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The MI SYNTAX score for risk stratification in patients undergoing primary percutaneous coronary intervention for treatment of acute myocardial infarction: A substudy of the COMFORTABLE AMI trial

Michael Magro [a,b,1], Lorenz Räber [a,1], Dik Heg [c,n], Masanori Taniwaki [a], Henning Kelbaek [d], Miodrag Ostojić [e], Andreas Baumbach [f], David Tüller [g], Clemens von Birgelen [h], Marco Roffi [i], Giovanni Pedrazzini [j], Ran Kornowski [k,l], Klaus Weber [m], Bernhard Meier [a], Thomas F. Lüscher [o], Patrick W. Serruys [b], Peter Jüni [c,n], Stephan Windecker [a,n,*]

[a] Department of Cardiology, Bern University Hospital, Bern, Switzerland
[b] Thoraxcenter, Erasmus University Hospital, Rotterdam, The Netherlands
[c] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[d] Cardiac Catheterization Laboratory, Rigshospitalet, Copenhagen, Denmark
[e] Department of Cardiology, Clinical Center of Serbia, Belgrade, Serbia
[f] Bristol Heart Institute, Bristol, United Kingdom
[g] Cardiology Department, Triemlispital, Zurich, Switzerland
[h] Thoraxcentrum Twente, Twente University, Enschede, The Netherlands
[i] Division of Cardiology, University Hospital, Geneva, Switzerland
[j] Cardiocentro, Lugano, Switzerland
[k] Rabin Medical Center, Petach Tikva, Israel
[l] Tel Aviv University, Tel Aviv, Israel
[m] Herzzentrum Bodensee, Kreuzlingen, Switzerland
[n] Clinical Trials Unit, Department of Clinical Research, University of Bern, Bern, Switzerland
[o] Cardiology Department, University Hospital Zurich, Zurich, Switzerland

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ABSTRACT

Background: To investigate the performance of the MI Sxscore in a multicentre randomised trial of patients undergoing primary percutaneous coronary intervention (PPCI).

Methods and results: The MI Sxscore was prospectively determined among 1132 STEMI patients enrolled into the COMFORTABLE AMI trial, which randomised patients to treatment with bare-metal (BMS) or biolimus-eluting (BES) stents. Patient- (death, myocardial infarction, any revascularisation) and device-oriented (cardiac death, target-vessel MI, target lesion revascularisation) major adverse cardiac events (MACEs) were compared across MI Sxscore tertiles and according to stent type.

The median MI SXscore was 14 (IQR: 9–21). Patients were divided into tertiles of $Sxscore_{low}$ (≤10), $Sxscore_{intermediate}$ (11–18) and $Sxscore_{high}$ (≥19). At 1 year, patient-oriented MACE occurred in 15% of the $Sxscore_{high}$, 9% of the $Sxscore_{intermediate}$ and 5% of the $Sxscore_{low}$ tertiles ($p < 0.001$), whereas device-oriented MACE occurred in 8% of the $Sxscore_{high}$, 6% of the $Sxscore_{intermediate}$ and 4% of the $Sxscore_{low}$ tertiles ($p = 0.03$). Addition of the MI Sxscore to the TIMI risk score improved prediction of patient- (c-statistic value increase from 0.63 to 0.69) and device-oriented MACEs (c-statistic value increase from 0.65 to 0.70). Differences in the risk for device-oriented MACE between BMS and BES were evident among $Sxscore_{high}$ (13% vs. 4% HR 0.33 (0.15–0.74), $p = 0.007$ rather than those in $Sxscore_{low}$: 4% vs. 3% HR 0.68 (0.24–1.97), $p = 0.48$) tertiles.

Conclusions: The MI Sxscore allows risk stratification of patient- and device-oriented MACEs among patients undergoing PPCI. The addition of the MI Sxscore to the TIMI risk score is of incremental prognostic value among patients undergoing PPCI for treatment of STEMI.

1. Introduction

The risk of adverse events among patients presenting with acute myocardial infarction has been thoroughly assessed by means of clinical variables incorporated into the TIMI risk score during the thrombolysis

* Corresponding author at: Department of Cardiology, Bern University Hospital, 3010 Bern, Switzerland.
E-mail address: stephan.windecker@insel.ch (S. Windecker).
[1] MM and LR contributed equally to this manuscript.

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era [1,2]. The advent of primary percutaneous coronary intervention (PPCI) as the preferred reperfusion strategy among patients with ST-segment elevation myocardial infarction (STEMI) identified angiographic variables obtained at the time of the intervention to be of additional prognostic significance in observational studies [3].

The SYNTAX score (Sxscore) quantifies angiographic characteristics and disease complexity among patients undergoing PCI and has been shown to predict MACE during follow-up in patients with stable and unstable coronary artery diseases [4]. Among patients with stable coronary artery disease, the combined use of clinical and angiographic variables in the global risk assessment further improved the predictive value [5]. Among STEMI patients, the addition of angiographic characteristics quantified by the MI Sxscore improved the TIMI risk model for prediction of major adverse cardiac events in a recent study including observational data from 669 consecutive STEMI patients [6]. The performance of such a model in all-comer STEMI trials remains to be examined. We therefore validated the MI Sxscore in a contemporary, multicenter trial of STEMI patients undergoing primary PCI, the COMFORTABLE AMI trial [7].

2. Methods

2.1. Study population

The COMFORTABLE AMI trial included patients 18 years of age or older who had a history of chest pain of more than a 10 min duration and associated ST segment elevation of >1 mm in ≥2 contiguous leads, new left bundle branch block or true posterior MI, who underwent primary percutaneous coronary intervention (PCI) within 24 h of symptom onset. In addition, there was angiographic presence of at least one acute infarct related artery (IRA) with one or multiple coronary artery lesions in a native coronary artery with a diameter between 2.25 and 4.0 mm, which could be treated with one or multiple stents. Exclusion criteria included use of vitamin K antagonists, mechanical complications of myocardial infarction, acute myocardial infarction secondary to stent thrombosis (ST), planned surgery within 6 months of PCI unless dual antiplatelet therapy could be maintained throughout the peri-surgical period and non-cardiac comorbid conditions with life expectancy <1 year. Further study details are described in detail elsewhere [7,8].

Angiography was digitally recorded and analysed in a central core laboratory. The MI Sxscore was assessed by experienced analysts using the web based programme www.syntaxscore.com as previously described. Angiographic documentation of patients included in the COMFORTABLE AMI trial was scored as described previously. In brief, the MI Sxscore for each patient was calculated by two independent and blinded, interventional cardiologists, taking into account the patency of the infarct related artery. An infarct related artery (IRA) with TIMI flow of 0 or 1 was scored as a total occlusion with thrombus. The CABG Sxscore was calculated by determining the standard Sxscore in native coronary vessels and subtracting points based on the importance of the diseased coronary artery segment (Leaman score) that are supplied by a functioning bypass graft. Points relating to intrinsic coronary artery disease, such as bifurcation disease or calcification, remained unaltered [9]. The interobserver and intraobserver variabilities of the Sxscoring team were previously reported as moderate (kappa statistic 0.56) and substantial (kappa statistic 0.70). The trial randomly assigned 1161 patients with acute ST-segment elevation myocardial infarction (STEMI) to treatment with biolimus-eluting stents with a biodegradable polymer (BioMatrix; Biosensors Inc., Morges, Switzerland) and bare-metal stents (BMSs) using the same platform design (Gazelle, Biosensors Inc., Morges, Switzerland).

2.2. Primary and secondary endpoints

The primary clinical end points of this study were patient-oriented MACE, defined as the composite of all-cause death, any reinfarction (MI) and any revascularisation, and device-oriented MACE, defined as a composite of cardiac death, target vessel reinfarction (TV-MI) and ischaemia-driven target-lesion revascularisation (TLR). Secondary endpoints included all-cause and cardiac deaths, target-vessel reinfarction (TV-MI), any reinfarction, composite of death or recurrent MI, ischaemia-driven target-lesion (TLR) and target vessel revascularisation (TVR), and ARC-defined definite and definite or probable stent thrombosis (ST) [10]. Details of the definitions of the primary and secondary endpoints used for adjudication of events by the independent clinical events committee (CEC) are reported elsewhere [8].

2.3. Statistical analysis

Continuous variables are presented as mean ± 1SD or as median and interquartile ranges. Categorical variables are presented as counts and percentages. To characterise differences between different Sxscores, the study cohort was divided into three groups according to MI Sxscore tertiles; $Sxscore_{high}$, $Sxscore_{intermediate}$ and $Sxscore_{low}$. Analyses of variance (ANOVA, for continuous variables), Kruskal–Wallis tests (for non-parametric variables) and Chi-squares tests (for categorical variables) were used to describe differences between the 3 groups. Comparisons involving the 2 stents were performed using unpaired t-tests.

Cox regression analysis was used to determine the risk ratio of Sxscore tertiles for the primary endpoint as well as individual endpoints at 30 days and 1 year. This was performed for the whole cohort as well as individually for each of the randomised groups

Table 1
Baseline characteristics of the COMFORTABLE AMI population according to SYNTAX score tertiles.

	Baseline characteristics			
	Syntax score			
	Low (0–10) N = 394	Intermediate (11–18) N = 374	High (19–52) N = 364	p value[a]
Baseline characteristics				
Age, years	58.7 ± 12.2	60.5 ± 11.0	62.6 ± 11.7	<0.001
Male gender	302 (77%)	297 (79%)	298 (82%)	0.21
Diabetes	47 (12%)	65 (17%)	58 (16%)	0.09
Insulin-dependent	8 (2%)	6 (2%)	11 (3%)	0.45
Hypertension	172 (44%)	178 (48%)	182 (50%)	0.21
Hypercholesterolaemia	224 (57%)	219 (59%)	194 (54%)	0.38
Smoker at any time	303 (77%)	293 (79%)	253 (71%)	0.02
Current smoker	209 (53%)	194 (52%)	157 (44%)	0.02
Ex-smoker	94 (24%)	99 (27%)	96 (27%)	0.61
Renal failure	65 (17%)	69 (19%)	69 (19%)	0.63
Family history of CAD	128 (33%)	122 (34%)	110 (31%)	0.68
Body mass index, kg/m^2	27.4 ± 4.4	27.2 ± 4.1	27.0 ± 4.3	0.46
Previous myocardial infarction	13 (3%)	22 (6%)	27 (7%)	0.04
Previous PCI	14 (4%)	16 (4%)	14 (4%)	0.87
Previous CABG	7 (2%)	5 (1%)	2 (1%)	0.33
Clinical presentation				
Time from symptom onset to balloon inflation, min	228.0 (159.0–354.0)	236.0 (163.5–392.0)	244.0 (170.0–400.0)	0.64
Resuscitation prior to hospital arrival	10 (3%)	6 (2%)	9 (2%)	0.61
Pulse rate, bpm	75.3 ± 15.1	76.0 ± 16.0	77.4 ± 16.9	0.20
Blood pressure, mm Hg				
Systolic	128.5 ± 22.6	131.4 ± 22.9	129.1 ± 23.5	0.19
Diastolic	77.5 ± 14.8	79.1 ± 14.2	77.9 ± 15.6	0.35
Cardiogenic Shock	0 (0%)	2 (1%)	10 (3%)	0.001
Killip class II, III or IV	20 (5%)	14 (4%)	39 (11%)	<0.001

Data is expressed in numbers and (percentages) or means ± 1 standard deviation. PCI = Percutaneous coronary intervention, CABG = coronary artery bypass.
[a] p value calculated using ANOVA for continuous variables or Kruskal–Wallis test for non-parametric variables and Chi-square test for categorical variables.

receiving BMS and the drug eluting stent. Event curves employing the Kaplan–Meier method were then generated to depict the differences across the MI Sxscore tertiles for the primary end point MACE and its components. To explore the effect of stratification in MI Sxscore tertiles, differential outcomes between BMS and biolimus-eluting stents were explored.

In a separate analysis, variables in the TIMI risk score including age >74, history of diabetes, hypertension or heart failure, systolic blood pressure <100 mm Hg, heart rate >100 beats per minute, Killip classes II–IV, body weight <67 kg, anterior STEMI and time to treatment of >4 h were used to assess the additional predictive value of the MI Sxscore as determined by the c-statistic. The performance of the model combining the TIMI risk score with the MI Sxscore in this all-comer randomised trial was compared to values achieved with the model studied using published previously data from an observational study. We used this comparison as a method of validation for the model [6].

All statistical tests were 2-tailed, and p values were significant at <0.05. Analysis was performed using STATA version 12.1 (StataCorp).

3. Results

Complete angiographic analysis of the MI Sxscore was performed in 1132 of 1161 patients enrolled in the COMFORTABLE AMI trial. The median (interquartile range) MI Sxscore of the entire patient cohort was 14 [9–21], and was not different between patients randomised to BES and BMS (15.1 vs. 14.8, p = 0.54). The $Sxscore_{low}$ tertile was composed of 394 patients with scores up to 10, the $Sxscore_{intermediate}$ tertile of 374 patients with scores ranging from 11 to 18, and the $Sxscore_{high}$ tertile of 364 patients with scores ranging from 19 to 52. Baseline clinical characteristics according to MI Sxscore tertiles are summarised in Table 1. Patients with higher MI Sxscores were older, and had a higher prevalence of diabetes, history of previous myocardial infarction, cardiogenic shock and signs of heart failure.

Angiographic characteristics across the three tertiles are summarised in Table 2. Patients with higher MI Sxscores were more likely to present with anterior myocardial infarction with the left anterior descending coronary artery (LAD) as the infarct related artery (IRA), an occluded IRA or a reduced TIMI 0/1 flow. Similarly, a higher number of stents was implanted into longer coronary artery segments, and there were more bifurcations and a higher number of treated vessels among patients in the $Sxscore_{high}$ group.

While a final post-procedure TIMI flow of 0/1 was present in only 1% of the $Sxscore_{high}$ group, a poor myocardial blush grade (MBG 0/1) was present in 9% of patients in this group, which was more frequent than that in the other tertiles (3% in the $Sxscore_{intermediate}$ group and 2% in the $Sxscore_{low}$ group, <0.001). The peak creatinine kinase also correlated with higher tertiles of MI Sxscore (Fig. 1).

We observed no differences in medication intake across the MI Sxscore tertiles at 1 year except for oral anticoagulants, which were more frequently prescribed in the highest MI Sxscore tertile.

Similar differences in baseline and procedural characteristics across MI Sxscore tertiles were observed in an analysis stratified according to stent type (Supplementary Tables 1 and 2 for bare metal stents and Supplementary Tables 3 and 4 for biolimus eluting stents).

Table 2
Angiographic and procedural characteristics of the COMFORTABLE AMI according to Sxscore tertiles.

	SYNTAX score			
	Low (0–10) N = 394	Intermediate (11–18) N = 374	High (19–52) N = 364	p value[a]
Angiographic characteristics pre-procedural				
Anterior STEMI	99 (25%)	112 (30%)	206 (57%)	<0.001
Infarct related artery, IRA				
Left main	1 (0%)	1 (0%)	3 (1%)	0.41
Left anterior descending	120 (31%)	124 (33%)	220 (60%)	<0.001
Left circumflex	70 (18%)	73 (20%)	46 (13%)	0.033
Right coronary	214 (54%)	194 (52%)	124 (34%)	<0.001
TIMI 0 or 1	165 (42%)	274 (73%)	305 (84%)	<0.001
Treated vessels incl. IRA[b]				0.012
1-Vessel disease	381 (97%)	357 (95%)	334 (92%)	0.005
2-Vessel disease	12 (3%)	15 (4%)	29 (8%)	0.005
3-Vessel disease	0 (0%)	2 (1%)	1 (0%)	0.36
Left main disease	1 (0%)	1 (0%)	3 (1%)	0.41
Procedural characteristics				
Number of stents implanted in IRA	1.3 ± 0.5	1.5 ± 0.8	1.6 ± 0.8	<0.001
Total stent length in IRA, mm	23.9 ± 10.8	28.3 ± 14.4	30.0 ± 14.7	<0.001
Average stent diameter in IRA, mm	3.2 ± 0.5	3.2 ± 1.4	3.2 ± 0.4	0.37
Bifurcation treatment in IRA	26 (7%)	29 (8%)	44 (12%)	0.02
Thrombectomy	240 (61%)	226 (60%)	240 (66%)	0.24
GP IIb/IIIa Inhibitors	179 (45%)	173 (46%)	173 (48%)	0.85
Intra-aortic balloon pump	3 (1%)	7 (2%)	18 (5%)	0.001
Multivessel stenting	12 (3%)	16 (4%)	30 (8%)	0.004
Angiographic characteristics post-procedural				
TIMI 0 or 1	1 (0%)	0 (0%)	3 (1%)	0.15
Corrected TIMI frame count at end procedure, fps	24.9 ± 15.3	25.7 ± 20.5	26.4 ± 21.3	0.61
Myocardial blush grade 0 or 1	9 (2%)	12 (3%)	31 (9%)	<0.001
Follow-up				
Complete revascularisation within 90 days[b]	3 (1%)	11 (3%)	16 (4%)	0.007
Medication at 1 year				
Aspirin	365 (97%)	340 (97%)	326 (97%)	0.83
Clopidogrel	171 (46%)	160 (45%)	147 (44%)	0.84
Prasugrel	132 (35%)	137 (39%)	129 (38%)	0.53
Beta-blocker	290 (78%)	280 (80%)	273 (81%)	0.47
ACE-inhibitors	219 (59%)	216 (61%)	223 (66%)	0.10
Statins	347 (93%)	328 (93%)	307 (91%)	0.64
Oral anticoagulant	8 (2%)	7 (2%)	19 (6%)	0.008

Data is expressed in numbers and (percentages), mean ± 1 standard deviation or median and (interquartile range). STEMI = ST elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction; GP = glycoprotein; PCI = percutaneous coronary intervention CABG = coronary artery bypass graft; and IRA = infarct related artery.

[a] p value calculated using ANOVA for continuous variables and Chi-square test for categorical variables.

[b] n = 28 requiring PCI and n = 2 requiring coronary artery bypass graft.

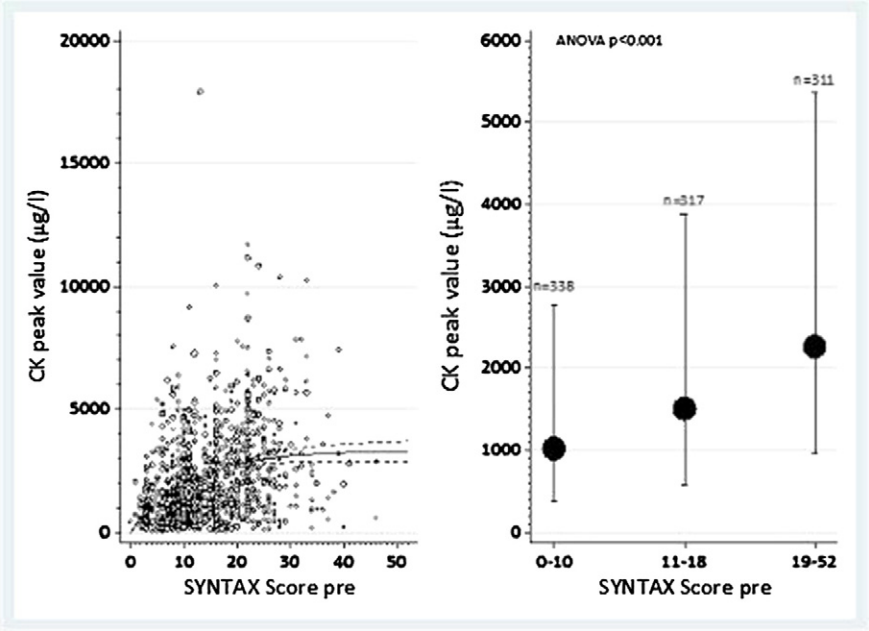


Fig. 1. SYNTAX score and infarct size based on peak creatinine kinase values. The left plot shows the relation of peak enzyme release and Sxscore while the right plots show the peak enzymes in tertiles of Sxscore.

3.1. Clinical outcomes

Clinical outcomes stratified according to the MI Sxscore tertiles are shown in Tables 3 (30 days) and 4 (1 year). Patient-oriented MACE (Fig. 2) was more common in the $Sxscore_{high}$ than in the $Sxscore_{low}$ tertiles at 30 days and 1 year (HR 2.38, 95% CI (1.26–4.49), p = 0.007). Device-oriented MACE (Fig. 3) was also more frequent in the $Sxscore_{high}$ than in the $Sxscore_{low}$ tertiles at 30 days and 1 year (HR 3.05, 95% CI 1.02–5.10, p < 0.001). Patients with MI Sxscores of ≤10 had a rate of device-related MACE as low as 2% at 30 days and 4% at 1 year. Conversely, rates of device-oriented MACE among patients with a MI Sxscore ≥19 were 4% and 8% at 30 days and 1 year, respectively. Differences in patient-oriented MACE were driven by a higher risk of death or reinfarction (9% in the $Sxscore_{high}$ group, 5% in the $Sxscore_{intermediate}$ group and 4% in the $Sxscore_{low}$ group, p < 0.001) as well as any revascularisation among patients in the highest risk tertile (9% in the $Sxscore_{high}$ group, 6% in the $Sxscore_{intermediate}$ group and 3% in the $Sxscore_{low}$ group, p = 0.002). Cardiac mortality was higher in the $Sxscore_{high}$ tertile compared to the $Sxscore_{low}$ tertile, HR 2.51 (1.03–6.10) p = 0.0423. The risk of repeat revascularisation was higher in the $Sxscore_{high}$, compared with the $Sxscore_{intermediate}$ and $Sxscore_{low}$ tertiles at 1 year ((9%) vs. 23 (6%) vs. 12 (3%) p = 0.002; $Sxscore_{high}$ vs. $Sxscore_{low}$ HR 3.24 (1.68–6.25), p = <0.001).

Definite and probable stent thromboses (STs) occurred early (within 30 days) in 26 patients and late (30 days to 1 year) in 8 patients. Early definite and probable STs were diagnosed in 13 (4%) of the $Sxscore_{high}$, 7 (2%) of the $Sxscore_{intermediate}$ and 6 (2%) of the $Sxscore_{low}$ (p = 0.081). Definite and probable STs at one year were recorded in 13 (4%) of the $Sxscore_{high}$, 9 (2%) of the $Sxscore_{intermediate}$ and 10 (3%) of the $Sxscore_{low}$ groups (p = 0.58).

3.2. Risk stratification according to TIMI score and MI Sxscore

A 10-point increase in the MI Sxscore was associated with an increased risk of patient- (HR = 1.83, 95% CI 1.43–2.32, p < 0.001) and device-oriented MACEs (HR of 1.48, 95% CI 1.10–1.98, p = 0.009).

Table 3
Clinical outcome at 30 days in the COMFORTABLE AMI trial according to Sxscore tertiles.

	SYNTAX score			Cox's regression				
	Low (0–10) N = 394	Intermediate (11–18) N = 374	High (19–52) N = 364	Intermediate vs. low		High vs. low		Overall
				HR (95% CI)	p value	HR (95% CI)	p value	p value
30 days follow-up								
Device-oriented MACE	6 (2%)	9 (2%)	16 (4%)	1.59 (0.57–4.48)	0.376	2.92 (1.14–7.46)	0.025	0.060
Patient-oriented MACE	6 (2%)	14 (4%)	25 (7%)	2.49 (0.96–6.49)	0.061	4.61 (1.89–11.24)	0.001	0.002
All cause death	3 (1%)	5 (1%)	9 (2%)	1.77 (0.42–7.42)	0.433	3.27 (0.89–12.09)	0.075	0.172
Cardiac death	3 (1%)	5 (1%)	8 (2%)	1.77 (0.42–7.42)	0.433	2.91 (0.77–10.96)	0.115	0.269
Reinfarction (any)	2 (1%)	4 (1%)	11 (3%)	2.14 (0.39–11.66)	0.381	6.04 (1.34–27.25)	0.019	0.027
Reinfarction in IRA	2 (1%)	3 (1%)	6 (2%)	1.60 (0.27–9.56)	0.608	3.27 (0.66–16.21)	0.147	0.288
Death or reinfarction (any)	5 (1%)	9 (2%)	20 (5%)	1.92 (0.64–5.73)	0.241	4.40 (1.65–11.71)	0.003	0.005
Revascularisation (any)	3 (1%)	9 (2%)	14 (4%)	3.20 (0.87–11.81)	0.081	5.15 (1.48–17.92)	0.010	0.033
Revascularisation in IRA, clinically indicated	3 (1%)	4 (1%)	9 (2%)	1.41 (0.32–6.32)	0.650	3.28 (0.89–12.11)	0.075	0.131
Stent thrombosis all	6 (2%)	7 (2%)	13 (4%)	1.24 (0.42–3.69)	0.697	2.37 (0.90–6.23)	0.081	0.152
Definite	3 (1%)	4 (1%)	7 (2%)	1.41 (0.32–6.32)	0.650	2.54 (0.66–9.84)	0.176	0.350
Definite/probable	6 (2%)	7 (2%)	13 (4%)	1.24 (0.42–3.69)	0.697	2.37 (0.90–6.23)	0.081	0.152
Probable	3 (1%)	3 (1%)	6 (2%)	1.07 (0.22–5.28)	0.938	2.18 (0.55–8.73)	0.269	0.429
Possible	0 (0%)	0 (0%)	0 (0%)					

Device-oriented MACE: cardiac death, repeat TLR clinically indicated, or MI in IRA; and patient oriented MACE: all cause death, reinfarction and revascularisation. IRA: infarct related artery. p value from Cox's regression Chi-square test.

Table 4
Clinical outcome 1 year in the COMFORTABLE AMI trial according to Sxscore tertiles.

	SYNTAX score			Cox's regression				
	Low (0–10) N = 394	Intermediate (11–18) N = 374	High (19–52) N = 364	Intermediate vs. low		High vs. low		Overall
				HR (95% CI)	p value	HR (95% CI)	p value	p value
1 year follow-up								
Device-oriented MACE	14 (4%)	22 (6%)	30 (8%)	1.68 (0.86–3.29)	0.128	2.38 (1.26–4.49)	0.007	0.026
Patient-oriented MACE	20 (5%)	33 (9%)	53 (15%)	1.79 (1.03–3.13)	0.039	3.05 (1.82–5.10)	<0.001	<0.001
All cause death	10 (3%)	11 (3%)	17 (5%)	1.17 (0.50–2.75)	0.719	1.87 (0.86–4.08)	0.117	0.235
Cardiac death	7 (2%)	10 (3%)	16 (4%)	1.52 (0.58–3.99)	0.396	2.51 (1.03–6.10)	0.042	0.107
Reinfarction (any)	8 (2%)	8 (2%)	14 (4%)	1.07 (0.40–2.85)	0.892	1.95 (0.82–4.66)	0.131	0.219
Reinfarction in IRA	6 (2%)	5 (1%)	6 (2%)	0.89 (0.27–2.91)	0.845	1.10 (0.35–3.41)	0.868	0.939
Death or reinfarction (any)	16 (4%)	18 (5%)	31 (9%)	1.20 (0.61–2.36)	0.588	2.17 (1.19–3.96)	0.012	0.021
Revascularisation (any)	12 (3%)	23 (6%)	34 (9%)	2.08 (1.04–4.18)	0.040	3.24 (1.68–6.25)	0.000	0.002
Revascularisation in IRA, clinically indicated	9 (2%)	13 (3%)	15 (4%)	1.54 (0.66–3.61)	0.318	1.85 (0.81–4.23)	0.144	0.340
Stent thrombosis all	12 (3%)	13 (3%)	21 (6%)	1.16 (0.53–2.53)	0.719	1.93 (0.95–3.93)	0.069	0.134
Definite	4 (1%)	4 (1%)	7 (2%)	1.06 (0.27–4.24)	0.933	1.91 (0.56–6.53)	0.301	0.488
Definite/probable	10 (3%)	9 (2%)	13 (4%)	0.96 (0.39–2.36)	0.926	1.43 (0.63–3.26)	0.398	0.577
Probable	6 (2%)	5 (1%)	6 (2%)	0.89 (0.27–2.91)	0.845	1.10 (0.35–3.40)	0.874	0.942
Possible	4 (1%)	5 (1%)	8 (2%)	1.33 (0.36–4.95)	0.671	2.21 (0.67–7.34)	0.195	0.389

Device-oriented MACE: cardiac death, repeat TLR clinically indicated, or MI in IRA; and patient oriented MACE: all cause death, reinfarction and revascularisation. IRA: infarct related artery. p value from Cox's regression Chi-square test.

Risk ratios of the individual TIMI risk score components were particularly predictive of death with little additional value in terms of the c-statistic by adding the MI Sxscore (without: 0.783; with 0.787). However, the model improved the prediction of patient- (0.623 to 0.692) and device-oriented outcomes (0.65 to 0.695) after addition of the MI Sxscore. The hazard ratios for the components and the c-statistics are shown in Table 5. The c-statistics of the score in observational studies is comparable (0.61) [6].

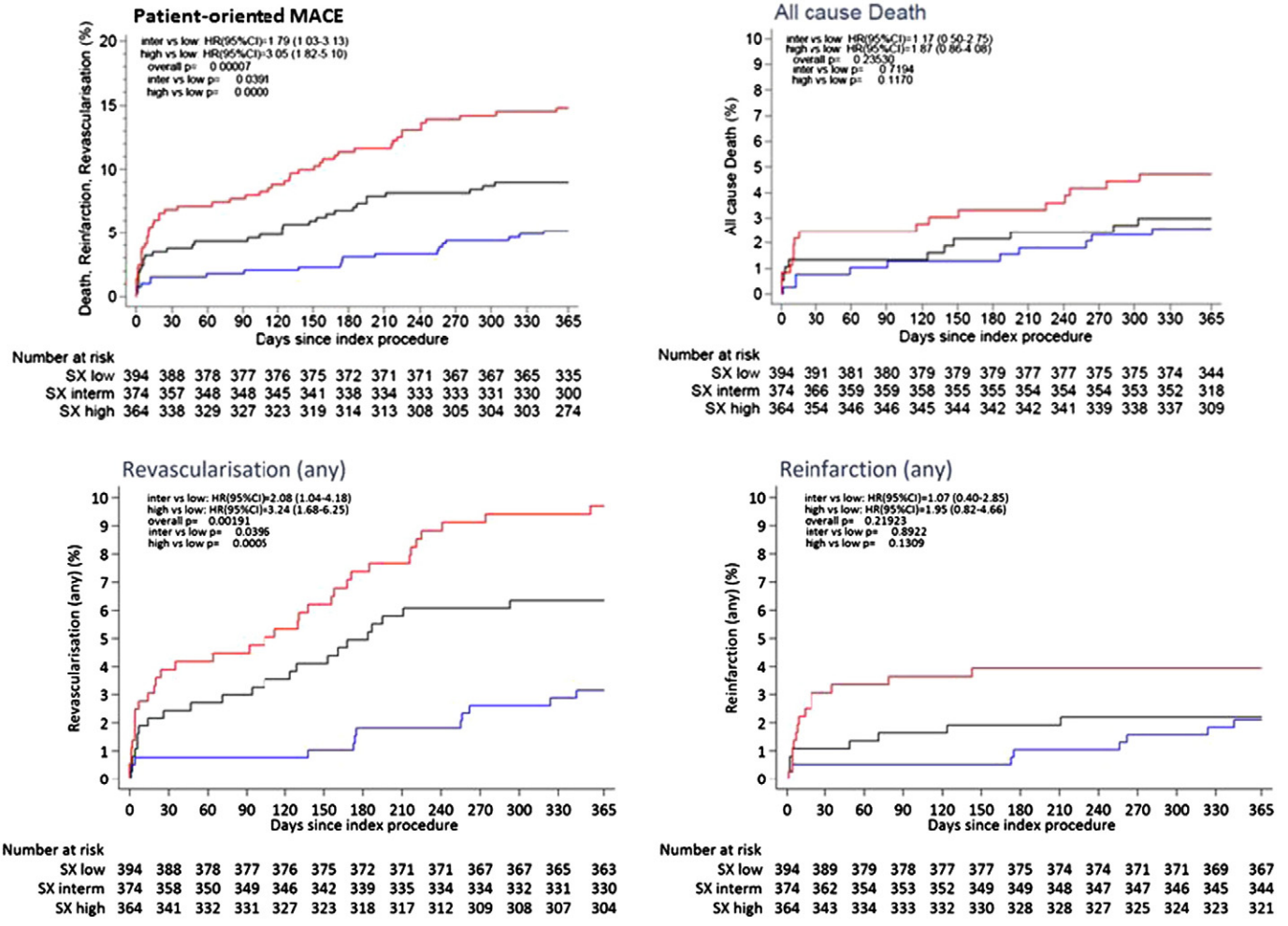


Fig. 2. Kaplan–Meier event curves and log rank tests for patients presenting with STEMI and categorised in tertiles of the MI Sxscore for 1 year patient-oriented major adverse cardiac events (MACEs) with its components separately shown; all-cause mortality, revascularisation and reinfarction. Red curve indicates MI $Sxscore_{high}$, black curve indicates $Sxscore_{intermediate}$ and blue curve indicates MI $Sxscore_{low}$.

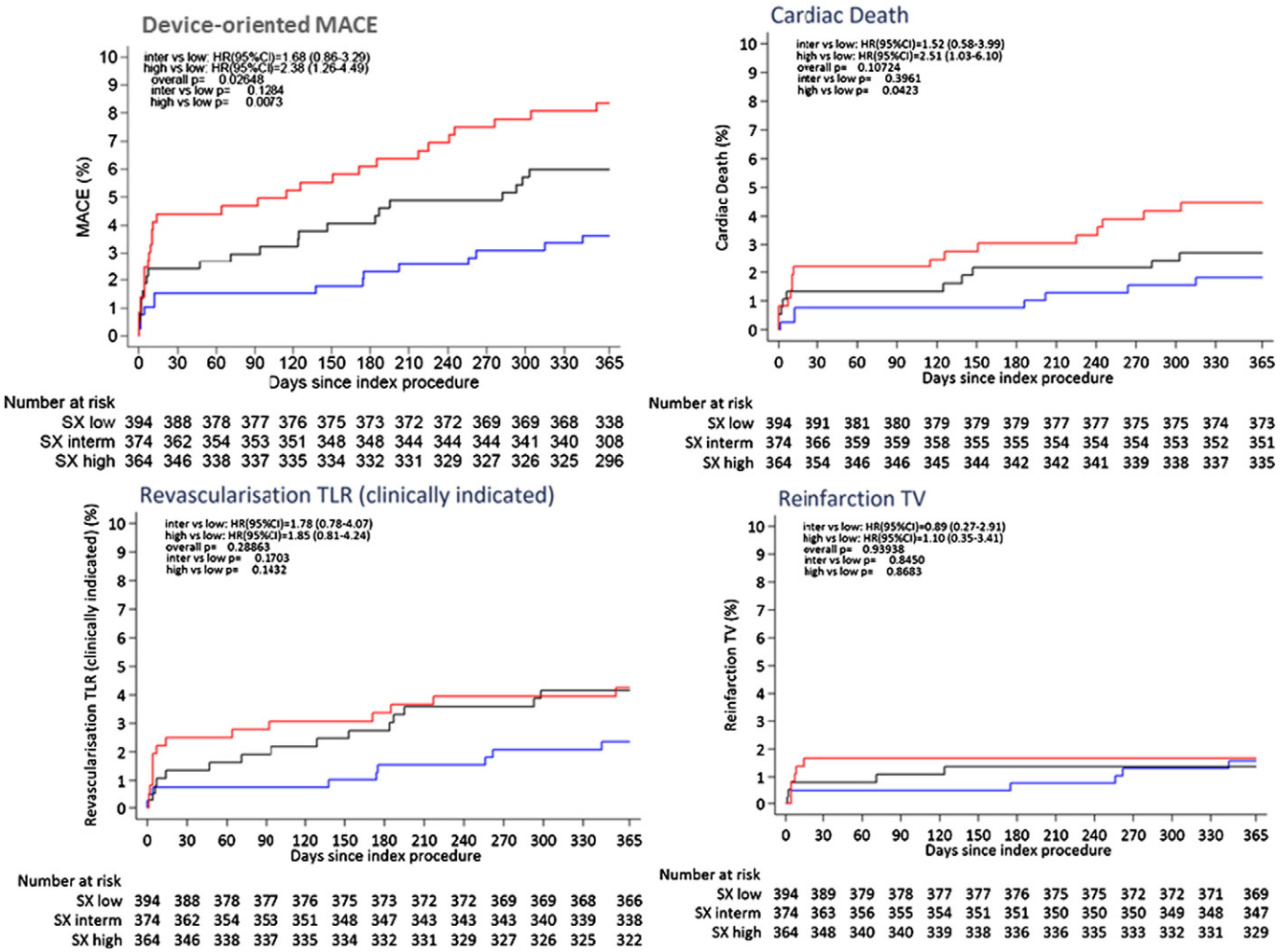


Fig. 3. Kaplan–Meier event curves and log rank tests for patients presenting with STEMI and categorised in tertiles of the MI Sxscore for 1 year device-oriented MACE with its components separately shown; cardiac death, target lesion revascularisation-TLR and target vessel reinfarction. Red curve indicates MI $Sxscore_{high}$, black curve indicates $Sxscore_{intermediate}$ and blue curve indicates MI $Sxscore_{low}$.

3.3. Performance of the MI Sxscore according to stent type

The MI Sxscore was available in 564 patients randomised to BMS and 568 patients randomised to biolimus-eluting stents. Patient-oriented MACE occurred more frequently with both stent types in the higher MI Sxscore tertiles (BMS $Sxscore_{low}$ vs. $Sxscore_{intermediate}$ vs. $Sxscore_{high}$ = 6% vs. 10% vs. 18%, p = 0.002; biolimus-eluting stents: 4% vs. 7% vs. 12% p = 0.029). Device-oriented MACE was more common among higher MI Sxscore tertiles treated with BMS ($Sxscore_{low}$ 4% vs. 7% vs. 13% p = 0.007) but not for DES ($Sxscore_{low}$ 3% vs. 5% vs. 4% p = 0.669). The difference in outcome between the two stent types was more evident among patients in the highest tertile compared to the lower tertiles (Fig. 4 and Supplementary Fig. 1; biolimus-eluting stents vs. BMS patient-oriented MACE: 12% vs. 18% (diff. 6%) in $Sxscore_{high}$; 6% vs. 4% (diff. 2%) in $Sxscore_{low}$; device oriented MACE: 13% vs. 4% (diff. 9%) in $Sxscore_{high}$; 4% vs. 3% (diff. 1%) in $Sxscore_{low}$).

4. Discussion

The MI Sxscore emerged as an important tool for risk stratification of STEMI patients treated by primary PCI in contemporary practise in the present study. Quantification of the extent and severity of coronary artery disease as well as the localisation and patency of culprit lesions and diseased segments other than the IRA proved useful to predict early and late major adverse cardiovascular events. Moreover, the risk assessment was complementary to the clinical TIMI risk score. Differences in clinical outcome, both in terms of patient- and device-oriented MACEs between stent types were most evident in the highest MI Sxscore groups.

Although the Sxscore was originally designed to evaluate revascularisation options among patients with multivessel disease, its application in all comer trials has allowed risk stratification across the entire range of patients with various clinical and angiographic characteristics [11,12]. A considerable proportion of patients included in such trials have stable coronary artery disease with a low risk for recurrent events. However, differences in outcome between stent types may be more easily elucidated among high-risk patients. Indeed, the MI Sxscore was found to provide additional value in risk stratification in the present all comer STEMI trial. Moreover, the present study confirms the discriminative value of the MI Sxscore among STEMI patients as previously suggested in observational studies [6,13].

The present analysis shows that patients with high MI Sxscore have an increased risk of mortality from cardiac causes. Patency of the IRA as well as multivessel disease are both known to impact on mortality among STEMI patients [14,15]. Both factors are integral parts of the MI Sxscore and likely contribute to its predictive value in terms of cardiac mortality. Since a low TIMI flow adds to the score, patients in the higher

Table 5
Hazard ratios for mortality and patient and device-oriented MACE at 1 year for the TIMI risk variables, Sxscore and the respective c-statistics for prediction of endpoints with and without the MI Sxscore.

	All-cause death				Patient-oriented MACE				Device-oriented MACE			
	Model 1 without SX		Model 1 with SX		Model 2 without SX		Model 2 with SX		Model without SX		Model with SX	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Parameters												
Intercept	0.004 (0.002–0.011)	<0.001	0.003 (0.001–0.009)	<0.001	0.027 (0.015–0.048)	<0.001	0.017 (0.008–0.034)	<0.001	0.048 (0.031–0.076)	<0.001	0.022 (0.012–0.039)	<0.001
TIMI STEMI risk score parameters												
Age 65–74 years	1.335 (0.545–3.271)	0.528	1.281 (0.520–3.153)	0.590	1.031 (0.528–2.010)	0.929	0.973 (0.497–1.905)	0.937	1.298 (0.783–2.151)	0.312	1.188 (0.711–1.983)	0.511
Age >74 years	3.843 (1.682–8.781)	0.001	3.580 (1.556–8.236)	0.003	2.677 (1.396–5.132)	0.003	2.427 (1.255–4.693)	0.008	2.326 (1.346–4.018)	0.002	2.008 (1.145–3.522)	0.015
History of diabetes, hypertension or heart failure	2.494 (1.125–5.531)	0.024	2.402 (1.081–5.338)	0.031	1.508 (0.884–2.572)	0.132	1.448 (0.846–2.479)	0.177	1.383 (0.904–2.115)	0.135	1.312 (0.852–2.020)	0.218
Blood pressure < 100 mm Hg	1.784 (0.627–5.077)	0.278	1.822 (0.637–5.212)	0.263	1.939 (0.905–4.155)	0.089	1.966 (0.911–4.242)	0.085	1.621 (0.837–3.139)	0.152	1.688 (0.860–3.310)	0.128
Heart rate >100 pulses	2.603 (0.970–6.988)	0.058	2.474 (0.907–6.753)	0.077	1.116 (0.417–2.984)	0.827	1.036 (0.378–2.840)	0.945	1.163 (0.528–2.559)	0.708	1.092 (0.482–2.472)	0.833
Killip II, III or IV	3.437 (1.410–8.374)	0.007	3.023 (1.210–7.549)	0.018	2.535 (1.201–5.352)	0.015	2.174 (1.012–4.669)	0.046	2.030 (1.054–3.911)	0.034	1.610 (0.817–3.175)	0.169
Body weight <67 kg	1.264 (0.543–2.939)	0.587	1.325 (0.570–3.082)	0.513	0.725 (0.338–1.554)	0.409	0.756 (0.354–1.617)	0.472	0.948 (0.534–1.681)	0.854	0.987 (0.554–1.757)	0.964
Anterior, anteroseptal or anterolateral MI	2.006 (1.015–3.964)	0.045	1.792 (0.890–3.611)	0.103	1.572 (0.942–2.623)	0.084	1.327 (0.782–2.252)	0.295	1.355 (0.896–2.050)	0.150	1.035 (0.672–1.596)	0.875
Time to Treatment >4 h	2.208 (1.022–4.771)	0.044	2.154 (0.993–4.674)	0.052	1.201 (0.711–2.030)	0.494	1.152 (0.678–1.957)	0.601	1.345 (0.883–2.046)	0.167	1.269 (0.827–1.946)	0.275
SYNTAX score (per 10 points)			1.309 (0.889–1.928)	0.172			1.477 (1.100–1.983)	0.009			1.827 (1.436–2.323)	<0.001
Concordance statistic C	0.783		0.787		0.653		0.695		0.623		0.692	

Device-oriented MACE: cardiac death, repeat TLR clinically indicated, or MI in IRA; and patient oriented MACE: all cause death, reinfarction, revascularisation odds ratios from logistic regression with C = Harrell's c concordance statistic. Age <65 years is the reference category. N = 1132 patients each model.

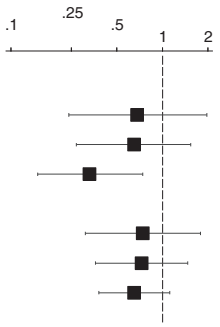
tertiles of the MI Sxscore are more likely to present with an occluded infarct related artery, an angiographic characteristic known to be associated with larger infarct sizes, and poorer prognosis. The higher prevalence of cardiovascular events among STEMI patients with multivessel disease is most likely multifactorial. First, the number of diseased vessels is often a reflection of the extent and severity of coronary atherosclerosis. Patients with multivessel disease therefore bear a higher risk of future events related to coronary artery disease progression or related to incomplete revascularisation, which is more prevalent in patients with higher baseline SYNTAX score, as previously shown in acute coronary syndrome patients [16]. Incomplete revascularisation is known to impact outcome in patients with residual coronary artery disease. Timely treatment of residual non-culprit coronary artery disease (within 90 days of the primary PCI) has therefore been advocated by the COMFORTABLE AMI study group. Since by definition high MI Sxscore patients often have multivessel disease and therefore residual disease, the risk of cardiovascular events related to non-culprit vessel disease certainly has an impact on the patient related outcome and therefore is an important determinant of the prognostic power of the MI Sxscore. Second, the increased procedural complexity reflected in a higher number of stents, a longer stent length and a higher rate of bifurcation treatment observed in the higher SXscore tertiles of this trial expose patients to an increased risk for re-stenosis and stent thrombosis [17,18]. Multivessel disease and high MI Sxscores were associated with a higher prevalence of the 'no-reflow' phenomenon, which reflects impaired myocardial reperfusion with its attendant effects on cardiovascular outcome [19]. In fact, in the present study, poor reperfusion as measured by TIMI flow at the end of the procedure and myocardial blush grade was more common in the higher Sxscore tertiles. The larger infarct size as determined by cardiac biomarkers in patients with the higher MI Sxscores observed in the current analysis lends support to the pathophysiological role of multivessel disease, IRA patency and myocardial reperfusion and provides insights on their link to clinical outcome.

The trend for a higher risk of early stent thrombosis among STEMI patients with high Sxscores observed in the present study corroborates the findings of a pooled analysis of 7 studies with 6496 patients [20]. In a subanalysis of 2093 acute coronary syndrome (ACS) patients in this study, higher rates of ST were observed in high Sxscore groups. The risk of ST among ACS patients treated with drug-eluting stents has been consistently higher than that in patients with stable coronary artery disease [17]. A large thrombus burden, frequently associated with impaired TIMI flow which is more prevalent in high Sxscore patients, plays an important role in the pathogenesis of stent thrombosis [21]. In addition, patients with high Sxscores often undergo treatment of bifurcations and implantation of longer stents, both risk factors for stent thrombosis. Moreover, the individual response to antiplatelet treatment is frequently impaired among diabetic patients, those with high BMI, and the elderly, characteristics predominantly present in patients in the highest Sxscores [22,23]. Interestingly, we observed a trend towards a higher rate of ST in the early phase after primary PCI in the higher Sxscore tertiles. Timely identification of high risk patients may allow for implementation of preventive measures such as the use of GPIIb/IIIa inhibitors and thrombectomy devices.

The MI Sxscore applied to STEMI patients provides incremental predictive value over clinical variables integrated in the TIMI score as previously shown in registry data [6]. Predictive clinical risk variables and their application in risk scores initially focused on early survival after STEMI [1]. The availability of angiographic characteristics in the primary PCI era provided additional prognostic information including TIMI flow in the infarct related artery and the presence of multivessel disease as factors associated with increased mortality. The MI Sxscore provides a similar predictive value in terms of 1-year mortality as the traditional TIMI risk score (0.783 to 0.787). The MI Sxscore incorporates patency of the infarct related artery and the myocardial area at risk. Compared with patients with low MI Sxscores, patients in the highest tertile have almost double the incidence of anterior myocardial infarction

SYNTAX Subgroup Analyses of the 1-Year Rates of Major Adverse Cardiac Events Among Patients Randomized to Receive Either the Biolimus-Eluting Stent or the Bare-Metal Stent

	Biolimus-Eluting Stent N = 568		Bare-Metal Stent N = 564		HR (95% CI)	p-value
	n	events (%)	n	events (%)		
Device-oriented MACE						
SYNTAX 0-10	205	6 (2.9)	189	8 (4.4)	0.68 (0.24-1.97)	0,479
SYNTAX 11-18	175	8 (4.7)	199	14 (7.2)	0.65 (0.27-1.54)	0,326
SYNTAX 19-52	188	8 (4.3)	176	22 (12.6)	0.33 (0.15-0.74)	0,007
Patient-oriented MACE						
SYNTAX 0-10	205	9 (4.4)	189	11 (6.0)	0.74 (0.31-1.79)	0,506
SYNTAX 11-18	175	13 (7.6)	199	20 (10.2)	0.73 (0.36-1.47)	0,380
SYNTAX 19-52	188	22 (11.9)	176	31 (17.8)	0.65 (0.38-1.12)	0,123



Device- oriented MACE: cardiac death, repeat TLR clinically indicated, or MI in IRA
Patient-oriented MACE: death, reinfarction or revascularisation
IRA: infarct related artery
p-value from Cox's Regression chi-square test

Fig. 4. SYNTAX subgroup analyses of the 1-year rates of major adverse cardiac events among patients randomised to receive either the biolimus-eluting stent or the bare-metal stent.

and impaired TIMI flow of the IRA, which result in a larger infarct size and two-fold increased mortality during the first year. The combination of the MI Sxscore and the TIMI risk score afforded improved discrimination of patient- and device-oriented MACEs as compared with either score alone. Moreover, the combined score was superior in the prediction of cardiac death and myocardial infarction and repeat revascularisation procedures. The addition of angiographic information to standard clinical variables is easily obtainable in STEMI patients undergoing primary PCI and offers improved prediction of adverse events and prognosis. The use of BMS in STEMI has resulted in a higher incidence of device-oriented MACE when compared to DES [8]. Stratification of MI Sxscores according to implanted stent platform supports the notion that differences in clinical outcomes between stent types are more pronounced in the highest MI Sxscore tertile. The observation in differentiation of outcome between stent types is consistent with that of previous Sxscore analysis in the LEADERS and SIRTAX trials [12,24]. Thrombogenicity of the stent coating and suppression of neointima by drug elution may be particularly important in complex lesions with high thrombus load and may explain the lower ST event rates observed in BES implanted in high-risk patients. Similarly, the risk of restenosis and therefore repeat revascularisation procedures is more pronounced in patients with higher MI Sxscores.

4.1. Study limitations

Several limitations need to be considered in the interpretation of the present study. The present analysis focused on patient- and device-oriented composite outcomes. However, findings on individual endpoints including mortality and stent thrombosis have to be interpreted with caution due to the limited number of patients and events and should therefore be considered hypothesis generating. The evaluation of the MI Sxscore was performed by experienced assessors, and it is uncertain whether the same robustness can be maintained in routine clinical practise. We have not assessed the residual SYNTAX score following protocol mandated complete revascularisation within 3 months after primary PCI. Therefore we cannot conclude on the impact of incomplete revascularisation following treatment of ST-elevation patients. In the current study the relation of the MI Sxscore and microvascular reperfusion was drawn from angiographic data of myocardial blush grade and TIMI flow. The relation of the score with a non-angiographic and therefore more independent means of measuring microvascular reperfusion such as ST segment resolution or gadolinium enhanced magnetic resonance imaging-derived microvascular obstruction was not available but may be further evaluated and confirmed in future research.

5. Conclusions

The MI Sxscore is a validated risk stratification tool in the assessment of adverse cardiovascular outcomes among STEMI patients undergoing primary PCI throughout one year. It provides added prognostic value beyond clinical risk scores such as the TIMI risk score and shows the highest discrimination between stent types in the highest MI Sxscore.

Disclosures

Clinical Trials Unit (CTU Bern), which is part of the University of Bern, Bern, Switzerland, has a staff policy of not accepting honoraria or consultancy fees. However, CTU Bern is involved in the design, conduct, or analysis of clinical studies funded by Abbott Vascular, Ablynx, Amgen, AstraZeneca, Biosensors, Biotronic, Boehringer Ingelheim, Eisai, Ei Lilly, Exelixis, Geron, Gilead Sciences, Nestlé, Novo Nordisk, Padma, Roche, Schering-Plough, St. Jude Medical, and Swiss Cardio Technologies (33CM30–124112 and 310030–118353).

Dr. Baumbach reported being on advisory boards and receiving consultancy fees from Boston Scientific, Medicines Company, and Abbott Vascular; and receiving payment for lectures from Medicines Company and Japan Stent Inc. Dr. Tüller reported receiving travel expenses from Biotronik, Biosensors, Terumo, and Medtronic. Dr. von Birgelen reported board memberships and receiving lecture fees from Abbott Vascular, Medtronic, and Boston Scientific; receiving consultancy fees from Medtronic; unpaid consultancies from Abbott Vascular, Boston Scientific, Biosensors, Biotronik, and Cordis; receiving grants from Abbott Vascular, Boston Scientific, Biosensors, Biotronik, Cordis, Medtronic, and St. Jude Medical; payment for lectures from Abbott Vascular, Boston Scientific, Medtronic, and MSD; and receiving payment for development of educational presentations from Cordis. Dr. Roffi reported receiving grants from Boston Scientific, Abbott Vascular, Medtronic, and Biosensors; and payment for lectures from Lilly-Daiichy Sankyo. Dr. Lüscher reported receiving research grants for the institution from Abbott, Biosensors, Biotronik, Boston Scientific, and Medtronic, and consultant payments from AstraZeneca, Boehringer Ingelheim, Bayer, Merck, and Pfizer. Dr. Meier reported receiving research contracts for

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.05.029.

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