Chapter 2
ACE Inhibitor and Renin–Angiotensin System the Cornerstone of Therapy for Systolic Heart Failure

Claudio Borghi, Filippo Del Corso, Simone Faenza, and Eugenio Cosentino

Definition of Heart Failure

Heart failure (HF) can be defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a rate commensurate with the requirements of the metabolizing tissues, despite normal filling pressures (or only at the expense of increased filling pressures) [1]. HF can be also defined, clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function. The diagnosis of HF, according to the guidelines of the European Society of

C. Borghi (✉)
Cattedra di Medicina Interna, Ospedale S.Orsola.Malpighi, Via Albertoni 15, Bologna 40138, Italy

Department of Medicine, University of Bologna, Bologna, Italy
e-mail: claudio.borghi@unibo.it

F. Del Corso • S. Faenza • E. Cosentino
Department of Medicine, University of Bologna, Bologna, Italy

P. Perrone Filardi (ed.), ACEi and ARBS in Hypertension *and Heart Failure*, Current Cardiovascular Therapy 5,
DOI 10.1007/978-3-319-09788-6_2

Cardiology, can be difficult and is based on a criterion of clinical evaluation, which relies on the clinical history, physical examination and appropriate investigations [2]. For this reason is more important the need to obtain objective evidence of a structural or functional cardiac abnormality that is thought to account for the patient's symptoms and signs, to secure the diagnosis of HF.

From the point of view of the classification HF is divided into acute and chronic form. The chronic form is the most common form of HF and its clinical feature most obvious are certainly frequent exacerbations evolution sometimes to acute complications. In this situation the patient may be described as "decompensated" and when a chronic stable HF deteriorates suddenly, i.e. "acutely", usually leading to hospital admission, an event of considerable prognostic importance. In this condition the term of acute HF is used to indicate pathological conditions such as acute pulmonary edema (cardiogenic) and cardiogenic shock, however, very different from the perspective of pathophysiological and clinical. Therefore it would be advisable not to use the term to refer to acute HF in these situations, but it is advisable to choose the most appropriate terms of acute pulmonary edema and cardiogenic shock.

HF can also be classified on the basis of the prevailing characteristics of ventricular dysfunction. In most cases the HF is associated with systolic dysfunction of the left ventricle (LV) that, if determined by echocardiography or other imaging tests (e.g. Cardiac Magnetic Resonance, Single-Photon Emission Computed Tomography) is manifested by a depression of the left ventricular ejection fraction (LVEF). Often in patients with HF is present next to systolic dysfunction also diastolic dysfunction that may be more or less relevant and sometimes presents even in the absence of impaired systolic function. The diagnosis of HF from diastolic dysfunction is formulated based on the presence of symptoms and signs of heart and instrumental to the demonstration of a normal LVEF at rest. Furthermore some patients, particularly those with 'idiopathic' dilated cardiomyopathy, may also show substantial or even complete recovery of LV systolic function with therapy [including an angiotensin-converting enzyme

(ACE) inhibitor, beta-blocker, and mineralocorticoid receptor antagonist (MRA)].

Epidemiology, Incidence, Prevalence and Natural History of Heart Failure

HF is one of the issues most relevant clinical and health in industrialized countries. Infact the HF is the leading cause of hospitalization and is a major cause of disability in patients older than 65 years. Over the past 30 years, the prevalence of cardiovascular diseases has been generally decreasing, while that of HF has been progressively increasing. Approximately 1–2 % of the adult population in developed countries has HF, with the prevalence rising to ≥10 % among persons 70 years of age or older [3].

In industrialized countries, this amount is expected to rise inevitably because of the increase in the average age of the population and in view of the fact that the overall mortality resulting from cardiovascular events is being reduced, while the quod vitam prognosis of patients with HF is, albeit slightly, improved due to the more aggressive treatment.

With regard to the distribution of HF in terms of LV dysfunction that measured by echocardiography between sexes, 51 % of men but only 28 % of women had a LVEF <40 % [4] (Fig. 2.1).

The incidence of HF and its trends are highly variable. The incidence raw (not adjusted for age) in the general population ranges from 1 to 5 cases per 1,000 person-years (28–34), while the data from the largest population-based studies report an incidence ranging from 1 to 2 per 1,000 cases per year. The wide variability in the data of incidence is largely due to the use of diagnostic criteria is not unique and only partially defined. In addition, the incidence data could be made further inaccurate by several factors such as the low percentage of patients autopsied, the economic interest in excluding HF as a discharge diagnosis tab nosographic and the difficulty of framing this syndrome as a primary diagnosis or secondary.

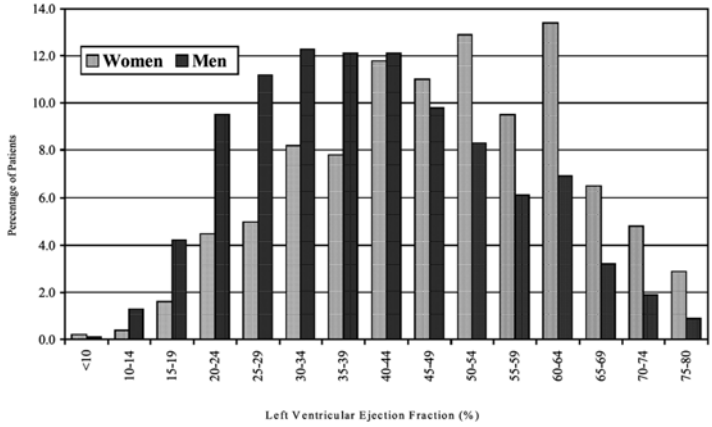

FIG. 2.1 Distribution of left ventricular ejection fraction measured in women and men enrolled in the EuroHeart Failure survey (From Cleland et al. [4])

One datum definitely ascertained is represented by the exponential increase in the incidence of HF with advancing age (Fig. 2.2). With regard to changes in the incidence of HF in time, the Framingham Heart Study showed only a slight decline in incidence during the last three decades, although it must be stated that this study was prior to the use of ACE inhibitors or thrombolytics.

The prevalence of HF is progressively increasing due to the aging of the general population. It is estimated that today the 9.1 % of individuals older than 80 years present a picture of HF and that in the future this percentage is set to grow further. In the United States, it was estimated that in 1997 people aged over 65 years were 33 million (of which about 7.9 million aged greater than or equal to 80 years) and that, by the year 2030, this number will increase to approximately 70 million (of which 18 million aged greater than or equal to 80 years). It may therefore be expected, even with conservative estimates, that, by that time, the number of elderly patients with HF will double, reaching a value of 3.6 million. The prevalence of HF varies from 3 to 20 individuals

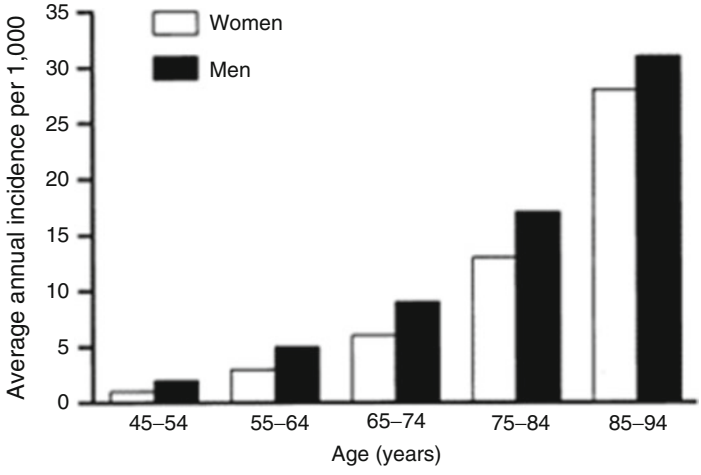

FIG. 2.2 The exponential increase in the incidence of HF with advancing age

per 1,000 people, with higher figures for individuals over the age of 65 years.

Before the modern era of treatment, 60–70 % of patients died within 5 years of diagnosis and 13.5 % died between admission and 12 weeks follow-up (Fig. 2.3). And there was frequent and recurrent admission to hospital: within 12 weeks of discharge, 24 % of patients had been readmitted (Fig. 2.4). Effective treatment has improved both of these outcomes, with a relative reduction in hospitalization in recent years of 30–50 % and smaller but significant decreases in mortality [4–7].

Aetiology of Heart Failure

The most frequent causes of HF are represented by coronary artery disease (CAD is the cause of approximately two-thirds of cases of systolic HF), cardiomyopathy and hypertension (HBP), while valvular heart disease, congenital heart disease

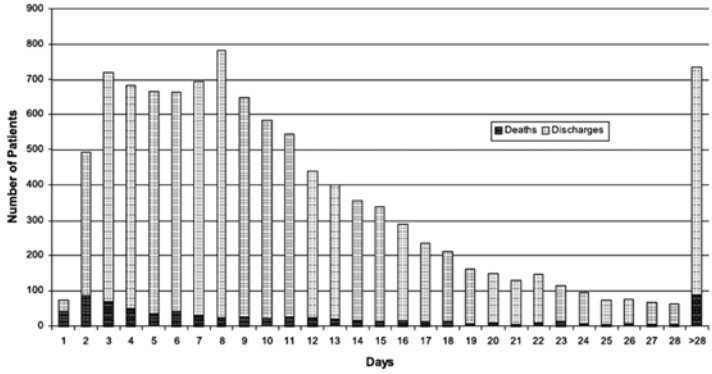

FIG. 2.3 Deaths on index admission and discharges from the time of admission (From Cleland et al. [4])

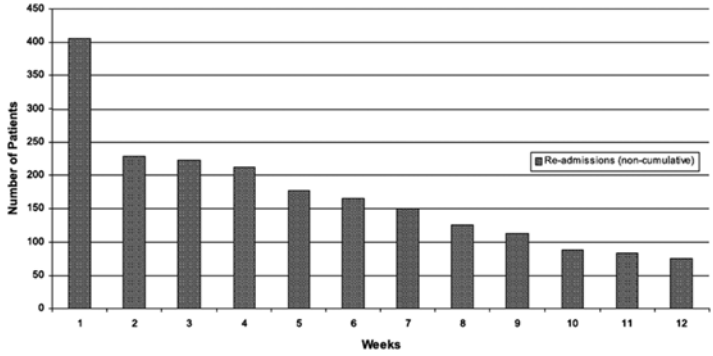

FIG. 2.4 First admission over 12 weeks for any reason from the time of index admission discharge (From Cleland et al. [4])

are more rare (Fig. 2.5). Other causes of systolic HF can be: previous viral infection (recognized or unrecognized), alcohol abuse, hemotherapy (e.g. doxorubicin or trastuzumab), and 'idiopathic' dilated cardiomyopathy (although the cause is thought to be unknown, some of these cases may have a genetic basis) [8]. According to data from the Framingham study HBP, associated or not with ischaemic heart disease, is

Coronary artery disease
Cardiomyopathy: • Familial: hypertrophic; dilated; arrhythmogenic right ventricular cardiomyopathy; restrictive; left ventricular non-compaction; • Acquired: myocarditis (inflammatory cardiomyopathy): infective, immune-mediated, toxic: drugs (e.g. chemotherapy, cocaine), alcohol, heavy metals; endocrine/nutritional; pregnancy; infiltration: amyloidosis, malignancy
Systemic arterial hypertension
Valvular heart disease: mitral; aortic; tricuspid; pulmonary
Congenital heart disease
Pericardial disease: constrictive pericarditis; pericardial effusion
Arrhythmia: Tachyarrhythmia (atrial and ventricular), bradyarrhythymia (sinus node dysfunction) **Conduction disorders:** atrioventricular block
High output states: anaemia; sepsis; thyrotoxicosis; Paget's disease; arteriovenous fistula; Beri-beri
Volume overload: renal failure; iatrogenic (e.g. post-operative fluid infusion)
Endocardial disease: endomyocardial diseases with hypereosinophilia [hypereosinophilic syndromes (HES)]; endomyocardial disease without hypereosinophilia [e.g. endomyocardial fibrosis (EMF)]; endocardial fibroelastosis

FIG. 2.5 Causes of HF

the most common cause of HF in the United States. By contrast in Europe, as reported from studies conducted in England and Sweden, the predominant cause of HF is represented by chronic ischaemic heart disease, HBP or cardiomyopathy represent the etiology of HF in percentages lower than 10 %. The data relating to SEOSI, observational epidemiological study conducted in Italy on HF in a population of nearly 4,000 patients referred to hospital centers specialize, identified in the etiology of ischaemic heart disease more frequent with a percentage of 42 % of patients while a role less obvious is found for HBP (20 %), dilated cardiomyopathy (15.3 %) and valvular heart disease (14 %), respectively [9]. Among the plausible reasons for the discrepancies classificative in terms of etiology of HF are certainly numbered the mode of interpretation of the results of epidemiological studies. In particular the role of arterial hypertension is certainly prevalent in all those conditions as the Framingham study in which the development of HF is related to the finding of HBP in each phase of the natural history regardless of the fact that the same has acted as a risk factor for the development of ischaemic heart disease.

In contrast, the role of the same HBP is greatly reduced from those studies (mainly in Europe) in which the development of HF is attributed to the ultimate cause that is responsible for it (e.g., chronic ischaemic heart disease, myocardial infarction [MI] or cardiomyopathy) regardless of the presence anamnestic or clinic HBP.

Pathophysiology of Heart Failure

HF is a complex syndrome with a multifactorial genesis characterized by an inability of the heart to adapt to changes in the metabolic needs of the tissues and supported by hemodynamic changes and different neurohormonal systems, in which the symptoms related to reduced functional capacity and the water retention dominate the clinical picture accompanied with reduced survival. HF can be achieved

with alterations in pump function or systolic or diastolic function or filling or, as more often happens, both resulting mainly depression of intrinsic ventricular contractility or changes in mode of contraction. Through the therapeutic restoration of intrinsic contractility of the myocardium can get the simultaneous improvement of systolic function and diastolic function.

Besides the reduction of the intrinsic contractility, a further primary cause of depression of ventricular function can also be the asinergia that makes uneven and asymmetric, and therefore asynchronous, the contraction of the ventricular myocardium for the presence of areas which are contracted little or nothing (zones of hypokinesia and akinesia) or which are contracted with excessive delay (asynchronous areas). The asynchronous contraction of the myocardium, mostly due to ischemic infarction or ventricular arrhythmias, depresses the pump function of the ventricle.

The appearance of alterations of myocardial function affects the development of a series of adaptation mechanisms functional, structural and neurohormonal which are initially able to compensate for the impaired myocardial, but that in a second time can represent elements responsible for a further progression of the disease.

In the initial phase of HF, all conditions characterized by an impaired intrinsic contractility (or inotropism), by distensibility (compliance), by the synergy of contraction of the ventricular walls, by an excessive hemodynamic load or by the association of some of these conditions, induce the heart to resort to various compensatory mechanisms of adaptation, immediate or delayed, aimed to preserve its pump function.

If the overload systolic or diastolic are not removed, the phase of functional insufficiency follows a second phase of re-structural adaptation, characterized by a stimulation of the synthesis of myocytes, resulting in hypertrophy (and according to some authors, also hyperplasia) of the muscle cells and hyperplasia of interstitial component, mainly fibroblasts and

matrix collagen. The wall stress also causes a stimulus to gene expression involving oncogenes, myocardial protein (ANP, BNP, angiotensin II). The combination of these processes conditions the development of a parietal hypertrophy. In the terminal stages of HF the maladaptive changes occurring in surviving myocytes and extracellular matrix after myocardial injury (e.g. MI) lead to pathological 'remodelling' of the ventricle with dilatation and impaired contractility, one measure of which is a reduced ejection fraction (EF), that it is a sign of LV systolic dysfunction [10, 11].

What characterizes untreated systolic dysfunction is progressive worsening of these changes over time, with increasing enlargement of the LV and decline in EF. Two mechanisms that underlie these events: the occurrence of further events leading to additional myocyte death (e.g. recurrent MI) and the systemic responses induced by the decline in systolic function, particularly neurohumoral activation. Two key neurohumoral systems activated in HF are the renin–angiotensin–aldosterone system and sympathetic nervous system. Initially this neuro-hormonal mechanisms have a compensatory function, aimed at maintaining an adequate perfusion to vital organs, but in the long term influence a number of physiologic abnormalities counterproductive as the retention of sodium and water, peripheral vasoconstriction and degenerative processes of myocardial muscle. In addition to causing further myocardial injury, these systemic responses have detrimental effects on the blood vessels, kidneys, muscles, bone marrow, lungs, and liver, and create a pathophysiological "vicious cycle" (Fig. 2.6), accounting for many of the clinical features of the HF syndrome, including myocardial electrical instability. Interruption of these two key processes is the basis of much of the effective treatment of HF [10, 11].

In this contest it is clear that the renin-angiotensin system (RAS) plays a central role in the pathophysiology of HF. Therefore to know the mechanisms that underlie this system is an important element to understand and choose the best therapeutic strategy for HF.

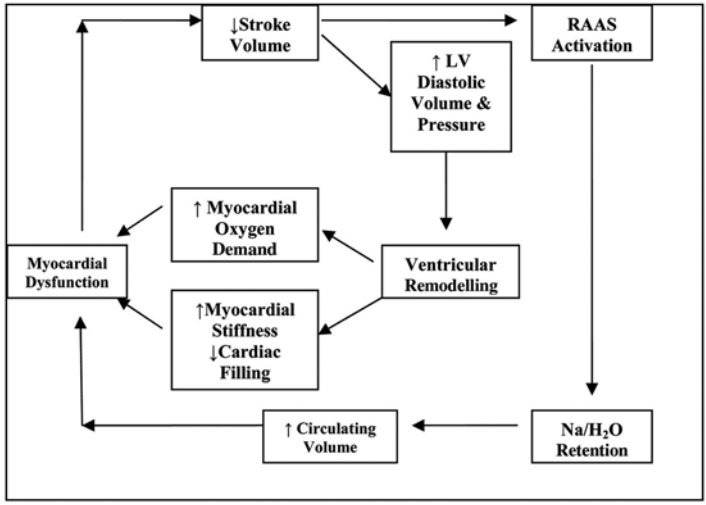

FIG. 2.6 The "vicious cycle" of the HF

The Renin-Angiotensin System

The RAS contributes in the contest of the HF to the increase of the peripheral vascular tone and hydrosaline retention concomitantly with the activation of the sympathetic nervous system. The reduction in cardiac output that characterizes HF causes an increase in plasma renin activity, levels of angiotensin II and aldosterone, which contribute to the development of the adverse effects that characterize HF. In Fig. 2.7 are depicted the different routes of production of angiotensin II which results from the activation of the system over that in circulating level also by an activation of the same at the tissue level, with local production of angiotensin II capable of performing a action vasoactive and trophic. The extent of activation of plasma ACE may reflect incompletely and partially the corresponding tissue activity in particular in patients with HF. Infact in this patient, from the very early stages, it could be observed a predominant local activation of the RAS with production of angiotensin II, even for alternative ways of

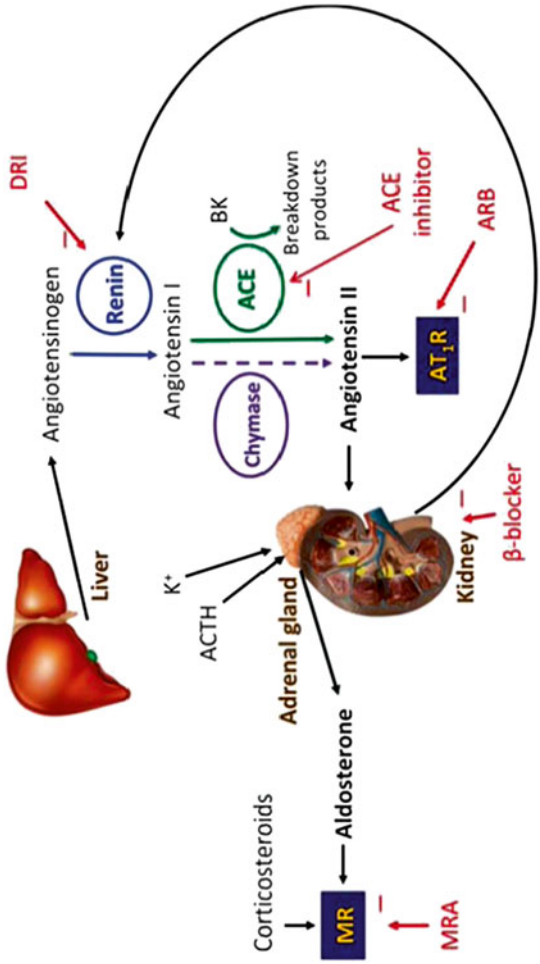

FIG. 2.7 The classical renin–angiotensin–system. *DRI* direct renin inhibitor, *ARB* angiotensin receptor blocker, *MRA* mineralocorticoid receptor antagonist, K^+ potassium ion, *ACE* angiotensin converting enzyme, *ACTH* adrenocorticotropic hormone (corticotropin), *BK* bradykinin, AT_1R angiotensin II type 1 receptor, *MR* mineralcorticoid receptor (From McMurray [12])

production and non-employees from the ACE (es. chimasi) that seem particularly important at the tissue level where they could be responsible for the production of angiotensin II by up to 90 %. The RAS is, as can be imagined, also activated in the heart, where it has been hypothesized to contribute to ventricular remodeling phenomena described in the previous paragraph. Indeed angiotensin II is able to stimulate the growth of cardiomyocytes, in turn facilitated by the release of norepinephrine induced by angiotensin II at the level of the sympathetic nerve endings. The biological actions of angiotensin II are realized through the interaction with 4 subtypes of receptors called AT1-AT4, but at present most of the effects of angiotensin II appear mediated by the AT1 receptor, while for the AT2 receptor have been hypothesized antiproliferative and vasodilators effects. The blockade of the AT1 receptor inhibits the action of angiotensin II at the receptor level, and allows a more efficient blockade of angiotensin II. In particular, one of the dominant effects of angiotensin II is represented by the stimulus to the production of aldosterone which has assumed great importance in patients with HF because of its ability to stimulate the reabsorption of sodium, but especially to induce the development of myocardial fibrosis with consequent the progression of myocardial structural alterations described in the previous paragraph. These changes are directly related to the progression of HF in hemodynamic level.

Focus on Blockade of the Renin–Angiotensin System

The objectives of the treatment of HF are varied and represented by the reduction of the symptoms, the prevention of the progression of the disease, by improving the quality of life, reduction in the frequency of hospitalization and especially by the prolongation of survival. In particular, the availability of drugs able to effectively interfere with the neurohumoral activation has allowed antagonize or modu-

late some of these systems to localization cardiac and extracardiac and responsible for the onset, the clinical expression and progression of the disease. In this context, ACE inhibitors represent the class of drugs most widely used among those used in the treatment of HF.

The clinical efficacy of ACE inhibitors follows to the unique mechanism of action that is articulated in an inhibition of the production of angiotensin II (potent vasoconstrictor and growth factor) which is associated with an inhibition of the degradation of the vasodilator bradykinin features of property resulting from the release of nitric oxide and prostacyclin. ACE inhibitors also reduce the activity of the sympathetic nervous system by inhibiting the action of angiotensin II which is capable of promoting the release of norepinephrine and inhibit the resorption (re-uptake). In addition, drugs of this class cause an increase in the density of the ß-adrenergic receptors (through mechanisms of up-regulation) and improve the heart rate variability, the response of the baroreceptor and autonomic function (including the vagal tone).

ACE inhibitors also exhibit antiproliferative effects (reduction of vascular and cardiac hypertrophy and extracellular matrix proliferation) and reduce ventricular remodelling after myocardial infarction [13, 14]. In the hypertrophied heart reduce cardiac hypertrophy and improve diastolic function.

Moreover ACE inhibitors decrease renal vascular resistances and increase renal blood flow and promote Na^+ and water excretion by the relatively greater effect in dilating postglomerular efferent than afferent arterioles, leading to a reduction in glomerular capillary hydrostatic pressure and glomerular filtration rate (GFR) [15]. So prevent progression of microalbuminuria to overt proteinuria [16], attenuate the progression of renal insufficiency in patients with a variety of non-diabetic nephropathies [17] and prevent or delay the progression of nephropathy in patients with insulindependent diabetes mellitus [18, 19].

In most patients ACE inhibitors are well tolerated, however, several adverse reactions may occur. They can also

appear at any time during treatment, even in patients already chronically treated with ACE inhibitors. The most common adverse reaction associated with their use in the elderly population is orthostatic hypotension (prevalence, ~ 50 %), especially during the first few days of treatment or after a dose increase. Dry cough appears in 5–10 % of patients, this is the most common adverse reaction associated with increased concentration of kinins, and is not dose-dependent. If the cough persists and interferes with quality of life, therapy with ACE inhibitors may be suspended and replaced by the administration of angiotensin II receptor blockers. Hyperkalemia due to a decrease in aldosterone secretion is rarely found in patients with normal renal function but it is relatively common in those with congestive HF and in the elderly. This side effect is also more frequent in patients with renal impairment, diabetes, receiving either K^+ or potassium K^+-sparing diuretics, heparin or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Angioedema is a rare but potentially life-threatening and appears related to an accumulation of bradykinin. Symptoms range from mild gastrointestinal disturbances to severe dyspnea and death. Finally ACE inhibitors, taken during the second or third trimester of pregnancy, may present some teratogenic effects.

Trials That Support the Use of Angiotensing-Converting Enzyme Inhibitors

The evidence supporting the use of ACE inhibitors in patients with HF is based on the results of wide prospective clinical studies (Fig. 2.8). This trials have demonstrated and repeatedly confirmed that ACE inhibitors are effective in reducing morbidity and mortality and are also able to improve the quality of life in patients with asymptomatic LV dysfunction or suffering from a overt congestive HF resulting from a reduced systolic function of the LV or when it is a result of a MI.

Trial	Year	N.pz	Class NYHA	Follow up (months)	Admission (RR, %)	Total deaths (RR, %)
CONSENSUS (enalapril 18.4 mg/die)	1987	253	IV	6	NA	↓ 27 p=.003
SOLVD-T (enalapril 16.6 mg/die)	1991	2569	II-III	41	↓ 26 p<.0001	↓ 16 p=.0036
SOLVD-P (enalapril 16.7 mg/die)	1992	428	I-III	37	↓ 44 p<.001	↓ 8 p=NA
SAVE (captopril18-150 mg/die)	1992	2231	I	42	↓ 22 p=.019	↓ 19 p=.019
AIRE (ramipril 15-10 mg/die)	1993	2006	II-III	15	NA	↓ 27 p=.002
TRACE (trandolapril 1-4 mg/die)	1995	1749	I-IV	24	NA	↓ 22 p=.001
SMILE (zofenopril 15-60 mg/die)	1995	1556	I-IV	12	NA	↓ 29 p=.011

FIG. 2.8 Main trials on ACE inhibitors. *NA* not available

Two key randomized controlled trials [Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) [20] and Studies of Left Ventricular Dysfunction (SOLVD)-Treatment] [21] assigned about 2,800 patients with mild to severely symptomatic HF to placebo or enalapril. This trials show how the addition of enalapril to conventional therapy in patients with severe congestive HF can reduce mortality and improve symptoms. The beneficial effect on mortality is due to a reduction in death from the progression of HF (Fig. 2.9).

In particular the CONSENSUS evaluate the influence of the angiotensin-converting-enzyme inhibitor enalapril (2.5–40 mg per day) on the prognosis of severe congestive HF (New York Heart Association [NYHA] functional class IV). The trial randomizes 253 patients in a double-blind study to receive either placebo (n = 126) or enalapril (n = 127). Conventional treatment for HF, including the use of other vasodilators, was continued in both groups. Follow-up averaged 188 days (range, 1 day to 20 months). The crude mortality at the end of 6 months (primary end point) was 26 % in the enalapril group and 44 % in the placebo group: a reduction of 40 % (P = 0.002). Mortality was reduced by 31 % at 1 year (P = 0.001). By the end of the study, there had been 68 deaths in the placebo group and 50 in the enalapril group: a

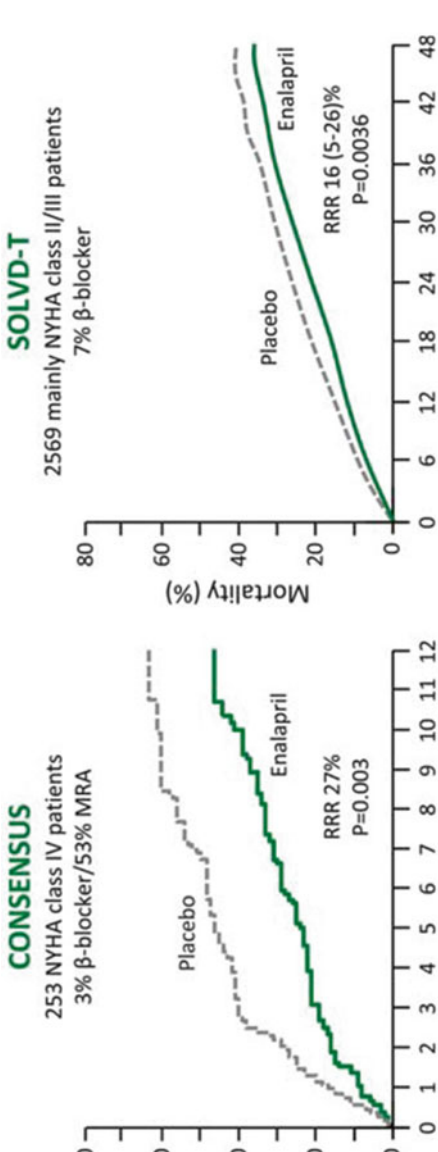

FIG. 2.9 Trials comparing an angiotensin-converting enzyme (ACE) inhibitor to placebo in patients with systolic heart failure. Outcome is cumulative mortality (From The CONSENSUS Trial Study Group [20] and The SOLVD Investigators [21])

reduction of 27 % (P = 0.003). The entire reduction in total mortality was found to be among patients with progressive HF (a reduction of 50 %), whereas no difference was seen in the incidence of sudden cardiac death. A significant improvement in NYHA classification was observed in the enalapril group, together with a reduction in heart size and a reduced requirement for other medication for HF.

In the SOLVD-Treatment were enrolled patients in New York Heart Association functional classes II and III. They received conventional treatment for HF were randomly assigned to receive either placebo (n = 1,284) or enalapril (n = 1,285) at doses of 2.5–20 mg per day in a double-bind trial. The follow-up averaged 41.4 months. There were 510 deaths in the placebo group (39.7 %), as compared with 452 in the enalapril group (35.2 %) (reduction in risk, 16 %; 95 % confidence interval, 5–26 %; P = 0.0036). Although reductions in mortality were observed in several categories of cardiac deaths, the largest reduction occurred among the deaths attributed to progressive HF (251 in the placebo group vs. 209 in the enalapril group; reduction in risk, 22 %; 95 % confidence interval, 6–35 %). There was little apparent effect of treatment on deaths classified as due to arrhythmia without pump failure. Fewer patients died or were hospitalized for worsening HF (736 in the placebo group and 613 in the enalapril group; risk reduction, 26 %; 95 % confidence interval, 18–34 %; P less than 0.0001).

Other important information on the effectiveness of ACE inhibitors in patients with HBP and CAD come to us from the results of the SMILE study. The SMILE project involved more than 3,500 patients with CAD and demonstrated that zofenopril treatment may reduce mortality and morbidity in patients with MI [22]. In particular this trial have demonstrated that the zofenopril has a primary role for prevention and treatment of cardiovascular diseases, thanks to interesting anti-ischemic effect, on blood pressure control and cardiovascular protection. The extent of the benefit of zofenopril treatment was significantly more evident in patients with history of HBP compared with the normotensive population (Fig. 2.10) [23] as well as in patients with diabetes [24]

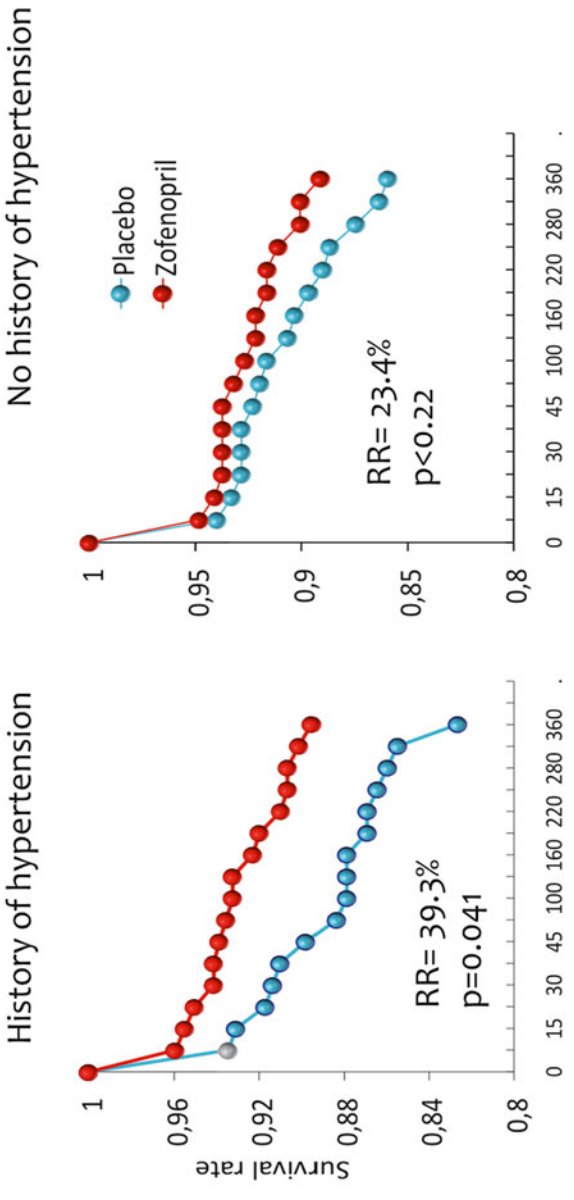

FIG. 2.10 Role of Zofenopril in reducing the incidence of events by approximately 40% in subjects with a history of hypertension (From SMILE Study Investigators [23])

probably owing to the favorable effects of better blood pressure and glycol-lipidic control with zofenopril in patients where HBP and metabolic abnormalities complicated MI.

In the Assessment of Treatment with Lisinopril And Survival (ATLAS) trial, 3,164 patients with New York Heart Association class II to IV HF and an EF $\leq$ 30 % were randomized with either low doses (2.5–5.0 mg daily) or high doses (32.5–35 mg daily) of the ACE inhibitor, lisinopril, for 39–58 months. Patients in the high-dose group had a nonsignificant 8 % lower risk of death (P = 0.128) but a significant 12 % lower risk of death or hospitalization for any reason (P = 0.002) and 24 % fewer hospitalizations for HF (P = 0.002) [25].

These findings are supported by a meta-analysis of smaller, short-term, placebo-controlled randomized controlled trials (RCTs), which showed a clear reduction in mortality within only 3 months [26]. It has also been documented by these RCTs that ACE inhibitors improve symptoms, exercise tolerance, quality of life, and exercise performance.

Additional support for the use of ACE inhibitors comes from an RCT in patients with a low EF but no symptoms of HF ("asymptomatic LV systolic dysfunction") and three large (5,966 patients in total) placebo-controlled, randomized, outcome trials in patients with HF, LV systolic dysfunction, or both after acute MI [27]. In the SOLVD-Prevention trial (which randomized 4,228 patients with asymptomatic LV systolic dysfunction), there was a 20 % RRR in death or HF hospitalization. In the myocardial infarction trials, which used captopril [Survival and Ventricular Enlargement (SAVE)], ramipril [Acute Infarction Ramipril Efficacy (AIRE)], and trandolapril [TRAndolapril Cardiac Evaluation (TRACE)], there was a 26 % RRR in death and a 27 % RRR in death or HF hospitalization [2, 28].

Very recently the results of the SMILE 4 comparing two different ACE-inhibitors, zofenopril and ramipril, in patients with left ventricular dysfunction after acute MI [29, 30] have suggested the possibility that the capacity of ACE-inhibitors to improve the mortality and morbidity in patients with CHF

can be significantly affected by the structural properties of the ACE-inhibitors. In particular the cumulative incidence of death and hospitalization for CV causes has resulted significantly reduced in patients treated with zofenopril whose antiischemic properties along with a more effective tissue penetration and antioxidant effect may have some remarkable impact on the protection of cardiac structure and function. The observations of the SMILE 4 study have been confirmed in a population of elderly patients with chronic CHF [19] where again the treatment with zofenopril was associated with a better survival in comparison to ramipril after adjustment for the most important confounding factors. These data open a new perspective in the treatment of patients with CHF where the choice of the ACE-inhibitor should not exclusively based on the main mechanism of action but also on the possibility that some additive properties can play some role by improving the capacity of the drugs to reach the tissue targets and by exerting some additional cardioprotective effects that can improve left ventricular function beyond the average expected by the pharmacological class.

ACE-Inhibitors Compared with Angiotensin Receptor Blockers

The clinical efficacy of ACE inhibitors has been compared with that of direct angiotensin-II receptor antagonists in several trials.

The second losartan in HF survival study (ELITE-2) showed equivalent effect on mortality and morbidity between losartan and captopril and less adverse events in losartan: mortality in 3,152 patients with chronic HF was similar in losartan and captopril, after a follow-up of 555 days (11.7 % vs. 10.4 %, respectively) [31].

In the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) 5,477 patients, with confirmed acute MI and HF during the acute

phase or a new Q-wave anterior infarction or reinfarction, were randomly to receive losartan or captopril. The trial show how there isn't a non-significant difference in total mortality in favour of captopril (18 % and 16 % respectively) [32].

In the VALIANT trial 15,703 patients with MI complicated by LV systolic dysfunction, HF or both were randomised to receive captopril or valsartan or the combination of both drugs. The trial shows how valsartan is as effective as captopril between the three groups with regard to mortality or other clinical outcomes [33].

On the contrary, in the Candesartan in HF: Assessment of Reduction in Mortality and morbidity (CHARM)-added trial, the addition of candesartan to an ACE inhibitors lead to a clinical important reduction in relevant cardiovascular events in patients with CHF and reduced left-ventricular ejection fraction, although mortality was not reduced [34]. Since no differences have been demonstrated to date between ACE inhibitors and angiotensin-II blockers, ACE inhibitors should remain the first-choice treatment in patients with HF [35].

Use of the ACE Inhibitors in the Hearth Failure: ESC and ACCF/AHA Guidelines

According to the **ESC (European Society of Cardiology) guidelines for the diagnosis and treatment of acute and chronic HF**, an ACE inhibitor is recommended, in addition to a beta-blocker, for all patients with an EF ≤40 % to reduce the risk of HF hospitalization and the risk of premature death (class of recommendation I, level of evidence A) [2, 20, 21, 34–36].

From the ESC guidelines [35]:

- indication for a patients should get an ACE inhibitor: EF ≤40 %, irrespective of symptoms;
- contraindications: a history of angioedema, bilateral renal artery stenosis, serum potassium concentration >5.0 mmol/L, serum creatinine >220 mmol/L (~2.5 mg/dL), severe aortic stenosis.

	Starting dose (mg)	Target dose (mg)
ACE inhibitor		
Captopril[a]	6.25 t.i.d.	50 t.i.d.
Enalapril	2.5 b.i.d.	10–20 b.i.d.
Lisinopril[b]	2.5–5.0 o.d.	20–35 o.d.
Ramipril	2.5 o.d.	5 b.i.d.
Trandolapril[a]	0.5 o.d.	4 o.d.

Fig. 2.11 Evidence-based doses of disease-modifying drugs used in key randomized trials. [a]Indicates an ACE inhibitor where the dosing target is derived from post-myocardial infarction trials. [b]Indicates drugs where a higher dose has been shown to reduce morbidity–mortality compared with a lower dose of the same drug, but there is no substantive placebo-controlled randomized controlled trial and the optimum dose is uncertain. *b.i.d.* bis in die (twice daily), *o.d.* omni die (once every day), *t.i.d.* ter in die (three times daily)

- First to use an ACE inhibitor in HF is important to check renal function and serum electrolytes. Within 1–2 weeks of starting treatment can be useful re-check renal function and serum electrolytes.
- Dose up-titration (Fig. 2.11):
  - Consider dose up-titration after 2–4 weeks. Do not increase dose if significant worsening of renal function or hyperkalaemia. Re-check renal function and serum electrolytes 1 and 4 weeks after increasing dose. More rapid dose up-titration can be carried out in patients in hospital or otherwise closely supervised, tolerability permitting.
  - In the absence of above problems, aim for evidence-based target dose or maximum tolerated dose.
  - Re-check renal function and serum electrolytes in the following months.
- Potential adverse effects:
  - Worsening renal function: if necessary, reduce ACE inhibitor dose or discontinue.

- Hyperkalaemia: control if the patient takes other agents causing hyperkalaemia, e.g. potassium supplements and potassium-sparing diuretics, e.g. amiloride, and stop.
- Symptomatic hypotension (e.g. dizziness) is common, often improves with time, and patients should be reassured. Consider reducing the dose of diuretics and other hypotensive agents. Asymptomatic hypotension does not require intervention.
- Cough: if an ACE inhibitor causes a troublesome cough, switch to an angiotensin receptor blockers (ARB).

In the combination therapy must pay attention to some associations, infact some treatments may cause harm in patients with symptomatic (NYHA class II-IV) systolic HF: the addition of an ARB or renin inhibitor, to the combination of an ACE inhibitor AND a MRA is NOT recommended because of the risk of renal dysfunction and hyperkalaemia. (Class III, Level C).

In acute HF after stabilization of the clinical, in patients with an EF ≤40 % an ACE inhibitor is recommended to reduce the risk of death, recurrent MI, and hospitalization for HF. (Class I, Level A).

Management of other particular conditions and comorbidity in HF with preserved EF:

- In patients with ventricular arrhythmias it is recommended that treatment with an ACE inhibitor (or ARB), beta-blocker, and MRA should be optimized. (Class I, Level A).
- Dysglycemia and diabetes are very common in HF, and diabetes is associated with poorer functional status and worse prognosis. So in this patients, diabetes may be prevented by treatment with ACE inhibitors [36].
- For the treatment of HBP in patients with symptomatic HF (NYHA functional class II–IV) and LV systolic dysfunction one or more of an ACE inhibitor (or ARB), beta-blocker, and MRA is recommended as first, second, and third-line therapy, respectively, because of their associated

benefits (reducing the risk of HF hospitalization and reducing the risk of premature death). (Class I, Level A)
- In patient with kidney dysfunction and cardiorenal syndrome the GFR is reduced in most patients with HF, especially if advanced, and renal function is a powerful independent predictor of prognosis in HF. So the ACE inhibitors frequently can cause a fall in GFR, although any reduction is usually small and should not lead to treatment discontinuation unless marked.

On the other side of the ocean also the **ACCF/AHA (American College of Cardiology Foundation/American Heart Association) guidelines of the HF** recognize an important role of ACE inhibitors [37].

In this guidelines patients are classified according to four stages, which reflects the growing appreciation for the importance of the prevention of HF:

- Stage A: patients at high risk for developing HF but without structural heart disease or symptoms of HF;
- Stage B: patients with structural heart disease but without signs or symptoms of HF;
- Stage C: patients with structural heart disease with prior or current symptoms of HF;
- Stage D: patients with end-stage disease who require specialized treatment strategies (refractory HF).

In the *Stage A* ACE inhibitors are recommended for the treatment of elevated blood pressure, diabetes mellitus, obesity, dyslipidemia and vascular risk.

In the *Stage B* in all patients with a recent or remote history of MI or acute coronary syndrome and reduced EF, ACE inhibitors should be used to prevent symptomatic HF and reduce mortality. (Class I, Level A). And they should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. (Class I, Level A).

Current evidence supports the use of ACE inhibitors and (to a lower level of evidence) beta-blocker therapy to impede maladaptive LV remodeling in patients with stage B HF and low LVEF to improve mortality and morbidity [38]. At 3-year

follow-up, those patients treated with ACE inhibitors demonstrated combined endpoints of reduced hospitalization or death, a benefit that extended up to a 12-year follow-up [39].

ACE inhibitors are also recommended in patients with HF with reduced EF (HFrEF) and current or prior symptoms (*Stage C*), unless contraindicated, to reduce morbidity and mortality. (Class I, Level A).

Their use in patients with HBP is also reasonable to control blood pressure in patients with HF preserved EF (HFpEF). (Class IIa, Level C)

ACE inhibitors can reduce the risk of death and reduce hospitalization in HFrEF.

- Patients should not be given an ACE inhibitor if they have experienced life threatening adverse reactions (i.e., angioedema) during previous medication exposure or if they are pregnant or plan to become pregnant.
- Dose up-titration:
  - clinicians should prescribe an ACE inhibitor with caution if the patient has very low systemic blood pressures (systolic blood pressure <80 mmHg), markedly increased serum levels of creatinine (>3 mg/dL), bilateral renal artery stenosis, or elevated levels of serum potassium (>5.0 mEq/L).
  - Treatment with an ACE inhibitor should be initiated at low doses, followed by gradual dose increments if lower doses have been well tolerated.
  - Renal function and serum potassium should be assessed within 1–2 weeks of initiation of therapy and periodically thereafter.

- The majority of the adverse reactions of ACE inhibitors can be attributed to the two principal pharmacological actions of these drugs: angiotensin suppression and kinin potentiation. Other types of adverse effects may also occur (e.g., rash, taste disturbances, cough). With the use of ACE inhibitors, particular care should be given to the patient's volume status, renal function, and concomitant medications.

In controlled clinical trials that were designed to evaluate survival, the dose of the ACE inhibitor was not determined by a patient's therapeutic response but was increased until the predetermined target dose was reached [20, 21, 24]. Clinicians should attempt to use doses that have been shown to reduce the risk of cardiovascular events in clinical trials. If these target doses of an ACE inhibitor cannot be used or are poorly tolerated, intermediate doses should be used with the expectation that there are likely to be only small differences in efficacy between low and high doses. Abrupt withdrawal of treatment with an ACE inhibitor can lead to clinical deterioration and should be avoided.

In conclusion, ACE-inhibitors are a cornerstone in the treatment of congestive heart failure and their favorable impact affect both mortality and rate of hospital admission thereby improving the overall prognosis and the economic budget. The advantage of ACE-inhibitors is related to their activity of blockade of the over-activated neuro-humoral system both in the plasma and at the tissue level. In addition the more integrated mechanism of action of

References

1. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008;10:933–89.
2. Guidelines ESC. for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787–847.

3. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;93:1137–46.
4. Cleland JG, Swedberg K, Follath F, Komajda M, Cohen-Solal A, Aguilar JC, Dietz R, Gavazzi A, Hobbs R, Korewicki J, Madeira HC, Moiseyev VS, Preda I, van Gilst WH, Widimsky J, Freemantle N, Eastaugh J, Mason J. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure survey programme – a survey on the quality of care among patients with heart failure in Europe. Part 1: patient characteristics and diagnosis. Eur Heart J. 2003;24(5):442–63.
5. Stewart S, MacIntyre K, Hole DJ, Capewell S, McMurray JJ. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail. 2001;3:315–22.
6. Stewart S, Ekman I, Ekman T, Oden A, Rosengren A. Population impact of heart failure and the most common forms of cancer: a study of 1 162 309 hospital cases in Sweden (1988 to 2004). Circ Cardiovasc Qual Outcomes. 2010;3:573–80.
7. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, Chalmers JW, Capewell S, McMurray JJ. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. Circulation. 2009;119:515–23.
8. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. 2011;8:1308–39.
9. Survey on heart failure in Italian hospital cardiology units. Results of the SEOSI study. SEOSI Investigators. Eur Heart J. 1997;18(9):1457–64.
10. McMurray JJ. Clinical practice. Systolic heart failure. N Engl J Med. 2010;362:228–38.
11. Shah AM, Mann DL. In search of new therapeutic targets and strategies for heart failure: recent advances in basic science. Lancet. 2011;378:704–12.
12. McMurray JJ. CONSENSUS to EMPHASIS: the overwhelming evidence which makes blockade of the renin-angiotensin-

aldosterone system the cornerstone of therapy for systolic heart failure. Eur J Heart Fail. 2011;13(9):929–36.
13. Paul M, Ganten D. The molecular basis of cardiovascular hypertrophy: the role of the renin–angiotensin system. J Cardiovasc Pharmacol. 1992;19 Suppl 5:S51–8.
14. Schiffrin E, Deng L. Comparison of effects of angiotensin I-converting enzyme inhibition and b-blockade for 2 years on function of small arteries from hypertensive patients. Hypertension. 1995;25:699–703.
15. Matsuda H, Hayashi K, Arakawa K. Zonal heterogeneity in action of angiotensin-converting enzyme inhibitor on renal microcirculation: role of intrarenal bradykinin. J Am Soc Nephrol. 1999;10:2272–82.
16. Keane WF, Shapiro BE. Renal protective effects of angiotensin-converting enzyme inhibition. Am J Cardiol. 1990;65:49I–53.
17. Ruggenenti P, Perna A, Gherardi G, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies and non-nephrotic proteinuria. Lancet. 1999;354:359–64.
18. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensinconverting enzyme inhibition on diabetic nephropathy. N Engl J Med. 1993;329:1456–62.
19. Pitt B, Poole-Wilson PA, Segl R, on behalf of the ELITE II Investigators. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000;355:1582–7.
20. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med. 1987;316:1429–35.
21. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. N Engl J Med. 1991;325:293–302.
22. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med. 1995;332:80–5.
23. Borghi C, Bacchelli S, Esposti DD, Bignamini A, Magnani B, Ambrosioni E. Effects of the administration of an angiotensin-converting enzyme inhibitor during the acute phase of myocardial infarction in patients with arterial hypertension. SMILE

Study Investigators. Survival of Myocardial Infarction Long-term Evaluation. Am J Hypertens. 1999;12(7):665–72.
24. Borghi C, Bacchelli S, Esposti DD, Ambrosioni E, SMILE Study. Effects of the early ACE inhibition in diabetic nonthrombolyzed patients with anterior acute myocardial infarction. Diabetes Care. 2003;26:1862–8.
25. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Ryden L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation. 1999;100:2312–8.
26. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA. 1995;273:1450–6.
27. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med. 1992;327:685–91.
28. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moye L, Braunwald E. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet. 2000;355:1575–81.
29. Borghi C, Ambrosioni E, Novo S, Vinereanu D, Ambrosio G, SMILE-4 Working Party. Comparison between zofenopril and ramipril in combination with acetylsalicylic acid in patients with left ventricular systolic dysfunction after acute myocardial infarction: results of a randomized, double-blind, parallel-group, multicenter, European study (SMILE-4). Clin Cardiol. 2012;35:416–23.
30. Borghi C, Cosentino ER, Rinaldi ER, Cicero AF. Effect of zofenopril and ramipril on cardiovascular mortality in patients with chronic heart failure. Am J Cardiol. 2013;112(1): 90–93.
31. Dickstein K, Kjekshus J, OPTIMAAL Steering Committee for the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Lancet. 2002;360:752–60.

32. Pfeffer MA, McMurray JJV, Velasquez EJ, et al., for the Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349:1893–906.
33. McMurray JJV, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003;362:767–71.
34. López-Sendón J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kjekshus J, Lechat P, Torp-Pedersen C, Task Force on ACE-inhibitors of the European Society of Cardiology. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The Task Force on ACE-inhibitors of the European Society of Cardiology. Eur Heart J. 2004;25(16):1454–70.
35. Guidelines ESC. for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29(19):2388–442.
36. McMurray JJ, Holman RR, Haffner SM, Bethel MA, Holzhauer B, Hua TA, Belenkov Y, Boolell M, Buse JB, Buckley BM, Chacra AR, Chiang FT, Charbonnel B, Chow CC, Davies MJ, Deedwania P, Diem P, Einhorn D, Fonseca V, Fulcher GR, Gaciong Z, Gaztambide S, Giles T, Horton E, Ilkova H, Jenssen T, Kahn SE, Krum H, Laakso M, Leiter LA, Levitt NS, Mareev V, Martinez F, Masson C, Mazzone T, Meaney E, Nesto R, Pan C, Prager R, Raptis SA, Rutten GE, Sandstroem H, Schaper F, Scheen A, Schmitz O, Sinay I, Soska V, Stender S, Tamas G, Tognoni G, Tuomilehto J, Villamil AS, Vozar J, Califf RM. Effect of valsartan on the incidence of diabetes and cardiovascular events. N Engl J Med. 2010;362:1477–90.
37. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American

College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147–239.
38. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, Wagoner LE, Givertz MM, Liang CS, Neibaur M, Haught WH, LeJemtel TH. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. N Engl J Med. 2000;343(4):246–53.
39. Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. JAMA. 2002;287:1003–10.

http://www.springer.com/978-3-319-09787-9

ACEi and ARBS in Hypertension and Heart Failure
Perrone Filardi, P. (Ed.)
2015, X, 150 p. 19 illus., 13 illus. in color., Softcover
ISBN: 978-3-319-09787-9