Chapter 2

Current Concept of Revascularization in STEMI Patients with Multivessel Coronary Artery Disease: Evidence Base and Our Own Randomized Trial Results

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Additional information is available at the end of the chapter

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Abstract

The use of personalized approach for the optimal revascularization strategy in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel coronary artery disease (MVCAD) is based on complete revascularization by using latest generation drug-eluting stents, with the choice between multivessel primary stenting and staged stenting strategy. The chapter includes theoretical rationale, original single-center study, an original calculator for choosing optimal revascularization strategy, and a clinical case example.

Keywords: ST-segment elevation myocardial infarction, multivessel stenting, personalized approach, calculator

1. Introduction

The current guidelines recommend culprit vessel revascularization as a standard treatment option in primary percutaneous coronary intervention (PPCI) [1–6]. Nevertheless, patients with ST-segment elevation myocardial infarction (STEMI) and multivessel coronary artery disease (MVCAD) constitute up to 50% of all STEMI cases [7, 8]. As known, MVCAD is associated with an adverse short- and long-term outcome after STEMI [9–11]. The definition and criteria of MVCAD, timing for nonculprit vessel revascularization, and a number of other tactical issues are actively discussed in the recent literature [5, 6]. There are three established PCI approaches for treatment of MVCAD and STEMI: (1) PPCI of infarct-related artery (IRA) only (culprit vessel revascularization only, CO) with percutaneous coronary intervention (PCI) of noninfarct-related artery based on findings ischemia (spontaneous or during noninvasive

stress-testing); (2) multivessel primary stenting (MPS): IRA is opened with the further dilatation of other significantly narrowed arteries during the same PPCI procedure; (3) multivessel staged stenting (MSS): the IRA only is treated during the first PPCI procedure with subsequent complete revascularization during the second intervention. In this chapter, we justify the use of personalized approach for the optimal revascularization strategy in patients with STEMI and MVCAD using the latest generation of drug-eluting stents (DES) with choosing MPS or MSS according to our original calculator. The chapter includes theoretical rationale, original single-center study, an original calculator for choosing optimal revascularization strategy, and a clinical case example.

2. The evolution of treatment strategies and guidelines for revascularization in patients with STEMI and MVCAD. The current evidence base. What do we know?

Earlier results of trials comparing MPS and CO approaches were controversial [12–19], probably due to the heterogeneity of patient samples, variable endpoints, distinct inclusion criteria and different study protocols. European and American Cardiology Societies for 2010–2013 [1–3] recommended limiting PPCI to the vessel with a culprit stenosis with the exception of cardiogenic shock and persistent ischemia after PCI. Moreover, performance of PPCI in a noninfarct artery was considered harmful [2].

However, randomized controlled trial (RCT) results [20–23] demonstrated usefulness and safety of multivessel stenting in patients with STEMI and MVCAD, both with MPS and MSS approaches. The current guidelines were updated by this data [4–6].

MPS approach was tested in two randomized controlled trials: PRAMI (Preventive Angioplasty in Acute Myocardial Infarction) [20] and CvLPRIT (Complete Versus Culprit-Lesion Only Primary PCI) [21]. In PRAMI trial, combined endpoint defined as cardiac death, nonfatal recurrent myocardial infarction (MI), or refractory angina at mean follow-up of 23 months occurred in 21 (9%) patients treated with MPS approach compared to 53 (22%) patients treated with CO approach (hazard ratio (HR): 0.35; 95% confidence interval (CI): 0.21–0.58) [20]. Authors concluded that MPS approach significantly reduces the risk of adverse cardiovascular events, as compared to PCI limited to IRA [20]. In the CvLPRIT trial, authors showed that major adverse cardiac events (MACE) including all-cause mortality, recurrent MI, heart failure, and ischemic-driven revascularization at 12 months follow-up occurred in 15 (10%) patients treated with MPS approach compared to 31 (21%) patients treated with CO approach (HR: 0.45; 95% CI: 0.24–0.84) [21]. In concordance with the PRAMI trial, researchers concluded that complete revascularization is beneficial for patients with STEMI and MVCAD in comparison with CO approach [21].

The MSS approach was also tested in two randomized controlled trials: DANAMI 3 PRIMULTI (Third Danish Study of Optimal Acute Treatment of Patients With ST-segment Elevation Myocardial Infarction) [22] and PRAGUE-13 (Primary Angioplasty in Patients Transferred From General

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Community Hospital to Specialized PTCA Units With or Without Emergency Thrombolysis) [23]. In the DANAMI 3 PRIMULTI trial, the MSS approach was based on the fractional flow reserve (FFR) value ≤ 0.80. Combined endpoint, defined as recurrent MI, all-cause mortality, and ischemia-driven revascularization at 27 months follow-up occurred in 40 (13%) patients treated with MSS approach and in 68 (22%) patients treated with CO approach (HR: 0.56; 95% CI: 0.38–0.83) [22]. Therefore, the MSS approach in patients with STEMI and MVCAD reduced the risk of adverse outcomes [22]. However, PRAGUE-13 trial did not find significant differences between MSS and CO approaches (frequencies of primary composite endpoint including all-cause mortality, recurrent MI, or stroke at 38 months follow-up were 13.9% vs. 16.0%, respectively) [23].

All these findings provided the possibility for endorsement (class IIb) of MPS and MSS strategies to patients with STEMI and MVCAD by European and American Cardiology Societies since 2014 [4] and 2015 [5], respectively. Moreover, in 2016, the American Cardiology Society accepted appropriate use criteria for coronary revascularization in patients with acute coronary syndrome considering revascularization of arteries with nonculprit stenosis at initial procedure or during the initial hospitalization [6]. According to these criteria, (1) stable patients immediately following PCI of culprit artery and one or more additional severe/intermediate (50–70%) stenoses may be defined as appropriate for MPS approach; (2) asymptomatic patients after successful treatment of culprit artery by PPCI and one or more additional severe/intermediate (50–70%) stenoses are appropriate for MSS approach if having ischemia on noninvasive testing/FFR ≤ 0.80; (3) asymptomatic patients after successful treatment of culprit artery by PPCI and one or more additional severe stenoses may be appropriate for MSS approach [6].

Hence, both MPS and MSS approaches have sufficient evidence base for being applied to patients with STEMI and MVCAD and are included in recent clinical guidelines. However, there is a number of unresolved issues such as stent choice, effect of residual SYNTAX score, timing of staged PCI, and the choice between two multivessel stenting approaches. Addressing these issues is crucially important for personalized treatment of STEMI and MVCAD.

3. Unresolved issues and prospects for revascularization in STEMI patients

3.1. Multivessel stenting versus staged revascularization with second-generation drug-eluting stents in ST-elevation myocardial infarction patients: results of randomized trial

3.1.1. Study population

The purpose of this open-label safety/efficacy randomized clinical trial (NCT01781715) is to determine outcomes of 136 consecutive patients with STEMI and multiple coronary artery disease (CAD) undergoing multivessel stenting in primary PCI or staged PCI with second-generation DES (Resolute Integrity™ Stent, Medtronic). Primary endpoints of this study were: (1) all death (cardiac and noncardiac), (2) any MI (STEMI and non-STEMI), (3) TVR. Secondary: (1) composite rate of all death, any MI and TVR, (2) stent thrombosis (ST).

We examined patients with STEMI and multivessel CAD undergoing primary PCI. Between October 2011 and October 2014 in our 24 h catheterization laboratory randomized 136 patients with multivessel CAD (defined as ≥70% diameter stenosis of two or more epicardial coronary arteries or their major branches by visual estimation with diameter ≥2.5mm). Inclusion criteria were (1) Subject must be at least 18 years of age; (2) Subject is able to verbally confirm understandings of risks and benefits of treatment of either multivessel stenting or staged PCI using the zotarolimus-eluting stent (Resolute Integrity™ Stent, Medtronic) and he or she or his or her legally authorized representative provides written informed consent prior to any study-related procedure; (3) Subject must have significant stenoses (≥70%) of two or more than two coronary arteries and requiring primary PCI for acute ST elevation myocardial infarction (STEMI) within 12 h; (4) Target lesions must be located in a native coronary artery with visually estimated diameter of less than 2.5 mm and more than 4.0 mm; (5) Target lesion(s) must be amenable for percutaneous coronary intervention.

Exclusion criteria were as follows: (1) Single lesions; (2) Acute heart failure Killip III-IV; (3) ≥50% left main stenosis; (4) Small vessels' diameter (<2.5mm); (5) The patient has a known hypersensitivity or contraindication to any of the following medications: heparin, aspirin, clopidogrel or ticagrelor, zotarolimus. Included were patients with the presence of prolonged (more than 30 min) chest pain, started less than 12 h before hospital arrival and ST elevation of at least 1 mm in two or more contiguous limb electrocardiographic leads or 2 mm in precordial leads.

Procedure success was defined as the achievement of an angiographic residual stenosis of less than 20% and a thrombolysis in myocardial infarction (TIMI) flow grade 3 after treatment of the lesions. Before the procedure patients were treated with loading doses of aspirin, clopidogrel or ticagrelor, unfractioned heparin. Post-PCI medical oral treatment included aspirin, statins, and clopidogrel or ticagrelor, which was recommended for 12 months in all cases after second-generation zotarolimus-eluting stent implantation. Signed informed consent for primary PCI and for the study was obtained from all patients before the procedure. Soon after every diagnostic angiography, the eligible patients were randomly allocated to two different strategies: 1. Multivessel stenting in primary PCI (MS primary): the IRA was opened followed by dilatation of other significantly narrowed arteries during the same procedure. 2. Multivessel stenting in staged revascularization (MS staged): the IRA only was treated during the primary intervention while the complete revascularization was planned in a second procedure (10.1 ± 5.1 days). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institution's human research committee.

3.1.2. Definitions and endpoints

Clinical and procedural data were collected by reviewing hospital records and angiographic runs stored in DICOM CDs. The primary endpoint of the study was the incidence of major adverse cardiac events (MACE) defined as cardiac or noncardiac death, reinfarction, and repeat coronary revascularization. For repeat revascularization we included all PCI or CABG occurring after the baseline procedure and justified by recurrent symptoms, reinfarction, or objective

evidence of significant ischemia on provocative testing. In the staged group we classified as repeat revascularization only unplanned procedures. Follow-up was obtained by outpatient visits or phone interviews.

We estimated clinical and angiographic criteria of ST. The incidence of ST was assessed throughout the follow-up period, according to the conventional ARC (Academic Research Consortium) classification [24]. Clinical criteria consisted of acute onset of chest pain persisting for >15 min and/or accompanied by ST-segment elevation or depression of at least 1 mm in two contiguous leads in the distribution of the target vessel. All patients with the clinical suspicion of ST underwent immediate coronary angiography to confirm the diagnosis followed by PCI.

Angiographic criteria of stent thrombosis consisted of partial or complete occlusion within the previously implanted stent with evidence of fresh thrombus. Within the first 18 h after index MI, recurrent MI required recurrent symptoms of myocardial ischemia associated with recurrent ST-segment elevation or depression of at least 1 mm in two contiguous limb electrocardiographic leads or 2 mm in precordial leads lasting at least 30 min. After 18 h, recurrent MI was defined as appearance of new Q waves, new left bundle-branch block, and/or enzyme evidence (level of creatine kinase MB fraction and/or troponin) of MI.

3.1.3. Statistical analysis

Continuous variables are presented as mean ± SD, categorical variables as percentages. For the endpoint "death" patients were censored at death or December 2015 if alive. For MACE patients were censored at the date of first MACE or at the end of follow-up. Follow-up was 100% complete. We used Chi Squared and Mann Whitney "U" test for statistical analysis to compare clinical, demographic, angiographic, PCI characteristics, and outcomes in groups. All analyses were performed using STATISTICA 8.0 (StatSoft, Tulsa, OK, USA).

3.1.4. Results

3.1.4.1. Baseline characteristics

In general population the mean age was 59 ± 10.6 (31–88) years; 92 (67.2%) were men. The incidence of diabetes mellitus in study cohort was 22.1%. The MS primary group included 67 patients, and the MS staged group 69 patients. The elective procedure in the MS staged group was performed on average 10.1 ± 5.1 days after the primary PCI. We evaluated the results in two study groups (MS primary vs. MS staged).

Table 1 shows the baseline clinical and demographic characteristics in study groups. Patients of MS primary and MS staged group were comparable for all clinical and demographic characteristics. The majority of patients in both groups were male, had hypertension and acute heart failure Killip 1.

Table 2 shows the baseline angiographic characteristics and special features of PCI. Mean SYNTAX score in the groups did not exceed 19 points, which corresponds to an intermediate

Variables	MS primary (n = 67)		MS staged (n = 69)		P
	n	%	n	%	
Age, years	58.6 ± 10.2		59.1 ± 11.1		0.6
Male	48	71.6	43	62.3	0.3
LVEF, %		50.7 ± 9.2		51.8 ± 7.3	0.5
Hypertension	64	94	61	88.4	0.4
Diabetes mellitus	16	23.9	14	20.3	0.8
Peripheral artery disease	13	19.4	20	29	0.3
Previous MI	10	14.9	4	5.8	0.2
Previous stroke	0	0	2	2.9	0.5
Acute heart failure (Killip II)	10	14.9	8	11.6	0.8

Table 1. Patient clinical and demographic characteristics.

Variables	MS primary (n = 67)		MS staged (n = 69)		P
	n	%	n	%	
Three-vessel disease	32	47.8	31	44.9	0.9
SYNTAX score	19.1 ± 7.9		18.6 ± 7.1		0.9
SYNTAX score ≥23 points	18	26.9	16	23.2	0.8
Contrast medium, ml	325.8 ± 110.2		373 ± 154.5		0.06
Mean number of stents	2.6 ± 0.5		2.7 ± 0.6		0.7
Total mean stent length, mm	57.5 ± 13.4		58 ± 16.2		0.6
Mean stent diameter, mm	3.3 ± 0.4		3.3 ± 0.5		0.3

Table 2. Baseline angiographic characteristics and special features of procedures.

severity of coronary lesions. About half of the patients in each group had 3-vessel CAD. Total mean stent length in each group exceeded 57 mm. There were no statistically significant differences between angiographic characteristics in the groups.

3.1.4.2. Events

Follow-up was completed in 100% of patients. Over the 12-month observation, there were no significant differences in frequency of adverse cardiovascular events among groups. After a follow-up of 12 months, there was only one noncardiac death in MS staged group (colon cancer). At the same time, fatality outcomes in the groups did not exceed 3% (**Table 3**). Survival free of MI and re-PCI was 62 (92.5%) patients in MS primary group and 67 (97.1%) in MS staged group (p>0.05).

Variables	MS primary (n = 67)		MS staged (n = 69)		P
	n	%	n	%	
All death	2	3	2	2.9	0.9
of them within 30 days	2	100	1	50	–
Cardiac death	2	3	1	1.4	0.6
MI	5	7.5	2	2.9	0.6
of them within 30 days	1	20	2	100	–
TVR	2	3	1	1.4	0.6
of them within 30 days	0	0	0	0	–
Non-TVR	0	0	1	1.4	0.9
of them within 30 days	0	0	1	100	–
Combined endpoint (cardiac death + MI + TVR)	4	5.9	3	4.3	0.7
Stent thrombosis (on the number of patients)	4	5.9	2	2.9	0.7
of them within 30 days	1	25	2	100	–

Table 3. 12-month outcomes.

3.1.5. Discussion

The main finding of the present randomized study is that after a follow-up of 12 months, in STEMI patients with multiple coronary lesions treated with multivessel PCI (primary and staged (10.1 ± 5.1 days)) with second-generation DES (Resolute Integrity), revascularization had satisfactory outcomes in two different strategies of PCI despite the initial severity of patients, including a high frequency of occurrence of diabetes (22.1%) and the average length of the stented segment 57.8 ± 14.6 mm.

According to previous guidelines, PCI should be performed only in IRA, at least in patients without cardiogenic shock [25]. This recommendation was based on the hypothesis that single-vessel PCI has a more favorable benefit-to-risk ratio and better financial implications. Some studies suggest that the more conservative strategy of treating only the IRA could avoid complications arising from longer procedures, such as the larger use of contrast medium with a potentially increased risk of contrast-induced nephropathy, the increased administration of radiation, as well as the danger of ischemia in noninfarcted myocardial regions [15, 18].

There is no randomized data to definitely answer the issues about the specific scientific merits of any of the approaches (multivessel stenting in primary PCI or staged PCI) [26]. And there is no evidence base for second-generation DES in STEMI patients with multivessel CAD, but in recent years, with the development of new advanced devices the outcome of multivessel PCI has markedly improved [17, 19].

However, the results of recent randomized trials challenged these recommendations [1, 4, 27]. The approach to the choice of revascularization strategy in patients with STEMI and MVCAD was detailed in 2014 ESC/EACTS Guidelines on myocardial revascularization [4]. The basic position of the recommendations is that the primary percutaneous coronary intervention (PCI) should be limited to infarct-related artery (IRA) (excepting cardiogenic shock or persistent ischemia, IIa class, level of evidence B) [4]. However, in patients with ischemia in noninfarct area primary PCI should be also performed for nonculprit lesions up to one week after admission (evidence grade IIa, Level B). Moreover, it is possible to carry out revascularization of nonculprit lesions at the time of primary PCI (evidence IIb class, level B) [20]. These standards came with the publication of the data from a randomized trial describing the preventive importance of PCI in nonculprit lesions (PRAMI) [1]. Nevertheless, the PRAMI trial does not respond to a key question—in which cases do we need to perform MS?

To the best of our knowledge the present study is the first that estimates throughout a follow-up the multivessel stenting during primary PCI and multivessel staged (10.1 ± 5.1 days) PCI with second-generation DES in STEMI patients with multivessel disease. We found that aggressive approach (multivessel stenting at the time of primary PCI or staged PCI) in STEMI patients with Resolute Integrity stents is associated with low risk of MACE in 12-month follow-up period. It is clear when compared with the published data. Twelve-month incidence of MACE in STEMI patients with multivessel disease in general cohort (BMS and DES) is 23.9–28%, re-MI 1.6–8.8%, death 3.3–6.3%, ST 1.8–4.3% [12, 15, 18]. In our study, we observed 12-month MACE, re-MI, death, and ST in 5.1, 5.1, 2.9, and 4.4% of patients, respectively.

Indeed, the inflammatory reaction arising during acute coronary syndromes and responsible for plaque instability is not limited to the culprit lesion, but involves the entire coronary tree [28]. Our results suggest that the multivessel approach (primary and staged) with second-generation DES is safe and possibly less expensive than an incomplete approach by reducing the probability of further unplanned procedures. We suppose that multivessel revascularization could decrease the risks and discomfort for patients associated with new unscheduled procedures. This hypothesis was also confirmed in the PRAMI trial. In PRAMI trial it was shown that in patients with STEMI and multivessel coronary artery disease undergoing infarct artery PCI, preventive PCI in noninfarct coronary arteries with major stenoses significantly reduced the risk of adverse cardiovascular events, as compared with PCI limited to the infarct artery [20].

In two other randomized trials, investigators have specifically assessed the value of preventive PCI in patients with acute STEMI undergoing PCI in the infarct artery. In one study, 69 patients were randomly assigned (in a 3:1 ratio) to preventive PCI (52 patients) or no preventive PCI (17 patients) [29]. At 1 year, in the preventive-PCI group, there were nonsignificant reductions in the rates of repeat revascularization (17 and 35%, respectively) and cardiac death or myocardial infarction (4 and 6%, respectively). In the other trial, 214 patients were randomly assigned to one of three groups: no preventive PCI (84 patients), immediate preventive PCI (65 patients), and staged preventive PCI performed during a second procedure about 40 days later (65 patients) [17]. At 2.5 years, the rate of repeat revascularization was

less frequent in the immediate—and staged—preventive-PCI groups combined, as compared with the group receiving no preventive PCI (11 and 33%, respectively), and there was a non-significant decrease in the rate of cardiac death (5 and 12%, respectively). The results of these studies are consistent with those of our study.

3.1.6. Conclusions

There is no doubt about the fact that the results of revascularization in STEMI patients with multivessel CAD may be improved by using the latest generation of DES (Resolute Integrity™ Stent, Medtronic). It is clear that further research in this area should be directed to the search criteria according to which it would be possible to choose a strategy of revascularization for PCI differentiated. Also important is to have an objective angiographic criteria indicating sufficient volume of revascularization performed in the hospital period with primary or staged multivessel stenting. In this context, in the next section of this chapter will be presented the relevant data of our own study—prognostic role of initial and residual SYNTAX score in STEMI patients after primary PCI.

4. Prognostic role of initial and residual SYNTAX score in patients with ST-segment elevation myocardial infarction after primary percutaneous coronary intervention

4.1. Methods

We recruited 327 consecutive patients and carried out a single-center registry study. The study was performed in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The local ethical committee approved the study and all the participants provided written informed consent after receiving a full explanation of the study. Criteria of inclusion were (1) hospital admission within 12 h of STEMI onset requiring the performance of primary PCI; (2) MVCAD defined as hemodynamically significant (≥70%) stenosis of two or more coronary arteries; (3) technical ability to perform PCI. Criteria of exclusion were (1) acute heart failure Killip class III-IV (pulmonary edema and cardiogenic shock); (2) left main coronary artery stenosis ≥50%. Before PCI, all patients received a loading dose of acetylsalicylic acid (250–500 mg) and clopidogrel (600 mg). Successful PCI was defined as the reduction of stenosis to <20% and a TIMI flow grade 3. After the PCI, all the patients received aspirin, statins, and clopidogrel during 1 year of follow-up.

We first evaluated the prognostic value of initial SYNTAX score that was calculated before PCI. Patients were divided into two groups depending on the severity of coronary lesions: SYNTAX ≤ 22 points (n = 213) and SYNTAX ≥ 23 points (n = 114). We then evaluated residual SYNTAX score that was calculated after PCI. Likewise, patients were stratified into two groups: SYNTAX ≤ 8 points (n = 243) and SYNTAX ≥ 9 points (n = 74). The SYNTAX score was assessed using a calculator (http://www.rnoik.ru/files/syntax/index.html).

4.2. Results

4.2.1. Baseline characteristics

Table 4 demonstrates the baseline clinical and demographic characteristics in study groups. As shown, patients with severe coronary atherosclerosis (SYNTAX ≥ 23**)** were characterized by (1) older age; (2) decreased left ventricular ejection fraction (LVEF); (3) more frequent past medical history of MI; (4) more severe acute heart failure compared to those with SYNTAX ≤ 22.

Table 5 shows a comparison of clinical and demographic characteristics of patients after primary PCI. Patients with SYNTAX ≥ 9 were characterized by (1) older age; (2) higher prevalence of females; (3) decreased LVEF; (4) more frequent past medical history of MI and peripheral artery disease compared to those with SYNTAX ≤ 8.

Variables	**Patients (n = 327)**				**P value**
	Initial SYNTAX ≤ 22 (n = 213)		**Initial SYNTAX ≥ 23 (n = 114)**		
	n	**%**	**n**	**%**	
Age, years	59.1 ± 9.9		60.9 ± 10.6		0.08
Male gender	142	66.6	74	64.9	0.8
LVEF, %		52.5 ± 7.2		48.4 ± 8.8	0.000009
Arterial hypertension	188	88.3	103	90.3	0.7
Diabetes mellitus	47	22	20	17.5	0.4
Peripheral artery disease	56	26.3	33	28.9	0.7
Past medical history of MI	21	9.8	29	25.4	0.0001
Past medical history of stroke	8	3.7	3	2.6	0.8
Acute heart failure (Killip class II)	17	7.9	21	18.4	0.009

Table 4. Patient clinical and demographic features (initial SYNTAX score groups).

Variables	**Patients (n = 317)**				**P value**
	Residual SYNTAX ≤ 8 (n = 243)		**Residual SYNTAX ≥ 9 (n = 74)**		
	n	**%**	**n**	**%**	
Age, years	58.8 ± 9.9		63.1 ± 10.6		0.001
Male	76	31.3	34	55.9	0.03
LVEF, %		51.4 ± 7.6		49.2 ± 9.2	0.08
Hypertension	218	89.7	68	91.9	0.7
Diabetes mellitus	45	18.5	20	27	0.2
Peripheral artery disease	59	24.3	28	37.8	0.03
Previous MI	31	12.8	17	23	0.05
Acute heart failure (Killip II)	29	11.9	10	13.5	0.9

Table 5. Patient clinical and demographic features (residual SYNTAX score groups).

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Analysis of the angiographic parameters and features of revascularization revealed a direct relationship between the initial SYNTAX ≥ 23 and residual SYNTAX ≥ 9 (**Table 3**). In comparison with residual SYNTAX ≤ 8 patients, those with SYNTAX ≥ 9 patients had (1) a higher prevalence of initial SYNTAX ≥ 23; (2) more frequent three-vessel disease; (3) more rare use of multivessel stenting strategy; (4) less percentage of successful PCI in IRA (**Table 6**).

4.2.2. Events

Within 1 year of follow-up, five deaths were reported in initial SYNTAX ≤ 22 group (**Table 7**). Four of them were due to MACE; the fifth was from cancer. Cases of cardiac death were due to (1) rupture of the myocardium on the second day after unsuccessful PCI of IRA; (2) stent thrombosis; (3) sudden cardiac arrest. We also observed seven nonfatal MI (**Table 4**). Three of them developed as a result of stent thrombosis, two as a result of destabilized nonculprit lesions, one as a complication of elective PCI, and one occurred 2 months after the

Variables	Residual SYNTAX ≤ 8 (n = 243)		Residual SYNTAX ≥ 9 (n = 74)		P value
	n	%	n	%	
Three-vessel disease	119	49	62	83.8	0.0001
Initial SYNTAX score	18.9 ± 7.7		26.8 ± 7.7		0.0000001
Procedure success	235	96.7	66	89.2	0.02
Multivessel stenting	80	32.9	7	9.5	0.0001
Staged PCI	163	67.1	67	90.5	0.0001
Mean time between PCI, days	80.1 ± 49.5		80.1 ± 46.4		0.9

Table 6. Baseline lesions and angiographic characteristics (residual SYNTAX score groups).

Variables	Initial SYNTAX ≤ 22 (n = 213)		Initial SYNTAX ≥ 23 (n = 114)		P value
	n	%	n	%	
Death from all causes	5	2.3	12	10.5	0.004
Cardiovascular death	4	1.9	11	9.6	0.003
Myocardial infarction	7	3.3	12	10.5	0.02
Repeated target vessel revascularization	10	4.7	9	7.9	0.4
Repeated nontarget vessel revascularization	2	0.9	2	1.8	0.9
Stent thrombosis	4	1.9	10	8.8	0.008
Combined endpoint*	10	4.7	12	10.5	0.008

*All death + MI + TVR.

Table 7. Outcomes after 1 year of follow-up (initial SYNTAX score groups).

index event. Six out of ten cases of repeated target vessel revascularization were caused by the development of in-stent restenosis (**Table 4**). Four other cases were associated with stent thrombosis. Twelve deaths were reported in patients with initial SYNTAX ≥ 23; eleven of them were caused by MACE while the twelfth was due to stroke (**Table 4**). Out of these, eleven deaths, five were the result of stent thrombosis, three were the result of an unsuccessful PCI and progressive acute heart failure, two patients died due to myocardial rupture, and the last case was associated with air embolism of the right coronary artery. Only one case of repeated target vessel revascularization out of nine was the result of in-stent restenosis, while the other eight were performed in patients with stent thrombosis (**Table 7**).

Initial SYNTAX score ≥ 23 was significantly associated with a higher risk of death from any cause, cardiac death, recurrent MI, stent thrombosis, and combined endpoint (**Table 8**).

There was a significantly higher frequency of death from any cause, recurrent MI, and repeated nontarget vessel revascularization among patients with residual SYNTAX ≥ 9 compared to those with residual SYNTAX ≤ 8 (**Table 9**).

Residual SYNTAX ≥ 9 successfully predicted MACE such as death, recurrent MI, and repeated nontarget vessel revascularization (**Table 10**).

Major adverse cardiovascular outcomes	**OR (95% CI)**
Death from any cause	4.9
Cardiac death	5.6
Recurrent myocardial infarction	3.5
Stent thrombosis	5.0
Combined endpoint	2.4

Table 8. Prognostic factors of MACE based on the initial SYNTAX score.

Variables	**Residual SYNTAX ≤ 8 (n = 243)**		**Residual SYNTAX ≥ 9 (n = 74)**		**P value**
	n	**%**	**n**	**%**	
Death	7	2.9	10	13.5	0.001
Myocardial infarction	10	4.1	8	10.8	0.05
Repeated target vessel revascularization	11	4.5	9	12.2	>0.05
Repeated nontarget vessel revascularization	6	2.5	7	9.5	0.02
Stent thrombosis	5	2.1	5	6.8	>0.05

Table 9. Outcomes after 1 year of follow-up (residual SYNTAX score groups).

Major adverse cardiovascular outcomes	OR (95% CI)
Death	3.4 (1.5–7.9)
Recurrent myocardial infarction	2.7 (1.2–6.1)
Repeated nontarget vessel revascularization	2.6 (1.2–5.5)

Table 10. Prognostic factors of MACE based on the residual SYNTAX score.

4.3. Discussion

The main objective of this study was to determine the value of initial and residual SYNTAX score for prediction of adverse revascularization outcomes in patients with STEMI and MVCAD. To the best of our knowledge, there is little evidence demonstrating the prognostic value of initial and residual SYNTAX score in STEMI patients who underwent primary PCI. Meanwhile, there is a need for objective criteria including the severity of coronary lesions, which could optimize the choice of revascularization strategy for these patients [30, 31].

Here we showed that initial SYNTAX ≥ 23 points can predict the development of MACE within 1 year of follow-up. Patients with SYNTAX ≥ 23 had significantly higher incidence of adverse outcomes such as death, MI, and stent thrombosis. However, residual SYNTAX score can be even more informative since it reflects the completeness of myocardial revascularization and risk of adverse events in the short- and long-term follow-up. Residual SYNTAX score ≥ 9 was significantly associated with an increased risk of death, recurrent MI, and repeated nontarget vessel revascularization. High residual SYNTAX score was more prevalent in groups with a predominance of female patients, three-vessel coronary disease, peripheral atherosclerosis, past medical history of MI, and reduced LVEF. It is known that these clinical and demographic indicators themselves have an adverse effect on long-term prognosis after MI [30, 31]. However, it cannot be excluded that adverse cardiovascular events are more dependent on revascularization completeness in the hospital period and, therefore, on residual SYNTAX score at the time of discharge from the hospital. It is important to note the direct association of the initial SYNTAX score ≥ 23 with residual SYNTAX score ≥ 9 points. We suggest that patients with initial severe coronary atherosclerosis are likely to retain a high residual SYNTAX at the end of hospitalization.

This highlights the need for complete revascularization in the early stages, including MS strategy (simultaneous and staged a tightly limited time interval between PCI), as well as a combination of primary PCI with subsequent coronary bypass surgery. Moreover, patients with high residual SYNTAX score may need more efficient schemes of anticoagulant and antiplatelet therapy with the use of modern drugs (bivalirudin, ticagrelor, prasugrel). Considering the desirability of multivessel PCI strategy targeting not only IRA but also nonculprit lesions in a limited time interval [4], we assume that the target value of residual SYNTAX score in STEMI patients to the end of in-hospital period is ≤ 8 points. This algorithm is particularly reasoning given a sufficiently high proportion of unsuccessful PCI in patients with severe initial and residual SYNTAX (10.8%).

4.4. Conclusions

Both initial and residual SYNTAX score can predict death from all causes and/or MACE in patients with STEMI and MVCAD. Patients with high initial SYNTAX score tend to have a high residual SYNTAX score. Therefore, the patients with high initial SYNTAX score require complete revascularization and efficient antiplatelet therapy. Probably, it is required to develop a model of differentiated selection of the optimal revascularization strategy for STEMI patients to reduce the residual SYNTAX score to the end of in-hospital period to ≤ 8 points using primary multivessel stenting or staged PCIs. These results may be useful for risk stratification in patients with STEMI and MVCAD. In this context, in the next section of this chapter will be presented the relevant data of our own study—personalized choice of optimal strategy revascularization in STEMI patients with MVCAD.

5. Personalized choice of optimal revascularization strategy in patients with STEMI and MVCAD

5.1. Methods and statistical analysis

Having recruited 327 consecutive patients, we carried out a single-center registry study. Criteria of inclusion were (1) hospital admission within 12 h of STEMI onset requiring the performance of PPCI; (2) MVCAD defined as hemodynamically significant (≥70%) stenosis of ≥ 2 coronary arteries; (3) technical ability to perform PPCI. Criteria of exclusion were (1) acute heart failure Killip class III-IV, i.e., pulmonary edema and cardiogenic shock; (2) left main coronary artery stenosis ≥ 50%. Before PPCI, all patients received a loading dose of acetylsalicylic acid (250–500 mg) and clopidogrel (600 mg). Successful PPCI was defined as the reduction of stenosis to < 20% and a TIMI flow grade 3. After the PCI, all the patients received aspirin, statins, and clopidogrel during 1 year of follow-up. Patients were divided into two groups: treated with MPS approach (n = 91) and treated with MSS approach (n = 236). The second stage of PCI in those who were treated with MSS approach was carried out 3–6 months after PPCI. After 12 months of follow-up, both cardiac and noncardiac death, recurrent MI, and repeat coronary revascularization were defined as primary endpoints. Repeated revascularization was performed utilizing PCI after the baseline procedure due to the recurrent symptoms, recurrent MI, or significant ischemia at provocative testing. In patients treated with MSS approach, we defined only unplanned procedures as repeated revascularization. Follow-up was conducted by outpatient visits or phone interviews.

We collected the data on age, gender, acute heart failure (Killip class), left ventricular ejection fraction, SYNTAX score, peripheral atherosclerosis (PA), past medical history of myocardial infarction or stroke, arterial hypertension, diabetes mellitus, MVCAD, and use of drug-eluting stents.

Risk stratification models were obtained using stepwise logistic regression with the calculation of ROC curve and area under the curve (**Figures 1** and **2**).

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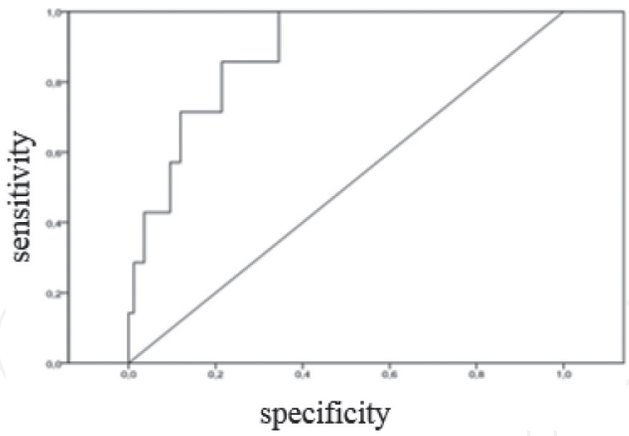

Figure 1. ROC curve of the model calculated for MPS strategy.

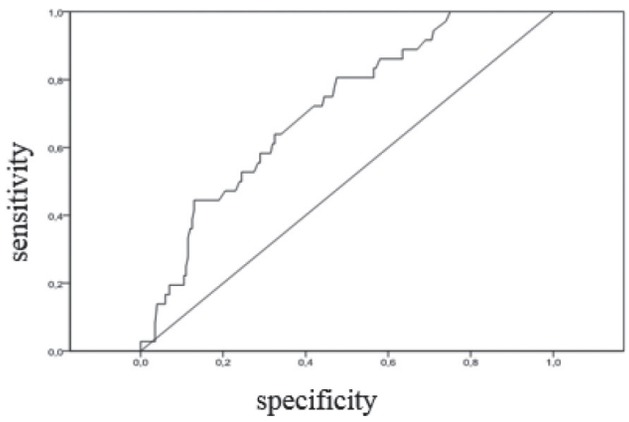

Figure 2. ROC curve of the model calculated for MSS strategy.

We further developed an original calculator for choosing the optimal stenting strategy (Microsoft Excel).

5.2. Results

5.2.1. Baseline characteristics

Patient groups did not have any significant differences in clinical or demographic characteristics (**Table 11**) as well as in angiographic features (**Table 12**) and characteristics of vascular access or implanted stents (**Table 13**).

Strikingly, there were no significant differences in outcomes between two revascularization strategies (**Table 14**).

Prognostic coefficients for each group of patients are presented in **Table 15**.

The values of prognostic coefficients were directly related to the risk of adverse outcome (**Table 15**). Past medical history of MI, severe coronary atherosclerosis (SYNTAX score ≥ 23), elderly age, and

female gender showed significant predictive ability of an adverse outcome for patients treated with MPS, while past medical history of MI or stroke, PA, arterial hypertension, three-vessel disease, and the use of non-DES were the predictors of an adverse outcome in those treated using MSS approach. The following clinical case represents an example of utilizing interactive calculator for the selection of the optimal revascularization strategy in a patient with STEMI and MVCAD.

5.3. Clinical case: using a calculator for a personalized selection of the optimal revascularization strategy in a patient with STEMI and MVCAD

Female, 64 years old, was admitted to the hospital with STEMI. The time from onset of symptoms to hospital admission was 4 h. The patient had a number of cardiovascular risk factors: diabetes, hypertension, PA (two-sided stenosis of internal carotid arteries), and residual effects of stroke. ECG showed signs of ST-segment elevation in leads V1–V5 > 2 mm. Ejection fraction on echocardiography was 33%.

Variables	MPS (n = 91)		MSS (n = 236)		P
	n	%	n	%	
Age, years	59.2 ± 10.2		60.1 ± 10.2		0.6
Male gender	62	68.1	154	65.3	0.6
LVEF, %		51.1 ± 8.8		50.7 ± 7.8	0.97
Arterial hypertension	79	86.8	208	88.1	0.9
Diabetes mellitus	17	18.7	49	20.8	0.8
Peripheral artery disease	20	21.9	68	28.8	0.4
Past medical history of MI	9	9.9	40	16.9	0.3
Past medical history of stroke	0		12	5.1	0.5
Acute heart failure (Killip class II)	11	12.1	28	11.9	0.8

LVEF—left ventricular ejection fraction; MI—myocardial infarction.

Table 11. Patient clinical and demographic features.

Variables	MPS (n = 91)		MSS (n = 236)		P
	n	%	n	%	
Three-vessel disease	50	54.9	132	55.9	0.9
SYNTAX score	18.9 ± 7.5		21.5 ± 8.6		0.1
LAD-IRA	36	39.5	86	36.4	0.8
Cx-IRA	17	18.7	53	22.5	0.8
RCA-IRA	38	41.7	97	41.1	0.9

IRA—infarct-related artery; LAD—left anterior descending artery; Cx—circumflex artery; RCA—right coronary artery.

Table 12. Baseline angiographic characteristics.

Variables	MPS (n = 91)		MSS (n = 236)		P
	n	%	n		n
Femoral access	43\91	47.3	255\472	54.6	0.5
Radial access	46\91	50.5	212\472	45.4	0.6
Shoulder access	2\91	2.2	5\472	1	0.7
Successful PCI	84\91	92.3	444\472	94.1	0.9
Contrast medium, ml	328.2 ± 120.7		364.1 ± 165.5		0.07
The average number of stents implanted in IRA	1.3 ± 0,5		1.4 ± 0,6		0.7
DES in IRA	48	52.7	125	52.9	0.9
The average number of stents implanted in non-IRA	1.2 ± 0.5		1.4 ± 0.7		0.7
DES in non-IRA	41	45	116	49.2	0.7
The average length of IRA stented segment, mm	28.9 ± 12.6		29.3 ± 13.7		0.8
The average length of non-IRA stented segment, mm	24.2 ± 11.7		28.1 ± 15.4		0.5
The average diameter of IRA stent, mm	3.3 ± 0.4		3.4 ± 0.5		0.8
The average diameter of non-IRA stent, mm	3.2 ± 0.5		3.2 ± 0.4		0.9

Table 13. Characteristics of vascular access and implanted stents in patient groups.

According to angiography data, multiple coronary disease occurred: subtotal lesion of the proximal and distal segment of right coronary artery (RCA), thrombotic occlusion of the proximal segment of left anterior descending (LAD) artery with blood flow TIMI 0, subtotal bifurcation stenosis of circumflex (Cx) artery (**Figure 3**).

Variables	MPS (n = 91)		MSS (n = 236)		P
	n	%	n	%	n
Death from all causes	3	3.3	14	5.9	0.5
Cardiac death	3	3.3	12	5.1	0.7
MI	3	3.3	16	6.8	0.3
Target vessel revascularization	4	4.4	13	5.5	0.9
Nontarget vessel revascularization	0	0	4	1.7	0.5
Combined endpoint*	7	7.7	24	10.2	0.6
Stent thrombosis	3	3.3	11	4.7	0.8

*Combined endpoint—death, MI and unplanned revascularization (TVR and non-TVR).

Table 14. Outcomes after 1 year of follow-up.

Risk factor	Presence of risk factor	Prognostic coefficients for MPS	Prognostic coefficients for MSS
Elderly age	No	0.031	0.132
	Yes	0.192	0.195
Female	No	0.048	0.169
	Yes	0.138	0.134
Acute heart failure (Killip class)	1	0.079	0.144
	2	0.091	0.214
Peripheral atherosclerosis	No	0.071	0.132
	Yes	0.1	0.203
Past medical history of MI	No	0.049	0.1353
	Yes	0.3	0.25
Arterial hypertension	No	0.125	0.043
	Yes	0.072	0.165
Diabetes mellitus	No	0.068	0.15
	Yes	0.111	0.163
Past medical history of stroke	No	–	0.147
	Yes	–	0.273
Three-vessel disease	No	0.064	0.097
	Yes	0.091	0.189
SYNTAX score ≥23	No	0.045	0.150
	Yes	0.16	0.156
LVEF	(3) ≤40%	0.111	0.077
	(2) 41–49%	0.148	0.224
	(1) ≥50%	0.036	0.128
DES	No	0.075	0.182
	Yes	0.078	0.041

MI—myocardial infarction; LVEF—left ventricular ejection fraction; DES—drug-eluting stents.

Table 15. Prognostic factors of unfavorable outcome depending on the revascularization strategy.

Using our original calculator, we counted the probability of an adverse outcome for MPS and MSS strategies (**Figure 4**). As seen from **Figure 4**, MPS strategy was selected as favorable, while MSS strategy showed a poor prognosis for the patient.

Hence, the patient underwent multivessel stenting of LAD, Cx and RCA (five DES implanted in total) (**Figure 5**).

The patient's conditions were satisfactory. On the 14th day, the patient was discharged from the hospital. There was no angina but patient experienced chronic heart failure II-III functional

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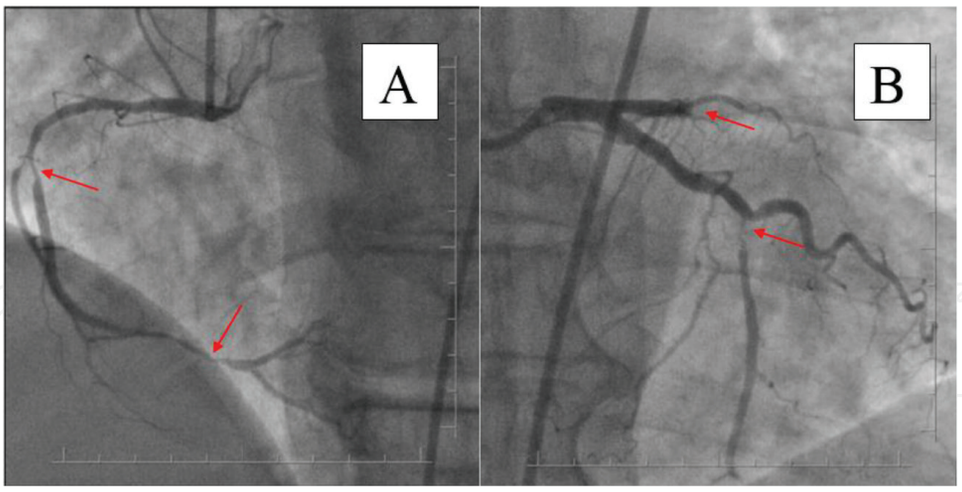

Figure 3. Angiography of the patient with STEMI and multiple coronary disease. A: Subtotal lesion of the proximal and distal segment of right coronary artery; B: Thrombotic occlusion of the proximal segment of left anterior descending artery and subtotal bifurcation stenosis of circumflex artery.

class (NYHA classification). Current diabetes and arterial hypertension were adequately controlled with proper medications. After 2 years, the patient underwent repeated coronary angiography. There were no stenoses of coronary arteries (**Figure 6**). According to echocardiography, LVEF was 45%, with a remained anterior wall hypokinesis.

Therefore, we successfully selected an optimal revascularization strategy. This restored the function of anterior myocardial wall, prevented destabilization of Cx and RCA stenosis, and provided a satisfactory quality of life.

5.4. Conclusions

Here we defined the risk factors of an adverse outcome and designed a calculator for the personalized choice of the optimal revascularization strategy for patients with STEMI and MVCAD.

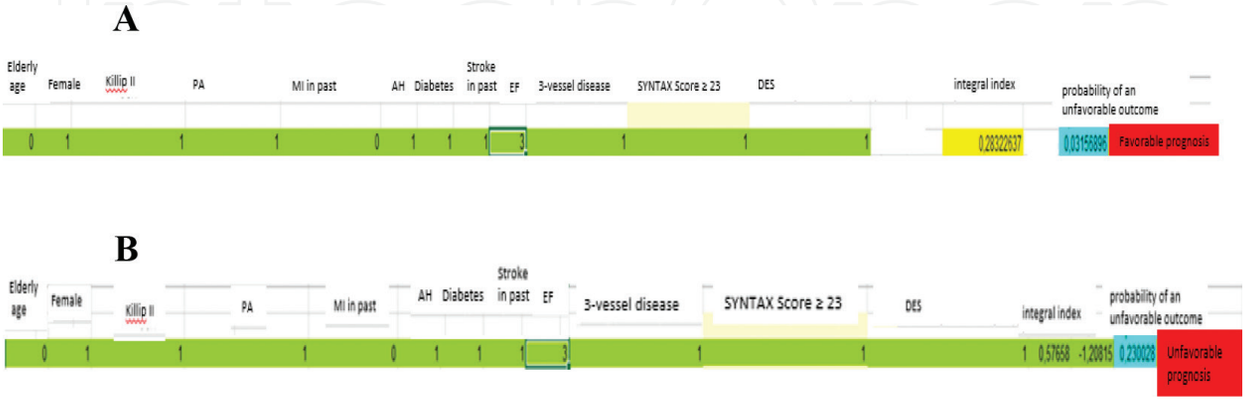

Figure 4. Using the model to calculate the probability of unfavorable prognosis for MPS (A) and MSS strategies (B); 1—presence of factor; 0—absence of factor; 3—LVEF ≤ 40%; PA—peripheral atherosclerosis; MI—myocardial infarction; AH—arterial hypertension; EF—ejection fraction; DES—drug-eluting stents.

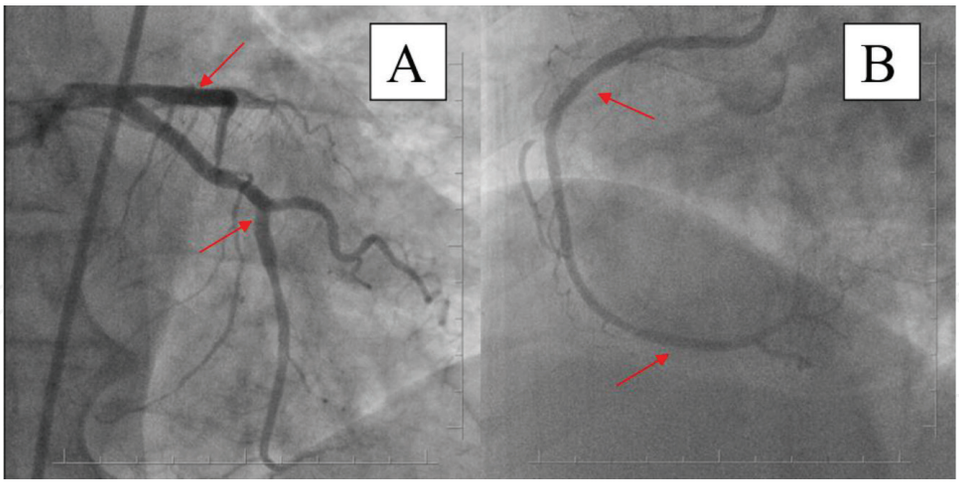

Figure 5. Angiography of the patient with STEMI after stenting. A—LAD and Cx; B—RCA.

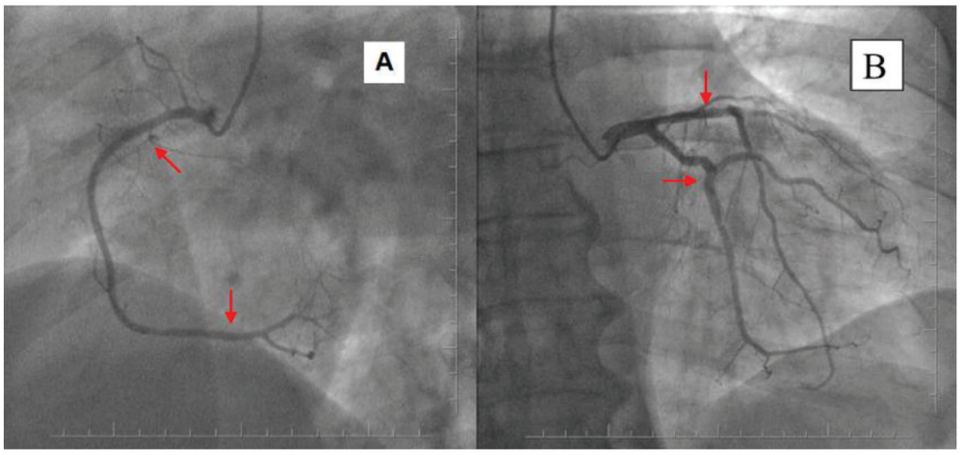

Figure 6. Angiography of the patient with STEMI 24 months after stenting A—RCA; B—LAD and Cx.

6. Conclusions

Around 50% of patients with STEMI have MVCAD that significantly worsens prognosis. There are three treatment approaches to these patients: culprit vessel intervention only, with ischemia-based PCI of non-IRA, MV stenting either at the time of PPCI or as a planned, staged procedure. Both MPS and MSS have evidence base and are approved by the current clinical guidelines. Treatment of culprit vessel only leads to worse outcomes. Complete revascularization, achievable through either MPS or MSS, is the key aim that was confirmed by our single-center registry study of initial and residual SYNTAX score. However, the choice between MPS and MSS is a crucially important issue. Here we defined the risk factors of adverse outcomes after either of these strategies and developed an original calculator for the choice of an optimal stenting strategy. Moreover, we carried out a randomized clinical trial and revealed that results of revascularization in patients with STEMI and MVCAD may be improved by using the latest generation DES such as Resolute Integrity™ Stent.

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Hence, we justify the use of personalized approach for the optimal revascularization strategy in patients with STEMI and MVCAD using the latest generation of DES with choosing MPS or MSS according to our original calculator.

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