STATE UNIVERSITY OF MEDICINE AND PHARMACY
„NICOLAE TESTEMITANU"
DEPARTMENT OF INTERNAL MEDICINE,
DISCIPLINE OF CARDIOLOGY

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CHRONIC CORONARY SYNDROMES

Methodical recommendation

Chisinau, 2022

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Centrul Editorial-Poligrafic *Medicina*
2022

CZU

The paper was discussed and approved by
the Quality management board of the „Nicolae Testemitanu”
State University of Medicine and Pharmacy
Proces-verbal nr. 05 from 08.04.2022

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The elaboration was designed as a methodical guide for medical students from the Faculty General Medicine, for the discipline of Cardiology on the theme „Ischemic heart disease, Chronic coronary syndromes” and contains up-to-dated information regarding the definitions, classification, diagnosis and treatment of various clinical forms of disease included in the curriculum.

Chronic coronary syndromes: Methodical recommendation / Marcel Abraş, Snejana Vetrilă, Victoria Sadovici, Andrei Grib; State University of Medicine and Pharmacy „Nicolae Testemitanu”, Department of Internal Medicine, Discipline of Cardiology. – Chişinău: CEP *Medicina*, 2022. – 48 p.: fig., tab.
Referințe bibliogr.: p. 33 (4 tit.). – 50 ex.
ISBN 978-9975-82-283-1.
616.12-07-08(075)
C 48

ISBN CEP *Medicina*, 2022

Preface

This paper reflects a topic of great importance in cardiology - ischemic heart disease - and was designed to update the information from the previous methodological elaboration – „Stable angina pectoris". The new edition points out current criteria for the diagnosis and management of chronic coronary syndrome as a modern clinical concept that emerges from the recent recommendations of the European Society of Cardiology.

Chronic coronary syndromes is an innovative term in cardiology that includes a group of clinical situations caused by atherosclerosis of the coronary arteries, which requires an approach with great care, because only a thorough examination of the patient will be able to define the optimal therapeutic management.

The symptoms of the disease are well known, but proper interpretation of the pain syndrome is often difficult, especially in certain categories of patients, such as young people, women and in the presence of comorbidities.

The complex evaluation of these patients include both non-invasive and invasive methods of examination, which help to stratify risk and decide upon the therapeutic strategies, which are the only way to reduce mortality, improve the prognosis and quality of life of these patients.

In this work, we have presented the pathogenesis and the clinical features of different variants of chronic coronary syndromes, we successively pointed out the therapeutic strategy in these patients, gradual and dynamic assessment of vital risk and of the prognosis. We have described in detail the recommended drug groups to be administered at different stages of the disease. Successful management by applying coronary angioplasty or coronary artery bypass could substantially improve the disease prognosis and survival in patients with chronic coronary syndromes.

We wish medical students remarkable success in the field of medicine and we want to believe that the material presented will be really useful.

CONTENTS

DISCIPLINE TRAINING OBJECTIVES ON THE THEME

„Ischemic heart disease. Chronic Coronary Syndrome"

At the level of knowledge and understanding

The student needs to know

- definition of the disease
- incidence and epidemiology
- aetiology
- risk factors
- pathogenesis
- clinical manifestations, methods of investigation: (symptoms, clinical signs, syndromes, in the order provided by the patient examination scheme, laboratory and instrumental examination data (non-invasive and invasive), mechanisms (pathogenesis) of symptoms, syndromes and changes detected at the laboratory and instrumental examination
- the peculiarities of clinical and paraclinical examination of the patient;
- classification proposed by the European Society of Cardiology, other classifications; classification criteria, particularities of clinical manifestations for each form/stage/grade/ provided for classification;
- clinical variants, atypical forms and their characterization;
- the evolution of the disease;
- their complications and manifestations, mechanisms and circumstances of occurrence;
- possible emergencies: clinical picture, causes and mechanism of onset;
- positive diagnosis: diagnostic criteria, diagnostic algorithm;
- differential diagnosis and differentiation criteria;
- requirements for the correct formulation of the diagnosis;
- treatment
- Indications for hospitalization, physical regimen, diet and

alimentary regimen, pathogenetic treatment, symptomatic treatment (drugs, doses, mode of administration, mechanism of action, side effects and their prevention, contraindications, duration of treatment)

- Interventional treatment (general principles, indications, contraindications, complications
- Surgical treatment (general principles, indications, contraindications, complications).
- Medical recovery (stages, methods);
- Primary and secondary disease prevention

SELF-ASSESSMENT QUESTIONS

Try to answer the following questions before studying the material in this given methodological guide. Fill in the answers after finding out about the proposed material.

1. How patients describe the feeling of the chest pain in angina pectoris?
2. When does the anginal pain occur?
3. When angina pectoris pain stop, slow down?
4. Where is this pain located?
5. What risk factors suggest ischemic heart disease?
6. How does angina is classify by the Canadian Cardiovascular Society?
7. What is the main method of investigating to confirm stable angina pectoris?
8. Indication for angiography of coronary arteries in stable angina pectoris patients?
9. What pharmacological treatment do you suggest to a patient with stable angina?
10. Enumerate invasive methods treatment stable angina pectoris

DEFINITION AND CLASSIFICATION

Coronary artery disease (CAD), also called ***ischemic heart disease (IHD),*** is defined as an imbalance between blood demand and supply to

the myocardium due to total or partial obstruction of the coronary arteries, usually caused by progression of atherosclerosis. *Acute coronary syndromes* or *chronic coronary syndromes* clinically present the disease.

The European Society of Cardiology (SEC) introduced the term **chronic coronary syndromes (CCS)** in 2019 the new definition referring to what was previously labelled as *stable coronary artery disease*. Clinical presentation of CCS is characterized by constrictive retrosternal pain, called ***angina pectoris***, when the need for myocardium in oxygen exceeds the supply. Clinical manifestations of CCS occur in the presence of coronary obstructions greater than 50 % on the trunk of the left coronary artery or greater than 70 % on one or more of the main coronary arteries. However, ⅓ of patients do not have significant epicardial coronary involvement, but instead they may have *vasospastic* or *microvascular angina pectoris.*

Clinical classification (scenarios) of chronic coronary syndrome (ESC Guideline, 2019)

- Patients with suspected CAD and *stable anginal symptoms*, and/or dyspnea;
- Patients with new *onset of heart failure* (HF) or left ventricular (LV) dysfunction and suspected CAD;
- Asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS, or patients with *recent revascularization*;
- Asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization;
- Patients with angina and suspected *vasospastic or microvascular disease*;
- *Asymptomatic subjects* in whom CAD is detected at screening.

All of these scenarios are classified as a CCS but involve different risks for future cardiovascular events (e.g. death or myocardial infarction), and the risk may change over time. The risk may increase as a consequence of insufficiently controlled cardiovascular risk factors, suboptimal lifestyle modifications and/or medical therapy, or unsuccessful revascularization. Alternatively, the risk may decrease as a

consequence of appropriate secondary prevention and successful revascularization. Hence, CCS is defined by the different evolutionary phases of CAD, excluding situations in which an acute coronary artery thrombosis dominates the clinical presentation (i.e. ACS).

EPIDEMIOLOGY

Worldwide, cardiovascular disease (CVD) is the leading cause of death, accounting for about ⅓ of deaths. In Europe, CVD is estimated to be responsible for 45 % of mortality, with ischemic heart disease being the most common cause of death. The same scenario is followed in Romania, where the data that come mainly from death certificates show that CVD is the main cause of death.

IHD is a rare disease under the age of 40, but its prevalence increases with age from 5-7 % in women aged 45-64 to 10-12 % between the ages of 65-84, and, respectively, from 4-7 % in men aged 45-64, to 12-14 % among those aged 65-84. Until the 1960 s, the incidence of ischemic heart disease was steadily increasing, but subsequently, as a result of targeted and effective identification and treatment of cardiovascular risk factors, the disease is declining.

PATHOPHYSIOLOGY

Myocardial ischemia occurs as a result of an imbalance between the demand and supply of oxygen to the heart muscle. The determinants of myocardial oxygen consumption are heart rate, systolic pressure and myocardial contractility, and myocardial ischemia can be triggered or precipitated by certain factors such as physical exertion, emotions, mental stress, fever, chills, thyrotoxicosis, tachycardia, etc.

The main cause of poor oxygen supply is atherosclerosis of the epicardial coronary arteries. Transient coronary vasoconstriction (dynamic stenosis) complements fixed stenosis caused by the presence of atherosclerotic plaque, which causes an additional reduction in coronary blood flow. Angina pectoris is the result of a continuous series of events that take place in a few seconds - ischemic cascade, triggered by transient myocardial ischemia: arterial occlusion - LV diastolic dysfunction - systolic

dysfunction in the irrigated territory of the stenosed artery - occurrence of T-wave and ST segment changes, which is displayed by angina pain. The onset of angina pain is secondary to the release of ischemic metabolites, such as adenosine, bradykinin, hydrogen ions, which irritates the terminals of the cardiac sensory nerves. When normal blood flow resumes, the events remit in the opposite direction of their occurrence.

Myocardial ischemia in vasospastic angina is due to the spasm of the epicardial coronary arteries, which can occur on vessels with or without significant stenosis. The most commonly involved factors are endothelial dysfunction, abnormal vegetative nervous system response, inflammation and oxidative stress. Rarely the artery has a portion with intramuscular trajectory (muscle bridge) and myocardial ischemia can be caused by its compression by a muscle bundle.

Microvascular angina is due to dysfunction of the coronary microcirculation (small vessels less than 0.4 mm), which is not visualized at the coronary evaluation.

Pathology

The most important and common cause of myocardial ischemia is *coronary stenosis*, based on the atherosclerotic process. The morphological entity of this process is atherosclerotic plaques, which can be stable and unstable. The stable plaque has lipid content and is covered with a dense fibrous capsule; it is also called „uncomplicated" and is the substrate of chronic coronary syndromes. The unstable plaque is a „complicated" plaque, and its vulnerability is due to a thin fibrous capsule with abundant lipid deposits and the presence of intense inflammatory activity inside it, metalloprotease secreting cells degrading the collagen tissue matrix of the capsule and promoting its rupture. These plaques can evolve to fissure, ulceration, thrombosis, sub-intimal haemorrhage or spasm and is the substrate of acute coronary syndromes.

Other less common causes of myocardial ischemia are: coronary embolism, dissection of the ascending aorta or coronary artery, coronary arteritis, myocardial muscle bridges, penetrating or non-penetrating heart trauma, but also congenital coronary artery abnormalities.

THE CLINICAL PRESENTATION

Chronic coronary syndrome is clinically manifested by chest pain, called **angina pectoris**, a phenomenon that meets 4 characteristics depending on location, type, relationship to exertion, aggravating or ameliorating factors.

The criteria for defining angina pectoris are:

- *location:* most frequently it is retrosternal, with irradiation to both arms, more frequently in the left shoulder and arm, neck and mandible, sometimes it appears in the epigastrium and less often - posterior thorax;
- *type:* pressure or constriction on a large surface, of different intensity, from mild to intense pain;
- *triggers:* physical exertion, emotions, cold, meal intake, the pain improves at rest;
- *duration:* less than 20 minutes. Usually, anginal pain ceases after 1-3 minutes of rest or administration of sublingual nitro-glycerine, but can persist for up to 10 minutes after cessation of intense exertion.

Some patients may have anginal equivalents, as an expression of myocardial ischemia (dyspnoea that occurs under the same conditions as pain and disappears after nitro-glycerine administration, palpitations), in the absence of chest pain. Atypical symptoms are common in women, elderly and diabetic patients.

Typical angina pectoris meets at least 3 criteria, and angina pectoris is atypical if less than three of the four characteristics are met. Non-coronary pain meets only one of the above criteria.

Microvascular angina generally has symptoms similar to those experienced by patients with coronary heart disease, but there are several features that may suggest this type of angina pectoris:

- high angina threshold variability;
- pain irradiates in the sub mammary region; pain is associated with palpitations;
- the pain does not subside immediately at rest;
- the pain does not subside or may even worsen with sublingual

nitro-glycerine.

Vasospastic angina (Prinz metal) occurs in young patients who have few cardiovascular risk factors and is closely associated with smoking. Angina occurs at rest, early at night or in the morning, very rarely occurs at exertion. The pain is manifested with episodes that are frequently repeated over a period of 3-6 months, followed by the temporary or permanent disappearance of angina sensations.

Silent myocardial ischemia is reported in situations when myocardial ischemia is not accompanied by angina, being found especially in elderly patients, with neurological pathologies (peripheral neuropathies - diabetic patients, inhibition of spinal or supraspinal pain) or in patients with multiple comorbidities.

Classification of the Canadian Society of Cardiology for stable angina pectoris

1. *Class I*: Angina only during strenuous or prolonged physical activity. It is absent in normal physical activity. Equivalence of energy consumption of 7-8 METs.
2. *Class II*: Slight limitation, with angina only during vigorous physical activity. Equivalence of an energy consumption of 5-6 METs.
3. *Class III*: Symptoms with everyday living activities, ie, moderate limitation. Equivalence of an energy consumption of 3-4 METs.
4. *Class IV*: Inability to perform any activity without angina or angina at rest, i.e., severe limitation. Equivalence of an energy consumption of 1-2 METs.

Physical examination of the patient with CCS may identify the presence of various risk factors for atherosclerosis, such as obesity (overweight, waist circumference); dyslipidaemia (xanthelasma, xanthoma's, corneal ring); hypertension, peripheral vascular damage (shortness of breath, changes in peripheral pulse). During the angina attack, reversible signs may appear and disappear after spontaneous or therapeutic intervention, such as abnormal systolic pulses in the precordial area, alternating pulse, atrial or ventricular gallop, and systolic murmur of mitral regurgitation due to ischemic papillary muscle dysfunction.

PARACLINICAL DIAGNOSIS

Laboratory testing is required for the identification of cardiovascular risk factors and for prognostic evaluation. Haemoglobin and haematocrit dosing is used to identify patients with anaemia, which is often a precipitating factor in angina attacks. It is also important to evaluate thyroid function, thyroid dysfunction being correlated with the manifestations of anxiety.

Evaluation of the complete lipid profile (total cholesterol, LDL, HDL, triglycerides), glycaemia, glycosylated haemoglobin, creatinine and liver transaminases also serve to identify cardiovascular risk factors. Dosage of markers of myocardial necrosis (troponin, preferably high sensitive) is indicated for the exclusion of an acute myocardial infarction, in case of clinical suspicion.

Electrocardiogram (ECG) at rest will be performed in all patients with angina, with or without chest pain (figure 1). During the angina crisis, ST segment elevation (ST segment elevation in Prinz metal angina) and/or changes in the T wave (negative T waves or positivity of previously negative T waves - pseudo normalization) are most frequently found. In the absence of chest pain, 50-69 % of patients with typical angina pectoris may have a normal electrocardiogram, and 25 % have minor electrocardiographic changes. In the remaining 15 % of patients, major electrocardiographic changes can be detected, caused by old myocardial infarctions, ventricular hypertrophies, pacemaker rhythms or bundle branch blocks.

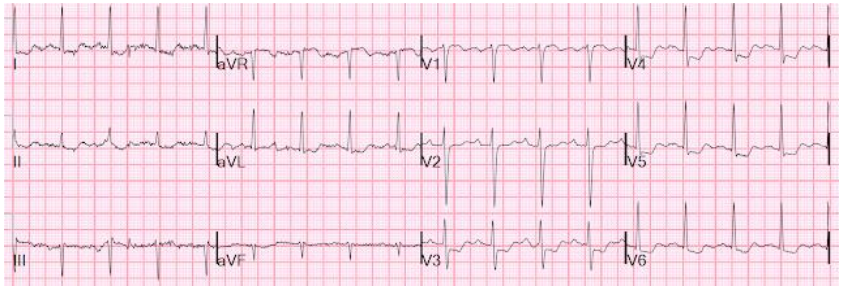


Figure 1. **Electrocardiogram recorded during angina attack.**

Echocardiography is a valuable examination because, by assessing cardiac structure and function, it can provide important information for the diagnosis and prognosis of patients with angina pectoris: changes of the heart kinetics, associated valvopathy, left ventricular hypertrophy, and overall left ventricular systolic function. Sometimes, echocardiographic examination allows the visualisation of the initial segment of the coronary arteries, but the clinical relevance of these images is limited for the time being, given that there are rare cases where stenosis at the proximal site in the coronary circulation can be identified by echocardiography.

Stress electrocardiogram (ECG exercise test) is indicated for the evaluation of electrocardiographic changes on exertion and is particularly useful in patients with angina in the presence of a normal ECG at rest. The increase in myocardial O_2 consumption can be induced by physical exercise (treadmill, cycle ergometer) or pharmacological induced (dobutamine) in the case of those incapable of physical exertion.

The ECG exercise test is limited to patients with electrocardiographic changes (RBBB, WPW syndrome, pacemaker rhythm, or pre-existing ST-segment elevation).

The result of the exercise test is interpreted „positive" according to the clinical (*table 1*) or electrocardiographic (*figure 2*) criteria of ischemia.

Table 1.

Clinical criteria for the positive exercise test.

Exercise-induced hypotension
Angina or exercise-induced angina equivalents
The appearance of 3, 4 heart sounds or heart murmur during exertion

In addition to the ECG changes presented above, frequent ventricular premature beats, multifocal premature beats, or moderate-effort ventricular tachycardia (less than 70 % of maximum heart rate) are suggestive for a positive exercise test for myocardial ischemia.

The result of the exercise test is interpreted as „negative" in the absence of any of the clinical or electrocardiographic criteria listed above.

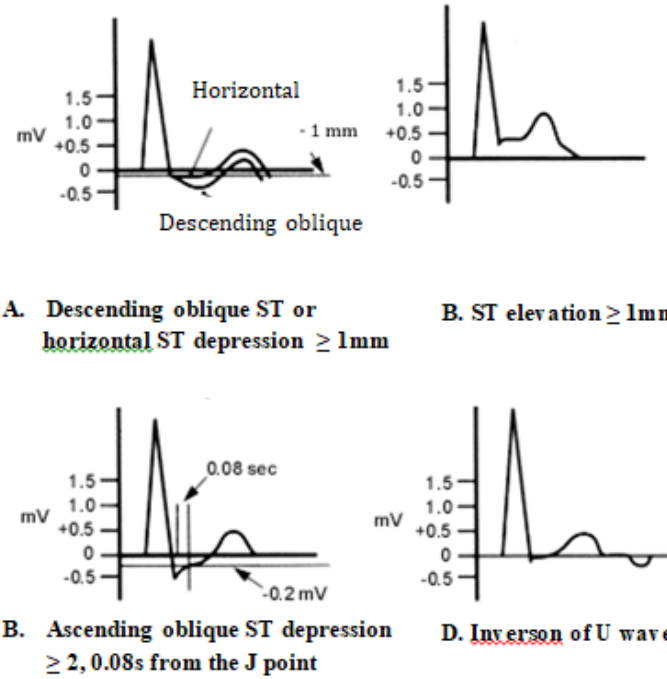


Figure 2. ECG criteria for positive exercise test.

The test result can be interpreted as „inconclusive" in case of ECG changes that are not suggestive of ischemia:

The test may be considered „uninterpretable" when the patient or examiner is unable to complete the test before the objectives have been met. In this case, alternative diagnostic methods should be considered.

Holter ECG monitoring is useful to determine episodes of silent ischemia, ST-segment elevation that occurs in vasospastic angina pectoris, or for cardiac arrhythmias.

In case when the exercise test can't be performed, other methods of investigation are recommended: pharmacological exercise tests. Pharmacological exercise tests use imaging techniques such as echocardiography or perfusion scintigraphy. During the test the patient is administered a sympathomimetic substance - dobutamine or a coronary dilator - adenosine or dipyridamole. The above mentioned tests are

recommended for patients with major left bundle branch block, preexcitation or pacemaker, for those who cannot perform the exercise ECG test, for patients with a history of percutaneous coronary intervention (PCI) or coronary artery by-pass graft surgery (CABG). These tests are of diagnostic superiority for the detection of ischemic coronary heart disease, and have a high negative predictive value. Exercise echocardiography has a sensitivity of 80-85 % and a specificity of 84-86 %. ECG and echocardiographic recordings are made at each stage of the test. Myocardial contrast can be used in the absence of effort for better contouring of the endocardium and identification of changes in parietal kinetics; myocardial velocities can be measured (by tissue Doppler), myocardial deformation parameters - strain and strain rates. These techniques are complementary to standard echocardiography for the detection of ischemia and improve the accuracy and reproducibility of stress echocardiography.

Exercise test myocardial perfusion scintigraphy uses Thallium (TI201) as radiotracer, which is preferentially fixed in the well-irrigated myocardium, the ischemic areas appearing as hypo fixation (cold) areas, or Technetium (Tc99m), which highlights the areas of myocardial necrosis, for which the tracer has affinity (hot, hyper fixation areas).

In combination with the exercise test, photon emission computed tomography (SPECT) is superior to myocardial perfusion scintigraphy for locating and quantifying ischemia. This method reflects the difference in myocardial uptake of the radiotracer and thus reveals the difference in myocardial perfusion between different areas. Myocardial hypoperfusion is defined by a reduction in radiotracer uptake during exercise testing compared to resting scintigraphy, and increased uptake into the lungs means severe and extensive IHD. The infusion SPECT has a sensitivity of 85-90 % and a specificity of 70-75 %.

Nuclear stress magnetic resonance (NMR) can be used in the absence of concluding results by routine examinations, the investigation aims to determine ischemia-induced parietal kinetics or dobutamine induced perfusion changes.

Positron emission tomography (PET) studies ischemia and myocardial viability at the cellular level. Cellular metabolites, for

example glucose, are used and the ischemic myocardium is identified, being considered the gold standard in the evaluation of myocardial viability, but it is less used due to the high cost.

A computerized tomography coronary angiogram (Angio CT) is a non-invasive imaging method which evaluates the coronary arteries using iodinated radiological contrast. It allows the visualization of calcium deposits in the coronary arteries, reveals the presence of intraluminal stenoses, the morphology and composition of atherosclerotic plaques. Except situations where CAD can only be ruled out on the basis of clinical evaluation, Angio CT imaging is recommended as an initial diagnostic test. The choice of the initial non-invasive diagnostic test is based on the pre-test probability, the test's ability to diagnose CAD, the patient's characteristics, experience, and local test availability.

Coronary angiography is an invasive method, which is performed by selective coronary catheterization (*figure 3*), providing anatomical information about the presence of stenosis and / or lesions in the coronary arteries. This method helps to define the therapeutic options: drug treatment or myocardial revascularization.

The examination is performed by arterial approach (puncture by Salinger technique in the radial, brachial or common femoral artery), with the introduction of atraumatic diagnostic catheters made of polyurethane and intubation of the ostium of the coronary arteries. Through these catheters, radiopaque contrast substance is injected and the coronary lumen is visualized in different projections, which allows the evaluation of the areas with filling defect or with the absence of contrast filling (coronary stenosis or coronary occlusion).

Coronary angiography allows the identification of the anatomical site of coronary stenosis, the estimation of their severity, the number of affected vessels, the state of the distal vascular bed after stenosis, but also the presence of collateral circulation.

Recommendation for coronary angiography (European Society of Cardiology Guideline, 2019)

1. Coronary angiography is recommended for patients with high clinical probability of CAD, refractory to optimal drug therapy

or if the patient develops typical angina at the minimum threshold of physical exertion, and the initial clinical evaluation shows a high risk of adverse events.

2. Coronary angiography is indicated if the non-invasive assessment suggests a high risk for adverse events and also for the determination of revascularization options.
3. Coronary angiography is required for patients with suspected CAD in cases where non-invasive testing has been inconclusive or, exceptionally, for patients practicing certain professions, due to professional regulatory considerations.

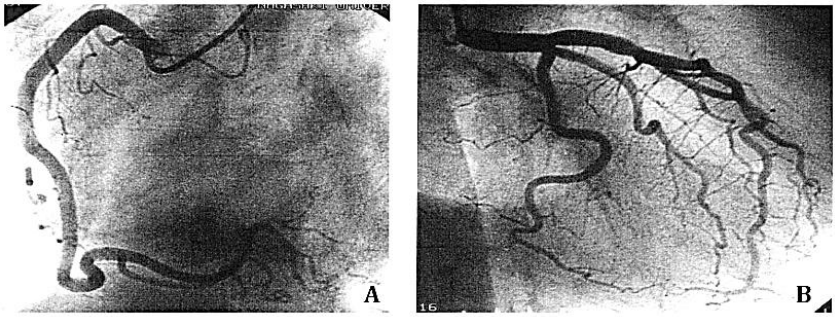


Figure 3. Angiography of the right (A) and left (B) coronary artery.

If the coronary angiography failed a definite diagnosis, complementary techniques such as: intravascular ultrasonography and optical coherence tomography can be used, that allow the evaluation of the vascular wall but also the measurement of the coronary flow reserve that determines the hemodynamic significance of stenosis.

Coronary angiography should not be performed in patients who refuse invasive procedures, who prefer to avoid a subsequent revascularization procedure, who are not candidates for PCI or CABG, or in whom a revascularization procedure will not improve functional status or quality of life.

Fractional flow reserve (FFR). Fractional flow reserve is defined as the pressure after the (distal to) stenosis relative to the pressure before the (proximal to) stenosis. The result is an absolute number; an FFR of

0.80 means that a given stenosis causes a 20 % drop in blood pressure. In other words, FFR expresses the maximal flow down a vessel in the presence of a stenosis compared to the maximal flow in the hypothetical absence of the stenosis. Coronary pressure-derived coronary FFR is currently the standard for functional assessment of lesion severity in patients with intermediate-grade stenosis (around 40-90 %) without evidence of ischemia in non-invasive tests or in those with multivascular disease. The diagnostic accuracy of FFR is similar to myocardial perfusion scintigraphy, but with a better spatial resolution. It is derived from the ratio between the value of aortic and coronary pressures measured during maximal hyperaemia, which is obtained by administration of intravenous or intracoronary adenosine. The limit value for defining the hemodynamic significance of stenosis is ≤0.80.

Intravascular imaging for the evaluation of stenosis. Intravascular ultrasonography (IVUS) is an intravascular imaging technique with an axial resolution of about 150 μm. IVUS imaging allows real-time tomographic evaluation of vessel size, lumen surface, and the composition and volume of the atherosclerotic plaque. Compared to optical coherence tomography (OCT), it has a more limited spatial resolution, but a better penetration and a potential advantage in vessel calibration. OCT is a mode of light-based intravascular visualization with an axial resolution higher than IVUS (15 vs. 150 μm). The disadvantage of OCT imaging is that it requires complete emptying of the lumen and has more limited penetration, which may restrict the assessment of the full pattern of the atherosclerotic plaque and influence the accurate calibration of the vessel.

Chest radiography is not essential for diagnosis, but may show heart failure or may be useful in the differential diagnosis of angina pectoris.

Differential diagnosis of angina comprises other situations of chest pain. Angina pain should be differentiated from:

- Pericarditis: the pain is accentuated by coughing, deep breathing, change in body position and does not improve with nitroglycerine intake. The auscultation of a pericardial friction rub

suggests the real diagnosis.

- Aortic dissection: very violent chest pain, maximum intensity from onset, irradiates in the back and is frequently associated with hypertension, aortic insufficiency, neurological signs or intermittent peripheral arterial pulse deficit. Echocardiographic evaluation, CT or cardiac MRI allow the diagnosis.
- Pleuritic chest pain (mediastinal tumours, pleurisy, pneumothorax, pulmonary thromboembolism, pulmonary infarction) - pain is exacerbated during respiratory movements and is sometimes associated with pleural effusion.
- Tracheobronchitis: retrosternal burning sensation accentuated by cough.
- Gastrointestinal diseases (reflux/oesophageal spasm, biliary colic, gastric/duodenal ulcer, pancreatitis) - pain is related to diet and can be relieved by antacid intake.
- Musculoskeletal pathology: cost sternal syndromes (Tietze syndrome/costochondritis): pain lasts seconds/hours and is reproduced by pressure, shoulder arthritis - pain is reproduced/ accentuated by its movement; cervical radiculitis: pain localized precordial, accentuated by deep inspiration/chest movements, lasts days /hours.
- Emotional disorders: stinging/chest tightness with retrosternal or precordial localization, lasts few hours and correlates with fatigue/stress.

The ESC Guidelines (2019) also introduced a new concept defined as „clinical likelihood of coronary heart disease". Depending on the patient's sex, age, and the nature of the symptoms, there are several factors that determine the clinical likelihood of coronary heart disease:

- decreased likelihood: normal exercise ECG; no coronary calcium by (Angaston score = 0).
- increased likelihood: risk factors for CVD (dyslipidaemia, diabetes, hypertension, smoking, family history of CVD); resting

ECG changes (Q wave or ST segment or T changes); LV dysfunction suggestive of CAD; Abnormal exercise ECG; coronary calcium by CT.

Treatment of chronic coronary syndrome

The major objectives of the treatment of chronic coronary syndromes are:

- improving the quality of life by increasing the tolerance to physical exercise, decreasing the frequency and intensity, or even disappearance of the angina episodes;
- prevention of complications of CAD (myocardial infarction, arrhythmias, heart failure, death) that limit long-term survival.

In order to achieve these objectives, lifestyle changes, control of cardiovascular risk factors, drug treatment and myocardial revascularization are required (interventional or surgical) - when there is evidence of persistence of inducible myocardial ischemia.

NON-PHARMACOLOGICAL TREATMENT

The first step is the thorough information of the patient and his family regarding the significance of angina pectoris and the importance of diagnosis and recommended therapeutic measures. Attitude training is required in the event of an angina attack, which involves discontinuation of the activity that caused the angina and the use of sublingual nitrates. The patient should be aware of the side effects of nitrates and seek medical attention if the angina symptoms persist after 10-20 minutes of rest and/or if they are not relieved by sublingual nitrates.

It is important to manage the risk factors by quitting smoking, adopting a low saturated fat diet, low in calories and/or hypoglycaemic (in the presence of dyslipidaemia, obesity, and diabetes), moderate alcohol consumption and systematic exercise (at least 30 minutes a day of continuous physical activity). It is necessary to correct anaemia and hyperthyroidism as well as to treat diabetes and hypertension. In patients with diabetes or kidney disease the target value of systemic blood pressure will be <130/80 mmHg.

DRUG TREATMENT

Drugs used to relieve symptoms (attenuation or elimination of angina) in patients with chronic coronary syndrome, called anti-ischaemic drugs are divided into 7 subcategories: nitrates, beta-blockers, calcium channel blockers, potassium channel activators, inhibitors of sinus node (ivabradine), metabolic agents (trimetazidine, ranolazine), molsidomine. The choice of anti-ischemic medication in patients with chronic coronary syndromes should be selected according to heart rate, blood pressure and left ventricular function.

Beta-blockers and/or calcium channel blockers remain the first-line drugs in the treatment of patients with chronic coronary syndromes. Beta-blockers are recommended for patients with left ventricular dysfunction or reduced ejection fraction. Prolonged-acting nitrates cause tolerance and lose their effectiveness, which requires their prescription with a free interval between doses of about 10-14 hours.

Beta-blockers should be initiated in the first 24 hours after admission to all patients who do not have: signs of heart failure, a severely diminished left ventricular ejection fraction, increased risk of cardiogenic shock or other contraindications to beta-blockers, such as: bronchial asthma, PR interval> 0.24 seconds, grade II or III atrioventricular block. Beta blockers reduce myocardial oxygen consumption by reducing the heart rate at rest, by decreasing inotropism, and blood pressure. Beta-blockers prolong the diastole, so the time of diastolic perfusion of the coronary arteries and, respectively, the myocardial perfusion of the ischemic areas increase.

The most used beta-blockers in angina pectoris are those that preferentially block cardiac beta 1 receptors, such as metoprolol, bisoprolol and nebivolol, but also carvedilol, which also has alpha 1 blocker action. The choice of beta-blocker treatment also depends on how it is eliminated, nebivolol and bisoprolol being eliminated mainly by the kidneys, and carvedilol and metoprolol - by the liver, which is why the latter are preferred especially in patients with renal impairment. The starting doses are 50-100 mg/day for metoprolol, 2.5-5 mg/day for

bisoprolol, or 6.25-12.5 mg/day - for carvedilol, divided into 1-2 doses. The dose may be increased progressively depending on the blood pressure and heart rate until the target ventricular rate is reached.

Antiplatelet are aspirin, which exerts an antiplatelet effect by inhibiting cyclooxygenase and thromboxane synthetase A2. It is administered in doses of 75-150 mg, the lowest effective, the risk of gastrointestinal bleeding being almost double at a dose of 162.5 mg/day vs placebo. Proton pump inhibitors may be combined to prevent gastrointestinal bleeding in patients with. Aspirin will be administered routinely to all patients with stable angina, with or without symptoms, but in the absence of contraindications. Clopidogrel is a thienopyridine derivative that is given at a dose of 75 mg/day (after a loading dose of 600 mg), in case of aspirin allergy or in combination with stent-type intravascular implants or in acute coronary syndromes. The risk of gastrointestinal haemorrhage is lower with clopidogrel compared with aspirin (1.99 vs 2.66 %, after 1.9 years of treatment, CAPRIE study: Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events). Newer representatives of the lien pyridine class – prasugrel and ticagrelor have evidence from studies showing a stronger and faster inhibition of platelet activity and a lower non-response rate than clopidogrel, which is accompanied by a more sustained effect during the maintenance phase and a more rapid decrease in plasma concentration after discontinuation of the medication.

Treatment with lipid-lowering drugs is guided by cardiovascular risk and LDL cholesterol levels. Statins - simvastatin, 40 mg/day, pravastatin, 40 mg/day, rosuvastatin, 10 mg/day and atorvastatin, 80 mg/day - are recommended in patients at high cardiovascular risk, and the dose will be increased until the target is reached (LDLc <1.8 mmol/l, or its decrease by at least 50 %, if LDL-c is between 1.8 and 3.5 mmol/l in patients with diabetes), provided tolerable. Hepatic and muscular cytolysis enzymes should be evaluated periodically to control for possible side effects. Other lipid-lowering drugs that can be used in stable angina pectoris are: ezetimibe, which reduces intestinal absorption of

cholesterol and is administered in combination with statins (in case of side effects the dose of statin will be reduced); fibrates - fenofibrate, 160 mg (proven efficacy in diabetic patients with hypertriglyceridemia), gemfibrozil which has proven beneficial in patients with insulin resistance and torcitabine (increases HDL cholesterol levels). The combination of lipid-lowering agents is recommended in patients with severe dyslipidaemia and increased risk of cardiovascular mortality (> 2 %).

Calcium channel blockers have anti-anginal action through the vasodilating effect, by blocking the influx of calcium into the muscle cell. Depending on their action, they are divided into dihydropyridines, which have a predominantly vascular action and non-dihydropyridines - which, in addition to the vascular effect, also have an important cardiac action - negative inotropic, chronotropic and dromotropic. In the case of stable angina pectoris, it is especially recommended to use non-dihydropyridine calcium blockers, such as verapamil and diltiazem, which control angina with the same effectiveness as beta-blockers, but, unlike them, do not prolong survival. In contrast, dihydropyridine calcium channel blockers such as amlodipine, felodipine, lercanidipine can be used in combination with beta-blockers in hypertensive patients. Be careful, though, because diltiazem or verapamil are not associated with beta-adrenergic blockers due to the increased risk of severe bradycardia or precipitation of heart failure. Nitrates and calcium channel blockers are indicated for patients with vasospastic angina pectoris, and beta-blockers should be avoided. The most commonly used doses of calcium channel blockers are: diltiazem, 120-360 mg/day, verapamil, 160-480 mg/day, amlodipine, 5-10 mg/day, lercanidipine (10-20 mg/day), in depending on heart rate and blood pressure, respectively.

Nitrates act by releasing nitric oxide, its vasodilating effect being more pronounced on the veins than on the arteries. Through the vasodilation effect on the lower limbs, nitrates reduce the venous return, the pre-charge and the diastolic dimensions of the heart, the final result being the decrease of the myocardial oxygen demand. They dilate both healthy coronary arteries and narrowed coronary arteries, favouring the

redistribution of blood through the collaterals, from well-irrigated myocardial areas to ischemic areas, especially at the subendocardial level. Chronic administration of nitrates may induce tolerance. This occurs after a few days-weeks in the case of oral doses and after a few hours - in the case of intravenous administration, but the effect can be avoided by the uneven, asymmetrical distribution of medication doses. The most common side effects of nitrates are headache and hypotension. Nitrates have several forms of administration and can be short or long acting.

Sublingual and spray nitroglycerin formulations provide immediate relief of effort angina. At the onset of angina symptoms, the patient should rest in a sitting position (standing promotes syncope, and lying down enhances venous return and preload) and take nitroglycerin (0.3–0.6 mg tablet sublingually and not swallowed, or 0.4 mg spray to the tongue and not swallowed or inhaled) every 5 min until the pain disappears, or a maximum of 1.2 mg has been taken within 15 min. Nitroglycerin can be administered for prophylaxis before physical activities known to provoke angina. Isosorbide dinitrate (5 mg sublingually) has a slightly slower onset of action than nitroglycerin due to hepatic conversion to mononitrate. The effect of isosorbide dinitrate may last ≤1 h if the drug is taken sublingually or persist for several hours if the drug is taken by oral ingestion. Nitro-glycerine for intravenous use is administered according to blood pressure and heart rate values, in doses of 5-100 pg/minute. The rate of intravenous administration of Nitro-glycerine may be increased by 10 pg/minute every 3-5 minutes, until angina disappears or systolic blood pressure drops below 100 mmHg. Intravenous administration of Nitro-glycerine is also indicated in the treatment of myocardial infarction, left ventricular failure and hypertensive crisis.

Long-acting nitrates such as isosorbide 5-mononitrate and isosorbide dinitrate are administered orally to prevent angina attacks at doses of 40-120 mg daily. To prevent nitrate tolerance, two daily intakes are recommended, at regular intervals, preferably in the morning and at

noon, or a single dose of nitrate retard is given in the morning to cover the active part of the day and to remain free during at night.

Potassium channel activators nicorandil has a nitrate-like vasodilation mechanism of action, the studies has proven that the drug reduces the death, AMI and hospitalization for stable angina pectoris, when given in combination with other drugs (recommendation class IC).

Sinus node inhibitors are an alternative drug for beta-blocker intolerant patients, it reduces the heart rate by directly inhibiting the If channels of the sinus node. A drug from this class is ivabradine, which has been shown to be as effective as beta-blockers in reducing angina symptoms (the BEAUTIFUL study: Morbidity- Mortality Evaluation of the If inhibitor ivabradine in patients with coronary heart disease and left ventricular dysfunction) (IIaB).

Metabolic agents such as trimetazidine and ranolazine are used as second line therapy in patients with stable angina pectoris refractory to other therapeutic classes; they have no hemodynamic effects, but improve myocardial cell metabolism and may have an additive effect in combination with beta-blockers (recommendation class IIbB).

Molsidomine it is a vasodilator, having as mechanism of action the release of nitric oxide. Daily doses are 2-8 mg/day in 2-4 doses. It does not cause tolerance, but may cause more pronounced hypotension compared to nitrates.

According to ESC recommendations, drug treatment in angina pectoris will be indicated and monitored individually. Thus, sublingual nitro-glycerine will be administered to all patients in angina attack, depending on tolerance; the dose of one drug will be optimized before supplementing another drug; the combination two drugs is recommended, before adding the third; myocardial revascularization will be indicated in symptomatic patients who cannot be controlled with two drugs.

REVASCULARIZATION THERAPY IN CHRONIC CORONARY SYNDROME

Myocardial revascularization plays a central role in the management of CCS on top of medical treatment, but always as an adjunct to medical therapy without supplanting it. The two objectives of revascularization are symptom relief in patients with angina and/or improvement of prognosis.

Both the anatomy and the functional assessment of the severity of the coronary lesion are required for the revascularization decision. Revascularization by percutaneous coronary intervention (PCI) or coronary artery by-pass graft surgery (CABG) is more effective for controlling angina, reducing the use of anti-anginal drugs, restoring exercise capacity and improving the quality of life compared to drug therapy alone. Revascularization by either PCI or CABG also aims to effectively eliminate myocardial ischemia and its adverse clinical manifestations among patients with significant coronary stenosis, and to reduce the risk of major acute cardiovascular events including MI and cardiovascular death.

In patients with multi-vascular damage or common trunk injury, the complexity of the coronary anatomy and the risk of angioplasty is calculated using the SYNTAX score (Appendix 1). A score < 22 shows a low risk for PCI intervention. Superiority of CABG compared to PCI was demonstrated in diabetic patients with CCS and tri-coronary atherosclerotic lesions and in non-diabetic patients with common left coronary trunk lesion and a Syntax score ≥ 33 or with tricoronary lesions and a Syntax score of > 22. The final decision will be made by a multidisciplinary team, informing the patient about the risks and benefits of each revascularization method and taking into account patient's preferences.

PCI consists of implanting a stent in the site of significant coronary stenosis, expanding the atherosclerotic plaque and restoring the arterial integrity (Figure 4, 5). The method requires an arterial approach identical to that required for coronary angiography, thus involving similar local complications.

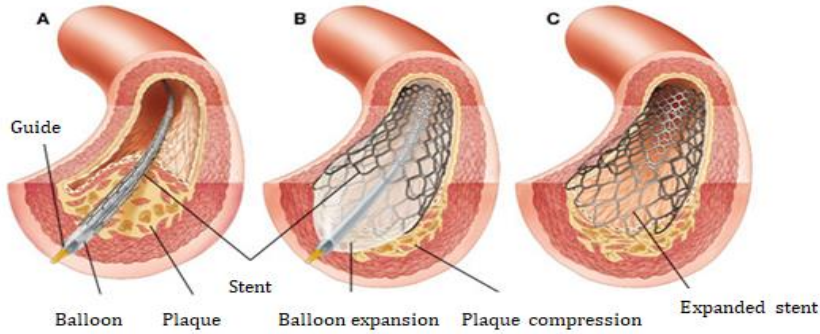
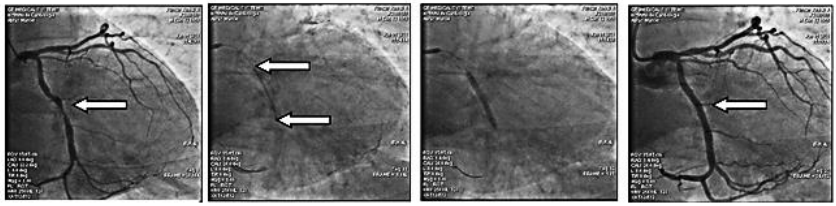


Figure 4. **PCI steps:**

A. Guide crossing through the atherosclerotic plaque with stent positioning at the level of the stenosis; B. Stent expansion; C. Complete restoration of the artery.



A. Severe stenosis of the Cx artery | B. Stent placement | C. Stent expansion | D. Cx artery after angioplasty

Figure 5. **PCI on the circumflex artery (Cx)**

Coronary stents have been developed to prevent arterial recoil and restenosis after balloon dilation. Stents can be classified into 3 large families: bare-metal stents (BMS), drug-eluting stents (DES) and bioresorbable vascular scaffolds (BVS).

A. Bare metal stents (BMS)

The first stents were made of stainless steel and, despite their thick profile and low flexibility, showed superiority over simple balloon angioplasty, eliminating sudden occlusion and having a lower rate of restenosis, confirmed in 2 historical studies published in 1993 (BENESTENT and STRESS). However, they have not been universally adopted due to the high incidence of acute and subacute intra-stent

thrombosis. This problem has been overcome by the introduction of dual antiplatelet therapy, which combines ticlopidine or clopidogrel with aspirin. At medium and long-term follow-up, BMSs carry a significant risk of intra-stent restenosis, reported in the 15-30 % of treated lesions.

B. Drug-eluting stents (DES)

The logical response to neointimal hyperplasia as a major determinant of coronary stent restenosis was the application of impregnated antiproliferative agents on the surface of the stents. So, in addition to the fact that stents act as permanent vascular scaffolds, they have become effective local platforms for drug administration. Thus, a revolutionary paradigm shift in the history of interventional cardiology was achieved.

- First-generation DES stents: sirolimus-eluting and and paclitaxel-eluting stents have further improved the results of percutaneous coronary intervention (PCI) by improving early results and reducing the risk of restenosis. Both were made of stainless steel, with a strut thickness > 130 μm.
- Second-generation DES stents: zotarolimus-eluting and everolimus-eluting stents. For these stents the platform was changed from stainless steel to metal alloys (cobalt-chromium or platinum-chromium), which meant a reduction in strut thickness and greater flexibility. Polymers consist of new, more biocompatible molecules, such as zotarolimus, everolimus and novolimus, with faster drug release and earlier endothelial coating.
- Polymer-free drug-eluting stents (PF-DES): A new strategy to eliminate polymer-mediated complications has been the development of polymer-free DES with a porous surface loaded with antiproliferative drug, which is released directly from these pores after implantation.
- Degradable polymer stents: they are coated with biodegradable polymers (such as poly-DL-lactide-co-glycolide or PLLA), can offer the advantage of a conventional DES - in the early stage

and behave like a BMS - in the later stages. Degradation of the bioresorbable polymer occurs simultaneously with the controlled release of the antiproliferative drug in the early post-implantation phase. After complete release of the drug and biodegradation of the polymer, only the metal platform remains in the coronary artery.

C. Bioresorbable vascular scaffolds (BVS)

Fears of late adverse events in the persistence of metal platforms in the coronary vessel have aroused interest in fully bioresorbable scaffold technology, which is a real revolution in interventional cardiology. BVS can be made of polylactic acid or metal alloy (magnesium, iron or zinc), being covered with a polymer and impregnated with an antiproliferative drug. The basic concept was the creation of a device that ensures the local delivery of drugs and mechanical support of permanent DES in the first 12 months and then completely reabsorbed after 24-36 months, allowing the restoration of normal luminal diameter and vasomotor function.

Despite the initial optimism, however, a number of disadvantages of polylactic acid-based scaffolds have emerged. Their radial strength is weaker than the strength of the DES, so recoil can be a problem in the case of rapid absorption. The latter resulted in higher rates of thrombosis and myocardial infarction at 1 year. Metal BVS become more attractive because they have the potential to overcome the limitation of polymeric BVS, being equipped with more radial force and thinner struts. However, the use of BVSs is limited only in controlled clinical trials or trials and there is still a long way to go before they can be used in routine clinical practice.

Dual antiplatelet therapy in PCI

Dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 receptor inhibitor, is the cornerstone in the treatment of patients undergoing elective PCI. The loading dose with aspirin is 150-300 mg, and that of clopidogrel - 600 mg, administered immediately before performing PCI. Maintenance doses of 75-100 mg aspirin and 75 mg clopidogrel, in combination, should be maintained for up to 6 months in

most cases of revascularization in CCS, regardless of stent type. The duration of treatment may be reduced to 1-3 months in the latest generation of active stents in patients at high risk of bleeding, or it may be extended in patients at high ischemic risk, including patients undergoing PCI after acute coronary syndrome.

Coronary artery by-pass graft surgery

Revascularization by coronary artery by-pass graft surgery (CABG) involves suturing arterial or venous grafts distal to the area with stenosis, a maneuverer that leads to the restoration of normal blood supply in coronary arteries with significant hemodynamic lesions (*Figure 6*).

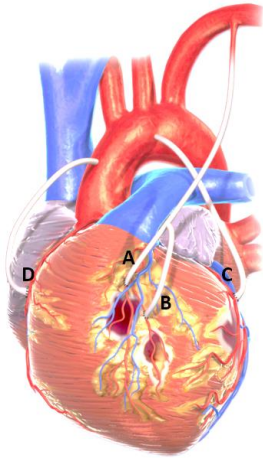
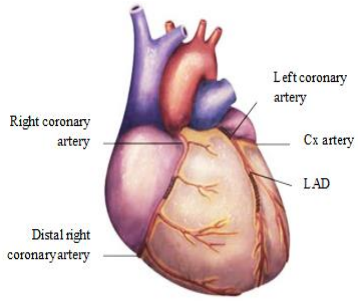
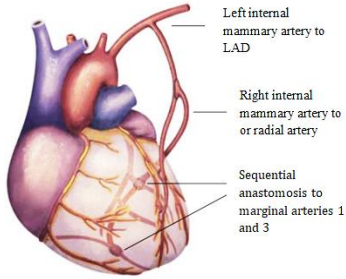


Figure 6. **Quadruple CABG: arterial graft in „Y" a.** Left internal mammary artery on the anterior descending artery (A), with segment of the left radial artery on the first diagonal branch (B), saphenous venous graft on the circumflex artery (C) and on the right coronary artery (D).

Over the last decades the clinical results of CABG have been significantly improved by the increasing application of arterial grafts and the improvement of extracorporeal circulation devices, by vigilant myocardial care, off-pump manoeuvres and effective postoperative pharmacotherapy. The complications induced by surgical treatment are presented in the *Table 2*. Long term safety is better for arterial grafts (usually the internal mammary artery - branch of the left or right subclavian artery, but also segments of the radial or gastro-epiploic artery) compared to venous (inverted internal saphenous vein segments, proximal to aorta and distal to the target coronary artery) due to the

difference in wall structure of the two types of vessels, the arterial being more appropriate to the existing pressure regime in the systemic circulation in which the grafts are connected. Classically, CABG requires cardioplegia (cardiac arrest), during which time the patient is connected to the extracorporeal circulation through the heart-lung machine. In the last decade, surgical techniques without cardioplegia have been introduced (surgery on beating heart with a classical approach - sternotomy or mini-invasive - intercostal approach and robotic surgery). CABG has shown better clinical outcomes in diabetic patients and those with more complex coronary lesions, with several clinical, anatomical, and technical issues that should be considered by the multidisciplinary team in the process of decision making (*Figure 7*). The decision of surgical myocardial revascularization must take into account several factors such as: patient age, comorbidities, history of CABG, fragility or immobilization of the patient, the possibility of obtaining a complete and lasting revascularization, but also the patient's desire, after appropriate counselling by the multidisciplinary team.





Favours P

Clinical features

Presence of severe comorbidities (inadequately reflected by scores)

Old age / disability / low life expectancy

Anatomical and technical aspects

Multiple arterial disease with SYNTAX score 0-22

Favours CABG

Clinical features

Diabetes

Decreased LV function (EF ≤35%)

Contraindications for DAPT

Stent diffuse, recurrent restenosis

Anatomical and technical aspects

Multiple arterial disease with SYNTAX score ≥23

Anatomy that would probably result in incomplete revascularization by CABG	Anatomy that would probably result in incomplete revascularization by PCI
Chest deformities or severe scoliosis	Severe calcified coronary lesions that may limit the expansion
Sequelae of thoracic irradiation	**The need for concomitant interventions**
Porcelain aorta	Pathology of the ascending aorta with surgical indication
	Concomitant cardiac surgery

Figure 7. **Aspects to be considered by the multidisciplinary team in making the decision to revascularize by PCI or CABG in patients with CCS and tricoronary and / or common trunk lesions.**

Table 2.

Complications of the CABG

Complications linked to the by-pass procedure
Post-perfusion neurologic syndrome
Sternal wound dehiscence
Acute myocardial infarction (by embolus, hypoperfusion or graft thrombosis)
Late graft stenosis
Acute kidney failure (by embolus or hypoperfusion)
Stroke (by embolus or hypoperfusion)
Hydrothorax, pneumothorax or hemothorax
Cardiac tamponade
General complications associated to cardiac surgery
Rhythm abnormalities, more often atrial fibrillation
Conduction abnormalities
Complications associated to general surgery
Infection at the incision site, mediastinitis, other forms of sepsis
Deep vein thrombosis
Post anesthesia complications
Keloid scar
Chronic pain in the site of incision

PRIMARY AND SECONDARY PREVENTION

Adequate control of modifiable risk factors leads to a significant decrease in mortality even in high-risk patients. A healthy lifestyle means a healthy diet, regular physical activity, but also adequate control of cardiovascular risk factors (smoking, diabetes, hypertension, dyslipidaemia, obesity). It is also recommended to inform the patient about the severity of the disease and the importance of personal contribution to their own health. Cardiovascular prevention treatment should be started as soon as angina pectoris is suspected. Antiplatelet agents (most commonly aspirin) and statins will be used, and in special categories of patients (hypertensive patients with left ventricular systolic dysfunction, diabetes mellitus or chronic kidney disease) ACE, sartans and beta blockers will be used.

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SELF-EVALUATION TESTS

1. Secondary prevention in patients with stable angina pectoris include:

A.B-blockers
B. Antiplatelet agents
C. Thrombolytics
D. Statins
E.A-blockers
Correct answer: A, B, D

2.CM. Mark the correct statements about microvascular pectoris:

A. Typical angina pain
B. Positive stress test
C. Angiography: normal coronary arteries
D. It occurs mainly in women
E. It occurs mainly in men
Correct answer A, B, C, D

3.CM. Mark the correct statements about coronary atherosclerotic lesion:

A. Haemorrhagic rash
B. Lipid stripe
C. Urticarial plaque
D. Fibrous plaque
E. Complicated atheromatous plaque
Correct answer: B, D, E

4.CM. Name the forms of acute coronary syndrome:

A. silent angina pectoris
B. Unstable angina pectoris
C. Acute myocardial infarction
D. Microvascular angina
E. Stable angina
Correct answer: B, C

5.CM. Select the painful clinical forms of ischemic heart disease:

A. Stable angina pectoris
B. Unstable angina pectoris
C. Acute myocardial infarction
D. Arrhythmias
E. Heart failure
Correct answer: A, B, C

6.CM. Select painless clinical forms of ischemic heart disease:

A. Vasospastic angina
B. Rhythm and conductibility disorders
C. Stable angina pectoris
D. Ischemic heart failure
E. Silent ischemia
Correct answer: B, D, E

7.CM. Select the symptoms specific for angina pectoris:

A. Dyspnoea
B. Chest pain
C. Low back pain
D. Burning sensation in the chest
E. Fever
Correct answer: A, B, D

8.CM. Select the factors involved in the pathogenesis of angina pectoris:

A. Decreased coronary flow
B. Liver failure
C. Respiratory insufficiency
D. Renal injection
E. Coronary stenosis
Correct answer: A, E

9.CM. The pathophysiology of the onset of coronary insufficiency is marked by:

A. Atherosclerosis of coronary arteries
B. Claude-Bernard-Horner syndrome
C. Vascular spasm
D. Pancoast-Tobias syndrome
E. Blood clotting disorder
Correct answer: A, C, E

10.CM. Select the procoagulant endothelial factors in ischemic heart disease:

A. Tissue thromboplastin
B. Willebrand factor
C. Heberden nodules
D. Endothelin
E. Platelet activating factor
Correct answer: A, B, E

12.CM. Select ECG changes during angina attack:

A. P *pulmonale*
B. ST depression
C. P *mitralis*
D. Negative T wave
E. ST elevation
Correct answer: B, D, E

13.CM. Angina pectoris pain can irradiate to the following regions:

A. Left shoulder
B. Lumbar region
C. Left scapula
D. Left arm
E. Occipital area
Correct answer: A, C, D

14.CM. Select the drugs indicated for reducing the preload in decubitus angina pectoris:

A. Diuretics
B. Thrombolytics
C. Nitrates
D. Digitalis
E. Statins
Correct answer: A, C

15.CM. The treatment of stable angina pectoris includes:

A. Nitrates
B. β-blockers
C. Diuretics
D. Calcium channel blockers
E. α-blockers
Correct answer: A, B, D

16.CM. Mark the criteria for positive exercise test:

A. Typical angina pectoris pain
B. Horizontal ST depression
C. Kayser-Fleischer ring
D. Left ventricular hypertrophy
E. Long QT interval
Correct answer: A, B, D

17.CM. Select the first line treatment of vasospastic angina:

A. Nitrates
B. A - blockers
C. Calcium channel antagonists
D. Thrombolytics
E. Diuretics
Correct answer: A, C

18. Note the aims to coronarography:

A. To examine the carotid arteries
B. To examine the coronary arteries and coronary aortic bypass grafts
C. To examine the celiac trunk
D. To examine the descending aorta
E. To examine the ascending aorta

Correct answer: B

19. Mark the information provided by coronary angiography:

A. The statement of the carotid wall arteries thickness
B. The endothelial thickness
C. Content of the atherosclerotic plaque
D. Coronary stenosis
E. Ejection fraction

Correct answer: D

20. Patients at high risk for coronary heart disease established by non-invasive investigations are recommended for:

A. Cardiac magnetic resonance
B. Coronary angiography
C. Cardiac computed tomography
D. Exercise scintigraphy test
E. Stress echocardiography (pharmacological or physical exertion)

Correct answer: B

21. Coronary angiography is recommended in the following situations:

A. Survivors of a resuscitated cardiopulmonary arrest
B. Patients with severe ventricular arrhythmias
C. Revascularized patients with early recurrence of moderate and severe angina symptoms
D. Patients with uncertain diagnosis after non-invasive tests or with contradictory results by several non-invasive methods, those with intermediate or high risk of ischemic coronary heart disease

E. Patients with Canadian class I or II angina, responding to drug treatment

Correct answer: A B C

22. Mark the indications for coronary angiography in stable angina pectoris:

A. Patients with angina who cannot perform non-invasive tests and the risk cannot be stratified by other methods
B. Patients with Canadian-grade angina I or II, with intolerance or refractory to drug treatment
C. Patients of high-risk professions (pilots, bus drivers, etc.) with abnormal stress tests, but without high-risk characteristics.
D. Patients with Canadian-class angina I/II and/or responding to drug treatment
E. Patients with angina pectoris grade III or IV, ameliorated under treatment in class I or II

Correct answer: ABCE

23. Select the absolute contraindications to coronary angiography:

A. Uncontrolled hypertension
B. Refusal of a competent mental patient to consent to the procedure
C. Chronic renal failure from diabetic nephropathy
D. Decompensated congestive heart failure or pulmonary edema
E. Acute stroke

Correct answer: B

24. Select the relative contraindications for coronary angiography:

A. Acute renal failure
B. Allergic reaction to lidocaine
C. Active gastrointestinal bleeding
D. Acute stroke

E. Documented anaphylactic reaction to the contrast substance

Correct answer: ACDE

25. Mark the score indicated for the assessment of the anatomical complexity of coronary heart disease and the long-term risk of mortality and morbidity after coronary angioplasty:

A. GRACE score
B. EUROSCORE II score
C. SYNTAX score
D. Score Crusade
E. STS score

Correct answer: C

26. Select the indications for coronary angiography as a diagnostic procedure:

A. Stable angina pectoris of Canadian class III or IV with high likelihood of ischemic coronary heart disease and inadequate drug control
B. Patients with severe valvular pathology before surgery
C. Patients with supraventricular arrhythmias
D. Revascularized patients without early recurrence of symptoms
E. Patients at increased risk of restenosis after angioplasty performed in a high-risk area

Correct answer: EBA

27. Select the situations where coronary angiography is not indicated:

A. Patients with angina who cannot perform non-invasive tests and whose risk cannot be stratified by other methods
B. Canadian class II angina patients with intolerance to drug treatment not responsive to specific medication
C. To assess the risk of cardiovascular disease in the next 10 years
D. Patients with ameliorated angina pectoris from class III or IV ameliorated under treatment in class I or II

E. Patients at increased risk of adverse events in non-invasive assessments but with mild to moderate symptoms

Correct answer: C

28. Select the possible complications after coronary angiography:

A. Death
B. Ventricular fibrillation
C. Hematoma at the puncture site
D. Anaphylactic shock
E. Chronic renal failure

Correct answer: ABCD

29. Select the scores that are being used for the assessment of in-hospital mortality after CABG.

A. GRACE score
B. Euro SCORE II score
C. Syntax score
D. Crusade score
E. STS score

Correct answer: BE

30. Post-CABG coronary angiography is recommended in patients with:

A. Ischemic symptoms and/or abnormal levels of biomarkers suggestive of perioperative MI
B. Extensive ischemic ECG changes
C. New onset parietal kinetics disorders
D. Low amplitude of the R wave from V 4 to V 6
E. Hemodynamic instability

Correct answer: ABCE

31. Select the correct dosage of Clopidogrel before and after PCI:

A. Loading dose 600 mg orally, maintenance dose 100 mg / day.
B. Loading dose 600 mg orally, maintenance dose 75 mg / day.

C. Loading dose 300 mg orally, maintenance dose 75 mg / day.
D. Loading dose 150 mg orally, maintenance dose 75 mg / day.
E. Loading dose 75 mg orally, maintenance dose 75 mg / day.

Correct answer: B

32. Select the correct dosage of Acetylsalicylic acid before and after PCI:

A. Loading dose 150-300 mg per os, maintenance dose 75-100 mg / day.
B. Loading dose 100 mg per os, maintenance dose 75 mg / day.
C. Loading dose 450 mg per os, maintenance dose 100 mg / day.
D. Loading dose 150 mg per os, maintenance dose 150 mg / day.
E. Loading dose 75 mg per os, maintenance dose 75 mg / day.

Correct answer: A

33. Select the possible associations for double antiplatelet therapy:

A. Aspirin + Clopidogrel
B. Aspirin + Ticagrelor
C. Aspirin + Eptifibatide
D. Aspirin + Prasugrel
E. Aspirin + Enoxaparin

Correct answer: ABD

34. Select the methods of the functional assessment of the severity of intermediate-grade coronary lesions:

A. IVUS (intravascular ultrasound)
B. OCT (optical coherence tomography)
C. FFR (fractional flux reserve)
D. Cardiac MRI
E. Angio CT

Correct answer: C

CLINICAL CASE 1

Complete myocardial revascularization in tri-coronary involvement by PCI in several steps

Patient A., 73 years old male, complains of constrictive retrosternal pain at during mild physical exercise (functional class III), which ameliorates after sublingual Nitro-glycerine 0.5 mg administration, and which upon continuation of exercise is associated with dyspnoea. The patient suffered a non-Q MI 14 years ago. The patient is currently treated with angiotensin converting enzyme inhibitors, antiplatelet agents, and prolonged-release nitrates. The electrocardiogram reveals sinus rhythm with a rate of 60 beats per minute, intermediate electrical axis of the heart, segmental ST elevation by 0.5 mm, followed by the negative „T" wave in D II, D III, aVF. Echocardiography showed: moderate dilation of the LA, thickening and induration of the aortic walls and aortic valve, hardened mitral valve leaflets. The overall ejection fraction of the LV was 55%. Abnormal diastolic function of the LV was established, as well as mitral valve regurgitation grade II, tricuspid valve regurgitation grade I-II and pulmonary valve regurgitation grade I. Taking into account the high clinical likelihood of CAD, typical angina refractory to medical treatment, as well ECG changes at rest, the patient was examined by invasive coronary angiography to visualize the vascular bed and establish subsequent treatment management (*fig. 8*).

Triple atherosclerotic lesions were detected by coronary angiography: severe stenosis at the origin of the circumflex artery (aCx), with retrograde perfusion of the distal segments through intra- and extra system collaterals -I A; critical stenosis at the bifurcation of the left anterior descending artery (LAD) with the diagonal branch I - II A; critical right coronary artery stenosis (RCA) - III A. The Syntax score was calculated as intermediate (25 points), the cardiac surgery risk was assessed as low (1.5 % mortality risk). The multidisciplinary team consisting of cardiologist, interventional cardiologist and cardiac surgeon first recommended the CABG procedure. The patient refused the surgical

method and was recommended the PCI as an alternative revascularization in several steps.

In the first step, the chronic occlusion on aCx was approached. After crossing the occlusion with an angioplasty guide, serial dilations were performed with semi-compliant balloons and implantation of the second generation drug-eluting stent, size 3.0-23 mm (IB), subsequently post-dilated with a non-compliant balloon at high pressures with a good result at the end of the procedure (IC).

In the second step, critical stenosis of the proximal segment of the RCA was addressed. After crossing the stenosis with a guide wire, serial dilations were performed with semi-compliant balloons and implantation of a second generation drug-eluting stent 2.5-22 mm (II B), with a good result at the end of the procedure (II C).

In the third step, the critical stenosis from the LAD bifurcation with the diagonal branch I was approached. After crossing the stenosis with two guide wires, the dilation of the LAD stenosis in segment I-II was performed with a semi-compliant balloon. Subsequently, a second generation drug-eluting stent was implanted, size 3.5-24 mm (III B), with a „window" in the stent cells towards the diagonal branch I, using the „kissing-balloon" technique. A good final result was achieved (III C).

In the fourth step, severe stenosis of the aCx was addressed. After crossing two angioplasty guides in the distal aCx and LAD, stenosis dilation was performed on aCx. Subsequently, the „cullotte" technique was applied, with the implantation of two second generation drug-eluting stents, 3.5-24 mm from the common trunk to aCx and 3.5-20 mm from the common trunk to LAD (IV A). After performing the „kissing-balloon" (IV B), the stents were inflated proximally with a non-compliant balloon at high pressures, obtaining a good final result (IV C).

In conclusion, the given patient benefited from complete myocardial revascularization by PCI in 4 stages, with the implantation of 5 pharmacological second generation stents, achieving a good angiographic and clinical result, despite the fact that he had complex

triple coronary atherosclerotic lesions and the first recommendation was CABG.

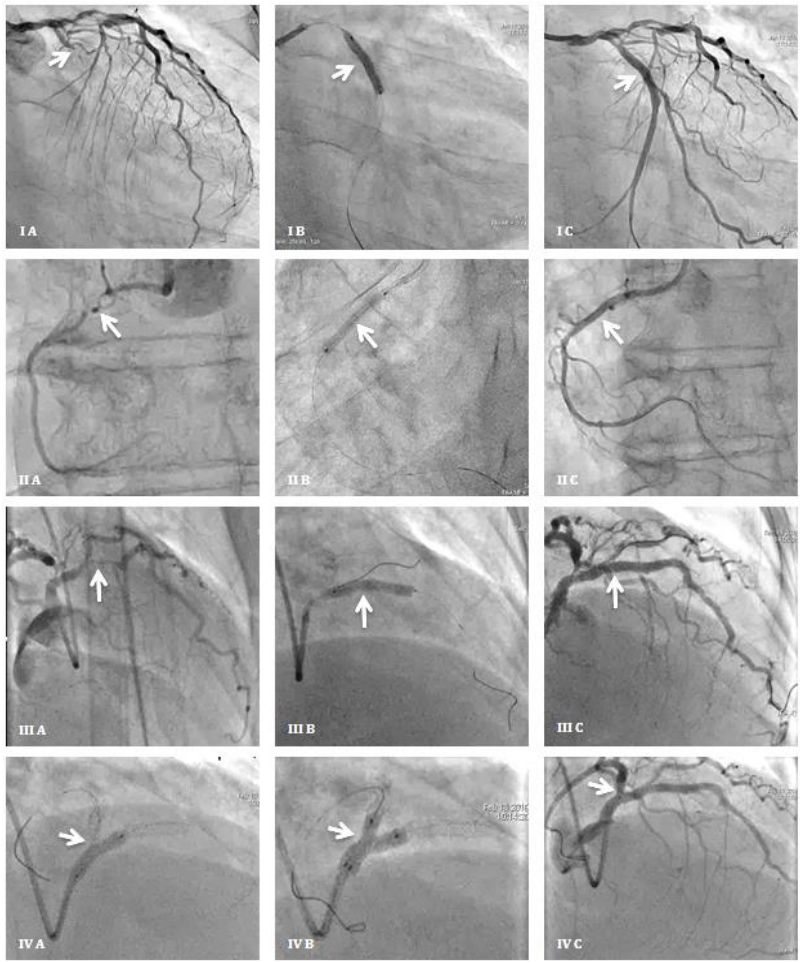

Figure 8. **PCI in 4 stages, with complete myocardial revascularization**

Conclusion to the case

- Patients who refuse CABG revascularization should be offered an
- alternative to revascularization.

- PCI in complex triple coronary atherosclerotic lesions needs to be staged.
- High-performance percutaneous techniques and devices offer the chance to achieve complete revascularization even in the case of complex lesions, which essentially improves the prognosis of patients, compared to the patients who are incompletely revascularized.

CLINICAL CASE 2

The hemodynamic significance of atherosclerotic lesions and intravascular imaging techniques in PCI.

Patient B., 61 years old male, complains of constrictive retrosternal pain and dyspnoea at medium physical exercise (functional class II), which is relieved by rest and nitro-glycerine administered sublingually; the patient also complains of lower limbs oedema that occurs in the evening. The medical history of the patient is marked by PCI on LAD, aCx and RCA. He has been hypertensive for several years, with maximum blood pressure values of 220/100 mmHg. The patient also suffers from insulin-independent type 2 diabetes, III degree obesity and dyslipidaemia. His permanent treatment includes antianginal, antiplatelet and antihypertensive drugs. The electrocardiogram reveals a sinus rhythm with a heart rate of 90 b/min, the cardiac axis is shifted to the left. Echocardiography results: moderate dilation of the LA, induration of the walls of the ascending aorta, aortic and mitral valve; Moderate LV hypertrophy (IVS 12 mm, posterior wall of the LV 11 mm); the overall contraction function of the LV is sufficient (EF = 51%); impairment of LV relaxation; mitral valve regurgitation grade II, aortic valve grade I, tricuspid valve grade II and pulmonary valve grade I. Considering the history of CAD with PCI on 3 arteries, typical angina pectoris accompanied by dyspnoea, the patient was evaluated by coronary angiography in order to visualize the vascularisation of the myocardium bed and establish subsequent management (*Figure. 9*).

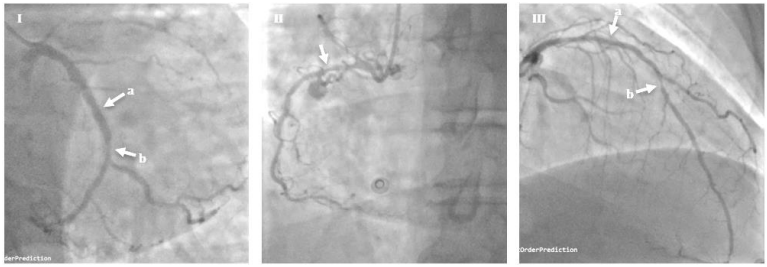

Figure 9. **Coronary angiography: moderate stenosis on aCx segm.** II (I b) and on LAD segm. III (III b), intrastent moderate restenosis on RCA segm. I (II) and on LAD segm. II (III a). Stent previously implanted on aCx segm. II with minimal signs of intrastent restenosis (I a).

The ECG exercise test could not be performed due to patient's obesity. Thus, in the absence of documentation of myocardial ischemia and in the presence of medium-grade stenosis, fractional flow reserve (FFR) was measured on aCx and LAD (Figure 10). The latter is an invasive index of hemodynamic significance of stenosis severity, measured using a pressure wire sensor. The FFR value is the ratio between the aortic pressure (Pa) and the coronary pressure appreciated distally by the stenosis (Pd), on the background of maximum hyperemia. It was found that stenosis on the segment. II al aCx is hemodynamically insignificant (FFR> 0.80), and that on LAD segm. III is hemodynamically significant (FFR ≤0.80).

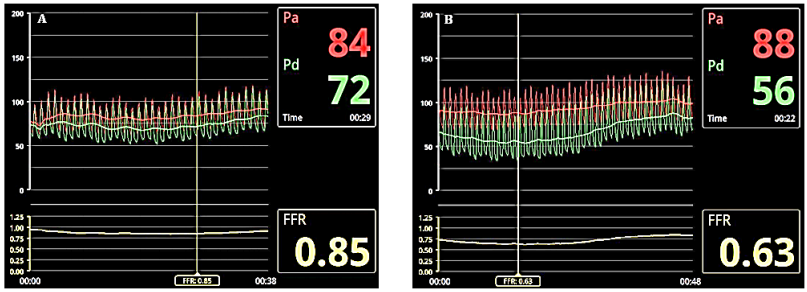

Figure 10. **FFR measurement on aCx segm.** II (A) and LAD segm. III (B).

Subsequently, PCI was used on LAD segm. III (figure 11). After predilution of the stenosis with a semi-compliant balloon, for the

calibration of the stent, the technique of intravascular imaging by optical coherence tomography (OCT) was used. A dissection of dilated stenosis (A) was visualized, which was covered with a second-generation drug eluting stent, measuring 2.5-33 mm. The final angiographic result after stenting was evaluated by OCT, which found the expansion and correct positioning of the stent in the lumen of the vessel (B).

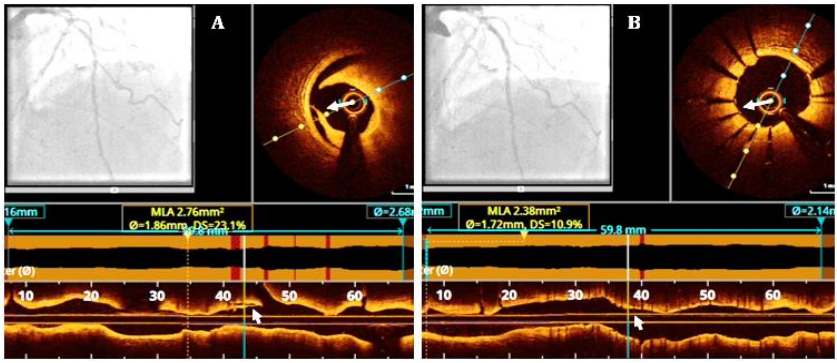

***Figure 11*. PCI on LAD guided by intravascular imaging by OCT:** image after balloon dilation (A) and after stenting (B).

- **Conclusion to the case**
- FFR measurement, performed in addition to coronary angiography, can be applied to document inducible ischemia (in the absence of non-invasive exercise testing).
- Assessment of the hemodynamic significance of intermediate stenosis is mandatory to decide which of them need to be revascularized and which can be delayed.

Intravascular imaging techniques objectify and optimize PCI results.

USMF „Nicolae Testemițanu”
Centrul Editorial-Poligrafic *Medicina*
Formatul hârtiei 60x84 $^{1}/_{16}$ Tiraj: 50 ex.
Coli de autor: 1,8 Comanda nr. 152
Chișinău, bd. Ștefan cel Mare și Sfânt, 165