

# Management of patients with heart failure\*

## *Manuseio do paciente portador de insuficiência cardíaca*

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### ABSTRACT

The treatment of heart failure (HF) has advanced greatly in recent decades. Today, based on evidence, it includes beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and spironolactone. For symptomatic patients, we must add a diuretic and/or digitalis. For these medications to be effective they must be used in full doses. The objective of this study was the correct treatment modifies the natural history of the disease, reducing its morbidity and mortality. To check its effectiveness, symptoms reduction, reversal of, increase of ejection fraction and reduction of heart rate are assessed. When there is no improvement of these characteristics, or the treatment is inadequate and must be improved, or the clinical picture is very serious, there is a poor prognosis. Early detection of HF allows measures to be taken in order to modify the natural history of the disease. Thus, we should encourage the correct treatment since early stages of the disease, preventing progression to advanced and refractory forms.

**Keywords:** Heart failure/drug therapy; Heart failure/prevention & control; Stroke volume; Heart rate; Cardiovascular agents/therapeutic use; Angiotensin-converting enzyme inhibitors

### RESUMO

O tratamento da insuficiência cardíaca (IC) avançou muito nas últimas décadas. Hoje, baseado em evidências inclui o uso de betabloqueadores, inibidores da enzima conversora de angiotensina, bloqueadores do receptor da angiotensina II e espironolactona. Para os pacientes sintomáticos devem-se acrescentar um diurético e/ou digital. Para que esses fármacos sejam efetivos devem ser empregados em doses plenas. O objetivo deste estudo foi observar o

tratamento correto modifica a história natural da doença, reduzindo sua morbidade e mortalidade. Para verificar sua efetividade, avalia-se a melhora dos sintomas, reversão da dilatação cardíaca, aumento da fração de ejeção e redução da frequência cardíaca. Quando não há melhora destas características, ou o tratamento é insuficiente e deve ser melhorado ou que o quadro clínico é muito grave e o paciente terá, então, um prognóstico sombrio. A detecção precoce da insuficiência cardíaca permite que medidas sejam tomadas a fim de modificar a história natural da doença. Deve-se, portanto encorajar o tratamento correto desde os estágios iniciais da doença, prevenindo a progressão para formas avançadas e refratárias.

**Descritores:** Insuficiência cardíaca/quimioterapia; Insuficiência cardíaca/prevenção & controle; Volume sistólico; Frequência cardíaca; Fármacos cardiovasculares/uso terapêutico; Inibidores da enzima conversora da angiotensina.

### INTRODUCTION

The understanding of heart failure (HF) has increased greatly in recent years. Today its pathophysiology and natural history are better understood, and we have new therapeutic options. Therefore, we are able to change the course of the disease<sup>(1,2)</sup>.

The Framingham study remains an important source for HF epidemiology. The collected data shows that approximately 2.5% of the population aged 45 years or more is affected by the disease, and that it is more frequent among the elderly<sup>(3)</sup>. In Brazil, HF is the leading cause of cardiac admission among patients over 65 years<sup>(1,2)</sup>.

In the population evaluated in the Framingham study, hypertension preceded the onset of symptoms in 70% of men and 78% of women, while coronary disease was the etiology in 59% of men and 48% of women. With better control of hypertension, ischemic heart disease has become the leading cause of heart failure in adults<sup>(3)</sup>, which was observed in large multicenter studies, and also in the Brazilian Registry of Heart Failure named BREATHE (Figure 1). In Brazil we must always include Chagas disease as a cause of HF.

### NATURAL HISTORY AND PROGNOSTIC FACTORS

Heart failure is a very debilitating disease<sup>(1,4)</sup>. The analysis of quality of life, with the use of questionnaires, in different diseases, identified HF as one of the most debilitating diseases, overcoming diabetes and chronic obstructive pulmonary disease. Dyspnea, fatigue and edema cause a lot of discomfort to the patients, explaining this finding.

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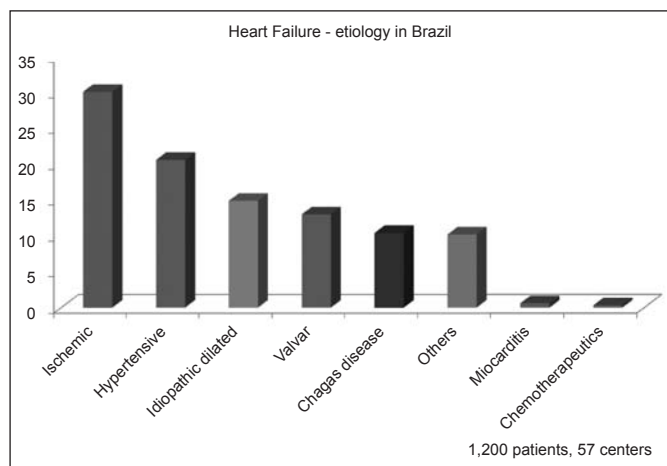


Figure 1 - Etiology of heart failure in patients in Registry BREATHE.

HF is a syndrome of malignant features, with high mortality in advanced forms<sup>(5)</sup>. In the past several studies have shown that mortality reached 50% in one year in patients in functional class (FC) IV of the New York Heart Association Classification. In our experience in this 21<sup>st</sup> century dealing with critically ill patients, we observed a mortality rate of 32% in the first year of follow up. It must be highlighted that this result was obtained in a population treated according to the most updated guidelines, but the disease remains with features of malignancy in advanced forms<sup>(6)</sup>. The natural history can be modified with the correction of baseline heart disease, the control of aggravating factors of HF, or the correct medication<sup>(7)</sup>.

However, it is important to note that, in its initial forms, its course is not so bad, a fact that should be considered when making a more aggressive decision. There is good evidence to prove good evolution in asymptomatic or mildly symptomatic patients, despite signs of severe cardiac impairment (e.g. ejection fraction of less than 25%)<sup>(8,9)</sup>, with data from the studies SOLVD prevention and survival and ventricular enlargement (SAVE) documenting this<sup>(9,10)</sup>. These studies demonstrated that ventricular dysfunction is a frequent finding. More than 6,000 asymptomatic patients and with ejection fraction of less than 40% were enrolled. Of these, about 35% had HF manifested in four years, demonstrating that not all patients with ventricular dysfunction present significant physical limitations. The analysis of evolution in the placebo group in these studies provided information about the natural history of the disease, since the first clinical manifestations of HF<sup>(9)</sup>. High mortality rates, described in advanced forms, are not seen in asymptomatic patients, even in those with significant ventricular dysfunction. Data from these two studies shows that these patients mortality in four years will be of less than 15% (Figure 2). Thus, at the time of therapeutic orientation, it is not possible to make analogies with the more advanced forms. Also, a proposal of transplant is not indicated in asymptomatic patients, as the risk of this procedure will be possibly greater than that observed in the natural history of the disease in its early stages.

Among symptomatic patients, the course of the disease is not similar; the more symptomatic, the worst the evolution. It is possible to stratify patients based on clinical and laboratory data. Thus,

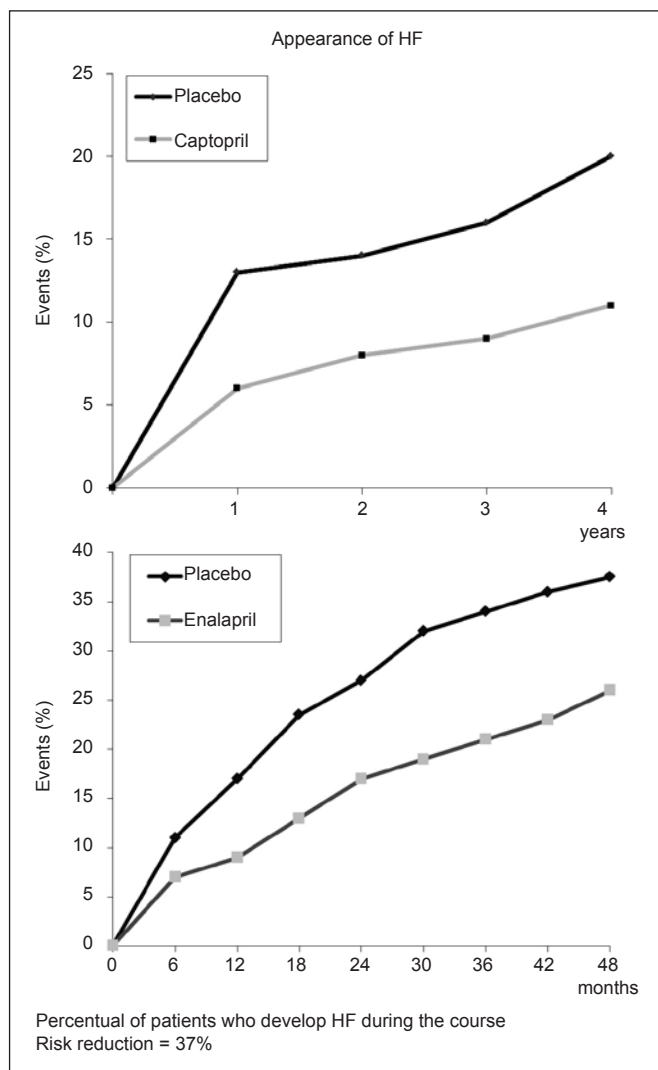


Figure 2 - In the study SOLVD prevention and SAVE the minority of patients developed heart failure in four years.

those with greater physical ability, demonstrated by the effort time during the ergometric test, the distance rode in the 6-minute test, or the oxygen consumption by spirometry, have better outcomes. Data of cardiac function also stratifies patients in terms of prognosis. The lower the cardiac output, the higher the pulmonary capillary pressure, the higher the peripheral resistance, the lower the ejection fraction and, therefore, the higher the mortality. Anatomy is also useful in this stratification, since cardiomegaly and increased heart chambers identify high-risk groups<sup>(8-12)</sup>.

Based on several studies that analyzed HF patients' survival, it was possible to identify some indicators of poor prognosis. These serve as severity criteria, useful for identifying patients who need more intense care or even those who would be candidates for surgical treatment of HF. In Table 1 we present some of these indicators that, when present, indicate a worse prognosis<sup>(13)</sup>.

The ejection fraction is an indicator that is easily obtained with the use of different methods. Echocardiographic evaluation, although very dependent on the experience of the examining physician, assists in patient stratification. Ejection fraction itself is not well correlated with functional classes. The joint analysis of

Table 1 - Prognostic factors in heart failure.

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History
Age > 65 years
Duration of symptoms
Etiology of HF
Greater intensity of symptoms
Diabetes mellitus
Associated Pulmonary disease
Multiple hospital admissions
Lack of compliance
Anemia
Physical examination
S3 present
High resting heart rate (> 70 beats / min)
Low systolic blood pressure
Ascites
Ketone breath
Cachexy
Clinical/Hemodynamic Profile types B and C
<b>Chest X-ray</b>
Marked cardiomegaly (cardiothoracic ratio > 0.55)
<b>Functional</b>
Smallest distance in 6 minutes
Oxygen consumption < 14 ml/kg/min
Increase in VE/VCO <sub>2</sub> in ergospirometry
<b>Laboratory Data</b>
Serum sodium < 130 mEq/L
Creatinine > 2.5 mg/dL
Hemoglobin < 11 g%
Elevated levels of BNP/proBNP
Renin
Liver enzyme and bilirubin
Uric acid
Electrocardiogram
Atrial fibrillation
Sustained and nonsustained ventricular tachycardia
Left bundle branch block
Echocardiography
Ejection fraction < 30%
LV Progressive dilatation
Enlarged LV diastolic and systolic diameter
<b>Hemodynamics</b>
Increased pulmonary artery pressures
Increased pulmonary capillary pressure
Low cardiac Output and index
Increased pulmonary vascular resistance

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ejection fraction and functional class allows to better identifying patients with poor prognosis (e.g. patients with ejection fraction of less than 35% on echocardiography in functional class IV). Increased ventricular diameters also identify patients with poor prognosis. In peripartum cardiomyopathy, patients presenting with ventricular diameters greater than 70 mm had a much higher mortality rate than those with lower ventricular dilation<sup>(14)</sup>. Patient evolution differs according to the etiology of the disease. Patients with an ischemic cardiomyopathy appear to have worse

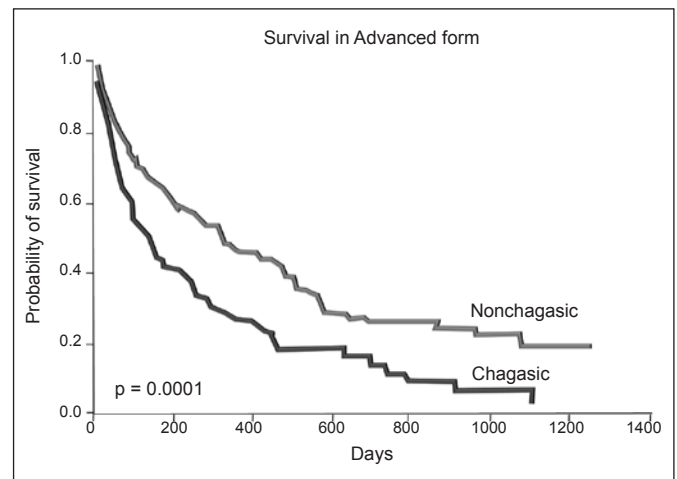


Figure 3 - Survival curve of patients admitted with advanced heart failure at Hospital Auxiliary de Cotoxó showing that patients with Chagas disease have worse outcomes.

outcomes than those with dilated cardiomyopathy. On experience with the InCor (Instituto do Coração) patients, those with HF due to Chagas disease have a worse evolution (Figure 3)<sup>(15)</sup>. Therefore in patients with HF, the identification of the etiology is essential because it allows, in many cases, to assess prognosis and guide treatment.

The assessments that measure cardiac reserve provide a better identification of patients according to their prognosis. Oxygen consumption equal to or less than 10 mL/kg/min identifies patients with indication for heart transplantation<sup>(16)</sup>. In this line of dynamic testing we have the six-minute walk test, which is easier to be performed, but is much less accurate. In this test, patients who walk less than 300 meters have more cardiac decompensations and increased risk of death.

Hypotension is another excellent prognostic indicator. Those in need for inotropic support or who remain with pressure of approximately 90 mmHg exhibit higher mortality rates<sup>(17,18)</sup>.

The association of prognostic factors better identifies patients' potential for progress<sup>(17,18)</sup>.

## DIAGNOSIS

Heart failure is a predominantly clinical syndrome, with the symptoms being the best way to diagnose it<sup>(19)</sup>. Even with all the technological and scientific advances of recent years, the analysis of symptoms and signs remains as the main way to diagnose HF, with no supplementary examination being able to uniquely and objectively define the presence of this syndrome.

The most frequent clinical findings in HF are: reduced exercise tolerance, clinically manifested by dyspnea and fatigue, and water retention, resulting in pulmonary rales, elevated jugular venous pressure, and peripheral edema. Dyspnea is the most frequent symptom in chronic heart failure (CHF), and is dependent on the degree of left ventricular dysfunction. It presents as dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and dyspnea at rest. Due to its high sensitivity (100%), the absence of dyspnea makes the diagnosis of CHF unlikely. Among patients seen in the emergency department with acute dyspnea,

about 50% have CHF as a cause. Thus, it is important that, in patients with dyspnea and suspected HF, differential diagnosis is performed with other causes of dyspnea, through a careful clinical assessment.

Due to its high specificity, some of the physical examination findings are useful to confirm the diagnosis of heart failure: deviation of the heart apex to the left, gallop rhythm, jugular venous distension, and the presence of hepatojugular reflux. However, these signs have low sensitivity, with their absence being of low value to rule out HF.

The objective of the laboratory evaluation of HF is to establish the diagnosis, stratifying the severity of the disease, and to identify the presence of other comorbidities, such as myocardial ischemia, anemia, renal insufficiency, nephrotic syndrome, diabetes mellitus, thyrotoxicosis and hypothyroidism.

Among the initial complementary tests in the evaluation of patients with dyspnea and suspected HF, chest X-ray and electrocardiogram (ECG) are of great importance<sup>(20)</sup>. If they result normal they make the diagnosis of HF unlikely. Moreover, HF is strongly suggested in the presence of cardiomegaly and pulmonary vascular congestion on chest X-ray, and the presence of Q waves on the anterior wall or left bundle branch block on ECG. The development of tests for the detection of B-type natriuretic peptide (BNP and NT-proBNP) has helped in the diagnosis of heart failure<sup>(21,22)</sup>. The BNP is a polypeptide that has its production stimulated by the expansion of ventricular volume and pressure overload. The dosage of these peptides has been shown to be useful in the diagnostic evaluation of patients with dyspnea, and also provides relevant information regarding the prognosis and treatment of HF. The dosage of this marker is especially useful in the evaluation of patients with acute dyspnea and suspected pulmonary disease. The presence of normal levels of brain natriuretic peptide (BNP) (< 100 pg/mL) or NT-proBNP (< 300 pg/mL) rules HF out as the cause of dyspnea in the emergency room<sup>(21,22)</sup>. Values above 500 pg/mL of BNP and 1500 pg/mL of NT-proBNP are diagnostic of cardiac decompensation.

## TREATMENT

HF treatment has undergone several changes in recent years, with beta-blockers, Angiotensin-Converting Enzyme (ACE) inhibitors, angiotensin receptor blockers and spironolactone or eplerenone<sup>(1,2)</sup> forming the basis of modern treatment. For symptomatic patients, diuretics and digoxin<sup>(1,2)</sup> are added. The evidence based treatment aims at blocking neurohormonal stimulation and reversing the deleterious cardiac remodeling<sup>(23)</sup>.

Evidence indicates that a well-conducted treatment modifies disease progression. If the natural history of the syndrome is characterized by progressive worsening of quality of life, reduced work capacity, progressive increase in symptoms and increased risk of death with its progression, the correct treatment, with the use of these neurohormonal blockers, reverses this trend reducing morbidity and increasing survival of patients with HF<sup>(1,2)</sup>. But it is important to emphasize that these results are seen when the patient receives the correct treatment, with drugs prescribed in optimal doses. Low doses have no effect.

## TREATMENT OF HEART FAILURE

The treatment itself must be preceded by the diagnosis of underlying heart disease and the identification of triggering factors<sup>(1,2)</sup>. The diagnosis of ischemic cardiomyopathy leads to the investigation of ischemia, myocardial viability and possibility of bypass. The presence of infarction leads to the consideration of the presence of ventricular aneurysm and possibility of heart geometrical reconstruction. These interventions substantially modify patients' outcome<sup>(23)</sup>.

The triggering or aggravating factors must be investigated and treated. The presence of anemia, arrhythmia, fever, hyperthyroidism and infectious process triggers or aggravates HF, and its control reverses the situation<sup>(1)</sup>. We also have to analyze which medications patients use, as they can precipitate or worsen heart failure (calcium channel antagonists, non-steroidal anti-inflammatory drugs)<sup>(1,2)</sup>.

Among the factors that trigger decompensation, it is interesting to note that the most frequent is poor compliance, either to drug therapy or salt and fluids control. Due to the potential severity of HF, it is essential that patients and their families are counseled about the impact of the disease and the importance of the correct treatment, in order to change the natural history and allow survival with good quality of life.

The importance of compliance to the therapeutic guidelines is being increasingly documented with the results obtained by the Heart Failure Clinics<sup>(24)</sup>. In these Clinics, patients and families are, among other measures, instructed about triggering factors, the importance of diet and treatment compliance. With better adherence to guidance, patients under treatment have shown better clinical outcome, with significant reduction in readmissions and emergency department (ED) visits.

## NON-DRUG THERAPY

Dyspnea, hepatic congestion and edema are the symptoms of HF related to water retention, and the reduction of salt and fluids intake is of great help for its control. With the advent of more potent diuretics, fluid restriction does not appear necessary for most patients, but in advanced forms and in those non-responsive to treatment, they are of great help to control symptoms<sup>(1,2)</sup>. Patient's daily weighing allows early identification of water retention and hence the correction of the doses of diuretics.

Physical exercise is another measure that has had its importance reevaluated. Although being contraindicated in the past, modern evidence suggests that exercise is useful for the treatment of HF<sup>(16)</sup>. The Rehabilitation Service of *Instituto do Coração* (Incor) demonstrated that physical exercise reduces sympathetic activity, which is elevated in these patients, and increases peripheral blood flow by improving endothelial function<sup>(12)</sup>. Studies on its effectiveness in reducing morbidity and mortality did not gather a large number of patients, but showed that patients who practiced physical exercises had reduced hospital admissions and mortality rate. Thus, exercises should be prescribed for clinically stable patients as an adjuvant to drug therapy. In our Service we documented that exercise performed at home, following instructions received in the hospital, improves patients' quality of life and keeps lower levels of neurohormones<sup>(25)</sup>.



## DRUG THERAPY

A better understanding of the effects of several drugs available is modifying its degree of importance in treatment. Diuretics and digitalis have a role in the control of patients' symptoms.

### Digitalis and diuretics

Diuretics are the main drug to control congestive symptoms: edema, hepatomegaly, and dyspnea<sup>(1,2,26)</sup>.

Loop diuretics are undoubtedly essential for compensation. The dose to be prescribed depends on the magnitude of symptoms and response to the drug. Once the disease is controlled, longer-acting thiazides show to be more useful, keeping patients symptom-free for prolonged periods. In more severe cases, the combination of the two (loop diuretics and thiazides) provides more intense diuresis and reverses the congestive scenario<sup>(1,2,26)</sup>. The value of digoxin in the treatment of heart failure has been well established by the Digitalis Investigation Group (DIG) trial that documented that the drug had no impact on mortality rates, but provided a reduction in hospital admissions for cardiac decompensation<sup>(27)</sup>.

Digoxin is an easy-dosage drug, once a day, but is recognized as a narrow therapeutic index drug, thus having therapeutic levels that are very close to toxic levels. Digitalis intoxication is not rare, but in most cases it is easy to control.

In recent years, the retrospective analysis of the SOLVD and DIG studies have documented that levels of digoxinemia higher than 0.10 ng/dL were followed by higher mortality<sup>(28,29)</sup>. It is important to note that these values are within the limits considered therapeutic. Together, these studies showed that digoxin may not be as innocuous as is usually thought, and that its prescription must be judiciously considered. These findings lead to the conclusion that the drug may present more risks than previously thought; thus, the treatment must be conducted with lower doses of the drug. It is likely that 0.125 mg daily, the dose often prescribed by Brazilian doctors, is effective and less risky to patients. ACE inhibitors, beta-blockers and spironolactone are drugs that modify the Natural History of the disease and should be prescribed to all patients, provided there are no contraindications.

### ACE inhibitors

Based on the results of studies Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS), SOLVD and many others following them, inhibitors should be prescribed to all patients with ventricular dysfunction<sup>(8,11)</sup>. For symptomatic patients, they should be prescribed to reduce symptoms and the high mortality that characterizes this stage of the disease, and for asymptomatic patients, to prevent progression to symptomatic forms, and to reduce mortality. These benefits have been observed with all ACE inhibitors, thus proving to be an effect of this drug class<sup>(30)</sup>.

A key point in the prescription of these drugs is the dose. Low doses have not been tested and there is no evidence that they are effective. Moreover, several studies have documented that the full doses are effective and well tolerated by most patients. In patients with advanced disease, the full doses provide better outcomes than lower doses. Therefore it is recommended to seek to

achieve the doses indicated by large studies. With respect to the most often prescribed inhibitors, we should try to achieve doses of captopril of 50 mg tid, enalapril 20 mg qd or bid, or ramipril 10 mg. Patients who do not tolerate these doses should be kept at the highest dose tolerated<sup>(1,2)</sup>.

The main causes of intolerance to ACE inhibitors are cough, hypotension, renal failure and hyperkalemia. For patients with cough it is recommended to change to the angiotensin II receptor blockers. In cases of hypotension, the dose reduction and revision of diuretics control the disease in most patients<sup>(1,2)</sup>. In cases of high creatinine levels above 3.0 mg/dL, dose reduction may bring some improvement. If this elevation persists, the therapy with drugs such as the combination of hydralazine and nitrates, which does not alter renal function, is preferable.

### Angiotensin II receptor blockers

The therapeutic effect is very similar to that of ACE inhibitors. Studies comparing ACE inhibitors and angiotensin II receptor blockers (ARB) showed that both drugs provide very similar results in the reduction of morbidity and mortality in patients with heart failure<sup>(31-33)</sup>.

It is the drug of choice to replace ACE inhibitors when these cause coughing as a side effect<sup>31</sup>. In patients with impaired renal function or hyperkalemia with ACE inhibitors, it is very likely that this adverse effect is also observed with ARBs, since their mechanism of action in the kidney is very similar<sup>(1,2)</sup>.

Studies have shown, such as observed with ACE inhibitors, that full doses are of major importance. Clinical improvement has not been observed with low doses. Thus, it is recommended to prescribe losartan 150 mg/day, valsartan 320 mg/day, and candesartan 32 mg/day, just to mention the most often prescribed drugs for patients with heart failure<sup>(31-34)</sup>.

### Beta-blocker

At present, it is the main drug for the treatment of heart failure<sup>(1,2)</sup>. Its indications are based on numerous clinical trials that have demonstrated that beta-blockers associated with ACE inhibitors further reduce the morbidity and mortality associated with the disease<sup>(35-39)</sup>. The observed reduction in mortality is higher than 30%, a value twice higher than that seen with ACE inhibitors. This significant reduction in mortality is one of the factors that transformed beta-blockers in the most important drugs for heart failure treatment.

Another point of great importance to treatment with beta-blockers is the reversal of ventricular remodeling<sup>(39,40)</sup>. Beta blockers have been shown capable of reducing cardiac dilation and significantly increasing ejection fraction, reversing cardiac remodeling in about 75% of patients taking the drug. Although ACE inhibitors also modify cardiac remodeling, their impact on it is much less significant<sup>(39)</sup>.

Beta-blockers, unlike diuretics, digoxin, ACE inhibitors and ARBs, should not be prescribed to decompensated patients<sup>(1,2)</sup>. The drug should be started after cardiac compensation, with low doses and gradual increase until reaching the recommended doses. At the beginning of treatment beta blockers may worsen heart function, but in the long run they show significant improvement. The treatment is initiated with low doses to minimize this nega-

tive inotropic effect. The increase, with doubling of dose every 7 days, is very well tolerated by patients and allows the achievement of the desired target doses in 30 days<sup>(1,2)</sup>.

Four beta blockers have proven their effectiveness for the treatment of heart failure: bisoprolol, carvedilol, nebivolol and metoprolol succinate<sup>(35-38,41)</sup>. For beta blockers, the doses have also been shown to be of great importance<sup>(1,2)</sup>. The benefits observed with the drugs are more evident in full doses. Thus the target dose should be 25 mg twice daily for carvedilol, 200 mg once daily to metoprolol succinate, and 10 mg once a day for nebivolol and bisoprolol. Carvedilol should be initiated at a dose of 3.125 mg bid, metoprolol succinate is initiated at a dose of 12.5 mg daily, bisoprolol and nebivolol 1.25 mg daily. The dose should be doubled every 7 days until it reaches the target dose<sup>(1,2,39)</sup>. The more beta blockers are used, the more it turns out that beta-blockers are well tolerated and easy to administer. In many patients it is possible to set up the incremental doses without clinical reassessment.

Another important issue in modern treatment of heart failure is the attitude to be taken when a patient on beta-blocker has a cardiac decompensation: should we simply stop its administration? The answer in most cases is: it should not be interrupted, since in most cases of cardiac decompensation the predominant scenario is of congestion, which can be controlled with the use of diuretics<sup>(39)</sup>. Drug suspension should be considered only when patients have low cardiac output signals, first with 50% reduction of the dose. If the scenario of low output or shock persists the drug should be discontinued. There is evidence that abrupt discontinuation of beta-blockers may be deleterious and accompanied by increased mortality.

### **Spirolactone**

The third drug that is important in the treatment of heart failure is spironolactone, a drug that also provides the reduction of morbidity and mortality<sup>(42-44)</sup>. The dose tested was 25 to 50 mg, with no documentation that higher dosages are more effective, but that they are only accompanied by more side effects.

The combined use of ACE inhibitors, beta-blockers and spironolactone may be accompanied by cases of hyperkalemia, with blood control being mandatory at baseline to detect its presence. Hyperkalemia may occur even with the prescription of high doses of other diuretics.

Based on the studies RALES, EPHEBUS and EMPHASIS we currently have evidence that Aldosterone receptor block modifies the HF Natural History in patients with functional class II, III and IV, and in patients stratified as FC I after myocardial infarction<sup>(42-44)</sup>. The results of the studies EPHEBUS and EMPHASIS expanded the indication of aldosterone blockade in patients with post-myocardial infarction asymptomatic ventricular dysfunction, and in those classified in FC II<sup>(43,44)</sup>. These more modern studies show that the drug is effective in less symptomatic patients.

### **Hydralazine and nitrate**

Vasodilators entered into the era of evidence-based medicine in the treatment of HF with the V-HeFT study that documented that long-acting vasodilator drugs modify the natural history of HF, significantly reducing the mortality of patients with the disease<sup>(45)</sup>. This was the first large clinical trial to document the pos-

sibility to reduce the high mortality of HF.

Its efficacy in acute situations is largely proven; however, tolerance due to the chronic use of nitrates led to a change of strategy<sup>(46)</sup>. Concomitant use of hydralazine with nitrate, both in animal model and in patients with HF, prevents the development of nitrate tolerance and provides maintenance of favorable nitrates hemodynamic effects<sup>(47)</sup>. The finding that the combined use of nitrates and hydralazine, besides potentiating the hemodynamic vasodilating effects prevents nitrate tolerance, allowed it to be used in the HF chronic treatment<sup>(48)</sup>. Since this has been documented, the association of nitrate and hydralazine has been investigated in the treatment of HF, and V-HeFT I study documented that it significantly reduces mortality of HF patients<sup>(45)</sup>.

With the documentation, in the late 1980s, that ACE inhibitors were effective in the treatment of HF, the V-HeFT II study was elaborated, which compared the efficacy of the combination of nitrates and hydralazine to enalapril, a drug that induced a reduction in mortality in the study CONSENSUS<sup>(11,49)</sup>.

In the study V-HeFT I it can be seen that the combination of nitrate and hydralazine provided, in two years of treatment, a relative reduction of 31% in mortality, with its rate being reduced from 34% in the placebo group to 26% in the group treated with nitrate and hydralazine<sup>(45)</sup>. The V-HeFT II study showed that enalapril was more effective than the combination of hydralazine and nitrate in the reduction in mortality among HF patients, causing a relative reduction of 28% in mortality. The mortality of the group treated with nitrates and hydralazine was of 25%, with 18% in the group treated with enalapril<sup>(49)</sup>. Documentation stating that enalapril provided a more significant reduction in mortality than the combination of nitrate and hydralazine made ACE inhibitors the vasodilators of choice for the treatment of HF.

However, more careful analysis of the V-HeFT I and II studies results showed various interesting aspects that deserve a more detailed analysis. An interesting aspect is that the combination of nitrates and hydralazine provided a more significant increase in ejection fraction than enalapril, suggesting differences in the mode of action, and allowing the assumption that the two could be used in addition, possibly providing more intense results than the isolated use of each regimen<sup>(50)</sup>. This was further investigated in the A-HeFT study and in smaller studies documenting that the concomitant use of the two regimens provides an even higher improvement than the separate treatment regimens<sup>(51)</sup>.

The A-HeFT study demonstrated that black patients respond well to treatment with nitrates and hydralazine, documenting that their addition to the usual treatment caused a 43% reduction in mortality<sup>(51,52)</sup>. With these results we should always prescribe this combination to black patients. More recently, a study conducted in 2009 showed that in white patients with advanced HF, the addition of nitrate and hydralazine was associated with significant improvement and reduced mortality<sup>(53)</sup>. The mortality rate among patients treated with ACE inhibitors alone was of 41%, while in those who received the association of nitrate and hydralazine it was of 34%, a relative reduction in mortality of 35%<sup>(53)</sup>.

In HF, increased peripheral resistance has been increasingly documented as the main pathophysiological element responsible for the progression of ventricular dysfunction and high mortality presented by the disease. All studies employing vasodilators in

treatment optimization have documented improvement in patient outcomes<sup>(53)</sup>. Thus, if we have a patient who is not doing well with the usual treatment, the addition of vasodilators can be effective to change the evolution allowing some compensation<sup>(53)</sup>. The prescription of nitrate and hydralazine is also indicated for cases in which there is renal function impairment during the treatment of HF. The impaired renal function may prevent the prescription of ACE inhibitors, ARBs, and aldosterone blockers<sup>(1,2)</sup>. In this circumstance, the combination of nitrates and hydralazine becomes the only option in vasodilator treatment, of undoubted importance for the treatment of HF<sup>(1,2)</sup>. Renal dysfunction, either temporary or permanent, is a frequent finding in patients with HF<sup>(1,2)</sup>.

The set of data shows that nitrates, a medication with over 100 years of use in cardiology, remain a current medication and should be prescribed for better control of HF, a disease of unquestionable severity, in which the optimal treatment modifies its natural history.

### The need for documentation on treatment effectiveness

Although evidence indicates that the treatment can change the natural history of the disease, when we observe how doctors are treating patients with heart failure we see that most of them do not follow the guidelines, and do not prescribe drugs that effectively reduce disease morbidity and mortality rates. This is borne out in the reports of records on how patients are being treated in Europe and the United States, all pointing to less than 30% of patients receiving optimized treatment (Figure 4)<sup>(54,55)</sup>. There are numerous reasons for not prescribing the treatment, and among them we highlight the lack of knowledge about the severity of the disease, the fear of drug side effects and the lack of markers of treatment efficacy.

We observed if the guidelines for the treatment of heart failure were being followed in InCor outpatients, and we could see that, in 1999, although ACE inhibitors were being prescribed for almost all patients, beta-blockers and spironolactone were prescribed only for less than 30% of patients<sup>(56)</sup>. During the search carried out in October 2004, we observed a sevenfold increase in the prescription of beta-blockers, reaching 70% of patients, data that indicates that most physicians at InCor adhered to the guidelines for the treatment of heart failure. Analyzing the clinical practice of three doctors used to treat HF we could observe

that it is possible to prescribe the drugs for almost all HF patients treated in clinics and also prescribe them in target doses, indicated by the Guidelines and clinical trials. The 103 patients attended by this group of physicians had as average dose of carvedilol 49 mg/day and enalapril 28 mg/day<sup>(57)</sup>.

Whereas epidemiological data show that the HF patients outcome is much worse than the outcome of patients with many types of cancer (prostate, breast or bladder), it would not be risky to say that we do not adopt for patients with heart failure the same behavior that oncologists adopt to cancer patients<sup>(5)</sup>. Patients with heart failure should be informed of the potential severity of the disease, and that the treatment, according to the guidelines, can alter this natural history.

Patients with heart failure who have had cardiac decompensation need to be closely monitored by their physicians. They should be advised to weigh themselves frequently, and measure the waist and ankle in order to early detect cardiac decompensation. Weight increase by more than 1 kg in a day or two, increase of two or three centimeters in waist circumference and ankle indicate fluid retention, and that the dosage of diuretics and the amount of liquid ingested should be revised<sup>(58)</sup>. This simple guidance significantly reduces the ED visits and gives patients with the syndrome a better quality of life.

One must also adopt some markers to identify whether the patient is responding satisfactorily to the treatment prescribed, so that it can be intensified or changed to those in which the desired response is not achieved. Symptomatic improvement, fundamental to patients' quality of life, has not been shown to be a good indicator of good response to the prescribed therapy. Diuretics in the correct dose can give compensation to most patients; however, patients can keep presenting ventricular remodeling, by increasing ventricular dilation and reducing ejection fraction with consequent worsening of symptoms, now in a more advanced clinical situation, imposing greater difficulty to therapy.

The reversal of ventricular dilatation, or increased ejection fraction and decreased heart rate to values below 70 beats per minute have shown to be good markers of good cardiac response to treatment<sup>(59,61)</sup>. The outcome of patients who show this reduction is much better than in those who do not.

The use of these markers allows the earlier identification of those patients who are not responding satisfactorily to treatment, and thus its enhancement, or change, in order to achieve the desired response. Thus, if the use of the prescribed drug does not show reversal of ventricular remodeling, it is necessary to review the therapeutic regimen<sup>(59,60)</sup>, check if the patient is taking the medications properly, in the doses prescribed, and review if the doses of each drug are the optimal ones. In many cases this reversal is obtained by optimizing the treatment, or increasing the dose of ACE inhibitors or beta-blockers, which at first appeared to be prescribed in necessary doses. The same applies to the natriuretic peptide, either with the dosage of BNP or NT-proBNP<sup>(62,63)</sup>. This neurohormone reduction indicates that the treatment is optimized and that the outcome will be improved. In studies where the natriuretic peptide dosage was used as the guide for therapy efficacy compared to the usual treatment guided by clinical manifestations, it can be seen that to reduce BNP values it was necessary to prescribe higher doses of diuretics and ACE inhibitors, a

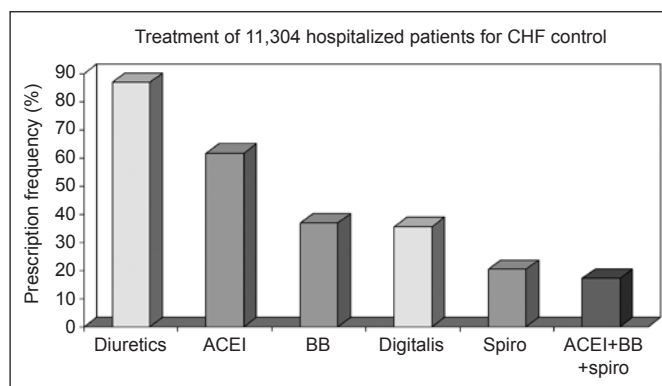


Figure 4 - EuroHeart Failure Survey.

requirement that is not identified in the group followed in the usual manner<sup>(63)</sup>. On follow-up, patients guided by natriuretic peptide levels had better outcomes, with reduced HF hospital admissions.

When the markers improvement is not reached, even with treatment optimization for heart failure, the patient with a severe form of the disease who will progress to non-responsive forms is identified. Similar to what is done with cancer patients, the family should be informed that the disease is progressing and that other measures are necessary, or that the prognosis is poor.

High HR is another indicator that the treatment can be incremented. The decompensated HF usually occurs along with high HR due to the activation of compensatory mechanisms, particularly by increased adrenergic activity<sup>(61)</sup>. In recent years, a growing number of studies has shown that HR above 70 beats per minute identifies patients at higher risk of adverse events<sup>(2,61)</sup>. The higher the HR, the higher the risk. Moreover, a reduction of HR reduces these risks<sup>(2,61)</sup>. A meta-analysis of studies with beta-blockers showed that part of the benefit of reversal of cardiac remodeling is related to HR reduction provided by the therapy<sup>(62)</sup>. Not only do beta-blockers reduce the heart rate, but also ivabradine, a sinus node I<sub>f</sub> channel inhibitor, has been shown to be effective in reducing HR in patients in sinus rhythm<sup>(61)</sup>. Thus, identification of HR above 70 bpm in a HF patient, on optimized treatment, identifies patients that should have their treatment incremented. In the presence of HR above 70 bpm we can increase the dose of the beta-blocker or prescribe ivabradine. The SHIFT study showed that prescribing ivabradine reduces HR and the incidence of events in these patients<sup>(61)</sup>. HR reduction with ivabradine also reverses cardiac dilatation<sup>(61)</sup>.

In HF, the HR that the patient develops when on treatment should be considered. It is an easily obtained variable, and the literature data have shown that even the HR that is not so high is a marker of poor prognosis<sup>(2,61)</sup>. Thus, in the presence of HR above 70 bpm, we should review the treatment and modify it in order to reduce the HR. The heart rate above 70 bpm indicates that the treatment should be incremented, since it suggests that the patient is not fully beta-blocked. In the presence of HR above 70 bpm, the prescription of digitalis, beta-blockers or ivabradine should be considered. Importantly, the prescription of ivabradine is the only one that had its effectiveness documented by the clinical study SHIFT<sup>(2,61)</sup>.

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