Relation Between Red Blood Cell Distribution Width and Cardiovascular Event Rate in People With Coronary Disease

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Background—Higher levels of red blood cell distribution width (RDW) may be associated with adverse outcomes in patients with heart failure. We examined the association between RDW and the risk of all-cause mortality and adverse cardiovascular outcomes in a population of people with coronary disease who were free of heart failure at baseline.

Methods and Results—We performed a post hoc analysis of data from the Cholesterol and Recurrent Events study. Baseline RDW was measured in 4111 participants who were randomized to receive pravastatin 40 mg daily or placebo and followed for a median of 59.7 months. We used Cox proportional hazards models to examine the association between RDW and adverse clinical outcomes. During nearly 60 months of follow-up, 376 participants died. A significant association was noted between baseline RDW level and the adjusted risk of all-cause mortality (hazard ratio per percent increase in RDW, 1.14; 95% confidence interval, 1.05 to 1.24). After categorization based on quartile of baseline RDW and further adjustment for hematocrit and other cardiovascular risk factors, a graded independent relation between RDW and death was observed (P for trend=0.001). For instance, participants with RDW in the highest quartile had an adjusted hazard ratio for death of 1.78 (95% confidence interval, 1.28 to 2.47) compared with those in the lowest quartile. Higher levels of RDW were also associated with increased risk of coronary death/nonfatal myocardial infarction, new symptomatic heart failure, and stroke.

Conclusions—We found a graded independent relation between higher levels of RDW and the risk of death and cardiovascular events in people with prior myocardial infarction but no symptomatic heart failure at baseline. **(*Circulation*. 2008;117:163-168.)**

Key Words: follow-up studies ■ mortality ■ myocardial infarction

Red blood cell distribution width (RDW) is a numerical measure of the variability in size of circulating erythrocytes.[1] This parameter is routinely reported as part of the complete blood count, but its use is generally restricted to narrowing the differential diagnosis of anemia.[2] A recent article reported a strong independent association between RDW and the risk of adverse outcomes in patients with heart failure, even after adjustment for hematocrit.[3] However, whether RDW is associated with adverse outcomes in persons without heart failure is unknown. We tested the hypothesis that higher levels of RDW were associated with risk of all-cause mortality and adverse cardiovascular outcomes in a population of people with coronary disease who were free of symptomatic heart failure at baseline.

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Methods

Study Design and Patients

This post hoc analysis of data from a previously conducted randomized trial was approved by the institutional review board at the University of Alberta. The Cholesterol and Recurrent Events (CARE) study was a randomized trial of pravastatin versus placebo in 4159 individuals with hyperlipidemia and a history of myocardial infarction[4] and has been described in detail elsewhere.[5] Briefly, men and postmenopausal women were eligible if they had had an acute myocardial infarction between 3 and 20 months before randomization, were 21 to 75 years of age, and had low-density lipoprotein cholesterol levels of 115 to 174 mg/dL (3.0 to 4.5 mmol/L), fasting glucose levels of ≤220 mg/dL (12.2 mmol/L), left ventricular

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Table 1. Baseline Characteristics of Participants by Quartile of RDW

	RDW Quartile 1 (n=1095)	RDW Quartile 2 (n=1022)	RDW Quartile 3 (n=1038)	RDW Quartile 4 (n=956)	*P*
Demographic characteristics and comorbidity					
Age, y	56.7±9.7	57.6±9.4	59.5±9.2	61±8.3	<0.001
Female sex	130 (11.9)	132 (12.9)	154 (14.8)	149 (15.6)	0.06
Black race	18 (1.6)	24 (2.4)	36 (3.5)	56 (5.9)	<0.001
Body mass index, kg/m^2	27.2±3.8	27.7±4.3	27.8±4.7	27.9±4.8	0.002
History of hypertension	416 (38.0)	410 (40.1)	446 (43.0)	479 (50.1)	<0.001
Current smoker	132 (12.1)	176 (17.2)	194 (18.7)	160 (16.7)	<0.001
History of diabetes mellitus	140 (12.8)	129 (12.6)	163 (15.7)	146 (15.3)	0.08
Medication use					
Pravastatin	563 (51.4)	516 (50.5)	515 (49.6)	464 (48.5)	0.60
β-Adrenergic blocker	455 (41.6)	408 (40.0)	411 (39.6)	352 (36.8)	0.18
Angiotensin-converting enzyme inhibitor	124 (11.3)	126 (12.3)	161 (15.5)	172 (18.0)	<0.001
Aspirin	937 (85.6)	863 (84.4)	872 (84.1)	751 (78.6)	<0.001
Thiazide diuretic	25 (2.3)	36 (3.5)	35 (3.4)	41 (4.3)	0.09
Lipid status					
Total cholesterol, mg/dL	209.1±16.8	209.2±17.3	208.5±16.8	207.1±17.5	0.03
LDL cholesterol, mg/dL	138.4±14.4	139.3±14.6	139.1±14.7	137.6±14.5	0.04
HDL cholesterol, mg/dL	38.9±8.6	38.7±9.0	39.0±9.3	38.7±9.4	0.86
Triglycerides, mg/dL	159.3±63.1	156.3±60.5	152.0±58.8	154.4±61.2	0.04
Renal function, blood pressure, and ejection fraction					
Glomerular filtration rate, mL · min^{-1} · 1.73 m^{-2}	73.8±15.1	73.2±15.2	71.4±15.0	68.8±15.9	<0.001
Serum creatinine, mg/dL	1.1±0.2	1.1±0.2	1.1±0.2	1.2±0.3	<0.001
Serum protein, per g/dL	7.3±0.4	7.3±0.5	7.3±0.5	7.3±0.5	0.30
Systolic blood pressure, mm Hg	127.6±17.1	127.7±17.5	129.3±18.4	131.2±19.2	<0.001
Diastolic blood pressure, mm Hg	78.6±9.8	78.3±10.0	78.5±10.1	78.8±10.8	0.79
Ejection fraction	53.6±11.6	53.9±11.9	52.8±12.1	51.6±12.6	<0.001
Laboratory parameters					
Hemoglobin, mg/dL	15.0±1.0	15.0±1.0	14.9±1.1	14.4±1.3	<0.001
Serum phosphorus, mg/dL	3.2±0.5	3.3±0.5	3.3±0.5	3.3±0.5	<0.001
Serum calcium, mg/dL	9.5±0.5	9.5±0.4	9.5±0.4	9.5±0.4	0.16
Serum albumin, mg/dL	4.2±0.2	4.2±0.2	4.2±0.2	4.1±0.2	<0.001

Values are mean±SD or n (%). LDL indicates low-density lipoprotein; HDL, high-density lipoprotein. RDW quartiles 1 to 4 were defined by 10.9% to 12.6%, 12.6% to 13.1%, 13.1% to 13.7%, and 13.8% to 23.2%, respectively.

ejection fractions of ≥25%, and no symptomatic congestive heart failure. After stratification according to clinical center, eligible and consenting participants were assigned by computer-generated random order in a double-blinded fashion to receive either 40 mg of pravastatin (Pravachol, Bristol-Myers Squibb) once daily or placebo. Treatment allocation was concealed with the use of a centrally maintained code.

Measurement of RDW and Kidney Function

Baseline levels of RDW were measured in fasting participants with the use of the Coulter STK-S analyzer at the CARE core study laboratory (normal range, 11.8% to 14.6%) (D. Gibson, written communication, 2007). Baseline RDW was considered as a continuous variable and in categories (quartiles). We estimated glomerular filtration rate using the following equation: $186 \times SCr^{-1.154} \times$age in years$^{-0.203} \times 1.210$ (if black) $\times 0.742$ (if female), where SCr is serum creatinine in mg/dL.[6] Proteinuria was defined by trace or greater protein on dipstick urinalysis.

Study Outcomes

The primary outcome for this analysis was all-cause mortality. We also considered several secondary outcomes including the development of symptomatic congestive heart failure, fatal or nonfatal myocardial infarction, ischemic or nonischemic stroke, and the composite of death from coronary heart disease (including fatal myocardial infarction, either definite or probable; sudden death; death during a coronary intervention; and death from other coronary causes) or nonfatal myocardial infarction confirmed by serum creatine kinase measurements. Deaths were reviewed by the outcomes committee without knowledge of the individual's treatment assignment or laboratory values.

Statistical Analysis

We used χ^2 or 1-way ANOVA, respectively, to test for differences in categorical or continuous factors between different categories of RDW. Multivariate linear regression was used to determine factors that were associated with baseline RDW levels. We then used Cox proportional hazards models to examine the association between RDW levels and the clinical outcomes, with follow-up beginning on the date of randomization. We performed models that adjusted for age, sex, and race. On the basis of our previous work,[7] a panel of additional variables that were associated with adverse clinical outcomes was selected a priori for use as covariates together with age, sex, and race in the fully adjusted models: smoking status; diabetic status; use of β-adrenergic blockers, angiotensin-converting enzyme inhibitors, and aspirin; glomerular filtration rate; presence or absence of proteinuria on dipstick urinalysis; systolic and diastolic blood pressure; hemoglobin; serum albumin; serum phosphate; waist to hip circumference ratio; left ventricular ejection fraction; fasting serum glucose; fasting serum triglyceride; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; total cholesterol; mean corpuscular volume; and randomization to pravastatin or placebo. Adjusted survival curves were produced for these final models with the mean of covariates method.[8] In sensitivity analyses, additional variables that were independently associated with RDW but were not selected a priori for inclusion were forced into the fully adjusted models. We determined that the proportional hazard assumption was satisfied by examining plots of the log-negative-log of the within-group survivorship functions versus log-time as well as comparing Kaplan-Meier (observed) with Cox (expected) survival curves. Values are reported as mean±SD or percentages; 95% confidence intervals (CIs) are provided where appropriate, and all probability values are 2-sided. Analyses were performed with Stata 8 SE software.

Role of the Funding Source

The CARE trial was an investigator-initiated study funded by Bristol-Myers Squibb, but this substudy on RDW was not industry supported. The authors had full access to and take full responsibility for the integrity of the data used in this analysis, and the rights to publication reside contractually with the investigators.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Baseline Characteristics

Of 4159 CARE participants, 4111 had RDW measured at baseline and were eligible for this analysis. The demographic characteristics of these remaining participants are shown in Table 1 (median duration of follow-up, 59.7 months). RDW ranged from 10.9% to 23.2% (median, 13.1%; interquartile range, 12.6% to 13.8%; mean, 13.4±1.1%), and 471 (11.5%) had RDW levels outside the normal range of 11.8% to 14.6% with RDW <11.8 (n=32 [0.8%]) and >14.6 (n=439 [10.7%]).

Patients with higher RDW levels tended to be older, were more likely to smoke, had higher body mass index, and had lower levels of hemoglobin and serum albumin. Other factors that were independently associated with baseline RDW level are shown in Table 2.

Association Between RDW Level and All-Cause Death

Higher levels of baseline RDW were associated with increased risk of all-cause death (adjusted hazard ratio per percent increase in RDW, 1.14; 95% CI, 1.05 to 1.24; P=0.002; Table 3). When participants were divided into 4 categories on the basis of their baseline quartile of RDW level, a graded relation between RDW and death remained. For example, the fully adjusted risk of mortality in the highest category of RDW was 1.78 (95% CI, 1.28 to 2.47) compared with the referent group (Table 3, Figure).

Table 2. Factors Associated With Higher Levels of RDW in Multivariable Linear Regression

	1% Increase in RDW	95% CI	P
Age, per 5 years	0.05	0.01 to 0.02	<0.001
Female vs male	−0.34	−0.45 to −0.23	<0.001
Glomerular filtration rate, per mL · min^{-1} · 1.73 m^{-2}	−0.01	−0.01 to −0.00	<0.001
Body mass index, per kg/m^2	0.02	0.01 to 0.02	<0.001
Prior hypertension	0.12	0.05 to 0.19	0.001
Current smoker	0.32	0.22 to 0.41	<0.001
Serum protein, per g/dL	0.16	0.08 to 0.24	<0.001
Hemoglobin, per g/dL	−0.24	−0.27 to −0.21	<0.001
Serum calcium, per mg/dL	0.16	0.07 to 0.24	<0.001
β-Blocker use	−0.11	−0.18 to −0.04	0.002
Left ventricular ejection fraction, per %	−0.00	−0.01 to −0.00	0.001
Aspirin use	0.16	0.07 to 0.25	<0.001
Serum phosphate, per mg/dL	0.18	0.11 to 0.26	<0.001
Serum total cholesterol, per mg/dL	−0.00	−0.01 to −0.00	0.001
Serum albumin	−0.48	−0.65 to −0.31	<0.001

Positive coefficients indicate a direct relation between the characteristic and higher levels of RDW.

Association Between RDW Level and Cardiovascular Events

Higher levels of baseline RDW were also associated with increased risk of the composite outcome of fatal or nonfatal myocardial infarction (P for trend=0.033). Participants with RDW in the highest quartile had a fully adjusted hazard ratio for experiencing myocardial infarction of 1.43 (95% CI, 1.03 to 1.99) compared with those with RDW in the lowest quartile. Baseline RDW was also independently associated with the risk of coronary death or nonfatal myocardial infarction (P for trend=0.001; Table 3). Participants with serum in the highest quartile had a fully adjusted hazard ratio for experiencing the composite outcome of coronary death or nonfatal myocardial infarction of 1.56 (95% CI, 1.17 to 2.08) compared with those with RDW in the lowest quartile. The risk of stroke was also independently increased in participants with RDW in the highest quartile compared with those with RDW in the lowest quartile (adjusted hazard ratio=2.58; 95% CI, 1.47 to 4.55).

Association Between RDW Level and New Congestive Heart Failure

Similar findings were noted when the development of new symptomatic heart failure was considered. Higher levels of RDW were associated with an increased risk of new heart

Table 3. Adjusted Association Between Quartile of RDW and Clinical Outcomes

	Unadjusted		Age, Race, and Sex Adjusted		Fully Adjusted*		
	Events, n (%)	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
All-cause death							
Quartile 1	62 (5.7%)	1		<0.001†	1		0.001†
Quartile 2	77 (7.5%)	1.29	0.92 to 1.80		1.29	0.92 to 1.82	
Quartile 3	100 (9.6%)	1.54	1.12 to 2.12		1.35	0.97 to 1.88	
Quartile 4	135 (14.1%)	2.16	1.59 to 2.93		1.78	1.28 to 2.47	
Per %		1.20	1.12 to 1.29	<0.001	1.14	1.05 to 1.24	0.002
Fatal coronary disease or nonfatal myocardial infarction							
Quartile 1	91 (8.3%)	1		<0.001†	1		0.001†
Quartile 2	105 (10.3%)	1.23	0.93 to 1.63		1.19	0.90 to 1.59	
Quartile 3	137 (13.2%)	1.59	1.22 to 2.08		1.39	1.05 to 1.83	
Quartile 4	146 (15.3%)	1.84	1.41 to 2.40		1.56	1.17 to 2.08	
Per %		1.13	1.06 to 1.21	<0.001	1.08	1.00 to 1.17	0.048
Stroke							
Quartile 1	21 (1.9%)	1		0.003†	1		0.004†
Quartile 2	31 (3.0%)	1.52	0.87 to 2.64		1.85	1.03 to 3.33	
Quartile 3	27 (2.6%)	1.17	0.66 to 2.08		1.30	0.71 to 2.37	
Quartile 4	52 (5.4%)	2.32	1.39 to 3.88		2.58	1.47 to 4.55	
Per %		1.18	1.05 to 1.33	0.004	1.20	1.05 to 1.37	0.006
Fatal or nonfatal myocardial infarction							
Quartile 1	75 (6.9%)	1		0.001†	1		0.033†
Quartile 2	83 (8.1%)	1.19	0.87 to 1.62		1.14	0.83 to 1.57	
Quartile 3	95 (9.2%)	1.36	1.01 to 1.85		1.20	0.88 to 1.65	
Quartile 4	105 (11.0%)	1.65	1.22 to 2.22		1.43	1.03 to 1.99	
Per %		1.11	1.02 to 1.20	0.014	1.07	0.97 to 1.17	0.17
Symptomatic heart failure							
Quartile 1	49 (4.5%)	1		<0.001†	1		0.001†
Quartile 2	56 (5.5%)	1.17	0.80 to 1.72		1.13	0.76 to 1.67	
Quartile 3	78 (7.5%)	1.49	1.04 to 2.13		1.23	0.85 to 1.78	
Quartile 4	119 (12.5%)	2.37	1.69 to 3.32		1.80	1.25 to 2.60	
Per %		1.23	1.15 to 1.32	<0.001	1.15	1.05 to 1.26	0.002

*Adjusted for age; sex; race; smoking status; diabetic status; use of β-adrenergic blockers, angiotensin-converting enzyme inhibitors, aspirin, and pravastatin; glomerular filtration rate; presence or absence of proteinuria on dipstick urinalysis; systolic and diastolic blood pressure; hemoglobin; serum albumin; serum phosphate; waist to hip circumference ratio; left ventricular ejection fraction; fasting serum glucose; fasting serum triglyceride; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; total cholesterol; and mean corpuscular volume.

†*P* for linear trend.

failure after adjustment for age, sex, and race (*P* for trend<0.001; Table 3) and in the fully adjusted model (*P* for trend=0.001; Table 3). Participants with RDW in the highest quartile had a fully adjusted hazard ratio for developing heart failure of 1.80 (95% CI, 1.25 to 2.60) compared with those with RDW in the lowest quartile.

Sensitivity Analyses

In sensitivity analyses, we adjusted for additional baseline factors that were found to be associated with RDW levels but were not included in the list of covariates that were selected a priori for inclusion in the fully adjusted model (body mass index, prior hypertension, serum total protein, serum calcium) and also for additional hematological parameters such as mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. These characteristics were forced into the aforementioned fully adjusted model but did not appreciably affect the association between higher levels of RDW and the increased risk of death (*P* for trend=0.001), new heart failure (*P* for trend=0.015), the composite of fatal coronary disease or nonfatal myocardial infarction (*P* for trend=0.003), or stroke (*P* for trend=0.004). However, in this model, the association between quartile of RDW and the risk of fatal or nonfatal myocardial infarction was attenuated and no longer statistically significant (*P* for trend=0.07).

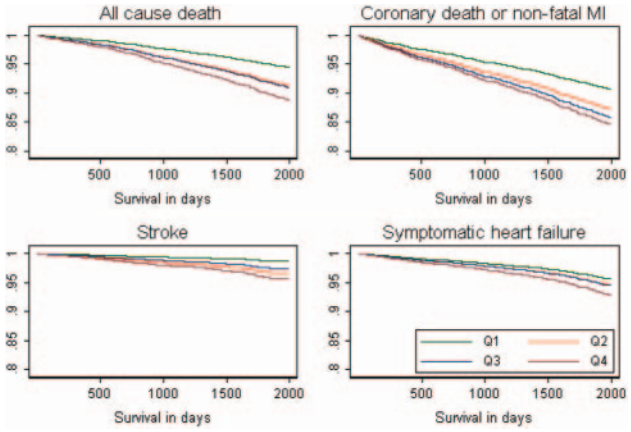

Figure. Fully adjusted time to clinical outcomes by baseline quartile of RDW. *P* for trend: all-cause death ($P=0.001$); coronary death or nonfatal myocardial infarction (MI) ($P=0.001$), stroke ($P=0.004$); symptomatic heart failure ($P=0.001$). Hazard ratios have been adjusted for age; sex; race; smoking status; diabetic status; use of β-adrenergic blockers, angiotensin-converting enzyme inhibitors, aspirin, and pravastatin; glomerular filtration rate; presence or absence of proteinuria on dipstick urinalysis; systolic and diastolic blood pressure; hemoglobin; serum albumin; serum phosphate; waist to hip circumference ratio; left ventricular ejection fraction; fasting serum glucose; fasting serum triglyceride; low-density lipoprotein cholesterol; high-density lipoprotein cholesterol; total cholesterol; and mean corpuscular volume.

Discussion

RDW reflects variability in the size of circulating red cells (anisocytosis) and is routinely reported by automated laboratory equipment used to perform complete blood counts.[1] We found a graded, independent association between baseline RDW level and the risk of all-cause death, the development of new heart failure, and coronary events in this population of individuals with previous myocardial infarction who were free of clinically evident heart failure of baseline, most of whom had RDW levels within the normal range. Adjustment for multiple potential confounders attenuated but did not eliminate the association between higher RDW levels and the adverse clinical outcomes. In addition to reaching statistical significance, the magnitude of the increased risk associated with higher levels of RDW was clinically relevant. For example, the risk of all-cause death in participants with RDW in the highest quartile was nearly 80% higher than those in the lowest quartile, similar to the adjusted risk of a recurrent cardiovascular event among CARE participants with C-reactive protein in the highest quintile compared with the lowest.[9] These findings are notable given that RDW is widely available to clinicians as part of the complete blood count and therefore incurs no additional costs, in contrast to other novel markers of cardiovascular risk.

Considerable attention has focused on the association between anemia and adverse cardiovascular outcomes in multiple patient populations.[10,11] In the present study, higher levels of RDW were associated with adverse outcomes even after adjustment for hemoglobin, making it unlikely that our findings are confounded by anemia. A previous analysis of 2 large populations of people with heart failure found a strong independent association between RDW and clinical outcomes including all-cause mortality,[3] similar to the findings in a small single-center study of hemodialysis patients.[12] Our study confirms and extends these findings in a population of patients who had no evidence of heart failure at baseline.

To reduce the risk of confounding, we adjusted for a comprehensive list of characteristics known to influence the risk of cardiovascular events. We also determined factors that were associated with higher levels of RDW at baseline and adjusted for these factors in analyses examining the association between RDW and clinical outcomes. Although this increases confidence in our finding that higher RDW is independently associated with adverse outcomes, the mechanism underlying this association is unclear. Identification of a putative mechanism is hampered by the lack of epidemiological studies demonstrating factors that are associated with anisocytosis. Overtly elevated RDW may represent nutritional deficiency (such as lack of vitamin B_{12} or folate) or recent blood transfusion.[13] However, most CARE participants had RDW values within the normal range, and we adjusted for mean corpuscular volume, which correlates with adequacy of vitamin B_{12} and folate stores. Therefore, we do not believe that either of these is a plausible explanation for our findings, although we did not directly assess nutritional status. Higher levels of RDW within the normal range may indicate accelerated red blood cell destruction or, more commonly, ineffective erythropoiesis.[2] We speculate that higher levels of RDW may reflect an underlying inflammatory state, which is associated with adverse clinical outcomes[14,15] and leads to impaired erythrocyte maturation.[16] However, this hypothesis will require confirmation in future studies, and more work is needed to explore determinants of RDW in populations with cardiovascular disease.

Strengths of our analysis include its relatively large size and the use of a central laboratory for all assays. In addition, outcomes were ascertained according to prespecified criteria by individuals who were unaware of RDW levels. However, our study also has some limitations that should be considered. First, this was a post hoc observational analysis, and therefore we cannot rule out the possibility of residual confounding. However, the hypothesis that RDW levels would be associated with adverse outcomes was formulated before analyses were started, reducing the risk of spurious conclusions. In addition, we adjusted for multiple potential confounders, including characteristics that were associated with RDW levels in the present data set. Second, this analysis concerns a select population of individuals with prior myocardial infarction who were eligible for a randomized trial and therefore may not be representative of the general population. Although our findings are similar to those reported from observational and clinical trial data from patients with clinically evident heart failure, additional studies should be done to confirm that the association between RDW and adverse outcomes exists in other populations.

In conclusion, we found a graded independent relation between higher levels of RDW and the risk of heart failure, cardiovascular events, and all-cause death in people with prior myocardial infarction but no evidence of heart failure at baseline. Further studies are required to determine the expla-

nation for the association between RDW and adverse clinical outcomes.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Red blood cell distribution width (RDW) is a numerical measure of the variability in size of circulating erythrocytes and is routinely reported as part of the complete blood count as an aid in the differential diagnosis of anemia. A strong independent association between RDW and the risk of adverse outcomes was recently reported in patients with heart failure. However, whether RDW is associated with adverse outcomes in other populations is unknown. In this study, we found a graded, independent association between baseline RDW level and the risk of all-cause death, the development of new heart failure, and coronary events in this population of individuals with previous myocardial infarction who were free of clinically evident heart failure at baseline, most of whom had RDW levels within the normal range. Adjustment for multiple potential confounders attenuated but did not eliminate the association between higher RDW levels and the adverse clinical outcomes. In addition to reaching statistical significance, the magnitude of the increased risk associated with higher levels of RDW was clinically relevant. For example, the risk of all-cause death in participants with RDW in the highest quartile was nearly 80% higher than those in the lowest quartile, similar to the adjusted risk of a recurrent cardiovascular event among Cholesterol and Recurrent Events study participants with C-reactive protein in the highest quintile compared with the lowest. These findings are notable given that RDW is widely available to clinicians as part of the complete blood count and therefore incurs no additional costs, in contrast to other novel markers of cardiovascular risk.

Relation Between Red Blood Cell Distribution Width and Cardiovascular Event Rate in People With Coronary Disease

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