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Red cell distribution width and risk for venous thromboembolism: A population-based cohort study

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ABSTRACT

Introduction: Red cell distribution width (RDW) has been associated with venous thromboembolism (VTE), but whether RDW is a predictor of first event of VTE is unknown. We investigated the association between RDW and incidence of first event of VTE in a population-based cohort.
Materials and Methods: RDW was measured in 27 042 subjects (aged 45–73 years, 60.6% women), without previous history of VTE or cancer within 5 years before follow-up, who participated in the Malmö Diet and Cancer study during 1991–1996. Incidence of VTE was identified from the patient register and the cause of death register during a mean follow-up of 13.8 years and studied in relation to RDW.
Results: During follow-up, 991 subjects (57.5% women) were affected by VTE (pulmonary embolism or deep venous thrombosis of the lower limbs). After adjustment for potential confounding factors the hazard ratios (HR) for VTE for the second, third and fourth RDW quartiles 1.15 (95% confidence interval 0.94–1.41), 1.41 (1.14–1.73), 1.74 (1.38–2.21), respectively, were compared with the bottom quartile of RDW. In the multivariate model subjects with the top 5% of RDW values compared with the bottom quartile had an even higher risk (HR = 2.51, 1.78–2.54). In receiver operating characteristic (ROC) analysis, the male specific area under the ROC curve (AUC) for RDW was 0.57 (95% CI 0.54–0.59). The female specific AUC was 0.56 (95% CI 0.53–0.58).
Conclusions: RDW was found to be associated with long-term incidence of first event of VTE among middle-aged subjects.

Introduction

Venous thromboembolism (VTE) is the third most common cause of death from cardiovascular disease after coronary heart disease and stroke [1]. Although a number of acquired and genetic risk factors for VTE have been identified, in 30–50% of cases VTE is idiopathic [1]. During the last few decades research has therefore concentrated on identifying new VTE risk factors and creating predictive models for VTE [2].

Erythrocytes, or red blood cells (RBCs), are constituents in clots and thrombi formed in vivo [3]. RBCs play a prothrombotic role in blood coagulation by increasing blood viscosity and forcing platelets towards the vessel wall [3]. Incorporation of RBCs into a fibrin clot affects clot structure and mechanical properties [3]. Even small structural differences of RBCs may have a large influence on pathophysiology [3]. Moreover, RBCs actively participate in thrombin generation [4]. A subfraction of red blood cells expresses phosphatidylserine on their surface. Unlike platelets, RBCs produce thrombin through the meizothrombin pathway, which has consequences in the context of clot formation and stabilization [4]. Polycythemia Vera has been associated with VTE [5], and hematocrit variations in the general population have been associated with VTE [6]. An increased focus on RBCs may therefore be justified, and may reveal novel mechanisms and risk factors for VTE.

Red cell distribution width (RDW) is a measure of the size variation as well as an index of the heterogeneity of the erythrocytes (i.e. anisocytosis) [7–9]. RDW is part of routine hematology laboratory tests and is used for classification of anemia [7–9]. Recent studies have shown that RDW is associated with increased mortality in a number of cardiovascular disorders such as coronary artery disease, stroke, peripheral artery disease, heart failure, pulmonary embolism, and pulmonary arterial hypertension, reviewed by Montagnana et al. [10]. It is however unclear whether anisocytosis might be the cause, or a simple epiphenomenon due to conditions such as inflammation, impaired kidney function, malnutrition, or oxidative damage [10]. Two studies have determined RDW in patients with pulmonary embolism (PE) [11,12]. Both studies found that a high RDW level, i.e. anisocytosis, was an independent predictor of early PE-related mortality [11,12]. Recently, RDW has been associated with venous thromboembolism (VTE) in two case–control studies [13,14]. These case–control studies cannot exclude the

Abbreviations: CI, confidence interval; HR, Hazard ratio; RDW, Red cell distribution width; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; MDC, Malmö Diet and Cancer study; CHD, coronary heart disease.

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possibility that anisocytosis was the result of the thrombotic event itself. To the best of our knowledge, there are no prospective studies on the association between RDW and risk of first event of VTE, i.e. deep venous thrombosis (DVT) and PE.

The purpose of the present study was to determine whether RDW is an independent predictor of first event of VTE in asymptomatic middle-aged subjects in the Malmö Diet and Cancer Study (MDC), which is a prospective cohort study in Malmö.

Materials and Methods

Study Population

The Malmö Diet and Cancer study (MDC) is a prospective cohort study from the city of Malmö in the south of Sweden. Sample characteristics, data collection, and clinical definitions for MDC have been described previously [15–22]. Briefly, 28 449 men (n = 11 246, born 1923–1945) and women (n = 17 203, born 1923–1950) attended a baseline examination between March 1991 and September 1996. Participants underwent sampling of peripheral venous blood, measurement of blood pressure and anthropometric measures and filled out a self-administered questionnaire. Information on RDW was available in 28 363 subjects [19]. Subjects with previous VTE (n = 360 subjects) at the baseline examination were excluded. Patients with diagnosis of cancer within 5 years before baseline were excluded (n = 448). Of the remaining 27 563 subjects (8 patients were diagnosed with both VTE and cancer before baseline), 521 subjects were excluded due to missing information on blood pressure, smoking habits, alcohol consumption, education level, civil status, hemoglobin value, and body mass index (BMI). Thus, the final study population in the analysis consisted of 27 042 (10 660 [39.4%] men and 16 382 [60.6%] women) subjects, aged 45–73 years.

Measurements and Definitions

Information on current use of statins, blood-pressure-lowering and anti-diabetic medications, physician-treated cancer, smoking habits, alcohol consumption, leisure-time physical activity, education level, and civil status were obtained from a self-administered questionnaire [15–22]. Weight and height were measured to the nearest 0.1 kg and 0.5 cm, respectively, with subjects wearing light clothing and no shoes. Current BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Blood pressure was measured using a mercury-column sphygmomanometer after 10 min of rest in the supine position. Hyperglycemia was defined as fasting whole blood glucose level greater than 109 mg/dL (i.e. 6.0 mmol/L), self-reported physician's diagnosis of diabetes or use of anti-diabetic medications. History of atrial fibrillation and also history of cardiovascular disease (CVD) at baseline was defined as diagnosis of atrial fibrillation and coronary heart disease (CHD) or stroke, respectively, in the Swedish National Hospital Discharge Register (SNHDR) [15,21,23]. Cancer during follow-up among individuals with first event of VTE (during follow-up) was obtained from Swedish Cancer Register. Subjects were categorized as current smokers (i.e. those who smoked regularly or occasionally) or non-smokers (i.e. former smokers and never smokers). High alcohol consumption was defined as >40 g alcohol per day for men and >30 g per day for women [15,19]. High education level was defined as completed secondary school and at least one year of education from college, university or higher (e.g. >12 years education), modified from reference [19] and [21]. Civil status was categorized into married or not [20]. Low level of physical activity was defined as the lowest tertile of a score revealed through 18 questions covering a range of activities in the four seasons. The evaluation of the questionnaire has been previously reported [19,22].

Red cell distribution width, mean corpuscular volume (MCV), hemoglobin, platelet and leucocyte concentrations were analyzed consecutively in fresh heparinized blood. Erythrocyte diameter was measured using a fully automated assay (SYSMEX K1000). Red cell distribution width was calculated as the width of the erythrocyte distribution curve at a relative height of 20% above the baseline. The intra-assay CV was 2.2%. Reference values were 36.4–46.3 fL in women and 35.1–43.9 fL in men [24].

Ascertainment of Venous Thromboembolic Events

All subjects were followed from the baseline examination until a first event of VTE, emigration, death or end of follow-up (December 31, 2008), whichever came first. VTE was defined as International Classification of Diseases – 8th revision (ICD-8 used before 1987), code 450 (PE), and 451 (DVT of the lower limbs) (ICD-9 used 1987–1996), code 415B (PE), and 451 (DVT of the lower limbs); and (ICD-10 used 1997–2008) I26 (PE), and I80 (DVT of the lower limbs) as the primary diagnosis. Patients with superficial thrombophlebitis were excluded (ICD-9 code 451A and ICD-10 code I80.0). The inpatient register, the outpatient register and the cause of death register were used to identify cases with VTE. All these registers have 100% coverage in Malmö during the whole follow-up time. A validation study has shown that a diagnosis of VTE in the SNHDR has a validity of 95% [25]. Such high validity has also been found for other cardiovascular disorders such as myocardial infarction (94%), stroke, heart failure, and atrial fibrillation [21,23,26–28]. The overall validity of the SNHDR is 87% [29]. A previous population-based prospective study was performed at the Malmö University Hospital in 1998–2006, of all in- and outpatients diagnosed with VTE in Malmö [30], i.e. at the same study center as the present study and with partially overlapping study periods. Among 1140 VTE patients, virtually all were diagnosed with an objective method such as phlebography, ultrasound or computer tomography [30]. Similar results were reported in another Swedish study that found that most Swedish patients with VTE are objectively diagnosed [31].

Statistical Analysis

Detailed information on the statistical analysis is found in the supplementary material. P-values were calculated with two-sided Student's t-test for continuous variables and with two-sided Fischer's exact test for dichotomized variables. Confidence interval for incidence rates were calculated with the OpenEpi version 2.3.1 according to Rothman/Greenland as described [32,33]. Cox proportional hazards regression was used to examine the association between RDW and incidence of VTE. Hazard ratios (HR) with 95% confidence interval (CI) were calculated [32]. The area under the ROC (receiver operating characteristic) curve (AUC) was used as a measure of the overall performance of the ROC curve because it reflects the probability that the diagnostic test will classify correctly [34]. Positive [sensitivity/(1-specificity)] and negative [(1-sensitivity)/specificity] likelihood ratios were also calculated to express the odds that a given value of a screening test outcome would be expected in a subject with or without VTE, respectively. Analyses were performed using IBM SPSS 21 (IBM, Armonk, New York, USA).

Ethical Approval

All participants provided written informed consent, and the study was approved by the ethics committee at Lund University, Lund, Sweden (LU 51/90). The MDC is registered in the US Library of Medicine as trial number NCT 01216228 (http://www.clinicaltrials.gov).

Results

Baseline Characteristics

Cardiovascular risk factors at the baseline examination for the middle-aged MDC cohort in relation to the sex-specific quartiles of