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Biomarkers for risk stratification in secondary cardiovascular prevention. A role of red blood cell distribution width and calcium score

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ABSTRACT

Background: Patients with coronary artery disease (CAD) are considered as high risk in terms of secondary cardiovascular prevention. However, obviously the risk is not homogenous across the whole group. Red blood cell distribution width (RDW) has been recently related to adverse outcomes in patients with atherosclerosis. Calcium score (CaS) may be used for risk stratification in primary prevention. The value of these biomarkers for prediction of cardiovascular outcomes in patients with CAD is unknown.
Methods: The study group comprised 269 consecutive patients with significant stable CAD. The primary endpoint was a composite of death or nonfatal myocardial infarction.
Results: Median post-discharge follow up was 43.2 months (IQR39.2–48.6). The primary outcome was observed in 27 patients including 13 deaths and 14 nonfatal myocardial infarction. According to ROC analysis the best cut-off value for RDW for prediction of the primary event was 14% [(AUC) = 0.69; 95% CI:0.63–0.75; p = 0.0002] and for CaS was 603 [(AUC) = 0.66; 95%CI:0.60–0.72; p = 0.001]. According to multivariable Cox regression analysis both RDW>14% (HR 2.6; 95%CI:1.1–5.9) and CaS>603 (HR 2.3; 95% CI:1.1–5.1) were independently correlated to the primary outcome. Subsequently, patients were categorized into three risk subgroups: LOW: CaS≤603 and RDW≤14–124(46.1%), MID: either CaS>603 or RDW>14–104(38.7%), and HIGH - CaS>603 and RDW>14–41(15.2%) patients. The respective risk of events according to Kaplan–Meier analysis were 4.03%, 9.62%, and 29.27% (p < 0.0001).
Conclusions: RDW and calcium score may be predictors of future cardiovascular events in patients with significant CAD. They may be useful tools for risk stratification and may indicate patients suitable for more aggressive secondary prevention measures.

Patients with diagnosed coronary artery disease (CAD), by definition are considered as high risk in terms of secondary prevention [1]. According to observational studies, mortality rates for CAD patient's population range from 1.2 to 2.4% per annum, and non-fatal myocardial infarction (MI) incidence ranges between 0.6% and 2.7% [2–8]. Cardiology guidelines recommend standardized medical intervention in all patients, comprising of antithrombotic therapy, statins and adequate controlling for risk factors of CAD or concomitant diseases [8]. However, according to common experience the risk related to coronary atherosclerosis is not uniform across the whole CAD population; patients with diffuse atherosclerosis and dynamic clinical manifestation likely differ from those with isolated single stenosis and stable angina. Those higher risk patients may likely benefit from more aggressive medical intervention, especially, that there are many new anti-atherosclerotic therapies in the pharma pipelines [9]. Lack of biomarkers for risk stratification of patients with significant CAD impedes development of novel, personalized therapies, and subsequently improvement of cardiovascular outcomes.

Red blood cell distribution width (RDW) is an indicator of heterogeneity in the size of circulating erythrocytes and is reported as

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a standard part of the complete blood count (CBC) laboratory test. Recent studies have showed that higher levels of RDW may be associated with increased atherosclerotic burden or risk of cardiovascular events in patients after myocardial infarction [10–12].

Calcium scoring is a tool which may be used for risk stratification in primary prevention. It quantifies coronary calcium which reflects atherosclerotic burden and is correlated with adverse outcomes during follow-up in asymptomatic patients without diagnosis of CAD [13]. It is unknown however, whether calcium score may predict cardiac events in patients with diagnosed CAD.

Therefore, we evaluated the value of these two biomarkers and their combination for prediction of cardiovascular outcomes in patients with significant coronary artery disease.

1. Methods

1.1. Study design and patient population

This is a retrospective analysis based on the prospective registry cohort. Our study group comprised 269 Caucasian, consecutive stable, symptomatic patients with significant CAD diagnosed based on computed tomography angiography between March 2009 and December 2009 from among 600 patients undergoing coronary CTA in our center during this time interval. Significant CAD was defined as at least one coronary stenosis of more than 50% in a major coronary artery diagnosed on CTA or calcium score above 800 (in these patients contrast coronary CTA was not performed, and they were admitted for invasive angiography). Patients presenting with acute coronary syndrome (ACS), a history of percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG) or significant arrythmia were excluded from the study. Clinical data including classic risk factors for the development of CAD such as age, sex, hypertension, dyslipidemia, diabetes mellitus, smoking and family history of CAD were recorded. Dyslipidemia was defined as total cholesterol levels 5.18 mmol/l or statin use. Hypertension was defined as a systolic blood pressure higher than 140 mmHg or a diastolic blood pressure higher than 90 mmHg, or use of antihypertensive medications.

Baseline RDW and hemoglobin were measured as a part of the automated complete blood count before computed tomography angiography using Roche Cobas Analyzer. Calcium score (CaS) was evaluated using Agatston method [14]. Invasive coronary angiography data included number of significant stenoses (>50%) in vessels more than 1.5 mm in reference diameter.

Out of the enrolled patients, 33(12.3%) had CABG and 143(53.2%) had PCI as the result of the index angiography, the remainder was managed medically based on the clinical status and functional ischemia testing. Those procedures were not counted as events.

All patients provided consent for the study, and the study was conducted according to Declaration of Helsinki.

1.2. Coronary Computed Tomography Angiography data acquisition

Coronary Computed Tomography Angiography (CTA) was performed with a dual source 2 × 64-slice scanner (Somatom Definition; Siemens Medical Solutions, Erlangen, Germany) with 330-ms rotation time, 0.6-mm collimation, and 100–120 kV of tube voltage, following calcium score study. In patients, for whom calcium score exceeded 800 contrast study was abandoned and such patients were referred routinely to invasive angiography. In all patients who had contrast study, sublingual nitrates (0.8 mg) were administered, if the heart rate was ≥70 beats/min, an intravenous bolus of metoprolol (increasing doses at 5 mg intervals, up to maximum dose of 20 mg) was given. From 60 to 80 mL of contrast agent iomeprol (Iomeron 400; Bracco) was injected intravenously at 6 mL/s. An electrocardiogram-gated retrospective acquisition protocol was used in all patients. Scan data were reconstructed routinely in mid to end diastole (60%–70% of R–R interval). Data sets that contained motion artifacts were individually optimized by changing the reconstruction window.

Coronary CTA analyses were performed off-line by experienced readers (MK, CK, JP), who evaluated all arteries with the reference diameter of above 1.5 mm for the presence of coronary stenosis above 50%.

1.3. Follow up and study endpoints

Patient's history data were obtained from the patients' interview and medical documentation. The follow up data were collected based on outpatient visits or using standardized telephone questionnaire at the mean of 43.2 months (IQR 39.2–48.6). The primary endpoint was a composite of death and nonfatal myocardial infarction [ST-elevation of ≥0.1 mV in >1 limb leads or of ≥0.2 mV in contiguous chest leads or new left bundle branch block (LBBB)] confirmed by medical records. Follow up data were available for all patients.

Assuming mean RDW at 13.4 ± 1.1%, 30 events would allow detection of 6% difference between events/non-events, with alpha 0.05 and power 80%. Based on previous literature, we assumed 11%(=30 patients) event rate over the planned follow-up period of 3.5 years, ultimately translating into 270 enrolled subjects [8].

1.4. Statistical analysis

Continuous data with normal distribution are presented as means (±SD). Non-normally distributed variables are presented as medians with interquartile ranges (IQR) and were analyzed as continuous after log transformation as appropriate. The best predictive values for RDW and calcium score were calculated based on ROC area under the curve analysis with the Youden index [15]. The predictive value of the variables was evaluated with Cox proportional hazards model. The independent effect of variables on primary outcome was calculated using Cox multivariate proportional hazards regression analysis, incorporating classic risk factors. Kaplan Meier curves were presented for the RDW and calcium score derived risk categories. The high risk categories for multivariable models made of classic risk factors or following addition of RDW and calcium score, were based on the cutoff points established by means of the respective ROC curves. This approach was to ensure the best possible risk categorization based on the classic risk factors. The net reclassification improvement was quantified as a sum of differences in proportions of individuals moving up minus the proportion moving down for people who develop events, and the proportion of individuals moving down minus the proportion moving up for people who do not develop events. Significance of the reclassification was tested using Mc Nemar test [16].

$P < 0.05$ was considered statistically significant. All analyses were performed using MedCalc Software (version 13.2.2, Ostend, Belgium).

2. Results

269 patients (107 female), mean age 66.24 (±7.87 years) were included in the analysis. During the follow-up, the primary outcome was observed in 27 (10.0%) patients, including 13 (4.8%) deaths and 14 (5.2%) nonfatal myocardial infarctions. The baseline study group characteristics and its relationship to the primary outcome are provided in Table 1. The revascularization directly following the index angiography did not correlate with the follow-up outcomes (log rank $p = 0.747$).