Renal Dysfunction and Anemia in Patients with Heart Failure with Reduced *versus* Normal Ejection Fraction

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Abstract

Background: The presence of anemia and renal dysfunction grants a bad prognosis for patients with heart failure and reduced ejection fraction (HFREF). The impact on patients with heart failure and normal ejection fraction (HFNEF) is not widely studied.

Objectives: To study the prevalence and the prognosis of anemia and renal dysfunction (RD) in patients with heart failure according to the type of ventricular dysfunction.

Methods: A total of 209 patients with chronic and stable heart failure were prospectively studied. Individuals with ejection fraction <50% were considered as HFREF patients. Anemia was defined, based on WHO criteria, as hemoglobin <13 g/dL for men and <12 g/dL for women. Renal function was calculated by means of the Simplified Modified Diet Renal Disease (sMDRD) formula. Hospitalizations, emergency admittances and obit by cardiac causes were considered as cardiac events.

Results: Ninety patients had HFREF and 119 had HFNEF. The glomerular filtration rate (GFR) was smaller in HFREF group (57.6 ± 66.2 *versus* 94.8 ± 36.6 mL/min/1.73m²; p=0.01). There was no difference in the prevalence of anemia between groups (23.3% *versus* 18.5%; p=0.34). Moderate to severe RD prevalence was higher in HFREF group (32.2% *versus* 16.8%; p=0.01). RD was the only factor associated with anemia that was independently associated with cardiac events (HR 2.52; 95%CI=1.27-5.2; p=0.01).

Conclusion: RD was less prevalent in HFNEF, while the prevalence of anemia did not differ between groups. RD was predictor of cardiac events independently on ejection fraction. (Arq Bras Cardiol 2010; 94(3):357-363)

Key words: Heart failure; anemia; renal insufficiency.

Introduction

Anemia and renal dysfunction (RD) are two prevalent comorbidities that worsen the development of heart failure[1-4]. Many physiopathological mechanisms have been proposed to explain the presence of anemia in patients with heart failure, like chronic diseases anemia[5], renal dysfunction, hemodilution[6], reduced production of eritropoetine by angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blockers (ARB)[7,8]. Independently on the mechanism, the presence of anemia grants bad prognosis[6].

RD is present in approximately 30% of patients with heart failure, and is also considered an important prognostic factor[9-11]. It unleashes inflammatory factors, hydrosalin overload and alterations on the metabolism of calcium and phosphorus, which may worsen the cardiac insufficiancy[12]. The renal dysfunction itself raises anemia, initiating a vicious circle called cardio-renal anemia syndrome by some authors, which has been associated with an increase in mortality rates[13-16]. Several studies assessed the influence of anemia and renal dysfunction in patients with heart failure and reduced ejection fraction (HFREF). However, these two variables interrelation has not been much studied in patients with heart failure and normal ejection fraction (HFNEF).

The objective of this study was to assess the prevalence and the prognostic impact of anemia and RD in patients with ambulatory chronic heart failure, according to the type of cardiac dysfunction.

Methods

Between December 2005 and February 2007, 230 patients with chronic heart failure were selected, as 114 were from a community attention program (family doctor) and 116 were from an ambulatory specialized in heart failure of a University Hospital. Inclusion criteria were Boston score higher than 8 points and patients older than 18 years old. Amongst the 230 patients, 21 were excluded because they did not fulfill the abovementioned Boston criteria, remaining 209 patients that were included in the study.

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At the first interview, all patients were submitted to complete anamnesis, physical exam, complete hemogram, biochemistry, thoracic X-ray, electrocardiogram and echocardiogram, as to determine the left ventricle ejection fraction (LVEF) by Simpson method. The participants who presented LVEF<50% were characterized as HFREF patients, and those with LVEF≥50% in the presence of any diastolic dysfunction degree determined by echocardiography were characterized as HFNEF patients. The stages of diastolic dysfunction were assessed according to the mitral flow pattern evaluated by conventional Doppler exam and characterized as stage I (normal), II (relaxing debt), III (pseudonormal) and IV (restrictive pattern).

Renal dysfunction and anemia definitions

The measurement of renal function was carried out by means of glomerular filtration rate (GFR) Simplified Modified Diet Renal Disease (sMDRD). For males, the formula 186 x serum creatinine$^{-1,154}$ x age$^{-0,203}$ was used; for black men: sMDRD x 1.212. For females, the formula sMDRD x 0.742 was used; for black women: sMDRD x 0.742 x 1.212). Later on, all patients were characterized according to their renal function: normal (GFR≥90 mL/min/1.73m^2), light renal dysfunction (GFR<90 and ≥60 mL/min/1.73m^2), moderate renal dysfunction (GFR<60 and ≥30 mL/min/1.73m^2), and severe renal dysfunction (GFR<30 mL/min/1.73m^2). Anemia was diagnosed based on WHO criteria, like hemoglobin rates <13g/dL for men and <12g/dL for women.

Cardiovascular events definition

Patients' inclusion was finished at the end of February 2007. A minimum 60-day follow-up was determined for the participants that were last included in this study. All patients were reassessed in April 2007, independently on their inclusion date, as to determine clinical outcomes in both groups. Mean follow-up was 12.4 ± 8 months. Non-planned hospitalizations, visits to the emergency room or obit due to cardiac events were considered to be outcomes.

Statistical analysis

The continuum variables were expressed as mean values and respective standard deviations and compared through Student's t-test or ANOVA. Categorical variables were expressed in absolute values and percentage, being compared by means of chi-square or Fisher's exact tests for samples with expected values inferior to 5. The variables that were statistically significant at univariate analysis were included in the multivariate analysis (logistic regression), as patients with and without anemia were compared. Multivariate analyses were carried out as to establish the independent value of variables with follow-up outcomes, by means of the analysis of Cox proportional hazards model. Anemia and RD were included in the multivariate models as categorical variables. GFR<6 mL/min/1.73m^2 was considered as presence of severe or moderate RD. The analysis was performed with the software Epi-Info 3.4 and SPSS version 11.0. Values of $p<0.05$ were considered statistically significant.

Bioethics

The present study was approved by the Ethics Committee of the hospital, in compliance with Helsinki declaration, under number 17906. All participants were informed about risks and benefits of the study and signed the informed consent.

Results

Basal characteristics

From 209 patients clinically diagnosed with heart failure, 90 (43.1%) had HFREF and 119 (56.9%) had HFNEF. Table 1 shows the patients' basal characteristics. As observed, HFREF patients presented higher prevalence of previous myocardium infarction, lower values of blood pressure and worse renal function. HFNEF patients were mainly women with higher levels of total cholesterol and higher prevalence of obesity and arterial hypertension. No significant differences were observed with regard to age or hemoglobin levels in both groups. The majority of patients were in functional class I or II (73%).

The medicines administered at the moment of inclusion in the study are presented in Table 2. Most of medicines used in heart failure treatment were more frequently prescribed for HFREF patients. HFNEF patients used more tiazidic diuretics. There was no significant difference in acetylsalicylic acid (ASA) prescription rate.

Renal dysfunction prevalence

Any RD (GFR<90 mL/min/1.73m^2) was present in 121 patients (57.9%), while moderate or severe RD were present in 23.3% of the whole sample. The classification of both groups' patients according to GFR is shown in Table 3. The prevalence of moderate or severe RD was twice higher among HFREF patients in comparison to HFNEF patients (32.2% *versus* 16.8%; p=0.01), as presented in Figure 1. In HFREF group, only 29 patients (32.2%) presented normal renal function *versus* 59 (49.6%) in HFNEF group (p=0.01). In HFNEF group, the distribution of creatinine values in stages II to IV of diastolic dysfunction, respectively, was 0.98 ± 0.26; 1.08 ± 0.3 and 1.26 ± 0.32 (p=0.02).

Anemia prevalence

The prevalence of anemia in the general studied population was 20.6%. There was no significant difference in the prevalence of anemia among HFREF patients in comparison to HFNEF patients (23.3% *versus* 18.5%; p=0.34). In HFNEF group, the distribution of hemoglobin in stages II to IV of diastolic dysfunction was 13.8 ± 1.03; 11.7 ± 1.12 and 10.9 ± 1.32 (p=0.04).

Factors associated with anemia

Table 4 shows a comparison between patients with and without anemia. Anemic patients were predominantly males, presented worse renal function and used diuretics more frequently in comparison to non-anemic patients. Through multivariate analysis, the only variable that was independently associated with anemia was presence of renal dysfunction, with Odds Ratio of 3.89 (95% confidence interval = 1.74 to 7.37; p=0.001). Ejection fraction was not associated with anemia.

Table 1 – comparison of the basal characteristics of patients from the both groups

Variables	HFREF (n=90)	HFNEF (n=119)	p-value
Male	52 (57.7%)	40 (33.6%)	0.001
Age (years old)	60.1 ± 13.22	61.7 ± 13.77	0.38
Functional class (NYHA)	2.2 ± 0.7	2.1 ± 0.6	0.88
Previous myocardial infarction	19 (21.1%)	13 (10.9%)	0.06
Arterial hypertension	64 (71.1%)	98 (82.4%)	0.07
Diabetes mellitus	24 (26.7%)	28 (23.5%)	0.35
Permanent atrial fibrillation	6 (6.7%)	3 (2.5%)	0.26
Obesity (BMI>30)	19 (21.1%)	42 (35.3%)	0.03
Cardiac frequency (bpm)	77 ± 15.3	79.4 ± 16.8	0.31
Systolic BP (mmHg)	131.1 ± 25.8	153.5 ± 28.3	<0.001
Diastolic BP (mmHg)	81 ± 14.7	88.9 ± 13.5	0.0001
Sodium (mEq/L)	139.4 ± 3.5	140.4 ± 3.1	0.08
Urea (mg/dL)	47.18 ± 32.34	35.92 ± 14.22	0.001
Creatinine (mg/dL)	1.19 ± 0.59	0.99 ± 0.38	0.004
GFR (mL/min/1.73m^2)	57.6 ± 66.2	94.8 ± 36.6	0.01
Hemoglobin (mg/dL)	13.5 ± 1.59	13.4 ± 1.53	0.58
Total cholesterol (mmol/L)	191.1 ± 56.8	209.5 ± 43.5	0.01
Ejection fraction (%)	42 ± 8.2	59 ± 7.3	<0.001

HFREF - heart failure with reduced ejection fraction; HFNEF – heart failure with normal ejection fraction; BMI - body mass index; BP - blood pressure; NYHA - New York Heart Association. GFR -glomerular filtration rate.

Table 2 – Main medications in use for both groups at the moment of inclusion in the study

Medication	HFREF (n=90)	HFNEF (n=119)	p-value
ACEI/ARB	85 (94.4%)	89 (74.8%)	0.001
Beta blockers	71 (78.8%)	58 (48.7%)	<0.0001
Espironolactone	32 (35.5%)	2 (1.6%)	<0.0001
Digoxine	50 (55.6%)	16 (13.4%)	<0.0001
Acetylsalicylic acid	31 (34.4%)	47 (39.5%)	0.57
Nitrate	22 (24.4%)	10 (8.4%)	0.001
Hidralazine	34 (37.7%)	33 (27.7%)	0.16
Diurectic	57 (63.3%)	34 (28.6%)	<0.0001
Tiazidic diuretic	17 (18.9%)	52 (43.7%)	0.0001

HFREF - cardiac insufficiency with reduced ejection fraction; HFNEF – heart failure with normal ejection fraction; ACEI - angiotensin converting enzyme inhibitor; ARB - angiotensin receptor blockers I.

Table 3 – Grades of renal dysfunction in both groups according to glomerular filtration rate established by sMDRD formula (mL/min/1.73m^2)

Renal function	HFREF (n=90)	HFNEF (n=119)	p-value
Normal (GFR>90)	29 (32.2%)	59 (49.6%)	0.01
Light dysfunction (GFR 90 to 60)	32 (35.5%)	40 (33.6%)	0.48
Moderate dysfunction (GFR 30 to 59)	26 (29%)	18 (15.1%)	0.024
Severe dysfunction (GFR<30)	3 (3.3%)	2 (1.7%)	0.7

HFREF - cardiac insufficiency with reduced ejection fraction; HFNEF – heart failure with normal ejection fraction; sMDRD - Simplified Modified Diet Renal Disease; GFR - glomerular filtration rate.

Prognostic value of RD and anemia

Seven patients (3.7%) died because of decompensate heart failure, and all of them were part of HFREF group (7.7% *versus* 0%; p=0.004). The presence of combinative outcomes was higher in HFREF group (34 [36.6%] versus 28 [24.3%]; p=0.037). In the univariate analysis, the main factor related to cardiovascular events were moderate or severe renal dysfunction, diabetes mellitus, previous myocardium infarction, being male and the presence of reduced ejection fraction. At the multivariate regression analysis by Cox proportional hazards model (Table 5), we observed that RD was independently correlated to cardiovascular events (*hazard ratio)*2.52 [95%CI = 1.27 to 5.2]; p=0.01), as well as reduced ejection fraction (HR=1.6 [95%CI=1.05 to 2.04], p=0.03). Anemia was not an event predictor, as we observed that the presence of outcomes in anemic versus non-anemic patients of 15 (34.8%) versus 47 (28.3%) patients, p=0.38. The events rate according to the presence of RD and anemia are shown in Figure 2.

Discussion

The relation between anemia and renal function in patients with heart failure has been reason for investigations. In the present study, we demonstrated that HFREF patients presented renal dysfunction more frequently than HFNEF patients, though the prevalence of anemia have been similar in both populations. Moreover, we demonstrated that RD was the only variable associated with anemia and that was an independent events predictor despite ejection fraction. Interestingly, HFNEF patients presented worse renal function and lower levels of hemoglobin in the most advanced stages of diastolic dysfunction.

Renal dysfunction prevalence

RD is frequent in patients with heart failure and is associated with worse prognosis in both ambulatory and hospital patients[1,16-23]. Advanced degrees of dysfunction are particularly frequent in decompensate patients. In ADHERE register[23], in which patients hospitalized due to decompensate

Table 4 – Comparison between anemic and non-anemic patients in the whole sample

Variable	With anemia (n=43)	Without anemia (n=166)	p-value
Male	26 (60.4%)	66 (39.7%)	0.023
Age (years old)	63 ± 14.3	59.9 ± 13.1	0.08
Functional class (NYHA)	2.2 ± 0.9	2.1 ± 0.9	0.31
Previous myocardial infarction	9 (21%)	23 (13.8%)	0.34
Arterial hypertension	34 (79%)	128 (77.1%)	0.62
Diabetes mellitus	14 (32.5%)	38 (22.9%)	0.26
Permanent atrial fibrillation	2 (4.6%)	7 (4.2%)	0.78
Hypotireoidism	2 (4.6%)	2 (1.2%)	0.37
BMI (kg/m^2)	27 ± 6.5	28.4 ± 5.5	0.22
Obesity	11 (25.6%)	50 (30%)	0.45
Cardiac frequency (bpm)	77 ± 15.6	78.7 ± 16.5	0.57
Systolic BP (mmHg)	139 ± 26.3	145 ± 30	0.24
Diastolic BP (mmHg)	82 ± 14.6	86.5 ± 14.5	0.068
Sodium (mEq/L)	139.6 ± 4	139.8 ± 3.4	0.81
Urea (mg/dL)	47.6 ± 31.5	38.4 ± 22	0.08
Creatinine (mg/dL)	1.3 ± 0.5	1 ± 0.45	0.0004
GFR (mL/min/1.73m^2)	65 ± 24.6	99 ± 55.5	0.0003
Severe or moderate RD	19 (44.2%)	30 (18%)	0.0006
Hemoglobin (mg/dL)	11.4 ± 1.03	13.9 ± 1.2	<0.0001
Total cholesterol (mmol/L)	179.2 ± 65.2	183.6 ± 74	0.75
Ejection fraction (%)	52.6 ± 18	54.7 ± 17.8	0.49
HFREF	19 (44.2%)	70 (42%)	0.86
ACEI/ARB use	39 (90.7%)	135 (81.3%)	0.21
Beta blockers use	29 (67.4%)	100 (60.2%)	0.34
Acetylsalicylic acid use	15 (34.8%)	63 (38%)	0.47
Diurectic	28 (65%)	63 (38%)	0.002
Tiazidic diuretic	13 (30.2%)	56 (33.7%)	0.82

ARB - angiotensin receptor blockers; RD - renal dysfunction; HFREF – heart failure with reduced ejection fraction; ACEI - angiotensin converting enzyme inhibitor; BMI - body mass index; NYHA - New York Heart Association; BP - blood pressure; GFR - glomerular filtration rate.

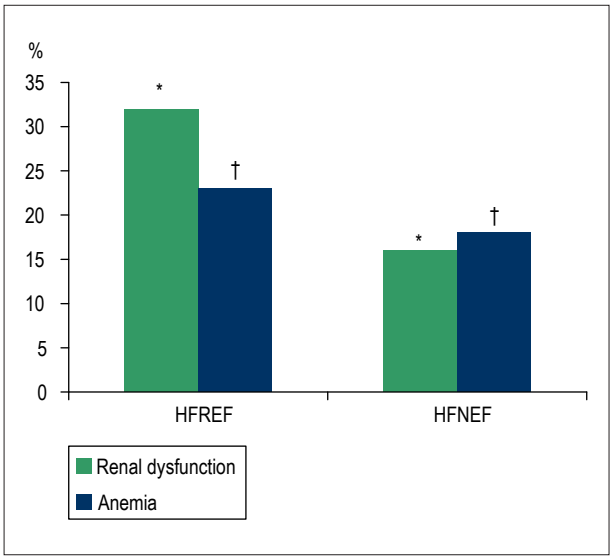

Figure 1 – *Prevalence of anemia and moderate or severe renal dysfunction in HFREF (n=90) and HFNEF (n=119) groups. *p=0.01; †p=0.34.*

Table 5 – Basal variables and its relation to cardiovascular events in analysis by Cox proportional hazard model. Significant variables are presented in boldface.

Variable	hazard ratio	95% confidence interval	p-value
Male	1.47	0.93 to 2.32	0.10
Age	1.02	0.96 to 1.04	0.60
Functional class (NYHA)	1.43	0.62 to 3.29	0.36
Previous myocardial infarction	1.36	0.72 to 2.47	0.30
Arterial hypertension	1.29	0.68 to 2.44	0.43
Diabetes mellitus	1.46	0.91 to 2.38	0.40
Permanent atrial fibrillation	1.30	0.74 to 2.30	0.36
Cardiac frequency	0.99	0.97 to 1.02	0.86
Systolic arterial pressure	0.97	0.95 to 1.02	0.24
Serum sodium	1.01	0.98 to 1.02	0.42
Moderate or severe RD	2.52	1.27 to 5.2	0.01
Anemia	1.23	0.76 to 1.98	0.39
Reduced ejection fraction	1.60	1.05 to 2.04	0.03

heart failure (with reduced or preserved LVEF) were included, 63.3% of patients presented GFR<60 mL/min/1.73m^2. In ambulatory patients, meta-analysis showed prevalence of any renal dysfunction in 51% of cases, and of severe or moderate dysfunction in 10%[1]. The prevalence of RD and its severity levels in the present study was similar to that found in the abovementioned meta-analysis.

When HFREF and HFNEF patients were compared, a higher prevalence for RD was found in the first group. After the stratification of patients in different stages according to GFR, we found that only the third part of HFREF patients presented normal renal function, as 32% presented moderate or severe renal dysfunction, against 16.8% in HFNEF group. This fact is consistent with what was observed by other authors[9,10,19].

It is important to emphasize that though it is more prevalent in HFREF patients, almost 20% of HFNEF patients presented moderate or severe endangering of renal function, which suggests that renal endangering in heart failure comprises other mechanisms besides low cardiac debt and bad renal perfusion typical of HFREF patients. Actually, it is known that the increase in central venous pressure, which leads to an increase in renal veins pressure, is one of the mechanisms involved in cardiac-renal syndrome and could explain its genesis in HFNEF patients[12,24].

Anemia prevalence

In the present study, we observed that 20% of patients presented anemia. Anemia prevalence in heart failure varies from study to study. It may be explained by the different diagnosis criteria and different clinical contexts. In a retrospective study with a hospital population, carried out in Brazil, it was found that 45% of the patients with heart failure presented anemia, as a cut of 12 g/dL was used independently on the sex[20]. In other Brazilian study, in which the cut was hemoglobin <13 g/dL for women and <12 g/dL for men, the prevalence of anemia reached 62.6%[25].

When the prevalence of anemia in HFREF and HFNEF was compared, there was no significant difference. Other authors have found similar results. In CHARM study[26], the prevalence of anemia in HFREF and HFNEF patients was 25% and 27%, respectively. In a Brazilian study carried out with patients with decompensate heart failure, the prevalence of anemia was significantly higher among HFNEF patients[27]. Our findings, however, confirm that the incidence of anemia in HFNEF patients is as frequent as in HFREF patients.

In a multivariate analysis, RD was the only factor that was independently associated with anemia. Though the objective of this study was not to establish the mechanisms involved in anemia genesis, these data suggest that RD plays an important role as anemia cause in patients with heart failure. Notwithstanding, as RD prevalence was lower in HFNEF patients, other mechanisms besides renal function may be implicated in this group.

Renal dysfunction and anemia as prognostic factors

In the current study, RD was independently associated with cardiovascular events, a fact that is well established in literature[1]. The prognostic impact of RD according to the type of ventricle dysfunction, however, is not yet well known. Although HFREF patients are considered to be more severe, some studies show that RD also has prognostic impact in HFNEF patients. Actually, it is described that reduced renal function may worsen the diastolic function[28]. In DIG study, there was a higher mortality rate related to RD among HFNEF patients in comparison to HFREF patients[19]. Grigorian et al[10], however, observed that heart failure prognostic was worse among patients with renal dysfunction independently on ejection fraction[10]. Silva et al[20], in a study carried out in Brazil, determined that the reduced ejection fraction of left ventricle and high levels of creatinine were associated with a higher mortality rate[20]. In our study, we found similar results, which shows that RD and reduced ejection fraction were independent event predictors. After analyzing all these studies, we concluded that renal function brings impact in heart failure development independently on LVEF.

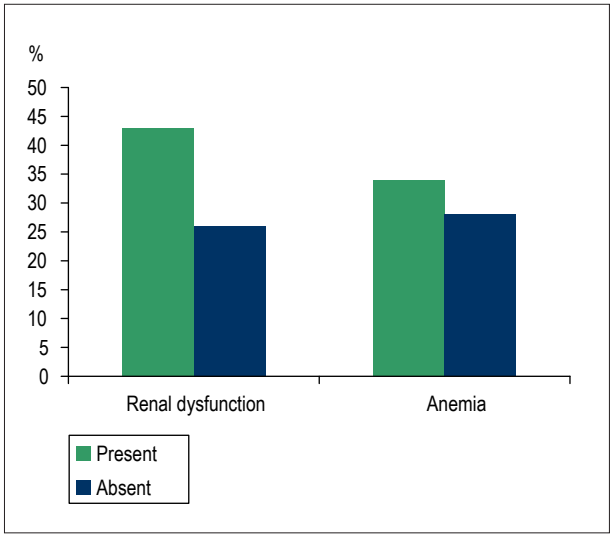

Figure 2 – Events rate in patients with moderate or severe renal dysfunction (GFR<60 mL/min/1.73m²) and anemia in the whole sample (n=209).

Anemia was not an event predictor in our sample, a result that is contrasting to those found by other authors. In CHARM study[26], anemia was predictor of events in both HFREF and HFNEF patients. Our relatively small sample may be an explanation for such findings. In fact, there were a larger number of events among anemic patients (34.8% *versus* 28.3%), but no statistical significance was reached. Based on prognostic data found in literature, the hypothesis of treating anemia in patients with heart failure became attractive. It is described that its correction in chronic renal patients delays and worsens renal function[29]. In patients with heart failure, the initial data were encouraging, showing that anemia correction ameliorated symptoms and functional capacity[20,30]. A recent study, however, did not show benefits in the increase of exercises tolerance, despite the tendency to mortality and heart failure hospitalizations reduction[31].

The present paper suggests that the renal function plays a much important role than anemia in the development of patients with stable chronic heart failure. Strategies on preservation of renal function are necessary and have been studied in literature in ambulatory and hospitalized patients[32-35], but there is no consensus on the benefits brought by these new drugs or procedures to renal function.

Limitations

No other mechanisms of anemia besides renal dysfunction were herein studied, so it is not possible to establish a cause or time relation between anemia and RD. Our relatively small sample may have contributed with type II error, mainly with regard to the prognostic value of anemia. The bigger proportion of HFNEF patients in relation to HFREF cannot be spread to general population with heart failure, for it is probably due to selection sloping, considering the greater

number of HFNEF patients referred from the primary attention program to this project.

Conclusions

The prevalence of renal dysfunction was higher among HFREF than in HFNEF patients. There was no difference in anemia prevalence in both groups. RD was the only factor associated with anemia in both groups, though it is not possible to establish a cause relation. RD and reduced ejection fraction of left ventricle were independently correlated to cardiovascular events in the presence or absence of anemia.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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