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Drug Treatment of Heart Failure: Assessment of Compliance with International Guidelines

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A B S T R A C T

Introduction: Recommendations are regularly updated and disseminated, but this is not sufficiently found in everyday practice. The aim of our study was to assess the quality of medical management of heart failure at the Military Hospital Avicenna of Marrakech according to the international guidelines.

Results: One hundred forty patients, mean age of 66 +/- 11,59 years, with a clear male predominance (70.2 %). heart failure with left ventricular systolic dysfunction accounted for (47.63 %). The prescription rate of the different drugs in heart failure patients was 65 % of patients taking a betablockers, 64 % for angiotensin-converting enzyme inhibitors (ACE), 51.8 % an anti-aldosterone 50 % a loop diuretic, 3.5 % Ivabradine and 12.3 % digoxin. 21 % of patients had a combination (ACE + BB) and 29 % a triple combination (IEC + BB + Anti-aldosterone). NYHA Class IV patients: 11.8 % were treated with the BB target dose; 7.4 % received the maximum recommended dose of ACE; 51.4 % were treated with anti-aldosterone; 54.4 % received a loop diuretic. Patients with severe LV dysfunction were 76 % on ACE, 68% on BB and 56 % on anti-aldosterone. Conclusion: In Morocco, despite limited resources, practitioners are trying to follow Western recommendations especially those of the European Society of Cardiology, the prescription rate of major drugs of heart failure is satisfactory.

Keywords: Heart failure - Guidelines - Medical management - Assessment.

INTRODUCTION

Heart failure (HF) is a major public health issue. Its prevalence in Europe ranges from 0.4% to 2% of the general European population and is 1% in France. The prevalence increases with age (1), and the extension of life expectancy increases the significance of this syndrome (2). The morbidity and mortality of HF surpass that of cancers (3). The median survival of a patient with HF is 5 years, but it is reduced in cases of progression to acute HF. The European Society of Cardiology and the French National Health Authority have clearly established and regularly updated guidelines for the management of HF. Based on large clinical trials, these guidelines highlight the beneficial effects of angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists. However, HF treatment remains too often suboptimal, with underutilization of modern drug therapies and/or prescriptions at too low doses. The aim of our study is to examine the drug treatment of chronic heart failure and to assess the degree of compliance with international guidelines among patients hospitalized in the cardiology department at Avicenne Military Hospital in Marrakech over a period of 4 years.

Patients and methods:

We conducted a retrospective descriptive single-center study over a period of 4 years, from August 2012 to September 2016, which included 114 patients hospitalized in the cardiology department at Avicenne Military Hospital in Marrakech for chronic heart failure, whether left-sided, right-sided, or global. We excluded from our study all patients under the age of 18, deceased patients, and incomplete records. Quantitative variables were described by specifying the sample size, mean, standard deviation, median, and extreme values. For qualitative and ordinal variables, the description included the sample size and the frequency of each modality. The number of missing data entries was also mentioned

Results:

Collection of clinical and paraclinical data: We collected data from 114 patients, of whom ¾ were between the ages of 50 and 79 (80%). The average age of the patients was 66 ± 11 years (ranging from 31 to 90 years), with a clear male predominance (70.2%). The number of patients with known diabetes was 43, representing 37.3%, all of whom had type 2 diabetes. The number of hypertensive patients was 49, representing 43%. Smoking was present in 14.9% of the patients, all of whom were men. Dyslipidemia was reported in 14.9% of the patients (n=17), with an average LDL cholesterol level of 1.57 mmol/L with a standard deviation of 0.35. Among women, 88.2% were postmenopausal. A total of 25.4% of the patients were obese (n=29), and 3

patients had a family history of coronary artery disease, representing 2.6%. Additionally, 41.2% (n=47) of the patients had a body mass index (BMI) > 25 kg/m². A total of 51.8% of the patients had between 2 and 3 prior hospitalizations for heart failure decompensation, while 36% had been hospitalized only once. The average duration of the last hospitalization was 6.38 days. Dyspnea was the main symptom, present in all patients, with 24.6% in NYHA Class III and 59.6% in NYHA Class IV. The average heart rate was 88 ± 19.58 beats per minute (33 to 180), and the average systolic blood pressure was 125 mmHg ± 22 (40 to 190).

Cardiac disorders were observed in 45.6% of patients (36% had atrial fibrillation, 9.6% had ventricular extrasystoles), myocardial ischemia in 31.6%, and conduction disorders in 18.5% (11.4% had left bundle branch block, 5.3% had right bundle branch block, and 1.8% had AV block). Left ventricular hypertrophy (LVH) was present in 11.4% of patients. **Echocardiography data** showed that the average left ventricular systolic ejection fraction was 45.86% ± 15 (10% to 80%), with 39.5% of patients showing good left ventricular systolic function. Left ventricular filling pressures were elevated in 22.8% of cases. **Biological data** revealed that BNP was measured in 72% of patients, with a positive result. Renal function was normal in 93.9% of the patients. The clinical and paraclinical characteristics of our population are summarized in Table I.

Etiologies and Factors of Heart Failure Decompensation: The main etiologies of heart failure were: valvular heart disease in 32 patients, representing 28.1% of cases, ischemic cardiomyopathy in 32 patients, dilated cardiomyopathy in 16 patients, representing 14%, and hypertensive cardiomyopathy in 6 patients, representing 5.3%. Table II presents the etiologies and triggering factors of heart failure in our patients.

Pharmacological Management: In terms of therapeutic management, all patients were placed on a low-sodium or sodium-free diet. Angiotensin-converting enzyme inhibitors (ACE inhibitors) were prescribed in 64% of the patients. Forty-seven patients received half of the maximum recommended dose of ACE inhibitors, representing 41.2%. Twenty patients received a quarter of the maximum recommended dose, representing 17.5%, while 6 patients received the full recommended dose, representing 5.3%. Ramipril was prescribed to 52.6% (n=60) of patients, trandolapril to 5.3% (n=6), while perindopril, captopril (2.6% each), and enalapril (0.9%) were less frequently prescribed. In our study, 6 patients were treated with ARBs (angiotensin II receptor blockers), representing 5.26%.

Beta-blockers were prescribed in 65% of cases. Bisoprolol was prescribed in 35.1% of cases, carvedilol in 24.6% (n=28), nebivolol in 4.4% (n=5), and atenolol in 1.8% (n=2) of patients. A total of 15.8% (n=18) of patients received the maximum recommended dose of beta-blockers, 34.2% (n=39) received half of the maximum recommended dose, and 15.8% (n=18) received a quarter of the maximum recommended dose. Of the patients who did not receive beta-blockers, 2 were bradycardic.

Aldosterone antagonists were prescribed in 51.8% (n=59) of patients, all of whom were treated with spironolactone. Among them, 38.6% (n=44) were on 25 mg/day of spironolactone, and 13.2% (n=15) were on 50 mg/day of spironolactone. Loop diuretics were prescribed in half of the patients (all were on furosemide; 28.1% were taking 40 mg/day and 12.3% were taking 80 mg/day).

The combination of ACE inhibitors and beta-blockers was found in 21% of the patients. The triple combination (ACE inhibitors + beta-blockers + aldosterone antagonists) was present in 29% of cases in our study. Ivabradine was prescribed to 4 patients (3.5%), and digoxin was prescribed to 12.3% (n=14) of patients. Table III summarizes the pharmacological management.

Evolution: The clinical evolution of the patients is summarized in Table IV. The average length of hospitalization was 6.38 ± 7.7 days, and the average follow-up duration was 9 ± 6.65 months. No in-hospital deaths were recorded during this period. Twenty-two patients were rehospitalized during this period. Follow-up difficulties were observed in 25.4% of the patients, related to treatment discontinuation, whether or not due to financial issues, failure to attend follow-up appointments, or loss to follow-up.

Pharmacological Management Based on Dyspnea Level (Figures 1, 2, and 3):

NYHA Class II Effort Dyspnea (3.5%) None of the patients in NYHA Class II were taking doses of 20 mg/day, 60 mg/day, 80 mg/day, or more than 100 mg/day of furosemide. Twenty-five percent (n=1) were taking 40 mg/day. Seventy-five percent (n=3) were treated with a beta-blocker (BB), and none of these patients received the maximum recommended dose of BB. Fifty percent (n=2) were treated with an ACE inhibitor (ACEi), and none of these patients received the maximum recommended dose of ACEi. Seventy-five percent (n=3) were treated with an aldosterone antagonist.

NYHA Class III Effort Dyspnea (24.6%) 3.6% (n=1) were taking a dose of 20 mg/day, 28.6% (n=8) were taking 40 mg/day, 10.3% (n=4) were taking 80 mg/day, and 3.6% (n=1) were taking a dose ≥ 100 mg/day of furosemide. None of the patients in NYHA Class III were taking a dose of 60 mg/day. Eighty-nine point three percent (n=25) were treated with a beta-blocker, and 28.6% (n=8) were treated with the maximum recommended dose of BB. Eighty-two percent (n=24) were treated with an ACE inhibitor, and 3.6% (n=1) of these patients received the maximum recommended dose of ACEi. Fifty-three point six percent (n=15) were treated with an aldosterone antagonist.

NYHA Class IV Effort Dyspnea (59.6%) 4.4% (n=3) were taking a dose of 20 mg/day, 32.4% (n=22) were taking 40 mg/day, 1.5% (n=1) were taking 60 mg/day, 20.3% (n=13) were taking 80 mg/day, and 6% (n=4) were taking a dose ≥ 100 mg/day. Sixty point four percent (n=41) were treated with a beta-blocker, and 11.8% (n=8) of these patients received the maximum recommended dose of BB. Fifty-eight point nine percent (n=40) were treated with an ACE inhibitor, and 7.4% (n=5) of these patients received the maximum recommended dose of ACEi. Fifty-one point four percent (n=35) were treated with an aldosterone antagonist.

Pharmacological Management Based on Left Ventricular Ejection Fraction (LVEF) (Figure 4):

In patients with severe left ventricular dysfunction, accounting for 21.9% of the total population: 76% (n=19) were treated with an ACE inhibitor (ACEi); 68% (n=17) were treated with a beta-blocker (BB); and 56% (n=14) were treated with an aldosterone antagonist.

In patients with moderate left ventricular dysfunction, accounting for 25.4% of the total population: 69% (n=20) were treated with an ACEi; 86.2% (n=25) were treated with a BB; and 69% (n=20) were treated with an aldosterone antagonist.

In patients with good left ventricular systolic function, accounting for 39.5% of the total population: 48.9% (n=22) were treated with an ACEi; 60% (n=27) were treated with a BB; and 40% (n=59) were treated with an aldosterone antagonist.

Discussion

Over the last twenty years, therapeutic approaches have evolved significantly. Treatment now focuses not only on symptomatic improvement but also on preventing symptom exacerbation, functional limitation related to heart failure, and reducing hospitalization rates and mortality.

The progression of heart failure (HF) is marked by episodes of worsening/remission depending on decompensating factors or self-aggravation. Its long-term prognosis is poor, with mortality potentially reaching 50% for patients in stage IV of the New York Heart Association (NYHA) classification. The advent of ACE inhibitors (ACEi), angiotensin II receptor antagonists (ARBs), and beta-blockers has improved survival and quality of life for patients, albeit at the cost of optimal treatment. These therapies are recommended as the foundational treatment for heart failure with reduced ejection fraction at all stages of the disease. The prescribed doses of beta-blockers and ACE inhibitors have increased, especially in diabetic patients, the elderly, and those in NYHA stage III. The proportion of patients receiving more than 50% of the target dose has also increased.

Adherence to guidelines is correlated with the number and duration of hospitalizations: the higher the adherence, the fewer and shorter the hospitalizations. Heart failure with reduced ejection fraction is the best codified in terms of treatment. It is recommended to start ACEi and beta-blockers as early as possible and to reach the target dose or the highest tolerated dose within the first six months. In our series, we closely adhered to these recommendations, comparing the prescription rate with those from other countries. The average prescription rate at discharge in England is 73% for ACEi alone, 85% for ACEi/ARB, and 82% for beta-blockers, excluding patients with contraindications to these medications. In our patients with left ventricular systolic dysfunction, ACE inhibitors were prescribed in 76%, beta-blockers in 68%, and aldosterone antagonists in 56% at the end of the follow-up. There was a progression in modifying treatment over time, with increasing doses for each class of therapy between hospital discharge and the consultation with the cardiologist (on average, 3 months later). The target dose was achieved in three times more patients (increasing from 5% to 15%), but this proportion remains insufficient. For the majority of them (56%), more than 50% of the target dose was prescribed.

There has been a significant and consistent increase in the prescription rate of ACE inhibitors and beta-blockers: from 62% and 37% in 2003 to 90.5% and 87.8% in 2014. The prescription rate for diuretics remained stable during this period (80%), while the rate for spironolactone increased from 31% to 42.7% in 2014. This indicates an improvement in the therapeutic management of heart failure patients, likely due to better awareness of international guidelines and the results of major therapeutic trials.

Most registries have found that only half of patients receive the recommended doses of ACE inhibitors. For beta-blockers, the proportion of patients receiving target doses has remained considerably low. This is consistent with the Euro Heart Failure Survey, where only 6% of patients eligible for the MERIT-HF trial received target doses of beta-blockers. The combination of diuretics, beta-blockers, and ACE inhibitors is also more frequently prescribed, increasing from 17.2% of treated patients in 2003 to 51% in 2007. The same trend is seen for the combination of ACE inhibitors and beta-blockers, used in 61% of cases in 2007 and 65% in 2009.

In our study, ACE inhibitors were prescribed to 64% of patients, which is consistent with several studies in the literature: CASE, IMPROVEMENT, and Maggioni et al. The efficacy of different ACE inhibitors in heart failure is generally similar, though it is less effective for captopril and enalapril. Table V summarizes the comparison of ACE inhibitor prescription rates with other studies. Beta-blockers are the second essential treatment for chronic heart failure and significantly reduce morbidity and mortality. In our study, beta-blockers were prescribed to 65% of patients.

Diuretics are recommended to reduce signs of congestion in patients with heart failure and reduced ejection fraction, but their effects on mortality have not been studied in randomized controlled trials. A Cochrane meta-analysis showed that, in patients with chronic heart failure, loop diuretics and thiazides seem to reduce the risk of death and worsening of heart failure compared to placebo. When compared to an active control, diuretics seem to improve exercise capacity (22). In our series, 38.6% of patients were on 25 mg/day of Aldactone and 13.2% were on 50 mg/day. (Table VII)

The combination of ACE inhibitors (ACEi) and beta-blockers was found in 61% of cases in the IMPACT-RECO study in 2009 (23) and in 21% of patients in our study, representing a 40% difference. Our results are similar to those of the IMPROVEMENT study in 2002, where the rate was 20% (Table VIII). The results of the SHIFT study (24) show that Ivabradine reduced the combined effect of mortality or hospitalization for heart failure in symptomatic patients with reduced ejection fraction or left ventricular ejection fraction < 35%, in sinus rhythm with a heart rate of at least 70 bpm, who had been hospitalized for heart failure in the previous 12 months, and were receiving a proven dose of beta-blockers (or the maximum tolerated dose) and an ACE inhibitor (or ARB). In our study, only 3.5% of patients were on Ivabradine.

Digoxin can be used in patients in sinus rhythm with symptomatic heart failure and reduced ejection fraction to reduce the risk of hospitalizations [95]. The prescription rate of recommended drugs (ACEi, beta-blockers, and anti-aldosterones) decreased as the NYHA class progressed. We also noted an

increase in the doses of loop diuretics as the NYHA class advanced. Based on these results, it seems that the more advanced the heart failure, the fewer the prescriptions for disease-modifying treatments, with a shift towards symptomatic treatment. This pattern is consistent with the 2005 MALHER Survey (23). The prescriptions of drugs in our series were similar between patients with systolic heart failure and those with heart failure with preserved ejection fraction.

The different components of medical treatment, either alone or in combination, including resynchronization, implantable defibrillator placement, and therapeutic education, are independent predictive factors for reduced mortality in heart failure (25).

Tables and figures

Table I: Clinical and Paraclinical Data

Parameters	Effectif (Pourcentage) N= 114
Age	66 +/- 11
Male sex	80 (70,2 %)
Cardiovascular Risk Factors	
Smoking	17 (14,9 %)
Diabetes	43 (37,3 %)
Dyslipidemia	17 (14,9 %)
Obesity	29 (25,4 %)
Hypertension (HTN)	49 (43 %)
Alcoholism	-
Average number of hospitalizations	
2 à 3	
Average hospitalization duration (Days)	
6,38	
Clinical Study	
Dyspnée II	04 (3,5 %)
Dyspnée III	28 (24,6 %)
Dyspnée IV	68 (59,6 %)
Global heart failure (HF)	50 (43,8 %)
Left-sided HF	30 (26,4 %)
Right-sided HF	20 (17,5 %)
Compensated HF	14 (12,3 %)
Systolic blood pressure (SBP)	125 mmhg +/- 22
Heart rate	88 +/- 19,58
Electrocardiogram	
Atrial fibrillation	41 (36 %)
Ventricular extrasystole	11 (9,6 %)
Signs of myocardial ischemia	36 (31,6 %)
Right bundle branch block (RBBB)	06 (5,3 %)

Left bundle branch block (LBBB)	13 (11,4 %)
Atrioventricular block (AV block)	02 (1,8 %)
Transthoracic echocardiography	
Elevated pulmonary artery pressures (PAP)	26 (22,8 %)
Left ventricular ejection fraction (LVEF)	45,86 % +/- 15
Normal LVEF	39,5%
Reduced LVEF	54 (47, 63 %)
Left ventricular hypertrophy (LVH)	26 (23 %)
Biology	
Elevated BNP	82 (72 %)
Normal renal function	106 (93 %)

Table II: Etiologies of Heart Failure and Causes of Decompensation

Parameters	Effectif (Pourcentage) N= 114
Etiologies	
Dilated cardiomyopathy	16 (14 %)
Valvular heart disease	32 (28 %)
Ischemic cardiomyopathy	32 (28 %)
Hypertensive cardiopathy	6 (5 %)
Unknown etiology	27 (23,7 %)
Cancer	01 (0,9 %)
Decompensation causes	
Diet deviation	20 (17,5 %)
Pulmonary infection	27 (23,6 %)
Hypertensive crisis	5 (4,4 %)
Ischemic episode	5 (4,4 %)
Arrhythmia	4 (3,5 %)
Unlabeled	52 (45,6 %)

Table III: Medication Management of Our Patients

Drugs	Effectif (Pourcentage) N= 114
ACE inhibitors	
Ramipril	60 (52,6%)
Trandolapril	06 (5,3%)
Perindopril	03 (2,6%)
Captopril	03 (2,6%)
Enalapril	01 (0,9%)
ARBs (Valsartan)	

06 (5,26 %)	
Beta-blockers	
Bisoprolol	40 (35,1 %)
Carvedilol	28 (24,6 %)
Nebivolol	05 (4,4 %)
Atenolol	02 (1,8 %)
Diuretics	
Spironolactone	59 (51,8 %)
Furosemide	57 (50 %)
Ivabradine	
04 (3,5 %)	
Digoxin	
14 (12,3 %)	
Drug combinations	
ACEI + BB	24 (21 %)
ACEI + BB + Anti-aldosterone	33 (29 %)

Table IV: Patient Evolution Under Treatment

Parameters	6 weeks	End of follow-up
FC	80 +/- 21,12	72 +/- 23,2
Systolic blood pressure (SBP)	131 +/- 30,24	128 +/- 29,3
Dyspnée I - II	82	87
Dyspnée III – IV	19	10
Réhospitalisation	-	22
Left ventricular ejection fraction (LVEF)	-	50,7 % +/- 20
Deaths	-	-

Table V: Prescription of ACE Inhibitors in Different Studies

Author or study, Year	ACEI prescription rate	Maximum recommended dose of ACEI	50% of maximum recommended ACEI dose
Etude de CASE, 2001	67%	NR	NR
Etude IMPROVEMENT, 2002	60%	NR	NR
Groote et al, 2007	71%	49%	NR
Etude FUTURE, 2012	82%	5%	37%
Maggioni et al, 2013	67%	29,3%	NR
Notre série, 2016	64%	5,3%	41,2%

Table VI: Prescription of Beta-Blockers in Different Studies

Auteur ou étude Année	Beta-blocker prescription rate	Maximum recommended beta-blocker dose	50% of maximum recommended beta-blocker dose
Etude IMPROVEMENT, 2002	60 %	NR	NR
Groote et al, 2007	65 %	18 %	47 %
Etude SHIFT , 2010	90 %	26 %	56 %
Etude FUTURE, 2012	74 %	5 %	56 %
Maggioni et al, 2013	88,9 %	17,5 %	NR
Notre série, 2016	65 %	15,8 %	34,2 %

Table VII: Prescription of Diuretics in Different Studies

Auteur ou Etude, Année	Loop diuretics prescription rate	Anti-aldosterone prescription rate
Etude sentinelle, 2002	61 %	21 %
Groote et al, 2007	83 %	35 %
FUTURE , 2012	86 %	29 %
Maggioni et al, 2013	NR	68,9 %
Notre série , 2016	50 %	51,8 %

Table VIII: Distribution by Double and Triple Combinations Prescription

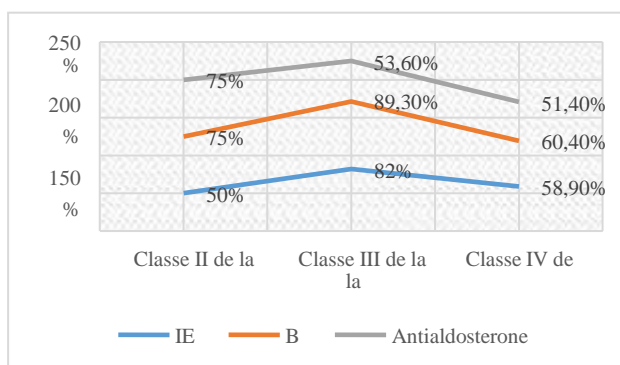| Auteur ou Etude, Année	Double combination (ACEI + BB)	Triple combination (ACEI + BB + Anti-aldosterone)
IMPROVEMENT, 2002	20%	35%
Etude sentinelle , 2002	14%	NR
Etude CNAM, 2008	NR	19%
IMPACT-RECO, 2009	61%	NR
Etude FUTURE,2012	52,8%	29%
Notre série , 2016	21%	28,9%

Figure1: Prescription Rates of Recommended Medications According to NYHA Class

Figure 2: Prescription Rates of Maximum Recommended Dose of ACE Inhibitors (IEC) and Beta-Blockers (BB) by NYHA Class
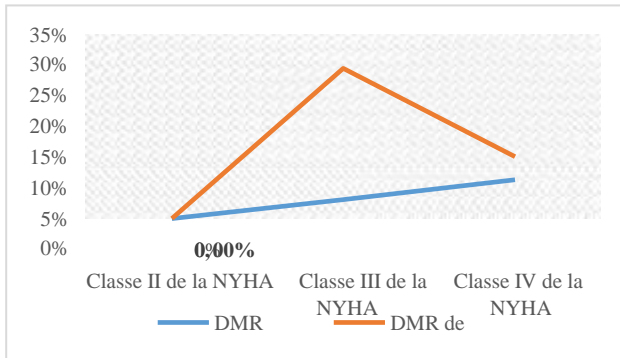

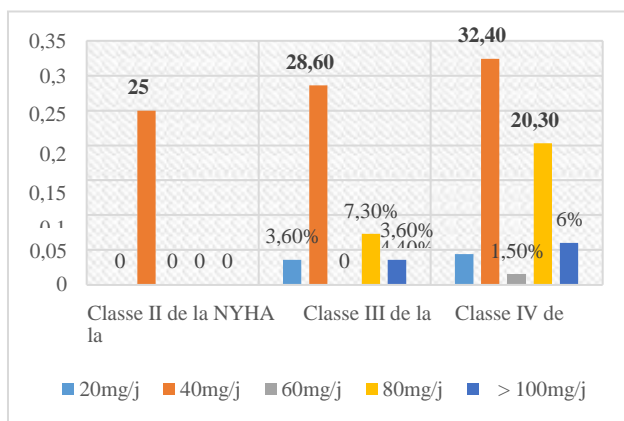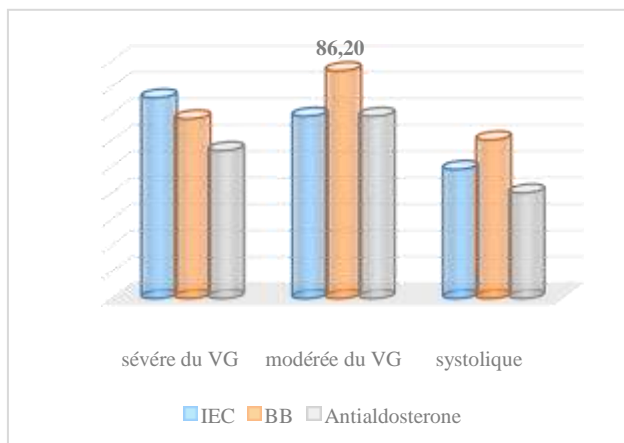**Figure 3:** Loop Diuretic Doses (in mg/day) Prescribed by NYHA Class

Figure 4: Prescription Rates of Recommended Medications Based on Left Ventricular Ejection Fraction (LVEF)

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