Heart failure

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Heart failure is common in adults, accounting for substantial morbidity and mortality worldwide. Its prevalence is increasing because of ageing of the population and improved treatment of acute cardiovascular events, despite the efficacy of many therapies for patients with heart failure with reduced ejection fraction, such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β blockers, and mineralocorticoid receptor antagonists, and advanced device therapies. Combined angiotensin receptor blocker neprilysin inhibitors (ARNIs) have been associated with improvements in hospital admissions and mortality from heart failure compared with enalapril, and guidelines now recommend substitution of ACE inhibitors or ARBs with ARNIs in appropriate patients. Improved safety of left ventricular assist devices means that these are becoming more commonly used in patients with severe symptoms. Antidiabetic therapies might further improve outcomes in patients with heart failure. New drugs with novel mechanisms of action, such as cardiac myosin activators, are under investigation for patients with heart failure with reduced left ventricular ejection fraction. Heart failure with preserved ejection fraction is a heterogeneous disorder that remains incompletely understood and will continue to increase in prevalence with the ageing population. Although some data suggest that spironolactone might improve outcomes in these patients, no therapy has conclusively shown a significant effect. Hopefully, future studies will address these unmet needs for patients with heart failure. Admissions for acute heart failure continue to increase but, to date, no new therapies have improved clinical outcomes.

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Introduction

Heart failure is a syndrome characterised by symptoms (such as breathlessness, ankle swelling, and fatigue) and signs (eg, raised jugular venous pressure, pulmonary crackles, and peripheral oedema) caused by structural or functional cardiac abnormalities that lead to elevated intracardiac pressures or a reduced cardiac output at rest or during stress. Heart failure is a leading and increasing cause of morbidity and mortality worldwide. General physicians and family doctors, and emergency physicians in cases of acute heart failure, care for most patients with heart failure.

Classification

Many clinical classification systems have been used for heart failure, including those based on symptom severity—eg, as assessed by the New York Heart Association functional classification system[1]—or on disease progression, as staged from A to D in the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines.[2] The ACC/AHA guidelines include patients at risk of developing heart failure (stage A) and those with structural heart disease but without signs and symptoms (stage B), as well as symptomatic patients (stage C) and those with advanced heart failure (stage D). The prevalence of stage B heart failure is at least 2–3 times higher than that of symptomatic heart failure.[3,4]

For practical purposes, the most important distinctions are those between acute and chronic heart failure and between patients with heart failure with reduced (≤40%) left ventricular ejection fraction and those with heart failure with preserved (≥50%) left ventricular ejection fraction. To date, almost every drug or device trial showing a beneficial treatment effect has enrolled patients with chronic heart failure with reduced ejection fraction. However, epidemiological data show that the prevalence of patients with preserved ejection fraction has increased, so that most patients admitted to hospital with heart failure have preserved, rather than reduced, left ventricular ejection fraction.[5,6] About 10–20% of patients with heart failure have intermediate ejection fraction values. The term mid-range ejection fraction has been used for patients with an ejection fraction of 40–49%.[1] Some of these patients' ejection fractions have improved from lower values.[7] The mortality of these patients can be lower than that of patients with a reduced ejection fraction, whereas their rate of readmission to hospital might be similar.[8]

Search strategy and selection criteria

We searched PubMed from June 1, 2016, to Dec 31, 2016 with the terms "heart failure" or "cardiac dysfunction" or "left ventricular dysfunction", in combination with the terms "guidelines", "statement", "epidemiology", "pathophysiology", "neurohormonal", "genetics", "genetic", "symptom", "sign", "diagnosis", "laboratory", "iron", "anaemia", "kidney", "renal", "creatinine", "nitrogen", "hepatic", "liver", "transaminases", "albumin", "sodium", "potassium", "chloride", "echocardiography", "Doppler-echocardiography", "imaging", "magnetic resonance", "coronary", "prevention", "hypertension", "diabetes", "treatment", "therapy", "drug", "trial", "diuretic", "ACE inhibitor", "aldosterone", "mineralocorticoid", "beta-blocker", angiotensin receptor blocker", "sacubitril/valsartan", "LCZ696", "ivabradine", "inotropic", "inotropes", "gene therapy", "regenerative", "devices", "LVAD", "vasodilator", "ularitide", and "serelaxin". We predominantly selected publications from the past 5 years, but did not exclude commonly referenced and highly cited older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and guidelines were also cited to provide readers with additional details and references.

Chronic heart failure

Epidemiology

Chronic heart failure affects about 2% of the adult population worldwide. The prevalence of heart failure is age-dependent, ranging from less than 2% of people younger than 60 years to more than 10% of those older than 75 years.[9–12] Increased values are found when the definition incorporates patients with asymptomatic left ventricular dysfunction, including an increase to 5·5% in people 60 years or older with systolic dysfunction and an increase to 36·0% in people 60 years or older with diastolic dysfunction.[3] Most patients with heart failure have a history of hypertension, coronary artery disease, cardiomyopathies, or valve disease, or a combination of these.[4,12,13] The calculated lifetime risk of developing heart failure is about 20%, and those with hypertension are at an increased risk.[13] As a result of ageing of the general population and improved treatment of acute cardiovascular events, the prevalence of heart failure is projected to increase by 25% in the next 20 years.[14] Costs related to the treatment of heart failure encompass 2–3% of the total expenditure of health-care systems in high-income countries and are projected to increase by more than 200% in the next 20 years.[14]

Patients with heart failure have a poor prognosis, with high rates of hospital admission and mortality. Implementation of evidence-based treatments (neurohormonal antagonists and implantable devices) has led to a reduction in the mortality rate of patients with heart failure, but rates remain high, from 6–7% per year in patients with stable heart failure to 25% or more per year in patients admitted to hospital with acute heart failure.[4,15–17]

	Mechanisms
Symptoms	
Breathlessness	Lung congestion due to raised left atrial pressure, respiratory muscle and chemoreceptor abnormalities
Orthopnoea	Increased venous return and lung congestion in the supine position
Paroxysmal nocturnal dyspnoea	The same as above plus respiratory centre depression
Fatigue	Skeletal muscle hypoperfusion and metabolic abnormalities
Palpitations	Tachyarrhythmias, reduced effort tolerance
Ankle swelling	Fluid retention
Early satiety; abdominal bloating	Fluid retention, increased right atrial pressure
Anorexia, depression, confusion	Fluid retention, cerebral hypoperfusion
Cachexia	Intestinal congestion, chronic cytokine and inflammatory pathway activation
Signs	
Elevated jugular venous pressure*	Increased right atrial pressure
Displaced apex beat	Left ventricular dilatation
Cardiac holosystolic murmur	Mitral or tricuspid regurgitation
Third heart sound, gallop rhythm	Increased left atrial pressure
Pulmonary crackles*	Increased left atrial pressure, lung congestion
Pleural effusion*	Fluid retention, increased left or right atrial pressure
Hepatomegaly	Increased right atrial pressure
Hepatojugular reflux	Increased right atrial pressure
Ascites	Fluid retention, increased right atrial pressure
Peripheral oedema	Fluid retention

*These signs are assessed with the patient in the sitting position.

Table 1: **Symptoms and signs of heart failure**

Pathophysiology

The pathophysiology of heart failure with reduced ejection fraction is that of a progressive condition; risk factors lead to cardiac injury and then the development of myocardial dysfunction (initially asymptomatic), and then to worsening symptoms until the patient develops end-stage heart failure. The risk factors are those of coronary artery disease, including hypertension, hypercholesterolaemia, diabetes, obesity, a familial history of heart failure, a predisposition to cardiomyopathies, and exposure to cardiotoxic agents (eg, alcohol, amphetamines, cancer treatment, and radiation).[1,2]

Cardiac injury can occur with any cardiovascular disease. Loss of myocyte cells and increased myocardial strain cause eccentric hypertrophy of the remaining myocytes, both directly and through neurohormonal activation, leading to fibrosis, progressive left ventricular dilatation, a change in the shape of the left ventricle from elliptical to spherical, and, often, functional mitral regurgitation. These changes, named left ventricular remodelling, result in increased myocardial oxygen consumption and reduced efficiency of myocardial contraction.[18,19] Neurohormonal activation causes renal sodium retention, fluid overload, and oedema. Concomitant renal dysfunction causes a reduced response to diuretics and worsened outcomes.[20,21] Gut congestion causes cachexia and contributes to activation of inflammatory pathways, leading to worse outcomes.[22]

Although heart failure is a heterogeneous condition with many different causes, all aetiologies lead to a final common pathway with similar mechanisms that become, at least partially, independent from the initial cause. Neurohormonal activation has a pivotal role, as results from clinical trials of neurohormonal therapies in heart failure have shown.[23,24]

The pathophysiology of heart failure with preserved ejection fraction remains highly debated and incompletely studied. Abnormalities of systolic function, such as impairment of global longitudinal strain, have also been shown in patients with preserved ejection fraction.[25,26] According to one hypothesis, comorbidities (eg, obesity, chronic kidney disease, iron deficiency, hypertension, diabetes, and chronic obstructive pulmonary disease [COPD]) cause a systemic proinflammatory state with

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production of reactive oxygen species by coronary microvascular endothelial cells, reduced nitric oxide bioavailability, and decreased protein kinase G activity. This proinflammatory state results in myocyte hypertrophy, titin hypophosphorylation, increased collagen deposition, and decreased left ventricular compliance.[27,28] However, data supporting this hypothesis are still developing.[29]

Symptoms and signs

The symptoms and signs of heart failure (table 1) are necessary but not sufficient for its diagnosis.[1,2] Many patients experience symptoms for weeks or months before receiving a diagnosis of heart failure, and are often initially treated for exacerbation of COPD, atypical pneumonia, deconditioning, or other conditions unrelated to heart failure. Treatment should be targeted to improve symptoms and outcomes. Physician assessments correlate poorly with patient-reported symptoms, so some suggest that instruments of patient-reported outcomes should be used routinely in clinical care.[30] Because of the low sensitivity and specificity of signs and symptoms of cardiac dysfunction, laboratory examinations and cardiac imaging are essential in the diagnosis of heart failure.

Diagnosis

Measurement of plasma concentrations of brain natriuretic peptide (BNP) or the N-terminal prohormone of BNP (NT-proBNP) is a mainstay for the diagnosis of heart failure (figure 1), with excellent sensitivity and negative predictive value.[1,31] Laboratory measurements can detect comorbidities that might have major effects on the clinical history of heart failure. The use of novel biomarkers[32] in clinical practice has not yet been established.

Heart failure is a clinical diagnosis and, consequently, echocardiograms do not independently diagnose heart failure, but they can provide essential data about cardiac anatomy and function. The main echocardiographic measurements are outlined in the appendix. Reduced ejection fraction is associated with all-cause mortality, deaths from cardiovascular disease and heart failure, and hospital admissions due to heart failure,[33,34] but a normal ejection fraction does not rule out heart failure, as in patients with heart failure with preserved ejection fraction. Tissue doppler imaging and speckle-tracking echocardiography enable the measurement of myocardial deformation, quantified as strain and strain rate, in different myocardial layers. Compared with the ejection fraction, global longitudinal strain is less load-dependent and more sensitive to detection of early impairment in left ventricular systolic function.[25,26,34]

Echocardiography is central in the diagnosis of heart failure with preserved ejection fraction, which requires the detection of structural abnormalities, left ventricular hypertrophy or left atrial enlargement, or signs of diastolic dysfunction.[35,36] Echocardiography also permits detection and assessment of concomitant valve disease and right ventricular function, and estimates of systolic pulmonary artery pressure, all of which affect prognosis.[34] Assessment of the size of the inferior vena cava and its inspiration-related collapse can help in estimation of intravascular volume status. Exercise, or pharmacological-stress, echocardiography is useful for assessment of coronary artery disease and diagnosis of heart failure with preserved ejection fraction in patients who report breathlessness and normal cardiac function at rest.[1,37]

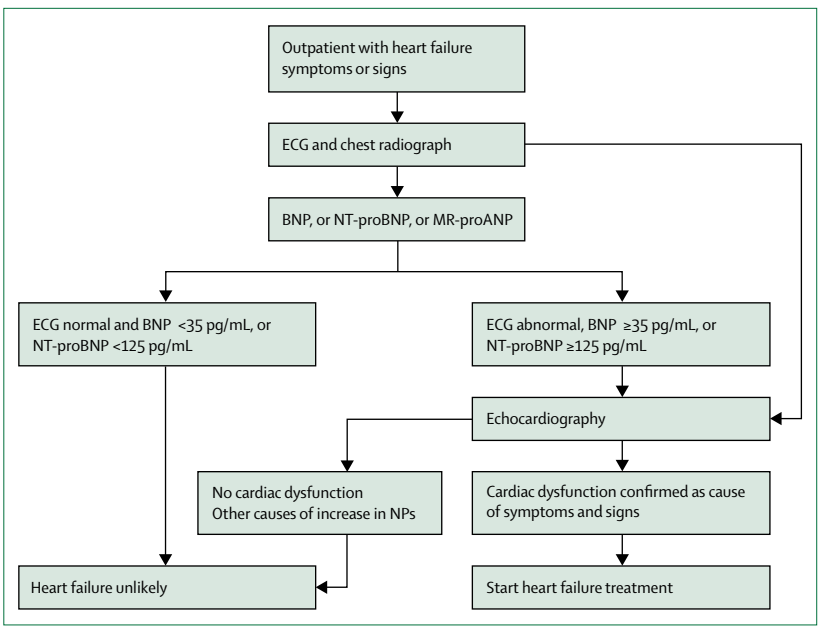

Figure 1: **Algorithm for the diagnosis of heart failure**
Different thresholds for heart failure diagnosis have been proposed for patients with non-acute and acute heart failure. Chest radiography is seldom the first option for diagnosis. MR-proANP concentrations of less than 120 pg/mL can be considered to rule out heart failure in the acute setting, although data supporting use of MR-proANP are scarce. Algorithm modified from references 1 and 31. BNP=brain natriuretic peptide. NT-proBNP=N-terminal prohormone of brain natriuretic peptide. MR-proANP=mid-regional pro-atrial natriuretic peptide. ECG=electrocardiogram. NPs=natriuretic peptides.

See Online for appendix

Cardiac MRI has better accuracy and reproducibility than echocardiography, with better tissue characterisation and spatial resolution that help in the diagnosis of inflammatory and infiltrative conditions. However, use of cardiac MRI is limited by its cost and incompatibility with some devices, including many implantable cardioverter defibrillators (ICDs) and pacemakers. Single-photon emission CT and PET are useful to assess myocardial ischaemia and viability. Gated single-photon emission CT allows measurement of ventricular volumes and global and regional systolic function. Coronary angiography and cardiac CT are used to diagnose coronary artery disease. Angiography is indicated in patients with angina or a medium-to-high pre-test probability of coronary artery disease and in those who are suitable for coronary revascularisation. Cardiac CT

might be indicated to exclude coronary artery disease in patients with a low-to-medium pre-test probability of that disease.[1,2]

Indications for endomyocardial biopsy are detailed elsewhere.[38] Cardiopulmonary exercise testing and the 6 min walking-distance test measure exercise tolerance in patients with heart failure, which has been associated with quality of life and prognosis.[1,39] Peak oxygen consumption and the slope of the correlation between minute ventilation and carbon dioxide production during exercise are major prognostic variables and are used as indications for heart transplantation.[39]

Prevention

Prevention of heart failure should be a primary target for health-care systems. Because heart failure is the final common pathway of almost all cardiovascular diseases, prevention of heart failure largely involves the prevention and treatment of hypertension and modifiable risk factors of coronary artery disease.[1,2] Benefits of antihypertensive treatment have been clearly shown.[40] In the SPRINT trial,[41] targeting of systolic blood pressure to less than 120 mm Hg in patients with hypertension who were at a high risk of cardiovascular events reduced mortality, cardiovascular events, and hospital admissions due to heart failure compared with targeting of systolic blood pressure to less than 140 mm Hg. In patients with cardiovascular risk factors, BNP screening and treatment of patients with high concentrations of BNP with renin-angiotensin-aldosterone system (RAAS) antagonists reduced rates of asymptomatic left ventricular dysfunction or overt heart failure.[42] In patients with coronary artery disease without left ventricular systolic dysfunction or heart failure, and in those with asymptomatic left ventricular dysfunction, regardless of its aetiology, angiotensin converting enzyme (ACE) inhibitors reduced the risk of new events and hospital admissions due to heart failure.[1,2]

Antidiabetic treatment has been associated with no effect on, or an increase in, heart failure and cardiovascular events. Two notable exceptions are the glucagon-like peptide-1 agonist liraglutide, and the sodium-glucose cotransporter 2 inhibitor empaglifozin. In the LEADER study[43] of 9340 patients with cardiovascular disease, chronic kidney disease, or both, liraglutide reduced the primary outcome of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke and the secondary outcome of cardiovascular death. Additionally, liraglutide reduced the number of hospital admissions due to heart failure, although not significantly.[43] In the FIGHT study,[44] 300 patients with heart failure with reduced ejection fraction who had been recently admitted to hospital were randomly assigned to liraglutide or placebo groups. During the 6 months of follow-up in that study,[44] there was no difference between the groups in the primary outcome or in its single components of death, readmission to hospital, and decrease in NT-proBNP concentrations, or in the other secondary endpoints.

In the EMPA-REG OUTCOME trial,[45] 7020 patients with a high cardiovascular risk were randomly assigned to either a placebo group or an empaglifozin group. Empaglifozin reduced the primary outcome of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke by 14%, as well as the number of cardiovascular-related deaths, hospital admissions due to heart failure, and all-cause deaths. However, the groups did not differ in the rates of non-fatal myocardial infarction or stroke alone. The effects were consistent across different categories (a history of heart failure or not) and among those taking different heart failure or antidiabetic medications.[45,46] Overall, the results of these trials suggest an effect for liraglutide on atherosclerosis and a more specific effect for empaglifozin on heart failure. Other studies are needed to clarify the value of these drugs for the treatment of heart failure. Empaglifozin is now recommended by European Society of Cardiology guidelines for the prevention of heart failure in diabetic patients.[1]

Prevention of worsening heart failure and recurrent hospital admission in patients with established heart failure continues to be a challenge. Multiple approaches have been developed with disparate results. Consistently, findings seem to support the usefulness of multidisciplinary care.[1,2] Natriuretic peptide-guided management has yielded conflicting outcomes, although some studies have shown improved survival, largely due to physicians using more appropriate treatment for chronic heart failure.[47,48] Implantable monitoring devices are now approved for patients with heart failure. Many of these devices monitor right ventricular, left atrial, or pulmonary artery pressures,[49] with the assumption that early detection of a rise in left ventricular filling pressure will prompt appropriate treatment and prevent the development of clinically evident heart failure. Home monitoring of pulmonary artery pressures with an implantable device has been shown to reduce hospital admissions in both patients with heart failure with reduced ejection fraction and in those with preserved ejection fraction, with persistent long-term benefits in a randomised trial.[50,51] Few consistent data have been obtained, to date, with devices that monitor lung water content.[52]

Treatment of chronic heart failure with reduced ejection fraction

Treatment of heart failure with reduced ejection fraction is mainly based on diuretics to relieve symptoms associated with congestion, and on neurohormonal antagonists and devices to improve outcomes. Neurohormonal antagonists are the backbone of medical treatment of heart failure, and include ACE inhibitors; angiotensin receptor blockers (ARBs); β blockers; mineralocorticoid receptor antagonists (MRAs); and, based on more recent data, angiotensin receptor blocker neprilysin inhibitors (ARNIs),[1,2,53] all of which have been shown to improve survival.

Improved heart-rate lowering with ivabradine is indicated in patients with an ejection fraction of 35% or

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less, persistent symptoms, sinus rhythm, and a heart rate of 70 bpm or more, despite maximally tolerated doses of a β blocker.[1,53,54] In the SHIFT trial[55] of 6558 patients with these characteristics, ivabradine reduced the primary endpoint of cardiovascular death or hospital admission due to heart failure by 18%, with a 26% reduction in hospital admission or death due to heart failure alone, but with no significant effect on cardiovascular death alone.

Use of the combined ARNI sacubitril/valsartan for chronic heart failure with reduced ejection fraction is supported by the results of the PARADIGM-HF trial.[23] In that trial, sacubitril/valsartan, compared with enalapril, reduced the combined primary endpoint of cardiovascular death or hospital admission due to heart failure by 20%, as well as its individual components and all-cause mortality. Compared with enalapril, sacubitril/valsartan was well tolerated—despite an increased incidence of hypotension (14·0% *vs* 9·2%)—with fewer increases in serum concentrations of creatinine and potassium, or reported coughs. Furthermore, the incidence of angio-oedema was only 0·4% with sacubitril/valsartan (*vs* 0·2% with enalapril).[24] Given the design of the trial with a run-in period, the published rates of adverse events probably underestimate the rates of adverse events in clinical practice, so extra care should be taken to check for hypotension in elderly patients and possible angio-oedema in more susceptible populations (ie, black and Asian people). According to the results of PARADIGM-HF,[1,53] sacubitril/valsartan should be used as a substitute for ACE inhibitors or ARBs in patients with heart failure with reduced ejection fraction and persistent symptoms. Previous concerns about neprilysin inhibition, including increasing β-amyloid protein concentration in the central nervous system—a possible risk factor for Alzheimer's dementia—have been partially addressed,[56] although further investigations will be done in other trials (eg, NCT01920711 and NCT02884206).[56] Consistent with the inclusion criteria of PARADIGM-HF, sacubitril/valsartan might be reserved for patients who are already on ACE inhibitors or ARBs as a substitute to these drugs (figure 2). To decrease the risk of angio-oedema, a washout period for the ACE inhibitor of at least 36 h is essential.

A detailed discussion of indications for ICDs and cardiac resynchronisation therapy goes beyond the aims of this Seminar, but these life-saving treatments are underused in many areas. Digoxin and oral vasodilators (nitrates and hydralazine) might still have a role in patients who remain symptomatic despite treatment with the various available drugs and devices. Further evidence regarding their efficacy and safety in the current era of heart failure treatment would be useful. A treatment algorithm for patients with heart failure with reduced ejection fraction is outlined in figure 2.

Optimal treatment of heart failure often requires a multidisciplinary team. Disease-management programmes must provide adequate education for the patient and their family, home support (particularly in the post-discharge phase), assessment of adherence to treatment, dietary advice, early detection of signs of decompensation, and readily available access to health-care services. Although a formal demonstration of efficacy through randomised trials has often been difficult, the clinical effect of these programmes is widely recognised[1,2] and they should be implemented in all patients, especially those with low social support. General measures—such as restricting sodium intake and doing aerobic exercise—are important. Regular exercise can improve clinical symptoms and functional capacity, and might reduce readmission to hospital.[1]

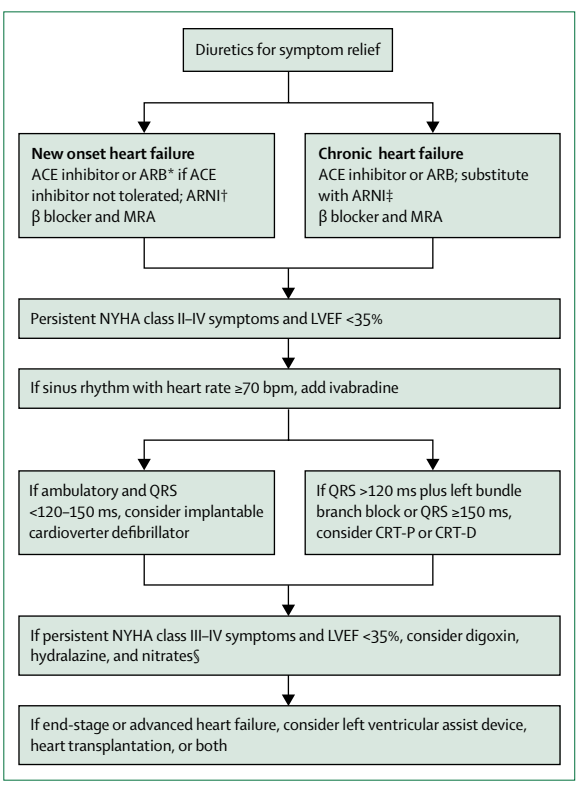

Figure 2: **Algorithm for the treatment of heart failure with reduced ejection fraction**

ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor blocker neprilysin inhibitor. MRA=mineralocorticoid receptor antagonist. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction. CRT-P=cardiac resynchronisation therapy-pacemaker. CRT-D=cardiac resynchronisation therapy-defibrillator. *ARBs are used in patients intolerant to ACE inhibitors. †No data exist about ARNIs as a first-line therapy in patients with new-onset heart failure. ARNIs are indicated in guidelines only for patients with persistent symptoms after treatment with ACE inhibitors or ARBs. However, ARNIs were associated with improved survival and reduced hospital admissions due to heart failure compared with ACE inhibitors or ARBs,[23] which might suggest use of ARNIs as a first-line therapy instead of ACE inhibitors. ‡In patients with chronic heart failure, ACE inhibitors or ARBs should be substituted with ARNIs, particularly in patients with persistent NYHA class II–IV symptoms and high BNP or N-terminal prohormone of BNP concentrations. §Hydralazine and nitrates have shown improved mortality in black people, so, in this patient population, it would be reasonable to initiate this treatment early in the algorithm after appropriate renin-angiotensin-aldosterone system antagonism and β blockade.

Treatment of advanced chronic heart failure with reduced ejection fraction

Patients with advanced chronic heart failure with reduced ejection fraction remain severely symptomatic and have severe cardiac dysfunction despite optimal treatment with drugs and devices.[57,58] These patients are candidates for heart transplantation when not contraindicated by age or major comorbidities. New-generation, continuous-flow left ventricular assist devices (LVADs) are now used not only as a bridge to transplantation but also as destination therapy. 2 year survival after primary LVAD implantation ranges from 78% in patients given the LVAD as a bridge transplant, to 61–62% of patients when it is implanted as definitive treatment.[59,60] Favourable outcomes have also been shown for LVADs in patients with non-inotrope-dependent heart failure and low exercise tolerance.[61] Right ventricular failure, infections, bleeding, and thromboembolic complications remain the main limitations of LVADs.[62] Further improvements are likely to occur in the coming years.[63,64]

Future directions for treatment

Vericiguat is a soluble guanylate cyclase stimulator that augments nitric oxide production. Vericiguat has been studied in phase 2 trials of patients with heart failure with reduced or preserved ejection fraction,[65,66] and is being evaluated in a large phase 3 trial of patients with reduced ejection fraction (VICTORIA; NCT02861534).

To date, no inotropic therapy has been shown to improve outcomes and most studies have shown increased adverse events and mortality with these drugs.[67] These adverse outcomes are probably related to the mechanisms of action of traditional inotropic agents, which indirectly increase contractility by increasing intracellular calcium concentrations rather than directly promoting more efficient contraction.[67] Omecamtiv mecarbil, a cardiac myosin activator that directly improves cardiac function, has shown favourable results in initial studies.[68] In a study of 450 patients with heart failure with reduced ejection fraction (COSMIC-HF),[69] 20 weeks of oral omecamtiv mecarbil decreased ventricular dimensions and volumes, increased stroke volume and ejection fraction, and reduced heart rate and NT-proBNP concentrations; omecamtiv mecarbil is being investigated in an outcomes trial of 8000 patients (GALACTIC-HF; NCT02929329). Results from the only outcome trial to test the efficacy of adenovirus-mediated sarcoplasmic reticulum calcium ATPase gene transfer for the treatment of chronic heart failure with reduced ejection fraction were neutral, although technical issues might have contributed to these results.[70] Cardiac regenerative therapy, through approaches based on cell delivery or in-situ reprogramming of endogenous cardiac fibroblasts, is under intense investigation. Small randomised, controlled, clinical trials of regenerative therapy have been done,[71,72] and further studies are warranted.

Hyperkalaemia can frequently restrict the use of RAAS inhibitors.[73] Two gastrointestinal-potassium binders that reduce potassium absorption might allow for improved tolerance of RAAS inhibitors and titration to increased doses.[74] New MRAs with improved cardiac selectivity have been compared with older agents in patients with heart failure and reduced LVEF.[75] The efficacy and safety of the new oral anticoagulants (compared with vitamin K antagonists) appear to be similar in patients with heart failure compared with the other patients in major trials of non-valvular atrial fibrillation.[76] Whether oral anticoagulants might also be useful to reduce thromboembolic risk and cardiovascular events in patients with heart failure and sinus rhythm is unclear.[77,78] Devices based on changes in sympathovagal cardiac stimulation are under investigation, although most have had neutral results.[49] Devices based on modulation of cardiac contractility or creation of left-to-right interatrial shunting have yielded promising results in small trials and will be assessed in larger studies.[79,80] Valve diseases are a common cause of heart failure and heart failure progression. Transcatheter treatment of aortic stenosis and mitral regurgitation is now possible, and tricuspid regurgitation might also soon be treated percutaneously. These less invasive procedures have increased the indications for treatment of valve disease and hence of heart failure, especially in elderly patients or patients with comorbidities in whom valve surgery might be contraindicated.[81] New surgical or interventional procedures to counteract left ventricular remodelling are also under investigation.[82]

Treatment of heart failure with preserved ejection fraction

No therapy has had a definitive, favourable effect on primary endpoints in outcome trials in heart failure with preserved ejection fraction. Symptom improvement remains a primary goal of treatment of these patients. Diuretics are the mainstay of treatment for patients with signs of congestion, but care must be taken to avoid an excessive decrease in left ventricular preload. Proper treatment of hypertension (perhaps with reconsideration of reduced target blood pressures[41]), coronary artery disease, and atrial fibrillation remain the best measure in patients with these comorbidities.[1,2]

Although no treatment has affected mortality or symptoms, hospital admissions due to heart failure were reduced in some trials.[1,83] In the TOPCAT trial,[84] spironolactone reduced the number of hospital admissions due to heart failure, with better results seen in patients enrolled on the basis of their BNP concentrations and in those from the Americas. In a subgroup analysis excluding patients enrolled in Russia and Georgia, spironolactone significantly reduced all-cause mortality, cardiovascular death, and hospital admission due to heart failure.[84]

Although progress has been made in understanding the phenotypes of heart failure with preserved ejection fraction,[85] improved characterisation of these patients is needed to improve selection of drug treatments on the basis

of cardiac and non-cardiac comorbidities (ie, hypertension, coronary artery disease, atrial fibrillation, diabetes, obesity) and pathogenetic mechanisms (ie, exercise tolerance, right ventricular dysfunction, increased pulmonary artery pressures).[27,86,87] Most drugs studied for the treatment of heart failure with preserved ejection fraction act on the availability of cyclic guanosine monophosphate and nitric oxide. Ongoing trials include the PARAGON-HF trial with sacubitril/valsartan (NCT01920711).[88] A phase 2b trial with vericiguat has been completed.[65] Favourable results have been obtained in initial studies with inorganic nitrites,[89] as opposed to nitrates, perhaps due to the absence of tachyphylaxis and reduced oxidative stress.[90]

Comorbidities

The prevalence of comorbidities in patients with heart failure and their effects on prognosis are increasing, particularly in patients with heart failure with preserved ejection fraction.[6,91,92] Comorbidities are associated with increased severity of heart failure symptoms, reduced tolerance to treatment, and worse prognosis. However, comorbidities might not have an independent prognostic value and, with a few exceptions to date,[40,93,94] their specific treatment has not affected clinical symptoms or improved outcomes. The main clinical implications of comorbidities in patients with heart failure are summarised in table 2.[1,20,21,40,45,46,74,93–95,98–102,104–109]

No evidence favours pharmacological rhythm control over rate control in the treatment of atrial fibrillation in patients with heart failure.[1,95] In the rate-control strategy, the optimal heart rate should be kept at 60–110 bpm and amiodarone is the second choice to β blockers or digoxin.[1,96] With respect to rhythm-control, ongoing large, randomised trials[1,97] comparing catheter ablation with pulmonary vein isolation versus medical therapy will help to establish the role of these different approaches.

Demographic variables also have a major role in patients with heart failure. Elderly patients with heart failure tend to be female and have distinct clinical characteristics, including an increased prevalence of hypertension and preserved ejection fraction. The prognostic value of some variables might also differ between elderly and younger patients.[110]

Acute heart failure

Definition

Acute heart failure is increasingly recognised as a distinct disorder with unique pathophysiology, treatments, and outcomes. Acute heart failure can be defined as the new onset or recurrence of symptoms and signs of heart failure, requiring urgent evaluation and treatment and resulting in unscheduled care or hospital admission.[1,111] Although the word acute suggests a sudden onset of symptoms, many patients might have a more subacute course, with gradual worsening of symptoms that ultimately reach a level of severity sufficient to seek unscheduled medical care.

Epidemiology

In high-income countries, acute heart failure is among the most common cause of admission to hospital in people older than 65 years. About 3 million people are admitted to hospital each year with a primary or secondary diagnosis of heart failure, and acute heart failure contributes to more than 7 million hospital days annually in the USA alone.[12] In-hospital mortality for acute heart failure can be greater than that for acute myocardial infarction and ranges from 2% to 20%. Mortality also remains high for more than 1 year after discharge compared with stable outpatients with chronic heart failure.[112,113] The prevalence of acute heart failure is projected to increase because of the same factors that are increasing the prevalence of chronic heart failure.

Pathophysiology

Acute heart failure is a heterogeneous syndrome that shares many characteristics and processes with chronic heart failure. The clinical course and prognosis of a patient with chronic heart failure is much worse after an episode of acute heart failure,[112] which suggests that acute heart failure has distinguishing aspects important to its pathophysiology—such as haemodynamics, renal function, and end-organ damage.

Symptoms and signs of poor perfusion are only present in about 5% of acute heart failure presentations (table 1). However, about half of patients with acute heart failure have reduced systolic function, representing a target for potential future therapies.[71,114] Most patients admitted to hospital with acute heart failure present with congestion, predominantly dyspnoea and peripheral oedema. Multiple factors contribute to congestion, including ventricular diastolic function, pulmonary venous pressure and resistance, decreased fluid clearance from the lungs and peripheral tissues, and intravascular volume status. Venous and arterial vasoconstriction with adverse volume redistribution have a major role in the haemodynamics of acute heart failure, providing the basis for the symptom benefit of vasodilators, whereas diuretics can address the increased intravascular volume secondary to fluid retention resulting from neurohormonal activation and renal dysfunction. Adequate reduction in congestion is essential for symptom relief and to reduce subsequent hospital admissions.[1,115]

The central role of renal dysfunction in the pathophysiology of acute heart failure has been a recent focus of research. Low cardiac output, altered intrarenal haemodynamics, tubuloglomerular feedback, and increased abdominal pressure or increased venous pressure can contribute to worsening renal function, but most evidence suggests that elevated central venous pressure (ie, the afterload on the kidney) is the most common dominant factor.[21,116,117] Worsening renal function often correlates with poor outcomes in acute heart failure, but not always; obtaining adequate decongestion, even at the expense of mild worsening renal function, can improve clinical outcomes.[118] By contrast, patients with worsening renal

	Examinations	Prognostic value	Therapeutic implications
Cardiovascular			
Atrial fibrillation	ECG, Holter monitoring	Yes, but not independent	Yes[1,95-97]
Ventricular arrhythmias	ECG, Holter monitoring	When life-threatening	Yes
Bradyarrhythmias	ECG, Holter monitoring	When life-threatening	Yes
Coronary artery disease	ECG, echocardiography, stress imaging	Yes	Yes; coronary-artery bypass grafting reduced 10 year mortality and cardiovascular-related hospital admissions versus medical treatment[93]
Hypertension	Laboratory, cardiac imaging	Yes	Yes[40]
Valve disease			
Mitral regurgitation	Echocardiography	Yes	Unknown
Aortic stenosis	Echocardiography	Yes	Yes
Tricuspid regurgitation	Echocardiography	Yes	..
Stroke	..	Yes	No
Non-cardiovascular			
Diabetes	Serum glucose, glycated haemaglobin	Yes, independent[98]	Yes, most antidiabetic agents, except metformin and including insulin, can worsen symptoms of heart failure; liraglutide reduced cardiovascular events;[43] empaglifozin reduced heart failure events in patients at risk of cardiovascular events[45,46,98]
Hyperlipidaemia	Serum cholesterol, triglycerides	Yes	No
Anaemia	Serum haemoglobin	Yes, uncertain if independent	No effect on outcomes and possible increase in thromboembolic events with recombinant human erythropoietin[99,100]
Iron deficiency	Iron, saturated transferrin, ferritin, hepcidin	Yes[101]	Ferric carboxymaltose treatment effective on symptoms, functional class, and hospital admissions due to heart failure in a meta-analysis[94,102,103]
Kidney dysfunction and worsening renal function	Serum creatinine, cystatin-c, markers of tubular injury	Yes, but must exclude an increase in serum creatinine caused by overdiuresis, hypotension, or initiation of an ACE inhibitor or ARB[20,21]	Yes, diuretics are less effective; ACE inhibitors, ARBs, MRAs, and thiazides are contraindicated in severe kidney dysfunction; digoxin dosing needs to be carefully monitored; novel oral anticoagulants contraindicated or dose adjustments needed[1,21,104]
Electrolyte disturbances	Serum sodium, potassium, chloride, magnesium	Yes[105,106]	Yes, ACE inhibitors or ARBs and MRAs might need dose adjustment or withdrawal, potassium binders might be useful[74]
Cachexia	Bodyweight, serum albumin, blood urea nitrogen	Yes	Unknown
Obesity	Bodyweight	Yes	Unknown
Hepatic dysfunction	Serum transaminases, bilirubin, alkaline phosphatases, γ-glutamyltranspeptidase	Yes[104,107]	Unknown
Chronic obstructive pulmonary disease	Pulmonary function testing	Yes	β blockers contraindicated with bronchial asthma. Consider other heart rate lowering agents if heart rate≥70 bpm
Sleep-disordered breathing	Sleep monitoring	Yes	Adaptive servoventilation has increased mortality in patients with predominant central sleep apnoea[108]
Depression	..	Yes	No
Infections	C-reactive protein, procalcitonin	Yes	Unknown[109]

Data based on specific references and on current guidelines.[1,2] ECG=electrocardiogram. ACE=angiotensin converting enzyme. ARB=angiotensin receptor blocker. MRA=mineralocorticoid receptor antagonist.

Table 2: **Comorbidities associated with heart failure**

function and persistent signs of congestion often have poor outcomes, presenting a dilemma for the practising clinician because it is difficult to know how much worsening renal function is too much.[21] Additional research into kidney injury and other biomarkers might provide guidance in the future. Diuretic resistance—ie, an insufficient diuretic response or a lack of decrease in bodyweight despite intravenous administration of diuretics at adequate doses—often coexists with kidney dysfunction, but has an independent association with poor outcomes.[119] A major advance in understanding the pathophysiology of acute heart failure has been the recognition of the role of end-organ damage in adverse outcomes. Acute heart failure represents a neurohormonal, cytokine, inflammatory, and oxidative stress storm in the setting of haemodynamic compromise, all of which contribute to end-organ damage. Markers of end-organ damage and dysfunction, namely cardiac troponins, serum transaminases, and renal markers, have been shown to be elevated in acute heart failure and correlate with decreased survival.[104] In-hospital worsening of heart failure is also related to poor outcomes both during hospital stay and post-discharge.[104,120] These findings have important implications for the treatment of acute heart failure, suggesting that early intervention (similar to the adage of time is myocardium in acute coronary syndrome) with the right therapeutics might reduce or prevent end-organ damage and improve long-term outcomes.

Diagnosis

Existing guidelines provide useful diagnostic algorithms for acute heart failure,[1,2,121,122] a clinical diagnosis that is not made on the basis of any single test. Physical examination remains important for diagnosis and treatment planning, especially for assessment of the signs of congestion, although with a low sensitivity and specificity. Electrocardiograms provide useful information about potential precipitants of acute heart failure and targets for specific therapies (ie, myocardial infarction or ischaemia, atrial fibrillation with rapid ventricular response, or other arrhythmias). Chest radiography can be very specific for the findings of acute heart failure, but has a poor sensitivity. Some studies[123,124] have suggested a valuable role for point-of-care ultrasonography, particularly lung ultrasonography, to assess left ventricular function, volume status, and the aetiology of dyspnoea. All guidelines recommend that patients presenting with acute heart failure have an echocardiogram, although more recent studies suggest that, once an echocardiogram has been done, repeat echocardiograms might have limited utility and should only be done when it is clear that the findings will directly affect management.[1]

The natriuretic peptides, BNP and NT-proBNP, have been shown to have excellent sensitivity in the diagnosis of heart failure. However, because of their low specificity, these biomarkers must be assessed in the context of other diagnoses (pulmonary embolism, right-ventricular strain, myocardial infarction) and patient characteristics (age, sex, renal function, obesity) that affect diagnostic thresholds. NT-proBNP assays might become preferable in the follow-up of patients on sacubitril/valsartan, given that this drug therapeutically increases BNP concentrations. Other biomarkers are also being investigated for their utility in acute heart failure.[32] Measurement of procalcitonin can assist in the differential diagnosis and guide therapy of pneumonia and acute heart failure in patients with dyspnoea.[109]

Therapeutics

The goals of treatment for a patient with acute heart failure are three-fold. First, immediate stabilisation and relief of symptoms. Current guidelines provide algorithms for this goal (figure 3).[1,122] Existing therapies (eg, diuretics and vasodilators) are fairly effective at improving early symptoms, although a large percentage of patients continue to have dyspnoea or subclinical

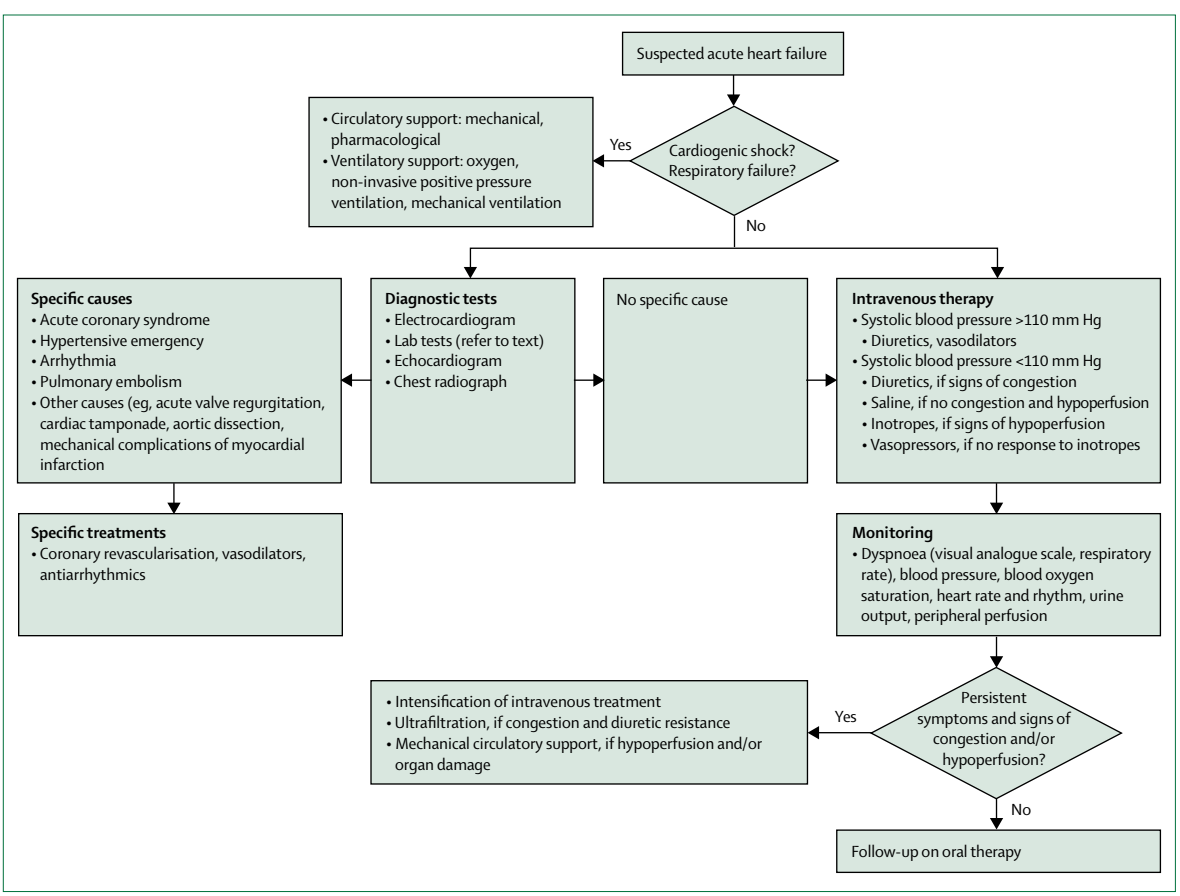

Figure 3: **Algorithm for the management of patients with acute heart failure**
Algorithm was modified from reference 122.

congestion despite treatment, as shown by persistently high plasma concentrations of BNP and NT-proBNP. This failure of treatment is frequently underappreciated by physicians. Patients without dyspnoea relief have poor short-term and long-term clinical outcomes,[125] suggesting that dyspnoea remains an important therapeutic target. Second, as already noted, a relatively recent concept in the management of acute heart failure is the goal of preventing in-hospital worsening heart failure[120] and other clinical events. No existing treatments have met this goal. Third, therapy should improve post-discharge outcomes. In a study of more than 123 000 patients admitted to hospital for acute heart failure in England,[126] improved adherence to six process measures (prescribing of ACE inhibitors and β blockers, performance of echocardiography, cardiology inpatient evaluation, and follow-up by a cardiologist and heart failure liaison) correlated with improved short-term outcomes, suggesting that processes of care can have an important effect on patient outcomes. Medications started before discharge have a much higher likelihood of being continued and being titrated to optimal doses as an outpatient than medications initiated after discharge,[1,2] so pre-discharge initiation of chronic, life-saving, and disease-modifying therapies might also improve clinical outcomes. Careful patient follow-up after discharge, with the intervention of a multidisciplinary team, has a pivotal role in patient outcomes.[1,2]

Diuretics continue to be a cornerstone of therapy for acute heart failure in patients with volume overload.[1,2,121,122] The DOSE study[127] enrolled 308 patients admitted to hospital with acute heart failure: patients treated with high-dose diuretic treatment (total daily dose of intravenous furosemide was 2·5 times the total daily dose of oral loop diuretic in furosemide equivalents) had greater dyspnoea relief and weight and fluid loss, but also a greater increase in creatinine, than did patients treated with low-dose diuretic therapy. No difference in responses was observed between patients assigned to bolus versus continuous infusions in that study. However, this absence of a difference might have been due to the clinical trial setting, in which bolus infusions were mandated and carefully monitored. In clinical practice, continuous infusions might still provide more reliable volume removal than bolus infusions. Unfortunately, the DOSE trial[127] was underpowered to assess clinical outcomes, so the long-term effects of these different strategies remain unknown. In the setting of diuretic resistance, sequential nephron blockade with thiazides or thiazide-like diuretics might be considered. Ultrafiltration is another option, but its efficacy is highly debated; the results of the CARRESS-HF study[128] suggest no benefit for ultrafiltration in patients with acute heart failure, worsened renal function, and persistent congestion, whereas the prematurely dis continued AVOID-HF trial[129] suggested reductions in hospital admissions with ultrafiltration in patients with acute heart failure.

Vasodilators have multiple potential benefits in patients with acute heart failure.[130] Data regarding the use of nitrates have been collected in small studies, of which many have been confounded by cases of acute heart failure caused by acute myocardial infarction. In a systematic review,[131] nitrate vasodilator therapy for the treatment of acute heart failure did not differ significantly from alternative interventions with regard to symptom relief and haemodynamic variables. After another extensive literature review, the UK National Institute for Health and Clinical Excellence recommended to "not routinely offer nitrates to people with acute heart failure".[132] Despite these analyses, other guidelines state that nitrate vasodilators should be administered to patients with acute heart failure and normal-to-elevated systolic blood pressure (≥110 mm Hg) to improve symptom relief.[1,2,121,122] Other studies have emphasised the importance of avoiding hypotension (eg, a systolic blood pressure of <90 mm Hg) in these patients, and the guidelines recommend careful blood pressure monitoring during administration of nitrate vasodilators.[1,2,122]

In the minority of patients with acute heart failure and signs of hypoperfusion, inodilators (ie, dobutamine, milrinone, enoximone, levosimendan) are indicated, although they have been shown to cause significant adverse effects, including tachycardia, supraventricular and ventricular arrhythmias, hypotension, myocardial ischaemia, and death.[133] Unfortunately, these agents remain the only pharmacological tools available to increase cardiac function, so they continue to be recommended for patients with impending or current cardiogenic shock.[1,2,121,122] In that context, vasopressor agents might be added to inodilators in treatment of select patients with a crucial need for vasoconstriction to maintain perfusion pressures, with some evidence supporting the preferential use of norepinephrine over dopamine.[134]

Many patients admitted to hospital with acute heart failure are already taking multiple oral medications for heart failure or other cardiovascular diseases. In the absence of symptomatic hypotension or cardiogenic shock, patients admitted to hospital with acute heart failure should continue taking β blockers, because discontinuation of β blockers in patients admitted to hospital with acute heart failure was associated with significantly increased in-hospital mortality, short-term mortality, and the combined endpoint of short-term readmission to hospital or mortality.[135] MRAs, ACE inhibitors, and ARBs can be continued if the patient does not have severe renal dysfunction or hyperkalaemia.

Other therapeutic recommendations include avoiding potentially harmful therapies. Opiates are not generally recommended because of their adverse effects on respiratory function and cognitive function.[136] One study[137] showed that intravenous fluids (median 1 L normal saline) were administered early in the hospital course in

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13 806 (11%) of 131 430 patients admitted to hospital for acute heart failure, and this treatment was associated with higher rates of critical-care admission, intubation, renal replacement therapy, and in-hospital death than treatment with diuretics alone. Calcium-channel blockers with negative inotropic properties, oral anti-arrhythmics (except for amiodarone), non-steroidal inflammatory drugs, or other agents that might interfere with renal function are generally contraindicated in patients with acute heart failure.

Future directions

Agents with vasodilating properties have continued to be actively developed.[130] In phase 2 and 3 trials,[138,139] patients treated with serelaxin, a recombinant version of the hormone relaxin, had significant improvements in the signs and symptoms of heart failure, including dyspnoea, decreased biomarker evidence of end-organ damage, decreased in-hospital worsening of heart failure, shortened duration of hospital stay, and increased 180 day survival. The potential beneficial effect of serelaxin on reduction in worsening of heart failure events and 180 day cardiovascular mortality is being investigated in the RELAX-AHF-2 trial (NCT01870778) of about 6600 patients.[140] Ularitide, an alternatively spliced atrial natriuretic peptide,[141] is being studied in a phase 3 trial of 2152 patients with acute heart failure (TRUE-AHF; NCT01661634). In a phase 2 dose-finding study[142] of 618 patients admitted to hospital for acute heart failure, no efficacious dose was identified for TRV 027, a biased ligand of the type-1 angiotensin II receptor, in the overall patient population. In the ATOMIC-AHF study,[68] omecamtiv mecarbil did not improve the primary endpoint of dyspnoea relief compared with the pooled placebo. However, dyspnoea improved in the high-dose cohort and an overall improvement in cardiac function was noted in that study.[114] A strategy of early initiation of MRAs in patients with acute heart failure is being tested in a randomised clinical trial.[143]

Conclusions

Heart failure continues to be a leading cause of morbidity and mortality worldwide. Symptoms and signs should be integrated with biomarkers and cardiac-imaging modalities for the diagnosis of heart failure where possible. Prevention of heart failure might be improved by better control of cardiovascular risk factors, including hypertension, possibly by lowering of systolic blood pressure targets in patients at increased risk of cardiovascular events and in those with diabetes, in whom empaglifozin has reduced heart failure events. Once symptomatic, patients with heart failure have a poor prognosis, particularly after hospital admission for acute heart failure. Survival of patients with heart failure with reduced ejection fraction can be improved by optimisation of oral medications, which involves ensuring that patients take the maximally tolerated dose (up to target doses) of known life-saving therapies (ACE inhibitors, ARBs, β blockers, or MRAs) and substituting ACE inhibitors or ARBs with sacubitril/valsartan if patients have persistent symptoms after treatment with ACE inhibitors or ARBs and high BNP or NT-proBNP concentrations. Substantial reductions in hospital admissions for heart failure can be achieved with addition of ivabradine to therapy in patients with a normal sinus rhythm heart rate (≥70 bpm) despite maximal tolerated (up to target) β blocker doses. The safety of LVADs is improving, making them an increasingly reasonable and valid option in patients with advanced heart failure. In the context of the increasing disease burden and persistently high morbidity and mortality, new treatments for heart failure with preserved ejection fraction and acute heart failure are desperately needed.

Contributors

Both authors wrote the manuscript and are responsible for the entire content. Both authors contributed equally to the manuscript.

Declaration of interests

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