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Research Article

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Cardiovascular risk estimated by UKPDS risk engine algorithm in diabetes

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Abstract: Since there is a high prevalence of type 2 diabetes mellitus (DM2), as well as CVD in Montenegro, we aimed to estimate CVD risk by United Kingdom Prospective Diabetes Study (UKPDS) risk engine algorithm in individuals with DM2. Furthermore, we aimed to explore whether non-traditional biomarker such as high sensitivity C-reactive protein (hsCRP) is superior for CVD risk prediction over old traditional risk factors. A total of 180 participants with DM2 (of them 50% females) were included in the current cross-sectional study. Biochemical and anthropometric parameters, and blood pressure were obtained. More males than females were classified at high UKPDS risk category ($p<0.001$). Also, about one third of diabetic patients (29.4%) were classified into the high-risk category. In multivariate regression analysis, triglycerides [Odds ratio (OR) =1.703, $p=0.001$] and creatinine concentration (OR=1.040, $p<0.001$) were independent predictors of CVD risk, whereas hsCRP was not correlated with CVD risk. HsCRP is not superior for CVD risk prediction by UKPDS risk engine algorithm over high triglyceride and creatinine levels in diabetic population, which suggests that the old traditional markers must not be underestimated when examining CVD risk in population with diabetes.

Keywords: Cardiovascular risk; Type 2 diabetes; UKPDS risk engine

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1 Introduction

Cardiovascular disease (CVD) represents the major cause of death in subjects with type 2 diabetes mellitus (DM2). It is estimated that almost three-quarters of individuals with DM2 die from CVD [1]. Therefore, assessment of CVD risk is of great importance for preventing adverse cardiovascular outcomes in this population group. Also, an assessment of CVD risk can be a useful tool for prevention of poor treatment of individuals at high-risk, as well as inappropriate treatment of subjects at low risk [2].

The CVD risk in DM2 patients has been estimated by various algorithms so far. The American College of Cardiology/AmericanHeartAssociation (ACC/AHA) calculator for CVD risk enables generation of sex- and race-specific risk predictions and also, represents the only US-based CVD risk prediction algorithm that has been validated in other US-based populations [3].

However, the two most widely used risk predictions in Europe are the Framingham risk score (FRS) and United Kingdom Prospective Diabetes Study (UKPDS) risk engine [4].

Although the 10-year FRS and ACC/AHA calculator include several established parameters, there are variables that are not included, but which may add significant contribution to CVD risk assessment exclusively in participants with DM2, such as levels of glycated hemoglobin (HbA1c) and duration of diabetes [4].

Furthermore, the UKPDS risk engine was developed for a large cohort of almost 5100 specifically newly diagnosed patients with DM2, during a median follow-up of 10.7 years [4], whereas FRS included almost 5580 individuals, but only 6% of them were known to have DM2. Therefore, it is speculated that FRS tended to underestimate risk for people with DM2 [5].

In comparison with Framingham and SCORE (Systematic Coronary Risk Evaluation) algorithms, the UKPDS risk engine was shown to be more precise in predicting CVD in a Hoorn study cohort of newly diagnosed DM2 subjects [6].

In line with this, there are discrepant results obtained from many studies, showing that the different CVD risk algorithms have variable precision in different popula-

tions when distinguishing subjects who are at high-risk from the other ones [7-12]. Moreover, a weak concordance between predicted and actual cardiovascular risk was also reported [13]. All these discrepant results may partly be explained by the fact that some ethnic groups have higher CVD risk than the others [14].

To our knowledge, there are no studies concerning the estimation of CVD risk by the UKPDS risk engine algorithm in population with DM2 in Montenegro. Even though it is a part of Mediterranean basis where Mediterranean diet is easily available, there is a high prevalence of DM2 [15], as well as CVD [16] in this developing country. Therefore, we aimed to estimate CVD risk by UKPDS risk engine in individuals with DM2. In addition, we sought for the utility of non-traditional markers [i.e., high sensitivity C-reactive protein (hsCRP)], over traditional ones for the best CVD risk prediction.

2 Materials and methods

2.1 Study population

This investigation derived from previous study which examined the utility of adiposity indexes in subjects with DM2 [17].

The current cross-sectional research included a total of 180 patients with DM2 (of them 90 females). The recruitment of participants with DM2 was done in the Primary Health Care Center in Podgorica, Montenegro, during their visit for laboratory analyses routine checkup in a period from October 2015 to May 2016.

The inclusion and exclusion criteria for diabetic participants were followed by 2016 American Diabetes Association Standards of Diabetes Care [18]. Subjects that met the inclusion criteria were volunteers with previously diagnosed DM2 or with at least two fasting plasma glucose levels ≥ 7.0 mmol/L, or random plasma glucose level of ≥ 11.1 mmol/L.

Participants with fasting glucose ≥ 5.6 mmol/L, but < 7.0 mmol/L, were asked to undergo oral glucose tolerance test (OGTT). Those subjects with plasma glucose level ≥ 11.1 mmol/L 2 hours after an OGTT were also included in the research, as well as those participants with glycosylated hemoglobin (HbA1c) ≥ 6.5% on two different measurements [18].

Participants with 2-h postload glucose < 11.1 mmol/L were excluded from the study. Also those with: HbA1c < 6.5%, type 1 diabetes mellitus, hsCRP > 10 mg/L, hypothyroidism or hyperthyroidism, subjects on chronic dialysis, kidney disease other than diabetic nephropathy, liver disease other than steatosis, a recent (6 months) history of acute myocardial infarction or stroke, ethanol consumption >20 g/day, usage of anti-inflammatory medications in the last 6 months, and pregnancy, were excluded from the investigation.

The Institutional Review Board of Primary Health Care Center in Podgorica, Montenegro approved the research protocol and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was signed by all subjects that participated in the examination.

Anthropometric measurements were obtained from each examinee [i.e., WC (cm), body height (cm), weight (kg) and BMI (kg/m2)], as described elsewhere [19].

2.2 Biochemical analyses

The blood samples were collected in a period from 7 to 9 o'clock in the morning after an overnight fast of at least 8 hours. Level of HbA1c was determined using immunoturbidimetric method (Roche Cobas 400, Mannheim, Germany) in a sample of a whole blood in K2EDTA. Serum levels of glucose, lipid parameters [i.e., triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c)], uric acid, and bilirubin, were performed on the same analyzer, using spectrophotometric assay. Serum hsCRP levels were measured nephelometrically (Behring Nephelometer Analyzer, Marburg, Germany).

The Modification of Diet in Renal Disease Study equation ($eGFR_{MDRD}$) was used for estimation of glomerular filtration rate, as following:

$eGFR_{MDRD}$ (mL/min/1.73 m2) = 186 × [serum creatinine (μmol/L) / 88.4]-1.154 × [Age (years)]-0.203 × 0.742 (if female) [20].

UKPDS risk engine (ver. 2.0) was calculated, as described elsewhere [21].

Variables that entered UKPDS risk engine equation were: age, sex, ethnicity, smoking status, atrial fibrillation status, diabetes duration, HbA1c, systolic BP, TC, and HDL-c. All participants were divided into three groups: low risk (< 15%), medium risk (≥15% and <30%), and high risk category (≥ 30%) [21].

2.3 Statistical analysis

Kolmogorov-Smirnov test was applied for testing the distribution of variables. Normal Gaussian distributed data were shown as mean [standard deviation (SD)] and com-

pared by one-way analysis of variance with Tukey-Kramer *post-hoc* test. For non-normal distributed data logarithmic transformation was performed to achieve normality and data were presented as geometric mean [95% Confidence Interval (CI)]. Those data were also compared using one-way analysis of variance with Tukey-Kramer *post-hoc* test. If the data were not normally distributed even after logarithmic transformation, they were presented as median (interquartile range) and compared using Kruskal-Wallis (three groups' comparisons) and Mann-Whitney (two groups' comparisons) tests. Chi-square test was applied for comparison of categorical variables that were presented as absolute frequencies. Possible correlation between CVD risk score and clinical parameters were tested with Spearman's non-parametric correlation analysis and results were given as correlation coefficient (ρ).

A receiver operating characteristic (ROC) curve analysis was applied to reveal clinical markers that could identify 10-year CVD risk in DM2 population. Area under curve (AUC) higher than 0.75 was considered as a good discrimination. The associations between presence of CVD risk (low and medium *vs*. high) and clinical parameters were evaluated by logistic regression analysis, adjusted for potential confounders which were not used for CVD risk calculations, but had clinical relevance to enter analysis.

Two-tailed $p<0.05$ was used as the criterion for a statistically significant differences and correlations. All analyses were done using the PASW® Statistic version 22 (Chicago, Illinois, USA).

3 Results

Table 1 shows distribution of DM2 patients according to low, medium and high CVD risk. Males and females were not equally distributed in risk categories. Results showed that more men than women were classified at high risk of UKPDS score. Furthermore, there were significant differences in insulin therapy usage in CVD risk categories ($p=0.009$), (Table 1). As it was expected, DM2 patients classified at high CVD risk category were older ($p<0.001$) and had DM2 for a longer period of time than those at low and medium risk ($p<0.001$), because ages and duration of diabetes entered the equations for risk score calculation.

Beside markers, which were used in risk scores calculations (TC, HDL-c and HBA1c), TG, LDL-c, creatinine, and $eGFR_{MDRD}$ were significantly different between low, medium and high CVD risk category. The TG levels were lower in the low than in the medium and high CVD risk category ($p<0.01$ and $p<0.001$, respectively). Similarly,

Table 1: Demographic characteristics of diabetic patients according to CVD risk

	Low risk < 15%	**Medium risk ≥15% <30%**	**High risk ≥ 30%**	**p**
N (male/female)	76 (23/53)	51 (26/25)	53 (41/12)	<0.001
Age (years)	56.00 (49.50-65.00)	63.00 (58.25-71.00)a,*	69.00 (63.00-77.00) a,b*	<0.001
BMI (kg/m2)	30.11 (27.03-36.64)	29.00 (27.15-32.18)	28.67 (26.39-32.01)	0.192
WC (cm)	107.00 (98.00-113.00)	105.00 (99.00-111.00)	105.00 (99.50-113.00)	0.883
SBP (mmHg)	135.00 (130.00-145.00)	130.00 (126.00-140.00)	132.00 (121.50-140.00)	0.155
DBP (mmHg)	80.00 (70.00-86.00)	80.00 (74.25-84.75)	80.00 (70.00-86.00)	0.709
Smoking habits (No/Yes)	59/17	38/13	41/12	0.911
Antihyperglycemics (No/Yes)	10/66	4/47	9/44	0.374
Insulin (No/Yes)	70/6	41/10	38/15	0.009
Hypolipidemics (No/Yes)	47/29	23/28	33/20	0.118
Antihypertensives (No/Yes)	25/51	13/38	13/40	0.507
Duration of diabetes (years)	2.00 (1.00-5.00)	6.00 (2.00-9.75)a,*	8.00 (4.00-12.25)a,*	<0.001

Data are presented as median (interquartile range) and compared by Kruskal-Wallis test
Smoking habits and drug usage are given as absolute frequencies and compared by Chi-square test
a – significantly different from low risk by Mann-Whitney test
b – significantly different from medium risk by Mann-Whitney test
* $p < 0.05$

the lower creatinine concentration was shown in the low than in the medium and high CVD risk category (p<0.01), (Table 2).

As expected, CVD risk score highly correlated with markers which were used in their calculations (age, TC, HDL-c, HBA1c), (Table 3). Also, CVD risk values highly positively correlated with TG level (p<0.01), creatinine concentration (p<0.01) and highly negatively correlated with $eGFR_{MDRD}$ (p<0.01).

Multivariate regression analysis was applied in order to examine independent predictions of clinical parameters that were significantly different between risk groups and that did not enter the equations for risk scores calculation (TG and creatinine), on CVD risk occurrence (low and medium *vs.* high). The $eGFR_{MDRD}$ was excluded for further logistic regression analysis because age was used for its calculation, the same as for risk score calculation. Multivariate adjustment was made for clinical parameters which had clinical relevance to CVD risk (BMI, WC, hsCRP, DBP and therapies usage). The TG (OR=1.703, p=0.001) and creatinine concentration (OR=1.040, p<0.001) kept independent prediction of the occurrence of CVD risk. According to R^2 obtained in logistic regression analysis, the model was able to explain variation in CVD risk by 31.7% (Table 4).

Table 3: Associations between CVD risk and clinical parameters using Spearman's correlation analysis

Variable	CVD risk
Age (years)	0.589**
BMI (kg/m²)	-0.131
WC (cm)	0.014
TC (mmol/L)	0.247**
HDL-c (mmol/L)	-0.415**
LDL-c (mmol/L)	0.297**
TG (mmol/L)	0.304**
Glucose (mmol/L)	0.399**
HbA1c (%)	0.471**
Uric acid (μmol/L)	0.036
Total bilirubin (μmol/L)	0.062
HsCRP (mg/L)	-0.081
Creatinine (μmol/L)	0.343**
$eGFR_{MDRD}$ (mL/min/1.73m²)	-0.232**

Data age given as coefficients of correlation Rho (ρ)
*p<0.05, **p<0.01

Table 2: Clinical parameters in diabetic patients according to CVD risk

	Low risk < 15%	Medium risk ≥15% <30%	High risk ≥ 30%	p
TC (mmol/L)	5.12±0.97	5.30±0,98	5.78±1.43[a†]	0.004
HDL-c (mmol/L)	1.34±0.32	1.14±0.30[a†]	1.01±0.26[a‡]	<0.001
LDL-c (mmol/L)	3.01±0.87	3.14±0.89	3.74±1.14[a‡,b†]	<0.001
TG (mmol/L)*	1.57 (1.43-1.72)	2.14 (1.87-2.47)[a†]	2.26 (1.94-2.65)[a‡]	<0.001
Glucose (mmol/L)**	6.90 (6.00-7.70)	7.20 (6.27-8.47)	8.90 (7.10-11.75)[c,d#]	<0.001
HbA1c (%)**	6.00 (5.50-6.65)	6.70 (5.90-7.90)[c#]	7.70 (6.60-9.67)[c,d†]	<0.001
Uric acid (μmol/L)	304.62±78.52	306.90±74.76	306.90±74.76	0.958
Total bilirubin (μmol/L)**	6.15 (4.60-8.10)	5.60 (4.12-7.93)	6.15 (4.60-8.10)	0.230
hsCRP (mg/L)**	1.89 (0.99-3.62)	1.30 (0.92-2.50)	1.43 (0.78-4.71)	0.467
Creatinine (μmol/L)**	71.00 (57.00-80.50)	76.00 (66.25-84.75)[c†]	81.00 (67.75-97.75)[c†]	<0.001
$eGFR_{MDRD}$ (mL/min/1.73m²)	87.04±20.83	80.20±20.25	76.42±25.36[a#]	0.029

Data are presented as arithmetic mean ± SD and compared by one-way ANOVA
* Log-normal distributed data are presented as geometric mean (95% CI) and compared by one-way ANOVA
** Skewed distributed data are presented as median (interquartile range) and compared by Kruskal-Wallis test
a - significantly different from the low risk group using post-hoc Tukey-Kramer test
b - significantly different from the medium group using post-hoc Tukey-Kramer test
c- significantly different from the low risk group using Mann-Whitney test
d- significantly different from the medium group using Mann-Whitney test
†p<0.01; ‡p<0.001; #p<0.05

A ROC analysis was performed to test TG and creatinine levels discriminatory abilities regarding CVD risk score (low and medium vs. high). Each of them showed poor accuracy regarding risk scores (AUC < 0.700, Table 5). When testing models with adjustment for confounders (BMI, WC, hsCRP, DBP and usage of therapies), discrimination of the applied procedures was approved (AUC > 0.750) and was considered as good (Table 5).

Table 4: Odds ratios (OR) after univariate and multivariate logistic regression analysis for parameters predicting abilities regarding CVD risk

	CVD risk		
Predictors	Unadjusted OR (95% CI)	p	Nagelkerke R^2
TG (mmol/L)	1.481 (1.146-1.993)	0.003	0.076
Creatinine (μmol/L)	1.034 (1.016- 1.053)	<0.001	0.154
Model	Adjusted OR (95% CI)	p	Nagelkerke R^2
TG (mmol/L)	1.703 (1.247-2.326)	0.001	
Creatinine (μmol/L)	1.040 (1.018- 1.063)	<0.001	0.317 (for Model)

Model: confounders BMI, WC, hsCRP, DBP (all continuous variables), therapies (all categorical variables) and predictors (TG and creatinine continuous variables)
SE-Standard Error

4 Discussion

In the current study, more males than females were classified at high-risk category of calculated UKPDS risk engine. Also, in our examination the UKPDS risk engine score classified 29.4% of individuals with DM2 at the high risk group. Higher risk in males was also found in other studies [5, 9]. Similarly, Kim et al. [22] reported 24% of subjects at high CVD risk when using the UKPDS risk score algorithm in Korean adults with DM2.

Ahn et al. [23] reported significant associations between UKPDS risk engine and carotid plaque and carotid artery intima-media thickness in Korean individuals with DM2, showing the importance of its assessment.

Since a great number of studies reported the utility of UKPDS risk engine score to determine CVD risk in individuals with diabetes [6, 23, 24], in our research we wanted to examine the associations between traditional (i.e., creatinine and TG) and non-traditional (i.e., hsCRP) cardiometabolic markers with the UKPDS risk engine score. In line with this, CVD risk values highly positively correlated with TG and creatinine concentrations and highly negatively correlated with $eGFR_{MDRD}$. In multivariate regression analysis TG and creatinine concentration kept independent prediction for the CVD risk occurrence. According to R2 obtained in logistic regression analysis, the model was able to explain variation in CVD risk by 31.7% (Table 4). Moreover, a ROC analysis showed that after adjustment for confounders, TG and creatinine levels have good discriminatory abilities (AUC > 0.750) regarding CVD risk score (low and medium *vs*. high risk), (Table 5).

In line with our results, Bansal et al. [25] showed that TG levels were associated with incident cardiovascular

Table 5: ROC analysis for single parameter and model discriminatory abilities regarding CVD risk

	CVD risk				
Predictors	AUC (95% CI)	SE	Sensitivity (%)	Specificity (%)	p
TG (mmol/L)	0.621 (0.528-0.713)	0.038	56.60	63.78	0.011
Creatinine (μmol/L)	0.654 (0.564-0.745)	0.046	32.08	92.91	0.001
Model	0.789 (0.719-0.859)	0.036	71.70	72.44	<0.001

Model: confounders BMI, WC, hsCRP, DBP (all continuous variables), therapies (all categorical variables) and predictors (TG and creatinine continuous variables)
SE-Standard Error

events, independently of levels of other lipids, and other traditional risk factors.

In a recently conducted large follow-up study (median period of 17.7 years), in individuals with DM2, high TG in addition to low HDL-c levels were related to a 1.54-fold greater hazard ratio for CVD [26] thus pointing out the significance of hypertriglyceridemia as a crucial traditional CVD risk factor [27]. On the contrary, this was not confirmed in those subjects who were free of DM2 [27]. In line with that, subclinical atherosclerosis is reported to be predominated among patients with both DM2 and hyperlipidemia, rather than among DM2 individuals who did not have additional CVD risk factors [28].

It is widely accepted that hypertriglyceridemia is a metabolic hallmark that leads to a consequent events of further atherogenic lipid profile [29]. With progression of insulin resistance, the increased lipolysis of TG in adipose tissue occurs, thus secreting more fatty acids, leading to increased production of TG-rich VLDL, higher concentrations of more atherogenic small dense LDL, as well as change in HDL composition and an increased clearance of HDL particles [30].

Higher levels of free fatty acids in addition to insulin resistance further lead to endothelial dysfunction, reduced production of nitric oxide, vasoconstriction, inflammation and therefore, initiation and progression of atherosclerosis [30].

In addition, our results are in line with previous studies showing an association of high creatinine levels and low eGFR levels with an increased risk of CVD [31, 32].

Schneider et al. [31] in a large observational study showed that DM2 patients with a doubling of serum creatinine levels were at an increased risk of CVD, in comparison with patients with DM2 whose serum creatinine did not double during follow-up.

Looker et al. [33] showed that, in addition to non-traditional biomarkers, eGFR, insulin therapy and HbA1c need to be included for the prediction of incident CVD in individuals with DM2.

Non-traditional biomarkers are of questionable significance regarding their utility in CVD risk assessment, since some previous studies reported the association of hsCRP with CV events occurrence [34, 35], whereas some other studies failed to verify this observation [36, 37].

In our current study, we reported that hsCRP had no incremental contribution to CVD risk prediction, compared to traditional risk factors. Cardoso et al. [34] suggested that hsCRP may be more reliable in risk stratification for secondary CVD prevention, but not in younger, lower-risk patients with DM2 treated at primary care. In several other studies, hsCRP was shown to be a signifcant predictor of CVD only among individuals without DM2 [38].

The possible explanations for such discrepancies may partly be explained by different populations, sample size, and different follow-up periods [34].

Some of the disadvantages of the current study are its cross-sectional design and the relatively small sample size. Moreover, individuals with DM2 in our study were not obtained from nationally representative sample. Therefore, longitudinal studies with nationally-representative sample are needed to confirm our observations. Furthermore, we were not able to measure urinary albumin excretion, as kidney function marker. However, even though screening for chronic kidney disease based on eGFR alone is not recommended in the general population, it may be effective in high-risk subjects, such as individuals with DM2 [39].

Although the UKPDS risk engine represents the most widely used tool for CVD risk estimation, it is of importance to mention the novel risk algorithm, the VILDIA score for patients with DM2. The latter includes several new biomarkers (e.g., 25-OH vitamin D3, NT-proBNP, Lp-PLA2 and renin) and was shown to provide better discriminatory power than the UKPDS risk engine for the prediction of 10-year survival. Therefore, studies in future are needed for the establishment of the best tool for CVD risk assessment in population with diabetes [40].

5 Conclusion

To the best of our knowledge, the reported herein is the first study that estimated CVD risk by the UKPDS risk engine algorithm in population with DM2 in Montenegro. About one third of diabetic patients (29.4%) were classified into the UKPDS risk engine high risk category. In addition, non-traditional parameter such as hsCRP was not correlated with cardiovascular risk, compared to old traditional risk factors such as high triglycerides and creatinine levels, which suggests that old traditional markers must not be underestimated when examining CVD risk in population with diabetes.

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