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ORIGINAL PAPER

Additive prognostic value of the SYNTAX score over GRACE, TIMI, ZWOLLE, CADILLAC and PAMI risk scores in patients with acute ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention

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Abstract This study evaluated additive prognostic value of the SYNTAX score over GRACE, TIMI, ZWOLLE, CADILLAC and PAMI risk scores in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI). All six scores were calculated in 209 consecutive STEMI patients undergoing pPCI. Primary end-point was the major adverse cardiovascular event (MACE—composite of cardiovascular mortality, non-fatal myocardial infarction and stroke); secondary end point was cardiovascular mortality. Patients were stratified according to the SYNTAX score tertiles ($\leq$12; between 12 and 19.5; >19.5). The median follow-up was 20 months. Rates of MACE and cardiovascular mortality were highest in the upper tertile of the SYNTAX score ($p < 0.001$ and $p = 0.003$, respectively). SYNTAX score was independent multivariable predictor of MACE and cardiovascular mortality when added to GRACE, TIMI, ZWOLLE, and PAMI risk scores. However, the SYNTAX score did not improve the Cox regression models of MACE and cardiovascular mortality when added to the CADILLAC score. The SYNTAX score has predictive value for MACE and cardiovascular mortality in patients with STEMI undergoing primary PCI. Furthermore, SYNTAX score improves prognostic performance of well-established GRACE, TIMI, ZWOLLE and PAMI clinical scores, but not the CADILLAC risk score. Therefore, long-term survival in patients after STEMI depends less on detailed angiographical characterization of coronary lesions, but more on clinical characteristics, myocardial function and basic angiographic findings as provided by the CADILLAC score.

Keywords SYNTAX score · ST-segment elevation myocardial infarction · Prognostic value

Abbreviations

CADILLAC	Controlled abciximab and device investigation to lower late angioplasty complications
GRACE	Global registry of acute coronary events
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular event
PAMI	Primary angioplasty in myocardial infarction
pPCI	Primary percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
SYNTAX	Synergy between percutaneous coronary intervention with taxus and cardiac surgery
TIMI	Thrombolysis in myocardial infarction

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Introduction

The SYNTAX score has been developed as a combination of several previously validated angiographic classifications aiming to grade the coronary anatomy with respect to the number of lesions and their functional impact, location, and complexity [1]. It was aimed to assist in patient selection

and risk stratification of patients with extensive coronary lumen obstruction undergoing revascularization [1–3].

The SYNTAX score was first used prospectively in the SYNTAX trial, which demonstrated different long-term event rates in CABG and PCI groups in regard to SYNTAX score tertiles. First published SYNTAX trial results showed that event rates were similar for lower (0–22) and intermediate (23–32) SYNTAX score tertile groups, but were significantly higher in the PCI group of the highest SYNTAX score tertile (≥33, indicating the most complex disease) [4]. Subsequently, after longer duration of follow-up (3-, 4-, and 5-years), the difference in primary end point event rates also appeared in the intermediate SYNTAX tertile group, in favor of CABG [5–7]. After this landmark study, it has been shown that SYNTAX score has predictive value in different clinical settings, including multivessel and left-main coronary artery disease [4, 8–14]. Nevertheless, the prognostic value of this scoring system has not been extensively validated in patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (pPCI). There are few recently published studies that have evaluated the SYNTAX score in the setting of pPCI [15–17], and only one study that compared its performance in the context of well-established clinical risk scores [18]. In fact, several scoring systems like GRACE [19], TIMI [20], ZWOLLE [21], CADILLAC [22] and PAMI [23], that include different patient, clinical or basic angiographic characteristics, were developed for risk stratification of patients with STEMI, but none of the previous studies have evaluated the relative prognostic merit of dedicated and sophisticated angiographic characterization represented by the SYNTAX score in relation to well known risk scores for STEMI patients.

The GRACE score was developed from a large unselected registry of patients from the entire spectrum of acute coronary syndromes (with 35.5 % of STEMI patients), and was primarily used for prediction of in-hospital all-cause mortality [19]. The TIMI risk score for STEMI is a simple scoring system derived on a highly selected STEMI patients treated with fibrinolytic therapy in the InTIME II randomized controlled trial [24], which was designed for the prediction of 30-day mortality [20]. The ZWOLLE risk score was derived from a registry of STEMI patients that underwent pPCI, and was devised for the prediction of their 30-day mortality [21]. The CADILLAC risk score is a more sophisticated tool constructed for the prediction of 1-year mortaliy of STEMI patients treated with pPCI, derived from the population of the CADILLAC randomized controlled clinical trial [22]. The PAMI risk score was derived from pooled data of various PAMI randomized controlled clinical trials and registries, constructed to predict 6-month mortality of invasively treated STEMI patients [23]. Overview of all these clinical risk scores is presented in Table 1.

Thus, the aim of this study was to assess additive prognostic value of the SYNTAX score over GRACE, TIMI, ZWOLLE, CADILLAC and PAMI risk scores in patients with STEMI undergoing pPCI.

Methods

This retrospective observational study included 209 consecutive patients with STEMI referred for pPCI, who were admitted to Catheterization laboratory of the Clinic for Cardiology, Clinical Center of Serbia, enrolled from January to April 2008. STEMI was diagnosed if the patient had typical symptoms of acute myocardial infarction lasting for more than 20 min accompanied by ST-segment elevation of more than 1 mm (0.1 mV) in two or more contiguous leads, or new, or presumed new left bundle branch block (LBBB). It was later confirmed by the rise and/or fall of cardiospecific biomarkers in peripheral blood (creatine kinase (CK), creatine kinase MB isoenzyme (CKMB) and troponin I). Patients with previous coronary artery bypass surgery and cardiogenic shock were not included in the study. Loading doses of aspirin and clopidogrel were administered in all patients prior to arrival to the Cath lab. Coronary angiography was performed immediately after admission and was followed by pPCI if appropriate. The procedure was performed using standard techniques. According to local pPCI protocol, only culprit lesion was treated during the index procedure. The decision whether to treat non-culprit lesions during staged procedure was based either on angiographic severity of the lesion (diameter stenosis of 50 % or more) or on subsequent non-invasive functional evaluation, and was left to the discretion of the operator. Antegrade blood flow in the infarct related artery was graded using the thrombolysis in myocardial infarction (TIMI) scale [25]. Total ischemic time was defined as a time interval from the onset of infarct symptoms to the first inflation of an angiographic balloon. It consists of "pain-to-first medical contact" (interval from the onset of infarct symptoms to presentation of a patient to health care provider) and "first medical contact-to-balloon" (interval from patient presentation to the first inflation of an angiographic balloon) time intervals. The study protocol was approved by our institution's medical ethical committee. All patients were informed about the procedure and provided informed consent.

Vital signs (heart rate and systolic/diastolic blood pressure) and Killip class findings were collected at the time of hospital presentation. Killip class I was defined as the absence of congestive heart failure, class II as the presence of rales and/or jugular venous distention, class III as the

Table 1 Overview of the GRACE, TIMI, ZWOLLE, CADILLAC, and the PAMI risk scores

Follow-up	GRACE In-hospital	TIMI 30-day	ZWOLLE 30-day	CADILLAC 1-year	PAMI 6-month
Primary end-point	Mortality	Mortality	Mortality	Mortality	Mortality
Studied population	Acute coronary syndromes (35.5 % STEMI)	STEMI	STEMI	STEMI	STEMI
Study used for the score construction	GRACE registry	InTIME II RCT	Registry	CADILLAC RCT	Pooled data from various PAMI RCTs and registries
Patient recruitment period	1999–2001	1997–1998	1994–2001	1997–1999	1990–1999
Number of patients	11,389	15,078	1,791	2,082	3,252
Reperfusion therapy	15.2 %	100 % (only thrombolytic therapy)	100 % (only pPCI)	100 % (only pPCI)	100 % (only pPCI)
Primary end-point rate	4.5 %	6.7 %	3.6 %	4.3 %	5.2 %
Number of variables for score calculation	8	10	6	7	5
Score includes angiographic characteristics	No	No	Yes	Yes	No
C-statistics	0.840	0.779	0.907	0.79	0.784

RCT randomized controlled trial

presence of pulmonary edema and class IV as a cardiogenic shock. Estimated glomerular filtration rate (eGFR) was calculated using Cockroft-Gault formula, and patients with renal insufficiency were defined as those who had eGFR less the 60 ml/min [22]. Anemia was diagnosed with hematocritical value less than 39 % for men, and 36 % for women [22]. In all patients, left ventricular ejection fraction (LVEF) was assessed by standard echocardiographic examination in the first 24 h after pPCI, using Simpson's biplane method. Severe left ventricular systolic dysfunction was defined as LVEF less than 40 % [22]. A 17-segment model was used to determine systolic left ventricular function [26]. Segmental wall motion was graded as follows: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. The wall motion score index (WMSI) was obtained by dividing the sum of individual visualized segment scores by the number of visualized segments.

The SYNTAX score calculation

The SYNTAX score was derived from the summation of the individual scorings for each separate lesion (defined as >50 % diameter stenosis in vessel larger than 1.5 mm), according to previously demonstrated and described methodology [1, 2]. For each patient, SYNTAX score calculation was based on initial diagnostic angiogram, for lesions visualized before wiring and primary angioplasty (i.e. before any intervention). Lesions located downstream the culprit lesion were included into calculation of the SYNTAX score only if they were visualized on initial diagnostic angiogram, regardless of their presence on subsequent angiograms (during/after the procedure). There is currently no consensus about SYNTAX score calculation in STEMI patients undergoing pPCI, since this group of patients was excluded from the initial SYNTAX score algorithm [1, 18]. For the purpose of the present study, in case of infarct related artery total occlusion, culprit lesion was scored as occluded artery of <3 months duration. The SYNTAX score was calculated using the SYNTAX score calculator which is available online (www.syntaxscore.com). All angiographic variables pertinent to calculation were computed by 2 interventional cardiologists who were blinded 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.

Clinical risk scores calculation

Five clinical risk scores (GRACE [19], TIMI [20], ZWOLLE [21], CADILLAC [22] and PAMI [23]) were calculated for each patient using their clinical and angiographic characteristics. All clinical scores were calculated solely by V.B. Variables included in calculation of these risk scores are presented in Table 2. All risk scores were calculated by summation of points given for each specific criteria presented in Table 2. The variables pertinent to SYNTAX score calculation are presented in Table 3.

Follow-up and clinical end-points

Data about in-hospital events were obtained from the hospital medical documentation. After discharge,

Table 2 Calculation and comparison of the GRACE, TIMI, ZWOLLE, CADILLAC and the PAMI risk scores

Criterion		GRACE	TIMI	ZWOLLE	CADILLAC	PAMI
Age	≥90	100	3	2	2	7
	80–89	91	3	2	2	7
	75–79	75	3	2	2	7
	70–74	75	2	2	2	3
	66–69	58	2	2	2	3
	65	58	2	2	–	3
	60–64	58	–	2	–	–
	50–59	41	–	2	–	–
	40–49	25	–	–	–	–
	30–39	8	–	–	–	–
	<30	–	–	–	–	–
Heart rate	<50	–	–	–	–	–
	5–69	3	–	–	–	–
	70–89	9	–	–	–	–
	90–100	15	–	–	–	–
	101–109	15	2	–	–	2
	110–149	24	2	–	–	2
	150–199	38	2	–	–	2
	≥200	46	2	–	–	2
Systolic blood pressure	<80	58	3	–	–	–
	80–99	53	3	–	–	–
	100–119	43	–	–	–	–
	120–139	34	–	–	–	–
	140–159	24	–	–	–	–
	160–199	10	>180	–	–	–
	≥200	–	Excluded	–	–	–
Killip's class	I	–	–	–	–	–
	II	20	2	4	3	2
	III	39	2	9	3	2
	IV	59	2	9	Excluded	2
Creatinine (mg/dl)	0–0.39	1	–	–	–	–
	0.4–0.79	4	–	–	–	–
	0.8–1.19	7	–	–	–	–
	1.2–1.59	10	–	–	–	–
	1.6–1.99	13	–	–	–	–
	2–3.99	21	–	–	–	–
	>4	28	–	–	–	–
Renal insufficiency (eGFR <60 ml/min, Cockroft-Gault formula)		–	–	–	3	–
History of diabetes mellitus, hypertension or angina	–	–	1	–	–	2 (only DM)
Cardiac arrest on admission		39	–	–	–	–
Elevated cardio-specific biomarkers		14	–	–	–	–
ST-segment deviation		28	–	–	–	–
Weight <67 kg		–	1	–	–	–
Anterior infarction or LBBB		–	1	1	–	2
Time to therapy >4 h		–	1	1	–	–
Baseline LVEF <40 %		–	–	–	4	–
Anemia		–	–	–	2	–
3 vessels disease		–	–	1	2	–
Final TIMI flow <3		–	–	1	2	–
Final TMI flow 0–1		–	–	2	–	–
Total		372	14	16	18	15

Table 3 Calculation of individual scorings for each separate coronary lesion with >50 % diameter stenosis

Segment weighting factor			
Segment no*	Segment*	Right dominance	Left dominance
1	RCA proximal	1	0
2	RCA mid	1	0
3	RCA distal	1	0
4	Posterior descending artery	1	n.a.
16	Posterolateral branch from RCA	0.5	n.a.
16a	Posterolateral branch from RCA	0.5	n.a.
16b	Posterolateral branch from RCA	0.5	n.a.
16c	Posterolateral branch from RCA	0.5	n.a.
5	Left main	5	6
6	LAD proximal	3.5	3.5
7	LAD mid	2.5	2.5
8	LAD apical	1	1
9	First diagonal	1	1
9a	First diagonal a	1	1
10	Second diagonal	0.5	0.5
10a	Second diagonal a	0.5	0.5
11	Proximal circumflex artery	1.5	2.5
12	Intermediate/anterolateral artery	1	1
12a	Obtuse marginal a	1	1
12b	Obtuse marginal b	1	1
13	Distal circumflex artery	0.5	1.5
14	Left posterolateral	0.5	1
14a	Left posterolateral a	0.5	1
14b	Left posterolateral b	0.5	1
15	Posterior descending	n.a.	1

Lesions adverse characteristic scoring	
Diameter reduction**	
Total occlusion	×5
Significant lesion (50–99 %)	×2
Total occlusion	
Age >3 months	+1
Blunt stump	+1
Bridging	+1
First segment visible beyond the occlusion	+1/per non-visible segment
Side branch (SB)	
Yes, SB <1.5 mm***	+1
Yes, both SB< and ≥1.5 mm	+1
Trifurcations	
1 diseased segment	+3
2 diseased segments	+4
3 diseased segments	+5
4 diseased segments	+6
Bifurcations	
Type A, B, C	+1
Type D, E, F, G	+2
Angulation <70°	+1

Table 3 continued

Lesions adverse characteristic scoring	
Aorto ostial stenosis	+1
Severe tortuosity	+2
Length >20 mm	+1
Heavy calcification	+2
Thrombus	+1
"Diffuse disease"/small vessels	+1/per segment number

SYNTAX score is calculated by summation of these individual scorings for all lesions [1]

×: Multiplication

+: Addition

* The definition of the coronary tree segments is based on the classification proposed by the American Heart Association and modified for the ARTS I and II trials. By this system the arterial tree is divided in 16 segments

** In the SYNTAX algorithm there is no question for % luminal diameter reduction. The lesions are considered as significant (50–99 % luminal diameter reduction) or occlusive

*** If all the side branches are 1.5 mm in diameter, no points are added since the lesion is considered as a bifurcation and it will be scored as such

follow-up data were collected by direct telephone interviews. For patients with clinical events in the follow-up period, events were adjudicated from the medical documentation of the respective hospitalization. The primary end-point was the major adverse cardiovascular event (MACE) defined as a composite of cardiovascular mortality, nonfatal myocardial infarction and nonfatal stroke. The secondary end-point was cardiovascular mortality with a demonstrable cardiovascular cause or any death that was not clearly attributable to a non-cardiovascular cause.

Statistical analysis

The normality assumption for continuous variables was evaluated by the Kolmogorov–Smirnov test. Continuous variables are presented as means and standard deviations for normally distributed variables or as medians and interquartile ranges (IQR) for non-normally distributed ones. They were compared using one-way ANOVA, or its non-parametric equivalent Kruskal–Wallis test. For ANOVA, Leven's test for homogeneity of variance was used to test for equality of variances. Categorical variables are presented as counts and percentages and were compared with the Chi square or Fisher's exact test.

To assess interobserver variability between two raters of the SYNTAX score, Cohen's kappa statistics [27] was used after tertile partitioning of their initial SYNTAX scorings. Cohen's kappa measures the agreement between the evaluations of two raters when both are rating the same object. The strength of interobserver agreement according to kappa values are usually given as follows: 0 = none, 0–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial, 0.81–1.00 = almost perfect [27].

Unadjusted and clinical risk score-adjusted survival curves for the SYNTAX score tertiles groups were generated by the Kaplan–Meier method, and further compared with the log-rank test. Two Cox proportional hazard regression models were formed: for MACE and for cardiovascular mortality prediction. Every studied scoring system (the SYNTAX, GRACE, TIMI, ZWOLLE, CADILLAC and the PAMI) was tested as univariable predictor in each Cox regression model. Furthermore, discriminatory power of the models was evaluated using the area under the receiving operating characteristic (ROC) curve (c-statistics) as an index of model performance. The c-statistics reflects the concordance of predictions with actual dichotomous outcomes, with the value of c-statistic of 1.0 indicating perfect, and 0.5 indicating random discrimination [28]. Proportional hazards assumption was formally tested using analysis of Schoenfeldt residuals for each variable in the models.

To test whether the addition of the SYNTAX score to each of the five studied clinical scoring systems in STEMI (the GRACE, TIMI, ZWOLLE, CADILLAC and the PAMI) improves the model significantly, the omnibus test of model coefficients was used to assess the improvement of the model. Two variables (the SYNTAX score and the respective clinical score) were entered into multivariable Cox regression models using forward stepwise (likelihood ratio) method of entry.

For all analyses, a two-sided $p < 0.05$ was considered statistically significant. All data were processed using the

Table 4 Patient characteristics according to tertiles of the SYNTAX score

	Total (N = 206)	Tertile 1, ≤12 (n = 72)	Tertile 2, >12 and ≤19.5 (n = 70)	Tertile 3, >19.5 (n = 64)	*p*
Male, n (%)	163 (79 %)	59 (82 %)	52 (74 %)	52 (84 %)	0.469
Age, years (SD)	58 (12.7)	55 (11.5)	57 (13.4)	63 (12.1)	0.001
Diabetes, n (%)	44 (21 %)	8 (11 %)	18 (26 %)	18 (28 %)	0.030
Hypertension, n (%)	142 (69 %)	45 (67 %)	47 (67 %)	50 (78 %)	0.134
History of smoking, n (%)	151 (73 %)	60 (86 %)	48 (69 %)	41 (64 %)	0.008
Dyslipidemia, n (%)	119 (58 %)	35 (49 %)	42 (60)	42 (66 %)	0.120
Family history of CAD, n (%)	103 (50)	36 (50 %)	40 (57 %)	27 (42 %)	0.224
BMI, kg/m^2 (SD)	27.3 (4.0)	26.4 (3.9)	27.9 (4.1)	27.7 (3.9)	0.049
Previous MI, n (%)	38 (18 %)	12 (17 %)	11 (16 %)	15 (23 %)	0.459
Previous stroke, n (%)	11 (5 %)	4 (6 %)	3 (4 %)	4 (6 %)	0.876
Previous PCI, n (%)	10 (5 %)	4 (6 %)	3 (4 %)	3 (5 %)	0.937
Total ischemic time, minutes, median, (IQR)	275 (248)	272 (228)	245 (205)	322 (293)	0.223
Pain-to-first medical contact, minutes, median (IQR)	80 (159)	90 (135)	60 (145)	105 (229)	0.427
First medical contact-to-balloon, minutes, median (IQR)	163 (98)	157 (93)	156 (105)	170 (90)	0.413
Infarct related artery, n (%)					
LMCA	2 (1 %)	1 (1 %)	0 (0 %)	1 (2 %)	0.017
LAD	89 (43 %)	21 (28 %)	30 (44 %)	38 (59 %)	
CX	19 (9 %)	9 (13 %)	7 (10 %)	3 (5 %)	
RCA	96 (47 %)	42 (58 %)	32 (46 %)	22 (34 %)	
Number of coronary arteries with stenosis ≥50 %, before pPCI, n (%)					
Single vessel disease	89 (43 %)	48 (67 %)	28 (40 %)	13 (20 %)	<0.001
Two vessel disease	65 (32 %)	19 (26 %)	28 (40 %)	18 (28 %)	
Three vessel disease	52 (25 %)	5 (7 %)	14 (20 %)	33 (52 %)	
TIMI flow grade					
TIMI 0 before/post PCI	155 (75 %)/ 4 (2 %)	38 (53 %)/ 0 (0 %)	56 (70 %)/ 1 (1 %)	61 (95 %)/ 3 (5 %)	<0.001/ 0.082
TIMI 1 before/post PCI	7 (3 %)/ 0 (0 %)	4 (6 %)/ 0 (0 %)	3 (2 %)/ 0 (0 %)	0 (0 %)/ 0 (0 %)	
TIMI 2 before/post PCI	21 (10 %)/ 8 (4 %)	13 (18 %)/ 2 (3 %)	6 (13 %)/ 1 (1 %)	2 (3 %)/ 5 (8 %)	
TIMI 3 before/post PCI	23(12 %)/ 194(94 %)	17 (23 %)/70 (97 %)	5 (15 %)/ 68 (98 %)	1(2 %)/ 56(87 %)	
Number of stents					
BMS	202 (98 %)	71 (99 %)	68 (97 %)	63 (98 %)	0.535
DES	2 (1 %)	1 (1 %)	1 (1.5 %)	0 (0 %)	
BMS + DES	1 (0.5 %)	0 (0 %)	1 (1.5 %)	0 (0 %)	
POBA only	1 (0.5 %)	0 (0 %)	0 (0 %)	1 (2 %)	
Ejection fraction, % (IQR)	50 (15)	55 (15)	50 (14)	45 (16)	<0.001
WMSI, median (IQR)	1.19 (0.31)	1.19 (0.19)	1.19 (0.31)	1.44 (0.38)	<0.001
Peak serum CK activity, U/L (IQR)	1,845 (2,250)	1,634.5 (1,912)	1,790.5 (2,292)	2,527 (3,016)	0.048
Heart rate, beats/min (SD)	80 (17)	77 (17)	78 (18)	85 (16)	0.011
SBP, mmHg (SD)	133 (25)	130 (19)	134 (26)	136 (30)	0.310
Creatinine, mg/dl (IQR)	1.15 (0.31)	1.13 (0.24)	1.11 (0.33)	1.29 (0.43)	0.016
Creatinine clearance, ml/min (IQR)	92.26 (49)	94.3 (37)	94.26 (54)	86.72 (55)	0.078
Cardiac arrest on admission	20 (10 %)	6 (8 %)	4 (6 %)	10 (16 %)	0.126

Table 4 continued

	Total (N = 206)	Tertile 1, ≤12 (n = 72)	Tertile 2, >12 and ≤19.5 (n = 70)	Tertile 3, >19.5 (n = 64)	*p*
Renal insufficiency (eGFR < 60 ml/min, Cockroft-Gault formula)	33 (16 %)	5 (7 %)	8 (11 %)	20 (31 %)	<0.001
Anemia	19 (9 %)	4 (6 %)	8 (11 %)	7 (11 %)	0.409
Killip class					
I	174 (84 %)	65 (89 %)	59 (84 %)	50 (78 %)	0.515
II	28 (13.5 %)	7 (10 %)	9 (13 %)	12 (19 %)	
III	4 (2 %)	1 (1 %)	2 (3 %)	1 (1.5 %)	
TIMI (IQR)	4 (3)	4 (2)	4 (3)	6 (4)	0.003
GRACE (IQR)	139.5 (39)	134.5 (32)	138.5 (39)	143.0 (49)	0.026
ZWOLLE (IQR)	2 (2)	1 (1)	2 (2)	3 (2)	<0.001
CADILLAC (IQR)	2 (4)	0 (2)	2 (4)	4 (7)	<0.001
PAMI (IQR)	2 (5)	2 (3)	2 (4)	4 (7)	<0.001

SD standard deviation, CAD- coronary artery disease, *BMI* body mass index, *LMCA* left main coronary artery, *LAD* left anterior descending artery, *Cx* left circumflex coronary artery, *RCA*right coronary artery, *IQR* interquartile range, *BMS* bare metal stent, *DES* drug eluting stent, *POBA* plain old balloon *angioplasty*, *pPCI* primary percutaneous coronary intervention, *WMSI* wall motion score index, *CK* creatine kinase

Table 5 Hard clinical events during follow up across the tertiles of the SYNTAX score

	Total (n = 206)	Lowest tertile, ≤12 (n = 72)	Intermediate tertile, >12 and ≤19.5 (n = 70)	Highest tertile, >19.5 (n = 64)	*p*
MACE	24 (12 %)	4 (6 %)	5 (7 %)	15 (23 %)	0.002
Cardiovascular mortality	17 (8 %)	3 (4 %)	1 (1 %)	13 (20 %)	<0.001
Non-fatal myocardial infarction	6 (3 %)	1 (1 %)	4 (6 %)	1 (2 %)	0.229
Non-fatal stroke	1 (0.5 %)	0 (0 %)	0 (0 %)	1 (2 %)	0.328

statistical package for social sciences, version 15 (SPSS, Chicago, Ill).

Results

Study population included 209 consecutive STEMI patients treated with pPCI. Survival status and follow-up could not be obtained in 3 patients (1.4 %). Thus, the final number of patients included in our analysis was 206 (163 (79 %) male, mean age 58 ± 13 years), as presented in Table 4.

The SYNTAX score was not normally distributed ($p < 0.001$), ranging from 0 to 52 (median 15.5, IQR 11.5). Patients were stratified according to tertiles of the SYNTAX score (lowest tertile: ≤12; intermediate tertile: >12 and ≤19.5; highest tertile: >19.5) and their characteristics are also presented in Table 4. There was substantial interobserver agreement between two raters in the assessment of the SYNTAX score (Cohen's kappa = 0.613; 95 % 2CI 0.523–0.703).

Patients in the highest tertile of the SYNTAX score (>19.5) were older, more commonly had diabetes, renal failure (eGFR <60 mL/min), three-vessel disease and the left anterior descending artery (LAD) as the culprit artery, and more commonly had initial TIMI 0 flow in the infarct related artery. Furthermore, these patients had lower ejection fraction and higher values of wall motion score index, peak CK serum activity, heart rate and serum creatinine. All clinical scores that were evaluated in studied population (the GRACE, TIMI, ZWOLLE, CADILLAC and the PAMI) were the highest in the upper SYNTAX score tertile group.

Clinical outcomes

The median follow-up for the studied patients (n = 206) was 20 months (IQR 3 months) after pPCI. The incidences of MACE, cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke across the SYNTAX score tertiles are presented in Table 5. Overall MACE rate was 11 % (23 events) and the rate of cardiovascular mortality was 8 % (16 deaths); rates of MACE and cardiovascular mortality were highest in the upper tertile of the SYNTAX score ($p < 0.001$ and $p = 0.003$, respectively).

Table 6 Univariable Cox-regression of the SYNTAX, GRACE, TIMI, ZWOLLE, CADILLAC and the PAMI risk scores for MACE and cardiovascular mortality (n = 206)

	B	*p*	HR (95 % CI)	C-statistics (95 % CI)
MACE				
SYNTAX	0.071	<0.001	1.074 (1.036–1.112)	0.763 (0.662–0.864)
GRACE	0.031	<0.001	1.032 (1.019–1.044)	0.757 (0.658–0.856)
TIMI	0.404	<0.001	1.498 (1.263–1.772)	0.726 (0.606–0.845)
ZWOLLE	0.272	<0.001	1.313 (1.176–1.466)	0.767 (0.672–0.862)
CADILLAC	0.260	<0.001	1.296 (1.198–1.403)	0.819 (0.658–0.856)[a]
PAMI	0.194	<0.001	1.214 (1.096–1.345)	0.705 (0.587–0.823)
Cardiovascular mortality				
SYNTAX	0.089	<0.001	1.093 (1.051–1.138)	0.782 (0.641–0.912)
GRACE	0.039	<0.001	1.040 (1.025–1.055)	0.820 (0.717–0.923)
TIMI	0.595	<0.001	1.813 (1.476–2.227)	0.858 (0.779–0.937)[b]
ZWOLLE	0.324	<0.001	1.82 (1.220–1.567)	0.824 (0.736–0.912)
CADILLAC	0.302	<0.001	1.353 (1.231–1.487)	0.880 (0.736–0.912)[b]
PAMI	0.266	<0.001	1.304 (1.165–1.460)	0.812 (0.703–0.921)

All presented C-statistics were significantly different from 0.5 ($p < 0.001$)

[a] Significantly higher prognostic value compared to the PAMI risk score ($p < 0.05$)

[b] Significantly higher prognostic value compared to the SYNTAX score ($p < 0.05$)

Cox proportional hazard model for MACE and cardiovascular mortality

All studied scoring systems (SYNTAX, GRACE, TIMI, ZWOLLE, CADILLAC and PAMI) were good univariable predictors of MACE in our population ($p < 0.001$) (Table 6). In studied population, the CADILLAC risk score showed the best discriminatory power, and it was the only studied clinical score which significantly better predicted MACE than the PAMI risk score, which had the least discriminatory power (c-statistics: 0.819 vs. 0.705, respectively; $p < 0.05$) (Table 6). There was no difference between discriminatory power of other studied scores (SYNTAX, GRACE, TIMI and ZWOLLE) and the PAMI score ($p > 0.05$) (Table 6). After excluding from analysis patients that had early MACE (≤30 days after index event), SYNTAX score was not significant univariable predictor of MACE in later follow-up (>30 days) (HR = 1.027; 95 % CI 0.949–1.113; $p = 0.508$). On the contrary, all studied clinical scores retained their predictive value for MACE occurring after 30 days of index event (GRACE: $p = 0.009$; TIMI: $p = 0.029$; ZWOLLE: $p = 0.003$; CADILLAC: $p < 0.001$; PAMI: $p = 0.032$).

Similarly, all studied scoring systems were significant univariable predictors of cardiovascular mortality in our population ($p < 0.001$) (Table 6). In particular, the CADILLAC and the TIMI risk scores (c-statistics: 0.880 and 0.858 respectively) had the best discriminatory power for cardiovascular mortality, and were better predictors than the SYNTAX score, which had the least power of discrimination (c-statistics: 0.782; $p < 0.05$) (Table 6). After excluding from analysis patients that died early from cardiovascular cause (≤30 days after index event), SYNTAX score was not significant univariable predictor of late (>30 days) cardiovascular mortality (HR = 1.059; 95 % CI 0.959–1.169; $p = 0.256$). On the contrary, all studied clinical scores retained their predictive value for late cardiovascular mortality occurring after 30 days of index event (GRACE: $p = 0.030$; TIMI: $p = 0.017$; ZWOLLE: $p = 0.007$; CADILLAC: $p < 0.001$; PAMI: $p = 0.014$).

Additive value of the SYNTAX score over other clinical scores

SYNTAX score was independent predictor of MACE and cardiovascular mortality and improved both models significantly when added to GRACE, TIMI, ZWOLLE, and PAMI risk scores (Table 7). However, in studied population, SYNTAX score did not improve the Cox regression models of MACE and cardiovascular mortality when added to CADILLAC score (Table 7). Unadjusted survival curves for MACE and cardiovascular mortality across SYNTAX score tertiles groups are presented in Figs. 1 and 2. Clinical risk score-adjusted MACE free survival curves across the SYNTAX score tertiles groups are presented in Fig. 3.

Discussion

Our study demonstrated that the SYNTAX score was significant univariable predictor of both MACE and cardiovascular mortality in patients with STEMI undergoing pPCI. The patients in the highest SYNTAX score tertile (>19.5) had significantly higher rates of MACE and cardiovascular mortality after pPCI in comparison to the lower and intermediate tertile. Furthermore, patients in the highest SYNTAX score tertile had the highest values of all studied clinical scores (i.e. the highest risk for adverse events) in comparison to the lower and intermediate one. In addition, even after risk adjustment for TIMI, GRACE,

Table 7 Addition of the SYNTAX score to the GRACE, TIMI, ZWOLLE, CADILLAC and the PAMI risk scores: multivariable Cox-regression for MACE and cardiovascular mortality (n = 206)

	B	*p*	HR (95 % CI)
MACE			
SYNTAX	0.049	0.007	1.051 (1.014–1.089)
GRACE	0.027	<0.001	1.027 (1.014–1.040)
Model improvement by adding SYNTAX score		0.011*	
SYNTAX	0.053	0.005	1.055 (1.017–1.095)
TIMI	0.339	<0.001	1.404 (1.177–1.674)
Model improvement by adding SYNTAX score		0.008*	
SYNTAX	0.051	0.006	1.052 (1.015–1.091)
ZWOLLE	0.238	<0.001	1.268 (1.122–1.434)
Model improvement by adding SYNTAX score		0.009*	
SYNTAX	–	0.165	–
CADILLAC	0.260	<0.001	1.296 (1.298–1.403)
Model improvement by adding SYNTAX score		ns*	
SYNTAX	0.056	0.004	1.056 (1.018–1.098)
PAMI		0.012	
Model improvement by adding SYNTAX score	0.145	0.017	1.156 (1.032–1.294)
Cardiovascular mortality			
SYNTAX	0.057	0.005	1.059 (1.017–1.102)
GRACE	0.033	<0.001	1.033 (1.017–1.050)
Model improvement by adding SYNTAX score		0.008*	
SYNTAX	0.059	0.005	1.061 (1.018–1.105)
TIMI	0.513	<0.001	1.670 (1.347–2.070)
Model improvement by adding SYNTAX score		0.009*	
SYNTAX	0.064	0.002	1.066 (1.024–1.110)
ZWOLLE	0.283	<0.001	1.327 (1.150–1.532)
Model improvement by adding SYNTAX score		0.003*	
SYNTAX	–	0.053	–
CADILLAC	0.302	<0.001	1.353 (1.231–1.487)
Model improvement by adding SYNTAX score		ns	
SYNTAX	0.660	0.002	1.068 (1.089–1.402)
PAMI	0.212	0.001	1.068 (1.089–1.402)
Model improvement by adding SYNTAX score		0.004*	

Method of variable entry—forward Stepwise (Likelihood Ratio)

* By omnibus test of model coefficients

ZWOLLE and PAMI scores, the SYNTAX score remained significant predictor of MACE and cardiovascular mortality. Most importantly, SYNTAX score significantly improved predictive value of TIMI, GRACE, ZWOLLE and PAMI risk scores for adverse cardiovascular events. However, SYNTAX score did not improve the predictive value of the CADILLAC risk score, neither for MACE nor for cardiovascular mortality.

Our study is the first that evaluated relative prognostic merit of the SYNTAX score over five well-established clinical risk scores for STEMI patients. To our knowledge, there is only one published study that tested additive prognostic value of the SYNTAX score over a clinical risk score in STEMI patients [18]. This particular study demonstrated that the SYNTAX score had a role in the risk stratification of patients with STEMI undergoing pPCI, and this was achieved through a combination with the PAMI clinical risk score. However, superior prognostic value of CADILLAC over PAMI has been demonstrated earlier [22] and confirmed in our study in regard to significantly better discriminatory power for prediction of MACE.

Although initially developed for quantification of angiographic severity of the stable CAD, the SYNTAX score was shown to have prognostic significance in various clinical settings, including stable CAD and acute coronary syndromes (ACS) [15, 17, 18, 29]. In stable CAD, the SYNTAX score is calculated prior to coronary intervention (either PCI or surgery), and demonstrated significant predictive value [4]. On the contrary, there are two different proposed methods for SYNTAX score calculations in

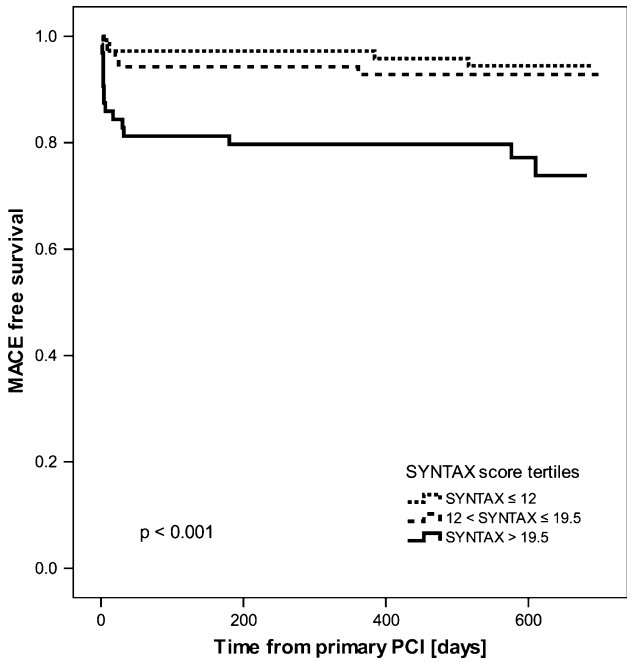

Fig. 1 Unadjusted MACE free survival across the SYNTAX score tertiles

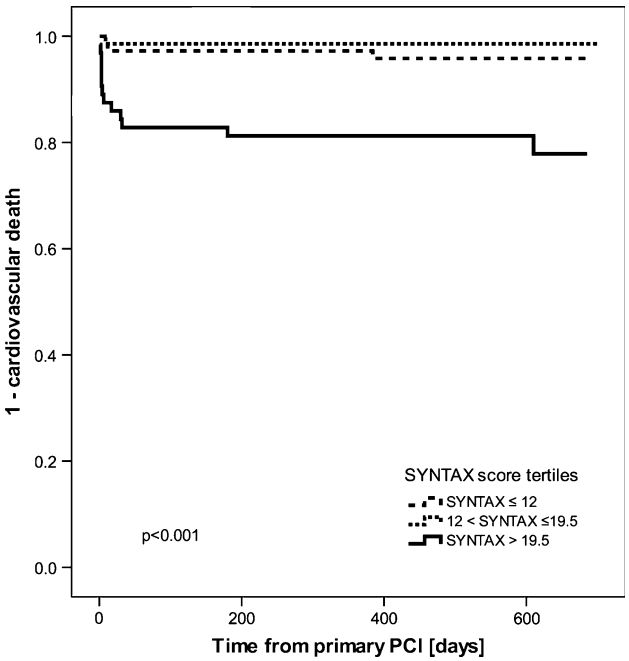

Fig. 2 Unadjusted survival (freedom from cardiovascular death) across the SYNTAX score tertiles

STEMI patients undergoing pPCI, which are based either on initial angiogram (before wiring and angioplasty) or after the guide wire has passed the infarct lesion/prior to stent deployment [15, 18]. In the present study, we calculated the SYNTAX score using initial diagnostic angiogram (before any intervention in the infarct related artery).

Our study population had similar distribution of the SYNTAX score as in previously published studies with patients with ACS. The SYNTAX score tertiles of our patients were: lowest tertile $\leq$12, intermediate tertile between 12 and 19.5, highest tertile >19.5. These tertiles were similar to those reported by Palmerini et al. [29] (lowest tertile <7, intermediate tertile between 7 and 13, highest tertile $\geq$13) for non-STEMI, Magro et al. [15] (lowest tertile <10, intermediate tertile between 10 and 20, highest tertile >20), and Garg et al. [18] (lowest tertile $\leq$9, intermediate tertile between 9 and 16, highest tertile >16) for STEMI patients. In all these studies, including the present one, the SYNTAX score was lower in comparison to values in cohort of patients with stable CAD in the landmark SYNTAX trial (lowest tertile <22, intermediate tertile between 23 and 32, highest tertile $\geq$33) [4].

There was substantial interobserver agreement between two raters in the assessment of the SYNTAX score (Cohen's kappa = 0.613), which is consistent with previously reported data [2, 30].

In regard to comparative value of different risk scores, the PAMI risk score, although developed on population of patients treated invasively, does not include any of the angiographic variables in the calculation, which may partially explain the significantly lower discriminatory power for MACE than that of the CADILLAC risk score (Table 6) which includes some of them (presence of three-vessel CAD and TIMI flow less than 3) (Table 2). The CADILLAC, ZWOLLE and the PAMI scores were developed exclusively on populations of patients undergoing invasive treatment of STEMI, while the populations from which the TIMI and the GRACE risk scores were derived included patients treated with fibrinolytic therapy. The TIMI, GRACE and the PAMI risk scores do not include angiographic characteristics of the patients (Table 2), which may partially explain why the SYNTAX score has additive prognostic information for prediction of long-term MACE and cardiovascular mortality when added to them. On the other side, both the CADILLAC and the ZWOLLE scores include some of the angiographic variables. Furthermore, the CADILLAC was developed from a high quality randomized controlled trial [31], while the ZWOLLE score was developed from a 'real-life' registry [21]. These characteristics of those two scores may be partially related to the fact that the SYNTAX score brings additive prognostic information for MACE and cardiovascular mortality only to the ZWOLLE but not to the CADILLAC risk score.

In our study population, prognostic information contained in the CADILLAC risk score, which is the most sophisticated of all studied clinical scores in the present study, was not significantly improved by the addition of the

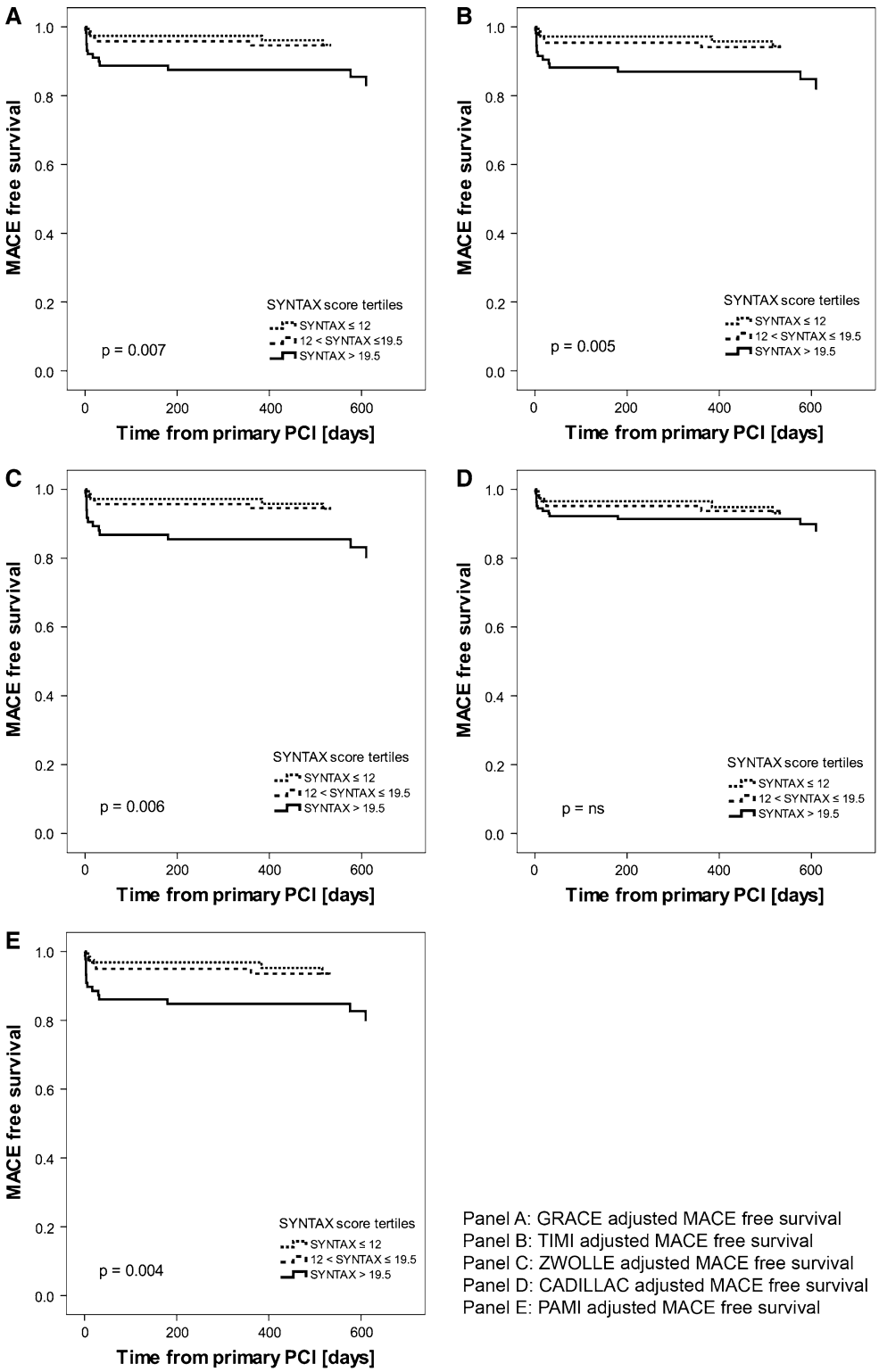

Fig. 3 Risk score-adjusted MACE free survival across the SYNTAX score tertiles

SYNTAX score. Similarly, it is of notice that the SYNTAX score had the least discriminatory power for cardiovascular mortality in our study, suggesting that long-term survival in patients after STEMI is not dependent only on the severity of coronary lesions, but also on other clinical characteristics, as proved by superiority of the CADILLAC score. In fact, it contains various angiographical and clinical parameters, including LVEF and anemia that no other studied score takes into account. Superiority of the CADILLAC risk score over the TIMI, PAMI and the ZWOLLE scores was previously demonstrated in terms of better accuracy in prediction of 30-day ($p = 0.02$) and 1-year

mortality ($p = 0.06$) [22]. Finally, one of the reasons for superior prognostic value of the CADILLAC risk score in our study population (with median follow up of 20 months) may be due to the fact that it is the only studied clinical scores that was initially derived for prediction of long-term (1-year) mortality, while others were constructed for shorter follow-up periods (Table 1).

Study limitations

This study is limited by its retrospective nature. Left ventricular ejection fraction in our study was assessed by echocardiography in the first 24 h after pPCI, while in the CADILLAC study, it was calculated using left ventriculography during the pPCI [22]. For the purpose of this study, an old definition of myocardial infarction was used, since the Universal definition of myocardial infarction [32] was not widely implemented in our institution at the time of enrollment (2008). Patients with cardiogenic shock were not included in the study, which was also the case in populations of patients from which the CADILLAC and the PAMI scores were derived [22, 23]. We used both MACE and cardiovascular mortality as our study end-points, while all the studied clinical risk scores were constructed to predict cardiovascular mortality only. The c-statistics method, although well suited for diagnostic purposes, may not be appropriate for prognostic models, because it does not incorporate dimension of time [33]. Although it might be interesting to differentiate the impact of the SYNTAX score on early and late cardiovascular outcomes, these subanalyses would be of limited value due to the small number of patients/events. Since the sample size of our study was relatively small, with small number of cardiovascular events, our findings should be considered as hypothesis generating and need to be further verified in a larger prospective trial, including patients with most severe clinical presentation during STEMI.

Conclusions

The SYNTAX score, per se, has a value in prediction of major adverse cardiovascular events and cardiovascular mortality in patient with STEMI undergoing primary PCI. Furthermore, the SYNTAX score improves prognostic performance of well-established GRACE, TIMI, ZWOLLE and PAMI clinical risk scores, but not CADILLAC risk score. Thus, long-term survival in patients after STEMI depends less on detailed angiographical characterization of coronary lesions, but more on clinical characteristics, myocardial function and basic angiographic findings as provided by the CADILLAC score.

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Conflict of interest None.

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