunction with an increased afterload. Nicardipine has a similar spectrum of use as nitrates, but may cause adrenergic activation (tachycardia), an increase in intrapulmonary shunt (hypoxaemia), and central nervous system complications.

Among the medications usually given to treat hypertensive crisis, β-blockers should not be advised in cases of concomitant pulmonary oedema. However, in some cases, and particularly in hypertensive crisis related to phaeochromocytoma, intravenous labetalol given as slow boluses of 10 mg while monitoring heart rate and blood pressure and followed by an infusion of 50–200 mg/h can be effective. Acute pulmonary oedema associated with hypertension, and in the absence of other complications, is often very easily treated and does not necessarily need admission to an intensive care unit.

11.6. Renal failure

Heart failure and renal failure frequently co-exist, and either one of them may cause the other. Heart failure causes renal hypoperfusion both directly and through the activation of neurohumoral mechanisms.[192] Concomitant therapies (e.g. diuretics and ACE-inhibitors through efferent glomerular artery dilatation, and non-steroid anti-inflammatory agents through inhibition of afferent glomerular artery dilatation) may also contribute to the development of renal failure. Initially, the autoregulation of renal blood flow and the constriction of the efferent glomerular artery may compensate for renal hypoperfusion but, at later stages renal function becomes critically dependent on afferent glomerular flow so that renal failure and oliguria are a common finding in patients with severe acute heart failure.[192–196]

Urinalysis may vary depending on the cause of renal failure. When renal failure is secondary to hypoperfusion, the urinary sodium/potassium ratio is characteristically less than 1. Acute tubular necrosis may be diagnosed on the basis of an increase in urinary sodium, reduction in urine nitrogen concentration and typical urinary sedimentation findings.

A mild-to-moderate impairment in renal function is generally asymptomatic and well tolerated. However, even a mild-to-moderate increase in serum creatinine and/or decrease in GFR are independently associated with a worse prognosis.[195,196]

Concomitant acute renal failure requires the recognition and treatment of its associated disorders. The prevalence of anaemia, electrolyte abnormalities, and metabolic acidosis is greater in patients with concomitant renal failure. Electrolyte abnormalities (hypo- and hyperkalaemia, and hypo- and hypermagnesaemia) and metabolic acidosis should be corrected as they may

cause arrhythmias, reduce the response to treatment, and worsen the prognosis.[197]

Renal failure also influences the response and tolerability of heart failure treatments, namely, digoxin and ACE-inhibitors, angiotensin receptor blocking agents, and spironolactone. Also pre-renal arterial stenosis and post-renal obstruction should be assessed. Administration of ACE-inhibitors is associated with an increased incidence of severe renal failure and hyperkalaemia in patients with concomitant renal failure. An increase in serum creatinine of more than 25–30% and/or achievement of levels >3.5 mg/dL (>266 μmol/L) are relative contraindications to the continuation of ACE-inhibitor treatment (see Section 10.3.5.)

Moderate-to-severe renal failure [e.g. a serum creatinine >2.5–3 mg/dL (>190–226 μmol/L)] is also associated with a reduced response to diuretics—a significant predictor of mortality in HF patients.[117] In such patients, it may be necessary to progressively increase the dose of the loop diuretics and/or add a diuretic with a different mechanism of action (e.g. metozalone). This may, however, be associated with hypokalaemia and a further decline in GFR.

In patients with severe renal dysfunction and refractory fluid retention, continuous veno-venous hemofiltration (CVVH) may become necessary. Combined with a positive inotropic agent this may increase renal blood blow, improve renal function, and restore diuretic efficiency. This has been associated with an increase in urine output, a reduction in symptoms, and in the left and right ventricular filling pressures and sympathetic stimulation and with an improvement in lung mechanical function, laboratory abnormalities (hyponatremia), and the response to diuretic therapy.[198,199] Loss of renal function may require dialysis treatment, especially in the presence of hyponatremia, acidosis, and overt uncontrolled fluid retention. The choice between peritoneal dialysis, haemodialysis, or filtration, is usually dependent on technical availability and on baseline blood pressure.[199]

Patients with heart failure are at the highest risk of renal damage after the administration of contrast media. This is ascribed to a decline in renal perfusion and a direct renal tubular damage caused by the contrast media. The most widely used preventive procedure, e.g. pre-procedural and post-procedural hydration may not be tolerated and the osmotic and volume overload of contrast material may favour pulmonary oedema. Other procedures which may prevent contrast-induced renal failure and which may be better tolerated in the patients with concomitant HF include the use of the smallest amounts of iso-osmotic contrast media, avoidance of nephrotoxic drugs like non-steroidal anti-inflammatory agents, pre-treatment with *N*-acetylcysteine,[200,201] and/or the selective DA_1 receptor agonist fenoldopam.[202] Peri-procedural haemodialysis is effective at preventing nephropathy in patients with severe renal dysfunction.[203] All these procedures have been shown to be effective only in small studies and larger trials are needed to confirm their efficacy.

Class IIb recommendation, level of evidence B

11.7. Pulmonary diseases and bronchoconstriction

When bronchoconstriction is present in patients with AHF, bronchodilators should be used. This is often the case in patients with concomitant lung problems, e.g. asthma, chronic obstructive bronchitis,[204] and lung infections. Bronchodilators may improve cardiac function, but should not be used instead of relevant AHF treatment. Commonly, initial treatment consists of 2.5 mg albuterol (salbutamol) (0.5 mL of a 0.5% solution in 2.5 mL normal saline) by nebulization over 20 min. This may be repeated hourly during the first few hours of therapy and thereafter as part of individual therapy as indicated.

11.8. Arrhythmias and AHF

There are no extensive reports on the prevalence of arrhythmias either as a cause or as a complicating factor in decompensated AHF. In the Euroheart Failure Survey, rapid atrial fibrillation was observed at index hospitalization in 9% of patients and 42% had a history of chronic or paroxysmal atrial fibrillation. The prevalence of all atrial tachyarrhythmias was 44%. Life-threatening ventricular arrhythmias were seen at index hospitalization in 2% and in the whole study population they were found as a concomitant early or acute problem in 8% of patients.[8]

11.8.1. Bradyarrhythmias. Bradycardia in AHF patients occurs most often in AMI, particularly with right coronary artery occlusion. In an AHF study of 131 patients, 34.3% of patients with bradycardia were AMI patients, who were generally younger than non-AMI bradycardia patients (67 ± 12 vs. 73 ± 13 years, $P = 0.025$).[205]

The treatment of bradyarrhythmias is usually initially with atropine 0.25–0.5 mg intravenously, repeated when needed. Isoproterenol 2–20 μg/min can be infused in cases of AV dissociation with low ventricular response, but should be avoided in ischaemic conditions. Slow ventricular rhythm in atrial fibrillation can be improved by intravenous theophylline 0.2–0.4 mg/kg/h as a bolus and then by infusion. A temporary pacemaker should be inserted if no response is achieved with medical therapy.[206] Ischaemia should be treated as soon as possible before or after inserting a pacemaker as indicated (*Table 12*).[207–210]

Class IIa recommendation, level of evidence C

11.8.2. Supraventricular tachycardia. Supraventricular tachyarrhythmias (SVTs) may complicate or cause AHF[203,211] On rare occasions persistent atrial tachycardias may cause decompensated heart failure requiring hospitalization. Similarly, atrial fibrillation with a rapid ventricular response may be the cause for a dilated cardiomyopathy and AHF.

In a survey among 123 consecutive elderly patients with pulmonary oedema, atrial fibrillation was present in 24.3% and was paroxysmal in 14.6%.[212] Paroxysmal atrial fibrillation was more common in patients with normal or near-normal ejection fraction than in patients with low ejection fraction (21.3 vs. 9.7%).[212] In CHF or worsening AHF, chronic atrial fibrillation is seen in 10–30% of patients, with the highest prevalence in advanced heart failure.[213]Supraventricular tachycardia,

Table 12 Treatment of arrhythmias in acute heart failure

Ventricular fibrillation or pulseless ventricular tachycardia	Defibrillate with 200–300–360J (preferably by biphasic defibrillation with a maximum of 200J). If refractory to initial shocks inject epinephrine 1 mg or vasopressin 40 IU and/or amiodarone 150–300 mg as injection
Ventricular tachycardia	If patient is unstable cardiovert, if stable amiodarone or lidocaine can be given to achieve medical cardioversion.
Sinus tachycardia or supraventricular tachycardia	Use β-blocking agents when clinically and haemodynamically tolerated: Metoprolol 5 mg intravenously as a slow bolus (can be repeated if tolerated) Adenosine may be used to slow AV conduction or to cardiovert re-entrant tachycardia On rare occasions: Esmolol 0.5–1.0 mg/kg over 1 min, followed by infusion of 50–300 μg/kg/min, or Labetalol 1–2 mg bolus, followed by infusion of 1–2 mg/min (to total of 50–200 mg). Labetalol also indicated in AHF related to hypertensive crisis or phaeochoromcytoma, with 10-mg boluses, to a total dose of 300 mg.
Atrial fibrillation or flutter	Cardiovert if possible. Digoxin 0.125–0.25 mg iv, or β-blocking agent, or amiodarone, may be used to slow AV conduction. Amiodarone may induce medical cardioversion without compromising left ventricular haemodynamics. Patient should be heparinized.
Bradycardia	Atropine 0.25–0.5 mg iv, to total of 1–2 mg. As interim measure, isoproterenol 1 mg in 100 mL NaCl infused to a maximum of 75mL/h (2–12 μg/min). If bradycardia is atropine-resistant, transcutaneous or transvenous pacing should be used as an interim measure. Theophylline may be used in AMI patients with atropine-resistant bradycardia with bolus of 0.25–0.5 mg/kg followed by infusion at 0.2–0.4 mg/kg/h

atrial fibrillation, flutter, and paroxysmal tachycardia are seen occasionally in AMI. Late onset (>12 h) is usually related to more severe heart failure (60% of those with Killip Class III or IV).[214]

11.8.3. Recommendations for treatment of SVTs in AHF. The control of the ventricular rate response is important in patients with atrial fibrillation and AHF, particularly in patients with diastolic dysfunction.[44]

Class IIa recommendation, level of evidence A

Patients with restrictive physiology or tamponade, however, may suddenly deteriorate with rapid heart rate reduction. Rapid rate control or cardioversion on clinical demand should be achieved (*Table 12*). The therapy of atrial fibrillation depends on the duration of the atrial fibrillation.[44]

Patients with AHF and atrial fibrillation should be anticoagulated. When atrial fibrillation is paroxysmal medical or electrical cardioversion should be considered after initial work-up and stabilization of the patient. If the duration of the atrial fibrillation is more than 48 h, the patient should be anticoagulated and optimal rate control achieved medically for 3 weeks before cardioversion. If the patient is haemodynamically unstable, urgent cardioversion is clinically mandatory, but atrial thrombus should be excluded by transesophageal echocardiography prior to cardioversion.[44]

Verapamil and diltiazem should be avoided in acute atrial fibrillation as they may worsen heart failure and cause third degree AV block. Amiodarone and β-blocking agents have been successfully used in atrial fibrillation for rate control and prevention of recurrence.[215,216]

Class I recommendation, level of evidence A

Rapid dizitalization should be considered especially when atrial fibrillation is secondary to AHF. Verapamil can be considered in the treatment of atrial fibrillation or narrow complex supraventricular tachycardia in patients with only slightly reduced ventricular systolic function.

Class I anti-arrhythmic agents should be avoided in patients with low ejection fraction and particularly in patients who have a wide QRS complex. Dofetilide is a new drug with promising results in medical cardioversion (59% cardioverted in dofetilide vs. 34% in placebo group) in one study and prevention of new atrial fibrillation,[217] but further studies are needed to evaluate its safety and efficacy in AHF.

β-Blocking agents can be tried in supraventricular tachycardias when tolerated.[218,219] In wide complex tachycardia, intravenous adenosine can be used in an attempt to terminate the arrhythmia. Electrical cardioversion of SVT with sedation should be considered in AHF with hypotension. AHF patients with AMI and heart failure, and patients with diastolic heart failure, do not tolerate rapid supraventricular arrhythmias.

Plasma potassium and magnesium levels should be normalized particularly in patients with ventricular arrhythmias.[197,220]

Class IIb recommendation, level of evidence B

11.8.4. Treatment of life-threatening arrhythmias. The importance of ventricular tachycardia or fibrillation as a cause of, or related to, AHF is unclear.

VF and VT require immediate cardioversion, with ventilator assistance if required, and in the case of a conscious patient with sedation (*Table 12*).

Amiodarone and β-blocking agents can prevent repetition of these arrhythmias.[197,215,216]

Class I recommendation, level of evidence A

In the case of recurrent ventricular arrhythmias and haemodynamically unstable patients, immediate angiography and electrophysiological testing should be

performed. In cases of a localized arrhythmic substrate radiofrequency ablation may eliminate the arrhythmic tendency although the long term effect cannot be ascertained (*Table 12*).[215,221]

Class IIb recommendation, level of evidence C

11.9. Peri-operative AHF

AHF in the peri-operative period is usually related to myocardial ischaemia and the effect of the aging of the general population over the last decade has exacerbated this problem.[222,223] The incidence of peri-operative cardiac complications including myocardial infarction and death is ~5% in patients with at least one of the following cardiovascular risk factors: age >70 years, angina, prior myocardial infarction, congestive heart failure, treatment for ventricular arrhythmias, treatment for diabetes mellitus, limited exercise capacity, hyperlipidaemia, or smoking.[224] The peak incidence occurs within the first 3 days after the operation.[223] Importantly, post-operative instability of coronary artery disease is usually silent, i.e. not associated with chest pain.

12. Surgical treatment of AHF

AHF is a severe complication of many cardiac disorders. In some of them surgical therapy improves prognosis if performed urgently or immediately (see *Table 13*). Surgical options include coronary revascularization, correction of the anatomic lesions, valve replacement or reconstruction, as well as temporary circulatory support by means of mechanical assist devices. Echocardiography is the most important technique in the diagnostic work-up (*Figure 3*).

Table 13 Cardiac disorders and AHF requiring surgical treatment

Cardiogenic shock after AMI in patients with multi-vessel ischaemic heart disease
Post-infarction ventricular septal defect
Free wall rupture
Acute decompensation of pre-existing heart valve disease
Prosthetic valve failure or thrombosis
Aortic aneurysm or aortic dissection rupture into the pericardial sac
Acute mitral regurgitation from
Ischaemic papillary muscle rupture
Ischaemic papillary muscle dysfunction
Myxomatous chordal rupture
Endocarditis
Trauma
Acute aortic regurgitation from
Endocarditis
Aortic dissection
Closed chest trauma
Ruptured aneurysm of the sinus of Valsalva
Acute decompensation of chronic cardiomyopathy requiring support by mechanical assist devices

12.1. AHF related to complications of AMI

12.1.1. Free wall rupture. Free wall rupture is documented in 0.8–6.2% of patients after AMI.[225] Usually sudden death occurs within minutes due to cardiac tamponade and electromechanical dissociation. The diagnosis is rarely established before the patient's death. However, in some cases the presentation of free wall rupture is sub-acute (thrombus or adhesions seal the rupture) giving an opportunity for intervention if the condition is recognized. Most of these patients have signs of cardiogenic shock, sudden hypotension, and/or loss of consciousness. In some patients rupture is preceded by chest pain, nausea, emesis, new ST segment elevation in the infarct related leads, or T-wave changes.[226] All these patients should undergo immediate echocardiography (*Figure 7A*). The clinical presentation, with a pericardial effusion of >1 cm depth and echo densities in the effusion confirm the diagnosis.[227] Temporary haemodynamic stabilization can be obtained by pericardiocentesis, fluids, and positive inotropes. The patient should be immediately transferred to the operating room without any further investigation. Free wall rupture has been also described as a rare complication of dobutamine stress echocardiography after AMI.[228]

12.1.2. Post-infarction ventricular septal rupture. Ventricular septal rupture (VSR) occurs in 1–2% of patients with AMI. Recent data suggest a lower incidence and an earlier presentation in the thrombolytic era.[229–231] VSR usually occurs in the first 1–5 days after MI. The first sign of VSR is a pansystolic murmur usually at the left lower sternal border in a patient with acute deterioration and signs of AHF/cardiogenic shock after an AMI (see *Figure 7A*).

Echocardiography will confirm the diagnosis and allow assessment of ventricular function, define the site of the VSR, the size of the left-to-right shunt, and the co-existence of mitral incompetence (*Figure 7B*).

Class I recommendation, level of evidence C

PAC oximetry with O_2 step-up will allow estimation of the pulmonary-to-systemic blood flow ratio (usually 2 or more).

Class III recommendation, level of evidence C for PAC for diagnosis if echocardiography is diagnostic

Class IIa recommendation, level of evidence C for PAC for monitoring

Haemodynamically compromised patients should have intra-aortic balloon counter-pulsation, vasodilators, inotropes, and (if necessary) assisted ventilation. Coronary angiography is usually performed because it has been demonstrated in some small retrospective studies that concomitant revascularization may improve late functional status and survival.[229,230]

Virtually all patients treated medically die. Surgery should be performed soon after the diagnosis in most patients. Hospital mortality is 20–60% in patients undergoing surgical repair. Improvements in surgical technique and myocardial protection improved outcome in recent series.[229,230]

There is a developing consensus that surgery should be performed as soon as the diagnosis is made, because the rupture can abruptly expand resulting in

cardiogenic shock, the most important determinant of adverse outcome.[231,232] The patients with VSR should be operated on urgently if they are in haemodynamically stable condition and immediately if they are in cardiogenic shock.

Class I recommendation, level of evidence C

Trans-catheter VSR occlusion has been used to stabilize critically ill patients with good results but more experience is needed before it can be recommended.[43]

Recently, left ventricular outflow tract (LVOT) obstruction with compensatory hyperkinesis of the basal segments of the heart has been described in some patients with apical anterior myocardial infarction as a cause of a new systolic murmur and cardiogenic shock. It persists until appropriate therapy decreases the LVOT obstruction (*Figure 7D*).[233]

12.1.3. Acute mitral regurgitation. Acute severe mitral regurgitation (MR) is found in ~10% of patients with cardiogenic shock after AMI.[234] The prevalence is uncertain in the general population of patients with AMI. It occurs 1–14 days (usually 2–7 days) after the infarction. In acute MR from complete papillary muscle rupture most of the non-operated patients die in the first 24 h.

Partial rupture of one or more papillary muscle heads is more common than complete rupture and has a better survival. In most patients the acute MR is secondary to papillary muscle *dysfunction* rather than to rupture. Endocarditis may also be a cause for severe MR and requires reparatory surgery.

Acute severe MR is manifested by pulmonary oedema and/or cardiogenic shock. The characteristic apical systolic murmur may be absent in patients with severe MR due to the abrupt and severe elevation of left atrial pressure. Chest radiography shows pulmonary congestion (this may be unilateral). Echocardiography will establish the presence and severity of MR and permit assessment of LV function. The left atrium is usually small or slightly enlarged. In some patients transesophageal echocardiography may be needed to establish the diagnosis.

A pulmonary artery catheter can be used to exclude VSR; the pulmonary capillary wedge pressure tracing may show large regurgitant V-waves. Ventricular filling pressures can be used to guide patient management (*Figure 7C*).

Class IIb recommendation, level of evidence C

Most patients need intra-aortic balloon counterpulsation for stabilization before cardiac catheterization and angiography. When a patient develops acute MR, operation should be done early because many patients deteriorate suddenly or develop other serious complications.[235] The patient with acute severe MR and pulmonary oedema or cardiogenic shock requires emergency surgery (*Figure 7E*).

Class I recommendation, level of evidence C

13. Mechanical assist devices and heart transplantation

13.1. Indication

Temporary mechanical circulatory assistance may be indicated in patients with AHF who are not responding to conventional therapy and where there is the potential for myocardial recovery, or as a bridge to heart transplant or interventions that may result in significant recovery of the heart function (*Figure 8*).

Class IIb recommendation, level of evidence B

Improvement in the design and function of the devices will increase the number of potential candidates for its short- and long-term use in the future.

13.1.1. Intra-aortic balloon counter-pulsation pump. Counter-pulsation has become a standard component of treatment in patients with cardiogenic shock or severe acute left heart failure that (i) do not respond rapidly to fluid administration, vasodilatation, and inotropic support; (ii) is complicated by significant MR or rupture of the interventricular septum, to obtain haemodynamic stabilization for definitive diagnostic studies or treatment; or (iii) is accompanied by severe myocardial ischaemia, in preparation for coronary angiography and revascularization.

Synchronized intra-aortic balloon counter-pulsation (IABC) is performed by inflating and deflating a 30–50 mL balloon placed in the thoracic aorta through the femoral artery. The inflation of the balloon in diastole increases aortic diastolic pressure and coronary flow while the deflation during systole decreases afterload and facilitates LV emptying. IABC may dramatically improve haemodynamics but its use should be restricted to patients whose underlying condition may be corrected (by, e.g. coronary revascularization, valve replacement, or heart transplant) or may recover spontaneously (e.g. myocardial stunning very early after AMI or open heart surgery, myocarditis).[236] IABC is contraindicated in patients with aortic dissection or significant aortic insufficiency. It should not be used in patients with severe peripheral vascular disease, uncorrectable causes of heart failure, or multi-organ failure.

Class I recommendation, level of evidence B

13.1.2. Ventricular assist devices. Ventricular assist devices are mechanical pumps that partially replace the mechanical work of the ventricle (*Table 14*). They unload the ventricle, thereby decreasing myocardial work, and pump blood into the arterial system increasing peripheral and end-organ flow.[237–239] Some devices include a system for extra-corporeal oxygenation.[240] New devices intended for the treatment of chronic (rather than acute) failure restrict the progression of ventricular dilatation. Recently, a number of devices have been developed for acute, short-term mechanical circulatory support in patients with acute or acutely decompensated heart failure. Some devices require a median sternotomy and complex surgery. Others simply extract blood from the arterial system pumping the

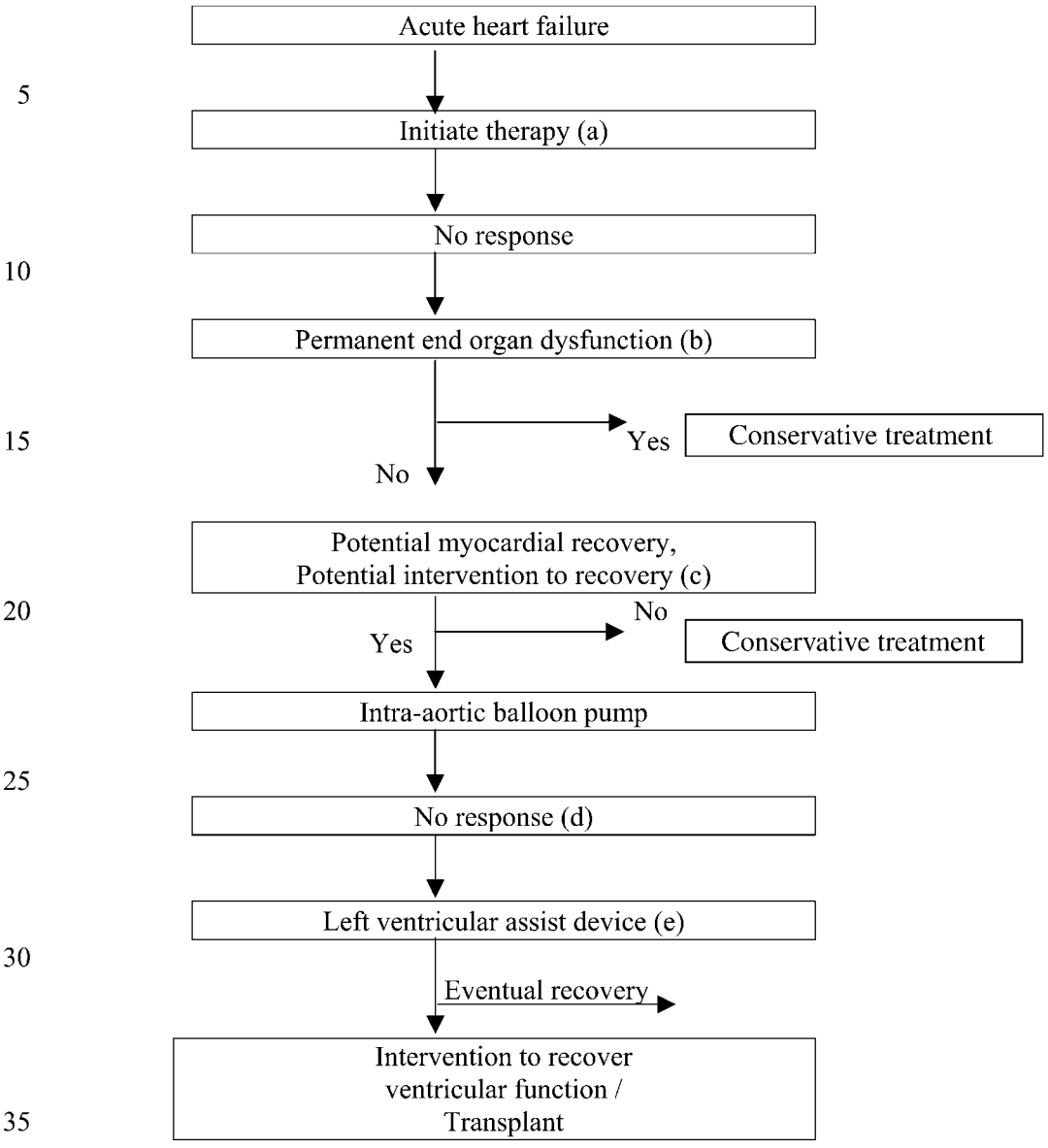

Figure 8 Selection of candidates for LV assist devices. (a) No response to conventional treatment of AHF, including appropriate use of diuretics and fluids, intravenous inotropics, and vasodilators. (b) End-organ dysfunction, including severe systemic disease, severe renal failure pulmonary disease or hepatic dysfunction, permanent central nervous injury. (c) Potential recovery of myocardial function or cardiac function, e.g. acute myocardial ischaemia, post-cardiotomy shock, acute myocarditis, acute valvular heart disease, or candidate to heart transplant. (d) Absence of clinical improvement after intra-aortic balloon pumping and mechanical ventilation. (e): Final indication may depend upon availability of device and experience of cardiovascular team.

blood again into the arterial or venous vascular system. In some patients, the haemodynamic and clinical improvement may be spectacular.

If recovery from AHF or transplantation is not possible, then the use of ventricular assist devices is unacceptable. The outcome of patients treated with a left ventricular assist devices vs. conventional treatment in a randomized clinical trial improved the prognosis of end-stage heart failure patients compared with conventional care, but was expensive and accompanied by frequent infections and thrombotic complications.[241] Experience is needed for the implantation and service of the pump and these devices should only be used within the framework of an institutional programme. *Table 14* summarizes the more frequently used systems and the main indications.

Class IIa recommendation, level of evidence B

Thromboembolism, bleeding, and infection are the most common complications associated with the use of ventricular assist devices.[237–239] Haemolysis and device malfunction are also frequent.

13.1.3. Selection of candidates for device therapy. Only patients with severe heart failure—not responding to conventional treatment of AHF including the appropriate use

Table 14 Mechanical assist devices

Device	System	Main indication	Comments
Extracorporeal			
Continuous flow pumps	Several	Short-term support	Easiest to use; cheapest
Centrifugal pumps	Several		Extensive experience May include extra corporeal membrane oxygenators Need for continuous monitoring Patient bedridden
Pulsatile	Thoratec Abiomed	Short-term support Post-cardiotomy LV and RV dysfunction Bridge to heart transplant	Easy to use; not expensive Need for continuous monitoring Patient bedridden
Intracorporeal			
Implantable, pulsatiles	Heart Mate Novacor	Long-term use possible Bridge to transplant Bridge to recovery	Expensive Patient may move and rehabilitate
Total artificial heart		No recovery expected No transplant candidate Alternative to transplant	Experimental Limited experience

of fluids, diuretics, intravenous inotropics, and vasodilators, as well as IABC and possibly mechanical ventilation—should be considered as potential candidates for mechanical support. Although transient haemodynamic and clinical improvement can be obtained in many cases, only patients with potential recovery of cardiac function should be considered as candidates for ventricular assist devices (*Figure 8*). These conditions include (i) acute myocardial ischaemia or infarction; (ii) shock after cardiac surgery; (iii) acute myocarditis; (iv) acute valvular dysfunction (particularly in the absence of previous chronic heart failure, when improvement in ventricular function is expected after spontaneous recovery or after appropriate interventions such as revascularization or valve replacement); (v) candidates for heart transplant.

Patients with permanent end-organ dysfunction, including severe systemic disease, severe renal failure, pulmonary disease, hepatic dysfunction, or permanent central nervous injury should not be considered for device therapy.

The selection of the specific device depends on the specific cardiac pathology, device availability, and surgical team experience.

13.2. Heart transplantation

Transplantation can be considered as a possibility in severe AHF known to have a poor outcome. This is the case in severe acute myocarditis or in postpuerperal cardiomyopathy or in a patient with major myocardial infarction with an initially poor outcome after revascularization. However, transplantation is not possible until the patient's condition has been stabilized with the aid of devices and artificial pumps.

14. Summary comments

The essential principles of the management of AHF are detailed in these guidelines and in the ESC Task Force guidelines for the diagnosis and treatment of CHF.

The clinical syndrome of AHF may present as acute *de novo* heart failure or as decompensated CHF with forward, left (backward), or right (backward) dominance in the clinical syndrome.

A patient with decompensated AHF failure requires immediate diagnostic evaluation and care, and frequent resuscitative measures to improve symptoms and survival.

Initial diagnostic assessment should include clinical examination supported by the patient's history, ECG, chest X-ray, plasma BNP/NT-proBNP, and other laboratory tests. Echocardiography should be performed in all patients as soon as possible (unless recently done and the result is available).

The initial clinical assessment should include evaluation of preload, afterload, and the presence of MR and other complicating disorders (including other valvular complications, arrhythmia, and concomitant co-morbidities such as infection, diabetes mellitus, respiratory diseases, or renal diseases). Acute coronary syndromes are a frequent cause of AHF and coronary angiography is often required.

Following initial assessment, an intravenous line should be inserted, and physical signs, ECG, and SpO_2 should be monitored. An arterial line should be inserted when needed.

The initial treatment of AHF consists of:

- Oxygenation with face-mask or by CPAP (SaO_2 target of 94–96%)
- Vasodilatation by nitrate or nitroprusside
- Diuretic therapy by furosemide or other loop diuretic (initially intravenous bolus followed by continuous intravenous infusion, when needed)

- Morphine for relief of physical and psychological distress and to improve haemodynamics
- Intravenous fluids if the clinical condition is preload-dependent and there are signs of low filling pressure. This may require testing the response to an aliquot of fluid.
- Other complicating metabolic and organ-specific conditions should be treated on their own merits.
- Patients with acute coronary syndrome or other complicated cardiac disorders should undergo cardiac catheterization and angiography, with a view to invasive intervention including surgery.
- Appropriate medical treatment by β-blocking agents and other medical therapy should be initiated as described in this report.

Further specific therapies (*Figures 5–7*, *Table 14*) should be administered based on the clinical and haemodynamic characteristics of the patient who does not respond to initial treatment. This may include the use of inotropic agents or a calcium sensitizer for severe decompensated heart failure, or inotropic agents for cardiogenic shock.The aim of therapy of AHF is to correct hypoxia and increase cardiac output, renal perfusion, sodium excretion, and urine output. Other therapies may be required, e.g. intravenous aminophylline or β_2-agonist for bronchodilation. Ultrafiltration or dialysis may be prescribed for refractory heart failure.

Patients with refractory AHF or end-stage heart failure should be considered for further support, where indicated (*Figures 7* and *8*) including: intra-aortic balloon pump, artificial mechanical ventilation, or circulatory assist devices as a temporary measure or as a' 'bridge' to heart transplantation.

The patient with AHF may recover extremely well, depending on the aetiology and the underlying pathophysiology. Prolonged treatment on the ward and expert care are required. This is best delivered by a specialist heart failure team that can rapidly initiate medical management and attend to the information needs of the patient and family.

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