

Red blood cell distribution width: A marker of anisocytosis potentially associated with atrial fibrillation

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Abstract

The incorporation of biomarkers in the actually used risk scores seem to be helpful for early identifying atrial fibrillation (AF) patients at higher risk. The aim of this critical review of the scientific literature is to investigate the potential clinical significance of red blood cell distribution width (RDW) in AF. A systematic electronic search was carried out to identify all articles describing an epidemiological association between RDW and AF in adult human populations. Data abstraction was conducted on a final number of 35 articles (13 cross-sectional, 12 prospective and 10 retrospective studies). The results of these epidemiological investigations were all virtually concordant to emphasize that an enhanced RDW value is not only a predictive factor and a marker of AF but its measurement may also be helpful for predicting the risk of developing many adverse complications in patients with AF, such as recurrence and duration of AF, hospitalization for heart failure, bleeding, left atrial thrombosis and stasis, thromboembolic events and mortality. AF patients with RDW values exceeding the local reference range may be more aggressively investigated and managed, in order to identify and attenuate the impact of possible underlying disorders causing both anisocytosis and AF.

Key words: Atrial fibrillation; Arrhythmia; Erythrocytes; Red blood cell distribution width

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Core tip: This critical review of the scientific literature aims to investigate the potential clinical significance of red blood cell distribution width (RDW) in atrial fibrillation (AF). We concluded that an enhanced RDW value is not only a predictive factor and a

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marker of AF but its measurement may also be helpful for predicting the risk of developing many adverse complications in patients with AF, such as recurrence and duration of AF, hospitalization for heart failure, bleeding, left atrial thrombosis and stasis, thromboembolic events and mortality.

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INTRODUCTION

Atrial fibrillation (AF) is the most common heart arrhythmia worldwide^[1]. Worryingly, AF is related to higher rates of stroke and mortality^[2]. Many risk scores and biological markers have been identified and developed to predict future AF events. Among the most frequently used and validated risk scores based on clinical parameters are CHADS2 [congestive heart failure, hypertension, age ≥ 75 years, diabetes, and stroke or transient ischemic attack (2 points)] and CHA2DS2-VASc [cardiac failure or dysfunction, hypertension, age 65-74 (1 point) or ≥ 75 years (2 points), diabetes mellitus, and stroke, TIA or thromboembolism (2 points) -vascular disease, and sex category (female)]^[3,4]. In addition, biomarkers may significantly contribute to obtain additional information regarding the risk that could influence the management of AF. Therefore, there is also an increasing interest in determining whether biomarkers themselves or in combination with clinical risk scores enhances prognostic accuracy for thromboembolism and mortality in AF patients^[5,6]. A wide range of biomarkers have been evaluated as predictors and/or prognostics, such as cardiac troponin I and T, natriuretic peptides, D-dimer, CRP, galectin-3, growth differentiation factor-15, among others^[1,5,7,8].

The incorporation of biomarkers in the actually used risk scores seem to be helpful for early identifying AF patients at higher risk (*i.e.*, enhanced risk for stroke, systemic embolic event or death), determining also their eligibility for anticoagulation and/or individualizing the most appropriate treatment strategy. Biomarkers are dynamic, and for that reason, they are also highly recommended to be included into management of patients with AF. Therefore, knowledge of new biomarkers related to AF may provide clinicians with more potential tools to quickly identify patients at higher risk of AF, attenuate its occurrence, improve its management, and decrease the risk of adverse events in patients with AF.

The search for hematological predictors of AF commenced in 1987 with the publication of a seminal study by Imataka *et al*^[9], who demonstrated that plasma volume and erythrocyte biology may be significantly perturbed in patients with AF. Ten years later, Takahashi *et al*^[10] first showed that erythrocyte size was altered both before and after the onset of chronic AF, thus leading to way to subsequent research aimed to define whether high heterogeneity of erythrocytes volumes, conventionally known as anisocytosis, may have clinical significance in AF.

Anisocytosis, defined as the presence of red blood cells (RBCs) with a broad heterogeneity of size and volume in peripheral blood, can be reliably estimated by the vast majority of modern hematological analyzers using different techniques, which provide a similar final index called RBC distribution width (RDW)^[11]. The RDW, which is not directly measured by the analyzers, but can be calculated as standard deviation (SD) of the mean corpuscular volume (MCV), and is usually expressed in absolute value (*i.e.*, RDW-SD) or as the coefficient of variation [*i.e.*, RDW-CV: (RDW-SD)/(MCV) $\times 100$]. Albeit largely instrument-dependent, the reference range of RDW-CV is usually comprised between 11.5%-14.5%^[12]. Increased RDW values, thus reflecting anisocytosis, may be due to many pathological conditions including congenital erythrocyte disorders (*i.e.*, β -thalassemia, sickle cell disease, hereditary spherocytosis), anemia (*e.g.*, due to iron, folate or vitamin B deficiencies), blood transfusions, some forms of hemolytic anemias, oxidative stress, inflammation and impaired renal function^[13-15]. Since the measurement of RDW has now become a useful part in diagnostic and prognostic assessment of many cardiovascular disorders such as acute coronary syndrome (ACS), heart failure and venous thromboembolism^[16,17], the aim of this critical review of the scientific literature is to investigate the potential

clinical significance of measuring RDW in patients with, or at risk of, AF.

SEARCH STRATEGY

A systematic electronic search was carried out using the three well-recognized and widely accessed scientific databases (*i.e.*, Medline interface PubMed, Web of Science and Scopus/EMBASE)^[18], with no date or language limits, to identify all articles which described the association between RDW and AF in epidemiological investigations involving human adult populations (cross-sectional, retrospective and prospective studies). The following keywords were used: "atrial fibrillation" AND "red blood cell distribution width" OR "RDW". The bibliographic references of selected items were also carefully checked for identifying additionally relevant documents. The title, abstract and full text of the articles were accurately reviewed by two authors (Lippi G and Cervellin G), and potential disagreement for inclusion was eventually resolved by the opinion of the third author. Although no meta-analysis was specified before the electronic search, since it was already clear that the studies could not be combined due to large heterogeneity in sample size, setting, and endpoints, it was our aim to explore whether this approach would still be possible after analyzing the data of the included studies.

SEARCH RESULTS

The search strategy retrieved a total number of 70 documents after elimination of replicates among the three scientific search platforms. Thirty five studies ought to be excluded since they did not match our search criteria (Figure 1). Data abstraction was hence conducted on a final number of 35 articles describing an epidemiological association between RDW and atrial fibrillation in adult populations, published between the years 2010 and 2019 (13 cross-sectional, 12 prospective and 10 retrospective studies) (Figure 1). It was finally decided that, as predictable, a meta-analysis was unfeasible due to large heterogeneity of the different studies (difference in nature, clinical settings, and endpoints, sample size from 49 to over 69000, no clear description of comorbidities in all studies, use of rather different RDW thresholds) (Table 1).

DESCRIPTION OF STUDIES OUTCOME

The first epidemiological investigation which could be identified in this critical literature review was published in 2010 by Horne and collaborators^[19]. In this prospective investigation, based on the Intermountain Heart Collaborative Study, a total number of 3927 patients undergoing coronary angiography were evaluated after 1 year and 30 d, with the aim of defining the frequency of incident cardiovascular disorders and complications (including AF). When patients were classified according to quintiles of RDW, the frequency of incident AF steadily increased from the lowest up to the highest (*i.e.*, from 2% to 14%) RDW quintiles. A highly significant trend towards increasing frequency of AF was consistently observed across RDW quintiles ($P < 0.001$).

Providência *et al*^[20] carried out a cross-sectional study including 247 patients presenting with symptomatic AF to the emergency department, who were then subjected to transesophageal echocardiography for ruling out left atrial appendage thrombus. Overall, left atrial appendage thrombus was evidenced in 21/247 (8.5%) of all AF patients, and its presence was found to be significantly more frequent in patients with RDW $\geq 15.0\%$ than in those with lower RDW values (14.8% *vs* 5.4%; $P = 0.013$).

Liu *et al*^[21] carried out another cross-sectional study including 133 patients with paroxysmal AF and 101 healthy controls. In multivariate logistic regression analysis, a RDW value $> 12.55\%$ was associated with a 63% enhanced risk of AF (odds ratio, 1.63; 95%CI: 1.01-2.61).

Ertaş *et al*^[22] retrospectively studied 132 patients undergoing nonemergency coronary artery bypass graft (CABG) surgery. A RDW $> 13.45\%$ was associated with a nearly 1.5-fold increased risk of new-onset AF (hazard ratio 1.48; 95%CI: 1.07-2.06). The same team of authors published another cross-control study, in which RDW was measured in 126 patients with non-valvular AF (39 with stroke and 87 without) and in 126 healthy controls with no AF^[23]. The value of RDW was found to be significantly higher in AF patients with (14.1% \pm 1.7%) or without stroke (14.3% \pm 1.8%) compared

Table 1 Summary and concise description of the studies

Authors	Study design	Study population	Endpoints	Outcome
Horne <i>et al</i> ^[19] , 2010	Prospective	3927 patients undergoing coronary angiography, endpoints collected at 30-d and 1-yr	Risk of developing cardiovascular diseases and complications	RDW positively correlated with the frequency of incident AF
Providência <i>et al</i> ^[20] , 2013	Cross-sectional	247 patients presenting with symptomatic AF	Association with outcomes of transesophageal echocardiography	High RDW associated with left atrial appendage thrombosis
Liu <i>et al</i> ^[21] , 2014	Cross-sectional	133 patients with paroxysmal AF and 101 healthy controls	Difference between groups	High RDW independently associated with AF
Ertas <i>et al</i> ^[22] , 2013	Retrospective	132 patients undergoing nonemergency CABG	Risk of new-onset AF until hospital discharge	RDW independently predicted the risk of developing AF
Ertas <i>et al</i> ^[23] , 2013	Cross-sectional	126 patients with AF (39 with stroke and 87 without) and 126 healthy controls	Difference among groups	RDW significantly higher in patients with AF than in controls, but non different between AF patients with or without stroke
Kurt <i>et al</i> ^[24] , 2014	Cross-sectional	320 patients with AF	Relationship with CHA2DS2-VASc score	High RDW independently associated with higher CHA2DS2-VASc score
Güngör <i>et al</i> ^[25] , 2014	Cross-sectional	117 patients with AF and 60 health control subjects	Difference among groups	RDW significantly higher in AF patients than in controls
Adamsson Eryd <i>et al</i> ^[26] , 2014	Prospective	27124 subjects free from AF at enrollment, followed-up for 13.6 yr	Risk of developing AF	RDW independently predicted the risk of developing AF
Sarikaya <i>et al</i> ^[27] , 2014	Cross-sectional	126 hypertensive patients (63 with AF and 63 without)	Difference among groups	High RDW significantly associated with AF
Gurses <i>et al</i> ^[28] , 2015	Prospective	299 AF patients undergoing cryoballoon-based ablation, followed-up for 24 mo	Outcome of cryoballoon-based ablation	RDW independently predicted the risk of recurrence and duration of AF
Korantzopoulos <i>et al</i> ^[29] , 2015	Prospective	109 patients undergoing elective cardiac surgery, followed-up throughout hospitalization	Risk of AF lasting > 5 min during hospitalization	RDW independently predicted the risk of postoperative AF
Wan <i>et al</i> ^[30] , 2015	Prospective	300 patients with AF followed-up for a median up period of 3.2 yr	Risk of adverse clinical outcomes	RDW independently predicted the risk of major adverse events and death
Lee <i>et al</i> ^[31] , 2015	Prospective	567 patients with newly diagnosed paroxysmal AF	Risk of adverse clinical outcomes	RDW independently predicted the risk of new-onset stroke, composite outcome and bleeding
Zhao <i>et al</i> ^[32] , 2015	Cross-sectional	90 AF patients, 24 with evidence of left atrial thrombus (<i>n</i> = 11) or left atrial spontaneous echo contrast (<i>n</i> = 13)	Evidence of left atrial thrombus or left atrial spontaneous echo contrast	RDW associated with presence of left atrial thrombus or left atrial spontaneous echo contrast
Aksu <i>et al</i> ^[33] , 2015	Prospective	49 patients with AF followed-up for 10 mo	Risk of AF recurrence	RDW predicted the risk of AF recurrence
Korantzopoulos <i>et al</i> ^[34] , 2016	Cross-sectional	101 patients with sick sinus syndrome (32 with AF)	Difference between groups	High RDW independently associated with AF
Karatas <i>et al</i> ^[35] , 2016	Retrospective	621 patients with myocardial infarction undergoing primary percutaneous coronary intervention	Risk of new-onset AF throughout hospitalization	RDW independently predicted the risk of new-onset AF
Yanagisawa <i>et al</i> ^[36] , 2016	Prospective	757 AF patients undergoing radiofrequency catheter ablation followed-up for 22 mo	Risk of adverse clinical outcomes	RDW independently predicted the risk of recurrent AF and major adverse events
Vizzard <i>et al</i> ^[37] , 2016	Retrospective	232 patients with stable heart failure 1 yr after enrolment	Risk of adverse events 1 yr after enrolment	RDW independently predicted the risk of cardiovascular death and/or hospitalization for heart failure

Geçmen <i>et al</i> ^[38] , 2016	Prospective	94 patients undergoing isolated on-pump CABG surgery followed-up until discharge from cardiovascular intensive care unit	Risk of postoperative AF	RDW independently predicted the risk postoperative AF
Zhang <i>et al</i> ^[39] , 2017	Prospective	172 patients with nonvalvular AF undergoing catheter ablation, followed-up for 3 mo	Risk of bleeding	RDW predicted the risk of bleeding events
Al-Kindi <i>et al</i> ^[40] , 2017	Retrospective	46720 patients with a diagnosis of HIV infection followed-up for development of cardiovascular complications	Risk of cardiovascular complications	RDW independently predicted the risk of AF
Liu <i>et al</i> ^[41] , 2017	Cross-sectional	99 patients with AF, categorized according to their CHADS2 and CHA2DS2-VASc scores	Association with risk of stroke	High RDW independently associated with higher CHADS2 and CHA2DS2-VASc scores
Saliba <i>et al</i> ^[42] , 2017	Retrospective	69412 patients with AF	Risk of death 2 yr after study entry	RDW independently predicted the risk of death; persistently increased RDW values at two time points stronger predictors of death than a single increased RDW value
Kaya <i>et al</i> ^[43] , 2017	Cross-sectional	619 patients with AF (325 with left atrial stasis and 294 without)	Association with left atrial stasis	High RDW independently associated with left atrial stasis
Cha <i>et al</i> ^[44] , 2017	Retrospective	5082 patients with AF	Risk of thromboembolic events during 5.2 yr	High peak RDW value during follow-up independently associated with the risk of thromboembolic events
Nam <i>et al</i> ^[45] , 2017	Cross-sectional	103 healthy control subjects and 117 patients with AF patients, 65 of whom with paroxysmal and 52 with persistent AF	Difference among groups	RDW values non significantly different between controls and all AF cases; RDW values significantly higher in patients with persistent than in those with paroxysmal AF
Wasilewski <i>et al</i> ^[46] , 2017	Retrospective	1734 patients with LVEF \leq 35% and without ACS	Risk of AF after 660 d	High RDW independently predicted the risk of AF
Kilicgedik <i>et al</i> ^[48] , 2018	Retrospective	358 patients after who underwent CABG surgery (57 with PSAF and 301 patients with non-PSAF)	Risk of AF after CABG surgery	High RDW was predictive of PSAF
Cerşit <i>et al</i> ^[47] , 2018	Retrospective	50 patients with AF and 62 age- and sex- matched controls, who had presented with ACS	Association and predictive value of RDW with AF in patients with ACS.	High RDW was associated with AF and had long-term predictive value
Ozsın <i>et al</i> ^[49] , 2018	Retrospective	93 patients who underwent off-pump CABG (24 patients with PSAF and 69 without PSAF)	Association and predictive value of RDW for development PSAF	Elevated RDW levels may be predictive of PSAF
Pilling <i>et al</i> ^[50] , 2018	Prospective	240477 healthy UK Biobank study volunteers aged 40 \pm 70 yr at baseline (follow-up \leq 9 yr)	Association of RDW with AF in healthy subjects.	High RDW was associated with AF and had long-term predictive value
Han <i>et al</i> ^[51] , 2019	Cross-sectional	303 patients with nonvalvular AF living at low altitude (3.5 m above the sea level) and high altitude (2260 m above the sea level).	Association of RDW with AF in subjects living at low and high altitude.	Elevated RDW levels were an independent risk marker for AF and is affected by type of AF and altitude
Jurin <i>et al</i> ^[52] , 2019	Prospective	579 patients with AF (non-permanent and permanent AF), with a median follow-up time of 21 mo	Association of RDW values with progression to permanent AF	RDW was independently associated with AF progression
Li <i>et al</i> ^[53] , 2019	Cross-sectional	106998 Chinese individuals	Relationship between RDW and AF	Elevated RDW is significantly related to higher prevalence of AF in a general Chinese population

AF: Atrial fibrillation; RDW: Red blood cell distribution width; LVEF: Left ventricular ejection fraction; CABG: Coronary artery bypass graft; ACS: Acute

coronary syndrome; PSFA: Post-surgery atrial fibrillation.

to the control population ($13.2\% \pm 0.9\%$), but its value did not differ among AF patients with or without stroke ($P > 0.05$).

Kurt *et al*^[24] measured RDW in 320 patients with AF and found that those with a higher CHA2DS2-VASc score had also significantly higher RDW values than those with a lower CHA2DS2-VASc score ($14.9\% \pm 2.7\%$ vs $13.6\% \pm 1.7\%$; $P < 0.001$). A highly significant correlation could be observed between RDW and CHA2DS2-VASc score ($r = 0.383$; $P < 0.001$). In multivariate analysis, a RDW value $> 14.05\%$ was associated with a 25% higher risk (odds ratio, 1.25; 95%CI: 1.11-1.42) of having high CHA2DS2-VASc score (*i.e.*, ≥ 2).

In an ensuing investigation, Güngör *et al*^[25] studied 117 patients with AF and 60 healthy control subjects, concluding that RDW values were significantly higher in AF cases than in controls (13.4% vs 12.6% ; $P = 0.01$). In multivariate regression analysis, a RDW $> 12.9\%$ was associated with a nearly 4-fold higher risk (odds ratio, 4.18; 95%CI: 2.15-8.15) of AF.

Adamsson Eryd *et al*^[26] carried out a large prospective study including 27124 subjects free from AF at enrollment, who were followed-up for a mean period of 13.6 years. Subjects in the highest quartile of RDW had a 33% enhanced risk (hazard ratio, 1.33; 95%CI: 1.16-1.53) of developing AF on follow-up compared to those in the lowest quartile. Moreover, each 1 SD increase of RDW value was associated with a 8% higher risk (hazard ratio, 1.08; 95%CI: 1.04-1.12) of incident AF.

Sarikaya *et al*^[27] studied 126 patients with hypertension (63 with AF and 63 without) and reported that RDW values were significantly higher in patients with AF than in those without ($15.1\% \pm 1.6\%$ vs $14.0\% \pm 1.1\%$; $P = 0.001$). In multivariate logistic regression analysis, a RDW value $> 14.2\%$ was found to be independently associated with 1.8-fold higher risk (odds ratio, 1.85; 95%CI: 1.22-2.79) of AF.

Gurses *et al*^[28] measured RDW in 299 patients with paroxysmal or persistent AF undergoing cryoballoon-based ablation, and who were then followed-up for a mean period of 24 mo. A RDW value $> 13.75\%$ was independently associated with both early (hazard ratio, 6.39; 95%CI: 3.41-11.97) and late (hazard ratio, 1.88; 95%CI: 1.41-2.50) recurrence of AF, enhanced left atrial diameter (hazard ratio, 3.09; 95%CI: 1.81-5.27), as well as with duration of AF (hazard ratio, 1.04; 95%CI: 1.01-1.07).

Korantzopoulos *et al*^[29] studied 109 patients undergoing elective cardiac surgery, who were then prospectively followed-up throughout hospitalization. In multivariate logistic regression analysis, a RDW $> 13.35\%$ was independently associated with a 46% higher risk (odds ratio, 1.46; 95%CI: 1.08-1.99) of developing postoperative AF during hospital stay.

Wan *et al*^[30] carried out a prospective study including 300 patients with AF who were followed-up at a median period of 3.2 years. Patients in the fourth quartile of RDW values had a 2.7-fold higher risk (hazard ratio, 2.70; 95%CI: 1.35-5.83) of major adverse events (all-cause mortality, ACS, stroke and major hemorrhage) and a 3.8-fold higher risk (hazard ratio, 3.83; 95%CI: 1.53-9.58) of death during follow-up.

Lee *et al*^[31] measured RDW values in 567 patients with newly diagnosed paroxysmal AF, who were followed-up for a median period of 4.8 years. In multivariate analysis, an increased RDW value (no indications provided on the cut-off used) was independently associated with 47% higher risk (hazard ratio, 1.47; 95%CI: 1.05-2.05) of new-onset stroke, 26% higher risk (hazard ratio, 1.26; 95%CI: 1.02-1.54) of composite outcome (mortality, new-onset stroke and hospitalization for heart failure), and 74% enhanced risk of bleeding (hazard ratio, 1.74; 95%CI: 1.28-2.36) throughout follow-up.

Zhao *et al*^[32] retrospectively analyzed a local echocardiology database for identifying all AF patients who underwent transesophageal echocardiography before catheter ablation or electrical cardioversion. The final study population consisted of 90 AF patients, 24 of whom had evidence of left atrial thrombus ($n = 11$) or left atrial spontaneous echo contrast ($n = 13$). The mean RDW value was found to be significantly higher in patients with these two complications than in those without ($13.0\% \pm 0.9\%$ vs $12.6\% \pm 0.8\%$; $P = 0.039$).

Aksu *et al*^[33] studied 49 patients with symptomatic paroxysmal AF who underwent cryoballoon ablation and were then followed-up for a mean period of 10 mo. Patients with AF recurrence on follow-up had significantly higher RDW values than those without ($16.1\% \pm 1.4\%$ vs $14.9\% \pm 0.5\%$; $P = 0.033$). Interestingly, the post-ablation RDW value remained almost unchanged in patients without recurrence of AF, but in those with AF recurrence the RDW significantly increased from $16.1\% \pm 1.4\%$ to $16.3\% \pm 2.4\%$ ($P < 0.05$).

In another study, Korantzopoulos *et al*^[34] measured RDW in 101 patients with sick

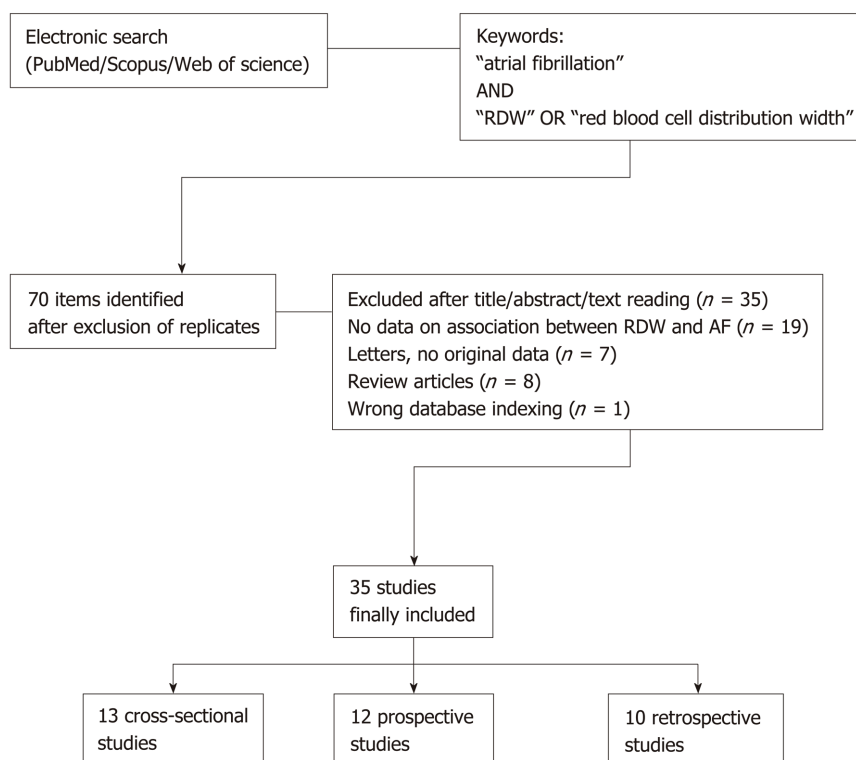


Figure 1 Search strategy and search results.

sinus syndrome (32 with AF), and found that a RDW value > 14.0% was independently associated with AF (odds ratio, 1.58; 95%CI: 1.06-2.85).

Karataş *et al*^[35] studied 621 patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, and who were followed-up throughout hospitalization. Patients with RDW > 13.4% had a 55% higher risk (odds ratio, 1.55; 95%CI: 1.20-2.01) of developing new-onset AF until hospital discharge.

Yanagisawa *et al*^[36] measured RDW in 757 patients undergoing radiofrequency catheter ablation for AF, who were then followed-up for a mean period of 22 mo. In multivariate linear regression analysis, a RDW value > 13.9% was associated with 20% higher risk (hazard ratio, 1.20; 95%CI: 1.01-1.40) of recurrent AF in patients with heart failure, whilst no significant association was found in those without heart failure. In patients with heart failure, a RDW value > 14.8% was also associated with 83% higher risk (hazard ratio, 1.83; 95%CI: 1.13-2.72) of developing major adverse events (all-cause mortality, hospitalization for heart failure and cerebral ischemia) during follow-up.

Vizzardi *et al*^[37] carried out a retrospective study including 232 patients with stable heart failure, whose clinical outcome was assessed 1 year after enrolment. In multivariate logistic regression analysis, a RDW value > 14.45% was independently associated with 3.9-fold enhanced risk (odds ratio, 3.89; 95%CI: 1.04-14.55) of cardiovascular death and/or hospitalization for heart failure in the first year after enrolment.

Geçmen *et al*^[38] carried out a prospective study including 94 patients undergoing isolated on-pump CABG surgery, who were followed-up until discharge from the cardiovascular intensive care unit. In univariate analysis, higher RDW values were associated with a 41% higher risk (odds ratio, 1.41; 95%CI: 1.01-1.96) of postoperative AF during cardiovascular intensive care unit stay. The cut-off value of RDW was unavailable in the publication and the association between RDW and postoperative AF was not tested in multivariate analysis.

Zhang *et al*^[39] measured RDW in 172 patients diagnosed with nonvalvular AF, who were followed up for 3 mo after catheter ablation. The overall number of bleeding events was found to be higher in patients with RDW values > 12.8% than in those with lower RDW values (11.8% vs 3.4%). Interestingly, the diagnostic efficiency (*i.e.*, area under the receiver operating characteristics curve; AUC) for predicting bleeding occurrence was higher for RDW than for activated partial thromboplastin time (0.737 vs 0.558; $P < 0.01$).

Al-Kindi *et al*^[40] used a large commercial database including electronic health

records of many participating hospitals, with the aim of identifying patients aged 18 years or older with a diagnosis of HIV and who had at least one available RDW measurement. The search allowed the extraction of a total number of 46720 records (mean or median follow-up period for development of cardiovascular complications is unavailable in the article). In these HIV patients, a RDW value > 14.5% was independently associated with a 96% higher risk (odds ratio, 1.96; 95%CI: 1.64-2.33) of incident AF.

Liu *et al*^[41] studied 99 patients with AF, divided into two groups according to their CHADS2 and CHA2DS2-VASc scores. In multivariate logistic regression analysis, a RDW value > 12.55% was found to be significantly associated with higher (≥ 2) CHADS2 score (odds ratio, 2.18; 95%CI: 1.14-3.22), whilst a RDW value > 12.75% was found to be significantly associated with higher (≥ 2) CHA2DS2-VASc score (odds ratio, 5.75; 95%CI: 3.70-7.79).

Saliba *et al*^[42] searched the electronic database for a large national health maintenance for identifying all patients diagnosed with AF in whom at least two RDW measurements were performed 1 year before study entry. Mortality data were retrospectively reviewed for up to 2 years after patients inclusion in the database. The electronic search identified a total of 69412 records. A RDW value > 14.5% was independently associated with a 49% increased risk (hazard ratio, 1.49; 95%CI, 1.43-1.55) of all-cause mortality during the follow-up period. More importantly, persistently increased RDW values at the two-time points were independently associated with an even higher risk of death during the same follow-up period (HR, 1.70; 95%CI: 1.61-1.79).

Kaya *et al*^[43] analyzed the data of 619 AF patients undergoing transesophageal echocardiography examination before cardioversion or AF ablation. In multivariate regression analysis, a RDW value > 13.7% was associated with a 67% increased risk of left atrial stasis (odds ratio, 1.67; 95%CI: 1.44-1.94).

Cha *et al*^[44] carried out a retrospective study including 5082 patients with non-valvular AF, who were followed-up for a mean period of 5.2 years. The RDW was measured several times during follow-up, allowing to identify nadir (*i.e.*, the lowest), peak (*i.e.*, the highest) and mean RDW values. Among the various RDW measures, a peak value $\geq 13.9\%$ was independently associated with a 66% enhanced risk (odds ratio, 1.66; 95%CI: 1.41-1.96) of thromboembolic events, including ischemic stroke and systemic embolism.

Nam *et al*^[45] carried out a cross-sectional study including 103 healthy control subjects and 117 patients with AF, 65 of whom with paroxysmal AF and 52 with persistent AF. Overall, no significant difference was found in mean RDW values between controls and AF cases ($13.4\% \pm 1.6\%$ vs $13.5\% \pm 0.8\%$; $P = 0.343$), whilst patients with persistent AF exhibited significantly higher mean RDW values than those with paroxysmal AF ($13.9\% \pm 0.9\%$ vs $13.3\% \pm 0.6\%$; $P < 0.05$).

Wasilewski *et al*^[46] performed a sub-analysis of the COMMIT-HF (COnteMporary Modalities In Treatment of Heart Failure) registry, including 1734 patients with left ventricular ejection fraction $\leq 35\%$ and without ACS at baseline, who were retrospectively investigated for a median period of 660 d. Patients in the highest RDW tertile had a more than double risk of developing AF on follow-up compared to those in the lowest tertile (44.1% vs 20.2% ; $P < 0.01$).

Cersit *et al*^[47] investigated the association between RDW and AF in 50 patients with and without AF after an ACS. RDW was significantly higher in patients with AF than the control group ($14.5\% \pm 2\%$ vs $12.6\% \pm 1\%$, $P < 0.001$). A RDW of > 11.7% also predicted AF (sensitivity 56% and specificity of 64%; AUC = 0.637, $P < 0.001$).

Kılıçgedik *et al*^[48] evaluated the RDW values in 358 patients who underwent CABG surgery [57 with post-surgery AF (PSAF) and 301 patients with non-PSAF]. Interestingly, RDW values were significantly higher in PSAF group. In multivariate analysis, RDW [OR:1.16 (95%CI: 1.0-1.36), $P = 0.05$] was found to be predictive for PSAF (68.4% sensitivity and 51.2% specificity; $P = 0.001$). Likewise, Ozsin *et al*^[49] analyzed the RDW levels in 93 patients who underwent off-pump CABG surgery. 24 patients developed PSAF while 69 did not. RDW was significantly correlated with PSAF and was also found to be predictive for PSAF (79.2% sensitivity and 65.2% specificity; $P = 0.001$).

Pilling *et al*^[50] analyzed the RDW levels in 240477 healthy volunteers (40 ± 70 at baseline) during a follow-up period of ≤ 9 years. Higher RDW levels ($\geq 15\%$ variation, $n = 6050$) was associated with AF (sHR 1.37: 1.21 to 1.55). RDW was also predictive of new-onset AF.

Han *et al*^[51] investigated the effects of low altitude (3.5 m above the sea level) and high altitude (2260 m above the sea level) on RDW levels of 303 patients with nonvalvular AF. RDW levels were higher in AF than control individuals ($P < 0.05$) and higher in persistent AF than paroxysmal AF ($P < 0.05$) in both low and high altitudes. Moreover, RDW, was independently associated with AF in low altitude

(RDW, OR: 1.687, 95%CI: 1.021–2.789; $P < 0.05$), whereas it was an independent predictor for AF (RDW, OR: 1.755, 95%CI: 1.179–2.613; $P < 0.05$) in high altitude.

Jurin *et al*^[52] recruited 579 patients with AF, 412 with non-permanent AF and 167 with permanent AF, and followed-up the patients with non-permanent AF during a median time of 21 mo. The main endpoint was progression of non-permanent AF to permanent AF. 109 patients (26.6%) progressed to permanent AF. Moreover, increased RDW levels showed a significant independent association with the progression to permanent AF (HR 1.19, 95%CI: 1.03–1.39, $P = 0.022$).

Finally, Li *et al*^[53] recently examined the relationship between RDW and AF in a general Chinese population (106998 subjects). The authors concluded that RDW was significantly related to a higher prevalence of AF; the OR (95%CI) of AF for increasing tertiles of RDW were 1.00 (reference), 1.08 (0.69, 1.67), and 2.65 (1.75, 4.07) (P for trend < 0.0001), respectively.

Taken together, the results of these epidemiological studies, as well as results from two systematic reviews and meta-analysis recently published^[54,55], are all virtually concordant to emphasize that an enhanced RDW value not only is a predictive factor and a marker of AF but its measurement may also be helpful for predicting the risk of developing many adverse complications in patients with AF, such as recurrence and duration of AF, hospitalization for heart failure, bleeding, left atrial thrombosis and stasis, thromboembolic events (including new-onset stroke) and mortality.

ANISOCYTOSIS IN ATRIAL FIBRILLATION: ACTIVE PLAYER OR BYSTANDER?

There are at least two biological explanations which can be brought for justifying the strong epidemiological association observed between anisocytosis and AF, either of which is plausible (Figure 2).

The first and rather predictable scenario is that the same causative factors for AF may also impair erythropoiesis, and thereby the observation of an increased RDW value may only be a coincident epiphenomenon in AF^[56]. For example, a high RDW value is commonplace in patients with recent blood transfusions or severe anemia^[13], and both RBC transfusion^[57] and anemia^[58] are associated with an excess incidence of AF, as consequence of onset of heart failure and impairment of renal function. Inflammation is probably the most frequent cause of anisocytosis^[59], but its contribution to the pathogenesis of AF is now almost unquestionable, since many inflammatory cytokines are known to impair atrial electrophysiology and structure^[60]. Oxidative stress is another important inducer of anisocytosis^[61], whilst the oxidation of myofibrillar protein and cardiomyocyte membrane lipids is also a well-recognized mechanism leading to AF^[62]. Finally, it is now clearly acknowledged that renal diseases may generate a kaleidoscope of inflammatory, neurohumoral, metabolic and hemodynamic stresses to the heart^[63], whilst impaired erythropoiesis and anisocytosis are also commonplace in patients with impaired renal function, mainly due to impaired erythropoietin production^[13] (Figure 2).

On the other hand, a support to the thesis that anisocytosis not only may be an innocent bystander in AF, but may also trigger, or contribute to worsening, AF has emerged from a discrete number of studies. Hirayama *et al* showed that the onset of arrhythmias is strongly associated with reduced erythrocyte deformability^[64], which is a conventional hallmark of anisocytic erythrocytes^[65]. A large variation of erythrocytes volume is also associated with a greater cholesterol content in the RBC membrane, which can then be directly transferred to atherosclerotic plaques enriched in erythrocytes^[66,67], thus finally promoting atherogenesis and ultimately predisposing to cardiac arrhythmias, since AF atherosclerosis and AF are now considered two strictly intertwined disorders^[68]. Finally, the presence of anisocytic erythrocytes has also been involved in the mechanisms underlying adverse cardiac remodeling^[69], thus leading to atrial fibrosis and predisposing the patients to a higher risk of developing AF^[70].

CONCLUSION

The value of the RDW can be automatically generated, along with the other parameters of the complete blood cell count, by the majority of modern hematological analyzers. It can therefore be considered an easier, faster and less expensive test compared to other potentially useful biomarkers in AF^[1]. Regardless of the fact that anisocytosis may be a simple bystander or an active player in the pathogenesis of AF and of its life-threatening complications, the current epidemiological evidence convincingly suggests that routine measurement of RDW may provide valuable

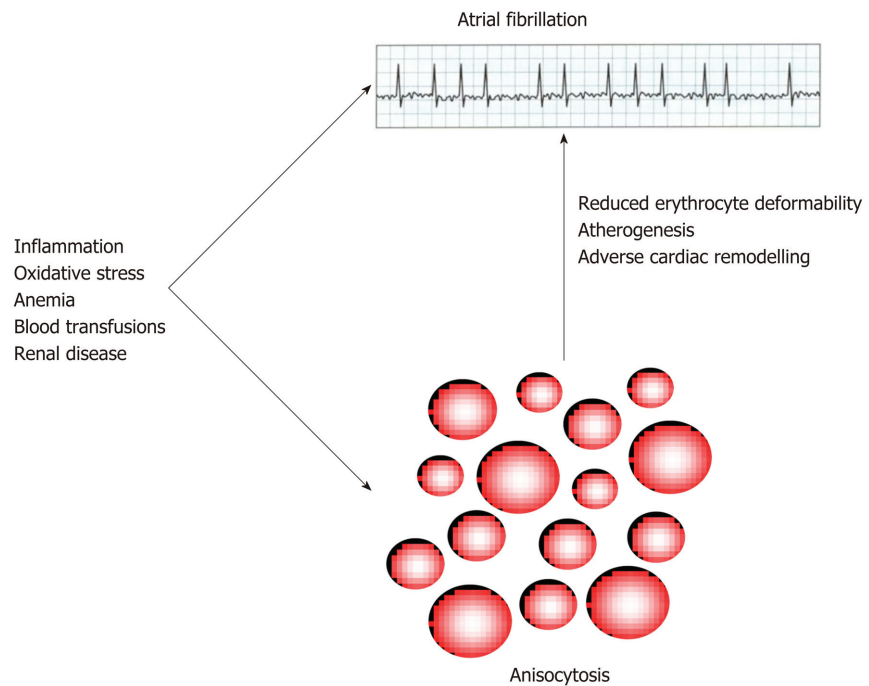


Figure 2 The interplay between atrial fibrillation and anisocytosis.

clinical information for diagnosis and management of AF, alone or combined with traditional risk scores such as CHADS2 and CHA2DS2-VASc^[71]. In particular, the strong and often independent association observed between high RDW values and unfavorable outcomes (*e.g.*, recurrence of AF, heart failure, bleeding, thromboembolic events and death) (Table 1), would lead us to conclude that AF patients with RDW values exceeding the local reference range may be more aggressively investigated and managed, in order to identify and reduce the impact of possible underlying disorders causing both anisocytosis and AF (Figure 2), and also for preventing the possible risk of adverse events potentially attributable to anisocytosis. Additional studies are then advised to define whether the inclusion of RDW within conventional risks scores may be effective in providing more accurate risk stratification in AF.

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