RED CELL DISTRIBUTION WIDTH FOR PREDICTING CARDIOVASCULAR DISEASE: A LITERATURE REVIEW

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ABSTRACT

Although the classical risk factors for cardiovascular disease (CVD) are very important, identification of potential novel risk factors could help clarify CVD pathophysiology, offer novel targets for intervention, and lead to improved risk stratification. Erythrocytes, or red blood cells (RBCs), are constituents of clots and thrombi formed *in vivo* but little is known about whether inherent properties of RBCs could affect the risk for CVD. The red cell distribution width (RDW) is a measure of the size variation and an index of the heterogeneity of erythrocytes, i.e. anisocytosis. Recently, a large number of studies have found an independent association beyond traditional risk factors between increased RDW (anisocytosis) and CVD. For instance, increased RDW has been associated with different CVDs such as coronary heart disease, stroke, heart failure, atrial fibrillation, peripheral artery disease, pulmonary arterial hypertension, and venous thromboembolism. RDW has also been associated with overall and cardiovascular mortality in different populations. RDW is influenced by many factors including traditional risk factors for CVDs, and it remains to be determined whether RDW is only a biomarker or also a pathogenic mediator for certain CVDs. Future Mendelian randomisation studies may provide a method for assessing the causal nature of increased RDW. Still, RDW is an inexpensive test measured routinely by automated blood cell counters and could be a useful predictor for CVD. In this article we present an overview of the literature about RDW and its association with CVDs.

Keywords: Cardiovascular disease, coronary heart disease, stroke, venous thromboembolism, red cell distribution width (RDW), biomarker, risk factor.

INTRODUCTION

Classical *in vitro* studies of the function of the coagulation system are performed in plasma, i.e. without erythrocytes or red blood cells (RBCs).[1] Few studies have therefore investigated the prothrombotic potential of RBCs. However, RBCs are constituents of clots and thrombi formed *in vivo*.[2-6] RBCs may play a prothrombotic role in blood coagulation by increasing blood viscosity and forcing platelets towards the vessel wall.[2-6] Incorporation of RBCs into a fibrin clot affects clot structure and mechanical properties. Even small structural differences in RBCs may have a large influence on pathophysiology.[2-6] Moreover, RBCs may actively participate in thrombin generation.[7] An increased focus on RBCs may therefore be justified, and may reveal novel mechanisms and risk factors for cardiovascular disease (CVD).

Mean corpuscular volume (MCV) is an index of RBC size.[8-12] Red cell distribution width (RDW) is a measure of the size variation and an index of the heterogeneity of erythrocytes (i.e. anisocytosis).[8-10] MCV and RDW are part of routine haematology laboratory tests and are used for classification of anaemia.[8-10] Recent studies have shown that RDW is associated with several CVDs such as coronary heart

disease (CHD), stroke, peripheral artery disease (PAD), heart failure (HF), venous thromboembolism (VTE), and pulmonary arterial hypertension (PAH).[11] The cause of these associations is still unclear. In this article we present an overview of the literature about RDW and its association with CVDs.

LABORATORY MEASUREMENT OF RDW

Modern automated blood cell counters calculate RDW from the RBC volume histogram as an index of heterogeneity.[12] RDW is often expressed as a percentage coefficient of variation (CV), and is calculated by dividing the standard deviation (SD) of the RBC volume by the MCV.[11] The result is multiplied by 100 in order to express it as a percentage.[12] The situation is complicated by there being RDW indices that are expressed in different ways. For several manufacturers, RDW is expressed as CV percentage.[12] RDW may also be expressed as a direct measurement of the width of the distribution, which gives a measure (in fL) that is independent of mean MCV.[12,13] The reference intervals differ between different manufacturers and may even vary between different instruments from the same manufacturer.[12-14] The lower reference limit for five different instruments varied between 10.7% and 12.9%, and the upper reference limit between 13.8% and 15.3%.[12,13] This is because different instruments use different algorithms to truncate the distribution in order to eliminate extreme values, which are often due to artefacts. The International Council for Standardization in Haematology has suggested a standardised statistical method for the analysis of RDW.[12,15,16] At present, any clinical use of RDW must be evaluated by comparison with reference values established for each model of analyser.

DETERMINANTS OF RDW

A number of haematological and non-haematological diseases have been associated with increased RDW (Table 1). Increased RDW (i.e. anisocytosis) is common in patients with deficiencies of iron, folate, and vitamin B12.[12,14] RDW has been used for differential diagnosis of anaemia. RDW is usually normal in thalassaemia traits and increased in iron deficiency anaemia.[12,14] Increased RDW is present in megaloblastic anaemia but RDW is usually normal in macrocytosis due to other causes.[12,14] However, there is a wide distribution of RDW values within a given disease, which has diminished its usefulness in differential diagnosis.[14] Increased RDW may be seen in other haematological disorders such as haemolytic anaemia, transfusion, sickle cell/beta thalassaemia, anaemia of chronic disorders, hereditary spherocytosis, and sickle cell anaemia,[11] and has also been associated with non-haematological diseases such as chronic hepatobiliary disease,[11] hypothyreosis,[17] hyperthyreosis,[17] Behçet's disease,[18] systemic lupus erythematosus,[19] and inflammatory bowel disease.[20]

Table 1: Haematological and non-haematological diseases associated with increased red cell distribution width.

Haematologic disorders	Non-haematological disorders
Iron deficiency anaemia[12,14]	Chronic hepatobiliary disease[11]
Megaloblastic anaemia (folate and vitamin B12 deficiency)[12,14]	Hypothyreosis[17]
Haemolytic anaemia[11]	Hyperthyreosis[17]
Sickle cell/beta thalassaemia[11]	Behçet's disease[18]
Transfusion[11]	Systemic lupus erythematosus[19]
Anaemia of chronic disorders[11]	Inflammatory bowel disease[20]
Hereditary spherocytosis[11]	Peripheral artery disease[48-51]
Sickle cell anaemia[11]	Stroke[52-57]
	Coronary heart disease[58-73]
	Heart failure[74-88]
	Atrial fibrillation[89-91]
	Pulmonary arterial hypertension[92-93]
	Venous thromboembolism[94-101]
	Hypertension[36-39]

It is, therefore, unsurprising that RDW correlates with inflammatory markers such as high-sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate, interleukin-6, soluble transferrin receptor, soluble tumour necrosis factor (TNF) receptor I, and soluble TNF receptor II (Table 2).[21-25] Increased levels of cytokines in inflammatory states promote anisocytosis by desensitising bone marrow erythroid progenitor cells and inhibiting RBC maturation.[11] In a study of patients with CHD, RDW did not correlate with hsCRP.[26] Instead, elevated levels of brain natriuretic peptide (BNP) were associated with increased RDW.[26] Increased RDW has also been associated with a number of other biomarkers (Table 2). In a study by Lippi et al.[27] RDW was independently associated with kidney function (estimated glomerular filtration rate). RDW has also been associated with microalbuminuria.[28] Among patients with HF, an association has been found between increased RDW and elevated troponin T levels.[29]

RDW has been associated with acquired and lifestyle factors such as increasing age, obesity, low cardiorespiratory fitness, smoking, being unmarried, and high alcohol consumption (Table 2).[30-34] It is also associated with obstructive sleep apnoea syndrome.[35] Hypertension has been associated with increased RDW.[36] RDW is especially increased in non-dipper hypertension patients.[37,38] An inverse relationship between lung function and RDW has been found.[39] An association has also been found between RDW and an unfavourable lipid profile, especially amongst women.[40] In another study, high RDW was associated with increased cholesterol content of the erythrocyte membrane.[41] An association has also been found between increased RDW and shorter telomere length.[42] Thus, RDW is associated with conditions, lifestyle factors, and biomarkers that are risk factors for CVDs and ageing (Table 2). Increased RDW may therefore be determined by epigenetic changes. The correlation between telomere length and RDW further suggests that the epigenetic changes associated with increased RDW reflect increased ageing, as shortened telomeres do.[42-44] It is possible that genetic factors affect RDW. Recently, a genome-wide association study of African Americans identified two variants (rs1050828 and rs10493739) on chromosomes Xq28 (*G6pD* gene) and 1p31.1, respectively, that are associated with RDW.[45]

Even though high RDW has been associated with increased incidence of several CVDs, this does not seem to be the case for incidence of diabetes.[46] A recent analysis by Engström et al.[46] of 26,709 nondiabetic participants from the population-based Malmö Diet and Cancer (MDC) Study showed that incidence of diabetes over a 14-year follow-up was substantially lower in subjects with high RDW. Thus, high RDW was a protective factor for new-onset diabetes. Low RDW was also associated with significantly higher waist circumference and glucose, insulin, and triglyceride concentrations.[46] By contrast, RDW was significantly and positively associated with HbA1c, with HbA1c increasing by 0.1% per 1 SD increase in RDW,[46] in accordance with recent data from nondiabetic participants in the National Health and Nutrition Examination Survey (NHANES) study.[47] A possible explanation for the positive association between HbA1c and RDW is that the RBC survival rates are on average higher in subjects with high RDW, leading to higher HbA1c due to increased duration of glucose exposure.[46]

Table 2: Laboratory markers and acquired and lifestyle-related factors associated with increased red cell distribution width.

Laboratory markers	Acquired and lifestyle-related factors
Inflammatory markers[21-25]	Age[33,34]
Brain natriuretic peptide[26]	Obesity[30]
Estimated glomerular filtration rate[27]	Low cardiorespiratory fitness[31]
Microalbuminuria[28]	Smoking[32,33]
Troponin T[29]	High alcohol consumption[33]
Unfavourable lipid profile[40]	Being unmarried[33]
HbA1c[46,47]	Obstructive sleep apnoea syndrome[35]
Short telomere length[42]	Lung function[39]
rs1050828 and rs10493739 variants[45]	

Table 3: Summary of published case-control studies, cohort-studies, and prognostic (mortality) studies showing associations of high red cell distribution width with risk of cardiovascular diseases and mortality.

Disease	Type of association (positive/negative)		
	Case-control studies	Cohort studies	Prognosis (mortality)
Peripheral artery disease	Positive[48]	-	Positive[51]
Stroke	Positive[52]	Positive[53]	Positive[55,56]
Coronary heart disease	-	Positive[60,73]	Positive[58,59,61-72]
Heart failure	-	Positive[33]	Positive[74-88]
Atrial fibrillation	Positive[90]	Positive[89,91]	-
Pulmonary arterial hypertension	-	-	Positive[92,93]
Venous thromboembolism	Positive[99,100]	Positive[101]	Positive[94-96]
Mortality among non-CVD patients and in the general population			
The general population	-	-	Positive[103-106]
Hospitalised patients	-	-	Positive[107]
Trauma and critically ill patients	-	-	Positive[108-113]
Sepsis	-	-	Positive[114]
Pancreatitis	-	-	Positive[115]
Hip fracture	-	-	Positive[116]
Kidney transplant recipients	-	-	Positive[117]

CVD AND INCREASED RDW

Increased RDW has been associated with an increased risk of a wide spectrum of CVDs in a large number of studies (Table 1).[33,48-102] Though initially quite unexpected, it is now unsurprising as studies have shown that increased RDW is associated with a large number of biomarkers and lifestyle factors associated with CVD (Table 2). As well as arterial CVDs, VTE[94-102] has been linked to increased RDW (Table 3).

PAD

In a cross-sectional study (the NHANES study), higher RDW values were independently associated with a higher risk of PAD.[48] Moreover, RDW significantly improved the risk prediction beyond that estimated by the American College of Cardiology/American Heart Association-defined PAD screening criteria.[48] In another study, RDW was found to be associated with the severity of atherosclerotic disease in patients with PAD.[49] However, Magri and Fava[50] found no association between RDW and PAD in diabetes patients. In a follow-up study of 13,039 outpatients with PAD at the Mayo Clinic, increased RDW was associated with mortality.[51] A 1% increment in RDW was associated with a 10% greater risk of all-cause mortality (HR 1.10, 95% CI 1.08-1.12, p<0.0001).

Stroke

In a case-control study, increased RDW was associated with ischaemic stroke.[52] Patients in the highest RDW quartile were significantly more likely to have a stroke compared with patients in the lowest quartile (OR 4.50, p<0.0001).[52] RDW was also a predictor for stroke in a follow-up study of 153 patients with HF.[53] Chen et al.[54] found that RDW was associated with all-cause mortality, but not with CVD (i.e. stroke and/or CHD). Increased RDW was also associated with poor prognosis or mortality among stroke patients in two studies,[55,56] though no association between RDW and stroke severity and functional outcome was observed in another study.[57]

CHD

In 2007, Anderson et al.[58] studied 29,536 consecutive patients undergoing coronary angiography. The highest RDW quartile compared with the lowest quartile had an increased risk of 30-day mortality (HR=1.8). Tonelli et al.[59] performed a *post hoc* analysis of data from the Cholesterol and Recurrent

Events study of patients with prior myocardial infarction (MI). Baseline RDW was measured in 4,111 participants who were randomised to receive pravastatin (40 mg, daily) or placebo and followed for a median of 59.7 months. A significant association was observed between baseline RDW and all-cause mortality (HR 1.14 per 1% increase in RDW).[59] The highest RDW quartile had an adjusted HR for death of 1.78 compared with the lowest quartile. Higher RDW was also associated with increased risk of coronary death/nonfatal MI, new symptomatic HF, and stroke.[59] A recent population-based study of 26,820 men and women reported that RDW was associated with an incidence of fatal acute coronary events.[60] However, no relationship was observed between RDW and nonfatal coronary events.[60] A large number of other studies have confirmed that RDW is a predictor for mortality in patients with CHD.[61-72] RDW was also found to be a predictor for incident CHD in healthy individuals in the NHANES study.[73]

HF

In 2007, Felker et al.[74] found that RDW was a prognostic factor regarding morbidity and mortality in the North American Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity study. An adjusted HR of 1.17 per 1 SD increase was found (p<0.001). This finding was replicated in a cohort of 2,140 HF patients from the Duke Databank, in which higher RDW was strongly associated with all-cause mortality (adjusted HR 1.29 per 1 SD, p<0.001). A large number of studies have confirmed that RDW is a predictor for poor prognosis in patients with acute and chronic HF.[33,74-88] In a large prospective study of 26,784 individuals, Borné et al.[33] found that RDW was an independent risk factor for incident HF in the MDC Study cohort. The HR for HF was 1.47 (95% CI 1.14-1.89) in the highest compared with the lowest RDW quartile.[33]

Atrial Fibrillation (AF)

In a study of 132 patients undergoing non-emergency coronary artery bypass grafting, preoperative RDW levels were significantly higher in patients who developed AF than in those who did not (13.9% versus 13.3%, p=0.03).[89] RDW was also associated with paroxysmal AF in a case-control study.[90] In a large prospective study of 26,124 individuals, Adamsson Eryd et al.[91] found that RDW was an independent risk factor for incident AF in the MDC Study cohort. The HR for AF was 1.33 (95% CI 1.16-1.53) in the highest compared with the lowest RDW quartile.[91]

PAH

Hampole et al.[92] found that RDW is independently associated with death in patients with PAH and performs better as a prognostic indicator than N-terminal pro-BNP. This was confirmed by Rhodes et al.[93] who found that RDW is a better predictor for mortality than other biomarkers in PAH.

VTE

Three studies have determined RDW in patients with pulmonary embolism (PE).[94-96] These studies found that high RDW was an independent predictor of PE-related mortality.[94-96] Two studies found an association between high RDW and chronic thromboembolic pulmonary hypertension.[97,98] RDW was also associated with VTE in two case-control studies,[99,100] but these case-control studies cannot exclude the possibility that anisocytosis was the result of the thrombotic event itself. A prospective cohort study by Zöller et al.[101] showed a graded independent association between RDW and risk of first VTE event among middle-aged subjects. After adjustment for potential confounding factors, the HRs for VTE for the second, third, and fourth RDW quartiles were 1.15 (95% CI 0.94-1.41), 1.41 (1.14-1.73), and 1.74 (1.38-2.21), respectively, compared with the lowest RDW quartile. In the multivariate model, subjects with the top 5% of RDW values had an even higher risk compared with the lowest quartile (HR 2.51, 95% CI 1.78-2.54).[101]

RDW was also associated with cerebral venous sinus thrombosis (CVST) in a diagnostic study of 138 patients referred to emergency services with complaints of headache.[102] Diagnosis of CVST was established by magnetic resonance venography. Diagnostic validity of RDW was found to be excellent in differentiating patients with CVST and primary headache, with a sensitivity of 91.9% and a specificity of 99%.

OVERALL MORTALITY

RDW has been shown to be a predictor for overall mortality in the general population.[103] Patel et al.[103] studied overall mortality among 8,175 adults 45 years or older who participated in the NHANES study. Compared with the lowest quintile of RDW, the adjusted HR for all-cause mortality was 1.1 (95% CI 0.9-1.3) in the second quintile, 1.2 (95% CI 1.0-1.4)

in the third quintile, 1.4 (95% CI 1.2-1.8) in the fourth quintile, and 2.1 (95% CI 1.7-2.6) in the fifth quintile.[103] Similar results have been found in other studies, including a meta-analysis.[104-106] Perlstein et al.[104] found a strong association between RDW and all-cause mortality in 15,852 adult participants in the NHANES III study. RDW was found to be a stronger risk factor for mortality in blacks and men compared to whites and women.[105] RDW is also a risk factor for mortality among older adults.[106] RDW has been shown to be a predictor for mortality in hospitalised patients (Table 3),[107] including patients with trauma and critical illness, sepsis and shock, acute pancreatitis, and hip fracture, as well as kidney transplant recipients.[108-117]

DISCUSSION

RDW is emerging as a potential biomarker not only for CVDs but also for predicting mortality in different patient groups and in the general population (Table 3). The methods for determining RDW are nowadays easily accessible and routinely performed using automated blood cell counters.[118] The mechanisms of the associations between CVDs and RDW are unclear. It is unlikely that only one mechanism is responsible because increased RDW is associated with several CVDs with different aetiologies. Still, it is possible that inherent properties of the RBC related to RDW may contribute to certain CVDs as RBCs are an important constituent of clots and thrombi formed *in vivo*.[2-6] Prospective studies show that high RDW, even after long-term follow-up, is a predictor for incident CVD.[33,60,73,91,101] Still, high RDW might not be the cause of CVD; it might just be a simple epiphenomenon due to conditions such as inflammation, impaired kidney function, malnutrition, or oxidative damage.[11] Clarification of the mechanisms behind the associations between high RDW and CVD may lead to new therapeutic opportunities. Recently, a genome-wide association study has found two gene variants associated with RDW. This indicates that RDW may also be affected by genetic factors. Mendelian randomisation studies may therefore be an important option for generating estimates for causal effects of RDW in different CVDs.[119]

Pros and Cons

RDW is a robust universal predictor for poor outcome for several CVDs (Table 3). On the other hand, this lack of specificity might become problematic if RDW is used for risk prediction in the clinic. Moreover, as we do not yet know why high RDW predicts CVD, we have no possibility for intervention regarding the cause of high RDW. The strength of RDW may be if it adds information to risk scores such as the Framingham Risk Score (FRS).[120] For instance, the FRS identifies only 70% of individuals at risk of CVD events and there is great interest in adding novel risk factors to improve its predictive capacity.[120,121] An important advantage is the low cost. Moreover, the analysis is quick and may easily be done in all laboratories on a modern automated blood cell counter. However, the method is not yet standardised, which is a major limitation that must be solved before the method can be introduced in the clinic.[12-14] Moreover, spurious RDW measurements may result from biases in determination of MCV, and a high-quality laboratory standard is necessary.[11,122]

Future Opportunities

An important issue for future research is the inclusion of RDW in risk score models such as the FRS. RDW has been shown to improve the Simplified Acute Physiology Score in critically ill patients.[123] RDW has also been included in other risk score models,[124,125] suggesting that this might be a possible avenue of clinical research. Due to the lack of standardisation it is important to develop a standardised method for RDW determination that will give results which are comparable between different manufacturers and laboratories.[12-16] Otherwise the clinical use of RDW will be limited. Perhaps the most important issue for future research is to elucidate the cause of the association between increased RDW and CVD. This might lead to the identification of new disease mechanisms and new treatments. For instance, although RBCs are constituents of clots and thrombi formed *in vivo*,[2-6] little is known about how different properties of RBCs affect arterial and VTE disorders. A special intriguing issue is why low RDW is associated with increased incidence of diabetes,[46] and at the same time HbAc1 is positively correlated with RDW.[46,47]

CONCLUSIONS

RDW is a novel and universal predictor for CVD and mortality. Clarification of the mechanisms underlying the association between RDW and CVDs may reveal new pathogenic mechanisms. There is an urgent need for standardisation before RDW can be used in clinical praxis as a novel risk factor that adds information beyond traditional CV risk factors.

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