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Department of Interventional Cardioangiology

ROBUST STUDY

PROTOCOL

of a multicenter, open-label, prospective, randomized, controlled non-inferiority study

CompaRison of corOnary BifUrcation treatment with and without Stenting using only drug eluTing balloons (ROBUST study)

VERSION 2.0.

November 6, 2025

Participating clinical study sites:

- **Center for Endosurgery and Lithotripsy (CELT), Moscow**
- **Moscow Regional Research and Clinical Institute (MONIKI)**
- **Scientific and Practical Center for Interventional Cardioangiology (NPCIC)**
- **Rostov Region Consultative and Diagnostic Center (Rostov-on-Don)**
- **Cardiac Surgery Clinic of the Amur State Medical Academy**
- **Scientific and Clinical Center No. 2 Russian Research Center of Surgery**
- **National Medical Research Center for Therapy and Preventive Medicine**
- **Clinic of the Central Clinical Hospital "RZD-Medicine"**

Sponsor: ROBUST is a physician-initiated study without financial support from medical companies.

1.1. SUMMARY:

Title	**A comparative non-inferiority study of endovascular treatment of coronary bifurcation lesions with and without stenting using drug-eluting balloons** Compa**R**ison of cor**O**nary **B**if**U**rcation treatment with and without **S**tenting using only drug elu**T**ing balloons (ROBUST study)
Study period	March 2026 – March 2027
Study aim	The aim of the study is to investigate the comparative efficacy and safety of PCI of a bifurcation stenosis using drug-eluting balloons in comparison with a stenting technique in patients with chronic coronary syndrome.
Hypothesis	1. PCI of coronary bifurcation stenosis using only drug-eluting balloons is reliably non-inferior ("not worse") in terms of acute and long-term outcomes, in comparison with stenting techniques using 2nd and 3rd generation drug-eluting stents. 2. PCI of coronary bifurcation stenosis with drug-eluting balloons may be associated with a lower complication rate (bleeding, late thrombosis) compared to stenting using drug-eluting stents
Study design	A multicenter, comparative, open-label, simple randomized, controlled study with a 1:1 allocation ratio
Methodology	A prospective, multicenter, randomized, controlled study in patients with bifurcation coronary artery stenosis eligible for revascularization by angioplasty and/or stenting. Patients will undergo PCI using one of the recommended bifurcation stenting techniques with 2nd and 3rd gen drug-eluting stents and angioplasty without stents using only drug-eluting balloons. Randomization will be 1:1 by random number generation using a web-based computer model. During the intervention, one of the intravascular imaging techniques (intravascular ultrasound - IVUS, optical coherence tomography - OCT) is recommended to optimize stenting and/or angioplasty. Follow-up coronary angiography will be done at 12 months after the primary coronary intervention to perform a qualitative analysis of the follow-up coronary angiography.
Patient population	The eligibility and inclusion criteria for patients with chronic coronary syndrome (CCS) in the study define the population of patients with coronary bifurcation stenosis who require myocardial revascularization. The total number of patients is 272, taking into account a 10% dropout

	rate.
Patient inclusion	No less than 136 patients (in each arm) should be included to achieve the required statistical significance of 0.80 (two-sided error criteria α=0.05).
Inclusion criteria	1. Patients with CCS with documented myocardial ischemia in area supplying by the target coronary artery, not older than 80 years and with an expected life expectancy of at least 1 year 2. Patients with single- or multivessel disease and "true" (**1.1.1; 1.1.0; and 0.1.1** according to the Medina classification) de novo bifurcation stenosis **> 50% and <100%** of the main coronary artery (excluding of the left main) or their large side branches. 3. Both main and side branches should be ≥ 2.0 mm and ≤ 4.5 mm in diameter (according to Quantitative coronary angiography - QCA or intravascular imaging) 4. Length of the main branch lesion should be no more than **30 mm** 5. The total length of the side branch should be no more than **7 cm,** and the side branch lesion length should be no more than **10 mm** 6. Patients without hereditary coagulopathies 7. With a recent (at least 3 months) history of acute coronary syndrome (ACS) 8. Signed informed consent by patient to participate in the study
Non-inclusion criteria	1. Patients with a single remaining artery supplying a large area of myocardium at risk, regardless of its caliber 2. Over 80 years of age 3. Bifurcation stenosis of the left main coronary artery and bifurcation lesions other than 1.1.1; 1.0.1, and 0.1.1 according to the Medina classification 4. The difference between the proximal and distal reference diameter of the main artery is > 1 mm 5. Pregnancy or breastfeeding 6. Severe valvular heart disease requiring surgical or percutaneous intervention within 1 year 7. Life expectancy less than 1 year. 8. Chronic renal failure (glomerular filtration rate less than 30 ml/min) 9. Concomitant cancer

	10. Heart failure > NYHA class II 11. In-stent restenosis in bifurcation lesions after previously performed PCI 12. Presence of thrombus containing Lesion 13. Without concomitant chronic occlusion (bifurcation included in the chronic coronary occlusion (CTO)) 14. Patients at high bleeding risk (according to the PRECISE-DAPT score) 15. LV ejection fraction according to echocardiography ≤ 0.4
Exclusion criteria	1. Anemia (Hb < 10 g/dL) 2. Thrombocytopenia and any coagulopathy 3. Episodes of significant bleeding and ongoing bleeding requiring modification of medical therapy 4. Acute coronary syndrome 5. PCI or coronary artery bypass grafting (CABG) performed according to clinical indications 6. Patient non-adherence to therapy, including antiplatelet and/or anticoagulant medications
Study endpoints	***The primary endpoint*** is a composite of all-cause death, myocardial infarction (MI), and clinically-driven target lesion revascularization at 12 months after initial procedure
	Secondary endpoints – 1. restenosis of the target lesion (main, side branch) 2. Target lesion thrombosis (definite, probable, possible according to the ARC classification). 3. Any repeat revascularization of target arteries 4. Components of the primary endpoint are cardiogenic death, any AMI 5. Bleeding defined according to the BARC 2-5 classification 6. PCI parameters – procedure duration, radiation dose, and amount of contrast agent
Investigational product	Investigational product is a sirolimus-coated coronary dilatation balloon catheter. It is planned to use a uniform drug-coated balloons to avoid the influence of the technological factor on study outcomes

Sample size calculation	To determine the number of patients to be included in the study, a power analysis was performed taking into account a 1:1 group allocation and literature data on the performance of similar stents. According to available literature data, the rate of the composite endpoint after bifurcation stenting has steadily improved over the past decade and currently is 9.6% with the use of second- and later-generation stents.[1] Previous studies do not provide definitive data on the rate of the primary MACE in patients undergoing balloon dilation of bifurcation lesions. However, an adverse event rate of 19% can be assumed based on the outcomes of "plain" balloon dilation in the general patient cohort. Assuming a composite endpoint rate of 0.096 and a non-inferiority margin of 4.7%, it was calculated that 244 patients (122 per study and control groups) would need to be enrolled to achieve statistical significance with type I and type II error levels of 0.05 and 0.2, respectively. Thus, the study power is 80%. To keep into account all incomplete or dropped-out cases, the sample size will be increased by 10%, resulting in a total of 272 patients (136 per group) to be included in the study. If a dropout rate of 20% is anticipated, the required sample size would be 306 patients (153 per group).
Evaluation of long-term outcomes	Assessment of the long-term outcomes will be using a telephone survey, a clinic visit, an instrumental examination and/or follow-up coronary angiography at 30 days, 6 months and 12 months after the procedure.
Estimated study duration	The patient enrollment phase of the study is expected to be completed by _31_ __March___ 2027.
Study initiation	__March___ 2026
Core laboratory	Tel.: E-mail:
Study reference Institutions	Clinic CELT, Moscow Moscow State Medical University (Sechenov University), Department of Interventional Cardioangiology
Contacts	Tel.: E-mail:

1.2. PRIMARY PROCEDURES AND STUDY TIMELINES

Evaluated criterion	Evaluation before the procedure	Procedure	Immediately after the procedure	Before discharge	1 month	6 months	12 months
Medical history, assessment of baseline laboratory tests and clinical data, and eligibility for study inclusion	√						
obtaining of clinical status (myocardial ischemia), non-invasive tests (MDCT, treadmill etc.), and laboratory tests (lipid profile, complete blood count)	√		√	√	√	√	√
Coronary angiography (including quantitative coronary angiography (QCA)	√	√	√		+/-	+/-	√
Percutaneous coronary intervention (PCI)		√			+/-	+/-	+/-
Intravascular imaging (IVUS, OCT)		+/-	+/-				+/-
High-sensitivity troponin assay		√	√	√			
Radiation dose, contrast agent volume, procedure duration		√	√				
Complications		√	√	√	√	√	√
Study endpoint evaluation					√	√	√
Assessment of angina functional class according to the CCS classification	√			√	√	√	√

1.3. STUDY GENERAL INFORMATION

The study was initiated by practicing physicians with extensive experience in coronary interventions for various types of lesions various types of coronary lesions, including bifurcation lesions, which are unequivocally considered complex. The study does not involve funding from any company, governmental or non-governmental organizations, or financial institutions.

Principal investigator:

Tel.:

Data collection and monitoring committee:

Tel.:
E-mail:

Tel.:
E-mail:

Core laboratory and clinical data analysis:
Core angiographic laboratory
Coordinator –
Tel.:
E-mail:

Signatures of coordinating investigators:
By signing below, I agree to the contents of the study protocol of a:

Multicenter, open-label, prospective, randomized controlled trial ROBUST

A comparative study of endovascular treatment of coronary bifurcation lesions with and without stenting using drug-eluting balloons

I commit to avoiding any abuse of influence or undue motivation of the subject, sponsor, monitor, other investigator(s), or other parties participating in or facilitating the conduct of the clinical study.

RESEARCHERS:

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Signatures of the principal investigators:

By signing below, I agree to conduct the study:

Multicenter, open-label, prospective, randomized controlled trial ROBUST

A comparative study of endovascular treatment of coronary bifurcation lesions with and without stenting using drug-eluting balloons

in accordance with the protocol, GCP rules, the Helsinki Declaration, and the laws of the Russian Federation.

1. Center for Endosurgery and Lithotripsy (CELT Clinic)
   _____ ()
2. NPCIC for Interventional Cardioangiology
   _____ ()
3. Scientific and Clinical Center No. 2 of the Russian Research Center of Surgery
   _____ ()
4. MONIKI
   _____ ()
5. AGMA Cardiocenter
   _____ ()

6. National Medical Research Center for Therapy and Preventive Medicine
   _____ ()
7. State Institution of the Rostov Region, Consultative and Diagnostic Center
   _____ ()
8. Clinic of the Central Clinical Hospital "RZD-Medicine"
   _____ ()

2. KEY INFORMATION OF THE STUDY:

2.1. INTRODUCTION:

Bifurcation lesions account for approximately 20-25% of all percutaneous coronary interventions[2]. Despite significant technological advances in instrumentation, the optimal treatment of bifurcation lesions remains challenging. On the one hand, both acute and long-term outcomes of PCI of bifurcation lesions are worse to those for non-bifurcation lesions, therefore, questions regarding the optimal stenting strategy persist. Furthermore, previous studies are difficult to interpret, since the lesions included in the studies differ across multiple criteria, and the outcomes may be influenced by numerous confounders, such as bifurcation angle, lesion extent in the main vessel, significant mismatch in calibers between the main and side branch, substantial difference in diameter between the proximal and distal segments of the main artery, etc. None of these factors are accounted for in the widely used Medina classification of bifurcations.

Currently, the recommended technique for bifurcation lesion treatment is provisional stenting of the main branch, with optional two-stent strategy, if necessary. However, all the aforementioned challenges in treating of bifurcation lesions, as well as the impact of main-branch stenting on the geometry and patency of the side branch, have renewed interest in the “leave nothing behind” concept, in particular, the use of drug-eluting balloons (DEBs). However, It should be emphasized, that data on the use of DEBs in the endovascular treatment of bifurcation lesions are scarce. A recently published systematic review with a focused meta-analysis included only 12 (!) completed studies over a 30-year period from 1990 to 2020, including randomized, observational, registry, and retrospective studies [3] To date, there are no comparative studies between treatment with DEBs alone and second- or later-generation drug-eluting stents.

Given the significant knowledge gaps and the lack of meaningful studies on the use of DEBs in bifurcation lesions, the aim of this study was to compare the acute and long-term outcomes of endovascular treatment of bifurcation lesions using second- and later-generation drug-eluting stents versus second-generation DEBs alone.

2.2. INVESTIGATORS AND ADMINISTRATIVE MANAGEMENT:

Sponsor: **ROBUST** is a physician-initiated study without financial support from companies

Coordinating research center: Department of Interventional Cardioangiology, I.M. Sechenov Moscow State Medical University (Sechenov University).

Principal coordinators:

Participating clinics:

- Scientific and Practical Center for Interventional Cardioangiology (NPCIC). **Principal Investigator:**
- Center for Endosurgery and Lithotripsy (CELT Clinic). **Principal Investigator:**
- Cardiac Surgery Clinic of the Amur State Medical Academy. **Principal Investigator:**
- Moscow Regional Research and Clinical Institute (MONIKI). **Principal Investigator –**
- Scientific and Clinical Center No. 2 Russian Research Center of Surgery. **Principal Investigator –**
- State Institution of the Rostov Region, Consultative and Diagnostic Center. **Principal Investigator:**.
- Central Clinical Hospital "RZD-Medicine". **Principal Investigator:**.

Data monitoring committee:

Data Monitoring and Protocol Compliance Committee –

Core (central) angiographic laboratory:

Scientific and Practical Center for Interventional Cardioangiology (NPCIC)

Adverse Event Evaluation Committee:

Center for Endosurgery and Lithotripsy (CELT Clinic)

Integration, data analysis and biostatistics:

2.3. PROTOCOL MANAGEMENT

The coordinating site (Department of Interventional Cardioangiology, Moscow State Medical University (Sechenov University)) and the principal investigators are responsible for preparing the final version of the protocol, the eCRF layout, and registering the study on the ***clinicaltrials.gov*** portal. The coordinating site and principal investigators will make corrections in the protocol if necessary and inform all principal investigators. These corrections may be accepted upon consensus among the principal investigators of the participating clinics. Principal investigators will coordinate the conduct of the study at all study sites, monitor study quality, and prepare publications.

An independent central angiographic laboratory, as well as an independent adverse event evaluation committee, will be established. The monitoring committee, together with the biostatistics expert, will oversee data collection, perform data interpretation and statistical analysis, supervise randomization, and support the performance of the eCRF.

An independent ethics committee will evaluate patient safety throughout the entire study.

2.4. STUDY AIM AND DESIGN: The aim of the study is to demonstrate the safety and efficacy (non-inferiority) of using drug-eluting balloons (DEBs) alone for the endovascular treatment of coronary bifurcation lesions in patients with CCS, compared with standard of care stenting techniques (provisional or two-stent strategy).

To address this objective, a multicenter, randomized controlled study with a non-inferiority design based on the primary clinical endpoint is planned. A non-inferiority design assumes that the primary endpoint rate in the experimental group is no less than the non-inferiority margin. The non-inferiority margin for the primary endpoint was calculated based on literature data and set at 4.7% for the comparison group undergoing bifurcation stenting[1,2,4].

The clinical site leading and organizing the study (core laboratory) is Scientific and Practical Center for Interventional Cardioangiology (NPCIC).

2.5. HYPOTHESIS: The use of drug-eluting balloons for the PCI of coronary bifurcation lesion in patients with CCS has been shown to be at least as effective and safe as currently accepted stenting techniques for treating these lesions. The effect will be assessed by measuring the difference in the rate of adverse events (MACE – Major Adverse Cardiac Events) between patients randomized to the drug-eluting balloon group and those randomized to the stenting group.

The null hypothesis states that the risk difference (R_1–R_0) between arms is greater than or equal to the non-inferiority margin of 4.7%. The alternative hypothesis is that the difference in adverse events between the groups will be less than 4.7%. The null hypothesis of no less efficacy of drug-eluting balloons compared with drug-eluting stents will be rejected if the upper limit of the 95% confidence interval for the risk difference (R_1–R_0) is less than 4.7%.

2.6. STUDY DESIGN: A simple, randomized, prospective, open-label, multicenter study including patients with chronic coronary syndrome and coronary bifurcation lesions (excluding the left main coronary artery), for whom percutaneous coronary intervention (PCI) is indicated, either with or without stenting.

Patients will undergo elective PCI according to current standards and recommendations for bifurcation stenting, and using drug-eluting balloons without stenting (stenting for only bail-out indications) under 1:1 randomization, comparing second- and later-generation drug-eluting stents with second-generation sirolimus-coated balloons. The use of intravascular imaging techniques (IVUS, OCT) during the index PCI is strongly encouraged but left to the operator’s discretion. The follow-up results will be assessed at 12 months after initial procedure.

At the 12-month follow-up, all patients will undergo follow-up coronary angiography for qualitative angiographic analysis, as well as non-invasive assessment of the patient's clinical status.

The overall observation period is 12 months, although further follow-up of patients beyond this

study is possible.

2.7. STUDY DESIGN AND PATIENT ENROLLMENT: ROBUST is a open label, multicenter, prospective, randomized, non-inferiority study including patients with chronic coronary syndrome and bifurcation lesions of epicardial coronary arteries, or their large branches (excluding the left main coronary artery) who are referred for PCI and stenting in routine clinical practice. Patients aged over 18 years who have signed informed consent and have a “true” bifurcation lesion of an epicardial artery or its large branch (diameter ≥ 2.5 mm and ≤ 4.5 mm with stenosis >50%) requiring PCI and/or implantation of a second- or later-generation drug-eluting stent will be included in the study.

Patients were included without restrictions on number of stents implanted, the number of target bifurcation lesions per patient (if meet the inclusion criteria), or the number of drug-eluting balloons used. One of the few study restrictions is that only patients with chronic coronary syndrome should enrolled in the study. The study must be approved by local ethics committees at each participating center. All patients must sign an informed consent with detailed steps of the PCI procedure, the characteristics of the devices used, potential risks, and expected outcomes.

The study flowchart is presented in Figure 1:

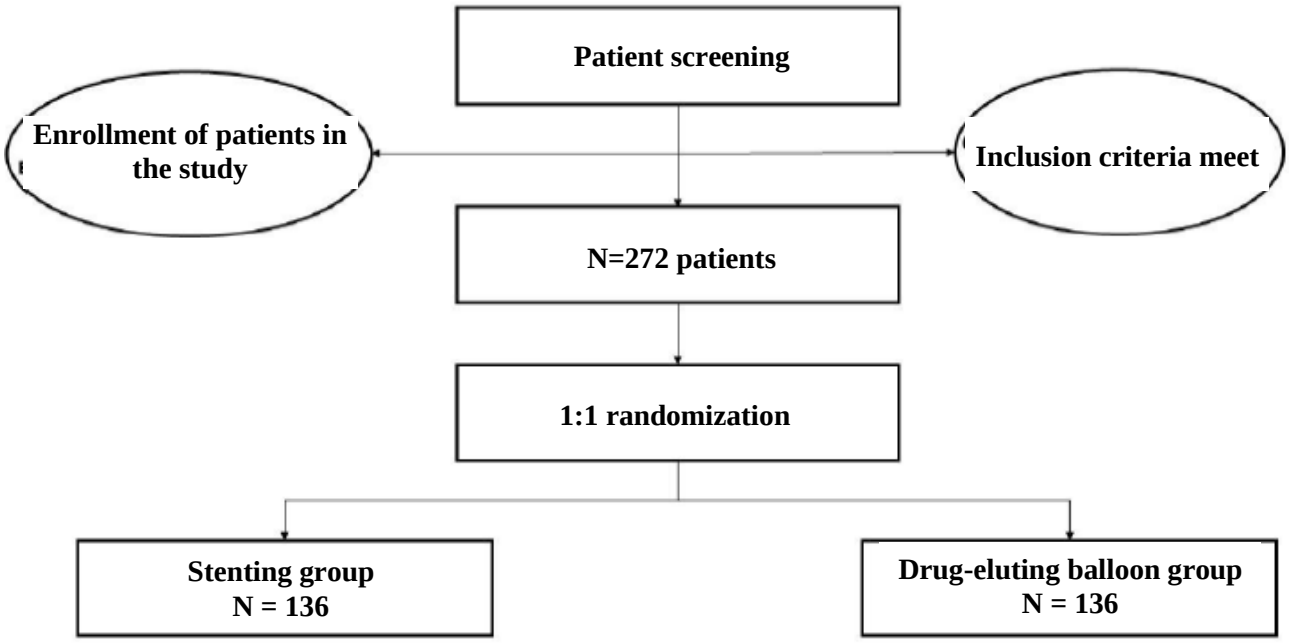

Fig. 1: Patient inclusion and randomization scheme

According to the patient inclusion scheme for the study (Fig. 1), **the selection criteria** for enrollment are:

- Patients of both sexes
- Age over 18 years
- Signed informed consent
- Life expectancy > 1 year
- Stable angina pectoris (angina class I-III according to CCS)

The patient **non-selection/exclusion criteria** are:

- Age >80 years
- Pregnancy, breastfeeding
- Patients not adherent to taking antiplatelet/anticoagulants and/or statins
- Severe comorbidity (including cancer) requiring major non-cardiac surgery within a year
- Anemia (hemoglobin level < 10 g/dL)
- Thrombocytopenia and/or any coagulopathy (including hereditary)
- Signs of ongoing bleeding
- Clinical symptoms or data indicating chronic heart failure II-IV according to NYHA at the time of selection for inclusion in the study
- Hospitalization for CHF within the last year

- History of CABG
- Acute coronary syndrome
- LV ejection fraction according to echocardiography ≤ 0.4
- Chronic renal failure (glomerular filtration rate less than 30 mL/min (according to Cockcroft-Gault)

Upon selection of patients according to the above criteria, the patient's baseline coronary angiogram should be evaluated for compliance with the inclusion and non-inclusion criteria.

Patient withdrawal from the study:

A patient may withdraw from the study at any time for any reason. However, their data may be used for statistical analysis. Furthermore, patient data may be excluded from the study if inappropriate inclusion is detected. The study may also be terminated if the Coordinating Study Site (CSS), the Department of Interventional Cardioangiology at I.M. Sechenov Moscow State Medical University (Sechenov University), receives corresponding recommendations from the independent ethics committee. Patient selection and inclusion in the study will occur during hospitalization (possibly within the first 24 hours, but not exceeding 7 days).

2.8. RATIONALE OF THE STUDY: Bifurcation studies relate to complex coronary lesions, endovascular treatment of which is associated with an increased risk of acute and delayed major cardiac complications, thrombosis, and restenosis in the main and/or side branch. The major challenges in the current treatment of PCI of bifurcation lesions are related to:

- non-optimal stenting techniques
- disruption of the geometry and anatomy of the artery at the bifurcation area (carina shifting)
- high restenosis rate at the side branch ostium, especially when a two-stent strategy was used (≈ 10-15%)[3]
- an increased risk of thrombosis and major cardiac complications – ≈ 5 % and ≈ 20%, respectively, according to world literature[5].
- significant treatment challenges in the follow-up period in cases of restenosis and/or in-stent occlusion.

Over the past decade, there has been a significant improvement in the outcomes of endovascular treatment of bifurcation lesions, primarily due to technological advances in instrumentation, intravascular visualization, operators growing experience and rigorous research in numerous randomized or registry studies. However, challenges persist, which are associated with the permanent implant – a foreign body within the arterial lumen (particularly a stent), which, on the one hand,

disrupts the natural geometry of the artery, associated to endothelial disfunction and, on the other, triggered chronic inflammation and resulted in acute and late complications (thrombosis, restenosis).

The recent advancement in drug-eluting balloon technology has revived interest among researchers in "metal-free" (or "less-metal") PCI. Data on the use of drug-eluting balloons in bifurcation lesions are scarce, and data from studies on metal-free PCI of bifurcation lesions are limited. Presumably, the PCI of bifurcation lesions using only drug-eluting balloons could potentially offer the following advantages:

- They do not disrupt the natural anatomy and geometry of the arterial bifurcation (no carina shifting)
- They do not impair endothelial function and preserved vasomotor activity
- There is no trigger for chronic inflammation (foreign metal body), which theoretically helps to reduce the rate of late thrombosis and restenosis

These potential benefits may translate into long-term clinical benefits reducing risk of major cardiac events (MACE), thrombosis, and restenosis. The **ROBUST** study aims to investigate the acute and long-term outcomes of PCI of bifurcation lesion using only drug-eluting balloons without stenting in comparison with currently adopted bifurcation stenting techniques, to prove the potential advantages of drug-eluting balloons in real clinical practice.

2.9. CHARACTERISTICS OF THE INVESTIGATIONAL DEVICES AND PERCUTANEOUS CORONARY INTERVENTION:

2.9.1 Sirolimus-coated drug-eluting balloon

A sirolimus-coated drug-eluting balloon SELUTION SLR™ (Cordis) is proposed as a test (experimental) instrument. The second-generation drug-eluting balloon technology provides controlled, measured, and reliable drug release for 60-90 days[6], which is comparable to the best-in-class second- and higher-generation metal drug-eluting stents coated with limus-family drugs[7]. Micro-reservoir technology (a blend of the biodegradable polymer PLGA with sirolimus) enables slow and controlled drug release synchronized with the biodegradation of the PLGA polymer. Cell Adhesion Technology (CAT technology) allows the micro-reservoirs to be secured on the balloon surface, preventing mechanical damage to the coating and avoiding drug loss during balloon delivery to the target site. The drug concentration is 1.0 μg/mm². The size range includes balloon diameters from 1.5 to 5.0 mm and balloon lengths from 10 to 40 mm. The manufacturer of the drug-eluting balloons is Cordis.

Second- and later-generation drug-eluting stents coated with limus-family drugs (sirolimus, everolimus, and biolimus) are being considered as a control (competitor) device. Implantation of the drug-eluting stents is performed using previously adopted bifurcation lesion stenting techniques

(single- or two-stent technique, with provisional stenting being preferred).

All information regarding the use of drug-eluting balloons, as well as deviations from the accepted protocol procedure, will be recorded in the primary documentation and electronic database.

2.9.2. Periprocedural medical therapy

All patients participating in the study should start receiving acetylsalicylic acid (aspirin) at a dose of 100 mg per day in combination with P_2Y_{12} platelet receptor inhibitors (clopidogrel) 75 mg per day at least three days before the scheduled procedure. Since the study includes patients with chronic coronary syndrome (CCS), the use of other more potent drugs (ticagrelor, prasugrel) should be justified. Patients with anemia (< 10 g/dL) and high bleeding risk (according to the PRECISE-DAPT score) should not include in the study. Anyway, the dosage and type of drugs prescribed within the framework of the DAPT remain at the discretion of the researchers in accordance with the local practice of the institution.

Patients who have not previously received 75 mg of clopidogrel for 7 days are prescribed 300-600 mg of clopidogrel (the dose is at the discretion of the physician) or 180 mg of ticagrelor as a loading dose before the index procedure.

Intraoperative anticoagulation will be achieved by administering unfractionated heparin at a dose of 70 to 100 U per kilogram of body weight. During the procedure Activated Clotting Time (ACT) obtained by portable ACT monitor device should be held at a level of more than 250 sec.

Use of IIb/IIIa receptor inhibitors are at the discretion of the operator. All patients will be prescribed DAPT, including aspirin at a dose 100 mg and clopidogrel at a dose of at least 75 mg or ticagrelor 90 mg twice daily after discharge for at least 6 months for stenting group and 1 months for DEB group of patients. Concomitant therapy is at the discretion of the physician.

All information regarding the type of drug therapy, its duration, as well as various types of deviations associated with the prescription of drug therapy, will be recorded in the electronic patient database.

2.9.3. Methods of randomization and allocation of patients into groups

Randomization will be performed using an electronic interactive system **BEFORE BALLOON PREDILATATION OR LESION PREPARATION (!).** If the patient meets the inclusion criteria and informed consent is obtained, the investigator logs into the system, where a unique patient identification number is recorded. At this point, the patient will be considered for enrolling in the study. But finally, after coronary angiography data is analyzed in the central (core) laboratory and if the inclusion criteria are met and exclusion criteria are absent, the investigator logs back into the system and randomizes the patient into one of the groups. Simultaneous randomization with other investigators is blocked by the system. At this point, the patient will be enrolled in the study.

Patients will be randomized in a 1:1 ratio to the drug-eluting balloon group and the stent group, respectively. If, after screening and analysis of coronary angiography data, a patient fails to meet the inclusion criteria and/or if meets exclusion criteria, the patient will be considered unsuccessfully screened and will not be included in the study. Follow-up will continue until discharge from the hospital. If an enrolled patient drops out at any stage of follow-up, their data will be included in the final analysis as ITT data.

First, it is necessary to determine whether the patient meets the eligibility criteria, which requires a questionnaire, physical examination, and diagnostic testing. The following procedures should be done: collection of medical history and medication history, laboratory test results, and assessment of physical status.

The informed consent should be signed in duplicate. One copy should be given to the patient participating in the study, and the other should be included in the investigator's file. The patient will be given sufficient time to review the informed consent and the opportunity to ask the investigator questions.

All data should be recorded in the primary documentation. Once all data is received and there is concordance with the inclusion criteria, the patient can be enrolled in the study. The system will assign a unique patient identification number. This unique numerical code will then be supplemented with additional numerical values reflecting the patient's individual characteristics and facilitating identification by the investigator, if necessary. The final unique code should be entered into the patient's file, as well as on a separate code sheet, which should be maintained on file at the site. Subsequently, if the patient meets the inclusion criteria and there were no exclusion criteria, randomization will be performed.

2.9.4. Transfer and analysis of angiographic data in the central (core) laboratory

Coronary angiography data from patients participating in the study should be send to a central (core) angiography laboratory. The central angiography laboratory will be established at the Scientific and Practical Center for Interventional Cardioangiology (NPCIC). Patient data must be blinded before transfer: patient information must contain only a unique identification number. Transfer will be performed in **DICOM** format by mail no later than 3 days from the date of coronary angiography.

To reduce the potential for bias in the interpretation of acute and long-term outcomes, as well as symptoms and signs, in patient management, which occurs when treatment is known in advance, this study **blinds** patients and the investigational devices to other investigators and to the patients. In this study, patient identification is not disclosed to other investigators until the end of the study.

2.9.5. Patient preparation before PCI

a. ***evaluation of the baseline clinical status:*** angina class, comorbidities, and the Frailty Index (if necessary), adherence to the treatment, medical history and previous treatments (discharge

summary from other healthcare facilities), peripheral pulse (on the radial arteries). Evaluation of patient compliance with the inclusion criteria for the study.

b. Laboratory tests:

Blood samples are collected upon admission before the target procedure (before inclusion in the study and informed consent). Laboratory tests and ECGs performed within 14 days prior to inclusion may be used for evaluation.

Complete blood count: red blood cell count, hemoglobin, platelet count, hematocrit, white blood cell count, lymphocyte count, C-reactive protein, ESR.

Blood chemistry: ALT, AST, total cholesterol (lipid profile), glucose, creatinine, CPK, CPK-MB or hs-Troponin I (preferred).

General examination and evaluation of general condition, symptoms (angina assessment using the SAQ questionnaire may be used), vital signs, height, weight, risk factors (hypertension, smoking), previous cardiovascular events, ECG, echocardiography, stress tests (if performed previously).

c. Myocardial necrosis biomarkers:

Samples of myocardial necrosis biomarkers will be collected and analyzed in a local laboratory according to established practices. All test results should be saved in the patient's medical record.

The following myocardial necrosis biomarkers may be applicable in this study:

- High sensitivity (hs) Troponin I
- CPK-MB

d. Pharmacological preparation:

Patients may take medications for comorbidities (e.g., diabetes) unless this conflicts with the patient's inclusion criteria. If there are signs and a diagnosis of chronic renal failure (decreased glomerular filtration rate), the patient should be hydrated according to the established regimen to reduce the risk of postoperative acute kidney injury (contrast-induced nephropathy, CIN).

All patients should receive dual antiplatelet therapy (DAPT) for at least 3 days (72 hours) prior to the scheduled PCI procedure. The choice of standard or potentiated (prasugrel, ticagrelor) DAPT is determined by local consensus of the treating physician and investigator. Triple therapy (anticoagulants + DAPT) is determined based on indications for the treatment of the patient’s concomitant diseases (for example, atrial fibrillation).

2.9.6. Coronary angiography procedure

The coronary angiography procedure should be performed taking into account the following conditions:

1. Before obtaining cine coronary angiograms, it is necessary to administer intracoronary 150-200 mcg of nitroglycerin (if central hemodynamic conditions allow).
2. Visualization of the target lesion should be performed in two orthogonal projections, where in

one of these projections the lesion will be fixed without foreshortening, with visualization of the distal segments of the branches involved in the lesion.

3. Cine coronary arteriography should be performed until the appearance of the venous phase (however many heartbeats are required).
4. When registered cine coronary angiograms, it is necessary to ensure that the tip of the catheter is located in the field of view to perform quantitative computed coronary angiography (QCA). It is necessary to visualize the catheter without filling it with contrast agent before start of cine angiography (there is no contrast agent in the catheter lumen before start of filming).
5. It is mandatory to obtain quantitative coronary angiography (QCA) before, immediately after, and 12 months later during follow-up coronary angiography. All native coronary angiograms in DICOM format, as well as those with quantitative data calculations (QCA), should be sent to the central core laboratory no later than three days after procedure completion.
6. Visualization of the coronary arteries should be “tight”, so it is necessary to use a sufficient amount and pressure for injection of contrast media (by hand or using a syringe injector).
7. All data should be documented in DICOM format. It is permissible to use coronary angiography data for 60 days prior to inclusion in the study (randomization is performed before PCI). However, previously performed coronary angiography should meet all the requirements described above in paragraphs 1-6.
8. Follow-up coronary angiography after 12 months should be performed used the same angulated projections as those used during the final imaging of the index PCI.

2.9.7. PCI procedure

Patients should be referred for PCI with a previously identified, hemodynamically significant target bifurcation lesion in a main coronary artery (or large secondary branches) that meets the anatomical inclusion criteria. A planned multistage procedure (PCI of other arteries) is not a contraindication to patient inclusion. The choice of access artery, guidewire types, and balloon catheters is at the discretion of the operator.

1. Preparation (predilation, atheroablation) of the lesion before using drug-eluting balloons

Predilation or preparation of the lesion is **a mandatory (!)** step in performing the procedure when using drug-eluting balloons. It is performed using balloons of a 1:1 diameter, matching the reference diameter of the arteries (main and side branch) involved in the target lesion. Predilation using balloons of the appropriate diameter is performed sequentially in the main and side branches. The use of the "kissing balloon" technique for predilation **is NOT ALLOWED!**

In case of stenting of the target lesion, direct stenting without predilation of either the main branch or the ostium of the side branch is permitted according to indications and at the discretion of the

operator.

The reference diameter of balloons for predilation is determined distal to the lesion, both in the main (parent) and in the side branch, using quantitative computed tomography (QCA) and/or intravascular imaging after **intracoronary administration of 200 mcg nitroglycerin.**

Optimal balloon predilation should meet the following conditions:

1. The balloon should be fully inflated, without any “constrictions” (filled with contrast agent) under the nominal pressure (defined by manufacturer and printed on the balloon catheter packaging) when it reaches the prespecified diameter.
2. After predilation, residual stenosis should be ≤ 30% as assessed visually (“eyeball”).
3. Antegrade blood flow should be at least TIMI III (according to the classification of Thrombolysis in Myocardial Infarction).
4. No antegrade blood flow limitimg dissection (type A-B according to the NHLBI classification).

The **length** of the drug-eluting **balloon** is selected taking into account the recommendation for complete coverage of the prepared segment (using atheroablation or balloon predilation), including 2-3 mm proximally and distally (the length of the drug-coated balloon should be 5-10 mm longer than the length of the predilation balloon).

The balloon inflation time required to ensure optimal and complete drug delivery to the vascular wall varies and is typically **30-60 seconds**, depending on the manufacturer's recommendations. However, balloon inflation time may depend on specific PCI parameters (the degree of ischemia during balloon inflation, cardiac arrhythmia, and deterioration of central hemodynamics). Anyway, the recommended inflation time (30-60 seconds) should be followed, but hemodynamic and ECG parameters should be taken into account first and foremost during balloon inflation.

When using intravascular imaging, it is necessary to perform a pullback in both the main (parent) and side branches. If the degree of the lesion does not allow for intravascular imaging, predilation with a smaller-diameter balloon (e.g., 2.0 mm) may be used to pass through the intravascular imaging transducer. Predilation is performed using the nominal pressure corresponding to the specified balloon diameter and specified in the manufacturer's table on the balloon catheter packaging. All cases of intravascular imaging (IVUS, OCT) and physiology should be sent to the central core laboratory for evaluation of the results and reviewed by the monitoring committee to assess the results (measurements) and the methodology for performing the intravascular examination.

In case of calcification or eccentric massive plaque in the area of target lesion, the operator could make a decision regarding use of atheroablation techniques (rotor) or special balloon catheters (cutting balloon, high-pressure non-compliant balloon). The decision to use these additional instruments is left entirely to the operator's discretion.

After predilation, the result of lesion preparation should assessed for the presence of residual

stenosis, dissection (type A-F according to the NHLBI classification) and blood flow (according to the TIMI classification) (Fig. 2). If intravascular imaging is used, the minimum cross-sectional area, the degree of residual stenosis, the presence and type of dissection, and the residual plaque mass (volume) are also assessed.

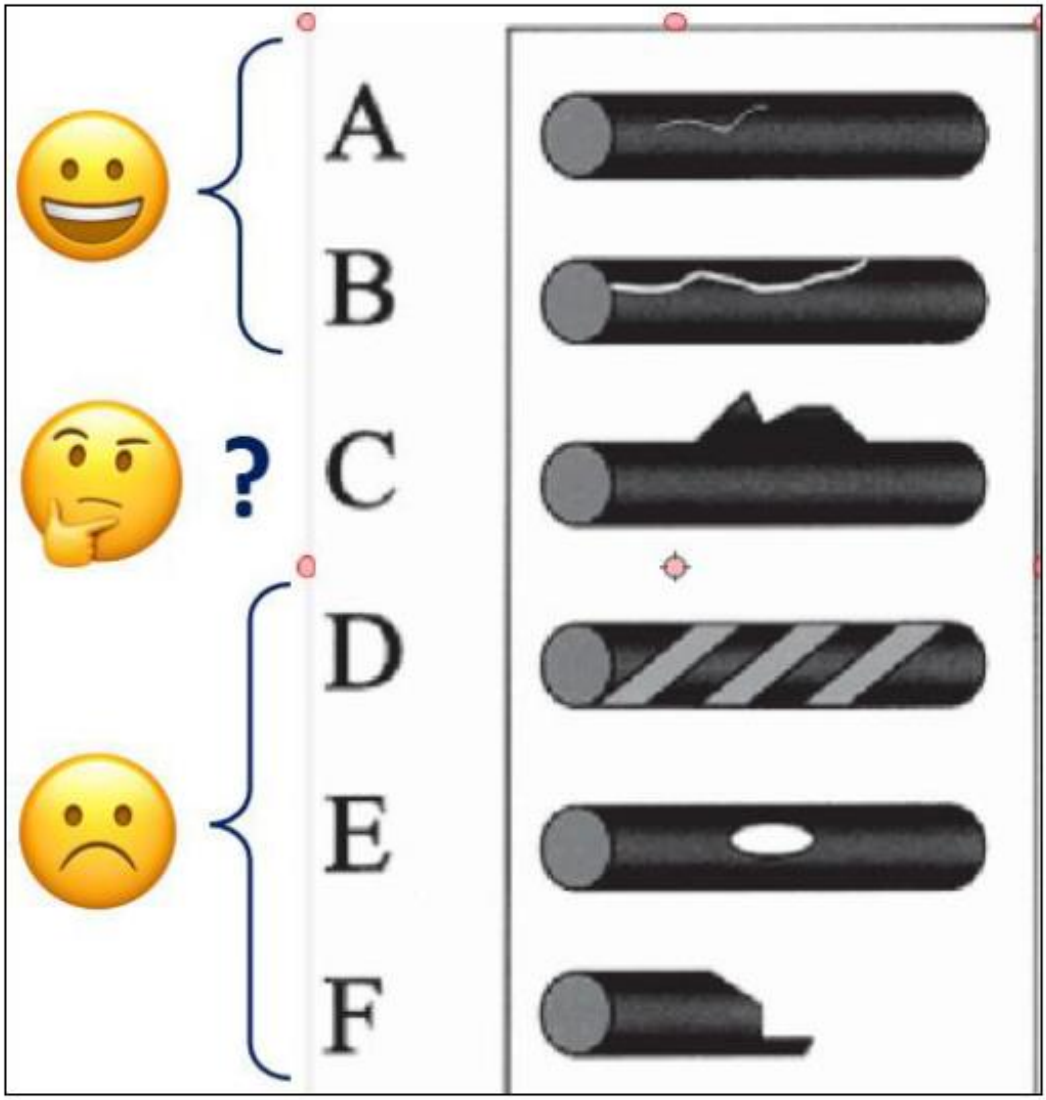

Fig. 2. Types of dissections after balloon angioplasty according to the NHLBI classification[9]:

Type A – minor "luminal haziness" within the dilated segment without impairment of blood flow (TIMI III)

Type B – a sign of "parallel" double lumen without retention of contrast agent at the dilation site after contrast washout (complete clearing of the dilated segment)

Type C – contrast extravasation beyond the arterial lumen, persisting after contrast washout

Type D – "spiral" dissection with the formation of a false channel with a delay in contrast throughout the entire segment of balloon dilation with a delay in the washout of the contrast

agent (TIMI <3)

Type E – a contrast defect within the dilated segment that was not observed before balloon dilation

Type F – inversion of the intimal-medial flap into the arterial lumen with complete occlusion of the lumen without antegrade blood flow (TIMI 0).

In case of significant residual stenosis (>30%), the operator may decide to perform additional preparation of the target lesion (high-pressure non-expandable balloon, cutting balloon, atheroablation) before using the drug-eluting balloon to reduce residual stenosis and/or recoil.

Since there are currently no criteria of intravascular imaging and physiology for evaluation of the optimal outcome after usage of a drug-eluting balloon, the final PCI outcome, in addition to intravascular imaging and physiology data, visual assessment (residual stenosis degree, TIMI 0-III blood flow) should be done using quantitative coronary angiography (QCA). According to the results of previous studies, the optimal PCI outcome is considered to be a residual stenosis degree of <30 % after drug-eluting balloon use and <10% after drug-coated stent implantation.[10]

Stenting can be used both in case of suboptimal outcome after balloon predilation (antegrade blood flow-limiting dissection) and as an emergency procedure ("bailout") after the use of a drug-eluting balloon.

2. *Implantation of stent(s) and use of drug-eluting balloons after predilation*

Following predilation and adequate lesion preparation, the final stage of PCI is the use of drug-eluting balloons or stents. The diameter of the drug-eluting balloons (stents) is determined based on the reference diameter of the main and side branches (5 mm distal to the distal lesion point in both arteries). The choice of stenting technique is at the operator's discretion, depending on the baseline anatomy of the bifurcation lesion and the results of predilation. Provisional stenting is the preferred technique; however, if necessary, a two-stent technique is permitted (the type of two-stent strategy is at the operator's discretion). Both provisional and two-stent strategies should be completed with the final kissing balloon (FKB) technique and proximal optimization (POT), as adopted by the consensus documents of the European Bifurcation Club[11]. In case of provisional stenting using the kissing balloon technique, a drug-eluting balloon of appropriate diameter (1:1 to reference diameter) should be used in the side branch, since previous studies have shown the benefit of inflating a drug-eluting balloon in the side branch to reduce the rate of MACE and restenosis at the side branch ostium in the follow-up period[12,13].

Since no radiopaque markers are used to define treated segment during angioplasty by drug-eluting balloon (unlike stenting), the proximal and distal positions of the inflated DEB (and,

consequently, the drug delivery segment) **SHOULD BE DOCUMENTED** by cine angiography. This is important for evaluation of the long-term angiographic outcome in the balloon dilation segment.

In case of using drug-eluting balloons, their diameter is selected at a 1:1 ratio to the reference diameter of both the main and side branches. As the final stage of stentless PCI of the target bifurcation lesion using drug-eluting balloons, the “mini-kissing” technique should be used (Fig. 3).

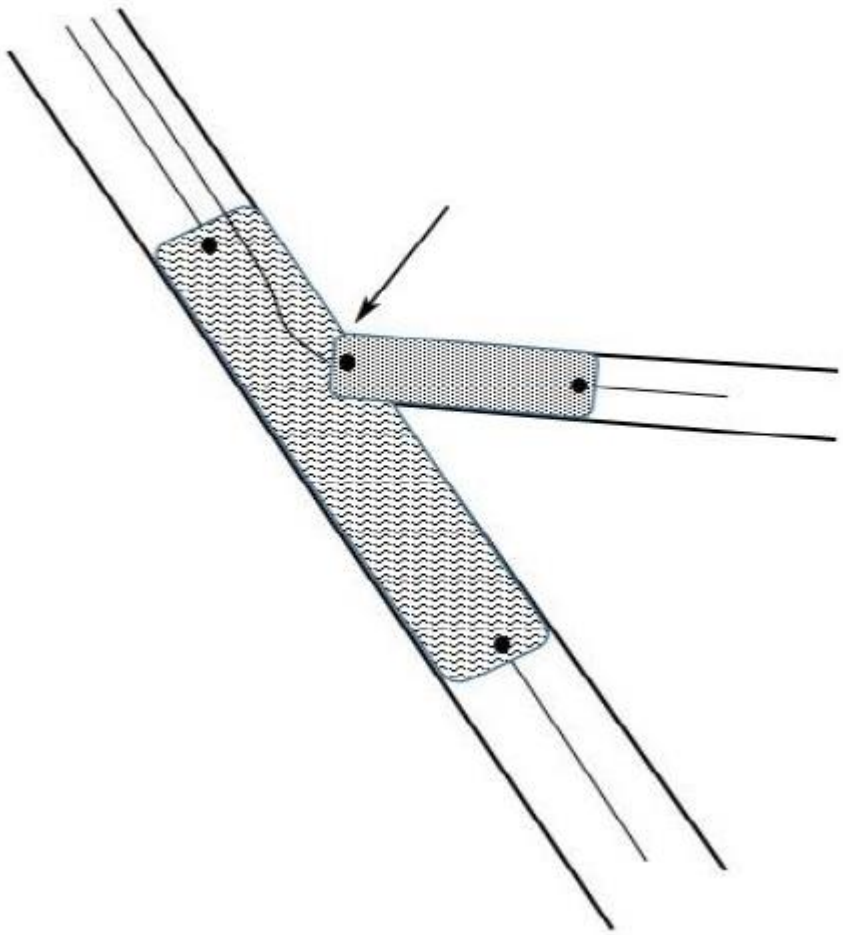

Fig. 3: Schematic representation of the final "mini-kissing" technique using drug-eluting balloons. To minimize balloon catheter protrusion from the side to the main branch, the proximal balloon marker in the side branch is positioned at the superior junction point (opposite the carina) of the main and side branch (indicated by arrow).

The FKB with drug-eluting balloons, shown in Fig. 3, is aimed to minimize mechanical trauma of the main artery and reduce the risk of flow-limiting dissection of the vessel wall. The drug-eluting balloon covers the superior junction of the side branch with the main artery (opposite the carina). Therefore, drug is interacted with whole circumference of the side branch ostium. The inflation pressure of the balloons is determined by the diameter/pressure relation table, according to the balloon manufacturer's data.

In case of unsatisfactory (complicated) outcome of the “mini-kissing” technique using drug-

eluting balloons, it is necessary to switch to stenting (the type and strategy of stenting remains at the discretion of the operator) (Fig. 4).

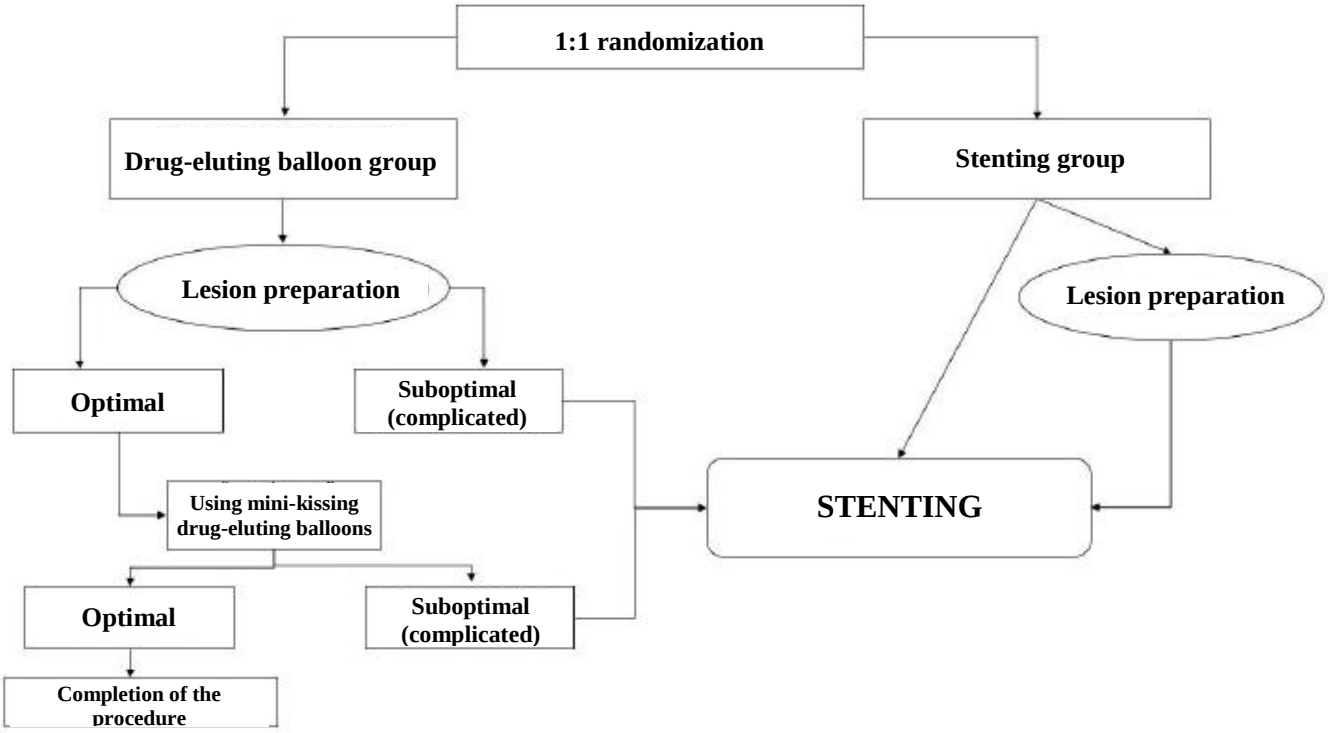

Fig. 4: Schematic representation of PCI stages in patient groups after randomization

An angiographic result obtained after lesion preparation or "mini-kissing" technique using drug-eluting balloons can be considered unsatisfactory (complicated), if it has the following characteristics:

- type C-F dissection according to the NHLBI classification[14].
- residual stenosis >30% according to QCA or intravascular imaging
- antegrade blood flow < TIMI III or FFR <0.8 (or noninvasive indexes <0.89).

If intravascular visualization use, the result can be considered unsatisfactory (complicated), if the following characteristics appeared:

- residual stenosis > 30%
- minimum cross-sectional area (CSA) < 70% of the reference CSA in the distal segment
- presence of dissection extended to the medial layer and >30% of the lumen circumference.

When physiology is used, the result of fractional blood flow reserve after hyperemic tests <0.8 and resting indices <0.89 can be considered as suboptimal.

If suboptimal (or complicated) immediate result is detected, emergency (bailout) stenting should be done using one of the recommended bifurcation stenting techniques. Such cases of emergency

stenting will be included in the "intention-to-treat" analysis.

The end of the procedure is determined by the time of removal of the guiding catheter. All stages of the PCI procedure should be carefully described and recorded in the corresponding fields of the electronic database (eCRF).

3. Evaluation of the final outcome

The final outcome (as well as intermediate ones) can be assessed angiographically (by "eyeball" or using QCA) or intravascular examination techniques (IVUS, OCT, physiology). The criteria described above are used to assess the angiographic result. Widely accepted IVUS or OCT criteria known from the literature are used to assess the immediate results after stent implantation [15] (Fig. 5).

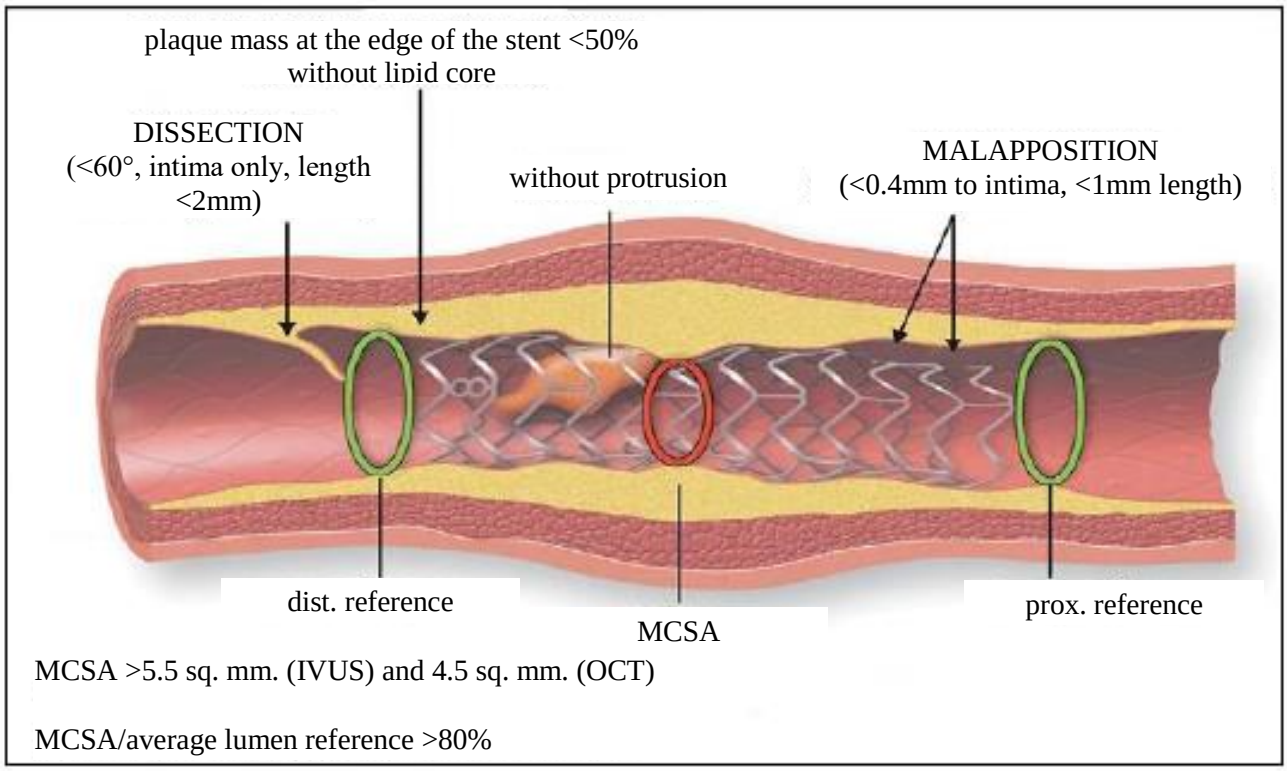

Fig. 5: Optimal stenting criteria based on intravascular imaging (IVUS, OCT). MCSA – minimum cross-sectional area.

Average reference = prox.reference + dist.reference/2

Currently, there are no clear intravascular imaging criteria for evaluation of immediate results after DEB angioplasty. However, IVUS and OCT can be useful option in angiographically indetermined cases. For example, Intravascular imaging could determine the extent of dissection and exact geometric parameters of the final lumen of both the main artery and the side branch.

In the case of using intravascular technique for evaluation of blood flow physiology, the result of FFR **≥ 0.8**[9] and resting indices **≥ 0.90** can be considered as satisfactory.

The immediate success (outcome) of PCI using DEB is assessed at patient discharge and

includes the following:

1. Successful use of the instrument (uncomplicated delivery of the balloon without significant resistance to the target lesion in <2 min, full balloon deployment under nominal pressure in 30-60 sec, easy uncomplicated removal without damage of the delivery system, residual stenosis in the dilation segment <30% with verification in the central (core) laboratory using quantitative coronary angiography (QCA)).
2. Absence of antegrade flow-limiting dissection (type C-F) and emergency stenting.
3. Absence of MACEs (cardiac death, periprocedural MI, repeat target lesion revascularization during index hospitalization, stroke, BARC bleeding 3 or 5 regardless of which PCI strategy was used).

The immediate success (outcome) of PCI using a drug-eluting stent is assessed at patient discharge and includes the following criteria:

1. Successful use of the instrument (uncomplicated delivery of the stent the target lesion in <2 min, full balloon/stent deployment under nominal pressure and, if necessary, additional successful post-dilation using a non-compliant balloon, without rupture of the balloon catheter and its unhindered removal (without damage of the delivery system). Final residual stenosis in the stented segment <10%, verified in a central (core) laboratory using quantitative coronary angiography (QCA)).
2. Absence of MACEs (cardiac death, periprocedural MI, repeat target lesion revascularization during index hospitalization, stroke, BARC bleeding 3 or 5 regardless of which PCI strategy was used).

4. Periprocedural pharmacotherapy for PCI

Before PCI, if necessary, premedication is administered to relieve or soften the patient's severe emotional state or anxiety. Typically, after puncture of the access artery and insertion of the sheath, unfractionated heparin is administered intravenously or directly through the sheath at a dose of 70-100 U/kg. If arrhythmia, hemodynamic disturbances or coronary artery spasm appeared, appropriate symptomatic therapy should be used. Any allergic reactions and adverse events associated with medications should be recorded in the adverse events reporting section of the electronic database. Platelet glycoprotein IIb / IIIa receptor blockers are used according to indications and at the discretion of the operator.

5. Postoperative follow-up period

In the intensive care unit after PCI, standard guideline directed medical therapy is delivered according to local practice. Monitoring of vital functions, identification and recording of adverse

events, registration of postoperative ECG (at least twice – immediate after PCI and at discharge), hs-troponin I, as well as other laboratory tests are mandatory, according to the table PRIMARY PROCEDURES AND STUDY TIMELINES shown in section 1.2..

In the post-discharge period, patients' condition will be assessed by outpatient visits or telephone contacts at 1, 6, and 12 months (±1 week). **Dual antiplatelet therapy (DAPT) is prescribed for 1 month in patients after the use of drug-eluting balloons[9] and for 12 months after stenting.** Standard or potent DAPT left at the discretion of the operator. **DAPT escalation/de-escalation is also at the discretion of the investigators, taking into account the clinical presentation and the nuances of the procedure. Triple therapy (anticoagulation+DAPT) is also at the discretion of the operator, taking into account the clinical presentation.**

By 12 months of follow-up (±1 week), all patients **in both groups should undergo control coronary angiography**. (See directions for performing coronary angiography in section 2.9.6. Coronary angiography.) When performing control coronary angiography, it is recommended to use parameters similar to those used for the index PCI (magnification, projection). After obtaining the appropriate quality of angiograms (see 2.9.6. Coronary angiography procedure), quantitative coronary image processing (QCA) should be performed.

On control coronary angiography, binary restenosis is assessed as >50% of the reference arterial diameter either within the stent (or in a segment dilated with a drug-eluting balloon) or at a distance of 5 mm from the stent edges. Restenosis at the side branch ostium is assessed similarly – i.e. > 50% diameter stenosis inside the distance of 10 mm from the side branch ostium (in case of provisional stenting or mini-kissing using drug-eluting balloons). In case of initial two stent strategy diameter stenosis > 50% of the side branch reference diameter at a distance of 10 mm from the stent edge in the side branch should be considered as a side branch restenosis.

Thrombosis of the treated segment (intra-stent or intra-balloon dilation segment) is assessed according to ARC Consortium on stent thrombosis and breaks up into three categories: definite, probable and possible[16]. Thereof, according to the timing of the thrombosis occurrence, acute (0-24 hours), subacute (within 30 days after discharge) and late (> 30 days after discharge) thrombosis is distinguished.

3.0. REQUIRED LEVEL OF EXPERTISE FOR STUDY PHYSICIANS

Physicians whose experience in endovascular treatment (stenting) of bifurcation lesions exceeds 70 procedures are eligible to participate in the study.

4.0. COLLECTION AND STORAGE OF RAW DATA

All data recorded in the study database require primary documentation (e.g., patient history,

ECG printout, laboratory reports, surgical protocol, coronary angiography and PCI procedure (on CD) or DVD. All data (copies) should be stored in the study patient's file. In the event of early withdrawal (up to 12 months) of a patient from the study for any reason, all data on treatment outcomes, adverse events, and medication should be saved. Any deviations from the protocol should be explained, and the reason should be specified in the database. Patients who do not meet the study participation criteria may be excluded after approval by the Project Directors.

5.0. EVALUATION OF STUDY ENDPOINTS

5.1. Composite primary endpoint -

It is a target lesion-related complication that occurs at 12 months of follow-up after the index PCI. It is defined as all-cause death, myocardial infarction (MI), and clinically-driven target vessel revascularization (TVR).

6.2. Secondary endpoint -

Target lesion-related – restenosis in target lesion (main, side branch) and thrombosis (definite, probable, possible according to the ARC definition),

Components of the primary endpoint - any repeat revascularization of the target vessel, cardiac death, any MI, bleeding 2-5 according to the BARC classification,

Parameters of the index PCI – procedure duration, radiation dose, amount of contrast media.

6.3. Other parameters to be evaluated -

The following parameters are to be evaluated using quantitative coronary angiography (QCA):

1. **Acute lumen gain** is the difference between the baseline and post-procedural values of the minimum lumen diameter (MLD)
2. **Net lumen gain** is the difference between the MLD value in the remote period (12 months) and its baseline value (pre-procedural)
3. **Late lumen loss** is the difference between the MLD value immediately after the procedure and in the long-term period (after 12 months)
4. **Change in the degree of stenosis** is the difference between the degree of stenosis in the treated segment immediately after the procedure and in the long-term period (after 12 months)

All quantitative coronary artery analysis (QCA) results in the target area will be obtained “in-stent” (in the balloon dilation area), including the 5 mm segment proximal and distal to the stent edge (balloon dilation) and throughout the entire “segment area” (as defined by the SYNTAX score coronary tree segmentation).

Thus, the angiographic endpoint should include the following:

- minimum lumen diameter, reference arterial diameter, percentage of stenosis – %DS (the

difference between the reference diameter of the vessel and minimum lumen diameter/reference vessel diameter x 100) and late lumen loss (the difference between the minimum diameter after the procedure and the long-term follow-up period).

- The rate of binary restenosis, defined as stenosis of 50% or more in the target lesion or segment at the angiographic follow-up period.

8.0. DEFINITION OF STUDY ENDPOINTS

Clinical endpoints will be evaluated according to the definitions below.

All-cause mortality **–** will be defined as an event for which the cause is unknown (unidentified death, death from unknown cause).

Myocardial infarction **–** diagnosis of myocardial infarction, as a component of a composite primary clinical endpoint, will be determined in the following cases:

- indications for hospitalization in other healthcare facilities with documented ECG data consistent with the development of AMI or with a new pathological Q wave in two or more ECG leads and/or indications of elevated levels of myocardial necrosis markers (creatine phosphokinase with MB fraction, high-sensitivity troponin I)
- with an increase in markers of myocardial damage (any concentration of creatine kinase above the upper limit of reference value along with an increased level of the MB fraction and/or an increase in the level of high-sensitivity troponin (hs-cTn) above the upper limit of the reference value in patients with normal baseline values (>99 percentile of the upper limit of the reference value), with or without a new pathological Q wave in two or more ECG leads, as well as taking into account clinical symptoms.
- in the absence of ECG data, Q Positive myocardial infarction is determined based on clinical data and an increase in myocardial necrosis markers.

Intraoperative (perioperative) myocardial infarction **–** defined as myocardial infarction associated with the PCI procedure (24-48 hours post-procedure) with the following characteristics:

- according to the definition by SCAI (Society for Cardiovascular Angiography and Interventions) perioperative MI is considered to be an absolute increase in the level of high-sensitivity cardiac Troponin (hs-cTn) ≥ 35 times the upper limit of the reference value (ULN) in combination with clinical and ECG symptoms of AMI or an absolute increase in the level of high-sensitivity troponin (hs-cTn) ≥ 70 times the upper limit of the reference value (ULN)[17].
- Additional signs may include: symptoms consistent with the development of myocardial infarction, or de novo ECG changes, or a de novo episode of complete left bundle branch block, or angiographic signs of coronary blood flow disturbances (no reflow, slow reflow) in main or side branch immediately after the PCI procedure

- De novo left bundle branch block, including cases where enzyme levels have not yet risen or where blood samples for specific cardiac markers in plasma have not been collected in time. All these parameters should be verified by a central (core) laboratory.

Myocardial infarction associated with probable or definite stent thrombosis **–** defined by coronary angiography or autopsy data, provided there is evidence of myocardial ischemia or documented ischemia, abnormal Q waves, or de novo hypokinesis/akinesis detected by echocardiography in the segment(s) supplied by treated artery. In addition, an increase of cardiac biomarkers by at least one level (above the 99th percentile of the upper reference limit) is taken into account.

Target vessel revascularization – target vessel revascularization will be defined as any repeat PCI or CABG in any segment of the target artery. **Indications for target vessel revascularization may only be clinical, based on evidence of ischemia determined by stress testing or symptoms of angina (clinically driven revascularization).**

Target lesion revascularization is any repeat PCI of the target lesion or CABG of the target artery performed for a late complication associated with the target lesion (restenosis, thrombosis). In cases of chronic coronary syndrome, **indications for target vessel revascularization may include** the presence of signs of ischemia determined by a stress test, or symptoms of angina (clinically indicated revascularization). Indications for target lesion revascularization should be determined **before control coronary angiography** as clinically indicated (ischemia-related) or indicated for other reasons. **In cases of recurrent angina in the form of acute coronary syndrome, cardiac-specific biomarkers should be assessed before repeat revascularization**. The algorithm for repeat revascularization is shown in Fig. 6.

An independent central angiographic laboratory should determine the degree of stenosis diameter corresponding to clinical indications. If the criteria are not met, the obtained results may be excluded from data analysis. The target lesion will be considered the segment at the site of stent implantation (balloon dilation), as well as up to 5 mm proximal and distal to the implanted stent (1 mm proximal and distal to the balloon dilation segment).

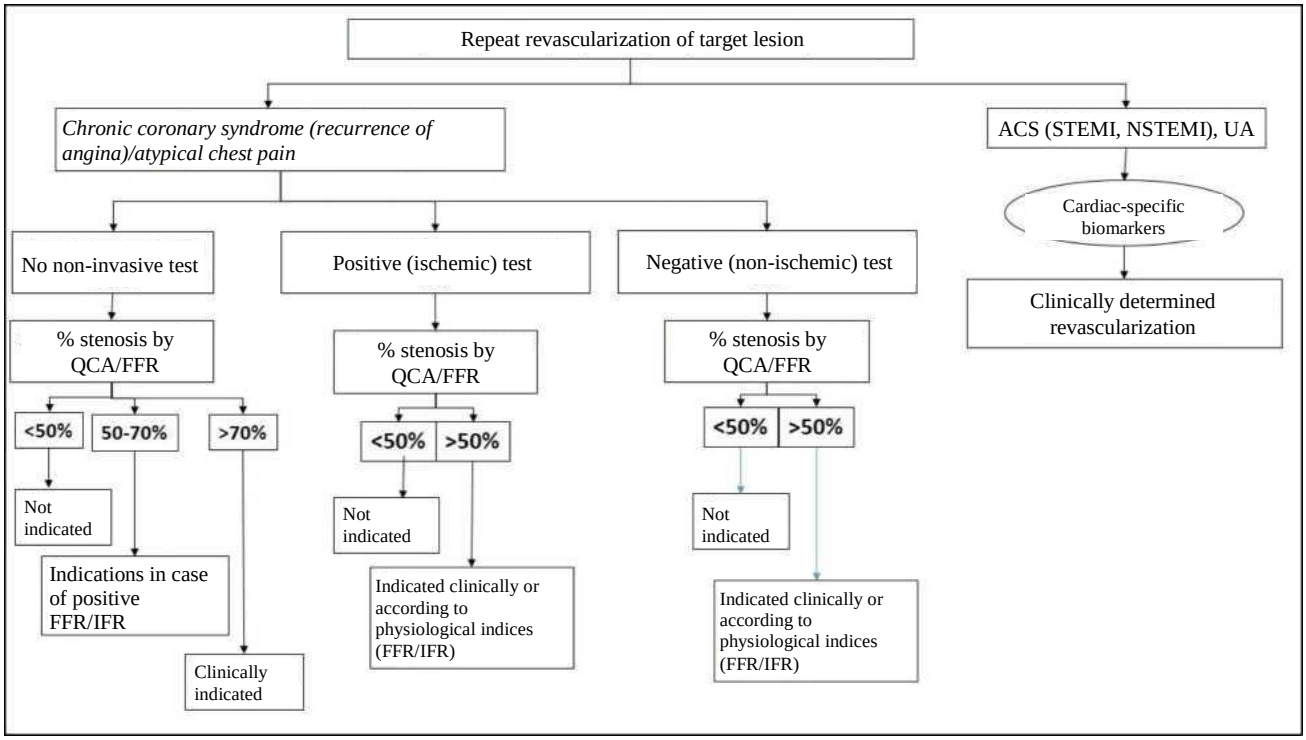

Fig. 6: Algorithm for performing repeat revascularization of the target vessel

***Target lesion restenosis* –** When using DEB, the restenosis diameter in the segment of the intervention (as well as up to 1 mm proximally and distally) should be ≥ 50% of the mean reference target artery diameter (assessed by the central angiography laboratory). In the case of stenting, restenosis is defined as ≥ 50% of the mean reference diameter of the target artery, taking into account a segment within 5 mm at the proximal or distal end of the stents.

***Target lesion thrombosis* –** thrombosis is defined as an event of occlusion at the site of the target lesion PCI that occurs after the completion of the intervention (PCI); specifically, from the moment of removal of the guiding catheter.

Target lesion/stent thrombosis will be classified as follows:

- acute thrombosis – 0-24 hours after PCI
- subacute (early) thrombosis – 24 hours – 30 days after PCI
- late thrombosis – 30 days-12 months after PCI

The same ARC (Academic Research Consortium) criteria apply in defining target lesion thrombosis, as in the case of stent thrombosis. In particular, ***definite, probable, and possible*** thrombosis[13].

Definite thrombosis is thrombosis confirmed by angiography, intravascular imaging, or pathological data.

Angiographic confirmation of stent thrombosis:

The presence of a thrombus originating in the stent or 5 mm proximally or distally to the stent (or 1 mm proximal and distal to the balloon dilation segment), as well as the presence of one of the following:

- sudden onset of ischemic symptoms at rest,
- de novo ECG changes confirming ischemia,
- increased levels of cardiac markers,
- non-occlusive thrombosis (filling defect of the coronary artery or local impregnation of contrast media in the lumen of the artery or visually detectable embolization of the distal bed),
- occlusive thrombosis (blood flow TIMI 0 or TIMI 1 in stent, proximally to stent or balloon dilation site).

2. Probable thrombosis is any case of unexplained death within the first 30 days, any myocardial infarction in the target artery area according to ECG data.

3. Possible thrombosis is a case of unexplained death after 30 days from the date of stenting.

The procedure will be considered successful in the case of:

- achieving a residual stenosis of less than 10% (<30% in the case of using drug-eluting balloons) after completion of PCI in the target lesion area and 5 mm distally and proximally to the lesion (1 mm proximally and distally to the balloon dilation segment).
- Clinical success of lesion treatment will be considered as achieving angiographic success combined with the absence of any in-hospital adverse events.

Target lesion thrombosis in the case of DEB PCI is defined as angiographically confirmed thrombus[*] localized in the target segment, including 1 mm proximally and distally to the site of application (inflation) of the drug-eluting balloon[10]. Or without angiographic confirmation, in the event of the development of the following symptoms within 48 hours after completion of PCI:

- acute onset of ischemic symptoms at rest
- appearance of new ischemic ECG signs indicating acute ischemia
- increase in the level of cardiac-specific biomarkers confirming the presence of acute myocardial injury[10].

In the late period, thrombosis of the treated segment (stented or dilated using a drug-eluting balloon) is determined according to the ARC (Academic Research Consortium) criteria, in particular, ***definite, probable and possible*** thrombosis.

The Adverse Event Evaluation Committee will have the authority to review submitted data and, if the adverse event criteria are not met, to invalidate them.

[*] A thrombus can be diagnosed by intravascular imaging (IVUS, OCT), especially OCT. However, if OCT reveals a small mural thrombus without disruption of antegrade blood flow, this symptom **cannot be considered thrombosis,** as it can be eliminated by anticoagulant or dual antiplatelet therapy without clinical consequences.

7.0. SAFETY PARAMETER RECORDING:

ECG recording:

A 12-lead ECG should be recorded during hospitalization before PCI, immediate after PCI and at discharge. If signs of myocardial ischemia are present, and repeated at any time. The ECG should also be recorded at each follow-up visits. The data (description) should be entered into the electronic patient database and stored in hard copy in the patient's file.

Medical therapy:

All data on medication administered during both the hospital and follow-up periods are to be recorded. Changes in medication treatment should also be recorded in the electronic database.

Laboratory tests:

Cardiac enzyme testing (hs-Troponin I or CPK-MB) should be performed in a local laboratory. The time of collection should be recorded in the patient's medical record and in the electronic database. Any other laboratory tests performed for vital signs in the hospital and at follow-up should also be recorded in the electronic database.

8.0. STUDY DATABASE:

Upon completion of each intervention, procedure parameters are to be prospectively recorded in the study database. All patient information should be blinded (only the identification code is provided). Participating sites will have access to the electronic database where data on patients included in the study will be recorded online. All database parameters are to be monitored by the lead institution at least once every three months.

9.0. DATA MONITORING:

The following information will be requested during the monitoring visit:

- patient demographic data;
- medical history and physical examination data;
- detailed information on all adverse events;
- all data on efficacy and safety;
- all data of study procedures and interventions, also related to the patient’s hospitalization at the institution, information about visits and all events related to the study;
- complete information on the patient's medication (including the patient's anesthesia record);
- data from all diagnostic procedures performed as part of the study;
- detailed information about the PCI performance;
- ECG data;

- angiography and PCI data recorded on CD in DICOM format;

Once entered into the electronic database, the data will be analyzed by the Study Monitors (SMs). If any inconsistencies or missing data are detected, a series of questions will be sent to the investigator. According to study requirements, the researcher should submit responses to these questions within one week.

10.0. REGISTRATION OF ADVERSE EVENTS:

Adverse events can be documented based on complaints from the patient or his legal representatives, symptoms identified by the physician, as well as the detection of pathological changes in laboratory test results.

The investigator should determine whether any signs of adverse events have occurred during patient visits and telephone contacts.

The investigator is responsible for identifying, recording in primary medical documentation, and reporting adverse events by entering information into the electronic database within five working days.

Adverse event reporting:

- If an adverse event occurs, the investigator should complete the appropriate page in the electronic database.
- Before reporting, the researcher should evaluate the severity of the event.

The adverse event severity rating scale is provided below:

- *mild:* signs or symptoms that are easily tolerated and resolve with symptomatic treatment;
- *moderate:* sufficient discomfort to affect usual activities, only partially relieved by symptomatic treatment;
- *severe:* inability to perform some daily activities, difficult to resolve with symptomatic treatment. The investigator should then determine whether there is a relationship between the investigational device and the adverse event.

Serious adverse event

A serious adverse event is recorded if it meets one of the following criteria:

- results in death
- is life-threatening. "Life-threatening" means any adverse event that could have been fatal at the time of its development; however, this definition does not imply that, if this manifestation had been more pronounced, it could hypothetically have led to death
- requires hospitalization or its prolongation
- results in persistent or significant disability/incapacity;
- is a congenital anomaly or acquired defect; or other medically significant conditions

that, in the opinion of the investigator, may threaten the patient or may require intervention to prevent one of the outcomes described above.

- Planned hospitalization is not a serious adverse event.

Recording and reporting of information about a serious adverse event:

In case of detection of a serious adverse event, the Investigator should record the most detailed information in the primary medical documentation and fill out the Serious Adverse Events Registration Form (Appendix No. 1) and send it within 24 hours by e-mail to _____ to the Coordinating center of the Study (Department of Interventional Cardioangiology, I.M. Sechenov Moscow State Medical University (Sechenov University).

The data will then be evaluated and submitted to the independent ethics committee. Signs of disease, symptoms, and/or changes in laboratory parameters that occurred prior to the use of the investigational device cannot be recorded as adverse events.

The investigator is responsible for identifying, documenting in the primary medical record, and reporting serious adverse events to the coordinating study site within 24 hours of becoming aware of the serious adverse event.

All procedures and analyses performed in this study are typically used in clinical practice and have well-defined safety profiles. Furthermore, all procedures performed in this study are commonly used in the study population, i.e., patients with coronary artery disease. Risk of catheterization and revascularization will be minimized by selecting experienced specialists who meet the study certification criteria.

11.0. DATA ASSESSMENT AND MONITORING:

11.1. Adverse Event Evaluation committee

The committee will be formed as an independent and multispecialty expert group responsible for evaluation of clinical events in the study. The primary goal is to ensure independent and ongoing oversight of clinical event data reported by investigators.

The members of the committee are authorized to perform the following:

- Determine the endpoint when the required amount of data is available;
- Make decisions in a timely, consistent and impartial manner;
- The expert group will review all endpoints on an ongoing basis. All committee members will be blinded to the patient's allocation to any of the study groups.

11.2. Independent Ethics Committee

To ensure that the study meets ethical and safety standards, the study will be also monitored by the independent ethics committee.

11.3. Statistical analysis

The analysis will be performed using the R software package (R Project for Statistical Computing). All statistical tests will be two-sided with a significance level of 5%. All confidence intervals will be calculated as two-sided 95% intervals. Continuous data will be represented by the number of observations, mean with standard deviation, median, and range of values. The precision of presentation is one decimal digit after the decimal point. Discrete values will be described by absolute and relative frequencies. Continuous parameters will be tested for normal distribution using the Shapiro-Wilk test. If continuous values are normally distributed, their comparison across treatment groups will be performed using the Student's t-test; otherwise, the nonparametric Wilcoxon test will be used. Discrete values will be compared using the chi-square test or Fisher's exact test (for unordered categories), or the Mantel-Haenszel statistic and other methods suitable for comparing ordered categories (the Mann-Whitney test).

11.4. Lost or incomplete data management

If there is no data on the occurrence of a clinical event at the time of the final visit, the date of the last contact will be considered the final visit.

12.0. LONG-TERM OUTCOME MONITORING:

It is planned to collect long-term outcomes from all patients included in the study. The nature, control time points, and type of control tests are described above (See section **1.2**. **PRIMARY PROCEDURES AND STUDY TIMELINES**). Almost all long-term outcome evaluation criteria require patient’s visit to the clinic.

13.0. START AND END OF INCLUSION OF PATIENTS IN THE STUDY:

It is planned to begin patient enrolment in the study on _March 2026. It is planned to completion the patient enrolment on March_2027.

14.0. PATIENT INFORMED CONSENT:

All patients sign informed consent after a preliminary explanation of the nature of the intervention, possible outcomes and complications. The study's objectives should be explained in detail in writing and orally, the procedures associated with the study should be described, and information provided about the potential risks and benefits for the patient if they participate in the study. The patient should also be informed that the study will involve third parties accessing anonymized personal data. The informed consent form should be signed and dated in duplicate by the patient and the principal investigator. One copy is given to the patient, the other one remains at the site.

15.0. PUBLICATION OF FINAL AND/OR INTERIM STUDY DATA:

No significant information related to the study may be published without prior approval from the lead clinical site and the principal investigators at the participating clinical sites. If consent is granted, all participating clinical sites should review and approve the proposed publication within two months.

16.0. ADMINISTRATIVE PROCEDURES:

Adverse Event Committee

To be established at the CELT Clinic – Center for Endosurgery and Lithotripsy. Tel.

Introduction of amendments to the protocol

Any study protocol amendments will be recorded as protocol amendments. Such amendments may only take effect after approval by the study coordinators.

Study monitoring

The investigator is responsible for the proper conduct of the study and the objectivity of the information recorded in the electronic database. The coordinating clinical site has the authority to appoint a monitor for data verification (primary documentation and electronic database). During monitoring visits, the investigator should provide access to primary documentation (medical records) and the electronic database.

Patient confidentiality

The data to be transferred should not contain the patients' personal data. All information related to study correspondence, as well as information recorded in the electronic database, should contain only an identification number.

Archiving

The investigator should retain all information related to the study for at least 5 years after completion of the study. Upon completion of the study, the investigator will be provided with a CD-ROM copy of each patient's data recorded in the electronic database. This data will include filled-in electronic forms, all comments on the electronic database, a list of all requests for data clarification, a signature list, and a list of all amendments made. These copies should be kept at the site for at least 5 years.

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STASTICAL ANALYSIS PLAN (SAP)

The Analysis will be done as intention to treat (ITT) and per protocol (PP) data.

The analysis will be performed using the R software package (R Project for Statistical Computing). All statistical tests will be two-sided with a significance level of 5%. All confidence intervals will be calculated as two-sided 95% intervals. Continuous data will be represented by the number of observations, mean with standard deviation, median, and range of values. The precision of presentation is one decimal digit after the decimal point. Discrete values will be described by absolute and relative frequencies. Continuous parameters will be tested for normal distribution using the Shapiro-Wilk test. If continuous values are normally distributed, their comparison across treatment groups will be performed using the Student's t-test; otherwise, the nonparametric Wilcoxon test will be used. Discrete values will be compared using the chi-square test or Fisher's exact test (for unordered categories), or the Mantel-Haenszel statistic and other methods suitable for comparing ordered categories (the Mann-Whitney test).

The null hypothesis states that the risk difference (R_1–R_0) is greater than or equal to the non-inferiority margin of 4.7%. The alternative hypothesis is that the difference in adverse events between the groups will be less than 4.7%. The null hypothesis of no less efficacy of drug-eluting balloons compared with drug-eluting stents will be rejected if the upper limit of the 95% confidence interval for the risk difference (R_1–R_0) is less than 4.7%.

PATIENT INFORMED CONSENT FORM

I, the undersigned _____

Give consent to the following medical interventional procedure

_____

Upon myself/my spouse/my dependent, informed by Dr. _____ .

My Doctor has provided me with a general explanation of the nature of this procedure and treatment process and the reasons for its indication based on my particular medical condition _____ .

My Doctor also informed me, that for the treatment of this medical condition the experimental product will be used. This product is not approved by FDA as safe and effective, and the treatment using this device is an experimental treatment. Nevertheless, the sirolimus drug coated balloon has received CE mark and has approved by European Regulatory Office as safe and effective product for using in clinical practice for percutaneous treatment of coronary atherosclerotic lesion. I am aware, that data regarding proposed operative treatment will be included in planned research. Certain information about my treatment may be shared with the clinical centers, involving in this research, but every effort will be made to keep my identity private. Hereby I confirmed, that my participation in this research program is absolutely voluntary.

I am also been informed, that there is a chance that the investigational device may improve late clinical results and reduce potential drawbacks inherent in standard of care for this type of lesion. However, there is no guarantee that I get benefit from this investigational treatment and in case of failure of investigational device stent will be implanted avoiding acute complications.

In late period after the procedure it is possible that I will not receive benefit other than receiving the standard of care associated with this treatment, or it could worsen my condition.

I also recognized that the following are serious side effects and complications that have been reported for the investigational device, including life-threatenig conditions:

- Cardiac death
- Myocardial infarction
- Artery thrombosis and dissection
- Arterial perforation and hemopericardium
- Bleeding, sometimes requiring blood transfusion
- Stroke
- Allergic reaction
- Device fragmentation, dislodgement or stuck
- Device thrombosis
- Hematoma and/or closure of the access artery

I acknowledge that the nature of my condition has been explained to me, along with the purposes, potential risks, benefits, and alternatives to the proposed treatment(s), including no treatment. I have been allowed to ask questions and have received satisfactory answers to all of my questions.

I understand that there are no guarantees about the outcomes of the treatment or procedure and that unexpected or unanticipated risks or complications may arise. I also recognize the right to change my decision to participate and withdraw my consent or refuse treatment at any time without penalty or loss of benefits warning in advance Dr. _____. During the treatment, if any new information

about the risks or benefits of the investigational device will appeared, Dr. _____ will inform me and discuss its significance. In certain situations, my doctor may need to stop the investigational treatment without my permission if:

- My condition gets worse.
- The investigational treatment is no longer safe.
- New information suggests that this investigational device does not work
- The investigational device is no longer available from the manufacturer.
- The independent supervisory committee decided prematurely stop the trial. If this happen, my doctor will inform me as soon as possible

By signing this form, I release the healthcare provider and facility, along with its staff, from any liability associated with the treatments or procedures, including the condition related to complications, provided that these services are performed with due care and by the best of medical practice.
I understand that my health information will be treated as confidential and shared only as required or permitted by law, including disclosures to health insurance providers for billing purposes.
I have read (or had read to me) this Consent to Treat Form. I fully understand its contents and implications. I acknowledge signing this consent voluntarily and with full knowledge of its significance.

Patient signature: _____ Date: _____

legally authorized representative signature (if applicable): _____ Date: _____

Physician/Healthcare provider signature: _____ Date: _____