

Value of the SYNTAX Score in ST-Elevation Myocardial Infarction Patients With a Concomitant Chronic Total Coronary Occlusion (from the EXPLORE Trial)



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‘To analyze the impact of additional coronary artery disease, quantified by the SYNTAX (SYnergy between PCI with TAXus and cardiac surgery) score, on left ventricular ejection fraction (LVEF) and long-term outcomes in a cohort of ST-elevated myocardial infarction (STEMI) patients with a concomitant chronic total coronary occlusion (CTO). A total of 302 STEMI patients were randomized to percutaneous coronary intervention of a CTO (CTO PCI) (n = 148) or conservative CTO treatment (n = 154). SYNTAX scores were calculated by an independent corelab (Cardialysis BV, Rotterdam) at two time-points: (1) at baseline, and (2) after primary PCI in the conservative CTO arm and after CTO PCI in the invasive arm (named ‘discharge SYNTAX score’). The population was divided in two groups (below or equal to the median SYNTAX score preprimary PCI, or above the median). At 4-month follow-up, the LVEF was significantly lower in patients in the group with a SYNTAX score above the group median (42.8% vs 48.5%, $p = 0.001$), and the SYNTAX score was an independent predictor for LVEF at 4 months (β -0.151 (SE 0.068), $p = 0.028$). In the group with a SYNTAX score above the group median the mortality rate was higher (10.1% vs 3.9%, $p = 0.025$), and there was a trend towards a higher MACE rate (15.4% vs 8.5%, $p = 0.063$). In conclusion, in this sub-analysis of the EXPLORE trial we observed a worse LVEF and a higher mortality rate for patients with a SYNTAX score above the median. We found that the SYNTAX score is an independent negative predictor for LVEF and an independent positive predictor for LVEDV at 4-month follow-up. © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) (Am J Cardiol 2019;123:1035–1043)

The presence of a concomitant chronic total coronary occlusion (CTO) contributes to a worse prognosis compared with multi-vessel disease (MVD) alone in ST-elevation myocardial infarction (STEMI) patients, either in a stable setting or in cardiogenic shock.^{1,2} The *Evaluating Xience and left ventricular function in PCI on occLusiOns after STEMI* (EXPLORE) randomized trial has investigated the impact of

additional percutaneous coronary intervention (PCI) early after primary PCI of a concurrent CTO on left ventricular ejection fraction (LVEF) and left ventricular end diastolic volume (LVEDV) at 4 months post-STEMI, compared with no early CTO PCI.³ In STEMI patients, it has been shown that a high SYNTAX (SYnergy between PCI with TAXUSTM and Cardiac Surgery) score is associated with worse outcomes (i.e., mortality, reinfarction, major adverse cardiac events [MACE]) at 1 year follow-up, and the SYNTAX score seems to be an independent predictor for mortality and MACE.⁴ Therefore, the impact of additional coronary artery disease (CAD) is important when determining the optimal treatment strategy and prognosis. The SYNTAX score is a widely accepted scoring tool for CAD assessment when multivessel revascularization is being considered, as suggested by the new ESC guideline on myocardial revascularization.^{5,6} We therefore investigated the value of the SYNTAX score in the EXPLORE trial.

Methods

The design, primary outcomes, and short-term clinical outcomes of the EXPLORE trial have been published

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See page 1042 for disclosure information.

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previously.^{3,7} In short, it concerns a multinational randomized controlled trial in STEMI patients admitted for primary PCI (pPCI), with a concurrent CTO in a noninfarct-related artery. After pPCI and clinical stabilization, patients were randomized after giving written informed consent to either CTO PCI within 7 days or no-CTO PCI within 4 months. Cardiac magnetic resonance imaging (CMR) was performed at baseline and at 4 months; in case of the inability to perform CMR at 4-month follow-up, alternative imaging was used (i.e., echocardiography, nuclear testing; Figure 1). In a subgroup of patients (n=180), serial (baseline and 4-month) CMR was available.⁸ The co-primary endpoint was LVEF and LVEDV at 4 months. PCI of additional noninfarct-related- and non-CTO-lesions was left at the discretion of the operator. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by institutional review boards of the participating institutes.

SYNTAX scores were calculated at *baseline* on the angiogram before primary PCI, and at *discharge* (this entails

the actual final residual coronary disease before discharge until 4-month follow-up).

To investigate the effect of early revascularization in this group of patients, assessment of all coronary artery disease at discharge in the invasive group was performed on the final angiogram after the CTO PCI procedure, and this assessment included all interventions before discharge. CAD assessment at discharge in the conservative group was performed after the primary PCI, or after any subsequent PCI during the same hospital admission. SYNTAX score calculation was performed by Cardialysis BV (Rotterdam, The Netherlands) using the predefined SYNTAX score calculation definitions and website (<http://www.syntaxscore.com/calculator/syntaxscore/frameset.htm>). Long-term follow-up (median 3.9 [IQR 2.9] years) has been published previously.⁹ Follow-up was collected via patient-telephone contact. All events were adjudicated by an independent critical event committee. Major adverse cardiac events (MACE) were defined as the composite of cardiac

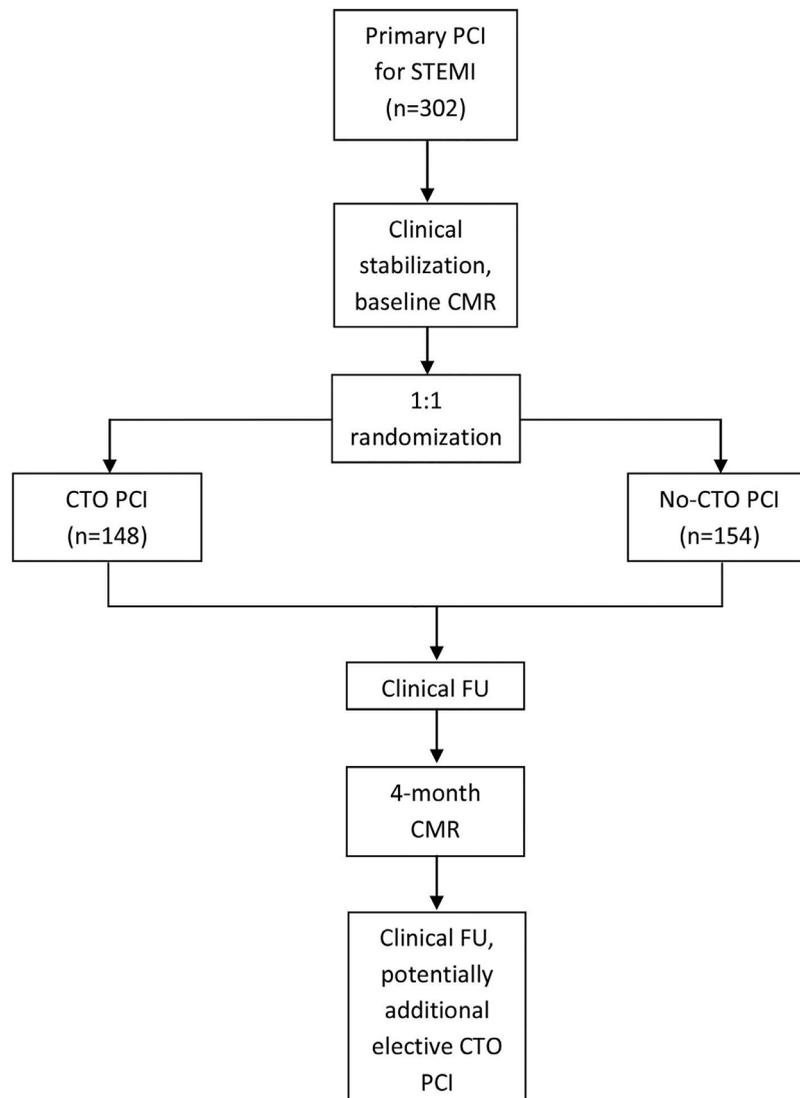


Figure 1. Study flowchart.

(CMR = cardiac magnetic resonance imaging; CTO = chronic total coronary occlusion; FU = follow-up; PCI = percutaneous coronary intervention, STEMI = ST-elevation myocardial infarction).

death, myocardial infarction (MI) and coronary artery bypass grafting (CABG).

For the purpose of the current analysis, the trial cohort was divided into 2 groups, 1 group with SYNTAX scores \leq the median and the second with SYNTAX scores $>$ the median. For a secondary analysis, patients were divided into groups according to the discharge SYNTAX score using a previously used and validated cut-off value (discharge SYNTAX score ≤ 8 and > 8).¹⁰ Continuous variables are displayed as mean (\pm SD) or median [IQR] in case of non-normal distribution of the variables, and were compared with the Student's *t*, or Mann-Whitney *U* test wherever appropriate. Categorical variables are reported as

numbers (%) and compared with the Fisher's exact- or chi-square test wherever appropriate. Survival analyses were performed using the Kaplan-Meier method, and differences in event rates were calculated using the logrank test. Long-term follow-up consisted of all available follow-up or was censored in case of completion of 5-year follow-up. The impact of the SYNTAX score pre-pPCI on 4-month LVEF and LVEDV was assessed using multivariable linear regression. A backward stepwise selection was performed after univariable selection (variables were selected because of their predictive value of LVEF and LVEDV at 4 months). A 2-sided alpha was calculated, which was considered significant when below 0.05. The statistical analyses were

Table 1
Baseline characteristics

	Syntax score pre-pPCI		p value
	\leq group median (n = 153)	$>$ group median (n = 149)	
Age (years, median, 1st-3rd quartile)	58 [50-66]	63 [53-69]	0.009
Men	125 (82%)	132 (89%)	0.107
Diabetes mellitus	20 (13%)	27 (18%)	0.267
Hypertension	61 (40%)	67 (45%)	0.415
Family history of CAD	76 (50%)	54 (36%)	0.020
Hypercholesterolemia*	49 (32%)	54 (52%)	0.468
Smoker			0.011
Current	85 (56%)	68 (46%)	
Previous	48 (31%)	41 (28%)	
Never	20 (13%)	40 (27%)	
Previous MI	22 (14%)	21 (14%)	1.000
Previous PCI	14 (9%)	11 (7)	0.678
Previous stroke	3 (2%)	8 (5%)	0.134
SYNTAX score before primary PCI (median, 1st-3rd quartile)	22.5 [18-26.5]	35.5 [32-39.8]	< 0.001
Discharge SYNTAX score (median, 1st-3rd quartile)	12.5 [9-16.8]	23.5 [18.5-28.5]	< 0.001
Peak CK-MB post pPCI (median, 1st-3rd quartile)	168.7 [52.7-300]	198 [56.8-420.5]	0.302
Peak troponin T post pPCI (median, 1st-3rd quartile)	3.1 [0.9-7.9]	3.5 [1.0-8.6]	0.786
SYNTAX score culprit lesion (median, 1st-3rd quartile)	8 [6-11]	11 [8-17.3]	< 0.001
Culprit coronary artery			0.097
LAD	60 (39%)	76 (51%)	
RCx	43 (28%)	30 (20%)	
Right	50 (33%)	43 (29%)	
Flow culprit lesion pre pPCI			< 0.001
TIMI 0 or 1	85 (56%)	114 (77%)	
TIMI 2 or 3	68 (44%)	35 (24%)	
SYNTAX score CTO lesion (median, 1st-3rd quartile)	9 [7.8-11.5]	10 [8.5-16]	< 0.001
CTO coronary artery			0.175
LAD	31 (20%)	44 (30%)	
RCx	46 (30%)	39 (26%)	
Right	76 (50%)	66 (44%)	
Flow CTO lesion at pPCI			0.489
TIMI 0 or 1	151 (99%)	149 (100%)	
TIMI 2	2 (1%)	0	
J-CTO categories of CTO lesion			0.253
Easy (0)	10 (7%)	6 (4%)	
Intermediate (1)	40 (26%)	30 (20%)	
Difficult (2)	50 (33%)	45 (30%)	
Very difficult (≥ 3)	53 (35%)	68 (46%)	
Three vessel coronary disease	38 (25%)	91 (61%)	< 0.001
Successful chronic total coronary occlusion percutaneous coronary intervention (n=147)	57 (75%)	51 (72%)	0.711

Baseline patient and angiographic characteristics per SYNTAX score group (above or below population median). (CAD = coronary artery disease; CTO = chronic total coronary occlusion; J-CTO = Japan-CTO; LAD = left anterior descending coronary artery; LVEF = left-ventricular ejection fraction; LVEDV = left-ventricular end-diastolic volume; MI = myocardial infarction; PCI = percutaneous coronary intervention; pPCI = primary percutaneous coronary intervention; RCx = ramus circumflexus coronary artery; TIMI = thrombolysis in myocardial infarction).

* LDL level > 2.5 mmol/L or receiving statin therapy.

Table 2
LVEF (panel A) and LVEDV (panel B) at baseline and 4 months follow-up in all patients with serial CMR recordings (n = 180)

	Below group median (n = 76)	Above group median (n = 71)	p value
Dissection CTO vessel	6 (7.9%)	6 (8.5%)	1.000
Thrombus CTO vessel	1 (1.3%)	0	1.000
Embolisation CTO vessel	0	0	-
Acute occlusion CTO vessel	0	0	-
Occlusion sidebranch CTO vessel	1 (1.3%)	1 (1.4%)	1.000
Dissection Donor artery	1 (1.3%)	0	1.000
Thrombus Donor artery	0	0	-
Embolisation Donor artery	0	0	-
Acute occlusion Donor artery	0	0	-
Occlusion donor artery	0	0	-

CTO = chronic total coronary occlusion.

carried out and figures were created with SPSS (version 24, IBM Corp., Armonk, NY) and Excel (version 14, Microsoft Corp., Redmond, WA).

Results

The median baseline (assessed before primary PCI) SYNTAX score was 29. Patients were subsequently divided into 2 groups, 1 with a SYNTAX score preprimary PCI \leq median (the 'low baseline SYNTAX score group'), and 1 $>$ median (the 'high baseline SYNTAX score group'). Overall baseline patient and angiographic characteristics for each of the groups are shown in Table 1. Baseline characteristics were well-balanced between groups. Table 2 depicts the imaging outcomes, showing that the LVEF post-pPCI was higher in the low baseline SYNTAX score group although this did not reach statistical significance (45.3% [34.9 to 51.2] vs 39.7% [30.7 to 49.1], $p = 0.058$). The baseline LVEDV was equal between the 2 groups.

Procedural success of additional CTO PCI was similar in the baseline SYNTAX groups (75% vs 72%, $p = 0.711$) (Table 1). The occurrence of CTO PCI procedural complications was similar between patients in the two baseline SYNTAX groups (13% vs 14%, $p = 1.000$) (Table 2).

At 4 months, median LVEF was 49% (41 to 54) in the low baseline SYNTAX group, and 43% (34 to 51) in the high baseline SYNTAX group ($p = 0.001$). The LVEDV was 199 ml (162 to 239) in the low baseline SYNTAX group, and 219 ml (176 to 255) in the high baseline SYNTAX group ($p = 0.012$) (Table 3). During the first 4 months of follow-up, 11% of the patients in the low baseline SYNTAX score group underwent revascularization of additional coronary artery lesions, compared with 25% of the patients in the high baseline SYNTAX score group ($p = 0.009$). When we divided the entire population in a low discharge SYNTAX score group (≤ 8) and a high discharge SYNTAX score group (> 8),¹⁰ we found that at 4 months the LVEF was similar between groups.

Figure 2 shows the LVEF and LVEDV in patients with serial CMR on baseline and 4-month follow-up (n = 180) per baseline SYNTAX group (n = 96 for the low baseline SYNTAX, and n = 84 for the high baseline SYNTAX score group), showing that in both the low baseline SYNTAX and high baseline SYNTAX group a significant increase in LVEF occurred from baseline to 4-month follow-up. In addition, both at baseline and 4-month follow-up the LVEF was significantly higher in the low baseline SYNTAX group. With regards to the LVEDV in this subpopulation, we observed that at baseline the LVEDV was similar between the low and high baseline SYNTAX groups but at 4-month follow-up the LVEDV had significantly increased in the high baseline SYNTAX score group.

At long-term clinical follow-up, the mortality rate was significantly higher in the high baseline SYNTAX score group (10% vs 4%, $p = 0.025$), and there was a trend toward lower MACE rates in the low group (9% vs 15%, $p = 0.063$; Figure 3). With regards to revascularization, there was no difference in neither survival nor MACE rates between the low and high discharge SYNTAX score groups (Figure 4). On long-term follow-up, 4% of patients in the low baseline SYNTAX group received implantable cardioverter-defibrillator (ICD)-therapy, compared with 10% of patients in the high baseline SYNTAX score group ($p = 0.042$).

On multivariable analysis, the baseline SYNTAX score had an independent negative predictive value for LVEF at 4-month follow-up. Corrected for baseline characteristics the baseline SYNTAX score had an independent positive predictive value for LVEDV at 4-month follow-up (Tables 4A and 4B).

Table 3
Primary outcomes of LVEF and LVEDV at baseline and 4-month follow-up per SYNTAX group, and per discharge SYNTAX score group

	SYNTAX score pre-pPCI		p value
	\leq group median	$>$ group median	
Left ventricular ejection fraction (%) at baseline	45.3 [34.9-51.2]	39.7 [30.7-49.1]	0.058
Left ventricular end-diastolic volume (ml) at baseline	207 [196-246]	210 [168-249]	0.754
Left ventricular ejection fraction (%) at 4 months	48.5 [40.6-53.9]	42.8 [33.8-50.5]	0.001
Left ventricular end-diastolic volume (ml) at 4 months	199 [162-239]	219 [176-255]	0.012
	Discharge SYNTAX score ≤ 8	Discharge SYNTAX score > 8	p-value
Left ventricular ejection fraction (%) at baseline	43.4 [35.3-48.2]	43.2 [32.2-50.6]	0.821
Left ventricular end-diastolic volume (ml) at baseline	216 [173-256]	206 [164-245]	0.375
Left ventricular ejection fraction (%) at 4 months	45.0 [40.3-52.9]	45.5 [36.2-52.4]	0.678
Left ventricular end-diastolic volume (ml) at 4 months	209 [174-245]	209 [168-250]	0.754

Primary outcomes per median SYNTAX score group. (LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume). Outcomes are depicted as median (1st to 3rd quartile).

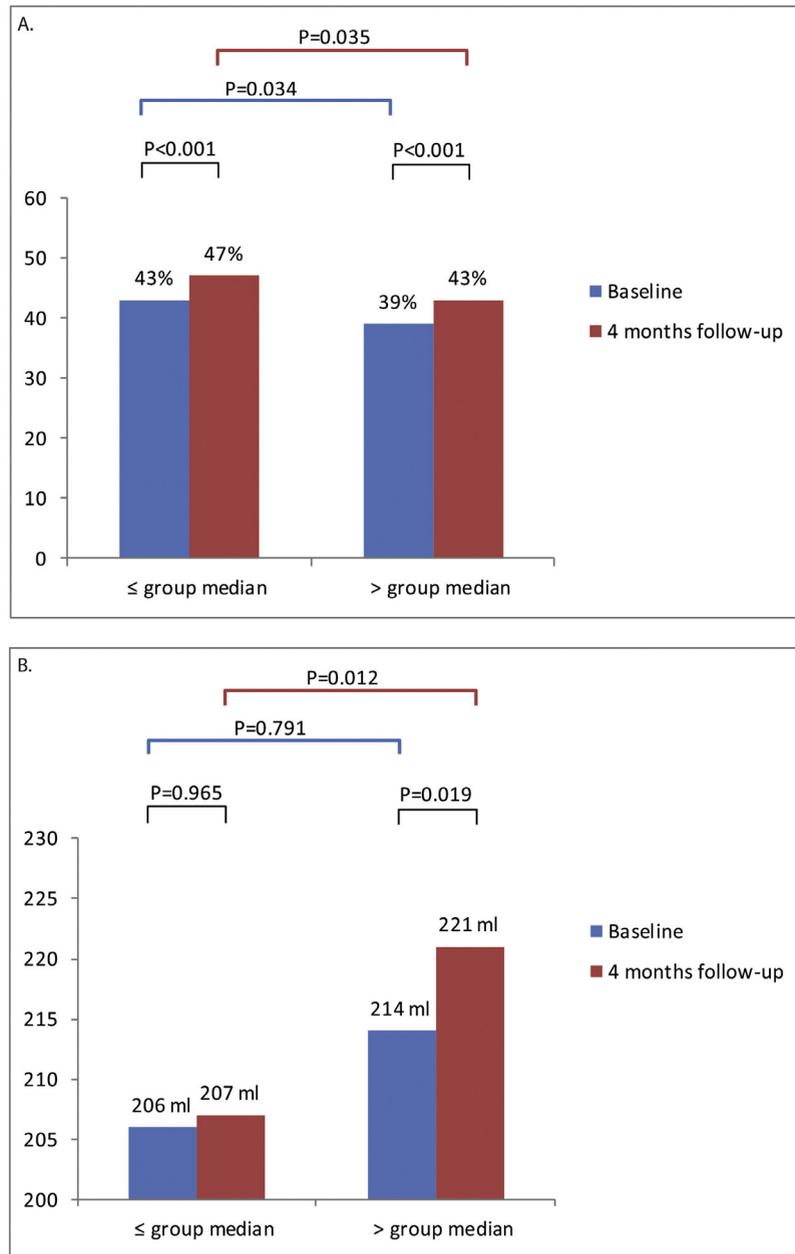


Figure 2. LVEF (panel A) and LVEDV (panel B) at baseline and 4 months follow-up in all patients with serial CMR recordings ($n = 180$). (CMR = cardiac magnetic resonance imaging; LVEDV = left ventricular end-diastolic volume [ml]; LVEF = left-ventricular ejection fraction [%]). Groups are based on the group median SYNTAX score preprimary PCI. Differences between groups and within groups are visualized.

There was no significant interaction between low- vs high-baseline SYNTAX score and randomized treatment assignment (CTO-PCI vs no-CTO-PCI) in terms of 4-month LVEF (p -interaction = 0.592), 4-month LVEDV (p -interaction = 0.723), nor long-term mortality (p -interaction = 0.813). Similarly, there was no significant interaction between low- vs high-discharge SYNTAX score and randomized treatment assignment (CTO-PCI vs no CTO-PCI) in terms of 4-month LVEF (p -interaction = 0.516), 4-month LVEDV (p -interaction = 0.645), nor long-term mortality (p -interaction = 0.939).

Discussion

The main findings of the current analyses were as follows: (1) STEMI patients with extensive coronary artery disease in addition to a concurrent CTO (high baseline SYNTAX score group) have significantly higher long-term mortality compared with STEMI patients with a concomitant CTO and less extensive additional coronary artery disease; (2) a high baseline SYNTAX score was associated with reduced baseline LVEF at baseline and at 4-month follow-up and with increased LVEDV at 4-month follow-up;

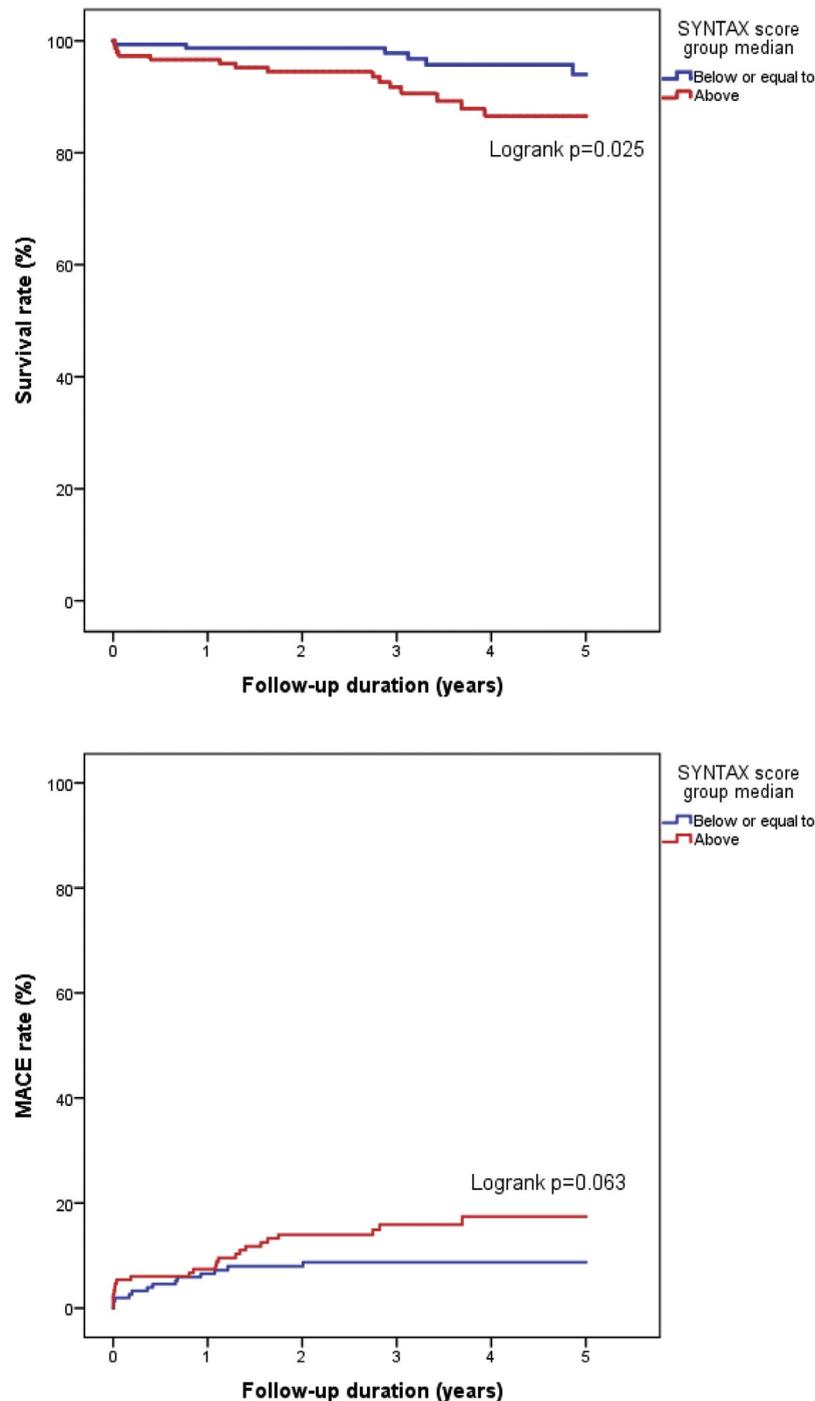


Figure 3. Long-term survival and MACE rates per median SYNTAX score group. (MACE = major adverse cardiac events; SYNTAX = SYnergy between PCI with TAXus and cardiac surgery).

(3) the baseline SYNTAX score was an independent negative predictor for LVEF, and an independent positive predictor for LVEDV at 4-month follow-up.

Several factors can either improve or impede outcomes after PCI, of which CAD severity is an important one. In the TAPAS (Thrombus Aspiration during Primary percutaneous coronary intervention in Acute ST-elevation myocardial infarction Study) and HORIZONS-AMI (Harmonizing

Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials, STEMI patients with a CTO had significantly more often three vessel disease compared with patients without a CTO, and this has been associated with higher mortality compared with STEMI patients with a CTO and two-vessel disease.^{11,12} Additionally, in these trials STEMI patients with a CTO in a noninfarct-related artery showed significantly more clinical signs of microvascular

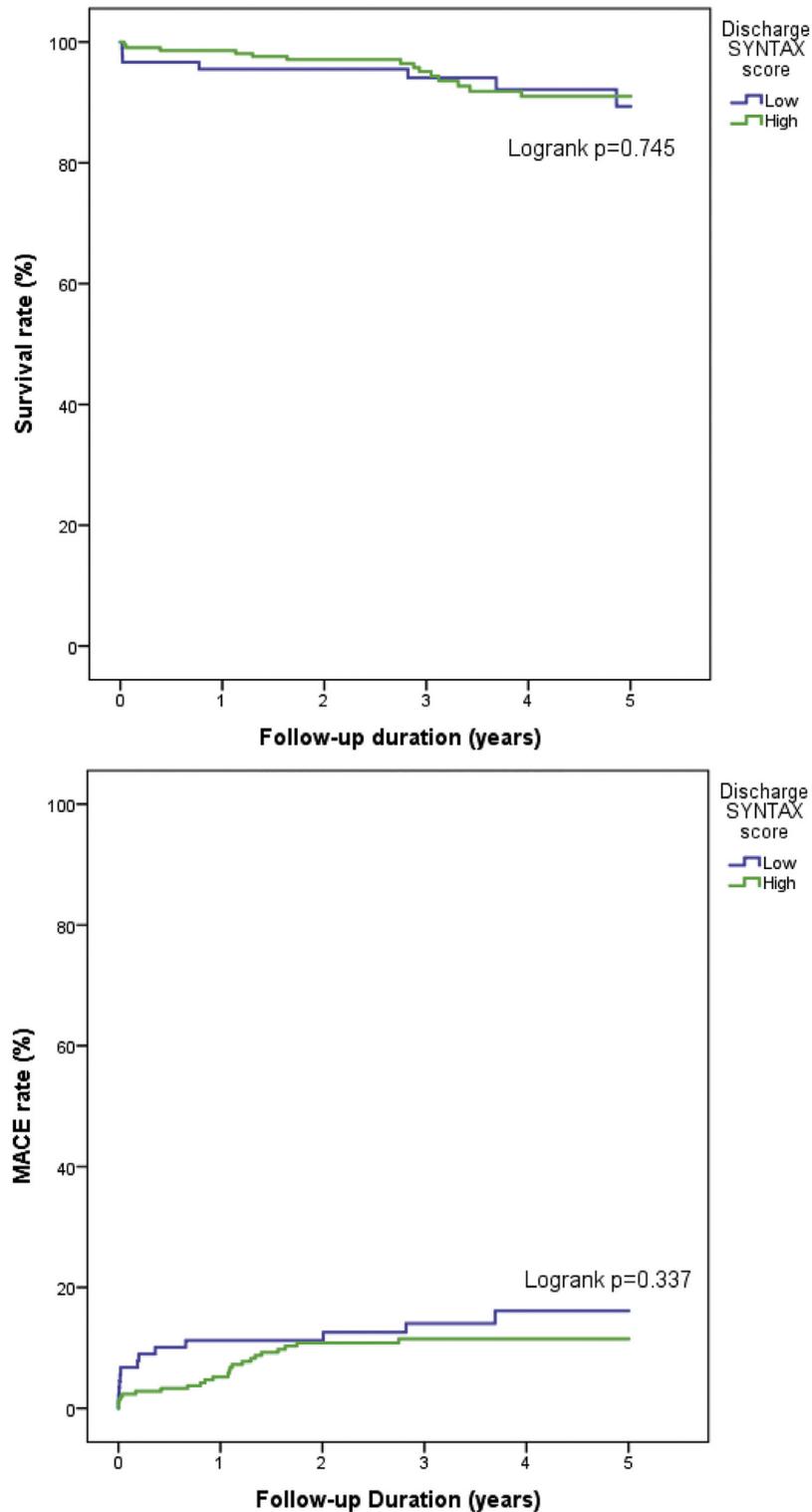


Figure 4. Long-term survival and MACE rates per discharge SYNTAX score group.
(MACE = major adverse cardiac events; SYNTAX = SYnergy between PCI with TAXus and cardiac surgery).

dysfunction (i.e., lower myocardial blush grade, more often incomplete ST-segment resolution and larger enzymatic infarct size) compared with STEMI patients without a CTO.^{11,12}

Regarding multivessel PCI in STEMI patients, several trials have been performed over the past few years (PRAMI, Cvlpit, DANAMI3-PRIMULTI, and COMPARE-ACUTE).¹³⁻¹⁶ These trials all showed that early

Table 4A
Influence of patient and angiographic characteristics on LVEF

Characteristic	Univariable			Multivariable		
	B	SE	p value	B	SE	p value
Age	-0.088	0.072	0.226	-		
Male gender	-0.393	2.039	0.847	-		
Hypertension	-2.475	1.459	0.091	0.376	1.280	0.770
Hypercholesterolemia	-2.086	1.528	0.173	-		
Diabetes mellitus	-5.340	2.035	0.009	0.786	1.810	0.664
LVEF at baseline	0.770	0.053	<0.001	0.739	0.054	<0.001
SYNTAX score pre pPCI	-0.378	0.076	<0.001	-0.151	0.068	0.028

This table shows univariable and multivariable analyses on the effect of baseline characteristics on LVEF (left ventricular ejection fraction) at 4-month follow-up. (pPCI=primary percutaneous coronary intervention; SYNTAX=SYNERgy between PCI with TAXus and cardiac surgery).

Table 4B
Influence of patient and angiographic characteristics on LVEDV

Characteristic	Univariable			Multivariable		
	B	SE	p value	B	SE	p value
Age	-0.364	0.370	0.327	-		
Male gender	37.365	10.185	<0.001	8.650	8.331	0.301
Hypertension	3.832	7.498	0.610	-		
Hypercholesterolemia	-5.495	7.833	0.484	-		
Diabetes mellitus	18.226	10.476	0.083	8.407	7.634	0.272
LVEDV at baseline	0.889	0.051	<0.001	0.870	0.051	<0.001
SYNTAX score pre pPCI	1.839	0.393	<0.001	0.695	0.291	0.018

This table shows univariable and multivariable analyses on the effect of baseline characteristics on LVEDV (left ventricular end-diastolic volume) at 4-month follow-up. (pPCI=primary percutaneous coronary intervention; SYNTAX=SYNERgy between PCI with TAXus and cardiac surgery).

PCI of additional lesions in the acute setting resulted in a significant decrease in MACE, but this was mainly driven by less repeat revascularizations. However, these trials excluded CTOs. Even though the EXPLORE trial was not powered for clinical events, this is the first randomized trial investigating the effect of early additional CTO PCI on functional and clinical follow-up.^{3,9} The SYNTAX trial¹⁷ showed that CABG was the preferred treatment strategy in patients with MVD and/or left main disease, mainly driven by a significantly lower rate of revascularization and major adverse cardiac or cerebrovascular events, and this was most profound in the high SYNTAX score tertile. Although this study was not carried out in STEMI patients, it still shows CABG could be considered if these patients also have a concurrent CTO and additional CAD.

In EXPLORE, the discharge SYNTAX score reflected the severity of CAD that all patients were discharged home with. Per protocol, no revascularization of the CTO was attempted until 4 months follow-up. Thus, the discharge SYNTAX score in the current analysis reflects the extent of residual CAD during the remodeling period up until the primary endpoint at 4 months. Until this point in time the discharge SYNTAX score shows that any residual CAD (CTO or not) does not necessarily lead to a worse prognosis. Beyond this follow-up point the discharge SYNTAX score

seems to lose its discriminative value to predict outcomes at long-term follow-up. This may be caused by additional revascularizations that have occurred beyond the 4 months follow-up moment.

Overall survival decreases in the high baseline SYNTAX score group compared with the low group. We observed that mortality rates seem to diverge at the beginning of the trial, possibly due to the CTO PCI procedure or due to complications related to the STEMI.³

In this subanalysis of the EXPLORE trial, all patients had a CTO lesion. Therefore, during the SYNTAX score calculations and analyses several important limitations of the SYNTAX score came to light. First, the distal part of the vessel beyond a CTO lesion forms a problem. In some patients this part of the vessel has been closed off of proper blood perfusion for years, resulting in smaller vessel diameters in some patients.^{18,19} If >75% of the distal part beyond a scored lesion is smaller than 2 mm, a multiplier is applied in the SYNTAX score, therefore potentially underestimating SYNTAX scores in the current population. And in case of some calcifications/lesions in the distal vessel, which could be quite common in CTO patients, it is difficult to score these lesions properly. In the hypoplastic distal vessel these lesions can comprise >50% of the lumen, but when the vessel shows positive remodeling over time after reperfusion, the lesion could only entail 20% of the lumen; a phenomenon that has been described before.¹⁹ If after CTO PCI the TIMI flow is improved from 0 to 2, the distal part of the vessel is not visible for proper scoring. Additionally, with emerging retrograde CTO PCI strategies a more proper scoring of the collateral vessels seems to be in place in CTO patient SYNTAX score calculations.

These analyses are subanalyses of the EXPLORE trial, with all associated limitations. Most importantly, the SYNTAX score has been developed to predict events during clinical follow-up, but the EXPLORE trial has not been powered on clinical events and long-term event rates are low. So all results and conclusions should be used with caution and only within the setting of the EXPLORE trial. Furthermore, not in all patients CMR was available resulting in low numbers in the subgroups, sometimes precluding the ability to demonstrate possible differences between SYNTAX scores. Also, patients randomized to the no-CTO PCI group were managed medically up until the 4-month primary end-point, and thus could undergo CTO revascularization after 4 months. This can impact clinical outcomes beyond the 4-month end-point, and thus should be taken carefully into account when interpreting the study results.

In conclusion, in this subanalysis of the EXPLORE trial we observed a worse LVEF and a higher mortality rate for patients with a SYNTAX score above the median. We found that the SYNTAX score is an independent negative predictor for LVEF and an independent positive predictor for LVEDV at 4-month follow-up.

Author disclosures

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