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Brief Communication

Relation of red blood cell distribution width to risk of major adverse cardiovascular events, death, and effect of alirocumab after acute coronary syndromes

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Elevated red blood cell distribution width (RDW) is associated with increased risk for major adverse cardiovascular events (MACE) and death in patients with cardiovascular disease. The ODYSSEY OUTCOMES trial compared alirocumab with placebo in 18,924 patients with recent acute coronary syndrome (ACS) and elevated atherogenic lipoproteins despite optimized statin treatment. This post hoc analysis determined whether RDW independently predicts risk of MACE and death in patients after recent ACS, whether RDW influences MACE reduction with alirocumab, and whether alirocumab treatment affects RDW. Associations of baseline RDW with risk of MACE and death were analyzed in the placebo group in adjusted proportional hazards models. Interactions of RDW and treatment on the risk of MACE and death were evaluated. An increasing quartile of RDW was associated with characteristics that predicted risk of MACE and death including age, hypertension, diabetes, atherosclerotic conditions and events, revascularizations, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein. After adjusting for baseline characteristics associated with the risk of MACE or death, baseline RDW remained independently associated with the risk of MACE and death in the placebo group (hazard ratios [95% confidence intervals] 1.08 [1.02–1.15] and 1.13 [1.03–1.24] per 1% increase of RDW, respectively, both $p < 0.001$). There was no interaction of RDW and treatment on MACE or death, nor did alirocumab affect RDW. RDW was associated with an increased risk of MACE and death, independent of established risk factors.

Introduction

Red blood cell distribution width (RDW) reflects the variability in red blood cell volumes. A normal RDW typically ranges from 12–15%, depending upon the testing laboratory.[1]

Elevated RDW has been associated with an increased risk for death and major adverse cardiovascular events (MACE) in patients with a history of cardiovascular disease.[2,3] The basis for this association is uncertain, but may include abnormal blood rheology or heightened inflammation. Elevated RDW has been associated with reduced red blood cell deformability and decreased microvascular perfusion, and resultant tissue hypoxia might explain increased cardiovascular risk.[4] RDW is also associated with markers of inflammation, including high-sensitivity C-reactive protein (hs-CRP),[5] but RDW was a stronger predictor of cardiovascular mortality than hs-CRP in an analysis from the National Health and Nutrition Examination Survey.[6]

Prior studies in patients with acute coronary syndrome (ACS) have found an association of RDW with the risks of MACE and death.[3,7,8] These studies involved 100 to 2500 patients, and most were conducted in a single center. An analysis of the multicenter EXAMINE trial in 5380 patients with diabetes and ACS showed that RDW was associated with MACE and death.[9] However, there is uncertain utility of RDW in estimating prognosis in a broad population of patients with ACS who receive high-intensity lipid-lowering therapy and other contemporary evidence-based treatments, and how the information provided by RDW may add to that offered by other characteristics including hs-CRP.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors reduce the levels of atherogenic lipoproteins and, in large randomized, placebo-controlled trials, have been shown to reduce the risk of MACE when added to statin treatment.[10,11] The goals of this post-hoc analysis from the ODYSSEY OUTCOMES trial were to determine whether RDW predicts risk of MACE or death in patients who are clinically stable after a recent ACS, whether RDW predicts the benefit of alirocumab in such patients, and whether alirocumab treatment affects RDW.

Materials and methods

The ODYSSEY OUTCOMES trial (clinicaltrials.gov identifier: NCT01663402) compared alirocumab with placebo in patients with a recent ACS and elevated atherogenic lipoproteins despite optimized statin treatment.[10] Randomization occurred 1−12 months after an ACS, a time when the acute phase response due to the event has waned.[12] The primary MACE outcome was the composite of death due to coronary heart disease, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, or unstable angina requiring hospitalization.[10] All-cause death was one of several secondary endpoints.

A standard complete blood count was obtained at randomization and at protocol-specified times thereafter. RDW was calculated as:

RDW = (standard deviation of red blood cell volume/mean red blood cell volume) × 100.

Blood lipids and hs-CRP were measured in samples obtained at baseline and at specified times thereafter.

Demographic and baseline characteristics, for all subjects and by baseline RDW quartile, were summarized by mean and standard deviation (SD) for continuous variables and by proportion for categorical variables. Missing baseline hs-CRP values were imputed by mean value of base-

line hs-CRP. Missing baseline RDW values were also imputed by mean value of baseline RDW. The imputation was performed so that all events of MACE or death could be included in the analyses. The associations of baseline RDW and risk of MACE or death in the placebo group were analyzed in proportional hazard models. For each outcome, 2 adjusted models were constructed. The first adjusted model included the variables significantly associated with the outcome, but specifically excluded hs-CRP. The second adjusted model contained all the variables of the first model and additionally was forced to include hs-CRP. Furthermore, the second adjusted model was recapitulated in 2 subsets of the trial cohort: those with baseline hs-CRP at or below the median (1.7 mg/L); and those with baseline hs-CRP above that value. Together, the adjusted models determined whether RDW predicted the risk of MACE or death independently of other clinical and laboratory variables, and whether the information contributed by RDW remained significant when hsCRP was considered. Pearson's coefficient was calculated for the correlation of baseline RDW and hs-CRP, as well as of baseline RDW and low-density lipoprotein cholesterol (LDL-C). The change in RDW from baseline to Months 12, 24, and 36 was analyzed using robust regression due to skewed distribution, including treatment and baseline RDW as covariates. The change in hs-CRP from baseline to Months 12, 24, and 36 was also analyzed, using robust regression due to the skewed distribution. To understand whether a differential treatment effect exists within the range of RDW or hs-CRP, baseline RDW and hs-CRP were divided into quartiles. The incidence rates of MACE and death were calculated for each quartile by treatment groups. Treatment hazard ratios (HRs) with 95% confidence intervals (CIs) for the effect of alirocumab versus placebo on MACE or death were calculated according to quartile of baseline RDW or baseline hs-CRP. Treatment HR were also calculated using proportional hazard models, incorporating stepwise selection of covariates from those listed in Table 1, and either explicitly excluding hs-CRP or forcing its inclusion. Treatment-by-baseline quartile interactions were also assessed. Adverse events were tabulated by treatments and baseline RDW quartiles. The analyses were performed using the intention-to-treat patient population and used SAS 9.4.

Results

Baseline characteristics of all patients, both overall and by RDW quartile, are shown in Table 1. RDW had a skewed distribution driven by an excess of higher values so that the mean of 13.9% was greater than the median of 13.8% (quartile [Q] 1, Q3 = 13.3%, 14.4%). Increasing quartile of RDW was associated with greater prevalence of characteristics predictive of the risk of MACE or death, such as age, hypertension, diabetes, and history of atherosclerotic conditions, events, and procedures. An increasing quartile of RDW was associated with levels of hs-CRP or LDL-C; however, these variables were also predictive of MACE and death.

Patients were followed for a median (Q1, Q3) of 2.8 (2.3, 3.4) years; 1,955 patients had MACE (alirocumab 903, placebo 1,052) and 726 died (alirocumab 334, placebo 392). Baseline RDW and hs-CRP were positively associated (Pearson correlation for log-transformed variables 0.1586, $p < 0.001$), and RDW was weakly but significantly correlated with baseline LDL-C (Pearson correlation for log-transformed variables 0.0218, $p = 0.0027$).

In unadjusted analyses depicted in Fig. 1, the risk of MACE or death in the placebo group increased nominally with baseline levels of RDW or hs-CRP. Table 2 shows that, in the placebo group, the unadjusted risk of MACE and death increased monotonically across quartiles of RDW and hs-CRP. For RDW, the risk of MACE was 1.8 times higher in quartile 4 than in quartile 1 (5.7 versus 3.1 per 100 patient-years) and the risk of death was 2.3 times higher in quartile 4 than in quartile 1 (2.3 versus 1.0 per 100 patient-years). Similarly, for hs-CRP, the risk of MACE was 1.7 times higher in quartile 4 than quartile 1 (5.4 versus 3.1 per 100 patient-years) and the risk of death was 2.6 times higher in quartile 4 than quartile 1 (2.2 versus 0.8 per 100 patient-years).

Table 3 shows the results of unadjusted and adjusted models for MACE and death in the placebo group. For each outcome, the first model adjusted for variables associated with the outcome except that hs-CRP was specifically excluded. The second (fully adjusted) model forced the inclusion of hs-CRP, as well as other variables significantly associated with the outcome. In the unadjusted model and both adjusted models, baseline RDW was significantly ($p < 0.001$) associated with the risk of MACE or death in the placebo group. The fully adjusted model demonstrated HR (95% CI) of 1.08 (1.01–1.15) and 1.14 (1.04–1.26) per 1% increase of RDW for MACE and death, respectively. An analysis stratified by baseline hs-CRP $\leq$1.7 mg/L (median) or $>$1.7 mg/L was conducted using the fully adjusted model. In the subgroup with baseline hs-CRP above median, there was a significantly greater risk of MACE and death per 1% increase in RDW, with HR (95% CI) of 1.09 (1.00, 1.18) and 1.21 (1.07, 1.36), respectively. In the subgroup of patients with baseline hs-CRP $\leq$ median, a 1% increase in RDW was associated with a directionally similar but numerically smaller HR for MACE and death of 1.06 (0.96, 1.17) and 1.02 (0.85, 1.22), respectively.

As shown in Fig. 1 and Table 2, alirocumab reduced the risk of MACE and death consistently versus placebo in each baseline RDW and hs-CRP quartile. There were no interactions of RDW quartile or hs-CRP quartile and treatment on MACE ($p = 0.99$ and $p = 0.16$) or death ($p = 0.64$ and $p = 0.59$). The absolute reduction in the risk of MACE with alirocumab versus placebo increased across quartiles of RDW from 0.5 to 0.8 per 100 patient-years, but similar trends were not apparent for reduction in death according to RDW quartile, or for absolute reduction in either MACE or death according to hs-CRP quartile.

A stepwise Cox regression model to determine the treatment effect of alirocumab according to baseline RDW selected the following baseline variables as significantly as-

Table 1 Baseline characteristics, overall and by RDW quartile.

Characteristic	All patients (n = 18,924)	RDW Q1 (11.3–13.3%) (n = 5,019)	RDW Q2 (>13.3–13.8%) (n = 4,930)	RDW Q3 (>13.8–14.4%) (n = 4,778)	RDW Q4 (>14.4–27.5%) (n = 4,197)	p value
Age, years, mean ± SD	58.6 ± 9.3	57.3 ± 9.2	58.2 ± 9.2	58.9 ± 9.1	60.2 ± 9.6	<0.001
Male, n (%)	4,762 (25.2)	1,182 (23.6)	1,153 (23.4)	1,181 (24.7)	1,246 (29.7)	<0.001
Body mass index, kg/m^2, mean ± SD	28.5 ± 4.9	28.2 ± 4.5	28.5 ± 4.7	28.6 ± 4.9	28.7 ± 5.4	<0.001
Hemoglobin A1c, %, mean ± SD	6.2 ± 1.2	6.2 ± 1.3	6.1 ± 1.2	6.2 ± 1.2	6.3 ± 1.2	<0.001
Current smoker, n (%)	4,560 (24.1)	1,213 (24.2)	1,221 (24.8)	1,153 (24.1)	973 (23.2)	0.368
Hypertension, n (%)	12,249 (64.7)	3,103 (61.8)	3,117 (63.2)	3,070 (64.3)	2,959 (70.5)	<0.001
Diabetes, n (%)	5,444 (28.8)	1,297 (25.8)	1,266 (25.7)	1,391 (29.1)	1,490 (35.5)	<0.001
Family history of coronary artery disease, n (%)	6,773 (35.8)	1,868 (37.2)	1,770 (35.9)	1,721 (36.0)	1,414 (33.7)	0.005
Myocardial infarction, n (%)	3,633 (19.2)	888 (17.7)	938 (19.0)	937 (19.6)	870 (20.7)	0.003
Percutaneous coronary intervention, n (%)	3,241 (17.1)	822 (16.4)	823 (16.7)	820 (17.2)	776 (18.5)	0.043
Coronary artery bypass graft, n (%)	1,047 (5.5)	249 (5.0)	244 (4.9)	274 (5.7)	280 (6.7)	<0.001
Ischemic stroke, n (%)	524 (2.8)	107 (2.1)	119 (2.4)	149 (3.1)	149 (3.6)	<0.001
Peripheral artery disease, n (%)	759 (4.0)	153 (3.0)	143 (2.9)	216 (4.5)	247 (5.9)	<0.001
Heart failure, n (%)	2,814 (14.9)	650 (13.0)	707 (14.3)	687 (14.4)	770 (18.3)	<0.001
LDL-C, mg/dL, mean ± SD	92.4 ± 31.0	91.1 ± 28.8	92.4 ± 30.7	92.3 ± 31.4	93.9 ± 33.2	<0.001
hs-CRP, mg/L, median (Q1, Q3)	1.7 (0.8, 4.0)	1.3 (0.7, 3.0)	1.5 (0.7, 3.4)	1.7 (0.8, 4.0)	2.3 (1.0, 5.3)	<0.001
RDW, %, median (Q1, Q3)	13.8 (13.3, 14.4)	13.0 (12.8, 13.2)	13.6 (13.5, 13.7)	14.1 (14.0, 14.3)	14.7 (14.7, 15.5)	<0.001
eGFR, mL/min/1.73 m^2, mean ± SD	79.7 ± 19.3	81.5 ± 18.0	80.7 ± 19.0	79.2 ± 19.3	76.8 ± 20.6	<0.001
Hemoglobin, g/L, mean ± SD	141.9 ± 13.9	144.6 ± 12.3	143.7 ± 12.6	142.2 ± 13.3	136.2 ±15.9	<0.001

eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; RDW, red blood cell distribution width; Q, quartile; SD, standard deviation.

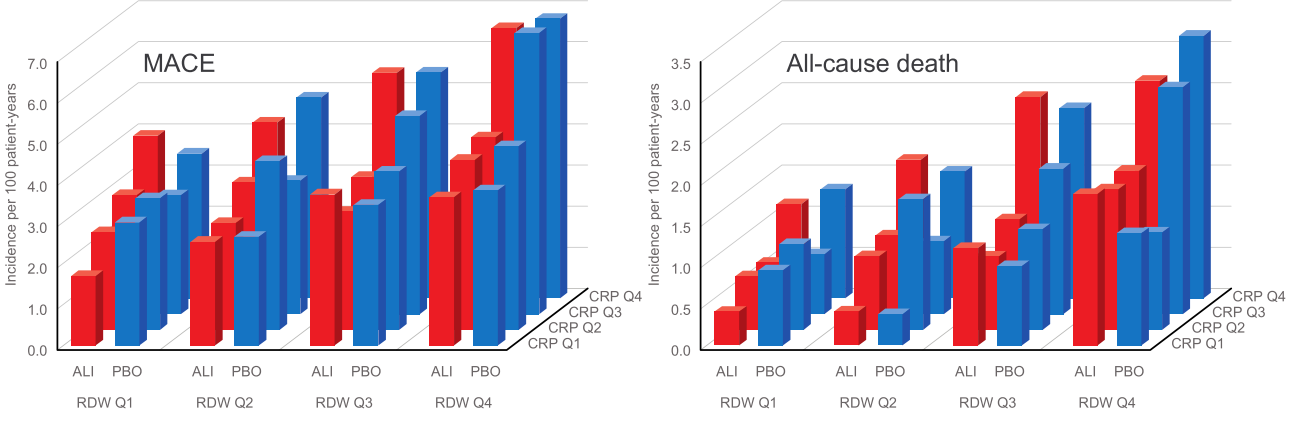

Fig. 1 Incidence rates of (A) MACE and (B) all-cause death per 100 person-years, according to baseline RDW value and hs-CRP quartile. ALI, alirocumab; hs-CRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular event; PBO, placebo; Q, quartile; RDW, red blood cell distribution width.

Table 2 Increased risk of MACE or death with increasing baseline RDW level and hs-CRP level. HRs are unadjusted. CI, confidence interval; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; MACE, major adverse cardiovascular events; RDW, red blood cell distribution width; Q, quartile. *RDW: minimum = 11.3%; Q1 = 13.3%; median = 13.8%; Q3 = 14.4%; maximum = 27.50%. hs-CRP: minimum = 0.20 mg/L; Q1 = 0.82 mg/L; median = 1.70 mg/L; Q3 = 3.96 mg/L; maximum = 252.00 mg/L.

Endpoint	Quartile*	Rate (per 100 person-years)		HR (95% CI) within each quartile
		Alirocumab	Placebo	
RDW				
MACE	Q1	2.6	3.1	0.83 (0.68, 1.01)
	Q2	3.1	3.7	0.84 (0.70, 1.01)
	Q3	3.8	4.4	0.86 (0.73, 1.03)
	Q4	4.9	5.7	0.86 (0.73, 1.01)
Death	Q1	0.7	1.0	0.68 (0.47, 0.99)
	Q2	0.9	1.1	0.87 (0.63, 1.21)
	Q3	1.4	1.6	0.90 (0.68, 1.18)
	Q4	2.1	2.3	0.89 (0.70, 1.14)
hs-CRP				
MACE	Q1	2.7	3.1	0.86 (0.70, 1.05)
	Q2	2.9	3.9	0.76 (0.63, 0.92)
	Q3	3.4	4.3	0.79 (0.66, 0.94)
	Q4	5.2	5.4	0.98 (0.84, 1.14)
Death	Q1	0.8	0.8	0.94 (0.65, 1.37)
	Q2	1.0	1.3	0.79 (0.57, 1.08)
	Q3	1.1	1.5	0.74 (0.55, 1.00)
	Q4	2.1	2.2	0.94 (0.74, 1.18)

Table 3 Risk of MACE and death per 1% increase of RDW in the placebo group.

Model	HR (95% CI) for MACE	HR (95% CI) for death
Unadjusted	1.20 (1.15, 1.27)	1.33 (1.25, 1.42)
Model 1: Adjusted for variables predictive of outcome, specifically excluding hs-CRP	1.11 (1.05, 1.17)	1.17 (1.07, 1.27)
Model 2: Adjusted for variables predictive of outcome, and hs-CRP	1.08 (1.01, 1.15)	1.14 (1.04, 1.26)
Model 2 in subgroup of patients with baseline hs-CRP <=1.7	1.06 (0.96, 1.17)	1.02 (0.85, 1.22)
Model 2 in subgroup of patients with baseline hs-CRP >1.7	1.09 (1.00, 1.18)	1.21 (1.07, 1.36)

Adjustment variables were those significantly associated with the risk of MACE or the risk of death. In Model 1 these variables were age, sex, hypertension, diabetes, smoking status, prior myocardial infarction, stroke, coronary bypass grafting, peripheral artery disease, baseline LDL-C, eGFR, hemoglobin A1c, hemoglobin, and body mass index. In Model 2, the adjustment variables were those of Model 1 and hs-CRP.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; RDW, red blood cell distribution width.

sociated with the risk of MACE in addition to RDW: age, sex, current smoking, hypertension, diabetes, family history of coronary artery disease, prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft, ischemic stroke, peripheral artery disease, heart failure, LDL-C, hemoglobin, hemoglobin A1c, and estimated glomerular filtration rate. A second model for MACE forced the inclusion of hs-CRP in addition to the variables included in the first model. Results of both adjusted models were consistent with those of the unadjusted model (Table 2) in showing significant association of baseline RDW with incidence of MACE or death in the placebo group but not with the treatment effect of alirocumab.

RDW decreased from baseline in both treatment groups but not significantly. Treatment with alirocumab or placebo did not affect RDW level over time (Table 4).

Discussion

This post hoc analysis from the ODYSSEY OUTCOMES trial demonstrates that RDW is positively associated with risk of MACE and death among patients who are clinically stable after a recent ACS. These associations remained significant after adjustment for other variables predictive of MACE or death, including demographic and medical history characteristics, LDL-C, and particularly hs-CRP. Alirocumab had no effect on RDW levels and reduced the risk of cardiovascular events when compared with placebo, irrespective of RDW level.

The present data add to the findings in previous analyses in several notable ways. First, RDW provided robust prognostics in a large, multinational population of patients with ACS, most of whom (89%) received high-intensity statin

Table 4 Treatment effects of alirocumab and placebo on RDW and hs-CRP.

Timepoint	Alirocumab (n = 9,451)	Placebo (n = 9,443)	Difference, LSM (SE) [95% CI]	p value
Baseline RDW, %, median (Q1, Q3)	n = 9,393 13.80 (13.30, 14.40)	n = 9,375 13.80 (13.30, 14.40)	–	–
RDW change from baseline, LSM (SE)				
Month 12	n = 7,561 −0.18 (0.01)	n = 7,861 −0.16 (0.01)	−0.02 (0.01) [−0.04, 0.00]	0.055
Month 24	n = 6,458 −0.25 (0.01)	n = 6,813 −0.23 (0.01)	−0.02 (0.01) [−0.04, 0.00]	0.13
Month 36	n = 3,133 −0.27 (0.01)	n = 3,323 −0.29 (0.01)	0.02 (0.02) [−0.01, 0.05]	0.25
Baseline hs-CRP, mg/dL, median (Q1, Q3)	n = 8,924 1.61 (0.78, 3.79)	n = 8,933 1.67 (0.79, 3.94)	–	–
hs-CRP change from baseline, LSM (SE)				
Month 4	n = 8,352 −1.40 (0.01)	n = 8,334 −1.43 (0.01)	0.04 (0.02) [0.00, 0.07]	0.032
Month 12	n = 7,579 −1.46 (0.01)	n = 7,932 −1.52 (0.01)	0.06 (0.02) [0.02, 0.10]	0.002
Month 24	n = 138 −1.03 (0.01)	n = 159 −0.92 (0.10)	−0.11 (0.15) [−0.41, 0.18]	0.463
Month 36	n = 535 −1.46 (0.06)	n = 548 −1.54 (0.06)	0.09 (0.083) [−0.08, 0.25]	0.303

CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; LSM, least squares mean; RDW, red blood cell distribution width; SD, standard deviation; SE, standard error.

therapy and the remainder who received maximum tolerated statin therapy. The trial population was also characterized by high utilization of other evidence-based therapies, including coronary revascularization and treatment with dual antiplatelet therapy, inhibitors of the renin-angiotensin system, and beta blockers. Second, in contrast to some prior observational cohort analyses, the outcomes reported here were blindly adjudicated. Third, the patients in the ODYSSEY OUTCOMES trial were randomized a minimum of 1 month after the qualifying ACS, thus at a time when acute phase effects on inflammatory markers such as hs-CRP should have waned.[13] Finally, both RDW and hs-CRP have been proposed as inflammatory markers that provide useful prognostic information after ACS and in chronic coronary heart disease. Our findings in fully adjusted models indicate that RDW contributes information on risk of MACE and death beyond that provided by hs-CRP, particularly among patients with elevated hs-CRP levels.

Historically, RDW was used as a means of anemia classification. In 2007, investigators from the North American Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity trial found an association between RDW level and cardiovascular death or hospitalization from heart failure in patients without anemia.[14] Following publication of those results and another analysis in patients with heart failure,[15] the association of elevated RDW levels with clinical outcomes was examined in patients with ischemic heart disease,[2] chronic dialysis,[16] diabetes,[17] stroke,[18] cancer,[19] inflammatory joint diseases,[20] and viral infections,[21] and in the general population.[22-24] In each case, the results demonstrated that an elevated RDW level was associated with an increased risk of MACE or death. The ODYSSEY OUTCOMES trial, consistent with existing literature, confirmed the association of RDW levels with CVD. Additionally, alirocumab significantly reduced CVD events at all RDW levels compared with placebo.

Despite robust associations of RDW with risk of MACE or death in fully adjusted analyses, the current data cannot determine whether RDW is a marker of other conditions that affect cardiovascular disease risk or if it reflects an abnormality of red blood cells that is directly related to the pathogenesis of MACE or death following ACS. In the former category, elevated RDW has been associated with chronic inflammatory conditions, and in the present analysis was indeed correlated with levels of hs-CRP. Other studies have correlated RDW with levels of interleukin-6 and fibrinogen.[5,15,25,26] As the life span of a red blood cell is roughly 120 days, elevated RDW levels may reflect inflammation over a period of months, unlike acute phase reactants such as hs-CRP or fibrinogen that reflect recent or ongoing inflammation. In the latter category, abnormal red blood cell morphology as marked by elevated RDW may be accompanied by reduced red cell deformability, and thereby microvascular dysfunction and compromised tissue perfusion.[4,27,28] In healthy

adults the omega-3 index, also known to affect membrane fluidity and deformability, was found to be inversely associated with RDW. [29] Furthermore, RDW may be inversely associated with fractional flow reserve independent of the severity of a coronary stenosis, also implying an adverse effect on microvascular function.[30]

Medications that may lower both RDW and hs-CRP levels include eicosapentaenoic acid[31] and colchicine.[32] Both of these agents also reduce cardiovascular risk,[33,34] but the association of levels and changes in RDW and treatment benefit have not been reported.

The present analysis of the ODYSSEY OUTCOMES trial shows that both RDW and hs-CRP levels are associated with an increased risk of MACE and death after a recent ACS. Although hs-CRP and RDW may both reflect inflammatory stimuli, they may predict risk of cardiovascular disease[6,35] and death[6,35] independently. When we controlled for baseline variables associated with MACE, including hs-CRP and LDL-C, RDW levels remained strongly predictive of cardiovascular events. Because RDW is provided with a standard complete blood count, this incremental information entails no added cost to medical care.

Although vascular inflammation influences atherosclerosis, and anti-inflammatory therapies have reduced MACE (canakinumab [CANTOS clinical trial],[36] colchicine),[33] alirocumab lowered levels of atherogenic lipoproteins and significantly reduced cardiovascular morbidity and mortality without a significant effect on markers of inflammation such as hs-CRP and RDW. These results support the notion that atherogenic lipoproteins and inflammatory targets are independent targets of therapy to reduce the risk of MACE.[37,38]

Limitations

In this analysis, adjustments were made only for baseline prognostic factors, and we did not consider any time-varying covariates affected by the course of treatment. This approach was used for the preservation of randomization and to prevent introduction of bias due to differential outcomes. We cannot exclude the possibility of residual confounding by factors not considered in this analysis. The mechanisms responsible for the association of RDW with cardiovascular risk remain uncertain and warrant further investigation.

Conclusions

This analysis of ODYSSEY OUTCOMES data shows that both RDW and hs-CRP are biomarkers that independently associate with the risk of cardiovascular events and death following an ACS. RDW, a routine element of laboratory data obtained in almost every patient, may therefore add to risk stratification and treatment decisions in patients with ACS. An RDW value of 14% or higher (approximately the highest quartile in this analysis) identifies patients at very high risk for MACE and death following ACS, despite optimized statin treatment and other evidence-based therapies.

Conflicts of Interest

P.M.M. reports receipt of research grants to his institution for the participation in the ODYSSEY OUTCOMES trial, as well as financial fees for serving as a medical monitor for the trial and associated support for travel related to trial meetings from Sanofi; consulting and speaking fees from Regeneron Pharmaceuticals, Inc. and Amgen; consultant fees from Esperion, Kaneka, and Stage II innovations; speaker fees from Amarin; advisor fees from Novartis for serving on their advisory committee; research grants to his institution from Ionis, FH Foundation, GB Life Sciences, Aegerion, Amgen, Kowa, Novartis, and Regeneron Pharmaceuticals, Inc.. P.G.S. reports grants and nonfinancial support (co-chair of the ODYSSEY OUTCOMES trial; as such, he received no personal fees, but his institution has received funding for the time he has devoted to trial coordination, and he has received support for travel related to trial meetings) from Sanofi; research grants and personal fees from Bayer (Steering Committee MARINER, grant for epidemiological study), Merck (speaker fees, grant for epidemiological studies), Sanofi (co-chair of the ODYSSEY OUTCOMES trial; co-chair of the SCORED trial; consulting, speaking), Servier (Chair of the CLARIFY registry; grant for epidemiological research), and Amarin (executive steering committee for the REDUCE-IT trial [Disease Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial]; consulting); and personal fees from Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Idorsia, Myokardia, Novo Nordisk, Novartis, Regeneron Pharmaceuticals, Inc. and AstraZeneca. P.G.S. also has a European application number/patent number, issued on October 26, 2016 (no. 15712241.7), for a method for reducing cardiovascular risk, all royalties assigned to Sanofi. A.M.Z. reports receiving fees for serving on a steering committee for the ODYSSEY OUTCOMES trial from Sanofi, and advisory board and speaker fees from Sanofi, Amgen, Boehringer Ingelheim, Bayer, Novartis, Pfizer, AstraZeneca, and Vifor. H.D.W. reports grant support paid to his institution for serving on a Steering Committee for the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) from Sanofi-Aventis and Regeneron Pharmaceuticals, Inc. for the ACCELERATE study (A Study of Evacetrapib in High-Risk Vascular Disease) from Eli Lilly and Company, for the STRENGTH trial (Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk Patients With Hypertriglyceridemia) from Omthera Pharmaceuticals, for the CAMELLIA-TIMI study (A Study to Evaluate the Effect of Long-term Treatment With BELVIQ [Lorcaserin HC] on the Incidence of Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects With Cardiovascular Disease or Multiple Cardiovascular Risk Factors) from

Eisai Inc, for the HEART-FID study (Randomized Placebo-Controlled Trial of FCM as Treatment for Heart Failure With Iron Deficiency) from American Regent, and for the ISCHEMIA Trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) and the MINT Trial (Myocardial Ischemia and Transfusion) from the National Institutes of Health USA. He also received grants to his institution and personal fees as Steering Committee member for the dal-GenE study (Effect of Dalcetrapib vs. Placebo on CV Risk in a Genetically Defined Population With a Recent ACS) from DalCor Pharma UK Inc, for the AEGIS-II study (The Safety and Tolerability of CSL112, a Reconstituted, Infusible, Plasma-Derived Human ApoA-I, After Acute Myocardial Infarction: The ApoA-I Event reducinG in Ischemic Syndromes I) from CSL Behring, for the SCORED trial (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) and the SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type2 Diabetes Post Worsening Heart Failure) from Sanofi-Aventis Australia Pty Ltd, and for the CLEAR Outcomes Study (Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid [ETC-1002] or Placebo) from Esperion Therapeutics Inc. H.D.W. was on the Advisory Boards for CSL Behring and Genentech, Inc. (an affiliate of F. Hoffmann-La Roche Ltd, "Roche"; Lytics Post-PCI Advisory Board at European Society of Cardiology. M.L. is an employee of Sanofi and may hold shares and/or stock options in the company. J.M. and G.M. are employees of Regeneron Pharmaceuticals, Inc. J.W.J. reports research grants from the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Commission Seventh Framework Programme; and research support from Amgen, Astellas, AstraZeneca, Daiichi-Sankyo, Lilly, Merck-Schering-Plough, Pfizer, Roche, and Sanofi. R.A.H. reports research grants (all DSMB related) from AstraZeneca, Janssen, and Bristol-Myers Squibb, serving on advisory boards for Gilead (uncompensated) and WebMD; and serving on the boards of directors (unpaid) for the American Heart Association and Stanford HealthCare. 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Contributors

All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy. Patrick M. Moriarty and Gregory G. Schwartz drafted the manuscript; contributed to conception or design; and contributed to acquisition, analysis, or interpretation. Jennifer McGinniss analyzed the data and wrote the methods section. All other authors contributed to conception or design; contributed to acquisition, analysis, or interpretation; and critically revised the manuscript.

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