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Development of one-year major adverse cardiac events risk index in patients with acute coronary syndrome and diabetes mellitus who underwent percutaneous coronary intervention

Razvoj indeksa rizika od velikih vaskularnih događaja tokom godinu dana posle perkutane koronarne intervencije kod bolesnika sa akutnim koronarnim sindromom i dijabetesom melitusom

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Abstract

Background/Aim. Patients with acute coronary syndrome (ACS) and diabetes mellitus (DM) have an increased risk of major adverse cardiovascular events (MACE) after percutaneous coronary intervention (PCI), which is not estimated sufficiently-multidimensionally in terms of type and severity of the ACS and/or DM and angiographic findings. The study was intended to validate and develop an index of metabolic, angiographic, anatomic and clinical risk factors for one-year MACE after conducted PCI in patients with ACS and DM. **Methods.** A prospective cross-sectional study was performed in patients with DM and ACS. In the PCI period the following risk factors were recorded: 1) age and metabolic variables – glycosylated hemoglobin (HbA1c), total cholesterol, and triglycerides levels in the blood; 2) endocrinological variables – DM therapy and type of DM; 3) ACS modality; 4) radiological/anatomical variable – SYNTAX score, and 5) clinical variables in modified age, creatinine, ejection fraction (ACEF) score. One-year MACE were recorded. **Results.** From a total of 136 consecutive patients, 55 of them developed at least one MACE in one-year follow-up. A high predictive risk index was evaluated that assessed particular or associated risks for one-year MACE (c statistic = 0.879) in the study population, defined by: SYNTAX score > 21, modified ACEF score > 1.38, HbA1c ≥ 8%, triglyceridemia ≥ 2.3 mmol/L in patients with insulin therapy, and ACS modality – unstable angina pectoris. The constructed risk index for one-year MACE (MACERI) had better predictive characteristics than SYNTAX score (c statistic = 0.798), as well as ACF score (c statistic = 0.744). **Conclusion.** MACERI can potentially have great application in future risk factors studies for one-year MACE in patients with DM and ACS who underwent PCI, because with it the effects of these factors are measured multidimensionally at valid and accurate manner.

Key words:
coronary artery disease; coronary angiography; diabetes mellitus; comorbidity; cardiovascular diseases; acute disease; risk factors.

Apstrakt

Uvod/Cilj. Bolesnici sa akutnim koronarnim sindromom (AKS) i dijabetes melitusom (DM) imaju povećan rizik od pojave velikih neželjenih kardiovaskularnih događaja (VNKD) nakon perkutane koronarne intervencije (PKI), ali on je nedovoljno višedimenzionalno procenjen u odnosu na vrstu i težinu AKS i/ili DM i angiografske nalaze. Ova studija je imala za cilj da validira i razvije indeks metaboličkih, angiografsko-anatomskih i kliničkih faktora rizika za VNKD u toku jedne godine posle sprovedene PKI kod bolesnika sa AKS i DM. **Metode.** Sprovedena je prospektivna studija preseka kod bolesnika sa DM i AKS, kojima su u periodu PKI evidentirani sledeći faktori rizika: 1) metaboličke varijable – nivoi glikoziliranog hemoglobina (HbA1c), ukupnog holesterola i triglicerida u krvi; 2) endokrinološke varijable – terapija DM i tip DM; 3) modalitete AKS; 4) radiološke/anatomske varijable – SYNTAX skor i 5) kliničke varijable u modifikovanom starost, kreatinin, ejekciona funkcija (engl. *age, creatinine, ejection fraction* – ACEF) skoru. VNKD su evidentirani do godinu dana posle PKI. **Rezultati.** Nakon PKI, od konsekutivno uključenih 136 bolesnika, njih 55 razvilo je bar jedan VNKD u periodu praćenja od jedne godine. Konstruisan je visoko prediktivni indeks rizika kojim su procenjeni zasebni ili združeni rizici

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od VNKD (c statistika = 0,879) u studijskoj populaciji, a koji su definisani SYNTAX skorom > 21, modifikovanim ACEF skorom > 1,38, HbA1c ≥ 8%, trigliceridemijom ≥ 2,3 mmol/L kod bolesnika na insulinskoj terapiji, kao i modalitetom ACS – nestabilna angina pektoris. Konstruisani indeks rizika (IR) od VNKD (IRVNKD) imao je bolje prediktivne karakteristike u odnosu na SYNTAX skor (c statistika = 0,798), kao i ACEF skor. **Zaključak.** IR-VNKD potencijalno može da ima veliku primenu u budućim istraživanjima faktora rizika od VNKD koji nastaju do jedne godine posle PKI kod bolesnika sa DM i AKS, jer se njime učinci ovih faktora višedimenzionalno validno i precizno mere.

Ključne reči:
koronarna bolest; angiografija koronarnih arterija; dijabetes melitus; komorbiditet; kardiovaskularne bolesti; akutna bolest; faktori rizika.

Introduction

Diabetes mellitus (DM) is the most important risk factor for coronary artery disease (CAD) and stroke [1]. Patients with DM have higher risk of CAD than non-diabetic patients [2]. More than 80% of all lethal outcomes in patients with DM are caused by atherosclerosis [1]. These patients more frequently have severe CAD and mortality from stroke than non-diabetic patients [1]. Having in mind their poor prognosis, in these patients the choice of the best CAD treatment (lifestyle correction, pharmacological therapy, revascularization, surgery) is of crucial importance [3]. Patients with severe CAD and DM often have multivessel disease and they are more frequently candidates for coronary artery bypass graft (CABG) surgery than non-diabetic patients [4, 5]. On the other hand, revascularization with the use of invasive percutaneous coronary intervention (PCI) is a more recent method in medicine due to its effectiveness in removing the most severe outcomes of coronary ischemia [6]. In order to closely monitor the treatment effects in patients with CAD and DM, and to improve medical decision-making in the choice between different alternatives and precise predictions related to the most important therapeutic outcome such as major adverse cardiac events (MACE), there was a need to develop unique angiographic and/or clinical instruments for CAD complexity measurement.

The SYNTAX score is an angiographic grading tool for determining the complexity of CAD in patients undergoing revascularization in combination with angiographic classifications aiming to grade the coronary anatomy with respect to the number of lesions, their location and functional impact of angiographically obstructive lesions [7–11]. In the SYNTAX trial after various longer follow ups, different "cut points" for the SYNTAX score are defined, which determine the level of risk for the primary outcome of CAD treatment. Thus, it is defined that patients with the SYNTAX score ≤ 22 have less complex CAD and better treatment outcomes [12–14]. The SYNTAX score has predictive value in different clinical settings including acute coronary syndrome (ACS) [7, 11, 15–21].

Modification of the original Age, creatinine, ejection fraction (ACEF) score [22] has recently been presented. The original ACEF score uses age, serum creatinine and ejection fraction of the left ventricle for adverse cardiovascular events prognosis in patients with DM and ACS. The modified ACEF score, uses creatinine clearance (CrCl) instead of serum creatinine providing a better assessment of renal function and improving predictive value in cardiovascular risk assessment, especially with regard to the prediction of the MACE development [23, 24].

However, there are no reports of the development of a predictive tool, which would combine the assessment of anatomical, clinical and metabolic risk factors for MACE in patients with ACS and DM. The aim of this study was assessment of the adequacy and criterion validity of a risk index which combines the SYNTAX score, the modified ACEF score and the metabolic risk factors for one-year MACE in patients with ACS and DM who underwent PCI.

Methods

Study design

The study was designed as a prospective, cross-sectional study in patients with ACS and DM who underwent PCI and who were monitored by one-year MACE. It was conducted in the period 2012–2014 at the Department of Cardiology and Invasive Cardiology, General Hospital Valjevo, Valjevo, Serbia. The study was approved by the local Ethics Committee and all the patients signed informed consent form.

Patients

The study population included patients who underwent PCI, men and women, older than 18, with ACS and DM. Patients had diagnosis of DM for at least one year according to current guidelines. ACS was defined as: acute myocardial infarction with ST elevation (STEMI) in the patient with characteristic symptoms of myocardial ischemia lasting for more than 20 min in association with persistent electrocardiographic ST elevation (STE) of more than 1 mm (0.1 mV) in two or more contiguous leads, or new, or presumed new left bundle branch block and subsequent release of biomarkers of myocardial necrosis; acute myocardial infarction without electrocardiographic ST elevation (NSTEMI) in the patients with characteristic symptoms of acute chest pain lasting for more than 20 min accompanied by ST depression of more than 1 mm (0.1 mV) and T wave inversion in two or more contiguous leads, with positive biomarkers of myocardial necrosis and unstable angina pectoris (UAP) in the patients with characteristic

Table 1

Description of continuous variables with the significance of the difference between MACE patients' groups

Variables	All patients (n = 136) mean ± SD	Patients with MACE		
		No (n = 81) mean ± SD	Yes (n = 55) mean ± SD	*p* (*t* value)
Age (years)	62.51 ± 9.35	60.73 ± 8.72	65.13 ± 9.70	0.007 (-2.758)
Total cholesterol (mmol/L)	5.85 ± 1.28	5.90 ± 1.27	5.78 ± 1.29	0.610 (0.511)
Triglycerides (mmol/L)	2.21 ± 1.27	2.24 ± 1.36	2.17 ± 1.14	0.732 (0.343)
HbA1c (%)	8.07 ± 1.18	7.7 ± 1.14	8.51 ± 1.12	0.000 (-3.726)
Creatinine clearance (mL/min)	9.85 ± 5.08	91.71 ± 4.86	89.58 ± 5.19	0.016 (2.436)
Left ventricular ejection fraction (%)	46.57 ± 8.35	49.52 ± 6.22	42.24 ± 9.22	0.000 (5.120)
SYNTAX score	23.26 ± 10.17	19.28 ± 6.87	29.13 ± 11.39	0.000 (-5.742)
Modified ACEF score	1.41 ± 0.44	1.25 ± 0.28	1.64 ± 0.53	0.000 (-4.975)

SD – standard deviation; HbA1c – glycosylated hemoglobin; MACE – major adverse cardiac events; ACEF – age, creatinine, ejection fraction.

symptoms of acute chest pain lasting for more than 20 min accompanied by electrocardiographic ST depression of more than 1 mm (0.1 mV) and T wave inversion in two or more contiguous leads, with negative biomarkers of myocardial necrosis. Patients with previous CABG or PCI on coronary arteries and patients with cardiogenic shock were not included in the study.

Procedures

According to the primary PCI (pPCI) protocol, only culprit lesion was treated during procedure. pPCI was performed in STEMI patients up to 48 hours from the onset of characteristic symptoms of myocardial ischemia. The decision whether to treat non-culprit lesions during pPCI in STEMI patients with multivessel disease was based on angiographic severity of the lesion (diameter stenosis of 50 % or more). The invasive PCI procedure (stenting) in NSTEMI patients was based on angiographic severity of the lesion (diameter stenosis of 50 % or more), exclusively for up to 72 hours from the onset of myocardial ischemia symptoms. The invasive PCI procedure in UAP patients was performed electively based on angiographic severity of the lesion (diameter stenosis of 50 % or more).

Outcomes

MACE, as a primary end point, was defined as all deaths, nonfatal myocardial infarction, nonfatal cerebrovascular insult (CVI) and repeated PCI or need for CABG that were assessed within one-year observation. After a one-year follow-up, patients were divided into two groups: patients with MACE and patients without MACE.

Variables – risk factors

Following risk factors were recorded for all the patients: age, gender, categories of ACS, categories of DM (type 1 or type 2), therapy of DM (with insulin or without insulin), glycosylated hemoglobin (HbA1c) in %, HbA1c ≥ 8% (unregulated DM), total cholesterol (mmol/L), total cholesterol ≥ 4.5 mmol/L (high level in diabetes), triglycerides (mmol/L), triglycerides ≥ 2.3 mmol/L (high or very high level), the SYNTAX score, the SYNTAX score > 21 and modified ACEF score.

Estimated glomerular filtration rate (eGFR) was calculated using Cockroft-Gault formula. Renal insufficiency was defined as eGFR < 60 mL/min. Left ventricular ejection fraction (LVEF) was assessed by echocardiographic examination in the first 24 h after pPCI, using Simpson's biplane method. Severe LVEF was defined as LVEF < 40%.

Modified ACEF score was calculated using the formula: years/EF +1 point for every 10 mL/min reduction in CrCl lower than 60 mL/min to 1.73 m^2 (to maximum 6 points). Therefore, CrCl between 50–59 mL/min to 1.73 m^2, 49–49 mL/min to 1.73 m^2, 30–39 mL/min to 1.73 m^2 will get 1, 2 or 3 points. The criterion value of modified ACEF for MACE detection was evaluated after completion of the study and was also used as a predictor variable of the above outcomes.

SYNTAX score was calculated in the manner described by Brkovic et al. [7]. All angiographic variables pertinent to calculation were computed by two interventional cardiologists who were blind to procedural data and clinical outcome. In case of disagreement, the opinion of the third observer was obtained, and the final decision was made by consensus.

Table 2

Frequency distribution by category variables with the significance of the difference between MACE patients' groups

Variables	Patients with MACE		*p* (χ^2)
	No (n = 81) f1 (%)	Yes (n = 55) f2 (%)	
Gender			
male	54 (66.7)	31 (56.4)	0.279
female	27 (33.3)	24 (43.6)	(0.223)
Acute coronary syndrome			
STEMI	30 (37.0)	14 (25.5)	0.152
NSTEMI	7 (8.6)	10 (18.2)	(3.768)
UAP	44 (54.3)	31 (56.4)	
DM – type			
1	2(2.5)	2(3.6)	1.000
2	79(97.5)	53(96.4)	
DM – therapy			
with insulin	23 (28.4)	21 (38.2)	0.265
without insulin	58 (71.6)	34 (61.8)	(0.231)
HbA1c ≥ 8 %			
no	46 (56.8)	13 (23.6)	0.000
yes	35 (43.2)	42 (76.4)	(14.659)
Triglycerides ≥ 2.3 mmol/L			
no	56 (69.1)	35 (63.6)	0.579
yes	25 (30.9)	20 (36.4)	(0.447)
Triglycerides ≥ 2.3 mmol/L in patients with insulin therapy			
no	78 (96.3)	47 (85.5)	0.050
yes	3 (3.7)	8 (14.5)	
Triglycerides ≥ 2.3 mmol/L in patients without insulin therapy			
no	59 (72.8)	43 (78.2)	0.480
yes	22 (27.2)	12 (21.8)	(0.499)
Total cholesterol ≥ 4.5 mmol/L			
no	11 (13.6)	11 (20.0)	0.349
yes	70 (86.4)	32 (80.0)	(0.996)
Left ventricular ejection fraction < 40%			
no	70 (86.4)	23 (58.2)	0.000
yes	11 (13.6)	11 (41.8)	(13.931)
Modified ACEF score > 1.38			
no	61 (75.3)	18 (32.7)	0.000
yes	20 (24.7)	37 (67.3)	(24.396)
SYNTAX score > 21			
no	61 (75.3)	14 (25.5)	0.000
yes	20 (24.7)	41 (74.5)	(32.915)
pPCI			
no	0 (0.0)	6 (42.9)	0.000
yes	30 (100)	8 (57.1)	
Stenting in NSTEMI patients			
no	0 (0.0)	6 (60.0)	0.035
yes	7 (100)	4 (40.0)	
Stenting in UAP patients			
no	2 (4.5)	23 (74.2)	0.000
yes	42 (95.5)	8 (25.8)	

DM – diabetes mellitus; HbA1c – glycosylated hemoglobin; STEMI – acute myocardial infarction with ST elevation; NSTEMI – acute myocardial infarction without ST elevation; UAP – unstable angina pectoris; pPCI – primary percutaneous coronary intervention; ACEF – age, creatinine, ejection fraction.

Statistical methods

Continuous numerical data sets were described by the mean and standard deviation. The attributive or ordinal variables were described by the frequency of outcomes and percentages. Univariable analysis was performed using Pearson χ^2 test or Fisher's exact test for categorical variables and Student *t*-test for continuous variables.

Binary logistic regression method with stepwise variable selection was used for multivariate analysis of MACE risk factors. All variables that had a $p < 0.1$ on univariable analyses were considered for inclusion in the final model.

The evaluation of the validity of the logistic regression model implied an assessment of its goodness-of-fit measure and its accuracy. Goodness-of-fit model was made by estimating the Nagelkerke R Square. The accuracy of the logistic regression model was assessed using discrimination and adequacy. Discrimination measures were conducted to prove how adequately a model can distinguish patients with MACE from patients without MACE. The analysis of the adequacy of logistic models and the estimation of the retention of variables or their interactions were made using the Hosmer-Lemeshow method. Discrimination validity of the predicted probabilities, obtained by logistic regression model and/or the newly constructed Major Adverse Cardiac Events Risk Index (MACERI), in distinguish MACE positive vs. MACE negative patients was estimated by Receiver Operating Characteristic (ROC) procedure. "Cut point" value, sensitivity, specificity, positive predictive value and negative predictive value were obtained by applying maximum Youden index. The testing of the significance of differences between the areas under the curve (AUC) or c statistic of the newly constructed MACERI in relation to the AUCs of other scales was performed by the DeLong method.

The accepted level of significance was $p \leq 0.05$. The statistical program IBM SPSS Statistics 20 (NY) was used for the data processing and MedCalc 12.5.0 (Belgium).

Development of MACERI

Once the model was developed using the regression equation, it was used to develop MACERI. We used the method described in the Framingham study [25] for conversion of the parameter of estimated regression model into an index. The number of points assigned to each variable equaled its regression coefficient divided by 0.5, followed by rounding to the nearest whole number. The points for each risk factor were then summed to obtain the total number of points (score) for a patient. Formula for back-transforming from logistic regression estimated score to probability was as follows:

$$\text{Estimated probability percentage} = 100 \times \frac{e^{logit}}{1 + e^{logit}}$$

where natural logarithm is presented with "e".

Results

The study included 136 consecutive patients with ACS and DM who were all subjected to PCI, of which 55 patients developed at least one MACE in a one-year follow-up period; 28/55 (50.9%) of the patients had two or more MACE. In the period of one year, 25/55 (45.45%) of patients underwent CABG treatment, while a repeated PCI was performed in 13/55 (23.64%) of the patients. 8/55 (14.55%) of the patients died, while 9/55 (16.36%) of the patients developed CVI. All patients involved in the study had multivessel CAD. Detailed descriptions of the study population characteristics are shown in Tables 1 and 2. Using the ROC procedure, we estimate a "cut point" for the modified ACEF > 1.38 (Table 3).

Compared to the non-MACE patients' group, patients with MACE were older and had higher values of the SYNTAX score, higher values for the modified ACEF scores, as well as all higher values for variables used to calculate the modified ACEF (Table 1). Patients with MACE also had higher average values of HbA1c (%) than the non-MACE patients. There was no differences between the groups of patients in the total cholesterol level (mmol/L) and level of triglycerides (mmol/L) (Table 1).

Compared to the non-MACE patients, the patients with MACE had more frequent unregulated diabetes (HbA1c > 8%) and cardiac insufficiency (LVEF = 40%), more frequent the SYNTAX score > 21 and the modified ACEF score > 1.38 and also less frequent pPCI and less frequent stenting in UAP patients and NSTEMI patients (Table 2). By

Table 3
Receiver operating characteristic (ROC) curve analysis of SYNTAX score, modified ACEF score and MACERI in the detection of major adverse cardiac events

Variables	AUC (95% CI)	SE for AUC	*p* (Z)	Cut point (95% CI)	SN (%) (95% CI)	SP (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
Modified ACEF score	0.744 (0.662–0.815)	0.045	0.000 (5.472)	> 1.38 (1.21–1.38)	62.7 (53.3–79.3)	75.31 (64.5–84.2)	64.9 (51.1–77.1)	77.2 (66.4–85.9)
SYNTAX score	0.798 (0.720–0.862)	0.041	0.000 (7.318)	> 21 (18.8–24.5)	74.55 (61.0–85.3)	75.31 (64.5–84.2)	67.2 (54.0–78.7)	81.3 (70.7–89.4)
MACERI	0.879 (0.812–0.929)	0.029	0.000 (12.070)	> 7 (5–7)	78.18 (65.0–88.2)	86.42 (77.0–93.0)	79.6 (66.5–89.4)	85.4 (75.8–92.2)

AUC – area under the curve; SE – standard error; CI – confidence interval; Z – normal distribution zed value; SN – sensitivity; SP – specificity; PPV – positive predictive value; NPV – negative predictive value; MACERI – major adverse cardiac events risk index; ACEF – age, creatinine, ejection fraction.

Table 4

Parameters for major adverse cardiac events risk on multivariable analysis with assigned points

Variables in the Equation	B	SE	Wald	df	*p*	Odds ratio	95% CI for Odds ratio		Appropriate points
							lower	upper	
Modified ACEF score > 1.38 (no) – reference									0
Modified ACEF score > 1.38 (yes)	1.952	0.521	14.054	1	0.000	7.044	2.538	19.546	4
Acute coronary syndrome			5.823	2	0.054				
STEMI – reference									0
NSTEMI	1.247	0.801	2.423	1	0.120	3.479	0.724	16.717	0
UAP	1.387	0.592	5.484	1	0.019	4.004	1.254	12.785	3
SYNTAX score > 21 (no) – reference									0
SYNTAX score > 21 (yes)	2.197	0.498	19.499	1	0.000	9.002	3.394	23.874	4
HbA1c ≥ 8% (no) – reference									0
HbA1c ≥ 8% (yes)	1.032	0.484	4.541	1	0.033	2.806	1.086	7.250	2
Insulin therapy by triglycerides ≥ 2.3 mmol/L (no) – reference									0
Insulin therapy by triglycerides ≥ 2.3 mmol/L (yes)	2.523	0.897	7.911	1	0.005	12.471	2.149	72.369	5
Constant	-4.164	0.790	27.761	1	0.000	0.016			

HbA1c – glycosylated hemoglobin; STEMI – acute myocardial infarction with ST elevation; NSTEMI – acute myocardial infarction without ST elevation; UAP – unstable angina pectoris; SE – standard error; CI – confidence interval.

using univariable testing, in all remaining variables no significant difference was found in the distribution of outcome rates between patients' groups.

By applying multivariable regression analysis, we identified four independent risk factors and one interaction between two risk factors for MACE and after which we made the allocation of appropriate points to form the MACERI (Table 4): 1) the modified ACEF score > 1.38; + 4 point; 2) UAP; + 2 points; 3) the SYNTAX score > 21; + 3 points; 4) HbA1c ≥ 8%; + 2 points, and 5) the interaction between insulin terapy and triglycerides ≥ 2.3 mmol/L; + 5 points. The above model showed moderate level of goodness-of-fit measure (Nagelkerke R Square = 0.537) and very good discriminating characteristics (Table 4) and adequacy (Hosmer-Lemeshow test χ^2 = 8.271; p = 0.219). The MACERI > 7 was the criteria for detection of very high MACE risk, that corresponded with estimated probability (or individual patient risk) for the MACERI > 0.44 (Tables 3 and 5). Based on 95% confidence interval for MACERI "cut point" in MACE detection (Table 3), we formed three levels of risk for the patient, as a low risk, increased risk and very high risk (Table 5). The average MACERI in the non-MACE patients' group was 4.65 ± 3.14, while in the group of patients with MACE was 9.62 ± 2.85.

By DeLong method, we found the difference in the AUC for the MACERI *versus* the AUC for the SYNTAX score (Difference between areas = 0.0814; 95% confidence interval from 0.00748 to 0.155; z = 2.158; p = 0.031). Also,

Table 5

Major adverse cardiac events risk index with risk levels categorization and estimated risk percentage *per* total points for a patient

Total points for a patient	Estimated risk percentage for a patient	Risk categorization by levels	Patients (n = 136) n (%)
0	1.53		
1	3.80		
2	4.18	Low risk	40 (29.4)
3	5.86		
4	9.87		
5	14.87		
6	23.50	Increased risk	42 (30.9)
7	30.47		
8	49.63		
9	61.11		
10	73.44		
11	79.30		
12	87.48		
13	92.47	Very high risk	54 (39.7)
14	95.15		
15	99.17		
16	99.98		
17	99.99		
18	99.99		

we found the difference in the AUC for the MACERI *versus* the AUC for the modified ACEF score (Difference between areas = 0.135; 95% confidence interval from 0.0522 to 0.218; z = 3.195; $p = 0.0014$). However, there was no difference in the AUC for the SYNTAX score compared to the AUC for the modified ACEF score (Difference between areas = 0.0536; 95% confidence interval from -0.0580 to 0.165; z = 0.942; $p = 0.346$).

Discussion

In our study, we first performed an assessment of the association of metabolic, anatomic –angiographic and clinical risk factors for the development of one-year MACE in patients with ACS and DM, who underwent PCI. We found that there was a combined impact of these risk factors in the study population and formed MACERI composed of the following significant risk factors: HbA1c > 8%, triglicerydes > 2.3 mmol/L in patients with insulin therapy, UAP diagnosis, the SYNTAX score > 21 and the modified ACEF score > 1.38.

In terms of HbA1c, our results support the recommendations of the American Diabetes Association (ADA) that in patients with DM and advanced microvascular (including ACS) and macrovascular complications, the target HbA1c values should be less restrictive (HbA1c < 8%) [26]. As the same ADA criteria were set for patients with frequent development of hypoglycaemia, ADA wants to prevent further compromise of multivessel CAD that would result from potential development of hypoglycaemia in patients with poor glucoregulation. Bearing in mind the "cut point" for the MACERI estimated in this study, we note that strict adherence to ADA recommendations potentially can avoid one-year MACE in patients with ACS and DM, even in cases where they additionally have the SYNTAX score > 22 or the modified ACEF score > 1.38.

In our study, a very high risk of one-year MACE in patients with insulin therapy and triglycerides ≥ 2.3 mmol/L was assessed. Since this risk is completely independent of the risk arising from HbA1c ≥ 8 %, this is the result of suboptimal insulin patients' therapy and their lifestyle. Therefore, we consider that correction of patient's lifestyle would be unsuccessful, and that they require intensive treatment with statins and fibrates at the same time in accordance with the recommendations of the European Association for Cardiovascular Prevention and Rehabilitation [27]. However, if these patients also have HbA1c ≥ 8%, there is a need to optimize their insulin therapy with the permanent measurement of glycemic profiles. This last point is highlighted taking into account "cut point" and scoring system for the MACERI that indicates that patients with insulin therapy and triglycerides ≥ 2.3 mmol/L associated with HbA1c ≥ 8% have a very high risk of a one-year MACE development, even when they have the SYNTAX score ≤ 22 and the modified ACEF score ≤ 1.38.

We evaluated that patients with UAP compared to the reference group of patients with STEMI had an increased risk for one-year MACE. The reason for this is seen in the reduced rate of invasive PCI in these patients compared to the patients with STEMI (28.8% vs. 57%, respectively). Therefore, in the future, it is important to consider more precise criteria for the implementation of invasive PCI in patients with UAP and DM, as our results suggest that more frequent stent placement in these patients could be beneficial in terms of reducing the risk of one-year MACE after PCI. It is also suggested that this risk in patients with UAP in relation to the reference category of patients with STEMI can be indirectly associated with a rarely implemented invasive PCI. Namely, all patients who underwent the invasive PCI certainly had a permanently monitored dual aggregation therapy in the observed one-year follow-up.

In this study, it was shown that there was no difference in AUC for the SYNTAX score versus AUC for the modified ACEF in the detection of risk of a one-year MACE. A similar result was demonstrated in Pivato et al. [24], who analyzed a mixed population with/without DM and ACS, but also a one-month follow-up after PCI. In any case, we showed that the MACERI had significantly better ROC characteristics, both in relation to the modified ACEF score and in relation to the SYNTAX score.

In the review of Yadav et al. [28], they emphasized the necessity to precisely determine the "cut point" for the SYNTAX score for MACE detection in patients with DM and ACS with longer follow-up period after PCI. We estimated that the "cut point" for the SYNTAX score in the one-year MACE was 22 (18.8 to 24.5). In the reports of other authors, the values for the SYNTAX score defined by the mentioned interval were similar, both in the prediction of MACE [17, 29], and in the assessment of associated risk factors in severe CAD forms [30, 31].

Study limitation

The limitations of this study are single center design, relatively small sample size, and non-inclusion in the evaluation of variables such as stent number, stent types, left main disease, culprit-only PCI and others. The performance of our studies, including the formation of attitudes of a variety of methods during PCI, and the definition of repeat revascularization as adverse events, corresponds to the time when said attitudes are still applicable and have been the subject of controversy [32]. However, such attitudes have now been overcome. As we did a cross-sectional study of risk factors for the development of MACE in the population of patients treated with PCI at that time, then we could not ignore this fact by simply avoiding repeat revascularization within MACE. We emphasize that our study was not an intervention study, hence there was no design, sample size, power and methodological basis for a clear assessment between the various procedures in the course of the PCI.

The major limitation of the SYNTAX score is that it estimates only anatomical complexity and distribution of coronary artery disease. The SYNTAX II score combines

clinical and anatomical risk estimation, but needs still to be validated in prospective cohorts.

Conclusion

Major adverse cardiac events risk index is highly adequate in predicting the most important one-year adverse events in patients with diabetes mellitus and acute coronary syndrome who underwent percutaneous coronary intervention. This index combines the risks that arise from metabolic, angiographic and clinical variables, and as such is more accurate in the prediction of mentioned events compared to the scales of which it is composed.

Conflict of interest

Authors declare that they have no conflict of interest.

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