Original Article

Major Clinical Characteristics of Patients Surviving 24 Months or More After Hospitalization due to Decompensated Heart Failure

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Objective

To study the major clinical characteristics of patients with heart failure who survived more than 24 months after hospitalization for compensation.

Methods

The study comprised 126 patients with heart failure in functional class III or IV, with a mean age of 51.7 years. Most patients were men (73%), had a mean ejection fraction (EF) of 0.36 and left ventricular diastolic diameter (DD) of 7.13 cm. The major clinical and laboratory characteristics were assessed, and, on follow-up, 25 (19.8%) patients, who survived more than 24 months after hospital discharge, were identified. Data of survivors (G1) were compared with those of patients who died (G2) before 24 months.

Results

In G1, the following levels were greater: serum sodium (138.3±3.4 vs 134.5±5.8 mEq/L; P=0.001); blood pressure levels (120.0 vs 96.7 mm Hg; P=0.003); and LVEF levels (0.40±0.08 vs 0.34±0.09; P=0.004); and the following levels were lower: urea (59.8 vs 76.3 mg/dL; P=0.007); prothrombin time (12.9 vs 14.8 seconds; P=0.001); LVDD (6.78±0.55 vs 7.22±0.91; P=0.003); and LA diameter (4.77 vs 4.99cm; P=0.0003). More survivors were found among patients with idiopathic cardiomyopathy and arterial hypertension than among patients with Chagas' disease and coronary artery disease. In multivariate analysis, the following variables remained as independent predictors of mortality: LVDD > 7.8 cm (HR 1.95); Na < 132 mEq/L (HR 2.30); and prothrombin time > 14 seconds (HR 1.69).

Conclusion

The study allowed predicting which patients with heart failure will have a good survival after hospital discharge and those with a greater chance of a long survival after discharge.

Key words

advanced heart failure, ventricular systolic dysfunction, survival, hyponatremia, shock

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Heart failure is currently recognized as a disease with a poor prognosis [1-5]. Initially, the disease evolves insidiously, but as patients become symptomatic, the prognosis becomes poor. Its advanced form has characteristics of malignancy and results in a shorter survival than different types of cancer [6].

In the natural history of heart failure, the need for hospitalization for compensation is associated with a greater heart impairment and failure of the mechanisms of compensation. The patients are hospitalized, have a poorer evolution, and their mortality is 2 to 3 times greater than that of those who require no hospitalization [3,7-10]. At our institution, we treat patients with heart failure who need hospitalization for compensation, a group with disease of greater severity and a worse prognosis.

We have observed that the survival of those patients, even with the new therapeutic schedules, remains small with less than 50% survival in the first year after hospital discharge [11,12]. However, some patients seem to challenge those results, surviving several years after hospitalization.

This study aimed at assessing the characteristics of patients with advanced heart failure hospitalized for compensation who survived longer (more than 2 years).

Methods

This study comprised 126 patients with heart failure in NYHA functional class IV nonconsecutively treated at the emergency unit of InCor. They were hospitalized for compensation at the Hospital Auxiliar de Cotoxó during the period 12/12/1993 to 09/25/1995. The patients had left ventricular dysfunction, signs of pulmonary and hepatic congestion, lower limb edema, and had been medicated at the emergency unit. Because their symptoms were not controlled with the therapy administered, they were hospitalized.

The inclusion criterion was the presence of systolic ventricular dysfunction of any etiology identified by values below 55% (cube method). The exclusion criteria were as follows: patients who died within the first 24 hours and those with acute coronary syndrome, valvular heart diseases with a surgical indication, congenital heart diseases, chronic renal failure or serum creatinine > 2.5 mg/dL, and fatal noncardiac diseases. All patients were clinically assessed on the day of hospitalization and underwent laboratory and echocardiographic assessments.

The major clinical characteristics of the population studied are shown in table I.

Most patients were of the male sex (73%). The patients' mean age was 51.1±14.2 years. Chagas' disease was the major etiology of ventricular dysfunction (44.4%). Shock was present in 31.7% of patients. On echocardiography, the mean left ventricular diameter was 7.14±0.9 cm, the ejection fraction was 0.36± 0.09, and 80.9% of patients had moderate or important mitral regurgitation.

Table II shows the results of the laboratory tests on the first day of hospitalization.

The renal function was reduced in most patients, with mean levels of urea and creatinine of 73.1±29.4 mg/dL and 1.48±0.39 mg/dL, respectively.

The patients were followed up at the outpatient care clinic of InCor after hospital discharge. All those who were not followed up at InCor were contacted (or their relatives) at the end of 1998 for assessing their clinical situation or death. The mean follow-up time was 15.3 ± 13.8 months.

As the study's objective was to assess the basal clinical characteristics of the patients who survived more than 2 years, the patients were divided into 2 groups: 1) group 1, comprising those who remained alive after 2 years; and group 2, comprising those who died within 2 years of follow-up.

The statistical analysis comprised the calculation of the mean, standard deviation, and minimum and maximum values of the continuous variables. The categorical variables were presented as frequency and percentage.

The 2 groups were compared; the Student *t* test was used for the continuous variables and the chi-square test was used for the categorical variables. For determining the predictors of mortality during the follow-up period, multiple regression analysis was performed with the Cox proportional hazards model, which was adjusted according to the clinical and laboratory characteristics of that population. The criterion used for selecting the variables in the multiple model was P<0.200 in the univariate analysis. The final model was constructed according to the Stepwise Forward technique, and the variables were maintained in the final model when the P value was <0.050. The Kaplan-Meier method was used for describing the survival rates for the relevant variables determined by regression analysis. The difference of survival between the groups was determined by the log-rank test. In all steps of the analysis, the significance level of 5% was adopted.

Results

On follow-up, 25 (19.8%) patients who survived more than 24 months after hospital discharge were identified. The major characteristics of the 2 groups are shown in table III.

No difference was found between the groups regarding age and sex. On univariate analysis, the following conditions were identified as predictors of mortality: Chagas' disease; reduced systolic blood pressure; reduced mean blood pressure; shock; left ventricular diastolic diameter greater than 7.8 cm; left atrial diameter greater than 5.7 cm; ejection fraction lower than 0.30; plasma sodium lower than 132 mEq/L; urea level greater than 55 mg/dL; and prothrombin time greater than 14 seconds (tab. IV).

No patient with ventricular diameter greater than 7.80 cm, left atrial diameter greater than 5.70 cm, ejection fraction lower than 0.30, and sodium level below 132 mEq/L was alive 24 months after hospital discharge (fig. 1, 2, and 3).

On multiple regression analysis using the proportional hazards

Table I - Major clinical characteristics of the population studied

Variable	n (%) variation	Mean/ standard deviation
Male sex	92 (73%)	
Age (years)	18 a 82	51.1±14.2
Duration of HF (months)	1-96	25.3±22.6
Heart rate (bpm)	46-150	95.3±19.1
Systolic blood pressure (mmHg)	0-190	101.4±32.9
Shock	40 (31.7%)	
Third cardiac sound	52 (41.3%)	
Ascites	49 (38.9%)	
Atrial fibrillation	40 (31.7%)	
LV diastolic diameter (cm)	5.2 a 9.6	7.1±0.9
Left atrial diameter (cm)	3.2 a 7.4	4.9±0.8
LV ejection fraction	0.11 a 0.58	0.36±0.09
Moderate/intense mitral regurgitation	102 (80.9%)	

Table II - Results of the laboratory tests

Variable	Variation	Mean/Standard deviation
Hemoglobin (g%)	7.8 a 18.4	13.6±1.9
Hematocrit (%)	27 a 94	42.9±7.2
Leukocytes (mL/mm3)	4.3 a 22	8.8±3.4
Prothrombin time (s)	11.4 a 33.8	14.5±3.1
Sodium (mEq/L)	119 a 147	135.3±5.6
Potassium (mEq/L)	2.7 a 6.9	4.4±0.7
Urea (mg/dL)	26 a 163	73.1±29.4
Creatinine (mg/dL)	0.8 a 2.4	1.48±0.35

Table III - Data of groups according to survival longer or shorter than 24 months

	> 24 months	< 24 months	P
n	25	101	
Age	50.9±17.2	51.1±14.0	0.9661
Male sex	17 (68%)	92 (73%)	0.7043
Idiopathic	9 (36%)	29 (23.01%)	
Hypertensive	7 (28%)	12 (9.5%)	
Chagas	6 (24%)	56 (44.4%)	
Ischemic	2 (8%)	21 (16.6%)	0.0005
Duration of disease	24.1±23.3	25.5±22.4	0.7818
Heart rate (bpm)	101.2±19.8	93.8±18.7	0.0982
Systolic BP	120.0±31.4	96.7±31.7	0.0039
Shock	3 (12%)	14 (34.9%)	0.0332
Third cardiac sound	11 (44%)	41 (40.6%)	0.9339
Ascites	6 (24%)	43 (42.6%)	0.1398
Atrial fibrillation	6 (24%)	34 (33.6%)	0.4905
LVDD (cm)	6.78±0.55	7.22±0.91	0.0032
LA (cm)	4.47±0.55	4.99±0.79	0.0003
LVEF	0.40±0.08	0.34±0.09	0.0048
Severe mitral regurgitation	20 (80%)	82 (81.2%)	0.8815
Hemoglobin (g%)	13.3±2.0	13.6±1.9	0.5457
Leukocytes	8992±3375	8776±3421	0.7769
Sodium (mEq/L)	138.3±3.46	134.5±5.8	0.0001
Potassium (mEq/L)	4.45±0.63	4.45±0.81	0.9973
Urea (mg/dL)	59.8±25.4	76.4±29.5	0.0076
Creatinine (mg/dL)	1.40±0.42	1.49±0.39	0.3387
Albumin (mg/dL)	3.32±0.64	3.28±0.61	0.7702
PT (s)	12.9±1.4	14.8±3.2	0.0001
Hospitalization (days)	15.8±15.1	19.4±13.8	0.2992

LVDD - left ventricular diastolic diameter; LA - left atrial diameter; LVEF - left ventricular ejection fraction; PT - prothrombin time.

Table IV - Univariate regression analysis of the mortality predictors in a 24-month follow-up

Variables	Death within 24 months: No (n = 25)	Death within 24 months: Yes (n = 101)	HR	95%CI	P
Age ≥50 years	14 (56.0%)	54 (53.5%)	0.87	0.58 – 1.29	0.480
Male sex	17 (68.0%)	75 (74.3%)	1.12	0.72 – 1.75	0.621
Etiology:					
Idiopathic	9 (36.0)	20 (19.8%)	0.61	0.37 – 1.00	0.050
Hypertensive	7 (28.0%)	5 (5.0%)	0.35	0.14 – 0.86	0.023
Chagasic	6 (24.0%)	50 (49.5%)	1.63	1.10 – 2.43	0.016
Ischemic	2 (8.0%)	19 (18.8%)	1.23	0.75 – 2.03	0.413
Valvular	1 (4.0%)	7 (6.9%)	1.50	0.70 – 3.26	0.298
Duration of disease >18 months	11 (44.0%)	49 (48.5%)	1.13	0.76 – 1.68	0.545
Heart rate >100 bpm	13 (52.0%)	28 (27.7%)	0.68	0.43 – 1.05	0.080
SBP <90 mm Hg	4 (16.0%)	39 (38.6%)	1.56	1.04 – 2.34	0.033
MBP <70 mm Hg	7 (28.0%)	53 (52.5%)	1.65	1.11 – 2.45	0.014
Shock	3 (12.0%)	37 (36.6%)	1.92	1.27 – 2.89	0.002
Third cardiac sound	11 (4.0%)	41 (40.6%)	1.01	0.68 – 1.51	0.959
Ascites	6 (24.0%)	43 (42.6%)	1.48	0.99 – 2.20	0.057
Arterial hypertension	4 (20.0%)	16 (18.0%)	1.04	0.60 – 1.79	0.883
Diabetes mellitus	6 (24.0%)	17 (16.8%)	0.70	0.41 – 1.17	0.173
Atrial fibrillation	6 (24.0%)	34 (33.7%)	1.07	0.71 – 1.63	0.747
LVDD >7.8cm	0 (0.0%)	23 (22.8%)	2.36	1.45 – 3.84	0.001
LA >5.7 cm	0 (0.0%)	17 (16.8%)	1.74	1.03 – 2.94	0.040
LVEF <0.30	0 (0.0%)	27 (26.7%)	1.92	1.22 – 3.02	0.005
Severe mitral regurgitation	20 (80.0%)	82 (81.2%)	1.07	0.65 – 1.76	0.796
Hemoglobin >15 g%	8 (32.0%)	26 (25.7%)	0.76	0.49 – 1.20	0.240
Hematocrit >45%	9 (36.0%)	33 (32.7%)	0.90	0.59 – 1.37	0.629
Leukocytes >10.000/mL	5 (20.0%)	25 (24.8%)	1.23	0.78 – 1.94	0.366
Sodium <132 mEq/L	0 (0.0%)	28 (27.7%)	2.39	1.51 – 3.77	<0.001
Urea >55.0 mg/dL	9 (36.0%)	73 (72.3%)	1.77	1.13 – 2.76	0.013
Creatinine >1.4 mg/dL	9 (36.0%)	47 (46.5%)	1.23	0.76 – 1.68	0.556
Albumin <3.3 mg/dL	14 (56.0%)	52 (51.5%)	1.04	0.70 – 1.55	0.837
PT >14 seconds	3 (12.0%)	43 (42.6%)	1.88	1.25 – 2.82	0.002

HR - hazard ratio; 95%CI - 95% confidence interval; SBP - systolic blood pressure; MBP - mean blood pressure; LVDD - left ventricular diastolic diameter; LA - left atrium; LVEF - left ventricular ejection fraction; PT - prothrombin time.

model, the following variables remained in the model as independent variables: left ventricular diastolic diameter greater than 7.8 cm (HR 1.95; P=0.009); plasma sodium lower than 132 mEq/L (HR 2.30; P<0.001); and prothrombin time greater than 14 seconds (HR 1.69; P=0.014) (fig. 4).

Discussion

Patients with heart failure who require hospitalization for compensation usually have the advanced form of the disease, and evolve with higher mortality rates than that of those who remained compensated on an outpatient care basis only [1-5, 7-10].

In population-based studies, 10% to 20% of patients with heart failure die in the first year of evolution, and this number may reach 50% in a 5-year follow-up [1-5]. When analyzing the survival of patients hospitalized with heart failure, the numbers are not encouraging, with a 30 to 40% mortality in the first year of follow-up [7-10].

The patients in this study originated from the emergency unit and were transferred to the ward when not compensated after emergency medication. The nonresponse to diuretics in the emergency treatment indicated the most severely ill patients. In this study, 60% of the patients died during the first year of follow-up, evidencing a population with severe disease. Our findings are in accordance with the literature that signals that the advanced form of heart failure is a disease with malignant characteristics [6].

The population in this study seems more severely ill than those usually described in epidemiological studies, or even in large assays, because no study reported mortality greater than 50% [1-5,7-10,13,14].

Although the population had great cardiac impairment, 19.8% of the patients survived more than 2 years. The survivors differed from those who died because, on clinical and laboratory examination on admission, they had higher blood pressure, a lower incidence of shock or hypotension, smaller left ventricular and atrial dilation, greater left ventricular ejection fraction, normal sodium levels, [Which is better? See change.] minor impairment in renal function, and normal prothrombin time.

The predictive factors of good or poor evolution are related to the pathophysiology of heart failure and to the mechanisms of disease progression [15-18].

The result of this study is relevant, because it shows that, through clinical assessment and routine laboratory tests, the population could be stratified and the patients with better evolution potential could be identified. This information has great practical connotations, because, as the patients with good evolution potential are identified, those with poor evolution potential are also identified. The latter are those who should be carefully followed up and who are the major candidates for heart transplantation or more aggressive procedures, necessary for trying to change the evolution of the disease.

The presence of hypotension or shock was an important predictor of poor outcome. The patients who manage to maintain arterial blood pressure signal a greater cardiac reserve, a fact associated with a better prognosis. In the literature, the reduction in blood pressure is identified as an independent prognostic factor in the studies with a population of patients hospitalized due to

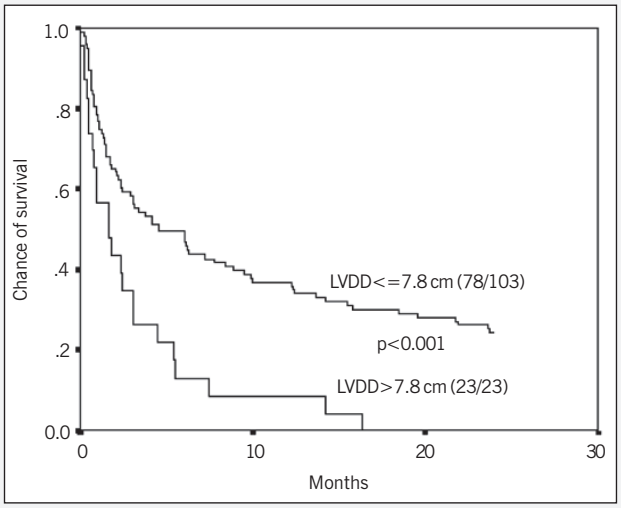

Fig. 1 - Survival curve for the left ventricular diastolic diameter greater or lower than 7.8 cm.

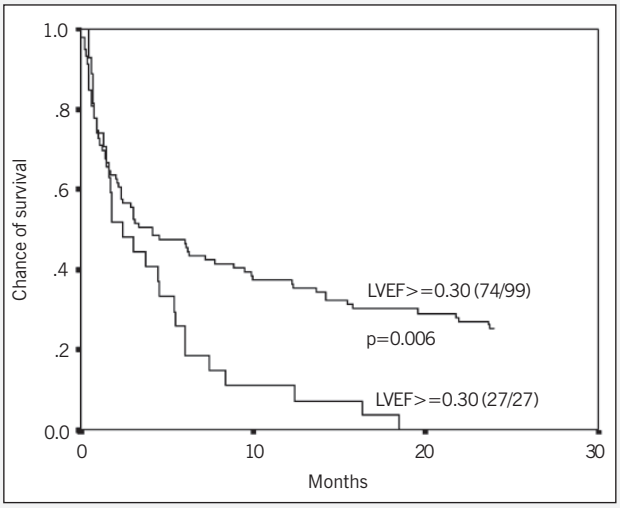

Fig. 3 - Survival curve for ejection fraction greater or lower than 0.30.

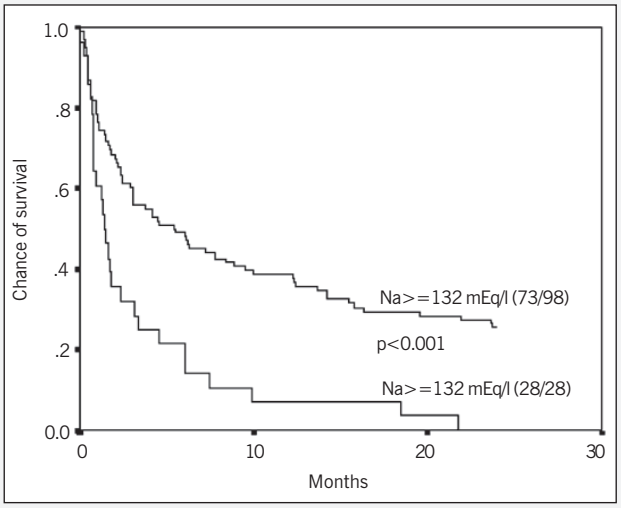

Fig. 2 - Survival curve for plasma sodium levels greater or lower than 132 mEq/L.

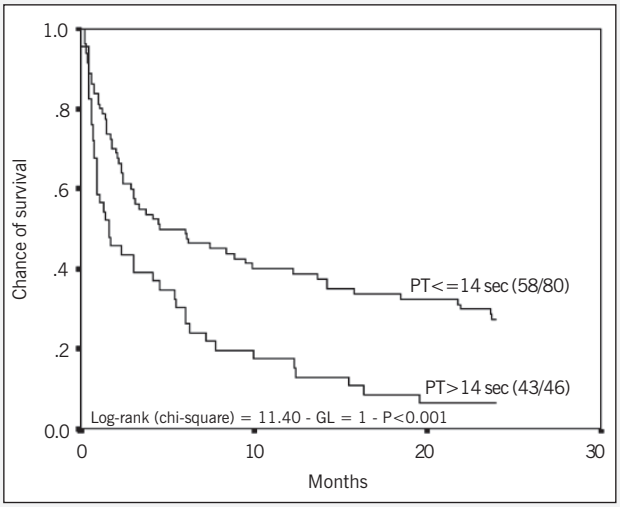

Fig. 4 - Survival curve for the prothrombin time longer or shorter than 14 seconds.

heart failure [3,7,19]. Blood pressure levels < 100 mm Hg are associated with greater mortality [3,7,19].

Cardiac function is another important prognostic determinant[5,10,15,16]. Our data show that patients with greater cardiac impairment, smaller cardiac dilation, and greater ejection fraction survive longer. This shows that for the population of patients with advanced heart failure, cardiac remodeling, which is more and more identified as a mechanism of disease progression, plays an unquestionable role in the natural history of the disease [5,10,15,16,20]. The patients with left ventricular diastolic diameter > 7.8 cm had a risk of death almost two times greater than that of patients with smaller dilation (HR 1.95) (fig. 1).

In laboratory tests, hyponatremia, an elevation in urea, and a more prolonged prothrombin time were associated with a worse prognosis. The surviving patients had no significant alterations in those tests. In the literature, hyponatremia and renal failure are frequently identified as independent predictors of the evolution of patients with heart failure [3,5,7,10,18-22]. Hyponatremia results from an increased neurohormonal stimulation, is always an important factor in prognostic stratification, and is frequently recognized as the most powerful factor for identifying those with the worst prognosis [5,7,10,18-20]. In the population studied, considering p level and the result of multivariate analysis, sodium was the factor with the greatest statistical expression, emphasizing the increased neurohormonal stimulation as an important prognostic determinant. Patients with hyponatremia had a 2.3-fold greater risk of death than those with normal sodium levels (fig. 2).

The presence of renal failure is frequently identified as an important prognostic factor in patients with heart failure, inducing an increase in mortality directly proportional to the degree of renal dysfunction [3,5,7,10,20-22].

Both the elevation in urea level and the extension of the prothrombin time result from low cardiac output and hepatic congestion in association with the cardiac dysfunction characteristic of heart failure [3,5,7,10,19,20]. In multivariate analysis, a prothrombin time greater than 14 seconds identified patients with a 1.69-fold greater risk of death than those with a prothrombin time not so prolonged (fig. 4).

When comparing the values found in the 2 groups of patients (survivors and nonsurvivors), some of the variables showed nonoverlapping values, which allowed the selection of values that identified severely ill patients, because the values were not found in

any survivor. Thus, left ventricular dilation greater than 7.8 cm identified patients who died without completing 2 years of survival; the same occurred for an ejection fraction lower than 0.30 and for a plasma sodium level lower than 132 mEq/L (fig. 1, 2 and 3).

Two studies, a Brazilian and a Canadian, that assessed the evolution of patients treated at an emergency unit also identified hyponatremia as an important independent predictor of poor evolution [19,20]. Hypotension, depressed renal function, and ventricular dilation were also identified as predictors of a bad evolution, suggesting that the variables identified are strong predictors of evolution in patients with decompensated heart failure and deserve the attention of the clinicians treating patients in this phase of the disease.

This study has limitations, such as the fact that most patients, although medicated with ACE inhibitors, were not receiving beta-blockers. Prescription of the latter might have allowed a greater number of patients to survive more than 24 months, and the variables identified as prognostic to have other values.

The recognition of the importance of the participation of cardiac remodeling, neurohormonal alterations, venous congestion and renal failure in determining the prognosis reinforces the role of the treatment for heart failure with neurohormonal blockers (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and aldosterone blockers) and beta-blockers, which are known to modify the identified factors, altering the evolution of the disease.

In conclusion, 19.8% of the patients with advanced heart failure survive more than 24 months after hospitalization for compensation. In patients hospitalized for decompensation, the parameters of cardiac remodeling, the sodium and urea levels, and the prothrombin time allow the identification of those with the greatest chances of surviving longer after hospital discharge. Assessment through clinical parameters and simple laboratory tests allows the stratification of patients with heart failure and the recognition of those who will have a better outcome.

References

1. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the framingham study. N Engl J Med 1971; 285: 1441-6.
2. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. N Engl J Med 2002; 347: 1397-402.
3. Muntwylwe J, Abetel G, Gruner C, Follath F. One-year mortality among unselected outpatients with heart failure. Eur Heart J 2002; 23: 1861-6.
4. Cowie MR, Mosterd A, Wood DA, et al. The epidemiology of heart failure. Eur Heart J 1997; 18: 208-25.
5. Kearney MT, Fox KAA, Lee AJ, et al. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. J Am Coll Cardiol 2002; 40: 1801-8.
6. McMurray JJV, Stewart S. The burden of heart failure. Eur Heart J 2002; 4 (suppl D): 50-8.
7. Wong PS, Davidsson GK, Timeyin J, et al. Heart failure in patients admitted to hospital mortality is still high. Eur J Intern Med 2002; 13: 304-10.
8. Jong P, Vowinckel E, Liu PP et al. Prognosis and determinants of survival in patients newly hospitalized for heart failure. A Population-Based Study. Arch Intern Med 2002; 162: 1689-94.
9. Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12220 index admissions in leicestershire 1993-2001. Heart 2003; 89: 615-20.
10. Baker DW, Einstadter D, Thomas C, Cebul RD. Mortality trends for 23505 medicare patients hospitalized with heart failure in northeast ohio, 1991 to 1997. Am Heart J 2003; 146: 258-64.
11. Canesin MF, Giorgi D, Oliveira Jr MT, et al. ambulatory blood pressure monitoring of patients with heart failure. A new prognosis marker. Arq Bras Cardiol 2002; 78: 83-9.
12. Del Carlo CH, Pereira-Barretto Ac, Cassaro-Strunz C, et al. Serial measure of cardiac troponin t levels for prediction of clinical events in decompensated heart failure. J Cardiac Fail 2004; 10: 43-8.
13. Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 999; 341: 709-17.
14. Packer M, Coats AJJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001; 344: 1651-8.
15. Mann DL. Heart failure as a progressive disease. In. Mann DL, ed. Heart Failure. A companion to Braunwald's Heart Disease. Philadelphia, Saunders, 2004: 123-8.
16. Cohn JN, Ferrari R, Sharpe N, et al. Cardiac remodeling-concepts and clinical implications: consensus paper from an international forum on cardiac remodeling. J Am Coll Cardiol 2000; 35: 569-82.
17. Böhm M, Kilter H, Kindermam M. Mechanism contributing to the progression of left ventricular dysfunction to the end-stage heart failure. Eur Heart J 2003; 5 (suppl I): 114-21.
18. Packer M, Lee WH, Kessler PD, et al. Role of neurohormonal mechanisms in determining survival in patients with severe chronic heart failure. Circulation 1987; 75 (suppl IV): IV 80-IV 92.
19. Brophy JM, Deslauriers G, Rouleau JL. Long-term prognosis of patients presenting to the emergency room with decompensated congestive heart failure. Can J cardiol 1994; 10: 543-7.
20. Vila Corta H, Mesquita ET, Cardoso R, et al. Emergency department predictors of survival in decompensated heart failure patients. Rev Port Cardiol 2003; 4: 495-507.
21. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol 2001; 38: 955-62.
22. Smith GL, Vaccarino V, Kosoborod M et al. Worsening renal function: what is a clinically meaningful change in creatinine during hospitalization with heart failure? J Cardiac Fail 2003; 9: 13- 25.