Introduction

In the past 20 years, enormous progress has been made in the understanding of the pathophysiology and treatment of the complex clinical syndrome of heart failure. It has been a bidirectional process, with improvements in the understanding of the pathophysiology suggesting new therapeutic approaches and the success and failures of clinical trials refining our hypotheses or even suggesting the involvement of new pathophysiological mechanisms.

In the past, heart failure was interpreted on the basis of a pathophysiological model according to which the hemodynamic abnormalities played a key role in determining the clinical presentation and the evolution of the disease. Therefore, the objective of pharmacological treatment was to improve these hemodynamic abnormalities. At the beginning of the '90s it became clear that the activation of the renin-angiotensin-aldosterone system and of the sympathetic system caused by the abnormality in cardiac function had deleterious clinical effects in the long term. Heart failure was therefore considered as a "neurohormonal" disorder and the objective of pharmacological treatment was to improve survival by antagonizing this reflex activation. More recently, even the so-called "neurohormonal" hypothesis has itself evolved in several ways.

In the present review the efficacy of each class of drug will be discussed in the light of the results of the most important clinical trials. In fact, from a practical point of view, since we learned so much from the published trials, it is very important that we know how these have been structured to evaluate the applicability of pharmacological treatments to individual patients.

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according to which the hemodynamic abnormalities played a key role in determining the clinical presentation and evolution of the disease. Therefore, the objective of pharmacological treatment was to improve these hemodynamic abnormalities. This has led to the widespread use of inotropic and vasodilator drugs. However, although all these drugs improved the hemodynamic profile and the symptoms of heart failure in acute conditions, they all (unexpectedly) failed to reach the objective of improving survival in medium or long-term clinical trials. At the beginning of the 90s it became clear that the activation of the renin-angiotensin-aldosterone system and of the sympathetic system caused by the abnormality in cardiac function had deleterious clinical effects in the long term. Heart failure was therefore considered as a "neurohormonal" disorder and the objective of pharmacological treatment was to improve survival by antagonizing this reflex activation.

More recently, the so-called "neurohormonal" hypothesis has itself evolved in several ways. First, new peptides such as the endothelins and other mediators that may not be considered hormones (such as cytokines) have been postulated to play a role in the progression of chronic heart failure, for example by setting into motion apoptotic processes (from the "neurohormonal" to the "neurohumoral" hypothesis). Second, the focus is less on the negative impact of these pathways on the blood vessels and on the kidneys and more on the negative effects on the heart: for example, spironolactone exerts beneficial effects not only by antagonizing systemic aldosterone but also directly by attenuating cardiac remodeling. Finally, it is now clear that CHF is also characterized by chronic heart failure, for example by setting into motion apoptotic processes (from the "neurohormonal" to the "neurohumoral" hypothesis). In this context, digitalis has been postulated to play a role in the progression of cardiac remodeling. However, is this the main mechanism of action of digitalis? The observation that high doses of the drug increase mortality is in contrast with this hypothesis, as is the observation that digitalis showed positive effects even in patients with a preserved left ventricular function (about 1000 patients with an ejection fraction > 45% enrolled in the DIG trial). In recent years a neurohormonal effect of digitalis has been delineated: the drug is able to increase baroreceptor sensitivity and reduce the adrenergic tone, and these effects might explain why this is the only positive inotropic drug which "survived" a large multicenter trial on CHF.

**Digitalis**

Although the digitalis glycosides have been used by physicians for more than 2 centuries, the role of these drugs and their mechanism of action in CHF is still a matter of debate.

Two important double-blind, placebo-controlled trials on the effects of digitalis in CHF patients were published in 1993: the PROVED and the RADIANCE trials. Both were "withdrawal" studies, demonstrating that the withdrawal of digitalis worsened the clinical conditions of the patients under chronic treatment with this drug; in the RADIANCE trial this conclusion turned out to be true even in patients treated with ACE-inhibitors and diuretics. However, neither of the two trials had the necessary statistical power to demonstrate the effects of digitalis on hard events. The DIG trial was designed to overcome the doubts on the safety and efficacy of digitalis; the study enrolled around 6800 CHF patients in sinus rhythm, with an ejection fraction < 45%. After an average follow-up period of 37 months, no difference in mortality was observed between digitalis and placebo (34.8 vs 35.1%) but hospitalizations due to worsening heart failure were significantly reduced by active treatment (26 vs 34%, p < 0.001); a trend towards a reduction in mortality due to heart failure with digitalis (11.6 vs 13.2%) was probably balanced by an increase in sudden death or death due to acute myocardial infarction. At subgroup analysis it turned out that the greater benefits were observed in patients with an ejection fraction < 25% and a more advanced NYHA functional class and these still remain the current indications for the use of digitalis in CHF patients in sinus rhythm. Although the DIG trial greatly contributed to the clarification of the role of digitalis in CHF patients, this study left many unanswered questions. First of all, the problem of optimal plasma levels: in a subgroup analysis (data reported in an interview to the principal investigator of the DIG trial) mortality was found to be substantially higher in patients with a plasma level > 0.2 ng/dl than in those with a plasma level < 0.1 ng/dl (63 vs 30%). This observation is strictly linked to the question of the mechanism of action of digitalis. It is well known that at the cellular level digitalis inhibits the transmembrane movement of sodium and potassium by inhibiting the adenosine triphosphate-dependent transport enzyme system; this enhances the exchange of intracellular sodium with extracellular calcium, therefore enhancing the activation of the contractile elements. However, is this the main mechanism of action of digitalis? The observation that high doses of the drug increase mortality is in contrast with this hypothesis, as is the observation that digitalis showed positive effects even in patients with a preserved left ventricular function (about 1000 patients with an ejection fraction > 45% enrolled in the DIG trial).

**Diuretics**

The rationale for the use of diuretics is the necessity to counteract salt and fluid retention which occurs in almost all patients with heart failure, with the only possible exception of the initial phases of the disease. The possibility of not administering these drugs is therefore limited to a small percentage of patients, even when the clinical conditions are stable: in several studies the withdrawal of diuretics or their substitution with ACE-inhibitors led to a worsening of the heart failure symptoms which rendered their rapid reintroduction in the therapeutic scheme necessary. Still, it is clear that diuretics are not an optimal form of treatment: they cause a reflex neurohormonal activation and may there-
fore increase the risk of sudden death. Large controlled randomized trials testing their efficacy and safety are lacking in heart failure patients; however, it is interesting to note that in the Captropil-Digoxin Multicenter Research, diuretics alone were not able to maintain a clinically stable profile for a long period of time, unless they were used in association with digitalis and captopril.

### Vasodilators

The rationale for the use of vasodilators in CHF patients is the frequent observation of an elevated preload and afterload in such patients, due to several, often coexisting, mechanisms: the increase in the adrenergic tone, the increase in the plasma levels of catecholamines, angiotensin II and vasopressin, fluid retention and others. The acute administration of vasodilators has always determined positive effects, in terms of both the clinical and hemodynamic improvement. Nonetheless, the results of chronic treatment with these drugs have been almost invariably disappointing, because of the rapid disappearance of the initial beneficial effects (due to tolerance) or because of the appearance of severe side effects; in some cases even unfavorable effects on mortality have been observed. This is true for almost any kind of vasodilator such as alpha-blockers (prazosin and minoxidil), direct vasodilators (idralazine), venodilators (nitrates), venodilators with positive inotropic effects (flosequinan), prostacyclin (epoprostenol), and calcium antagonists (nifedipine, verapamil, diltiazem, mibebradil). Nonetheless, there are vasodilators which may be used safely in CHF patients: third-generation calcium antagonists such as amlodipine may be used to treat CHF patients with coexisting angina or severe hypertension; nitrates may be used in patients with elevated pulmonary artery pressures, in association with hydralazine or ACE-inhibitors (to prevent the development of tolerance).

### Inotropic drugs

There are several groups of pharmacological substances sharing the capability of increasing cardiac inotropism. A classification based on their mechanism of action at the cellular level includes: 1) drugs increasing the intracellular cyclic adenosine monophosphate (cAMP) through beta-receptor stimulation, 2) drugs increasing the intracellular cAMP through the inhibition of phosphodiesterase which degrades cAMP, 3) drugs interfering with calcium metabolism, 4) drugs with multiple mechanisms of action. The rationale for their use in CHF patients is that a reduced inotropism is a common finding in most diseases which lead to the syndrome of CHF. In addition, many of these drugs also have vasodilator properties, therefore combining what once seemed to be the ideal characteristics of a drug for CHF patients. However, despite these favorable hemodynamic and clinical effects in acute settings, the results of chronic treatment with these drugs have been invariably negative and most trials documented an increase in cardiac mortality. In the Xamoterol in Severe Heart Failure Study (516 patients in NYHA class III or IV, average follow-up period 4 months) the beta-agonist xamoterol increased the incidence of fatal events. In the PRIME II trial (1906 patients in NYHA class III or IV, average follow-up period 6 months) ibopamine, a dopaminergic receptor stimulator, was associated with an increase in the risk of death (+26%). Enoximone, a phosphodiesterase inhibitor, was associated with an increase in the risk of death (mainly arrhythmic death). In the PROMISE trial (1088 patients in NYHA class III or IV, average follow-up period 6 months) milrinone determined a 28% increase in overall mortality and a 69% increase in sudden death. A dose-dependent increase in mortality was observed in advanced CHF patients treated with vesnarinone in the VEST trial (3853 patients in NYHA class II-IV, average follow-up period 9 months); interestingly, despite the negative effects on survival, vesnarinone significantly improved the quality of life at 2 and 4 months in this trial.

To explain the negative results of these trials one must first consider the pro-arrhythmic action which is shared by most inotropic drugs; however, in addition it is important to note that these drugs stimulate the work of a heart which already is in a condition of relative energy shortage and may accelerate cellular degenerative processes and thus cardiac remodeling.

### ACE-inhibitors (Table I)

Although ACE-inhibitors are vasodilator agents, they do represent a separate pharmacological class, characterized by the capability of antagonizing the neurohormonal activation in CHF. They block the enzyme which converts angiotensin I into angiotensin II, thus reducing the plasma and tissue levels of angiotensin II (and increasing kinin levels because the same enzyme is responsible for kinin degradation); as a consequence, not only do they antagonize the renin-angiotensin-aldosterone system, but they also reduce the sympathetic-adrenergic drive because angiotensin II has an important facilitating effect on adrenaline dismission by the nervous endings.

Regardless of the etiology of heart failure (primary dilated cardiomyopathy or ischemic heart disease) and of the NYHA functional class, the beneficial effects of ACE-inhibitors on symptoms, exercise tolerance and survival have been well documented in CHF patients. Two landmark trials, CONSENSUS and SOLVD-Treatment, showed convincing evidence that ACE-inhibitors reduce morbidity and mortality in all grades of CHF. The CONSENSUS trial (253 patients in NYHA class IV, average follow-up period 6 months) demonstrated, as
early as 1987, that enalapril reduces the cardiac and all-cause mortality in severe heart failure patients. The SOLVD-Treatment trial (2569 patients in NYHA class II-III and ejection fraction ≤ 35%, average follow-up period 41 months) demonstrated an improved survival with enalapril in patients with moderate to severe CHF. The SOLVD-Prevention trial (4228 patients in NYHA class I, average follow-up period 37 months) showed that ACE-inhibition may delay or prevent the onset of overt symptomatic heart failure (-37%), reduce cardiovascular hospitalizations (-44%), and non-significantly improve all-cause and cardiac death (-8 and -12%, p = NS) even in totally asymptomatic patients. Further studies demonstrated that ACE-inhibitors can improve survival and reduce cardiovascular events in patients with an impaired systolic function or overt heart failure after myocardial infarction (SAVE, AIRE, TRACE, SMILE). These trials convincingly showed that ACE-inhibitors may reduce the risk of myocardial infarction and emphasize the complex biological action of these drugs, which certainly goes far beyond the angiotensin II antagonism. The favorable impact of these drugs on the long-term survival in CHF patients has been confirmed in the AIREX and in the CONSENSUS 10-year studies, although in the long term the survival benefit tends to become attenuated: in fact, only 5 patients were alive after 10 years in the latter trial, all treated with enalapril. In the long run the average duration of life gained with enalapril treatment in the CONSENSUS patients was about 37 months. Similar findings were noted in the 12-year follow-up of the SOLVD trials.

Are there any unsolved issues with regard to ACE-inhibitor therapy for CHF? Given the large body of evidence accumulated with these drugs in over 10 years of multicenter trials, this could seem an unnecessary question. However, the answer is yes. A first point relates to the dosages of ACE-inhibitors. In clinical practice we tend to use doses which are sometimes much lower than the "target" doses indicated in the trials. The reason for the gap existing between clinical practice and the studies published in the literature is probably the fear of the side effects induced by ACE-inhibitors, mainly hypotension, which are considered to be dose-dependent more than the beneficial effects of these drugs. Although this problem has already been addressed by two studies, NETWORK and ATLAS, a definite answer has not yet been reached. The suggestion is to titrate the doses unless the side effects do really manifest. Another problem raised in recent years is that, despite their clinical efficacy, ACE-inhibitors are rather aspecific pharmacological inhibitors of the renin-angiotensin-aldosterone system: angiotensin II may in fact be generated by non-ACE-dependent biochemical pathways. These considerations form the rationale for the evaluation of the clinical efficacy of more specific pharmacological inhibitors of the renin-angiotensin-aldosterone system.

### Beta-blockers (Table II)

Once formally contraindicated in patients with CHF, these drugs are now one of the cornerstones of the therapeutic approach to heart failure. When the first studies suggesting a positive role for beta-blockers were published in 1975, heart failure was viewed as a "hemodynamic" disorder, and therefore the use of negative inotropic agents was considered detrimental. Years later, the rationale for the use of these drugs was clarified, as we learned that neurohormonal activation is an early phenomenon in CHF patients (it may occur before the development of symptoms) and, importantly, that it is not a mere consequence of the cardiac damage but it is also a determinant of the progression of the disease. A long-lasting sympathetic activation interferes with the mechanisms of signal transduction of the adrenergic receptors (decreasing the number of beta1-receptors, and uncoupling beta-receptors) and therefore reduces the efficacy of the adrenergic stimulation on the heart. In addition, a prolonged exposition to high catecholamine
levels may even exert a "toxic" effect on the myocytes, inducing myofibril damage and stimulating apoptotic processes. Changes in contractile proteins, with a greater expression of fetal isoforms of beta-myosin, are observed in advanced CHF and are also probably related to sympathetically hyperactivity. Beta-blocker administration may upregulate beta-receptors and may reverse the expression of the different isoforms of contractile proteins. Paradoxically, they may now be considered the most effective positive inotropic agents for CHF patients.

The first randomized studies with beta-blockers in CHF failed to demonstrate a survival benefit with metoprolol, bisoprolol and carvedilol; however, these studies did not have adequate statistical power\textsuperscript{41-43}. On the contrary, an impressive survival benefit was demonstrated with all these drugs in the following multicenter trials. In the four studies performed by the US Carvedilol Study Group (1094 patients in NYHA class II-III, average follow-up period 6 months), a 65% reduction in total mortality was observed in the carvedilol treated arm\textsuperscript{44}. In the CIBIS II trial (2647 patients in NYHA class III, average follow-up period 16 months) a 34% reduction in total mortality was observed in the group of patients treated with bisoprolol\textsuperscript{45}. In the MERIT-HF trial (3991 patients in NYHA class II-III, average follow-up period 12 months) a 35% reduction in total mortality was observed in the metoprolol treated arm\textsuperscript{46}. The most recently published COPERNICUS trial has extended the indications for the use of beta-blockers to patients with severe heart failure; the trial enrolled 2289 patients in NYHA class III-IV and with a left ventricular ejection fraction \( \leq 25\% \), and has been prematurely stopped because a 35% reduction in total mortality was observed in the actively treated arm\textsuperscript{47}. However, there has been one trial which showed a non-significant effect of beta-blockade on survival: the BEST trial which used bucindolol, a non-selective beta-blocker; a 10% reduction in total mortality was observed in the actively treated arm\textsuperscript{48}. The study raised several problems about racial differences in the responsiveness to this agent and about the differential efficacy of beta-blockers. The latter problem will be addressed in the ongoing COMET trial, directly comparing carvedilol and metoprolol.

In conclusion, there is overwhelming evidence that beta-blockers may improve survival in the different grades of CHF; this evidence is even more relevant because it has been obtained in patients already been treated with ACE-inhibitors. However, the use of these agents requires a very careful clinical approach, in terms of patient selection (they may have severe CHF but must be clinically stable) and in terms of follow-up (during the titration phase their clinical conditions must be checked frequently); in other words "start low and go slow".

**Angiotensin II receptor blockers (Table I)**

The advent of specific blockers for the angiotensin II receptor 1 was preceded by the hypothesis that a more specific pharmacological inhibition of the renin-angiotensin-aldosterone system could also lead to a greater clinical efficacy in CHF patients. As compared to ACE-inhibitors, these agents may in fact also block the action of non-ACE-generated angiotensin II. In addition, by selectively blocking the angiotensin II receptor 1 they leave unaltered the action of angiotensin II on receptor 2, which has been postulated to have potentially desirable actions, such as also induction of nitric oxide release. Despite this theoretical background, neither the ELITE II trial nor the RESOLVD trial confirmed the hypothesis of a superiority of angiotensin II receptor blockers versus ACE-inhibitors suggested by the ELITE investigators\textsuperscript{49-51}. The investigators of the Val-HeFT trial tested the hypothesis that the addition of angiotensin II receptor blockers to conventional therapy with ACE-inhibitors and beta-blockers could result in a clinical benefit. The trial (5010 patients in NYHA class II-IV) demonstrated that valsartan did not improve mortality but reduced the combined endpoint of mortality and morbidity, with a marked reduction (-27%) in the frequency of heart failure hospitalization\textsuperscript{52}. This benefit was not uniform: the greater advantage was observed in patients not receiving ACE-inhibitors, whereas no benefit and a negative trend were observed in patients already taking a combination of ACE-inhibitors and beta-blockers.
Anti-aldosterone agents (Table I)

In the RALES trial (1663 patients in NYHA class III or IV), the addition of low-dose spironolactone (25 mg) to conventional treatment with ACE-inhibitors and beta-blockers reduced the frequency of hospitalization (-35%) and prolonged survival (-30% in cardiac mortality and -29% in sudden death) in advanced CHF patients. Although a strong rationale for the therapeutic administration of anti-aldosterone agents in heart failure was known even before planning the RALES study (the prevention of the potassium sparing effect of frusemide, the synergistic action with loop diuretics, the systemic neurohormonal action), the results of this trial were still surprising and fostered many researches aiming at a better understanding of the negative effects of aldosterone and of the mechanisms through which spironolactone reduces mortality in CHF. Experimental and clinical studies have shown that aldosterone synthesis may take place in the myofibroblasts, determining cardiac concentrations which may be 17 times than the plasma levels (so that now aldosterone must not only be considered as a systemic hormone but also as a paracrine agent). This cardiac production may be strongly inhibited by spironolactone and it is possible that the anti-remodeling effects of spironolactone are attributable to the inhibition of the profibrotic effects of aldosterone at the cardiac level. More recently, the EPHEBUS trial demonstrated the efficacy of a new selective aldosterone receptor blocker, eplerenone, in patients with a recent myocardial infarction (6632 patients with an acute myocardial infarction complicated by systolic left ventricular dysfunction, NYHA class I-IV). Treatment with eplerenone was associated with a reduction in all-cause mortality (11.8 vs 13.6%, relative risk 0.85, p = 0.008) as well as in cardiovascular mortality and hospitalizations; in contrast to the data reported in the RALES trial using spironolactone, eplerenone was not associated with gynecomastia or sexual dysfunction. However, no head to head data as to which anti-aldosterone antagonist is optimal for heart failure patients are available.

Antiarrhythmic therapy (the prevention of sudden death)

A substantial proportion of heart failure patients (up to 30-40%) die suddenly, most probably of a lethal ventricular arrhythmia. The prevention of sudden death is therefore a major (and as yet unresolved) issue confronting contemporary cardiology. Overall, the impact of antiarrhythmic agents may be considered far from being satisfactory. Sodium channel blockers have at best a neutral effect on mortality, but may actually increase mortality in certain subsets of patients. Pure class III agents also either had negative effects (d-sotalol determined a 65% increase in the incidence of fatal events in the SWORD trial) or had no effect at all (as is the case of dofetilide in the DIAMOND trial). On the contrary, beta-blockers have been shown to produce a consistent and significant reduction in arrhythmic mortality in heart failure patients; sudden death was in fact reduced by 44% in CIBIS II and by 41% in MERIT-HF. Unlike other antiarrhythmic drugs these agents appear to induce no pro-arrhythmic effect and their action does not appear to be due to the suppression of ambient arrhythmias, the predominant action most likely being the reversal of sympathetic hyperactivity and the attenuation of the arrhythmogenic effects of myocardial ischemia. Amiodarone turned out to have only modest effects, despite the fact that in view of its array of pharmacological and electrophysiological properties, this drug might have been expected to markedly reduce mortality in the same subset of patients in whom beta-blockers proved to be highly effective. In the GESICA trial (516 patients with advanced heart failure primarily due to dilated cardiomyopathy, followed up for an average of 24 months), amiodarone reduced the total mortality (-28%, p = 0.024) and also induced a slight reduction in the incidence of sudden death (-27%, p = NS). In the STAT-CHF trial (674 patients with advanced heart failure due to different etiologies, followed up for an average of 45 months) amiodarone did not improve survival. In two large post-infarction trials, CAMIAT and EMIAT, the combination of amiodarone and beta-blockers was associated with the greatest improvement in survival, suggesting that the pharmacological properties of these drugs may be additive or even synergistic. Such an association is currently the best possible pharmacological approach to the prevention of sudden death in patients with heart failure.

Nowadays, however, the interest and the hopes in the field of preventing sudden death are shifted towards non-pharmacological options. The Antiarrhythmics Versus Implantable Defibrillators (AVID) and the Multicenter Automatic Defibrillator Implantation Trial (MADIT) demonstrated that implantable cardioverter-defibrillators reduce mortality in patients with a low left ventricular ejection fraction and spontaneous or inducible ventricular arrhythmias. Post-hoc analysis of both trials demonstrated that the greatest benefit was obtained in patients with the lowest ejection fraction. The MADIT II trial has recently been prematurely stopped because of overwhelming evidence of a survival benefit in implanted patients; in this trial patients with a low ejection fraction were enrolled regardless of the demonstration of repetitive arrhythmias. Will the prophylactic implantation of cardioverter-defibrillators in all patients with a low left ventricular ejection fraction therefore be the solution? Before answering such an important question it is necessary to wait for the results of other ongoing trials, such as the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which is comparing amiodarone vs implantable cardioverter-defibrillators in about 2500 patients in NYHA class III or IV and with an ejection fraction < 35%.
References