Original Article

The role of red blood cell distribution width in mortality and cardiovascular risk among patients with coronary artery diseases: a systematic review and meta-analysis

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Background: Red cell distribution width (RDW) might be a novel biomarker that reflects multiple physiological impairments related to atherosclerosis and coronary artery diseases (CAD). We conducted this systematic review and meta-analysis to evaluate the association of RDW between all-cause mortality and fatal/non-fatal cardiovascular disease (CVD) events in CAD patients.

Methods: Relevant studies were searched and identified in the MEDLINE and EMBASE databases. English-language prospective studies that reported risk estimates for RDW and mortality/CVD events were included. Data were extracted regarding the characteristics and clinical outcomes, and a quality assessment was conducted. Results were extracted for the highest versus lowest RDW level, and meta-analyses were carried out using random effects models.

Results: We identified 22 studies enrolling 80,216 participants. The study duration ranged between 1 month and 23 years. Of the 15 studies that were included in the meta-analysis, higher RDW indicated a significant increased risk for all-cause mortality in CAD patients: pooled risk ratio (RR) 2.20 (95% CI, 1.42-3.39; P<0.0004). The results for fatal, non-fatal and fatal/non-fatal events were: pooled RR 1.80 (95% CI, 1.35-2.41; P<0.0001), RR 1.86 (95% CI, 1.50-2.31; P<0.00001) and RR 2.13 (95% CI, 1.20-3.77; P=0.01). Heterogeneity was moderately present; however, sensitivity analyses for follow-up duration, CAD subtype, or RDW as dichotomous values showed similar results.

Conclusions: The meta-analysis indicates that higher RDW levels are associated with increased risk of mortality and CVD events in patients with established CAD.

Keywords: Red cell distribution width (RDW); coronary artery diseases (CAD); mortality; cardiovascular (CV); meta-analysis

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Brief summary

The red cell distribution width (RDW) is a quantitative measure of the size variation of circulating erythrocytes. Of note, RDW might be a novel biomarker that reflects multiple physiological impairments related to atherosclerosis and coronary artery disease. However, conflicting findings have been reported on the association of RDW with risk of subsequent cardiovascular (CV) events. We therefore conducted this systematic review and meta-analysis to synthesize all available evidence of prospective studies on this interesting issue.

Introduction

RDW is a quantitative measure of the size variation of circulating erythrocytes with higher values reflecting greater heterogeneity in cell sizes (1). RDW is routinely reported to physicians in clinical practice as part of the automated complete blood count (CBC), which mainly served as an auxiliary index in the differential diagnosis of microcytic anemia (2).

In addition to its traditionally known role, RDW is of interest for its potential impact on cardiovascular disease (CVD) and mortality risk in general population (3-5). A previous meta-analysis and prospective studies have showed that higher RDW, even within the normal reference range, was strongly associated with increased risk of death and CVD risk in community-dwelling adults (3-5). Of note, RDW significantly improved mortality risk prediction beyond established risk factors, as assessed by several indices of model calibration and discrimination. Although the exact mechanisms are unclear, this association is provocative because it is independent of numerous factors, including nutritional status, anemia, inflammation, and others co-morbidity diseases. Hence, it is possible that RDW is a novel biomarker that reflects multiple physiological impairments related to atherosclerosis and coronary artery diseases (CAD).

However, conflicting findings have been reported on the association of RDW with risk of subsequent CVD events during prospective follow-up of individuals with established CAD (3-5). With implications for drug development and secondary prevention, the pathogenesis of first and subsequent CVD events may not be precisely equivalent. We therefore conducted this systematic review and meta-analysis to synthesize all available evidence of prospective studies that report the association of RDW in relation to all-cause mortality and fatal/non-fatal CVD events in patients with prior CAD.

Methods

A prospective protocol of objectives, literature-search strategies, inclusion and exclusion criteria, outcome measurements, and methods of statistical analysis was prepared a priori according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and the Meta-analysis of Observational Studies in epidemiology (MOOSE) guideline (6,7).

Search strategy

Study data were obtained through the following ways: searching on PubMed (1948 to January 2013), EMBASE (1948 to January 2013) and Cochrane Library database included terms "red blood cell distribution width", "mortality" and "CV events" and their corresponding index words using the special features in titles and/or abstracts. Only human studies were included. To identify further potentially relevant studies missed by the electronic database search, reference lists of identified trials and review reports were manually screened and searches are based on English language only. In addition, we verified the search strategy by hand-searching the reference lists of primary studies, review articles, and clinical guidelines. Email-alerts with newly published articles from MEDLINE were checked until October 1, 2013.

Inclusion and exclusion criteria

Inclusion criteria were the following: (I) serum or plasma RDW was the determinant; (II) outcomes: all-cause mortality, fatal and/or non-fatal CV events such as CV death, myocardial infarction (MI), stroke, heart failure (HF) and readmission; (III) paper type: original prospective quantitative cohort study (i.e., no review, commentary, case reports, editorial); (IV) study performed in participants ≥18 years. We excluded studies that did not report any of the outcomes mentioned above. The titles and abstracts of studies identified by the search strategy were independently screened by two reviewers (LZ.L. and C.S.). Differences between authors were resolved by consensus or by consultation of an additional reviewer (X.Z.W).

Quality assessment and data extraction

A quality checklist was developed to determine the quality of the eligible studies based on the PRISMA Statement and the MOOSE guideline in combination with a previously

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Table 1 Quality checklist based on the PRISMA Statement and the MOOSE guideline

Selection bias
Is the study population clearly described in terms of age, gender, and setting?
Is the percentage of eligible subjects who participated in the study mentioned?
Are participants in the study similar to eligible non-participants, in terms of age, gender, and important disease characteristics?
Were reasons for loss to follow-up presented and assessed during the study for possible systematic attrition? (subjects that did not finish the study)
Information bias
Is a clear description provided of the measurement method?
Are clear definitions of each outcome variable provided?
Statistical analyses
Are statistical analyses adequate to answer the research question?
Were multivariable analyses performed? If yes, continue with question 9
Was it clearly described which variables were included in the (multivariable) model(s)?
Final question
Were there any other important flaws in the design or analyses of the study? If yes, study not included

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MOOSE, Meta-analysis of Observational Studies in epidemiology.

published quality checklist for observational studies (6-8) (see *Table 1*). Studies were scored based on nine quality criteria on a binary scale; including description of characteristics of the study population, assessment of exposure and outcome, confounding and potential flaws. The quality of each study was independently assessed by Y.S and W.Y.M and scores were compared for each item of the checklist. The scores were summed and quality was considered poor [0-4], moderate [5-6], or good [7-9]. Studies with potential flaws or rated as poor quality were not included.

Of the eligible studies, information including first author, years of follow-up, country of origin, name of the study, number of participants, participants' characteristics, determination of outcome, RDW concentrations and category, and outcome measures were recorded. When the report did not contain sufficient details to adjudicate the validity of the study, or outcome data were missing, attempts were made to contact the authors by email and in writing.

Data synthesis and statistical methods

Results reported as count data were presented for all-cause mortality, fatal CVD events and non-fatal CVD events: adjusted hazard ratio (HR), odd ratio (OR) or regression coefficients (β) and 95% confidence interval (CI). We extracted the results of the highest versus lowest RDW concentrations and used the lowest RDW category as the reference. If the study reported more than one estimate, only the result of the largest RDW difference was included. We transformed risk estimates by taking their natural logarithms and calculated the standard errors as follows: (Ln upper limit - Ln HR)/1.96. We weighted the natural logarithm of the risk estimates by generic inverse variance to account for the sample size and distribution of the included studies (9).

We used Review Manager 5.2 (The Cochrane Collaboration, Oxford, United Kingdom) to analyze the collected data. The results of the included studies were pooled and meta-analyses were carried out using fixed or random-effects models. Statistical heterogeneity between studies was assessed using the chi-square test with significance set at $P<0.10$ and heterogeneity was quantified using the I^2 statistic. I^2 values represent the proportion of total variation attributable to heterogeneity rather than chance whereby 0% is no observed heterogeneity and 100% maximal heterogeneity.

Potential publication bias was evaluated by visual inspection of a funnel plot. A priori sensitivity analyses were defined to evaluate the stability of the pooled estimates and to examine changes in results after excluding specific

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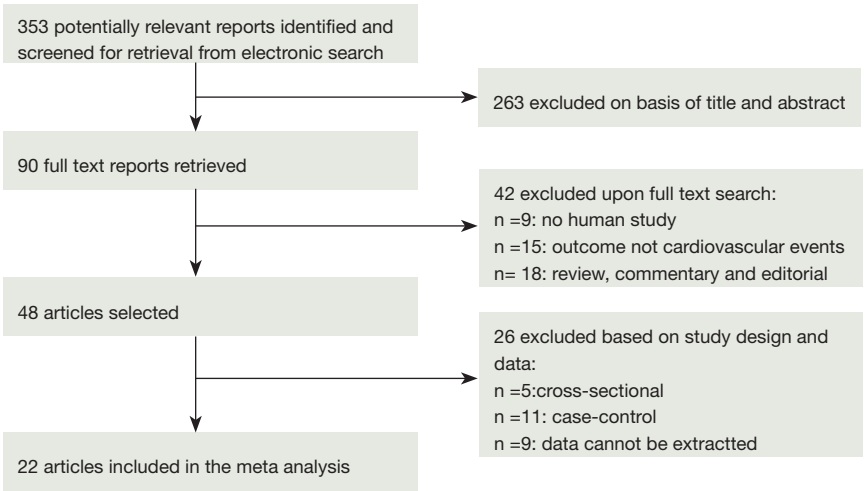

Figure 1 Flow diagram of the study selection process.

studies. The subgroup analyses were preplanned for: length of follow-up >4 years, subtype of CAD [acute coronary syndrome (ACS), coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI)] and RDW as dichotomous values. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Search results

The systematic literature search yielded 353 potentially relevant articles. *Figure 1* shows the flow diagram for the identification process. Briefly, 263 articles were excluded based on title and abstract. The remaining 90 studies were identified in full-text; 42 studies were excluded for study type and outcome. Then, another 26 studies were excluded based on study design (n=5 cross-sectional, n=11 case-control, n=9 data cannot be extracted). The hand search did not result in any additional articles. The email alerts yielded in two additional studies. Twenty-two studies were eligible for quality assessment and ranked according to their sum scores (see *Table 1*), of which 20 studies were grated as "good" and 2 as "moderate" quality. Agreement between the two reviewers was 97% for study selection and 96% for quality assessment of trials.

Study characteristics

Table 2 represents the main characteristics and results of the included studies on mortality and CVD events. Of the 22 studies (10-30), 15 investigated the relation between RDW and all-cause mortality, four and eight investigated fatal and non-fatal CVD events, respectively. Six studies investigated the relation between RDW and fatal and/or non-fatal CVD events. The total number of participants was 80,216. The population sizes of the studies, all published between 2007 and 2014, varied between 100 and 29,526. The mean study duration ranged between 1 month and 23 years. Overall, 22 different cohorts were used of which one included only men (12). Ten cohorts were conducted in Asia, six in the United States and four in Europe; mean age ranged between 55.6 and 66.6 years. Risk estimates (HRs/ORs), regression coefficients, and 95% CI were reported in 15 studies for RDW levels (highest *vs*. lowest) or dichotomous cut-off values of RDW, which were include in the subsequent meta-analysis. Additionally, risk estimates of RDW were reported as a continuous variable in seven studies.

RDW and all-cause mortality

Of the 15 studies that were included in the meta-analysis, all studies reported positive associations between high RDW concentrations and all-cause mortality, except one studies reported negative association (16). In the meta-analysis, the summary estimates for the highest compared with lowest category of baseline RDW indicated a significant increased risk for all-cause mortality in CAD patients: pooled risk ratio (RR) 2.20 (95% CI, 1.42-3.39; P<0.0004) (*Figure 2*). Heterogeneity was relatively high present (I^2 =93%).

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Table 2 Characteristics of studies included in the systemic review and meta-analysis

Study year	Follow-up/year	Country	Type of CAD	Patients	Mean age/year	Male (%)	Measurement outcomes	RDW levels	Results HR (95% CI)	Adjustments	Quality scores
Bekler 2014 (10)	1.5	Turkey	NSTE-ACS	237	61.1±11.9	75.5	CV death	14.1	1.55 (1.16-2.06)	Na	6/moderate
Benedetto 2013 (11)	11.8±4.1	Italy, United Kingdom	Isolated CABG	8,340	64.4±12.6	80.2	All-cause late death after discharge	12.9-13.4-14	2.91 (1.05-4.81)	Age; BMI <18.5 and >30 kg/m^2, GFR; chronic lung disease; diabetes, extracardiac arteriopathy; LV function	9/good
Cavusoglu 2010 (12)	2	US	CAG patients	389	65.6±10.0	100	All-cause mortality	14.4	2.69 (1.5-4.84);	Elderly status, high hs-CRP, presence of anemia, impaired LV function	8/good
Dabbah 2010 (13)	2.25	Israel	Patients with AMI	1,709	61.2±12.6	78.2	All-cause mortality; readmission	12.8-13.2-13.7-14.3	2.8 (1.6-4.7)	Age, gender, previous infarction, heart failure, history of diabetes, hypertension, smoking status, serum creatinine, anterior location of infarction, ST-elevation infarction, Killip class at admission, thrombolytic therapy, primary angioplasty, medical therapy, LVEF, baseline HB, and MCV	9/good
Tsuboi 2013 (14)	3.9	Japan	Stable CAD	560	66.6±10.2	80	All-cause mortality	12.1-13.1-14.2	2.66 (1.14-6.94)	Na	8/good
Lee 2013 (15)	1	Korea	AMI	5,196	64.5±11.9	67.3	MACE defined as death, non-fatal MI	12.6-13.1-13.9	6.18 (2.1-18.21)	Sex, age, HB, BMI, prior coronary heart disease, hypertension, diabetes mellitus, serum creatinine, total cholesterol, PCI, antiplatelet agents, β-blockers, and ACEI/arbs	9/good
Nabais 2009 (16)	0.5	Portugal	Patients with ACS	1,796	64.0±13.0	77.9	Death or MI	12.8-13.6	1.35 (0.86-2.11)	Age, renal failure, LVEF, Killip class, systolic blood pressure, heart rate, history of PCI	9/good
Ephrem 2013 (17)	3.8	US	NSTE-ACS patients	543	65.0±3.0	56	Readmission	16.3	1.35 (1.02-1.79)	Age, sex, race, type of insurance, creatinine, heart failure, hypertension, diabetes, and length of stay	9/good
Poludasu 2009 (18)	3.1±4.4	USA	PCI pts	859	62.2±10.4	49.4	Mortality	13.3-15.7	0.97 (0.33-2.87)	Na	7/good

Table 2 (*continued*)

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Table 2 (*continued*)

Study year	Follow-up/year	Country	Type of CAD	Patients	Mean age/year	Male (%)	Measurement outcomes	RDW levels	Results HR (95% CI)	Adjustments	Quality scores
Tonelli 2008 (19)	4.96	CARE study	Hyperlipidemia and MI	4,111	58.6±9.3	59.7	MACE (death, MI, stroke, HF)	12.6-13.4-13.8	1.78 (1.28-2.47)	Age; sex; race; smoking status; diabetic status; use of failure, hypaceis, aspirin, and pravastatin; GFR; proteinuria on dipstick urinalysis; systolic and diastolic blood pressure; HB; waist to hip circumference ratio; LVEF; fasting glucose; LDL-C; HDL-C; total cholesterol; and MCV.	9/good
Wang 2011 (20)	1 mon	Chinese	ACS	1,654	64.9±11.9	58.1	Cardiac death, HF, recurrent infarction	12.1-12.8-13.3	2.116 (1.427-2.137)	Age, gender, history of hypertension and diabetes, smoking status, BNP, LVEF, BMI, AMI on presentation, serum creatinine, peak CPK, number of diseased vessels, Troponin-I, hs-CRP, HB and medical therapy.	8/good
Isik 2012 (21)	0.5	Turkey	STEMI patients with primary PCI	100	61.3±12.8	77	Cardiovascular mortality	14	mid-term mortality 5.89 (1.63-21.24)	Age, sex, HB, hypertension, previous CAD, basal CK-MB, hs-CRP and d hyperten	7/good
Warwick 2013 (22)	5.8	UK	Isolated CABG patients	8,615	64.9±9.0	80.4	In-hospital mortality and long-term survival	13.5-14.2-15.3	1.05 (1.02-1.07)	Age; sex; race; smoking status; diabetic status; use of β-blockers, aceis, aspirin, and pravastatin; GFR; proteinuria on dipstick urinalysis; systolic and diastolic blood pressure; HB; serum phosphate; waist to hip circumference ratio; LVEF; serum triglyceride; LDL-C; HDL-C; total cholesterol; and MCV	9/good
Anderson 2007 (23)	4.9±3.1	IHC study	Suspected CAD	29,526	61.1±14.7	62	All-cause mortality	12.6-13.3-14	3.0 (2.3-3.9)	Na	8/good
Uyarel 2011 (24)	1.8±1.3	Turkey	Primary PCI for STEMI	2,506	55.6±11.8	82.8	Mace	14.8	1.831 (1.034-3.24)	Sex, age, time to reperfusion, DM, hypertension, smoking habit, GFR, multivessel disease, unsuccessful procedure, anterior MI, admission anemia, transfusion	9/good
Azab 2011 (25)	4	USA	NSTEMI	619	64.5±11.9	67.4	All-cause mortality	>14	1.104 (1.004-1.214) per 1 unit	Appropriate GRACE score, HB, serum glucose, LDL, LVEF, use of statin, use of aspirin, use of clopidogrel, prior CABG, prior coronary angioplasty and in-hospital bypass surgery	8/good

Table 2 (*continued*)

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Table 2 (*continued*)

Study year	Follow-up/year	Country	Type of CAD	Patients	Mean age/year	Male (%)	Measurement outcomes	RDW levels	Results HR (95% CI)	Adjustments	Quality scores
Ren 2013 (26)	1	Chinese	Stable angina	1,442	59.8±5.4	62.1	Mortality/ACS	11.7-12.5-13.1	1.544 (1.058-3.216) per quintiles	Age, gender, history of hypertension, diabetes or arrhythmia, the smoking status, BMI, blood pressure, the levels of serum creatinine, glucose, lipids, ALT, AST, hs-CRP and HB, number of diseased vessels, BNP level, the white blood cell count, an LVEF	9/good
Yao 2014 (27)	2.41	Chinese	CAD DES-PCI	2,169	60.2±10.9	67.7	Mace	12.27-13-13.5	1.37 (1.15-1.62)	Age, gender, DM, hypertension, peripheral vascular disease, number of vessels, multivessel disease, prior MI, GFR, LVEF, number of stents implanted, total stent length, and stent diameter	8/good
Osadnik 2013 (28)	2.5	Poland	Stable CAD/PCI	2,550	63.9±9.5	70.5	Mortality	13.1-13.6-14.1	1.23 (1.13-1.35) per 1%	Age, sex, heart failure, atrial fibrillation, hypertension, previous MI and PCI, previous CABG, previous stroke, diabetes, lipid abnormalities, obesity, CKD, smoking, NYHA class, heart rate, blood pressure, LVEF, number and type(s) of stent implanted, number of PCI vessels, HB, MCV	8/good
Arbel 2014 (29)	3	Israel	CAG pts	3,222	65.6±11.8	72.3	MACE (death, MI, stroke)	13.5	1.12 (1.07-1.18) per 1%	Age, gender and anemia status in addition to conventional cardiovascular risk factors, cardiovascular medications, metabolic variables, inflammatory variables, ACS status	9/good
Patel 2009 (3)	2.4±1.0	USA	Suspected CAD	2,584	63.0±11.0	66	All cause death	14.5	1.29 (1.19-1.38) per 1%	Na	7/good
Lappé 2011 (30)	8.4±15.2	USA	CAD	1,489	65.5±11.3	74.4	Mortality	13.2	1.37 (1.29-1.46) per quintile	Age, gender, diabetes, hypertension, dyslipidemia, smoking, family history of early CAD, and other risk factors: smoking, family history, hyperlipidemia	8/good

AMI, acute myocardial infarction; ACS, acute coronary syndrome; CAD, coronary artery disease; PCI, percutaneous coronary intervention; MACE, major adverse cardiovascular events; HF, heart failure; CABG, coronary artery bypass grafting; BMI, body mass index; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; MCV, mean corpuscular volume; HB, hemoglobin; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, brain natriuretic peptide; CK-MB, creatine kinase-MB; GFR, glomerular filtration rate.

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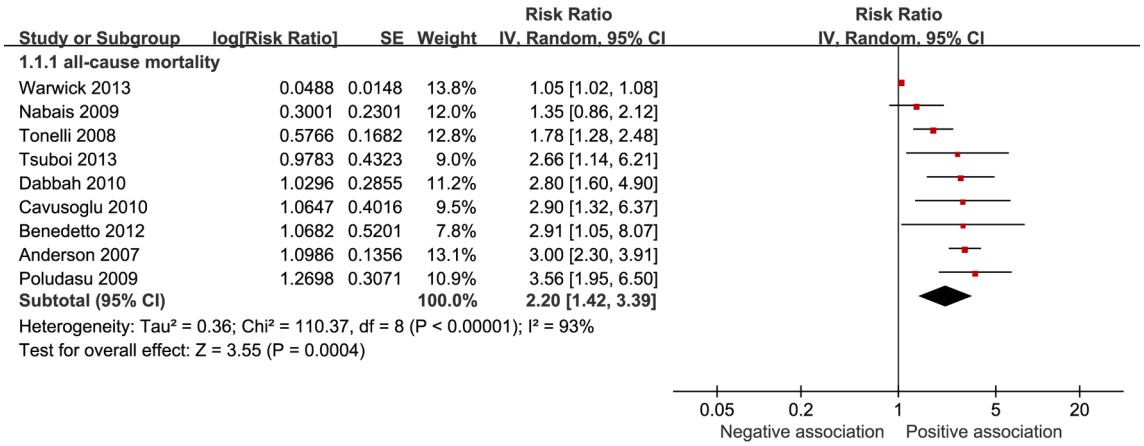

Figure 2 Pooled relative risk of RDW and all-cause mortality of the included studies. Risk ratios (RRs) are shown with 95% CIs. RDW, red cell distribution width.

RDW and fatal/non-fatal CVD events

Four studies investigated excess RDW level and fatal CVD events specifically (10,20,21,26). Eight studies (10,13,16,17,20,21,26,27) investigated high RDW and non-fatal CVD events and three studies (14,15,19,24) reported the association between RDW and fatal/non-fatal CVD events. All studies reported positive associations between high RDW concentrations and fatal CVD events. For non-fatal CVD events, six studies reported positive associations and in two studies (16,17) higher RDW was not significantly associated with non-fatal CVD events. One study reported cardiac events for HF and stroke separately. In the meta-analysis, the pooled estimates for the highest compared with lowest category of baseline RDW indicated a significant increased risk for fatal CVD events: pooled RR 1.80 (95% CI, 1.35-2.41; P<0.0001), with a moderate heterogeneity (I^2 =44%). The pooled estimate for non-fatal CVD events resulted in a slightly higher association: RR 1.86 (95% CI, 1.50-2.31; P<0.00001), with a low heterogeneity (I^2 =28%). The pooled estimate for the overall fatal/non-fatal CVD events resulted in a higher association: RR 2.13 (95% CI, 1.20-3.77; P=0.01; I^2 =66%) (see *Figure 3*).

Publication bias and sensitivity analysis

The funnel plot (*Figure 4*) for studies of RDW and all-cause mortality shows reasonable symmetry at the top of the funnel plot and a little asymmetry at the bottom, which suggest some evidence of publication bias for smaller studies.

The findings were similar whether fixed or random-effects models were used. However, sensitivity analyses for follow-up duration >4 years only marginally changed the results (*Figure 5*). The inclusion of studies with ACS patients attenuated the results; nonetheless, the estimate was still significant: RR 1.91 (95% CI, 0.93-3.89; P=0.08; I^2 =75%). The inclusion of studies with PCI patients resulted in a more pronounced estimate and negligible heterogeneity: HR 3.23 (95% CI, 1.98-5.27; P<0.0001; I^2 =0%). No sensitivity analyses were performed for fatal CVD events, because of too few studies.

Discussion

Our study provides the first systematic review and meta-analysis of prospective studies of RDW and total mortality, fatal and non-fatal CVD events in populations with established CAD. The meta-analysis indicates a significant increased risk for RDW excess and all-cause mortality and CVD events that range from 80% to 120%.

Our systematic review and subsequent meta-analysis has several strengths. This first systematic review gives a broad overview of all prospective studies on RDW in relation to all-cause mortality and fatal/non-fatal CVD events, and provides insight in its associated risks. The systematic review and meta-analysis were performed according to the PRISMA Statement and the MOOSE guideline and included a quality assessment-an important component to evaluate the methodological quality (31,32). The quality assessment allowed us to distinguish between poor, moderate and good quality studies and to the selection of

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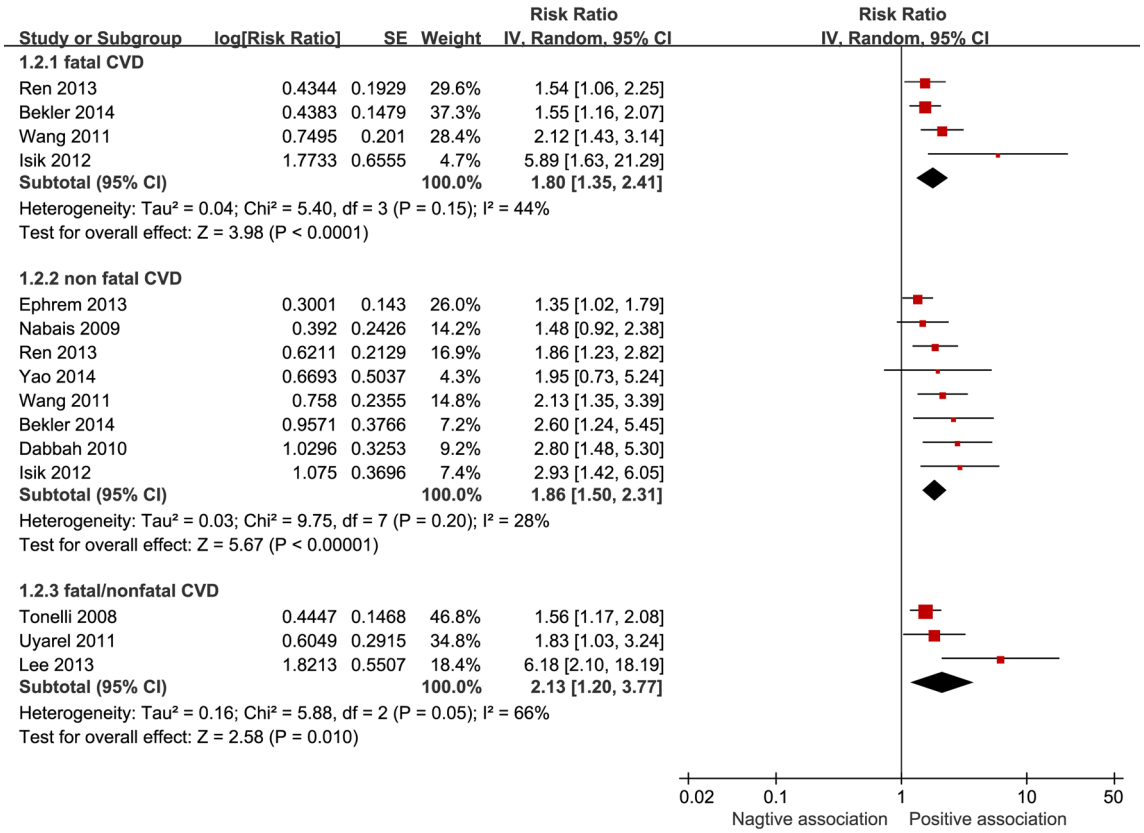

Figure 3 Pooled relative risk of red cell distribution width (RDW) and fatal cardiovascular (CV) events, non-fatal CV events and fatal/non-fatal CV events of the included studies. Risk ratios (RRs) are shown with 95% CIs.

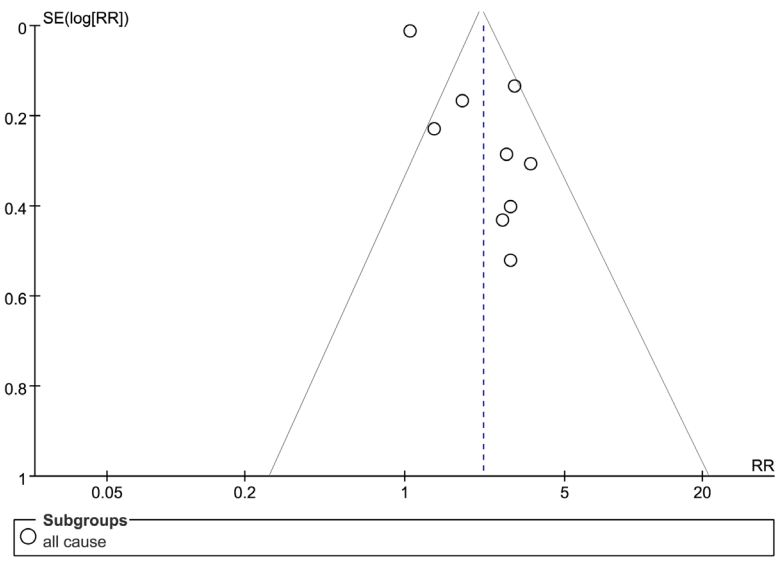

Figure 4 Funnel plot for red cell distribution width (RDW) and all-cause mortality. Each square indicates one study with its standard error indicating the weight of the study and its relative risk. The dotted lines represent 95% CI to visualize the symmetry around the pooled estimate.

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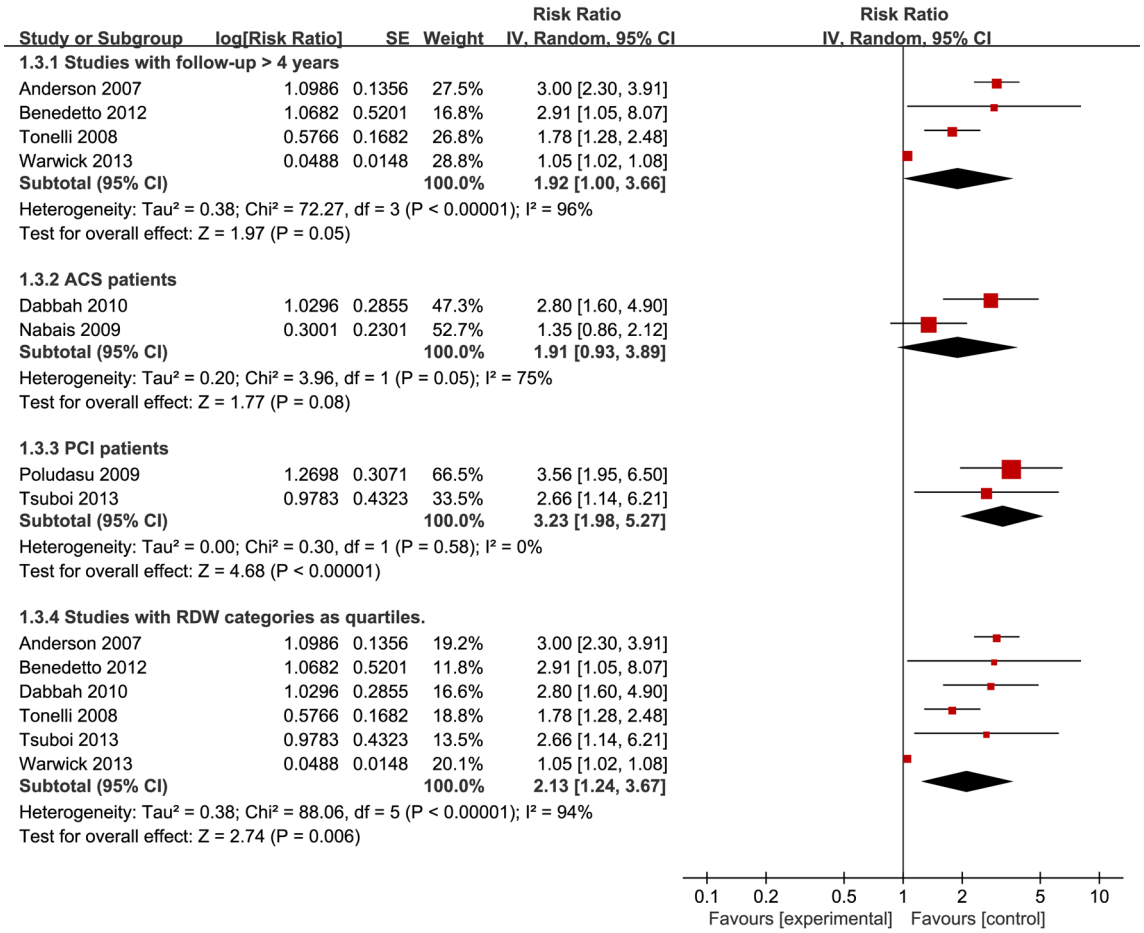

Figure 5 Forest plots of red cell distribution width (RDW) and all-cause mortality of the included studies: studies with follow-up >4 years; B, ACS patients; percutaneous coronary intervention (PCI) patients; studies with RDW categories as quartiles. Risk ratios (RRs) are shown with 95% CIs.

only moderate and good quality studies. This resulted in studies with multivariable adjusted risk estimates and a large number of included CVD cases >80,000. Moreover, the present analysis included only prospective cohort studies and most follow-ups lasted more than 23 years (30), which limits the problem of reverse causation bias.

The meta-analysis of observational studies might be influenced by heterogeneity. The variance between the included studies could partly be due to differences in study populations, RDW assays, outcome definitions, and adjustment for confounders. The use of random-effects models in our analyses adjusts in part for these variances between studies (9). Subgroup analyses were performed to test the stability of the pooled estimates. The positive association between higher RDW concentrations and CVD events was consistent given the similar pooled risk estimates for total mortality, fatal and non-fatal CVD events in both fixed and random models. This suggests that higher RDW level might be involved in pathological processes that lead to CVD. Of note, the inclusion of studies with PCI patients resulted in a higher HR, which might indicate that PCI patients are more prone to RDW excess and thereby have a higher risk of developing a secondary CVD event.

However, it should be noted that the results of our meta-analysis could not identify whether RDW is a causal factor for CVD. The studies in the meta-analysis used different approaches to define RDW categories. This might have affected our results, although we took into account the result of quartile 4 versus quartile 1 when available and used this approach consistently for all included studies. Sensitivity analyses for RDW and total mortality based on RDW quartiles resulted in a similar estimate than

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studies that used dichotomous cut-off values: pooled RR 2.13 (95% CI, 1.24-3.67). RDW cut-off values reflect a smaller difference in RDW concentration between RDW groups compared with RDW quartiles. However, pooling studies that reported cut-off values still showed a significant RR, which suggests that moderate elevations in RDW concentrations could play a role in the development of mortality risk of CAD patients.

Visual inspection of the funnel plot illustrates that studies with a smaller standard error at the top of the funnel plot were more symmetrically distributed than studies with a larger standard error at the bottom of the funnel plot (9). This suggests possible publication bias favoring smaller studies with significant results, which implies that the pooled estimate could be an overestimation of the true association; however, the power to detect publication bias is low given the limited number of studies. In addition, negative studies are less likely to be published and not all endpoints of the included studies were adjudicated and definitions of end points could be different between studies.

Based on the available prospective studies and the absence of randomized controlled trials, this meta-analysis highlights a risk factor for subsequent mortality and CVD events in populations with established CAD. Randomized controlled trials in these persons are therefore warranted to determine whether RDW-modifying therapies could result in less CVD events. It should be noted that lack of a gold standard to measure RDW hampers clinical decision making and treatment for subjects with high RDW concentrations. Nonetheless, more awareness should be given to individuals with a high RDW concentration in CAD populations.

Conclusions

Our meta-analysis supports that higher RDW concentrations are associated with increased risk of subsequent mortality risk and CVD events in established CAD patients. Despite the possibility of some publication bias, the results provide evidence for positive associations considering the quality, direction and magnitude of the associations of the included studies. Future studies should focus on RDW-modifying therapies to give more insight into the underlying mechanisms that might lead to CVD events.

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