Usefulness of Red Cells Distribution Width to Predict Worse Outcomes in Patients With Atrial Fibrillation

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Red cells distribution width (RDW) is a measure of red cell size variability, but little is known about the relation between RDW and outcomes in atrial fibrillation (AF).The aims of our study were to evaluate the association between RDW values, AF patients' profile and outcomes. Consecutive patients with ECG-confirmed AF were divided in 3 groups according to tertiles of RDW values (≤13.5%, 13.6% to 14.6%, >14.6%).We enrolled 457 patients, 61.9% males, median (interquartile range) age 74 (66 to 80). Both CHA_2DS_2-VASc and HAS-BLED scores increased progressively according to RDW tertiles. During follow-up, there was an increased risk for all-cause death and the composite end point in the highest RDW tertile (p <0.001 for both outcomes). On multivariate Cox regression analysis, the highest RDW tertile was independently associated with all-cause death (hazard ratio [HR] 3.23, 95% confidence interval [CI] 1.04 to 10.00) and the composite end point (HR 2.04, 95% CI 1.12 to 3.70). RDW as a continuous variable was also independently associated with all cause death and the composite outcome (HR 1.16, 95% CI 1.02 to 1.31 and HR 1.16, 95% CI 1.05 to 1.27, respectively). In conclusion, in a real-life AF population, RDW is associated with clinical factors indicating a worse profile and is independently associated with increased risks of all-cause death and other clinical events. **(Am J Cardiol 2019;124:1561−1567)**

Red cell distribution width (RDW) is a blood parameter that describes heterogeneity in red blood cell volume, usually used in anemia differential diagnosis.[1] More recently, RDW has emerged as a significant biomarker predictor of incident clinical conditions and events,[2] all-cause death[3] and cardiac, vascular and thrombotic conditions.[4−7]

Higher RDW values have been associated with an increased risk of incident atrial fibrillation (AF), whereby the incidence of new AF cases was progressively higher from the lowest to the highest RDW quartile, after a follow-up of 13 years.[8−10] In patients with paroxysmal or persistent AF, mean RDW was an independent predictor of late AF recurrence during follow-up.[11] Nonetheless, limited data are available on the relation between RDW and adverse outcomes in unselected "real world" AF patients. Limited data linking RDW and an increased risk of adverse outcomes in AF have been derived from highly selected cohorts.[12−14] The aims of our study were to evaluate factors associated with RDW values in a real-world AF patient cohort, and second, to investigate if RDW is an independent predictor of all-cause death and a composite end point.

Methods

From February 1st 2016 to August 31st 2017, we prospectively enrolled AF patients in 2 observational registries. The 2 registries, the first one promoted by the European Society of Cardiology (ESC)[15] and the second being a spontaneous, non-funded one, had similar design, being differentiated only by the time course, and were approved by the local ethics committee, and all the patients provided written informed consent. All patients were enrolled consecutively, with no overlap between the 2 registries. In both the registries, patients were eligible for inclusion being either inpatients and outpatients with age ≥18 years old and an electrocardiogram documenting an episode of AF in the 12 months before the enrollment. Patients could have been either in AF or in sinus rhythm at the time of enrollment and being seen for both AF and other admission reasons. Patients were excluded if they did not have any electrocardiographic proof of AF or had only atrial flutter as the only documented arrhythmia. No other exclusion criteria were applied to gather the studied population.

At enrollment, demographic, clinical, laboratory, and echocardiographic data, as well as pharmacological therapy

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were collected for each patient enrolled. Information about AF pattern, time since the first episode, symptoms and comorbidities were collected. After enrollment, all patients underwent a structured follow-up with clinical visits at 1-6-12 months and subsequently, every 6 months. All clinically relevant events were collected during the entire follow-up time. For patients not attending scheduled visits, telephone contact with patient or patient's relatives was established when possible, collecting follow-up information. In case of death, local community registries were examined in order to retrieve relevant information about the occurrence and causes of death.

According to baseline RDW values, patients were retrospectively subdivided according to RDW tertiles: (1) lowest tertile (T1): RDW ≤13.5%; (2) intermediate tertile (T2): RDW 13.6% to 14.6%; and (3) highest tertile (T3): RDW >14.6%.

AF was defined according to the more recently published ESC guidelines.[16] Anemia was defined for a hemoglobin value <10 g/dl. According to recommendations, creatinine clearance was calculated using the CKD-EPI equation and chronic kidney disease was defined as CKD-EPI <60 ml/min/1.73 m^2.[17] Valvular heart disease was defined as moderate-to-severe valvular disease, prosthetic heart valve(s) or heart valve surgical repair. Malignancy was defined by a history of previous or active cancer.

Left atrial dilation was categorized according to the American Society of Echocardiography and European Association of Cardiovascular Imaging 2015 guidelines; a left atrium was then defined severely abnormal when maximum indexed left atrial volume was >48 ml/m^2.[18] Heart failure (HF) was defined according to the typical clinical presentation at the time of clinical visit, also including in the same group patients with left ventricular ejection fraction less than or equal to 40%. Major bleeding was defined according to the International Society on Thrombosis and Hemostasis criteria.[19]

Thromboembolic risk at baseline was calculated according to CHA_2DS_2-VASc score (congestive HF, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74, and sex category [female]), whereas baseline bleeding risk was calculated according to HAS-BLED score (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, and drugs/alcohol).[20]

During follow-up, all concurrent clinical events were recorded. Study outcomes considered were all-cause death and a composite end point of all-cause death; hospitalization for thromboembolic events (both stroke and venous thromboembolic events); hospitalization for hemorrhagic events; and hospitalization for acute coronary syndrome.

Continuous variables were expressed as mean ± standard deviation (SD) when normally distributed or as median (interquartile range if not normally distributed according to Kolmogorov-Smirnov test, whereas categorical variables were reported as numbers and percentages.

To evaluate the clinical factors associated with RDW, a linear regression analysis was performed. First, a univariate analysis was performed with all the clinical variables available at baseline. Next, all variables with a $p < 0.10$ were included in the multivariate model.

Kaplan-Meier curves for cumulative survival for all-cause death and composite end point were built and RDW tertiles were compared according to the log-rank test. Cox regression analysis was performed to establish the independent predictors of all-cause death and composite end point. Two distinct models were computed (1) first using the categorized RDW tertiles, in which all other continuous variables were categorized according to clinical cut-offs; (2) second using continuous RDW, together with all other continuous variables. According to univariate analysis, all variables with a $p < 0.10$ were included in the multivariate one. In order to better analyze the impact of the various individual clinical factors, CHA_2DS_2-VASc and HAS-BLED scores were not entered in the regression models. To establish the relation between the 2 scores and RDW values, we exclusively performed a descriptive analysis and a univariate linear regression analysis.

To analyze the predictive ability of RDW, receiver operating curves (ROC) were fitted. According to the Youden Index the best fitting value was determined. A p value <0.05 was considered statistically significant. All analyses were performed using SPSS statistical software (version 18.0, Statistical Package for the Social Sciences, SPSS-PC Inc., Chicago, Illinois).

Results

A total of 457 patients were enrolled with 176 (38.5%) being inpatients from the cardiology ward.

AF patients were categorized according to the RDW tertiles, as follows: (1) 171 (37.4%) in the lowest tertile; (2) 141 (30.9%) in the intermediate tertile; (3) 145 (31.7%) in the highest tertile. Clinical characteristics of patients according to RDW tertiles were reported in Table 1. Patients were progressively older in relation to increasing tertiles. No difference was found in terms of oral anticoagulant therapy either at enrollment or at discharge across the RDW tertiles. A univariate linear regression analysis was first performed to identify the clinical factors associated with RDW values (Web Table 1). Several factors were identified at univariate analysis as associated with RDW, usually depicting both higher thromboembolic and bleeding risk (age, coronary artery disease, HF, peripheral artery disease, previous major bleeding, previous stroke/systemic embolism, history of malignancy, creatinine clearance, etc). Also some AF characteristics such as type of AF, AF duration and presence of AF at enrollment were associated with RDW (Web Table 1). On multivariate analysis history of malignancy and severe left atrium enlargement were directly associated with increasing RDW, with previous stroke/systemic embolism showing a borderline trend for the direct association ($p = 0.05$). Furthermore, hemoglobin levels were inversely associated with RDW values (Web Table 1). At baseline (Table 1), a progressively increasing CHA_2DS_2-VASc score and HAS-BLED score was found across the tertiles (both $p < 0.001$). The proportion with high bleeding risk (HAS-BLED ≥3) was progressively more prevalent ($p = 0.005$). Mean RDW increased progressively across CHA_2DS_2-VASc strata ($p < 0.001$) (Figure 1, Upper Panel), and the prevalence of the higher RDW tertile increased across the CHA_2DS_2-VASc strata (Web Figure 1). Similarly, progressively increasing mean RDW values were

Table 1
Baseline demographic, clinical and laboratory characteristics of patients enrolled in the study

Variable	Overall cohort (n = 457)	RDW tertiles			p
		Lowest (n = 171)	Intermediate (n = 141)	Highest (n = 145)	
Age, median (IQR) (*years)*	74 [66-80]	72 [64-78]	74 [66-81]	76 [69-83]	<0.001
Age ≥75 years	228 (49.9%)	72 (41.1%)	67 (45.5%)	89 (61.1%)	0.002
Women	176 (38.5%)	66 (38.6%)	60 (42.6%)	50 (34.5%)	0.374
Body mass index, median (IQR) (kg/m^2)	26 [23-29]	27 [23-29]	26 [24-29]	26 [24-29]	0.945
Hypertension	313 (68.5%)	112 (65.5%)	95 (67.4%)	106 (73.1%)	0.329
Diabetes mellitus	76 (16.6%)	16 (9.4%)	32 (22.7%)	28 (19.3%)	0.004
Dyslipidemia	190 (41.9%)	67 (39.4%)	59 (41.8%)	64 (44.8%)	0.634
Smoker	172 (37.7%)	61 (35.7%)	53 (37.6%)	58 (40.3%)	0.702
Coronary artery disease	128 (28.0%)	34 (19.9%)	41 (29.1%)	53 (36.6%)	0.004
Dilated cardiomyopathy	14 (3.1%)	9 (5.3%)	2 (1.4%)	3 (2.1%)	0.103
Heart failure	81 (17.7%)	27 (15.8%)	21 (14.9%)	33 (22.8%)	0.155
NYHA >2	34 (7.4%)	6 (3.5%)	6 (4.3%)	22 (15.2%)	<0.001
Valvular heart disease	62 (13.6%)	14 (8.2%)	17 (12.1%)	31 (21.4%)	0.002
Stroke/systemic embolism	61 (13.3%)	15 (8.8%)	22 (15.6%)	24 (16.6%)	0.082
Peripheral artery disease	72 (15.8%)	21 (12.3%)	24 (17.0%)	27 (18.6%)	0.269
Any bleeding	39 (8.5%)	11 (6.4%)	9 (6.4%)	19 (13.1%)	0.058
Major bleeding	15 (3.3%)	7 (4.1%)	2 (1.4%)	6 (4.1%)	0.328
Chronic obstructive pulmonary disease	36 (7.9%)	13 (7.6%)	8 (5.7%)	15 (10.3%)	0.337
Chronic kidney disease	131 (28.7%)	36 (21.1%)	33 (23.4%)	62 (42.8%)	<0.001
Malignancy	86 (18.9%)	24 (14.0%)	23 (16.4%)	39 (26.9%)	0.010
Liver disease	15 (3.3%)	6 (3.5%)	2 (1.4%)	7 (4.8%)	0.264
Type of atrial fibrillation					
First detected	56 (12.3%)	21 (12.3%)	18 (12.8%)	17 (11.7%)	0.010
Paroxysmal	68 (14.9%)	29 (17.0%)	22 (15.6%)	17 (11.7%)	
Persistent	149 (32.6%)	70 (40.9%)	42 (29.8%)	37 (25.5%)	
Permanent	184 (40.3%)	51 (29.8%)	59 (41.8%)	74 (51.0%)	
Atrial fibrillation at enrollment	270 (59.1%)	84 (49.1%)	83 (58.9%)	103 (71.0%)	<0.001
Atrial fibrillation history >1-month	357 (78.1%)	125 (73.1%)	110 (78.0%)	122 (84.1%)	0.061
Cardioversion procedures	190 (41.7%)	89 (52.0%)	54 (38.3%)	47 (32.6%)	0.001
CHA_2DS_2-VASc, median (IQR)	3 [2-5]	3 [2-4]	3 [2-5]	4 [3-5]	<0.001
CHA_2DS_2-VASc ≥1 (≥2 if female)	420 (91.9%)	153 (89.5%)	129 (91.5%)	138 (95.2%)	0.176
HAS-BLED, median (IQR)	1 [1-2]	1 [1-2]	1 [1-2]	2 [1-2]	<0.001
HAS-BLED ≥3	66 (14.4%)	16 (9.4%)	18 (12.8%)	32 (22.1%)	0.005
Hemoglobin, median (IQR) (g/dl)	13.6 (12.4-14.6)	14 (12.7-14.8)	13.9 (12.4-14.8)	13 (11.6-14.1)	<0.001
Anemia (hemoglobin <10 g/dl)	20 (4.4%)	1 (0.6%)	4 (2.8%)	15 (10.3%)	<0.001
White blood cells, median (IQR) ($10^3/\mu$l)	7.36 (5.90-8.85)	6.97 (5.71-8.46)	7.56 (6.32-9.06)	7.50 (5.89-9.10)	0.058
Platelets, median (IQR) ($10^3/\mu$l)	206 (172-249)	208 (174-248)	208 (174-264)	201 (169-239)	0.557
Hematocrit, median (IQR) (%)	40.8 (37.2-44.2)	41.2 (38.0-44.2)	41.2 (37.6-45.3)	39.1 (35.8-42.9)	0.001
CKD-EPI, median (IQR) (ml/min/1.73 m^2)	73.4 (56.7-86.5)	80.4 (63.7-91)	77.1 (61.8-86.3)	63.7 (46.2-79.7)	<0.001
Left ventricular ejection fraction, median (IQR)	55 (45-60)	59 (50-63)	55 (46-60)	55 (45-60)	0.008
Left ventricular ejection fraction <40%	71 (18.5%)	27 (18.5%)	17 (14.5%)	27 (22.5%)	0.288
Left ventricular end diastolic diameter, median (IQR) (mm)	51 (47-56)	50 (47-55)	51 (47-56)	53 (47-59)	0.385
Severe left atrium enlargement	164 (35.9%)	51 (29.8%)	49 (34.8%)	64 (34.8%)	0.029
Any anticoagulant at enrollment	334 (73.1%)	116 (67.8%)	110 (78%)	108 (74.5%)	0.118
Anticoagulant therapy at enrollment					0.157
No	123 (26.9%)	55 (32.2%)	31 (22%)	37 (25.5%)	
Vitamin K antagonist	109 (23.9%)	29 (17%)	39 (27.7%)	41 (28.3%)	
Nonvitamin K antagonist oral anticoagulant	187 (40.9%)	71 (41.5%)	59 (41.8%)	57 (39.3%)	
Heparin	38 (8.3%)	16 (9.4%)	12 (8.5%)	10 (6.9%)	
Any anticoagulant at discharge	411 (89.9%)	154 (90.1%)	126 (89.4%)	131 (90.3%)	0.960
Anticoagulant therapy at discharge					0.653
No	46 (10.1%)	17 (9.9%)	15 (10.6%)	14 (9.7%)	
Vitamin K antagonist;	107 (23.4%)	33 (19.3%)	36 (25.5%)	38 (26.2%)	
Nonvitamin K antagonist oral anticoagulant	285 (62.4%)	114 (66.7%)	86 (61%)	85 (58.6%)	
Heparin	19 (4.2%)	7 (4.1%)	4 (2.8%)	8 (5.5%)	
Any oral anticoagulant at discharge	392 (85.8%)	147 (86%)	122 (86.5%)	123 (84.8%)	0.915
Antiplatelet at discharge	94 (20.6%)	27 (15.8%)	32 (22.7%)	35 (24.1%)	0.141
Oral anticoagulant + antiplatelet at discharge	66 (14.4%)	22 (12.9%)	23 (16.3%)	21 (14.5%)	0.690
Antiarrhythmics	56 (12.3%)	31 (18.1%)	14 (9.9%)	11 (7.6%)	0.010

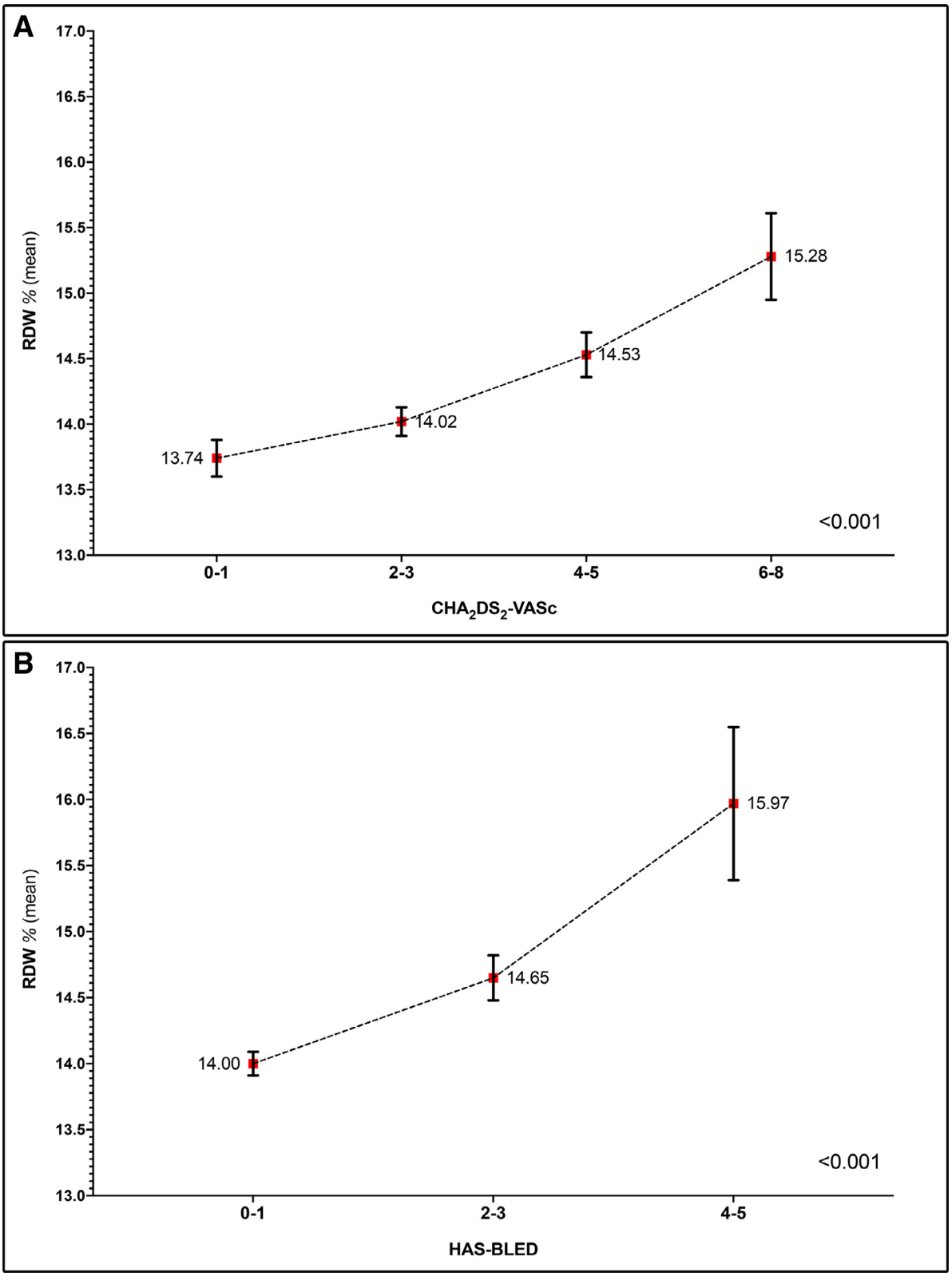

Figure 1. Red cells distribution width values according to CHA2DS2-VASc and HAS-BLED classes. RDW = red cells distribution width; markers stand for mean values and whiskers stand for standard error.

found across HAS-BLED strata (p <0.001) (Figure 1, Lower Panel), and the prevalence of the higher RDW tertile progressively increased across the HAS-BLED strata (Web Figure 2). On univariate linear regression analysis, both CHA_2DS_2-VASc (unstandardized Beta: 0.258, 95% confidence interval [CI] 0.163 to 0.352, t = 5.372, p <0.001) and

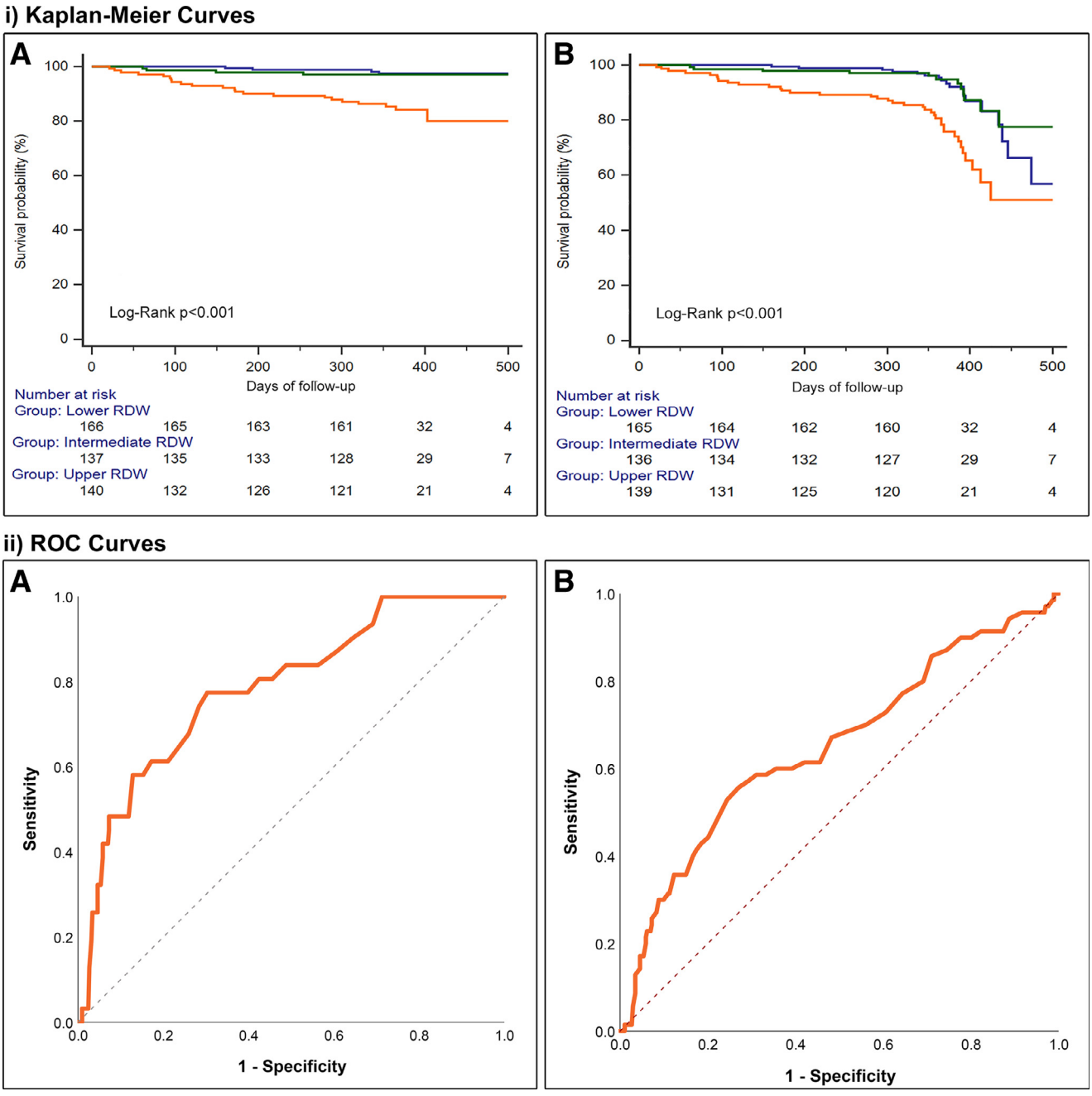

Figure 2. Follow-up analysis according to red cells distribution width. (*i*) Kaplan-Meier curves for outcomes according to red cells distribution width tertiles. RDW= red cells distribution width; A) All-Cause Death; B) Composite end point; Orange Line = Higher Tertile; Green Line = Intermediate Tertile; Blu Line = Lower Tertile. (*ii*) ROC curves for outcomes according to red cells distribution width. A) All-cause death; B) Composite end point.

HAS-BLED (unstandardized Beta: 0.406, 95% CI 0.229 to 0.582, t = 4.519, p <0.001) were directly associated with increasing RDW. Data about follow-up observation were available for 443 (96.9%) patients. After a median (interquartile range) follow-up of 370 (345 to 393) days, a total of 31 (6.1%) died and 70 (15.8%) sustained the composite end point (Web Table 1). Rate of all-cause death was significantly higher in the higher RDW tertile (16.4% vs 2.4% and 2.9% in lower and intermediate RDW tertile, respectively, p <0.001). The composite end point was higher in the higher RDW tertile (Web Table 1). Kaplan-Meier curves showed a significantly lower cumulative survival probability for both all-cause death and composite end point in the higher RDW tertile (Figure 2, Upper Panel). After univariate analysis, a Cox multivariate analysis was performed, both considering RDW tertiles and continuous values (Table 2). In the first model, after multiple adjustments, the highest RDW tertile was found to be associated with an increased risk for all-cause death (hazard ratio [HR] 3.23, 95% CI 1.04 to 10.00) and the composite end point (HR 2.04, 95% CI 1.12 to 3.70) (Table 2). In the second model, an increasing RDW was found associated with an increased risk of all-cause death (HR 1.16, 95% CI 1.02 to 1.31 for each percentage point increase) and composite end point (HR 1.16, 95% CI 1.05 to

Table 2
Multivariate Cox regression analysis for outcomes

With RDW tertiles	HR	95% CI	With RDW as continuous variable	HR	95% CI
All-cause death			All-cause death		
RDW tertiles			RDW (%)	1.16	1.02-1.31
Lowest (*ref.*)	–	–	Age (*years*)	1.07	1.01-1.31
Intermediate	0.99	0.24-4.07	CKD-EPI (per ml/min/1.73 m^2)	0.98	0.96-1.00
Highest	3.23	1.04-10.00	Valvular heart disease	2.78	1.27-6.09
Anemia	3.98	1.42-11.16	Peripheral artery disease	2.51	1.11-5.69
Peripheral artery disease	2.71	1.16-6.31			
Composite endpoint*			Composite endpoint*		
RDW tertiles			RDW (%)	1.16	1.05-1.27
Lowest (*ref.*)	–	–	CKD-EPI (per ml/min/1.73 m^2)	0.98	0.97-0.99
Intermediate	0.67	0.32-1.38	Valvular heart disease	2.15	1.25-3.69
Highest	2.04	1.12-3.70			
Valvular heart disease	2.14	1.23-3.74			

CI = confidence interval; HR = hazard ratio; for other abbreviations see Table 1.
* Composite of i) all-cause death; ii) hospitalization for thromboembolic events (both stroke and venous thromboembolic events); iii) hospitalization for haemorrhagic events; iv) hospitalization for acute coronary syndrome.

1.27) (Table 2). ROC curves (Figure 2, Lower Panel) showed that RDW had a good predictive ability for all-cause death (c-statistic: 0.786, 95% CI 0.703 to 0.869) (Figure 2, Lower Panel, A Panel). According to Youden Index, a RDW >14.5% had the highest sensitivity (77.4%) and specificity (69.7%) values for all-cause death prediction. RDW showed also a modest predictive ability for composite end point occurrence (c-statistic: 0.651, 95% CI 0.576 to 0.726). An RDW >14.6% had the higher sensitivity (55.7%) and specificity (73.0%) values for composite end point.

Discussion

In this study, derived from a contemporary, real-world cohort of AF patients, we found that several clinical factors indicating a worse clinical profile are associated with higher RDW values. Second, a significant association between baseline RDW values and a worse profile in terms of CHA_2DS_2-VASc and HAS-BLED scores was found. Third, higher RDW values were associated with an increased rate of all-cause death and of the composite end point of clinically relevant events. In literature the association between hemoglobin levels and RDW is clear and straightforward.[1,10] Nonetheless, several other conditions have been described as being associated with RDW, including cardiac disorders.[2,4] Our results show a relation between RDW and increased thromboembolic and bleeding risks. Several clinical factors, depicting both higher thrombotic and bleeding risk are involved (i.e., previous stroke, malignancy, impaired renal function, low hemoglobin, and severe left atrium enlargement) and a relation was also evident between CHA_2DS_2-VASc, HAS-BLED, and RDW values. Our results extend previous knowledge about the role of RDW in being associated with thrombotic and bleeding events. Indeed, anisocytosis (the morphological abnormality described by an increased RDW) can lead to an increased propensity for thrombotic and bleeding events and for the risk of venous thromboembolism a significant association with high RDW has been reported,[21,22] as well as an association between major bleeding events and high RDW.[23,24]

The association between RDW and risk of all-cause death in the general population has been established, also showing a significant "dose-response" relation.[3,25] Thus far, data about RDW and outcomes in AF patients have been limited.[12–14,26] Moreover, in many studies from literature on the relation between RDW and the outcome of AF patients some important clinical characteristics of AF patients were not analyzed, such as AF type,[14,26,27] or the analysis was limited to paroxysmal AF.[13]

In our study, we highlighted in a real-life cohort of unselected heterogeneous AF patients widely comparable with general AF observational cohorts,[15] a direct independent relation between RDW and the risk of all-cause death, as well as between RDW and the risk of a composite end point of relevant clinical events. Moreover, we analyzed a cohort of contemporary patients, whereas previous data referred to historical cohorts.[12–14,26] In the context of previously published results, our data extend the evidence of a prognostic utility of RDW in AF patients. This is also strengthened by the ROC curves and c-statistic values showing valuable predictive abilities for the outcomes considered.

In practice RDW could be used in refining baseline risk evaluation, in assessing AF patients' both thromboembolic and bleeding risk. According to the established relation between AF and inflammation and oxidative stress,[28,29] as well as the imbalance in inflammation and oxidative stress associated with increasing RDW,[30] RDW may act as a marker of increased risk for all major clinical events.

The study has several limitations due to its observational, even though prospective, nature. First, the small sample size and the reduced number of events partially limit the generalizability of our results. Further bias, despite the adjustments used in the statistical models, cannot be excluded. Lastly, the group with lower RDW was slightly more represented, but this is justified since the limit between the lower and intermediate tertiles was common to many patients.

In conclusion, in an unselected, real-life, AF population, RDW is associated with several clinical factors, in particular RDW is independently associated with increased risks of all-cause death and other clinical events.

Disclosures

VLM reports small speaker's fee for Bayer, Boehringer, Daiichi Sankyo, Mylan; MP reports consulting activity for Boehringer Ingelheim; GYHL has served as consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo, and as speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo; GB has received small speaker's fee from Medtronic, Boston, Boehringer, and Bayer, outside of the submitted work. The other authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.08.008.

1. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: a simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci* 2015;52:86–105.
2. Pilling LC, Atkins JL, Kuchel GA, Ferrucci L, Melzer D. Red cell distribution width and common disease onsets in 240,477 healthy volunteers followed for up to 9 years. *PLoS One* 2018;13:e0203504.
3. Patel KV, Ferrucci L, Ershler WB, Longo DL, Guralnik JM. Red blood cell distribution width and the risk of death in middle-aged and older adults. *Arch Intern Med* 2009;169:515–523.
4. Danese E, Lippi G, Montagnana M. Red blood cell distribution width and cardiovascular diseases. *J Thorac Dis* 2015;7:E402–E411.
5. Lippi G, Filippozzi L, Montagnana M, Salvagno GL, Franchini M, Guidi GC, Targher G. Clinical usefulness of measuring red blood cell distribution width on admission in patients with acute coronary syndromes. *Clin Chem Lab Med* 2009;47:353–357.
6. Montagnana M, Cervellin G, Meschi T, Lippi G. The role of red blood cell distribution width in cardiovascular and thrombotic disorders. *Clin Chem Lab Med* 2011;50:635–641.
7. Lippi G, Turcato G, Cervellin G, Sanchis-Gomar F. Red blood cell distribution width in heart failure: a narrative review. *World J Cardiol* 2018;10:6–14.
8. Güngör B, Özcan KS, İ Erdinler, Ekmekçi A, Alper AT, Osmonov D, Çalık N, Akyuz S, Toprak E, Yılmaz H, Yıldırım A, Bolca O. Elevated levels of RDW is associated with non-valvular atrial fibrillation. *J Thromb Thrombolysis* 2014;37:404–410.
9. Liu T, Shao Q, Miao S, Liu E, Xu G, Yuan R, Li G. Red cell distribution width as a novel, inexpensive marker for paroxysmal atrial fibrillation. *Int J Cardiol* 2014;171:e52–e53.
10. Adamsson Eryd S, Borné Y, Melander O, Persson M, Smith JG, Hedblad B, Engström G. Red blood cell distribution width is associated with incidence of atrial fibrillation. *J Intern Med* 2014;275:84–92.
11. Gurses KM, Yalcin MU, Kocyigit D, Evranos B, Ates AH, Yorgun H, Sahiner ML, Kaya EB, Ozer N, Oto MA, Aytemir K. Red blood cell distribution width predicts outcome of cryoballoon-based atrial fibrillation ablation. *J Interv Card Electrophysiol* 2015;42:51–58.
12. Wan H, Yang Y, Zhu J, Huang B, Wang J, Wu S, Shao X, Zhang H. The relationship between elevated red cell distribution width and long-term outcomes among patients with atrial fibrillation. *Clin Biochem* 2015;48:762–767.
13. Lee KH, Park HW, Cho JG, Yoon NS, Kim SS, Kim MR, Kim MC, Cho KH, Kim HK, Kim CH, Kim KH, Jun SJ, Kim WJ, Lee KJ, Jeong HC, Cho JY, Park KH, Sim D, Yoon HJ, Hong YJ, Kim JH, Ahn Y, Jeong MH, Park JC. Red cell distribution width as a novel predictor for clinical outcomes in patients with paroxysmal atrial fibrillation. *Europace* 2015;17(Suppl 2):ii83–ii88.
14. Saliba W, Barnett-Griness O, Rennert G. Red cell distribution width and all-cause mortality in patients with atrial fibrillation: a cohort study. *J Arrhythm* 2017;33:56–62.
15. Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, Potpara T, Dan GA, Kalarus Z, Diemberger I, Tavazzi L, Maggioni AP, Lip GYH, Investigators E-AL-TGR, Coordinators) SCN. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. *Europace* 2018;20:747–757.
16. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Group ESD. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J* 2016;37:2893–2962.
17. Boriani G, Savelieva I, Dan GA, Deharo JC, Ferro C, Israel CW, Lane DA, La Manna G, Morton J, Mitjans AM, Vos MA, Turakhia MP, Lip GY. Chronic kidney disease in patients with cardiac rhythm disturbances or implantable electrical devices: clinical significance and implications for decision making-a position paper of the European Heart Rhythm Association endorsed by the Heart Rhythm Society and the Asia Pacific Heart Rhythm Society. *Europace* 2015;17:1169–1196.
18. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1–39. e14.
19. Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, Lane DA, Levi M, Marin F, Palareti G, Kirchhof P, Collet JP, Rubboli A, Poli D, Camm J. reviewers: D. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. *Europace* 2011;13:723–746.
20. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH, Guidelines ECfP. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 2010;12:1360–1420.
21. Bucciarelli P, Maino A, Felicetta I, Abbattista M, Passamonti SM, Artoni A, Martinelli I. Association between red cell distribution width and risk of venous thromboembolism. *Thromb Res* 2015;136:590–594.
22. Zöller B, Melander O, Svensson P, Engström G. Red cell distribution width and risk for venous thromboembolism: a population-based cohort study. *Thromb Res* 2014;133:334–339.
23. Lee KR, Park SO, Kim SY, Hong DY, Kim JW, Baek KJ, Shin DH, Lee YH. Red cell distribution width as a novel marker for predicting high-risk from upper gastro-intestinal bleeding patients. *PLoS One* 2017;12:e0187158.
24. Fatemi O, Torguson R, Chen F, Ahmad S, Badr S, Satler LF, Pichard AD, Kleiman NS, Waksman R. Red cell distribution width as a bleeding predictor after percutaneous coronary intervention. *Am Heart J* 2013;166:104–109.
25. Patel KV, Semba RD, Ferrucci L, Newman AB, Fried LP, Wallace RB, Bandinelli S, Phillips CS, Yu B, Connelly S, Shlipak MG, Chaves PH, Launer LJ, Ershler WB, Harris TB, Longo DL, Guralnik JM. Red cell distribution width and mortality in older adults: a meta-analysis. *J Gerontol A Biol Sci Med Sci* 2010;65:258–265.
26. Saliba W, Barnett-Griness O, Elias M, Rennert G. The association between red cell distribution width and stroke in patients with atrial fibrillation. *Am J Med* 2015;128:e111–e198. 192.
27. Cha MJ, Lee HS, Kim HM, Jung JH, Choi EK, Oh S. Association between red cell distribution width and thromboembolic events in patients with atrial fibrillation. *Eur J Intern Med* 2017;46:41–46.
28. Siti HN, Kamisah Y, Kamsiah J. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). *Vascul Pharmacol* 2015;71:40–56.
29. Khan AA, Lip GYH. The prothrombotic state in atrial fibrillation: pathophysiological and management implications. *Cardiovasc Res* 2019;115:31–45.
30. Bujak K, Wasilewski J, Osadnik T, Jonczyk S, Kołodziejska A, Gierlotka M, Gąsior M. The prognostic role of red blood cell distribution width in coronary artery disease: a review of the pathophysiology. *Dis Markers* 2015;2015:824624.