Heart failure burden and therapy

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Heart failure (HF) is a syndrome with a broad spectrum of heterogeneous symptoms and signs resulting in a wide range of clinical expressions. The prevalence of HF is estimated to be 1–2% in developed countries, increasing with age. Heart failure is the leading cause of hospitalization for patients older than 65 years, raising concerns about the economic burden of this syndrome. This article provides a critical review of epidemiological and clinical aspects for HF; causes, comorbidities, and types of HF are also described. The systolic vs. diastolic, the acute vs. chronic approaches, and the connections between HF and left bundle branch block or atrial fibrillation are further detailed. In addition, a synthesis of the latest results and recommendations concerning the indication and the prescription of pharmacological (such as diuretics or rennin–angiotensin–aldosterone system inhibitors) and non-pharmacological treatments (particularly device therapy) is proposed.

Keywords
Heart failure • Epidemiology

Introduction

Epidemiological data are essential for clinical decision-making and for utilization and allocation of health care resources. They are also critical for planning prospective studies of therapeutic interventions and care management, particularly for sample size calculation and risk stratification.

The shortage of epidemiological data, together with the heterogeneity and confusing nomenclature of the heart failure (HF) syndrome, partly explains why the epidemiology of HF is poorly understood. Nearly all available epidemiological descriptions of HF are based on retrospective analysis of hospital records of patients admitted to hospital, or presenting to the emergency room with HF and only few observations are population based. Because of large variations in health care systems and in clinical practice among different western countries, one should caution against the generalization of data derived only from hospital records.

However important, epidemiological data limited to hospitalized patients do not provide information on the huge hidden part of the iceberg, which consists of mild and asymptomatic patients with HF. In epidemiological studies of hospitalized HF patients, case ascertainment relies on the diagnosis made by the managing physician. The lack of agreement on a definition of HF, as well as the lack of gold-standard diagnostic criteria, may result in a considerable heterogeneity in the diagnosis of HF in epidemiological studies. Ideally, the definition of HF should combine clinical features with an objective measure of cardiac performance and/or neuroendocrine markers. Available epidemiological data in HF describe only a fraction of patients with this syndrome and are not comprehensive. Epidemiological data describing patients with advanced HF are more likely to be comprehensive, because, at this stage of the disease signs and symptoms, ventricular dysfunction and neuroendocrine activation do coincide and diastolic failure without evidence of systolic failure is usually rare.

Randomized clinical trials of treatment for chronic HF (CHF) are the basis of many conceptions about HF epidemiology. Due to the selection bias of such studies—which preferentially recruit relatively young white men with coronary artery disease—epidemiology of HF in the real world cannot be derived from clinical trials.

Heart failure is a syndrome with a broad spectrum of heterogeneous symptoms and signs caused by a cardiac dysfunction and resulting in a wide range of clinical expressions, which made it harder for researchers to measure its real burden until a clear definition was drawn by the European Society of Cardiology Task Force.1 However, reports drawn on various data sets from registries,2 trials,3 population-based studies,4,5 and hospital-based studies,6 uniformly raise concerns about both the growing frequency and the severity of this syndrome.7

Occurrence of heart failure in developed countries

Heart failure is an urgent public health need with national and global implications. It is one of the most important causes of morbidity and mortality in the industrialized world. According to the European Society of Cardiology, within 51 European countries...
representing a population of 900 million, it is estimated that there are at least 15 million patients with HF. More than 5 million Americans have HF. According to the American Heart Association, an estimated 550,000 new cases occur each year in the USA.

The prevalence of HF is estimated at 1–2% in the Western world, and the incidence is estimated 5–10 per 1000 persons per year. Persons younger than 50 years are hardly ever found to have HF. In a recent US population-based study, the prevalence rate of HF was 2.2% (95% CI 1.6–2.8), increasing with age: 0.7% in persons aged 45–54 years, 1.3% in persons aged 55–64 years, 1.5% in persons aged 65–74 years, and 8.4% for those aged 75 years or older. Similar increasing prevalence trends were reported in the Rotterdam study: from 1% in persons aged 55–64 years to 13% in those aged 75–84 years. The rise in the incidence and prevalence of HF globally is the result of improved care of acute myocardial infarction combined with the ageing of the population and the emerging pandemic of cardiovascular disease in the developing countries.

**Awareness of heart failure**

Appropriate HF care, adequate resourcing of care, and research require recognition of its clinical, social, and economic importance not only by healthcare authorities and providers but also by the general public. Without recognition of symptoms and their seriousness, people with HF will not seek medical attention promptly. Awareness of the causes of HF may help to make appropriate lifestyle changes to reduce risk. In addition, awareness of treatment benefits could aid compliance and prompt patients to seek appropriate care. However, there is a lack of information on public awareness of HF. Studies have shown relatively poor understanding and treatment of HF by general practitioners. As part of the SHAPE programme, a survey has indicated that the awareness of most aspects of HF in the general population in Europe is low. There are clear misconceptions of the nature, severity, treatment options, and costs. Therefore, the general public is unlikely to demand appropriate measures by healthcare authorities and providers. A better understanding of HF could improve its prevention and management. Strategies to educate the public about HF are needed.

**Outcomes related to heart failure**

**Heart failure mortality**

The results of both the Framingham Heart Study and a population-based study in Olmsted County, Minnesota suggested decreases of age-adjusted mortality rates in patients after the onset of HF in the last decades. However, 5-year age-adjusted mortality rates after onset of HF remained high in those two studies, with higher rates in men (50% in men vs. 46% in women for the Olmsted County population based study). The vast majority of patients with HF die from cardiovascular causes; estimates vary from 50 to 90%, depending on the HF population studied. Among cardiovascular causes of death, sudden cardiac death poses a major threat, with up to 50% of HF patients dying of sudden cardiac death. Importantly, the relative contribution of sudden death to total death rate decreases when the clinical severity of HF increases. It is at its maximum (>50%) in patients with low left ventricular ejection fraction (LVEF) and NYHA class I and II and lowest in patients with advanced HF where patients die mostly from pump failure. This is an important element influencing the relative benefit, and, therefore, the indications for implantable cardiac defibrillators (ICDs).

**Heart failure hospitalization**

The hospitalization rate for HF is useful as a measure of the burden of HF, though it may vary with the prevalence, the incidence, and the survival in HF, variations in regional health care systems, and the discharge diagnosis coding practices. Heart failure hospitalization represents 1–2% of all hospital admissions, which makes it the leading cause of hospitalization for patients older than 65 years. Interestingly, admission numbers for HF peaked in the 1990s in Scotland, the Netherlands, and Sweden and then started to decline. For example, in a Dutch male population, the annual increase in hospitalization rate between 1980 and 1992 was estimated at 4.3%. It was followed by a small annual decrease of 1.5% in the years thereafter. This decline may be due to improved therapy and management of HF, but also to an increased home-based care by general practitioners for patients with terminal HF. However, the burden related to HF hospitalization remains huge: when patients are first diagnosed as having HF, they tend to be hospitalized for the disease as frequently as 21.3 events per 100 person-years in white people and up to 53.2 events per 100 person-years in black people.

**Prognostic factors**

The science of prognostication has been extremely active in HF over the last two decades. In the attempt to stratify patients by risk categories and aiming at applying a staged therapeutic strategy, a number of clinical and biological characteristics, clinical scores as well as a large and ever increasing number of biomarkers have been associated with outcome and a few have been developed as ‘predictors’ of outcome. A non-comprehensive list of factors assessing the severity of HF and shown to be related to outcome in patients with CHF includes age, gender, ethnicity, aetiology, co-morbidity, NYHA class, exercise capacity, peak VO2, poor quality of life, low body weight, left bundle branch block (LBBB), atrial fibrillation, non-sustained, sustained, and inducible ventricular tachycardia, increased PR and QRS duration, T-wave alternans, QT dispersion, low heart rate variability, depressed baroreflex sensitivity, history of HF hospitalization, resuscitated death, hyponatraemia, hypokalaemia, raised serum creatinine and blood urea nitrogen, transaminases, bilirubin and urates, anaemia, neuroendocrine activation, high serum BNP, low LVEF, abnormal diastolic function parameters, raised serum levels of markers of extracellular matrix metabolism, viable myocardium, and central haemodynamics. Prognostic analyses have been predominantly carried out on populations with LV systolic dysfunction (LVSD). Much less data are available for HF with preserved systolic function. Specific predictors of sudden death have also been developed. Beyond low LVEF, none has a strong enough predicting value to be the basis for indicating an ICD. Similarly, beyond low LVEF and wide QRS complex, none has a strong enough
predicting value to be the basis for indicating cardiac resynchronization therapy (CRT).

**Heart failure economics**

Heart failure has a huge impact on health-related quality of life and appears as an economic burden nowadays. Actually, in the USA, 17% of all medical expenditure, or $149 billion annually, and nearly 30% of Medicare expenditure are attributable to stroke, hypertension, HF, and other heart diseases. It is estimated that 1–2% of all healthcare expenditure is devoted to HF in developed countries, and the USA cost increased from $30.2 billion in 2007 to an estimated amount of $37.2 billion in 2009, the major part of the expenditure relating to hospitalizations with an estimated cost of $20.1 billion dollars in 2009.

**Causes and co-morbidity of heart failure**

Heart failure is associated with ischaemic heart disease (from 46 to 68%), arterial hypertension (from 53 to 66%), diabetes (from 27 to 38%), arrhythmia, especially atrial fibrillation (from 21 to 42%), and renal insufficiency (from 17 to 53%). Heart failure is associated with serious morbidities, such as renal failure, cancer, cirrhosis or hepatic insufficiency, or chronic obstructive pulmonary disease.

There are very little data from developing countries. Rheumatic heart disease remains a major cause of HF in Africa and Asia, especially in the young. Hypertension is an important cause in the African and African-American populations. Chagas’ disease is still a cause of HF in South America. However, as countries undergo socio-economic development, the epidemiology of HF becomes increasingly similar to that in Western countries.

**Different types of heart failure**

A common description of HF distinguishes different types of the syndrome according to its mechanism (systolic vs. diastolic), its aetiology (ischaemic vs. non-ischaemic) or its clinical presentation (acute vs. chronic).

**Systolic vs. diastolic heart failure**

Systolic HF is frequently distinguished from diastolic HF. However, as the terms systolic and diastolic HF are not mutually exclusive, they should not be considered as separate pathophysiological entities. It seems more appropriate to distinguish between HF with an impaired (low) left ventricular ejection fraction (HFLEF) and HF with a preserved left ventricular ejection fraction (HFPEF), which is more common in older individuals, in women, in individuals with hypertension, obesity, renal failure, anaemia, and atrial fibrillation. Whether HFLEF and HFPEF are distinct pathophysiological entities is still a matter of debate. Some view these as two different phenotypic expressions of the same disease with a continuum between diastolic failure and systolic failure. Clinical trials for heart failure have historically focused on HFLEF and drove the cardiology community to be 'systolocentric', thus contributing to view HFLEF and HFPEF as distinct respective entities. As a result, advances in HF therapy have been extraordinarily successful in HFLEF contrasting with the paucity of evidence-based therapy in HFPEF. Over the last two decades, the relative importance of these entities has changed substantially with an increase in the prevalence of HFLEF from 38 to 54% of all HF cases. The prognosis of patients suffering from HFPEF is as ominous as the prognosis of patients suffering from HFLEF.

**Chronic vs. acute heart failure**

Clinical trials for heart failure have historically focused on CHF, thus contributing to the view of acute HF syndromes (AHFS) simply as severe decompensated CHF. As a result, advances in HF therapy have been extraordinarily successful in CHF contrasting with the paucity of evidence-based therapy in acute HF. Eventually, the term AHFS, referring to de novo HF or decompensation of CHF, and initially perceived as an extension of CHF, is now regarded as a standalone disease, with its proper definition, and which has a poor short- and medium-term prognosis, especially for the most severely affected patients admitted to an intensive care unit, with an in-hospital mortality as high as 28%.

On the basis of pathophysiological targets, it was recently proposed to distinguish between ‘vascular’ and ‘cardiac’ acute HF with different initial clinical presentation. This is the basis of the ‘new’ concept of ‘Acute Heart Failure Syndromes’. These categories have also been shown to represent different outcomes: hypertensive acute pulmonary oedema has a lower mortality rate compared with decompensated HF or cardiogenic shock. Decompensated HF is the main driver of poor outcome in patients with CHF. Once admitted for an acute episode of HF, readmission rate and mortality are very high. The immediate post-discharge period is the most vulnerable period.

**Heart failure and left bundle branch block**

Approximately one-third of patients with HF present with conduction disturbances that result in a QRS duration of >120 ms. Most commonly (in ~25% of HF patients), this is exhibited as an LBBB pattern. This percentage is significantly higher than the estimated 1.5% prevalence of LBBB in the general patient population. In patients with CHF as well as in acute HF, the association between LBBB, and more generally between wide QRS complex and poor outcome have led to test and prove the hypothesis that CRT may benefit selected stable patients with severe CHF, LVSD, and increased QRS duration.

**Heart failure associated atrial fibrillation**

In a recent meta-analysis of atrial fibrillation and the risk of death in patients with HF including 20 studies, Wasywich et al. reported an overall odds ratio for death in patients with concomitant atrial fibrillation compared with patients in sinus rhythm varying from 1.33 (95% CI 1.12–1.59) for 9 randomized controlled trials (RCTs) to 1.57 (95% CI 1.20–2.05) for the 11 observational studies. Abnormalities of diastolic function, including shortened diastole due to high heart rates and loss of atrial kick, impaired LV systolic function due to heart rate irregularity and loss of A-V synchrony, and tachycardia associated with ventricular impairment could explain why the presence of atrial fibrillation may worsen HF outcome. Nonetheless, the adverse prognostic effect of atrial fibrillation is more pronounced in CHF patients with de novo atrial fibrillation.
fibrillation for patients with HF may not be a simple function of patient age, HF severity, or LVEF.49 However, considering that atrial fibrillation worsens HF and HF promotes atrial fibrillation, management of atrial fibrillation in patient with HF remains a major challenge.

**Pharmacological treatment of heart failure**

Pharmacological treatment of systolic HF is evidence based since the overwhelming majority of trials have been devoted to HF with LVEF <40 or 35%. The treatment of HF with preserved systolic function is less well defined than the treatment of systolic HF. Therefore, in HFPEF, the current recommendations are based on disease-oriented evidence, including pathophysiology, extrapolation of knowledge about other aspects of cardiovascular disease, data from small studies, and expert opinions. None of the treatment recommendations has been validated by RCTs. However, evidence is emerging that so far, effective drugs in HF with low LVEF are most likely to be equally effective in HF with preserved systolic function. Therefore, we will not separate HFLEF from HFPEF.

Pharmacological treatment of HF is directed at alleviating symptoms, treating congestion, preventing tachycardia, improving quality of life and survival. In addition, pharmacological treatment of HF with preserved systolic function is directed at normalizing blood pressure, promoting regression of LV hypertrophy, preventing tachycardia and maintaining atrial contraction.

**Diuretic therapy**52

Loop diuretics work by blocking the sodium–potassium chloride transporter in the ascending loop of Henle. They are potent natriuretic agents with high ceiling efficacy, have short onset and duration of action, and are therefore best suited to the treatment of acute pulmonary oedema and HF with severe congestion. Because of being safe in renal failure, loop diuretics are also the diuretics of choice in patients with concomitant renal dysfunction. Thiazide diuretics interfere predominantly with sodium reabsorption in the central part of the distal tubule. They have longer onset and duration of action, and much milder natriuretic effects. They are therefore used clinically in mild CHF in ambulatory patients. Because of being nephrotoxic, thiazide diuretics are contra-indicated in HF patients with renal dysfunction. Torasemide has higher bioavailability when compared with oral furosemide as well as additional anti-aldosteronergic effects.

In congested patients with HF, diuretics are extremely effective in relieving symptoms, reducing intracardiac pressures, and improving cardiac performance. Diuretics improve quality of life by providing relief from symptoms of HF. In non-congested patients, it is unclear whether the continued use of diuretics is useful. Continued use of diuretics may cause potentially detrimental vascular effects and neuroendocrine activation. The beneficial haemodynamic effects of chronic diuretic usage may outweigh the potentially adverse neuroendocrine stimulation in the non-congested patients who are already on angiotensin converting enzyme (ACE)-inhibitors and beta-blockers. On the other hand, diuretic withdrawal in stable patients may cause significant deterioration of haemodynamic parameters and worsening of HF. There is evidence supporting the notion that continuous diuretic therapy is needed for chronic therapy. It is possible, however, that if the patients had severe restriction of sodium intake, they could avoid diuretic therapy. Prolonged activation of the rennin–angiotensin–aldosterone system (RAAS) may lead to progressive salt/water retention and peripheral vasoconstriction. Diuretics should be used in combination with ACE-inhibitors on the assumption that the ACE-inhibitor will suppress the adverse neuroendocrine effects of the diuretic. The effect of diuretic therapy on mortality as well as HF hospitalization has not been properly studied. The use of non-potassium-sparing diuretics may be associated with a significantly increased incidence of sudden, presumed arrhythmic, death.

Electrolyte imbalance is the most common adverse effect of chronic diuretic therapy. Biochemical abnormalities include hypokalaemia, hyponatraemia, hypomagnesaemia, hyperuricaemia, and metabolic alkalosis. Diuretic-associated hypokalaemia may increase the risk of arrhythmic mortality in patients.

**Rennin–angiotensin–aldosterone system inhibition**

The RAAS is one of the major mechanisms in transition from risk factor to overt HF as well as of the progression of the disease and its lethal complications. Therefore, RAAS inhibitors may be useful at different stages of the disease; all the way through from preventing the disease at the stage of risk factor, to slowing the progression of the disease, once LV dysfunction is established, to the prevention of death and hospitalization at a later stage.

Despite optimal therapy, patients with HF experience clinically meaningful disease progression. Optimal therapy is based essentially on potent inhibitors of the RAAS. It is recognized that this requires a combination of agents blocking, respectively, the three main components of this system: decreasing rennin production with a beta-blocker, limiting angiotensin-2 production with an ACE-inhibitor and/or blocking angiotensin-2 AT1 receptors with an angiotensin receptor blocker (ARB) and opposing aldosterone effects with a mineralocorticoid receptor antagonist.

**Angiotensin-converting enzyme inhibitors**53

Angiotensin-converting enzyme inhibition improves survival, symptoms, functional capacity, and reduces hospitalization in patients with moderate and severe HF and LVSD. In a meta-analysis of 32 randomized trials comparing ACE inhibitors with placebo in HF patients, the pooled relative risk reduction in mortality was 17% when taking an ACE inhibitor. In the studies of LV function treatment trial (SOLVD treatment), 2569 patients with overt but stabilized HF and LVEF ≤35%, the average benefit from enalapril was 2.44 months of extended life. The SOLVD trials both show that the size of benefit is correlated with the LVEF: in the lower risk higher LVEF group with a normalized annual mortality of up to 15% the relative risk of mortality with enalapril was 0.88 (95% CI 0.80–0.97). In the higher risk lower LVEF group with a normalized annual mortality rate of more than 15%, the relative risk was 0.64 (95% CI 0.51–0.81).
Angiotensin-converting enzyme inhibitors are recommended as first-line therapy in patients with reduced LV systolic function expressed as a subnormal LVEF, i.e. <40–45% with or without symptoms. They should be up-titrated to the dosages shown to be effective in the large, controlled trials in HF and not titrated based on symptomatic improvement alone. In patients who have had myocardial infarction and have LV dysfunction, ACE inhibitors provide an important benefit. In a meta-analysis of the four trials in which more than 6000 patients were randomized after myocardial infarction with LV dysfunction to an ACE inhibitor or placebo, the risk ratio was 0.80 (95% CI 0.74–0.88). In the SOLVD trials, 65% of the patients included had had a myocardial infarction.

There is an improvement in symptoms and exercise tolerance when patients with symptomatic HF and a reported LVEF ≤35% are given an ACE inhibitor. Angiotensin-converting enzyme inhibitors seem to be cost-effective since trials consistently show a reduction in admissions to hospital for progressive heart disease. Although most evidence is derived from randomized trials of enalapril, no clinically important differences between the effectiveness of the various ACE inhibitors have been reported.

Before initiation of ACE inhibition, patients should have their blood pressure, renal function, and serum potassium measured. In the absence of fluid retention, ACE inhibitors should be given first. In patients with fluid retention, ACE inhibitors should be given together with diuretics. The dose of ACE inhibitors should always be initiated at the lower dose level and titrated to the target dose. When treatment is initiated, diuretics should be withheld for a brief period (at least 24 h) to allow any volume depletion to resolve. Because of the risk of hyperkalaemia, potassium supplements as well as potassium sparing diuretic drugs should be stopped in all patients who are being started on ACE inhibitors, regardless of the serum potassium concentration. These drugs may be restarted if the patient remains hypokalaemic on full therapeutic doses of ACE inhibitors. Potassium supplements should be considered only in patients with persistent low serum potassium concentration (<4.0 mmol/L). Potassium concentrations must be monitored a few days after drug initiation or up titration and until they are stable because of the risk of renal failure. Older age, severe LVSD, initial systolic blood pressure <100 mmHg, serum sodium <135 mmol/L and high doses of diuretic therapy are all risk factors for hypotension after the first dose of ACE inhibitors. In such conditions, patients may be considered for referral to hospital for assessment and supervised initiation of treatment. They should be given a small dose of a short-acting agent and monitored closely for 2 h. If the test dose is tolerated, they should be started on a small dose of a short-acting ACE inhibiting drug such as enalapril (2.5 mg twice daily) or captopril (12.5 mg three times daily). Patients who are not at high risk of hypotension after the first dose should be started on a small dosage of a drug such as enalapril (2.5 mg twice daily) or captopril (12.5 mg three times daily). Blood pressure, renal function, and serum potassium measurements should be repeated 1 week after initiation of treatment and again 1 week after each significant increase in dosage. Subsequently and in stable conditions, monitoring at least once a year seems appropriate. A mild to moderate rise in serum creatinine concentration of <50 μmol/L is to be expected when patients are initiated on an ACE inhibitor. A larger rise in serum creatinine as well as a serum potassium concentration of 5.5 mmol/L or more, or a documented fall in blood pressure when symptomatic (hypotension with dizziness or weakness), should lead to reassessment of volume status reassessed. The ACE inhibitor dose should be reduced or the drug discontinued. In patients who are hypovolaemic because of diuresis, the dose of any diuretic should be reduced and the ACE inhibitor may be tried again or re-up-titrated. Cough is common in patients taking these drugs, but it is also common in people with HF. Thus, patients who report cough while taking ACE inhibitors should be evaluated to see whether this resulted from pulmonary congestion before stopping treatment is considered. If cough is definitely traced to the ACE inhibitor use, patients should be changed to an ARB.

The implementation of these simple guidelines is far from optimal. In real life, ACE inhibitors are under prescribed, and/or prescribed at smaller than optimal doses. It is still a challenge to apply this therapy to the majority of patients.

In HF patients with preserved systolic function, ACE inhibitors cause regression of LV hypertrophy, decrease blood pressure, and prevent or modify cardiac remodeling; these actions provide strong theoretical support for the use of these agents in patients with diastolic dysfunction. So far, there have been few studies of ACE inhibitors in patients with diastolic dysfunction. In trials of hypertensive patients at high risk of and most likely with a certain degree of diastolic dysfunction, ACE inhibitors decreased the rate of new HF events as well as hospitalization for HF. This was the case in HOPE55 which included high-risk patients, and in EUROPA56 which included patients with coronary artery disease. Respectively, in these trials, ramipril up to 10 mg daily and perindopril up to 8 mg daily were effective in reducing HF events. In both trials, HF and LVSD patients were excluded. In the remainder of hypertension trials, evidenced by the recent meta-analysis,57 ACE inhibitors prevent new onset HF better than calcium channel blockers, diuretics, and first-generation beta-blockers.

The Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF) is the largest trial of perindopril in patients with diastolic failure.58 It aimed to assess the potential benefits of perindopril (2–4 mg) vs. placebo to treat CHF in elderly people, in the absence of any major left ventricular systolic dysfunction. Patients had an LVEF of >45% and were hospitalized for HF within the last 3 months. The trial had insufficient power and was fraught with many protocol violations. In the first year, when most patients were on assigned therapy, perindopril improved symptoms and exercise capacity, reduced hospitalizations for HF, and reduced total and CV hospital bed-days.

The large majority of conditions associated with LV diastolic dysfunction are compelling indications for ACE inhibitor therapy. This includes hypertension, diabetes, LV hypertrophy, and coronary artery disease. ACE inhibitor therapy is, thus, indicated throughout the spectrum of HF from preserved systolic function to asymptomatic and symptomatic NYHA class I to IV systolic HF.

AT1 receptor blockers59

Results of experimental work, confirmed by the findings of the RESOLVD pilot trial, have shown that inhibition of the effects of angiotensin-2 requires a combination of ACE inhibition and AT1
receptor blockade, and more recently the CHARM-added trial\textsuperscript{62} have confirmed that addition to conventional therapy, including an ACE inhibitor, of valsartan up to 360 mg daily or of candesartan up to 32 mg daily, respectively, produced further reduction in CV mortality and morbidity. Results were most remarkable on the reduction of HF hospitalization. Guidelines for management of CHF patients advise adding valsartan or candesartan to conventional treatment including an ACE inhibitor in symptomatic patients.\textsuperscript{8}

Substudies of ValHeFT provided interesting results on the potential mechanisms of the beneficial effects of valsartan.\textsuperscript{8} It provides sustained reductions in BNP and prevents substantial increases in plasma norepinephrine and plasma aldosterone over time, produces improvements in LV function, and reverses LV remodelling.

Although renal tolerance of ARBs is not superior to that of ACE inhibitors, cough is specific to ACE inhibitors and is the most frequent cause of ACE inhibitor therapy discontinuation. Results of a subgroup analysis of ValHeFT\textsuperscript{61} and of the CHARM-alternative trial\textsuperscript{62} demonstrated that the use of valsartan or of candesartan, in patients with CHF intolerant to ACE inhibitors, produced substantial clinical benefit on survival and CV hospitalization. Therefore, ARBs may offer a safe and effective alternative to ACE inhibitors in CHF patients intolerant to ACE inhibitors.

Taken together, the results of trials with ARBs suggest that they may be used alternatively to ACE inhibitor therapy in CHF patients intolerant to ACE inhibitors. Valsartan and candesartan may also be used in addition to ACE inhibitors and to other conventional treatments in symptomatic patients with CHF.

In patients with acute myocardial infarction and HF ELITE II and OPTIMAAL trials could not conclude the non-inferiority of losartan 50 mg once a day, compared with captopril 150 mg/day.\textsuperscript{63} This result is interpreted as being related to the use of a low and ineffective dose of losartan. On the other hand, VALIANT\textsuperscript{64} enrolled 14,703 patients with acute myocardial infarction complicated by HF, LV dysfunction or both and has shown that valsartan 160 mg b.i.d was as effective as a proven dose of captopril in reducing the risk of death and the risk of CV death, non-fatal infarction, or HF. As expected, valsartan produced significantly less cough, skin rash, and taste disturbances than did captopril. The evidence from VALIANT is that valsartan is a clinically effective alternative to an ACE inhibitor. VALIANT has also shown that combining valsartan with a proven dose of captopril produced no further reduction in mortality and more adverse drug events. Therefore, in acute myocardial infarction HF, it may be better to use valsartan or an ACE inhibitor, but not a combination of the two. It is unknown whether there are clinically important differences between the effectiveness of the various ARBs. So far, data are available from clinical trials only for valsartan and candesartan. Because they share a common mechanism of action, ARBs should be used with the same caution as ACE inhibitors with respect to their effects on blood pressure, renal function, and serum potassium (see above). The dose of ARBs should always be initiated at a low dose and titrated to the target dose or maximum tolerated dose.

In HF patients with preserved systolic function, ARBs cause regression of LV hypertrophy, decrease blood pressure, and prevent or modify cardiac remodelling; these actions provide strong theoretical support for the use of these agents in patients with diastolic dysfunction. The LIFE trial\textsuperscript{65} included hypertensive patients with LV hypertrophy. In subgroups of patients at high risk of and most likely having a certain degree of diastolic dysfunction, i.e. diabetic patients and patients with isolated systolic hypertension, losartan 100 mg was superior to atenolol in reducing the occurrence of HF events.

The CHARM-Preserved trial studied the effect of candesartan up to 32 mg daily in patients with preserved systolic function and with an HF hospitalization within 1 year before inclusion.\textsuperscript{64} After an average of 36.6 months follow-up, the study found no difference in cardiovascular mortality, but a small decrease in hospitalization for worsening HF among patients taking candesartan compared with placebo. The Irbesartan in Heart Failure with Preserved Systolic Function study has evaluated the utility of irbesartan in patients with diastolic HF and failed to show a significant benefit of ARB therapy.\textsuperscript{66}

### Aldosterone antagonists

Aldosterone promotes sympathetic activation, para-sympathetic inhibition, myocardial and vascular fibrosis, baroreceptor dysfunction, and vascular damage, and impairs arterial compliance. All classical RAAS inhibitors, even when used in combination, do not efficiently block the aldosterone system. This is also true of the new rennin inhibitors, the value of which, over or in addition to the other RAS inhibitors, is unclear.

In NYHA class III to IV CHF of any aetiology, spironolactone should be added to conventional therapy, including ACE inhibitors. The RALES trial\textsuperscript{67} has shown that an average dose of 25 mg is usually well tolerated and produces a decrease in hospitalization rate and all-cause mortality as well as sudden death rate. The benefit from spironolactone is consistent in a large variety of subgroups and is independent from the presence of fluid retention. However, patients with an important degree of cardiac fibrosis seem to benefit most from therapy.\textsuperscript{68}

Whether patients with milder HF may benefit from antialdosterone therapy remains open to investigation. The use of non-potassium sparing diuretics in hypertension and in HF increases, while the use of potassium sparing diuretics decreases the risk of sudden death; therefore, aldosterone antagonists should thus be recommended in combination with diuretic therapy.

More specifically, because aldosterone has an important pathophysiological role in the initial stage as well as during the progression of HF, it is very likely that antialdosterone therapy may be effective in preventing as well as slowing the progression of LV dysfunction and preventing asymptomatic HF from being symptomatic.

Thus, areas where the use of aldosterone antagonists may be of benefit and which should be investigated with proper clinical trials are: mild HF, HF with preserved systolic function, and early stages of cardiac remodelling where limitation of extracellular matrix turnover with aldosterone antagonists at low doses without haemodynamic effects may be useful in preventing HF.\textsuperscript{69}

Spironolactone should not be used when serum creatinine exceeds 250 mmol/L. Serum potassium and creatinine need to be monitored 1 week and 1 month after drug initiation and after
each dose escalation. Spironolactone is to be initiated at a low dose of 12.5 mg once a day and up-titrated to 25 mg once a day, which is the maintenance dose in the majority of patients. This may be increased to the maximum dose of 50 mg in patients still symptomatic and with normal serum potassium.

In recent reports of patients with CHF, the use of spironolactone in clinical practice has been associated with a relatively high incidence of serious hyperkalaemia resulting in renal failure, the need for dialysis, and death. However, in these reports, patients with renal dysfunction often were not excluded, serum potassium was not closely monitored, and the dose of spironolactone was not reduced if serum potassium increased to >5.5 mmol/L and was not discontinued if serum potassium was >6.0 mmol/L. It should also be noted that many of these patients who developed hyperkalaemia in clinical practice after starting spironolactone were older than those entered into RALES and, therefore, serum creatinine may not have accurately reflected the severity of renal dysfunction. Therefore, it is prudent to determine the estimated glomerular filtration rate before beginning an aldosterone blocker, especially in elderly patients.

Gynecomastia may occur in as many as 10% of the patients. It is usually well tolerated, but pain may lead to drug discontinuation. Erectile dysfunction, amenorrhea, disturbance of menses are other steroid-related adverse events. These are less frequent and usually not relevant in elderly HF patients.

The results of the Eplerenone Post-AMI Heart Failure Efficacy and Survival Study (EPHESUS) have important implications for the treatment of patients with systolic left ventricular dysfunction and survival Study (EPHESUS) have important implications for usually not relevant in elderly HF patients.

Heart failure burden and therapy

Device therapy for heart failure

In this EP-Europace Supplement, other articles address issues related to HF and device therapy.

Implanted biventricular pacemakers (CRT) with or without ICD improve survival and morbidity in patients with CHF, low LVEF, and wide QRS complex, who are optimally treated with pharmacological agents. Correspondingly, ICDs improve survival. There is only limited evidence in favour of device treatment in certain patient subgroups, such as the impact of ICD on outcomes in patients with reduced LVEF in NYHA class I or IV HF. Similarly, limited evidence exists for CRT in patients with only modest QRS prolongation or only modestly reduced LVEF. Despite evidence for a beneficial effect of device therapy in CHF, only a minority of eligible patients are currently offered these options.

New trials are exploring the use of the device therapy in milder HF patients at the time of an acute decompensation of CHF. The advantages of combining CRT with ICD in HF patients having an ICD indication are being explored in the MADIT-CRT and the RAFT trials.

Acute heart failure therapy

There is an unmet need for new pharmacological agents for the early management of acute HF that may improve both short- and long-term outcomes. So far, therapies commonly used for the treatment of AHFS present some well-known limitations and have been associated with an early increase in the risk of death. Innovative therapies with new mechanisms of action may safely and effectively reduce pulmonary congestion or improve cardiac performance in acute HF patients. In spite of promising findings, no new agent has demonstrated a clear benefit in terms of long-term clinical outcomes compared with placebo or conventional therapies. Therefore, guidelines for the treatment of acute HF are not evidence based. There is intense development of new agents specifically designed for acute HF, with several ongoing trials, and much discussion among experts and regulatory bodies about phase III clinical trial endpoints.

Perspective

Changes in the population age structure are anticipated in most developed countries, with large increases in the number of very elderly people who are those at greatest risk of developing HF. The survival of patients with HF has, finally, started to improve and hospital admission rates are declining. The incidence of myocardial infarction, the single most powerful predictor of future HF, is falling. However, survival after myocardial infarction is increasing. With the ageing of the population and decline in anti-inflammatory drug, a cyclooxygenase-2 inhibitor, or a potassium supplement, eplerenone should be discontinued. In patients with an estimated glomerular filtration rate between 30 and 60 mL/min and in patients with diabetes, including those with proteinuria, serum potassium should be monitored even more closely than normally recommended, as risk of hyperkalaemia increases with declining renal function.
mortality of other forms of cardiovascular diseases, it is likely that the incidence of HF and its impact on public health will continue to increase. Research has been very effective in delivering major advances in therapy of CHF with lower LVEF. This includes a number of drugs, mainly acting through inhibition of the RAAS. Device therapy adds to the benefit of drug therapy in CHF with lower LVEF. Two major areas with the greatest unmet needs are acute HF and HFPEF; these two being the next frontiers in HF research.

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References


