International Journal of Cardiology XX

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Red blood cell distribution width predicts new-onset anemia in heart failure patients ☆

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ARTICLE INFO

Article history:
Received 24 January 2011
Received in revised form 31 March 2011
Accepted 17 April 2011
Available online XX

Keywords:
Red blood cell distribution width
Anemia
Heart failure
Hemoglobin

ABSTRACT

Background: Hematologic abnormalities such as elevated red blood cell distribution width (RDW) as well as anemia are prognostically meaningful among heart failure (HF) patients. The inter-relationship between these hematologic abnormalities in HF is unclear, however. We therefore aimed to assess whether RDW is predicting changes in hemoglobin concentrations as well as onset of anemia.
Methods: 268 consecutive non-anemic patients with acutely decompensated HF (ADHF) were enrolled at hospital discharge and RDW was measured. At 6 month follow-up, change in hemoglobin as well as new-onset anemia was studied as a function of RDW at discharge.
Results: RDW at discharge correlated negatively with hemoglobin values at 6 months ($r = -0.220$; $p < 0.001$); a greater decrease in hemoglobin concentration occurred in those with higher values of RDW at discharge ($p = 0.004$), independently of baseline hemoglobin concentration and other risk factors. At 6 months, 54 patients (20%) developed new-onset anemia. RDW values at discharge were significantly higher among patients who developed new-onset anemia (15.1 ± 2.2 vs. 14.2 ± 1.4, $p = 0.005$). In integrated discrimination improvement analyses, the addition of RDW measurement improved the ability to predict new-onset anemia (IDI 0.0531, $p < 0.001$), beyond known risk factors as hemoglobin, renal function, age, diabetes mellitus, sex and HF symptom severity. In adjusted analyses, patients with RDW > 15% (derived from receiver operating characteristic analysis) had a tripling of the risk of new-onset anemia (OR = 3.1, 95% CI 1.5–5.1, $p = 0.002$).
Conclusion: Among non-anemic patients with ADHF, RDW measurement at the time of hospital discharge independently predicts lower hemoglobin concentrations and new-onset anemia over a 6-month follow up period.

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Anemia is common in patients with heart failure (HF) and most studies indicate a prevalence of more than 20% [1,2]. Among non-anemic patients with chronic HF, new-onset anemia increases over time from 14% at 1 year to 27% at 5 years [3]. In addition, new-onset anemia and decreasing in hemoglobin concentrations over time are associated with a higher risk of mortality [3–6]. However, the mechanisms underlying the development of anemia in HF patients are poorly known and a multifactorial interaction has been proposed [7]. Therefore, new-onset anemia represents an important issue with implications for the prognosis and the treatment of this disabling disease.

Red blood cell distribution width (RDW) is a numerical measure of the variability in size of circulating erythrocytes. Usually, red blood cells have a standard size, but disorders leading to ineffective erythropoiesis or situations of increased red blood cell destruction cause greater heterogeneity in red blood cell size, with a higher RDW value [8,9]. Recently, there has been growing interest in RDW, since higher RDW levels have been found to be associated with an increased risk of all-cause and cardiovascular mortality in patients with heart failure and other chronic diseases [10–13]. Among patients with chronic HF, Felker et al. identified RDW as a strong and independent predictor of mortality and adverse cardiovascular events [13]. Notably, our group has found an association between RDW and mortality in patients with acutely decompensated heart failure (ADHF) as well [14,15]. RDW may reflect neurohumoral activation, renal dysfunction, nutritional deficiencies, bone marrow dysfunction and chronic systemic inflammation; or could represent an integrative

☆ This study was supported by the national network of investigation on heart failure "REDINSCOR": Grant RD06/0003/0013, Instituto de Salud Carlos III, Ministry of Health, Madrid, Spain.
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doi:XX

measure of all these pathological processes occurring during the progression of HF [16–21].

Importantly, while anemia and RDW are both recognized prognostic factors in patients with HF, the specific interaction between these two measures is not known; specifically, while the risk associated with RDW appears to be independent of prevalent anemia [14,15], it is not known whether RDW merely marks patients at risk for future anemia. Accordingly, in the present study, we sought to evaluate whether RDW values in patients with ADHF predict future hematologic abnormalities, as a possible mechanistic insight to the prognostic value of RDW in these patients.

1. Methods

1.1. Study population and design

The study was approved by the local ethics committee, and informed consent was obtained from each patient at inclusion. The study population consisted of 288 consecutive non-anemic patients with ADHF (diagnosed clinically using current guidelines [19]) discharged from the department of cardiology from January 2002 to June 2004. Patients were eligible to be enrolled in this analysis if they were alive at 6 months after hospital discharge.

For the purposes of this analysis, anemia was defined using the World Health Organization criteria: hemoglobin level lower than 12 g/dL in women and 13 g/dL in men [20].

Patients were excluded from this study if they have had previous history of anemia, have received previous red blood cell transfusion or were on treatment for anemia, such as supplemental iron, folate or an erythropoiesis-stimulating agent.

Baseline clinical characteristics, biochemical and echocardiographic variables were prospectively recorded. Two-dimensional echocardiography was also performed in all subjects before hospital discharge. Left ventricular ejection fraction was measured using Simpson's biplane method.

Blood samples were collected for all patients when they had been stabilized on therapy and were ready to be discharged from hospital. After hospital discharge, patients received standard HF management as recommended by contemporary guidelines [19]. At 180 ± 14 days after discharge, patients were again seen, and a second blood sample was collected in all patients.

1.2. Biochemical measurements

Blood samples were extracted following an overnight fast and a 10-min rest in supine position. Samples were immediately processed for the determination of all biochemical parameters. RDW and hemoglobin were determined by the automated hematology analyzer XE-2100 (Sysmex, Kobe, Japan).

The normal range of RDW (%) in our laboratory was 11–16%. A modular analyzer (Roche Diagnostics, Manheim, Germany) was used for all biochemical measurements. Renal function was determined through the estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) using the abbreviated Modification of Diet in Renal Disease study equation [21].

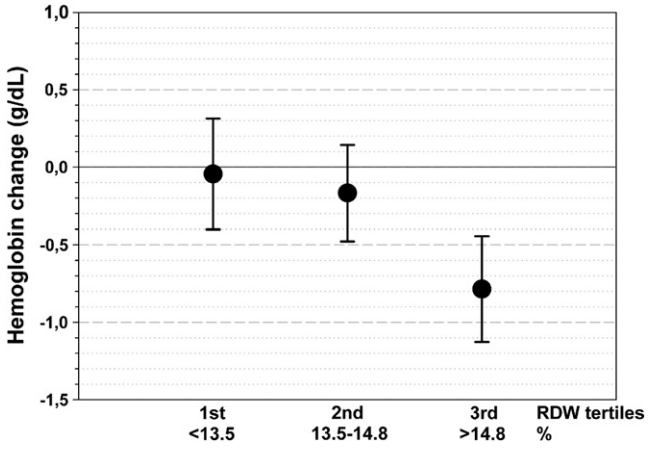

Fig. 1. Change in hemoglobin concentrations at 6 months as a function of RDW tertiles. A graded decrease in hemoglobin concentrations are noted with higher RDW values (p for trend = 0.004).

Table 1
Linear regression analysis for prediction of change in hemoglobin concentration at 6 months.

	Univariate		Multivariable	
	r	p value	β	p value
RDW,%	−0.220	<0.001	−0.211	<0.001
Hemoglobin, g/dL	−0.317	<0.001	−0.386	<0.001
Female	−0.178	0.003	0.180	0.002
NYHA class III–IV	−0.169	0.006	−0.126	0.031
eGFR, mL/min/1.73 m^2	0.118	0.053	0.077	0.205
Diabetes mellitus	−0.103	0.077	−0.108	0.057

GFR, glomerular filtration rate; NYHA, New York Heart Association; RDW, red blood cell distribution width.

Table 2
Baseline clinical characteristics according to new-onset anemia at 6 months.

Variable	New-onset anemia (n = 54)	No anemia (n = 214)	p value
Age, years	72 [64–78]	67 [55–76]	0.011
Male gender	36 (66%)	144 (67%)	0.931
Diabetes mellitus	24 (44%)	69 (32%)	0.092
Hypertension	38 (70%)	134 (62%)	0.208
Body mass index, kg/m^2	28.8 ± 4.18	28.7 ± 5.5	0.629
COPD	9 (16%)	50 (23%)	0.288
Prior stroke	5 (9%)	25 (11%)	0.614
NYHA III–IV	19 (36%)	59 (28%)	0.269
Prior heart failure	20 (37%)	59 (28%)	0.173
Ischemic etiology	23 (42%)	97 (45%)	0.718
Atrial fibrillation/flutter	19 (35%)	83 (39%)	0.626
Left bundle branch block	17 (31%)	62 (29%)	0.926
LVEF, %	35 [30–45]	38 [29–45]	0.671
LVED, mm	58 [51–63]	56 [50–61]	0.400
Left atrial size, mm	43 ± 8	47 ± 8	0.044
In-hospital inotropic use	2 (4%)	7 (3%)	0.960
Treatment at discharge			
Antiplatelet	33 (61%)	118 (55%)	0.429
Anticoagulation	17 (31%)	101 (37%)	0.438
Beta-blockers	28 (51%)	137 (64%)	0.110
ACE-I/ARB	46 (85%)	181 (84%)	0.912
Statins	25 (46%)	108 (50%)	0.584
Loop diuretics	42 (77%)	138 (64%)	0.102

Data are expressed as mean ± SD, median [interquartile range] and number (%). COPD is chronic obstructive pulmonary disease; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; LVED, left ventricular end-diastolic diameter; ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

1.3. Statistical analysis

For the purposes of the present analysis, both absolute change in hemoglobin (g/dL) as well as new-onset anemia at 6 months represented outcome measures.

Table 3
Baseline laboratory parameters according to anemic status at 6 months.

Variable	New-onset anemia (n = 54)	No anemia (n = 214)	p value
Hemoglobin, g/dL	13.8 [13.1–14.2]	14.2 [13.6–15.1]	<0.001
RDW,%	15.10 ± 2.20	14.18 ± 1.40	0.005
MCV, fL	89.8 [87.6–92.0]	90.8 [87.4–93.0]	0.304
MCH, pg/cell	30.2 ± 1.7	30.5 ± 1.9	0.126
Creatinine, mg/dL	1.00 [1.20–1.50]	1.13 [1.00–1.30]	0.134
eGFR, mL/min/1.73 m^2	59.84 ± 23.14	66.46 ± 20.55	0.040
Urea nitrogen, mg/dL	50 [37.50–74.75]	46 [35–59]	0.139
Sodium, mEq/L	137 [134–140]	138 [136–141]	0.166
Uric acid, mg/dL	7.5 [5.5–9.5]	7.3 [6.1–8.8]	0.868
Albumin, g/dL	3.65 ± 0.51	3.79 ± 0.48	0.146
Protein total, g/dL	6.59 ± 0.92	6.76 ± 0.74	0.268
C-reactive protein, mg/dL	1.55 [0.5–2.82]	1.25 [0.5–3]	0.453
Cholesterol, mg/dL	172 ± 43	172 ± 46	0.944

Data are expressed as mean + SD or median (quartiles). MCV, mean corpuscular volume; RDW, red blood cell distribution width; MCH, mean corpuscular hemoglobin; GFR, glomerular filtration rate; CRP, C-reactive protein.

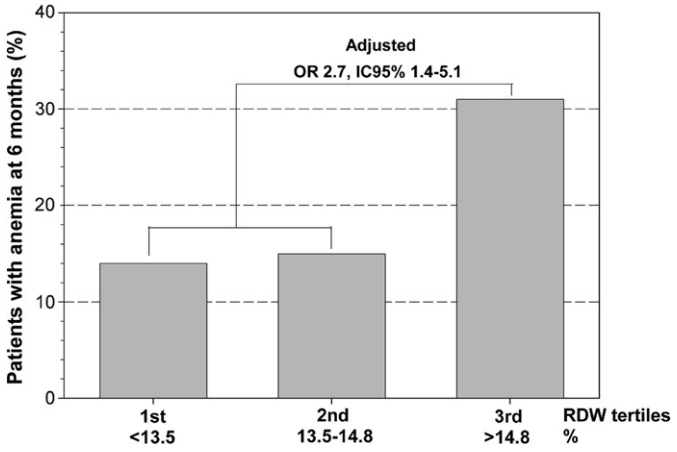

Fig. 2. New-onset anemia as a function of RDW tertiles. The highest RDW tertile (>14.8%) was associated with a higher risk of new-onset anemia than 1st and 2nd RDW tertiles.

All variables were tested for normal distribution using the Kolmogorov–Smirnov test. Continuous variables with normal distribution are expressed as mean ± standard deviation (SD), and those with skewed distribution as a median [interquartile range, (IQR)]. Baselines differences between anemic and non-anemic patients were assessed by Student's *t* test or Mann–Whitney *U* test for continuous variables, and the χ^2 test for categorical variables. Differences across RDW tertiles were tested using analysis of variance for hemoglobin values and the χ^2 test for new-onset anemia. Correlations were studied using Spearman's or Pearson's correlation, as appropriate. Single linear regression analysis was used to examine correlations between absolute hemoglobin change and each baseline variable. Multivariable linear regression was performed to determine variables independently associated with the absolute change in hemoglobin. Logistic regression analysis was used to evaluate the association between each baseline variable and the development of new-onset anemia. Multivariable logistic regression models were applied to determine the variables independently associated with the development of new-onset anemia. In both multivariable analyses, the variables included were those variables with $p<0.1$ in the univariable analysis. Receiver operating characteristic (ROC) curve analysis was constructed to determine the optimum cut-off points, which was identified as the point on the ROC curve that maximized both sensitivity and 1-specificity. Improvement in predictive accuracy by adding RDW was also evaluated by calculating integrated discrimination index [22]. Model performance for predicting anemia was evaluated by measures of calibration (Hosmer–Lemeshow statistic) and discrimination (C-index), both measures internally validated using the technique of bootstrap resampling. Confidence intervals (95% CI) are provided where appropriate. All probability values were 2-sided and a p-value of <0.05 was statistically significant. Statistical analysis was performed using SPSS v.15.0 software (SPSS Inc., Chicago, Illinois).

2. Results

2.1. Study population

The study population consisted of 268 non-anemic patients discharged from the hospital after admission due to ADHF. The median age of study subjects was 68 years, 67% were male and 44% had ischemic heart failure. Approximately one third had previous chronic heart failure, diabetes mellitus, advanced New York Heart Association (NYHA) functional class (III–IV) and/or atrial fibrillation. The median LVEF was 36% [30–45] and the mean eGFR was 65 ± 21 mL/min/1.73 m^2. At discharge or baseline, RDW values were 14.4 ± 1.6% and hemoglobin levels were 14.3 ± 1.1 g/dL.

2.1.1. Change in hemoglobin concentration at 6 months

At 6 months, the mean hemoglobin concentration was 13.92 ± 1.65 g/dL and the absolute change in hemoglobin concentration from baseline was −0.32 ± 1.63 g/dL. RDW values at discharge correlated negatively with both hemoglobin concentration at 6 months ($p<0.001$ $r_s=-0.260$) and the absolute hemoglobin change ($p<0.001$ $r_p=-0.220$). As showed in Fig. 1, tertile analysis of RDW values examined as a function of changes in hemoglobin concentration revealed that there was a greater decrease in hemoglobin at 6 months among non-anemic patients with elevated RDW values at discharge (p for trend = 0.004; Fig. 1). When we investigated the predictors of change in hemoglobin concentration by using linear regression analyses (Table 1); we found both RDW and hemoglobin at hospital discharge inversely correlated with change in hemoglobin levels between the two time points (β −0.211 and β −0.386 respectively, $p<0.001$ for both). No significant correlations were found with the mean corpuscular volume ($p=0.19$) and the mean corpuscular hemoglobin ($p=0.12$). Others independent predictors were female sex and advanced NYHA functional class.

2.1.2. RDW and new-onset anemia

A total of 54 patients (20%) developed new-onset anemia within 6 months after hospital discharge. Tables 2 and 3 show the clinical and laboratory characteristics at discharge, stratified by anemic status at 6 months. With respect to hematologic indices as a function of future anemia, concentrations of hemoglobin were significantly lower in those destined for future anemia, but were within normal limits (g/dL, 13.8 [13.1–14.2] vs. 14.2 [13.6–15.1], $p<0.001$). Mean corpuscular volumes and mean corpuscular hemoglobin were similar for both groups of patients.

Despite similar mean corpuscular volumes and mean corpuscular hemoglobin, among patients who developed future new-onset anemia, values of RDW at hospital discharge were significantly higher (15.1 ± 2.2 vs. 14.2 ± 1.4, $p=0.005$). Tertile analysis of RDW revealed that the highest tertile (>14.8%) was associated with a higher rate of new-onset anemia than the others 1st and 2nd tertile ($p=0.009$; Fig. 2). Baseline RDW percentage was associated with a higher risk of new-onset anemia (per%, OR 1.37, 95% CI 1.15–1.64, $p=0.001$). The results of logistic regression analysis for identifying baseline predictors of new-onset anemia are detailed in Table 4. Besides RDW, hemoglobin concentration, renal function (eGFR), age and diabetes mellitus were predictive. After entering in the multivariable analysis, both RDW and hemoglobin at baseline were the main determinants of a higher risk of new-onset anemia. Taking into account a model including hemoglobin, renal function, age, diabetes mellitus, sex and NYHA class, the addition of RDW was associated with a significant integrated discrimination improvement for the prediction of anemia (IDI = 0.053, $p<0.001$).

In the ROC analysis, RDW had an area under the curve of 0.62 for predicting future anemia (95% CI = 0.56–0.68, $p=0.007$) and the

Table 4
Logistic regression analysis for prediction of new-onset anemia at 6 months.

	Univariable		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
RDW,%	1.371 (1.146–1.641)	0.001	1.362 (1.114–1.665)	0.003
Hemoglobin, g/dL	0.609 (0.443–0.837)	0.002	0.609 (0.423–0.878)	0.008
Age, years	1.031 (1.007–1.056)	0.013	1.016 (0.988–1.045)	0.258
Diabetes	1.681 (0.915–3.089)	0.094	1.758 (0.904–3.421)	0.097
eGFR, mL/min/1.73 m^2	0.984 (0.980–0.999)	0.042	0.984 (0.965–1.004)	0.121

GFR, glomerular filtration rate; RDW, red blood cell distribution width.

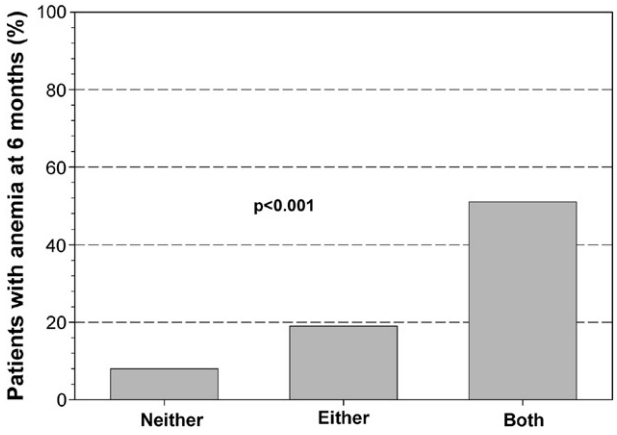

Fig. 3. New-onset anemia as a function of elevated RDW (≥15%) and low-normal hemoglobin (≤14 g/dL but > WHO anemia definition). The presence of neither (n = 90), either (n = 139) or both (n = 39) was associated with rising incidence of future anemia.

value of ≥15% was identified as the optimal cut-off point for prediction (sensitivity of 50%, specificity 75%, positive predictive value 33% and negative predictive value 86%). Patients with RDW at discharge above 15% had a tripling of the risk of new-onset anemia in adjusted analysis (OR 3.1, 95% CI 1.5–5.1, p = 0.002). ROC analysis for hemoglobin levels at discharge for predicting future anemia identified <14 g/dL as the optimal predictive value (sensitivity of 72%, specificity 57%, positive predictive value 30% and negative predictive value 89%). According to the presence of none, either or both predictors above or below the respective cut-off values, patients were classified as low, medium and high risk for new-onset anemia at 6 months (Fig. 3). This new ordinal variable demonstrated a good performance for prediction of new-onset anemia, as indicated by a C-index of 0.70 ± 0.039 (validated by bootstrapping of 200 samples), and adequate calibration (Hosmer–Lemeshow, p value of 0.35).

3. Discussion

The main finding of this work is that RDW emerges as an independent early marker of hemoglobin evolution and independently identified risk of new-onset anemia in patients discharged after an ADHF admission, providing predictive information for hematologic abnormalities beyond hemoglobin concentrations and other known risk factors.

Abnormalities of hematologic indices, including RDW and hemoglobin are prognostically meaningful in patients with HF, as has been described [1–6,13–15]. Indeed, anemia is a common comorbidity in HF patients, with a variable prevalence (15% to 70%) depending on the definition and sample selection, and when present in patients with HF, anemia has been consistently associated with an increased risk of mortality [5]. Beyond baseline anemia status, several studies have also evaluated the value of new-onset anemia or decrease in hemoglobin concentrations over time, showing that both conditions are associated with a subsequent higher risk for mortality in patients affected by HF [3,4]. Therefore, identification of those patients at higher risk for developing decreased hemoglobin or frank anemia is a relevant goal.

In this study, we examined RDW as predictor of reduced hemoglobin in mid-term follow-up, and RDW also served as a predictor of incident anemia in those with treated ADHF. We found in a non-anemic ADHF population, higher RDW values at discharge were associated with a decrease in hemoglobin levels and a higher risk of new-onset anemia, even after adjustment by simultaneous hemoglobin concentration and other baseline risk factors.

RDW has been previously related to ineffective erythropoiesis, but the mechanisms underlying this association have remained unclear. A strong association between RDW and inflammatory biomarkers was found in a large cohort of unselected adult outpatients (>35 years), as well as patients with inflammatory bowel disease [16,21]. In patients with chronic HF, Förhécz et al. recently reported multiple correlations between RDW and biomarkers of inflammation, ineffective erythropoiesis, undernutrition and renal function; after adjustment, the main correlates of RDW were soluble transferrin receptor and soluble tumor necrosis factor (sTNF) receptors, reflecting iron deficiency and inflammation as the main processes linked to high RDW [18]; these results were recently echoed in a large multicenter cohort of ambulatory patients with HF [19], although in other analyses, associations between inflammation, sTNF receptors, iron status and nutritional deficiencies were not found [15].

The association between RDW and outcome notwithstanding, the mechanistic reason for such adverse outcome remains somewhat unclear. The results of our work contribute to the field by identifying RDW as an independent early marker for reduction in hemoglobin and new-onset anemia in HF patients. We found that RDW values greater than 15% were indicative of a significantly higher risk of new-onset anemia, especially in those patients with hemoglobin concentration in the lower range of normality (<14 g/dL); thus, when used together RDW is additional to hemoglobin concentration for predicting incident anemia. Clinically, such a finding may have monitoring implications, as clinicians might be more able to identify those at highest risk for incident anemia by combining RDW and hemoglobin measures.

Besides a monitoring implication, our findings may also have therapeutic implications: while therapies for correcting anemia in the context of HF are under evaluation and may be of benefit [23,24], it is possible that at-risk HF patients might show superior outcome with earlier intervention for anemia, with a goal to prevent it, rather than responding to it [23,25,26] To this point, our work suggests that mechanisms leading to anemia could affect RDW at an earlier stage, before hemoglobin falls into the anemia range. In fact, Jankowska et al. have recently described a high prevalence (32%) of iron deficiency, absolute or functional, among non-anemic patients with chronic HF [27]. In this study, iron deficiency was related to poorer prognosis even in the absence of anemia [27]. Therefore RDW could be used in the design of further studies focused on therapeutic interventions aimed to correcting those meaningful related factors, as iron deficiency, before anemia is established.

Limitations of our study include the sample size and the fact that we do not provide information about erythropoietin levels, inflammatory measures other than C-reactive protein, neither iron nor nutritional indices. Nevertheless, the results of Förhécz et al. and Allen et al. suggest RDW as an integrative measure of activated processes related to inflammation and iron deficiency. These processes are well established as determinants of anemia in heart failure patients and characterize the pathophysiology link between RDW elevation and future new-onset anemia [7,28].

In conclusion, the present study supports RDW as an early marker of hemoglobin evolution in non-anemic patients with HF, predicting incident anemia at intermediate term follow up. As RDW is routinely reported as part of the complete blood count and its measurement requires almost no cost, this increases its potential applicability to clinical practice. Future studies are needed to define the mechanisms linking RDW, hemoglobin, and incident anemia in patients with HF.

Funding

This study was supported by the national network of investigation on heart failure "REDINSCOR": Grant RD06/0003/0013, Instituto de Salud Carlos III, Ministry of Health, Madrid, Spain. Dr. Januzzi is supported in part by the Balson Clinical Scholar fund.

Conflict of interest

None declared.

Acknowledgment

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [29].

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