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PARADIGM CHANGE FOR STABLE CORONARY DISEASE IN CHRONIC CORONARY SYNDROME. NOVELTIES IN THE GUIDELINES OF THE EUROPEAN SOCIETY OF CARDIOLOGISTS FROM 2019

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SUMMARY: Although the English physician Heberden described angina pectoris (AP) two and a half centuries ago, our understanding of this syndrome, as a cause, an optimal diagnostic approach and treatment, continues to develop. The new guidelines of the European Society of Cardiology(ESC) from year 2019 brings, first of all, a paradigm shift for stable coronary artery disease (SCAD) to the comprehensive term chronic coronary syndromes (CCS), which essentially means that chronic coronary artery disease (CAD) has complex clinical scenarios and may have periods of instability, at any evolutionary stage. The results of the essential COURAGE study and the latest studies: ISCHEMIA, ORBITA and metha-analysis on CCS as well as the key messages of the European Guidelines for Diagnosis and Treatment of Chronic Coronary Syndromes (CCS) shed light on the issue of coronary heart disease. Chronic coronary artery disease (CCAD) has long stable periods but due to acute atherothrombotic events, erosion or rupture of atherosclerotic plaque can progress to some of the acute coronary syndromes (ACS). The disease is chronic, usually progressive and therefore serious even in asymptomatic stages. The dynamic nature of CAD is manifested in various clinical presentations, which we categorize into either acute or chronic coronary syndromes. The paradigm shift emphasizes the fact that the dynamic processes of accumulation in atherosclerotic plaques and functional alterations of the coronary circulation can be modified by lifestyle changes, pharmacological therapy and myocardial revascularization (MR), which lead to stabilization or regression of the disease but unfortunately not complete cure. Careful evaluation of the anamnesis, characterization of anginal and other symptoms and evaluation of risk factors and manifestations of previous cardiovascular diseases (CVD), as well as assessment of the adequacy of physical activity and exercise tolerance, are of cardinal importance. The current guide to CCS identifies 6 leading and most common clinical syndromes: 1. Patients with suspected CCS and stable angina pectoris and / or dyspnea on exertion; 2. Patients with newly developed heart failure (HF) or left ventricular dysfunction (LVD) and suspected CAD; 3. Asymptomatic and symptomatic patients with stabilized symptoms lasting less than one 1 year after ACS or recent myocardial revascularization (MR); 4. Asymptomatic and symptomatic patients more than 1 year after ACS or MR; 5. Patients with AP and suspected vasospastic or microvascular disease; 6. Asymptomatic individuals in whom CAD was detected at screening. Each of these scenarios is classified as CCS and is a consequence of different evolutionary phases of chronic CAD, and has a different risk for future adverse cardiovascular (CV) events. Pre-test probability (PTP) of CAD, based on age, sex and quality of symptoms, has been revised and changed from the previous guide from year 2013. A new term has been introduced: Clinical probability of obstructive coronary artery disease (CPCAD) which includes both PTP and various risks factors of atherosclerotic CAD and serves to exclude or confirm the suspicion of CAD. The general methodological approach for initial diagnosis for patients with AP and suspected obstructive CAD involves 6 steps. STEP 1-Assessment of symptoms and signs to identify patients with possible unstable AP and other forms of ACS; STEP 2 is an assessment of the general condition and quality of life that decide on treatment planning; STEP 3 includes basic diagnostic procedures and assessment of left ventricular (LV) function of the heart; STEP 4 makes the determination of Pre-test and Clinical probability of obstructive CAD; STEP 5 is the selection of a

diagnostic test by physical or pharmacological stress via ECG and imaging methods including MSCT coronary angiography (CTA) to establish the diagnosis of CAD. Finally, STEP 6 is the assessment of the risk of adverse CV events, especially mortality, and based on that, make definitive therapeutic decisions with invasive coronary angiography (ICA) and possible MR. If obstructive CAD cannot be ruled out by clinical evaluation, either a noninvasive functional imaging test or anatomical imaging by CTA is performed as an initial test to exclude or confirm the diagnosis of CAD. Anatomical and functional assessment should be considered for a decision on RM, except in severe coronary stenosis> 90%. A high risk of adverse CV events identifies patients who would have great prognostic benefit from MR, even if asymptomatic. The role of myocardial revascularization (MR) has been placed in the context of recent evidence relating to the prognostic role of percutaneous coronary interventions (PCI) or coronary artery bypass graft (CABG) in this low-risk population. MR is reserved for patients where there is strong evidence to improve prognosis based on evidence of regional ischemia by perfusion imaging. Patients at high risk of mortality of 3% per year or more undergo coronary flow fractional reserve (FFR) or coronary flow reserve (CFR) due to perform MR even if they have no symptoms. The application of a healthy lifestyle reduces the risk of subsequent adverse CV events and is part of adequate secondary prevention therapy. Regular vaccination against influenza is necessary for everyone with CCS. Optimal medical therapy (OMT): non-pharmacological and pharmacological therapy of CCS is given great attention as the main type of treatment of CCS, not MR. The modern role of anti-ischemic (antianginal) drugs is emphasized: First lines - beta-blockers (BB) and calcium antagonists (CCB) with sublingual nitroglycerin, and Second lines - long-acting nitrates (LAN), with newer options: ivabradine, nicorandil, trimethazidine, allopuronol, etc. Drugs that improve the prognosis of CCS are statins and acetylsalicylic acid (ASA) and other antiplatelet drugs and recently low dose rivaroxaban and additionally angiotensin converting enzyme inhibitors (ACEI) and again BB in specific indications. Anti-ischemic treatment must be tailored to the individual patient based on comorbidities, other concomitant therapies, expected tolerances and adherence, and patient preferences. The choice of anti-ischemic drugs for the treatment of CCS should be adjusted to the heart rhythm, blood pressure and heart function. BB and ACEI are recommended for patients with LVD or HF with reduced left ventricular ejection fraction (HFrEF). Antithrombotic therapy is a key part of secondary prevention in patients with CCS. Patients with previous acute myocardial infarction (AMI), who are at high risk of ischemic events and low risk of fatal bleeding, should consider long-term dual antiplatelet therapy with aspirin and either P_2Y_{12} receptor inhibitor or a very low-dose rivaroxaban, unless there is an indication for oral anticoagulation, is atrial fibrillation (AF). Proton pump inhibitors are recommended in patients receiving only aspirin or a combination of antithrombotic therapy who are at risk of gastrointestinal bleeding. Statins are recommended for all patients with CCS, regardless of LDL level. ACEIs (or angiotensin receptor blockers, ARBs) are recommended in the presence of SI, diabetes, and hypertension and should be considered in patients at high risk for adverse events.

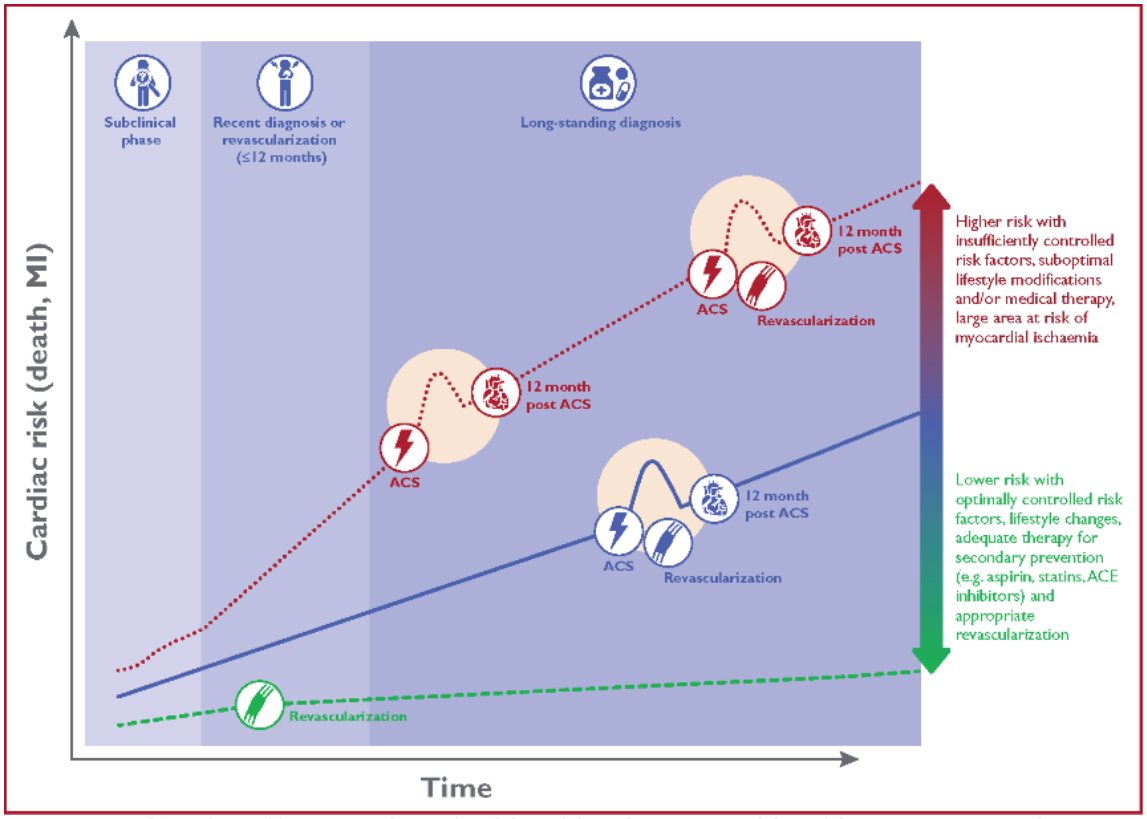
Keywords: Angina pectoris/stable, Angina Pectoris/Unstable, microvascular angina, angina pectoris with normal coronary arteriogram, ischemic heart disease, coronary heart disease, Acute coronary syndrome, Myocardial infarction, Myocardial ischemia/diagnosis/prevention and control/pharmacotherapy, Myocardial revascularization/percutaneous coronary intervention-PCI/coronary artery bypass-CABG

INTRODUCTION AND SIGNIFICANCE OF THE PROBLEM

The new 2019 European Society of Cardiology (ESC) guide for the diagnosis and management of chronic coronary syndromes [1] focuses on the new comprehensive term Chronic Coronary Syndromes (CCS) for all forms of chronic coronary artery disease (CCAD) except acute coronary syndromes [2,3], rather than only stable coronary artery disease (SCAD), as a previous ESC guide from 2013 [4]. The new guide of the European Association of Cardiologists from 2019 primarily brings a paradigm shift for stable coronary heart disease to the comprehensive term chronic coronary syndromes (CCS), which essentially means that CAD has complex clinical scenarios and can have periods of instability at any evolutionary stage. Essentially, the clinical presentation of coronary heart disease is categorized into either acute coronary syndromes (ACS) [2,3,5] or chronic coronary syndromes (CCS) [1]. Coronary heart disease (CAD) is a dynamic pathological process of appearance and growth of atherosclerotic plaques in epicardial coronary arteries, but also in their smaller intramyocardial branches [6,7, 8,9] (microvascular disease) with or without coronary vasospasm [10-13], without whether they are functionally fixed obstructive (stenotic) or non-obstructive [14,15]. This dynamic process leads to a functional alteration of the

coronary blood flow or myocardial ischemia. Myocardial ischemia can be reduced, stabilized or stagnation or regression of atherosclerotic plaques can be achieved through therapeutic interventions: optimal non-invasive medical ie. (medical therapy-OMT) which consists of lifestyle changes, reduction of risk factors and optimal pharmacotherapy (OPhT) and optimal invasive interventions - percutaneous or surgical myocardial revascularization (RM). [16-21]. CAD has long stable periods, but may also become unstable at some period due to acute atherothrombotic events — breakup or erosion of atherosclerotic plaque. However, the disease is chronic, most often progressive and therefore serious, even in clinically asymptomatic periods [1] (FIGURE 1).

FIGURE 1: CLINICAL PRESENTATION - CLINICAL SCENARIOS OF CHRONIC CORONARY SYNDROMES



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The dynamic nature of the CAD process results in different clinical presentations or clinical scenarios, acute coronary syndromes (ACS) [2,3,5] or chronic coronary syndromes (CCS) [1].

CLINICAL PRESENTATION - CLINICAL SCENARIOS OF CHRONIC CORONARY SYNDROMES (CCS).

The clinical presentation of CCS consists of 6 leading and most common clinical scenarios [1]:

1.Patients with suspected CAD and stable angina pectoris (AP) and / or dyspnea on exertion.

2. Patients with newly developed heart failure (HF) or left ventricular dysfunction (LVD) and suspected CAD.

3. Asymptomatic and symptomatic patients with stabilized symptoms up to 1 year after ACS or myocardial revascularization (RM).

4. Asymptomatic and symptomatic patients more than 1 year after ACS orRM.

5. Patients with AP and suspected vasospastic or microvascular disease.

6. Asymptomatic individuals in whom CAD was detected at screening.

Each of these scenarios is classified as CCS, is a consequence of different evolutionary phases of CAD and has a different risk for future adverse CV events (death or myocardial infarction) and this risk may change over time [1].

NEW CONCEPTS AND RECOMMENDATIONS FOR CCS

New concepts and recommendations for CCS and revised concepts and recommendations from the previous ESC guide in 2013 [4], in this 2019 ESC

guide [1], based on current available evidence from a large number of randomized studies, registers and expert consensus (cited a huge number of scientific papers: 529 references) have a holistic approach, give quite clear guidelines for the diagnosis and therapy of CCAD and systematically process all clinical presentations of CCAD in a clear and clinically applicable way. This ESC Guide and its recommendations should facilitate clinical decision-making by physicians in their day-to-day practice [1].

NEW MAIN RECOMMENDATIONS OF CLASS I (There is evidence and / or general agreement that a given treatment or procedure is benefitial, useful and effective: Wording to use: Is recommended or is indicated)

1. Non-invasive functional imaging diagnostic test for the detection of myocardial ischemia or coronary MSCT angiography should be the initial test for the diagnosis of CAD in symptomatic patients in whom obstructive coronary heart disease cannot be ruled out by clinical judgment alone.
2. It is recommended that the selection of the optimal test for the diagnosis of CAD be based on the Clinical Probability of CAD and other patient characteristics that affect test performance, local availability, and expertise.
3. Non-invasive functional imaging test for myocardial ischemia is recommended if coronary MSCT angiography shows CAD of uncertain functional significance or is non-diagnostic, inclusive.
4. Invasive coronary angiography (ICA) is recommended as an alternative test for the diagnosis of coronary artery disease (CHD) in patients with high clinical probability and severe symptoms refractory to medical therapy (nonpharmacological and pharmacological) or typical angina at low exercise and when clinical evaluation indicates at high risk of adverse CV events. Invasive functional assessment (FFR, iwFR) must be available and used to evaluate stenosis prior to coronary revascularization, except in the case of a very high degree of coronary stenosis ≥90% of the stenosis diameter.
5. In patients with atrial fibrillation (AF) with a CHA_2DS_2-VASc score ≥ 2 for males and ≥ 3 for females, non-vitamin K antagonists (NOAC, DOAC) are preferred if there are no contraindications.
6. After percutaneous coronary revascularization (postPCI) in patients with AF, NOACs: Apixaban 2 x 5 mg, Dabigatran 2 x150 mg, Edoxaban 60 mg and Rivaroxaban 20 mg once daily have an advantage over vitamin K antagonists (VKA) in combination with in combination with antiplatelet therapy (mono- or dual-DAPT at high hemorrhagic risk).
7. Proton pump inhibitors are recommended in patients at high risk of gastrointestinal bleeding, according to the HAS-BLED score, in the following subgroups: patients with aspirin monotherapy, dual antiplatelet therapy (DAPT) or oral anticoagulant monotherapy.
8. If the target value of serum LDL cholesterol is not reached with the maximum dose of statins, combination with ezetimibe is recommended, and in VERY HIGH RISK, a third drug PCSK9-inhibitor (Proprotein convertase subtilisin / kexin type 9) is added parenterally.
9. Sodium glucose-2-cotransporter inhibitors (SGLT2-I): empagliflozin, canagliflozin or dapagliflozin are recommended in patients with diabetes mellitus (DM) and CCS and cardiovascular disease.
10. Glucagon-like peptide-1 (GLP-1) receptor agonists liraglutide or semaglutide are recommended in patients with DM and CCS and cardiovascular disease.

NEW AND / OR REVISED CLASS IIa MAIN RECOMMENDATIONS (There is conflicting evidence and / or divergence of opinion about the usefulness / efficacy of a given treatment or procedure, but weight of evidence/opinion favor of usefulness / efficacy. Wording to use: Should be considered)

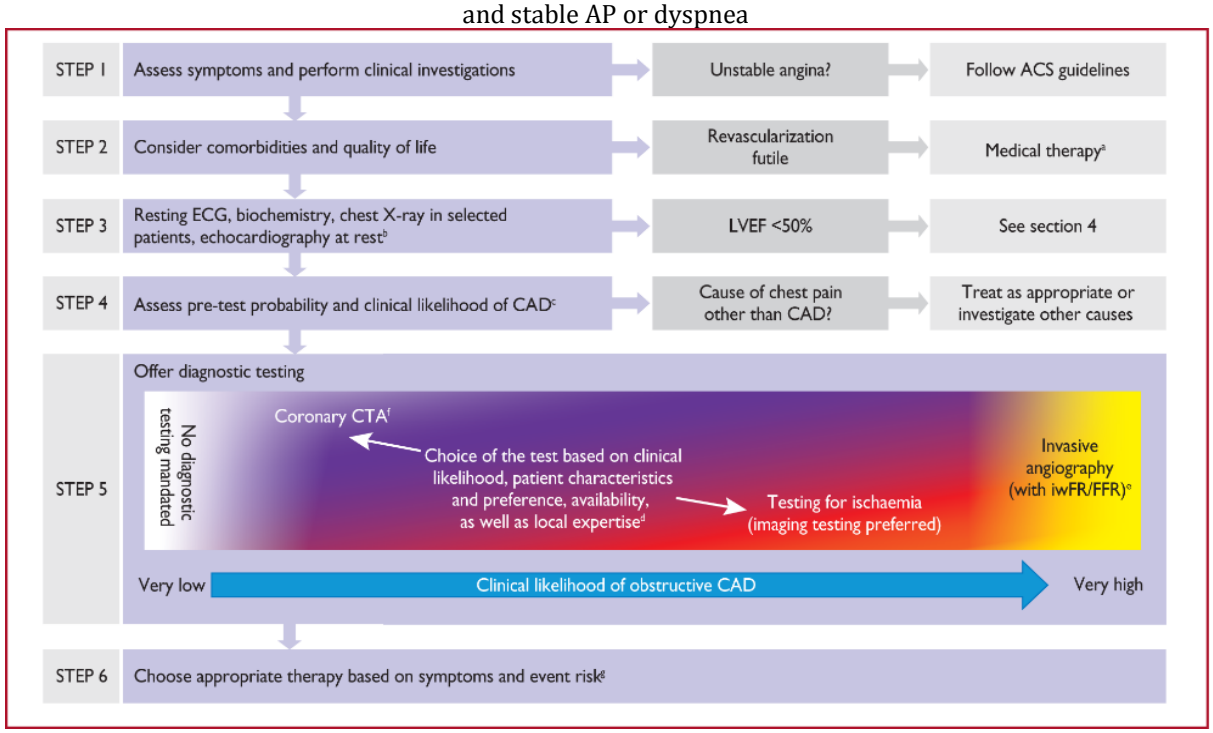
1. Invasive coronary angiography with the availability of invasive functional evaluation should be considered to confirm the diagnosis of CAD in patients with an uncertain diagnosis on noninvasive tests.
2. Coronary MSCT angiography should be considered as an alternative to invasive coronary angiography if other non-invasive tests are ambiguous or non-diagnostic.
3. The addition of another antiplatelet drug to aspirin for long-term secondary prevention should be considered in patients with a high ischemic risk and without a high risk of bleeding.
4. Long-term oral anticoagulant therapy (OAC) should be considered with AF and CHA2DS2-VASc = 1 for males and 2 for females, non-vitamin K antagonists (NOAC) are preferred, if there are no contraindications
5. In patients with AF and NOAC, where the risk of haemorrhagic risk outweighs the risk of stent thrombosis or ischemic stroke, a lower dose of NOAC should be given (Rivaroxaban 15 mg once

daily or Dabigatran 2 x 110 mg in combination with mono or double antiplatelet therapy).
6. In post-PCI patients with AF or other indications for OAC, triple therapy with aspirin, clopidogrel, and OAC should be considered for at least one month or longer when the risk of stent thrombosis outweighs the haemorrhagic risk, with a total duration of up to 6 months. both risks and is clearly stated on discharge from the hospital!
7. Angiotensin converting enzyme (ACEI) inhibitors should be considered in CCS patients at very high risk of adverse cardiovascular events.
8. Ranolazine, nicorandil, ivabradine and trimetazine are converted to IIa (from class IIb-utility / efficacy is much less based on evidence / views).

CLASS III MAIN RECOMMENDATIONS. There is evidence and / or general agreement that a given treatment or procedure is not useful/ effective and in some cases may be harmful: Wording to use: Is not recommended
1. Coronary MSCT / MDCT angiography is not recommended when there are extensive coronary calcifications, irregular heart rate, significant obesity, inability of the patient to hold his breath long enough and any other factors that would affect the failure to obtain a quality image.
2. Changes in the ST segment of the ECG during PSVT should not be used as evidence of CAD.
3. Outpatient ECG monitoring (Holter ECG) should not be routinely used in the examination of patients with suspected CCS.
4. Coronary calcium score via MSCT is not recommended for identification of persons with obstructive CAD.
5. Exercise ECG test (ergometric ECG stress test on a treadmill or bicycle) in patients with ≥0.1Mv (1mm) ST segment depression on an ECG at rest, or digitalis treatment is not recommended for diagnostic purposes of CCS.
6. Invasive coronary angiography (ICA) is not recommended as the only method for risk stratification in CCS.
7. Nitrates are not recommended for the treatment of CCS in patients with hypertrophic obstructive cardiomyopathy or in concomitant therapy with phosphodiesterase inhibitors (Sildenafil et al.).
8. The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with acetyl-salicylic acid (ASA) and oral anticoagulant therapy (OAC).
9. Coronary MSCT angiography is not recommended as a routine test to monitor patients diagnosed with chronic coronary syndrome (CCS).
10. Carotid echosonography with determination of intimomedial layer thickness is not recommended for CCS risk stratification.
11. In low-risk asymptomatic adult non-diabetics, coronary MSCT angiography or functional imaging tests for ischemia are not indicated for further diagnostic evaluation.
12. Routine determination of circulating cardiac biomarkers is not recommended for stratification of cardiovascular risk in patients with CCS.
13. The combination of drugs from the ACEI and ARB groups is not recommended for CCS.
14. In severe heart valve disease, stress stress tests should not be used routinely to detect CAD, due to low diagnostic benefit and potential risk of complications.
15. Sex hormone replacement therapy is not recommended for risk reduction in postmenopausal women.
16. Transmyocardial revascularization is not recommended for patients with severe AP refractory to optimal medical treatment (OMT) and myocardial revascularization (RM) strategies.

SCENARIO 1: PATIENTS WITH SUSPECT CAD-CCS AND STABLE AP and / or EFFORT DYSPNEA.
The procedure (algorithm) in 6 steps in the approach to initial care of patients with suspected CCS and stable AP or dyspnea on exertion is given in Figure 2.

FIGURE 2. **6-step procedure (algorithm)** in the approach to initial care of patients with suspected CCS and stable AP or dyspnea



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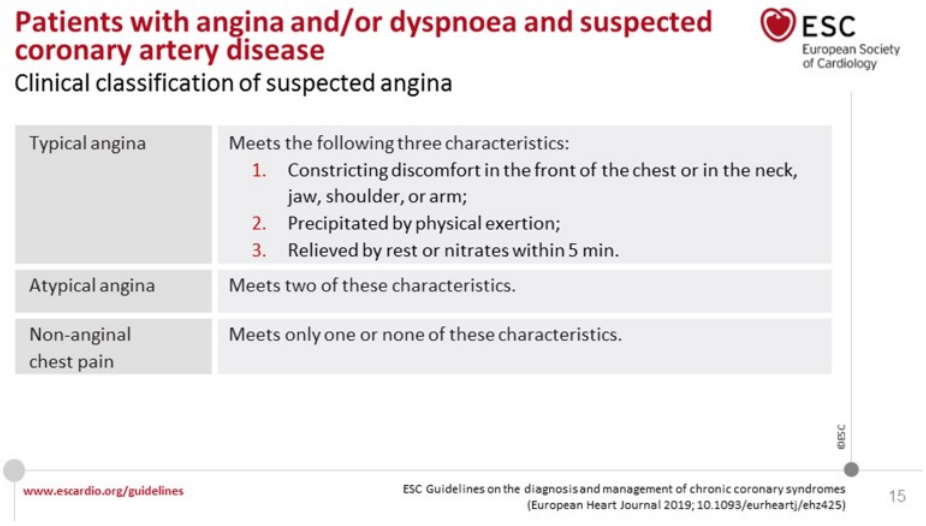
Instead of the previous 3 steps according to the ESC guide from 2013 [4,22], a procedure or algorithm has now been introduced in 6 STEPS [1] in the approach to initial care of patients with suspected CCS:

STEP 1: Assessment of symptoms (TABLE 1) uses the traditional clinical classification of suspected anginal symptoms: chest discomfort - discomfort (pain) on exertion usually shorter than 10 minutes (pain lasting seconds is usually not anginal) and conducting clinical trials, identifying patients with unstable angina and other forms of ACS. AP can paradoxically decrease with further effort (walk-through angina) or with the next effort (warm-up angina) [23].

TABLE 1. The traditional clinical classification of suspected anginal symptoms: chest discomfort



It should not be emphasized how important it is to quickly rule out other acute acute cardiac conditions: acute coronary syndrome (ACS) - unstable angina pectoris- identical pain as in AP but lasting> 20 minutes. One should always think of a dissecting aortic aneurysm, ie Acute

aortic syndrome (AAS), pulmonary embolism, pericarditis and myocarditis. In the differential diagnosis, consider non-cardiac diseases that may resemble anginal pain. The most common diseases that can mimic angina pectoris: gastroesophageal diseases (40%), thorax wall syndromes (Costochondritis and Titze syndrome), some lung diseases, pneumothorax, pleuritis and herpes zoster intercostalis

STEP 2- Consider the general condition and condition of the patient,

assess the quality of life and the presence of comorbidities that potentially affect the therapeutic decision. If performance of load tests and coronary revascularization are unlikely due to the general condition, immediately introduce OMT, especially antianginal pharmacological therapy.

STEP 3. Basic clinical supplementary trial.

Includes basic examination: electrocardiogram (ECG), in selected patient ambulatory ECG Holter monitoring, biochemical analysis, radiography of the thorax in selected patients. An ECG is crucial for the diagnosis of myocardial ischemia, typically a reversible horizontal depression of the ST segment in two or more adjacent ECG leads during or immediately after an anginal attack. The descending ST-segment depression is less specific and the slow-ascending depression is the least specific for the diagnosis of ischemia, while the fast-ascending ST-segment depression is a normal variant in tachycardia [24]; Holter ECG often reveals asymptomatic myocardial ischemia in the form of horizontal depression of the ST segment on exertion [24,25,26]; The ECG may also indicate indirect signs of CAD: pathological Q tooth [27]; left bundle branch block (LBBB) or atrioventricular (AV) blocks, extrasystoles [27]; In an episode of atrial fibrillation (AF) with asymptomatic myocardial ischemia - ST depression [28,29]. In contrast to AF, ST depression during paroxysmal supraventricular tachycardia (PSVT) is not predictive of ischemia. Echocardiographic assessment of left ventricular function (LV), primarily left ventricular ejection fraction (EF), is mandatory. When the EF is <50% the patient is referred directly for invasive coronary angiography (ICA). Transthoracic echocardiography (TTE) as the single most informative diagnostic method in cardiology has a crucial role in excluding alternative causes of chest discomfort [30] and for risk stratification. In the case of suboptimal echo imaging (<10% of cases), transesophageal echocardiography (TOE) and cardiomagnetic resonance imaging (CMR) are used [31].

STEP 4 Assessment of pre-test probability and clinical probability of CAD-CHD

The European Guide 2019 gives increased and renewed importance to the determination of pre-test probability (PTP) of obstructive coronary heart disease, but the classic PTP, Diamond and Forrester based on age, sex and nature of symptoms [31] have undergone major changes based on new evidence [32]. The mean PTP is 15% to 85%. Using the new table (TABLE 2) reduces the overestimation of the incidence of coronary heart disease. [1, 31, 32].

TABLE 2. NEW REVISED PRESTEST PROBABILITY

Foldyna B, Udelson JE, Karady J, et al. insights from the PROMISE trial. Eur Heart J Cardiovasc Imaging 2018; 20:574 581.

Patients with angina and/or dyspnoea and suspected coronary artery disease

ESC European Society of Cardiology

Pre-test probability of coronary artery disease

	Typical		Atypical		Non-anginal		Dyspnoea[a]	
Age	M	W	M	W	M	W	M	W
30–39	3%	5%	4%	3%	1%	1%	0%	3%
40–49	22%	10%	10%	6%	3%	2%	12%	3%
50–59	32%	13%	17%	6%	11%	3%	20%	9%
60–69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

[a] In addition to the classic Diamond and Forrester classes, patients with dyspnoea only or dyspnoea as the primary symptom are included. The dark green shaded regions denote the groups in which non-invasive testing is most beneficial (pre-test probability >15%). The light green shaded regions denote the groups with pre-test probability of CAD between 5-15% in which the testing for diagnosis may be considered after assessing the overall clinical likelihood based on modifiers of pre-test probability.

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ESC Guidelines on the diagnosis and management of chronic coronary syndromes (European Heart Journal 2019; 10.1093/eurheartj/ehz425)

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A new term, Clinical Probability of Obstructive Coronary Disease (CPCAD), is introduced, which uses different risk factors for CAD as modifiers of PTP probability. Reduction of probability for obstructive CAD: normal ECG test with physical load and normal calcium score of coronary arteries (Agatston = 0) [1, 33]. Factors that increase CPCAD:

A) dyslipidemia, diabetes, hypertension, smoking, family history of CAD and sudden death.

B) Changes in the ECG at rest: Q wave and changes in the ST segment and T wave.

C) Left ventricular dysfunction referring to CAD

D) Abnormal exercise ECG test

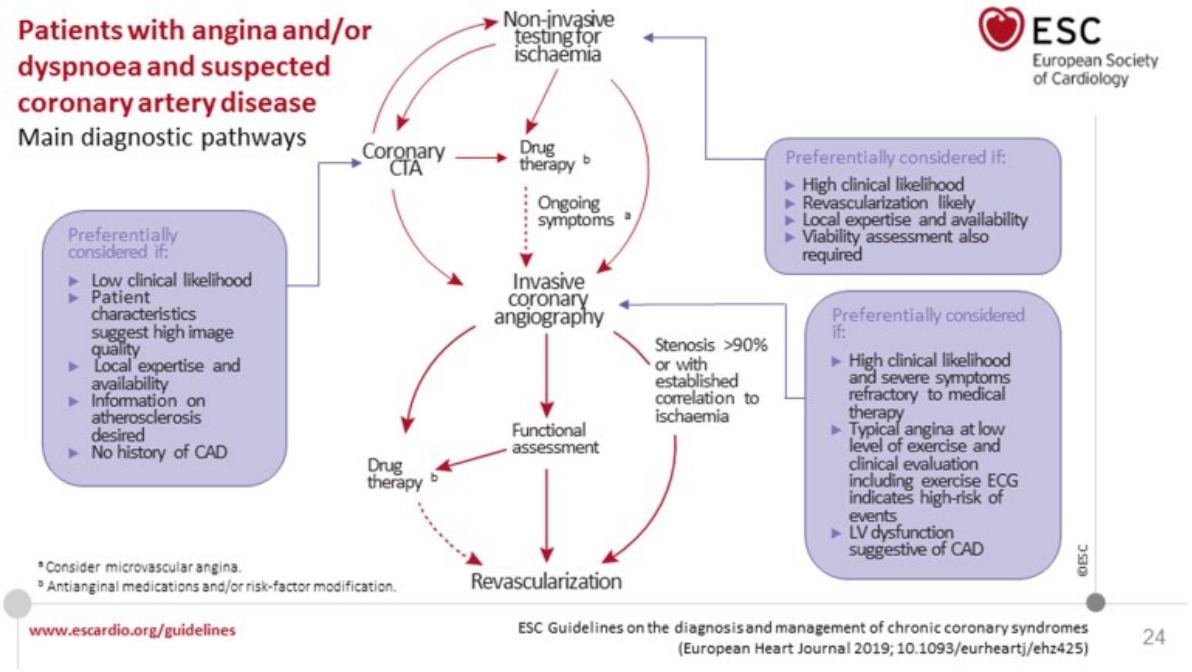
E) increased calcium score by CT

The selection of the initial non-invasive diagnostic test (functional or anatomical image) is based on PTP or CPCAD.

STEP 5. Selection of the optimal diagnostic test for diagnosing CAD

Selection of the optimal diagnostic test for diagnosing CAD, based on patient profile, local availability and expertise. [1, 36-42] is shown in Figure 3.

Figure 3. MAIN DIAGNOSTIC PATHWAYS IN SYMPTOMATIC PATIENTS WITH SUSPECT OBSTRUCTIVE CAD CCS



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In patients in whom revascularization is "futile" due to comorbidity and overall quality of life (STEP 2), the diagnosis of CAD can be made clinically and only OMT- optimal medical therapy is required. If the diagnosis of CAD is uncertain, making a diagnosis using non-invasive functional tests to record myocardial ischemia before treatment is a reasonable option; on the other hand in a patient with a high clinical probability of CAD, when symptoms have not responded to medical therapy or severe typical low-grade angina is present and / or initial clinical assessment (including echocardiogram and in selected patients ECG exercise test or Ergometric ECG test) indicates a high risk of adverse events, switch directly to invasive coronary angiography (ICA) without further diagnostic testing. Under such circumstances, the indication for MR should be based on appropriate invasive confirmation of the hemodynamic significance of the stenosis: FFR, CFR [43, 44].

Existing guidelines recommend the use of either noninvasive functional imaging imaging of ischemia or anatomical imaging using coronary CT angiography (CTA) as an initial test for the diagnosis of CAD. Functional non-invasive ischemia tests for the diagnosis of obstructive CAD are designed to detect myocardial ischemia by ECG changes, irregularities of wall movement using CMR stress or stress echocardiography, or perfusion changes by myocardial scintigraphy

(SPECT), positron emission cardiography or contrast CMR. Ischemia can be caused by physical exertion (erggometrically) or pharmacological stressors, either through increased myocardial function and oxygen demand, or by heterogeneity in myocardial perfusion by vasodilation. Non-invasive functional tests have high accuracy for detecting coronary stenosis that restricts flow compared to invasive functional examination by fractional flow reserve (FFR) [45].

However, insignificant coronary stenoses and atherosclerotic plaques not associated with ischemia remain undetected by functional testing and in the presence of a negative functional test, patients should receive risk factor modification based on ESC recommendations for CV prevention [6].

Anatomical non-invasive assessment

Anatomical noninvasive assessment by visualization of coronary arteries, imaging and lumen of the coronary artery wall can be reported using intravenous contrast agent by coronary CT angiography (CTA), which provides high accuracy for detecting obstructive coronary stenoses, as well as invasive coronary angiography [45A] the recordings are based on anatomy. However, stenoses that amount to 50 to 90% by visual examination are not necessarily functionally significant, ie. they do not always cause myocardial ischemia. [45.46]. Therefore, non-invasive or invasive functional testing is recommended for further assessment of angiographic stenosis detected by coronary CTA or ICA, unless high-grade stenosis (> 90% of diameter) is detected by invasive angiography. The presence or absence of non-obstructive coronary atherosclerosis on coronary CTA provides prognostic information and can be used for preventive therapy. [47].

The role of Exercise (ergo) ECG test

The ECG ergometric stress test has poorer diagnostic performance compared to diagnostic visualization tests and has limited power to rule out obstructive CAD. [45]. Therefore, these guidelines recommend the use of diagnostic imaging tests instead of exercise ECG as an initial test for the diagnosis of constructive CAD. Exercise ECG test can be considered as an alternative for the diagnosis of obstructive CAD, if visualization (imaging tests) are not available, bearing in mind the risk of false negative and false positive test results. [45]. Exercise ECG has no diagnostic value in patients with ECG abnormalities that prevent the interpretation of ST-segment changes.

Influence of clinical probability on the choice of diagnostic test

Each non-invasive diagnostic test has a certain range of clinical probability for obstructive CAD where the usefulness of its application is maximum. Test probability coefficients are a useful parameter of their ability to properly classify patients and can be used to facilitate the selection of the most useful test for any patient. [45]. Given the clinical probability of obstructive CAD and the probability coefficient of a particular test, a post-test probability for obstructive CAD after performing such a test can be assessed.

Using this approach, the optimal range of clinical probability for each test can be estimated, where patients can be reclassified from medium (15–85%) to any: low (<15%) or high probability of CAD> 85% after the test [45]. Coronary CTA is preferred in patients with a lower range of clinical probability of CAD (previously numerically PTP 15-65%), without prior diagnosis of CAD and important conditions associated with a high probability of good image quality. Coronary CTA detects subclinical coronary atherosclerosis, but can also rule out anatomically and functionally significant CAD.

Non-invasive functional tests for ischemia have the advantage because they directly show the area of myocardial ischemia by provoking ischemia. Before revascularization, functional assessment and [45]. schemes (non-invasive or invasive method) is required in most patients.

In addition to diagnostic accuracy and clinical probability, the choice of a non-invasive test depends on other patient characteristics, local expertise, and test availability. Some diagnostic tests may be better in some patients than others. For example, tachyarrhythmia and the presence of extensive coronary calcification are associated with an increased likelihood of non-diagnostic quality of the coronary CTA image and are not recommended in such patients. [51]. Stress echocardiography or SPECT myocardial perfusion imaging may be combined with dynamic TFO and may be desirable if additional information is available during the TFO ECG test. TFP cannot be used for diagnostic purposes in the presence of ECG abnormalities that prevent the assessment of ischemia. The risks associated with different diagnostic tests must be weighed for and against the benefit to the particular patient [52]. Similarly, contraindications for pharmacological stressors and contrast agents (iodine- and gadolinium-based contrast agents) chelates) should be considered. When testing is used appropriately, the clinical benefit of

accurate diagnosis and therapy outweighs the projected risks of testing itself [52].

Invasive examination

For strictly diagnostic purposes, ICA is required only in patients suspected of having obstructive CB in the case of unconvincing, ambiguous or inclusive non-invasive testing or, exceptionally, in patients of certain public occupations of special importance (drivers, pilots, machine workers, police officers). and the like), due to security and regulatory issues. [53]. However, ICA may also be necessary when a noninvasive assessment suggests a very high risk of adverse events to determine revascularization options. [53]. In a patient with a high clinical likelihood of CAD and symptoms not responding to medical therapy or with typical low-effort angina, and an initial clinical assessment indicating a high risk of events, early ICA without prior noninvasive risk stratification may be a reasonable solution to identify lesions that may be suitable for myocardial revascularization (FIGURE 3). Invasive functional assessment should complement the ICA, especially in patients with 50 to 90% coronary stenosis or multivessel disease, given the frequent discrepancies in the angiographic and hemodynamic severity of coronary stenosis. [53-58]. ICA should not be performed in patients with angina who refuse invasive procedures and avoid revascularization, who are not candidates for percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), or in whom myocardial revascularization is not expected to improve functional status or quality of life

STEP 6 After the diagnosis of CCS is made, the risk of adverse events is stratified by functional stress tests: isotopic stress-rest SPECT, the most available pharmacological stress echo dobutamine or dipyridamole and the least available cardiomagnetic resonance (CMR) stress with dobutamine and contrast perfusion. The decision on further treatment is based on determining the level of risk [1]. Definition of risk levels according to annual mortality: no ischemia, mortality from adverse events less than 1%; medium risk - annual mortality between 1% and 3%; high annual mortality is over 3% (Table 3).

TABLE 3. DEFINITION OF HIGH RISK LEVEL (HIGH EVENT RISK) FOR FUNCTIONAL IMAGE TESTS AND NON-INVASIVE ANATOMICAL CT CORONARY ANGIOGRAPHY

Patients with angina and/or dyspnoea and suspected coronary artery disease

ESC European Society of Cardiology

Definitions of high event risk for different tests

Exercise ECG	Cardiovascular mortality >3% per year according to Duke Treadmill Score.
SPECT or PET perfusion imaging	Area of ischaemia ≥10% of the left ventricle myocardium.
Stress echocardiography	≥3 of 16 segments with stress-induced hypokinesia or akinesia.
CMR	≥2 of 16 segments with stress perfusion defects or ≥3 dobutamine-induced dysfunctional segments.
Coronary CTA or ICA	Three-vessel disease with proximal stenoses, LM disease, or proximal anterior descending disease.
Invasive functional testing	FFR ≤0.8, iwFR ≤0.89.

www.escardio.org/guidelines

ESC Guidelines on the diagnosis and management of chronic coronary syndromes (European Heart Journal 2019; 10.1093/eurheartj/ehz425)

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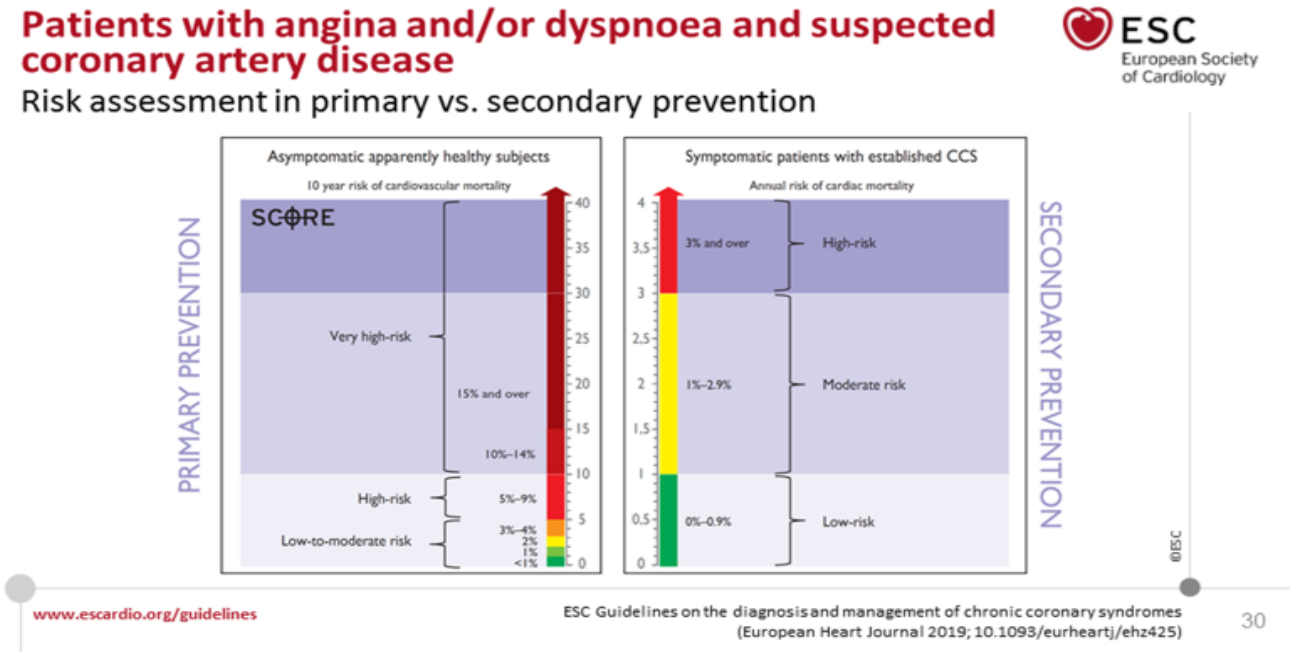
Figure 4. COMPARISON OF CV RISK LEVELS OF ASYMPTOMATIC PERSONS IN PRIMARY PREVENTION OF ADVERSE CV EVENTS AND IN ESTABLISHED CCS IN SECONDARY PREVENTION



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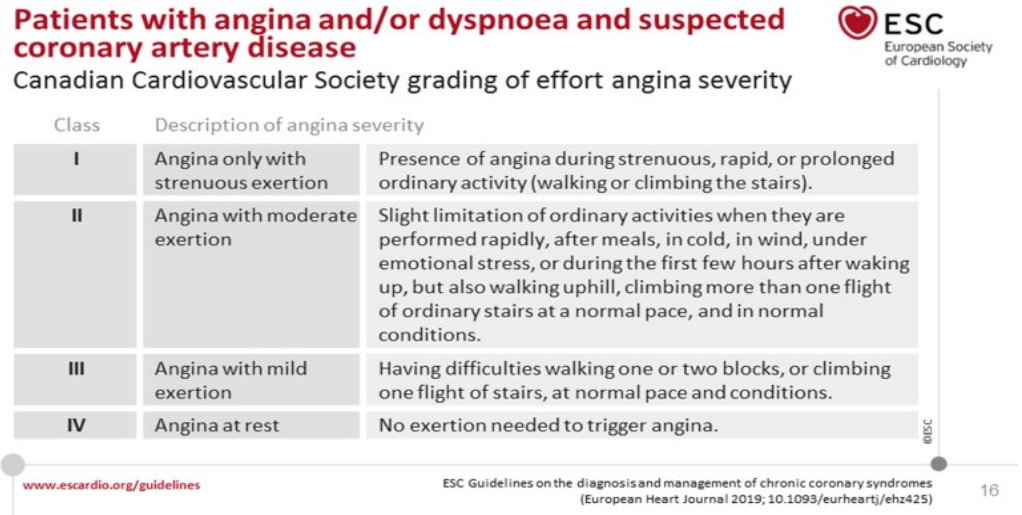
If the angina is very severe but not unstable, according to the well-known Canadian Classification of the Canadian Class IV Association (TABLE 4), with a pretest probability greater than 85% according to Bayes' theorem, ICA is performed immediately without previous noninvasive tests, but with coronary fractional flow reserve assessment. (FFR) [45, 56, 59].

TABLE 4. Classification of severity of angina pectoris and / or dyspnea on exertion according to the Canadian Cardiovascular Association



The role of coronary MSCT angiography is to rule out significant disease in patients with a lower intermediate probability of 15 to 50%. Finally, the choice of adequate therapy is made: lifestyle change, pharmacological therapy of CAD

and myocardial revascularization (MR), based on symptoms and risk of adverse CV events.

NON-PHARMACOLOGICAL MEASURES IN THE TREATMENT OF CHRONIC CORONARY SYNDROMES (for all ccs, especially for scenario 1)

The guide underlines the crucial role of a healthy lifestyle or other preventive measures to reduce the risk of consequent cardiovascular events and mortality [1], as shown in the essential studies COURAGE [60] and FAME [44]. Regular taking of medications for the treatment of hypertension, hyperlipidemia, diabetes, etc. should ensure the achievement of target values of blood pressure, LDL cholesterol, HDL, triglycerides and glycemia (HbA1c), which leads to stagnation and regression of atherosclerosis, which is discussed in detail in the ESC Guide for CV prevention 2016 [6].

The involvement of a multidisciplinary team in preventive work is recommended: cardiologist, general practitioner (GP), nurses, nutritionist, psychologist, psychotherapist and pharmacist (class I evidence B) [1]. The use of a healthy lifestyle, as a preventive intervention, reduces the risk of subsequent development of adverse CV events and mortality. The application of healthy behavior is important: smoking cessation, recommended physical activity, healthy diet, maintaining a healthy weight, which significantly reduces the risk of future cardiovascular events and death, and which is based on evidence. [1, 61, 62]. The benefits are obvious as early as 6 months after the index event [1, 61, 62]. Primary health care plays an important role in prevention, the EUROACTION study showed that a program coordinated by a primary care nurse improves the reduction of risk factors. [63].

Smoking cessation improves the prognosis in patients with HCV, including a 36% reduction in the risk of death for those who successfully quit. Measures to promote smoking cessation include brief tips and advice on behavioral intervention and pharmacological therapy including nicotine replacement. Patients should also avoid passive smoking. Short doctor's advice doubles the likelihood of smoking cessation in the short term, but more intensive advice and support (behavioral interventions, telephone support or self-help measures) is more effective than short advice, especially if continued for one month [62,63]. All forms of nicotine replacement therapy, bupropion, and varenicline are more effective in smoking cessation than self-control; combining a behavioral and pharmacological approach to smoking cessation is effective and recommended. [64].

Healthy eating [65]: Diet rich in vegetables, fruits and whole grains. Limit saturated fat intake to <10% of total intake. Limit alcohol to <100 g / week or 15 g / day.

Healthy body mass gain and maintain a healthy mass (BMI <25 kg / m2) or lose weight through recommended energy intake and increased physical activity.

Obesity is associated with shorter overall life expectancy and overweight is associated with the development of cardiovascular disease (CVD) [66]. Waist circumference is a sign of central obesity and metabolic syndrome [30] and is strongly associated with the development of CVD and diabetes. The recommended waist circumference is ≤94 cm for men and ≤80 cm for women. In people with CVD, intentional weight loss is associated with a significantly lower risk of adverse events [67].

Moderate alcohol intake (1-2 drinks per day) does not increase the risk of AMI.

Physical activity. The exercise is called "pollypill" because of its many beneficial effects on CV risk factors and the CV system [21, 68, 69, 70]. Physical activity reduces AP severity, improves oxygen transport in the myocardium and increases exercise capacity, and is an independent predictor of increased survival in men and women with CCS [21, 68, 69, 70]. Every 1 mL / kg / min increase in peak oxygen consumption was associated with a 14% reduction in CVD risk and an all-cause cause of death in women and men. [21]. Recommendations for physical activity for patients with CCS are 30 to 60 min of moderate-intensity aerobic activity ≥5 days per week. [6, 69]. Even irregular physical activity in leisure time reduces the risk of mortality in previously seated patients [72] and increasing activity is associated with lower CV mortality [73]. Strength exercises maintain muscle mass and function, and in addition to aerobic activity (fast walking, swimming, etc.), they give beneficial effects in terms of lowering insulin resistance, lipid levels and blood pressure.

CV rehabilitation based on physical exercise has constantly shown efficacy in reducing CV mortality and hospitalizations compared to the control group in patients with CAD and this benefit remains at the present time [74,75,76, 77].

Psychosocial factors. Patients with CAD have a twice-increased risk of depression and anxiety disorders compared to people without heart

disease [78]. Psychosocial stress, depression and anxiety are associated with poorer CCS outcomes. Clinical trials have shown that psychological (eg, counseling and / or cognitive-behavioral therapy) and pharmacological interventions with psychopharmaceuticals have had beneficial effects on depression, anxiety, and stress, with some evidence of reduced cardiac mortality and adverse events compared with placebo. [79,80,81].

Environmental factors. Air pollutants are estimated as one of the 10 leading risk factors for global mortality. Exposure to air pollution also increases the risk of AMI as well as hospitalization and death from HF, stroke and arrhythmias. [82]. Patients with CCS should avoid areas with heavy traffic due to pollution and noise [82,83]

Sexual activity. Patients with CCS are often concerned about the CV risk of sexual activity and / or sexual dysfunction. [84,85]. The risk of causing sudden death or AMI is very small, especially when sexual activity with a stable partner in a known environment is stress-free or without excessive food or alcohol intake [86]. Although sexual activity transiently increases the risk of MI, it causes only <1% of acute MI and <1.7% for sudden death during sexual activity. [86]. Energy expenditure during sexual activity is generally low to moderate (3 - 5 METs, metabolic equivalents) and climbing stairs to the second floor is often used as equivalent activity in terms of energy expenditure. Phosphodiesterase-5 inhibitors for the treatment of erectile dysfunction are usually safe in CCS patients, but are contraindicated in those who take nitrates and who have severe hypotension [86]. Healthcare professionals should ask patients about sexual activity, give them information and provide advice

Adhering to lifestyle modifications and taking medication regularly is a big challenge. A systematic review of epidemiological studies has shown that a significant proportion of patients do not adhere to regular CV medications and that 9% of cardiovascular adverse events in Europe can be attributed to poor patient adherence (compliance) to regular therapy [87, 88]. In older men with CKD, greater adherence to medication guidelines was positively associated with better clinical outcomes, independent of other conditions. Polypharmacy plays a negative role in adherence to treatment [88] and the complexity of the medication regimen is associated with non-adherence and a higher hospitalization rate [89]. Physicians who prescribe drugs should give preference to drugs that have proven their benefit with the highest level of evidence and those that are most beneficial to the patient, without significant side effects of the drug. Regime simplification helps adhere to treatment and there is evidence of the benefits of cognitive education strategies, electronically monitored feedback, and telephone support from nurses and technicians. Reviewing and controlling the type and dose of drugs by primary care physicians is a significant factor in helping all patients, especially patients with more comorbidities, to simplify the treatment regimen, detect drug interactions and minimize the risk of drug side effects [89,90,91]. Long-term support (intensive for the first 6 months, then every 6 months for 3 years) in the GOSPEL study (Global Secondary Prevention Strategies to Limit Recurrence after Myocardial Infarction) resulted in significant improvements in risk factors and a reduction in some adverse outcomes [20].

Sex hormone replacement therapy in menopausal women with CCS is not recommended.

Annual vaccination against influenza is recommended for all patients with CCS because it improves the prevention of AMI, reduces CV mortality in adults aged> 65 years

PHARMACOLOGICAL THERAPY OF CHRONIC CORONARY SYNDROMES SCENARIO 1

PHARMACOLOGICAL THERAPY OF CHRONIC CORONARY SYNDROMES: CLINICAL SCENARIO 1- Patients with suspected coronary heart disease and stable angina and / or dyspnea on exertion.

The goals of pharmacological treatment of patients with CCS are: to reduce the symptoms of angina and ischemia caused by physical exertion and exercise and to prevent unwanted CV events. Anti-ischemic drugs - but also lifestyle changes, regular exercise training, patient education and eventual revascularization - all play a role in minimizing or eradicating symptoms during long-term prevention. Prevention of cardiovascular adverse events: ACS, AMI, HFrEF, HFmEF, HFpEF), ventricular arrhythmias and heart blocks, VT, AF, stroke and CV deaths associated with CCS focuses on reducing the incidence of acute atherothrombotic events and and the development of LV dysfunction. Optimal pharmacological therapy (OPhT)can be defined as a treatment that satisfactorily controls symptoms and prevents CAD-related adverse events, with maximum patient adherence to treatment and with minimal drug side effects.

The modern role of first-line antianginal drugs: beta-blockers (BB) and calcium antagonists (CCB) and second-line long-acting nitrates (LANs) was highlighted, including new options: ivabradine, nicorandil, trimetazidine and ranolazine (and possibly allopurinol), and drugs that improve prognosis (acetylsalicylic acid (ASA) and other antiplatelet drugs, statins, ACEI, BB). There are two therapeutic goals in the treatment of CCS:

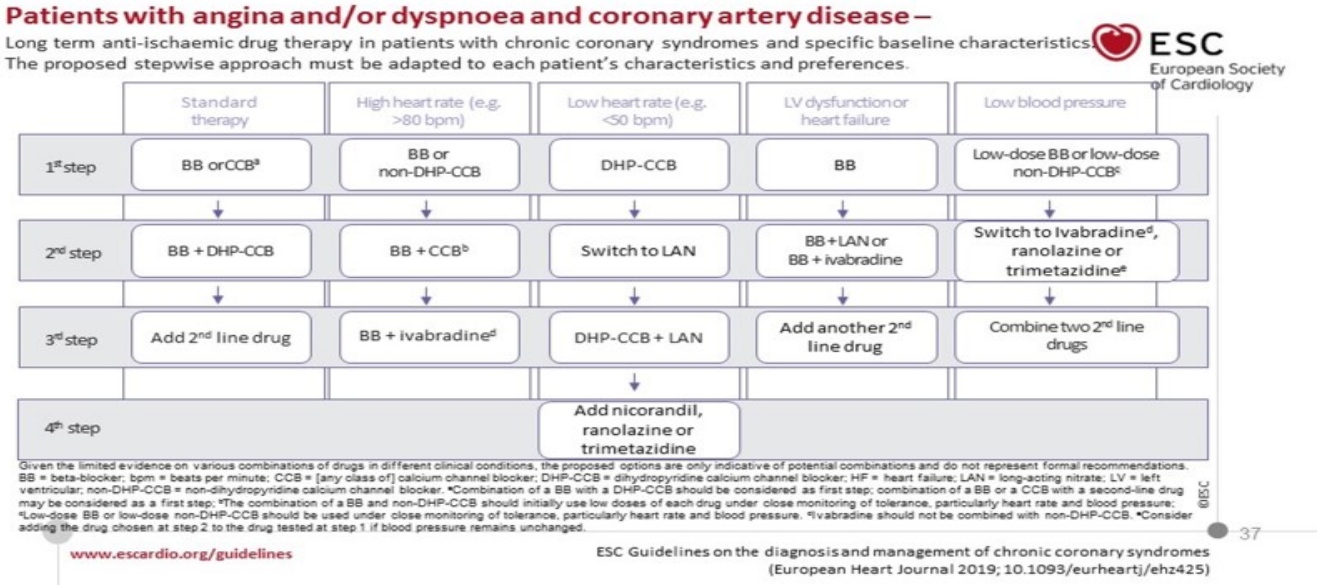
1. Improving the prognosis by reducing the risk of atherosclerosis progression and preventing acute coronary events and sudden death and prolonging life
2. Minimize symptoms with improved quality of life.

ANTI-ISCHEMIC (ANTIANGINAL) DRUGS

Immediate alleviation of anginal symptoms or prevention of symptoms under circumstances that are likely to cause angina is usually obtained by fast-acting formulations of nitroglycerin sublingually, which is one of the first-line antianginal drugs. However, there is no universal definition of optimal treatment in patients with HCV and drug therapy must be tailored to the individual characteristics and preferences of the patient. Initial drug therapy usually consists of one or two antianginal drugs in addition to drugs for the secondary prevention of CVD. [92-95]. The initial choice of antianginal drugs depends on the expected tolerance associated with the patient's profile and comorbidities, potential drug interactions used concomitantly in therapy, patient preferences after notification of potential adverse drug effects, and drug availability. Combination therapy with two antianginal drugs e.g. beta-blocker (BB) and calcium antagonist (CCB) are better than monotherapy with any class of antianginal drugs, but the effect in reducing clinical events remains unclear [95-98]. BB or CCB are recommended as first-line drugs, although to date no randomized controlled trial (RCT) has compared this strategy with alternative strategies that use initial prescribing of other anti-ischemic drugs or a combination of BB and CCB [92-95]. The results of a meta-analysis of 46 studies and 71 treatment comparisons, support the initial combination of BB and CCB. [98]. The same meta-analysis suggested several other initial first-line combinations of antiischemic drugs (long-acting nitrates, ranolazine, trimetazidine, and to a lesser extent, ivabradine) that may prove useful in combination with BB or CCB as first-line therapy, with no data for nicorandil. No study or meta-analysis has yet sufficiently assessed the impact of combining beta-blockers or CCBs with another line of anti-ischemic drugs against adverse events: morbidity or mortality [98]. Regardless of the initial strategy, the response to initial antianginal therapy should be reconsidered 2 to 4 weeks after starting treatment.

The algorithm of treatment with antiischemic drugs in patients with suspected CCS and stable angina and / or dyspnea on exertion is shown in TABLE 5.

TABLE 5 PHARMACOLOGICAL THERAPY OF CHRONIC CORONARY SYNDROMES



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FIRST LINE TREATMENTS CCS

SHORT-ACTING NITRATES are given for an acute AP attack on exertion. Sublingual tablets (lingvalete) and nitroglycerin spray provide immediate relief of angina on exertion. The nitroglycerin spray works faster than the sublingual nitroglycerin tablet [99]. At the onset of angina symptoms, the patient should rest in a sitting position (standing promotes syncope) and take nitroglycerin (tablet 0.3-0.6 mg sublingually, not swallowed, or 0.4 mg spray under the tongue and not swallowed and not swallowed. inhale) every 5 min until the pain ceases or a maximum of 1.2 mg is taken within 15 min. Within that time frame, if the angina lasts for more than 15 minutes, the patient must call an ambulance for hospital treatment, due to the suspicion of ACS. Nitroglycerin can be used for prophylaxis before physical activities that are known to cause angina

BETA BLOCKERS (BB-blockers of beta 1- β1-adrenergic receptors).

Selective β1-adrenergic receptor blockers are preferred in CCS. The efficacy of OMT in stable angina where BB is the central component of treatment is similar to the effect of percutaneous coronary intervention (PCI) with a stent, according to W. Boden, principal investigator of the COURAGE study [16, 60]. The dose of beta-blockers should be adjusted so that the heart rate is 55-60 beats per minute [100, 101]. Discontinuation should be gradual dose reduction and not abrupt. Abrupt cessation of intake due to an increase in the number of β1 receptors in the heart causes worsening of angina, sometimes even myocardial infarction. Dosing according to the target heart rate of 55-60 / min is common, but is acceptable below 50 / min in an individual patient without blocks. Target doses of β1-blockers in CCS: metoprolol 2 x 100mg. maximum 400 mg, bisoprolol 1 x 1.25-10 mg, maximum in Europe 30 mg, in the USA up to 40 mg; (L.Opie, Drugs for the Heart, 2013); nebivolol 1.25-5 mg x 1, up to a maximum of 15 mg in practice. BBs are effective in silent ischemia. During the effort, the goal is for the heart rate not to be over 100 / min. All BBs are potentially equally effective in CCS and selection is made according to comorbidities. BBs can be combined with dihydropyridine (DHP) CCBs to reduce DHP-induced tachycardia. Caution is warranted when a beta-blocker is combined with verapamil or diltiazem due to the potential for the development of worsening SI, excessive bradycardia, and / or atrioventricular block (formerly an absolute, now a relative contraindication). The combination of a beta blocker with nitrate reduces reflex tachycardia. The main side effects of beta blockers are fatigue, mental depression, bradycardia, AV block, bronchospasm, peripheral vasoconstriction, postural hypotension, impotence, and masking the symptoms of hypoglycemia. In comorbidities, the most selective β1 blockers bisoprolol and nebivolol are preferred. In patients with recent AMI and those with chronic SI with reduced EF (HFrEF), BB is associated with a significant reduction in mortality and cardiovascular events [102–104], about a 30% reduction in mortality and reinfarction, and a similar effect in ischemic SI. The benefit in patients with CAD without previous AMI or SI is less well established and placebo-controlled trials are lacking. [105]. A retrospective analysis of 21860 matching patients from the REACH registry did not show a reduction in cardiovascular mortality with beta-blockers in patients with CAD and risk factors, with or without previous AMI [106], but this is still the subject of debate and further research.

CALCIUM ANTAGONISTS (CCBs or calcium channel blockers).

While CCB improves the symptoms of myocardial ischemia, it has not been shown to reduce adverse events and mortality in patients with CCS [107]. However, they have been shown to have an advantage in the prevention of exercise ischemia over BB.

NON-DIHYDROPYRIDINE CALCIUM ANTAGONISTS (NE-DHP): VERAPAMIL AND DILTIAZEM

Verapamil has a number of approved indications, including all types of angina (on exertion, vasospastic and unstable), supraventricular tachycardia and hypertension. Indirect evidence suggests good safety, but with the risk of heart blocks, bradycardia and HF. Compared with metoprolol, antianginal activity was similar. Combined beta-blockade with verapamil is not recommended (previously absolutely contraindicated due to the risk of cardiac SA and AV blocks). Diltiazem, with its profile of effects, has advantages over verapamil in the treatment of exertion angina. Like verapamil, it acts by peripheral vasodilation, reducing afterload while preventing coronary vasospasm. It has a moderate negative inotropic, chronotropic and dromotropic effect. There were no test results comparing diltiazem and verapamil. The use of non-DHP is not recommended for CCB in patients with LV dysfunction

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CALCIUM DIHYDROPYRIDINE ANTAGONISTS (DHP-CCB)

Long-acting nifedipine

Nifedipine, a potent arterial vasodilator, is particularly well tested in hypertensive anginal patients when added with beta-blockade. In large placebo-controlled ACTION, the addition of long-acting nifedipine [60 mg once daily] to conventional angina treatment had no effect on prognosis. Long-acting nifedipine has been shown to be safe and has reduced the need for coronary angiography and cardiovascular interventions [108]. Relative contraindications for nifedipine are: small cardiac output (severe aortic stenosis, hypertrophic obstructive cardiomyopathy or HF); Careful combination with beta-blockade is usually feasible and desirable. Vasodilator side effects include headaches and ankle edema.

Amlodipine.

The very long half-life of amlodipine and its good tolerability make it an effective antianginal and antihypertensive drug taken once a day. There are few side effects, mostly ankle edema. In patients with CCS and without SI, amlodipine at a dose of 10 mg / day reduced the number of coronary revascularizations and hospitalization for AP in a 24-month study [109]. Exercise-induced ischemia is reduced more effectively with amlodipine, 10 mg / day, than with the beta-blocker atenolol, 50 mg / day, and their combination is even better. However, the CCB-BB combination is underused, as are other combinations of antichemical drugs, even in some studies that report that "optimal treatment of stable AP on exertion" has been applied [110]

SECOND LINE DRUGS

Long-acting nitrates for the prophylaxis of angina (eg, nitroglycerin patch, isosorbide dinitrate, and isosorbide mononitrate) are second-line drugs for relieving AP, when initial therapy with BB or NE-DHP CCB is contraindicated, poorly tolerated, or insufficient to control symptoms. There is essentially a lack of data comparing nitrates with BB and CCB, in order to draw firm conclusions about their relative efficacy [110]. When taken over a long period of time, long-acting nitrates cause tolerance with loss of efficacy, so it is necessary to prescribe a drug-free interval of 10-14 hours. The bioavailability of isosorbide dinitrate depends on inter-individual liver variability while isosorbide mononitrate, its active metabolite, is 100% bioavailable. Dose titration is essential to obtain maximum symptom control at a tolerable dose. Discontinuation should be a gradual dose reduction and not abruptly avoid worsening of AP. The most common side effects are hypotension, headache and redness. Contraindications include hypertrophic obstructive cardiomyopathy, severe aortic stenosis, and concomitant use of phosphodiesterase inhibitors (e.g., sildenafil, tadalafil, or vardenafil) or riociguata.

Molsidomin is an unfairly neglected drug (even in the new ESC guide from 2019 [1]), which acts similarly to nitrates, but does not develop tolerance to its action, has an effective anti-ischemic effect and good tolerability. Dosage 3 x 2mg to 4mg or retractable form 2 x 8mg. Unfortunately, there are no studies on the effect on the prognosis of CCS [111,112]

Ivabradine is not inferior to atenolol or amlodipine in the treatment of angina and ischemia in patients with CCS [111]. By adding ivabradine 7.5 mg twice daily, atenolol therapy provided better control of heart rate and anginal symptoms. Overall, the results of the study support the use of ivabradine as a second-line drug in patients with CCS, when they do not tolerate or have contraindications for BB.

Nicorandil is a nitrate derivative of nicotinamide, with antianginal effects similar to those of nitrates or beta blockers. Side effects include nausea, vomiting, and potentially severe ulceration of the oral, intestinal, and mucous membranes. In a placebo-controlled IONA study (n = 5126), nicorandil significantly reduced nonfatal AMI or hospitalization in patients with CCS, but there was no effect on death from ischemic heart disease or fatal AMI [113]. These results support the use of nicorandil as a second-line drug in patients with CCS.

Ranolazine is a selective inhibitor of late internal sodium current. Side effects include dizziness, nausea and constipation. In addition, ranolazine increases QTc, and should therefore be used with caution in patients with QTc prolongation or with QTc prolonging drugs. In a placebo-controlled study in 6560 patients with NSTEMI ACS, the addition of ranolazine to standard treatment did not prove effective in reducing primary outcomes and CV mortality, AMI, or recurrent ischemia. [114]. However, ranolazine in the relatively large CCS subgroup (n = 3565) significantly reduced recurrent ischemia and worsening angina [115]. These results support the use of ranolazine as a second-line drug in patients with CCS with angina despite frequently used antianginal agents such as beta-blockers, CCB, and / or long-acting nitrates. In contrast, there is a lack of evidence to support the use of

ranolazine in patients with CCS after PCI with incomplete revascularization

Trimetazidine reduces ischemia by affecting myocardial metabolism without hemodynamic effects, unlike many anti-ischemic drugs [116]. Trimetazidine 35 mg twice daily BB (atenolol) reduces exertion-induced ischemia [117]. It is contraindicated in Parkinson's disease and movement disorders.
A study of 1628 patients showed that treatment with trimetazidine along with other antianginal drugs resulted in a lower mean number of mild angina attacks.
Allopurinol, a xanthine oxidase inhibitor, has recently been proposed for the treatment of CCS. Allopurinol has a double effect of energy conservation, reduces the consumption of O2 in the myocardium by inhibiting xanthine oxidase and transfers from creatine phosphate to ATP. Norman et al [118] in a randomized study of 65 patients with CCS found that 600 mg / day of allopurinol prolongs the time to onset of ST depression and pain by reducing vascular oxidative stress. the development of acute myocardial infarction (ACS) in the elderly, especially when taken for more than 2 years [119,]. However, the role of allopurinol in reducing clinical events in CAD remains unclear [120].

PATIENTS WITH CCS AND LOW BLOOD PRESSURE
Therapy with anti-ischemic drugs should be started with very low doses, BB or non-DHP-CCB with vigilant monitoring of tolerance to these drugs, and in case of severe hypotension, therapy should be discontinued. Preference should be given to drugs that do not affect blood pressure, such as: Trimetazidine, Ranolazine and Ivabradine in patients with sinus rhythm

PATIENTS WITH CCS AND BRADICARDIA
Elevated resting heart rate is a strong independent risk factor for adverse events in patients with CCS and the therapeutic goal is a heart rate (SF) of less than 60 / min. But with HR <50 / min, drugs that have a negative chronotropic effect (BB and NON-DHP-CCB, ivabradine) should be avoided or used with caution if necessary. Treatment should begin with a very low dose. Drugs that do not have a heart rate slowing effect should be preferred (DHP-CCB, LAN, Trimetazidine, Ranolazine, Nicorandil)

PHARMACOLOGICAL TREATMENT TO IMPROVE PROGNOSIS AND PREVENT ADVERSE EVENTS

ANTI-PLATELET MEDICINES
Platelet activation and aggregation is the initiator of symptomatic coronary atherothrombosis, which is the basis for the use of antiplatelet - antiplatelet drugs in patients with CCS, given the favorable balance of prevention of ischemic events and increased risk of bleeding. Dual antiplatelet therapy (DAPT) with aspirin and oral P2Y12 inhibitors is the basis of antithrombotic therapy after AMI and / or PCI.
ACETYLSALICYLIC ACID (ASPIRIN) IN SMALL DOSES acts by irreversibly inhibiting platelet cyclooxygenase-1 and thus thromboxane, which occurs with a chronic dosage of ≥75 mg / day. Gastrointestinal side effects at higher doses justify a daily dose of 75-100 mg for the prevention of ischemic events in CAD patients with or without a history of AMI. As inhibition of cyclooxygenase-1 by aspirin is consistent and predictable in adequate patients, there is no need to test for platelet function.

P2Y12 INHIBITORS block platelet receptors P2Y12, which plays a key role in platelet activation and arterial thrombus formation. Clopidogrel and prasugrel are thienopyridine prodrugs that irreversibly block P2I12 with active metabolites. Clopidogrel is a well-known standard antiplatelet drug, but relatively often there is resistance to its action. Prasugrel does not show significant resistance, reduces ischemic events and stent thrombosis, but without affecting mortality, but therefore to the detriment of increased nonfatal bleeding. Ticagrelor is a reversibly binding inhibitor of P2Y12, which does not require metabolic activation. Ticagrelor has the most predictable and consistently high level of P2Y12 inhibition during maintenance therapy in susceptible patients and also has a faster onset of action compared to clopidogrel. Ticagrelor monotherapy appears to have similar efficacy and safety as aspirin in patients with previous PCI. Ticagrelor increases non-fatal but not fatal bleeding. Equivalent efficacy and similar safety of two doses of ticagrelor were explained by similar levels of platelet inhibition. Ticagrelor can cause dyspnoea, which is often transient and usually mild and tolerable, but sometimes a switch to thienopyridine is required. There are opinions and limited pharmacodynamic studies that support the unlicensed use of prasugrel or

ticagrelor in stable patients undergoing elective PCI who are at high risk for stent thrombosis.

DURATION OF DOUBLE ANTIAGREGATION THERAPY AFTER PCI

After 6 months, DAPT achieves an optimal balance of efficacy and safety in most patients [121]. Premature discontinuation of P2Y12 inhibitors is associated with an increased risk of stent thrombosis and is not recommended [121]. However, a shorter duration of DAPT may be considered in individuals at high risk for life-threatening bleeding given the very low risk of stent thrombosis after 3 months. However, the official position is: 12 months of DAPT recommended after ACS and PCI.

Greater benefit from prolonged therapy with clopidogrel or prasugrel has been observed in patients treated with AMI. The PEGASUS-TIMI 54 study showed that long-term therapy with ticagrelor 60 or 90 mg 2 x 1, initiated in stable patients more than 1 year after AMI, reduced ischemic events at the expense of increased multiple nonfatal bleeding. [121]. The 60 mg dose appears to be better tolerated and has been approved in many countries for this indication. Absolute reduction of ischemic events in CCS SCENARIO 4 with long-term ticagrelor (60 mg 2 x 1) with a low dose of ASA in high-risk patients after AMI with DM, peripheral arterial disease or multivessel CAD was demonstrated by Bhatt DL and associates in the subgroup of the mentioned study PEGASUS- TIMI 54. [122].

ORAL ANTICOAGULANT MEDICINES (AOK)

ANTICOAGULANT DRUGS IN SINUS RHYTHM

Anticoagulant drugs inhibit the action and / or production of thrombin, which plays a key role in both coagulation and platelet activation. Recently published studies have renewed interest in combining lower anticoagulant doses with antiplatelet therapy.

RIVAROXABANE IN SMALL DOSES. Rivaroxaban is a factor Xa inhibitor that has been studied at a low dose of 2.5 mg 2 x 1 daily in several populations of patients with sinus rhythm, and this dose is 1/4 of the standard dose used for anticoagulation in patients with AF. In the ATLAS ACS 2TIMI 51 study, rivaroxaban 2.5 mg 2 x 1, compared with placebo, reduced the complex outcome of AMI, stroke, or CV death in stabilized patients treated with aspirin and clopidogrel after ACS, with increased nonfatal bleeding, but with evidence reductions in cardiovascular mortality [123]. Subsequently, in the COMPAS study (124), the same regimen in combination with aspirin and clopidogrel, with or without rivaroxaban 2 x 5 mg, in patients with CCS showed reduced ischemic events at the expense of an increased risk of predominantly nonfatal bleeding. [124].

ANTICOAGULANT DRUGS IN ATRIAL FIBRILLATION

OAC is recommended for patients with AF and CCS to reduce ischemic stroke and other ischemic events. OAC in patients with AF has shown superiority over aspirin monotherapy or clopidogrel-based DAPT for stroke prevention and is therefore recommended for this indication. [124]. When administering OAC to a patient with AF and CCS, based on the CHA_2DS_2-VAS score and HASBLED score, non-vitamin K antagonists -NOAC (i.e., apicaban, dabigatran, edoxaban, or rivaroxaban) have an advantage over vitamin K (VKA) antagonists. [1]

Proton pump inhibitors

Proton pump inhibitors reduce the risk of gastrointestinal bleeding in patients treated with antiplatelet drugs and are given to anyone with a high risk of bleeding (HASBLED score) and monotherapy, to improve safety. [124]

STATINS

When target LDL cholesterol values cannot be achieved, it has been shown that the addition of ezetimibe reduces LDL cholesterol but also reduces CV events in patients with ACS, in diabetics [1] without further impact on mortality. In addition to exercise, diet, and weight control, which should be recommended to all patients, dietary supplements, including phytosterols, may lower LDL-C to a lesser extent, but no improvement in clinical outcomes has been shown [1]. Phytosterols are also used in patients with statin intolerance, which is a group with a higher risk of cardiovascular events. Studies from 2015 show that subtilinin-kexin type 9 proprotein convertase inhibitors (PCSK9) (evolocumab and alirocumab) are very effective in lowering cholesterol, lowering LDL-C in a consistently stable manner to <-1.3 mmol / L. In outcome studies, these agents have been shown to reduce cardiovascular and mostly ischemic events, with little or no effect on mortality. [1] Very low cholesterol is well tolerated and associated with fewer events, but the high cost of PCSK9 inhibitors and their unknown long-term safety has limited their low-density lipoprotein apheresis and new therapies such as mipomersen and lomitapid need further investigation. For patients undergoing PCI, a

high dose of atorvastatin reduces the incidence of periprocedural events [1].

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM BLOCKERS

ACE INHIBITORS can reduce mortality, AMI, stroke, and HF among patients with LV dysfunction, previous peripheral vascular disease, and high-risk DM. It is recommended that ACE inhibitors (or ARBs, angiotensin AT2 receptor blockers in cases of ACEI intolerance) be considered for the treatment of patients with CCS with coexisting hypertension, LVEF <40%, DM or chronic renal disease and insufficiency (CKD), unless contraindicated (eg severe renal impairment, hyperkalaemia, etc.). However, not all studies have shown that ACE inhibitors reduce all-cause mortality, as well as cardiovascular death, nonfatal AMI, stroke, or HF in patients with atherosclerosis and without impaired LC function. A meta-analysis, including 24 trials and 61961 patients, documented in CCS patients without HF [1] that renin-angiotensin system (RAS) inhibitors reduced cardiovascular events and death only compared to placebo, but not when compared to active controls. . Therefore, ACE inhibitor therapy in CCS patients without HF or high CV risk is generally not recommended unless necessary to achieve target blood pressure values.

Neprilysin is an endogenous enzyme that degrades vasoactive peptides such as bradykinin and natriuretic peptides. Pharmacological inhibition of neprilysin raises the level of these peptides, enhancing diuresis, natriuresis, myocardial relaxation, and antiremodeling and reducing renin and aldosterone secretion. The first drug in the class is LCZ696, which combines valsartan and sacubitril (a neprilysin inhibitor) in one tablet. patients with HF (LVEF <_35%) who remain symptomatic despite optimal treatment with ACE inhibitor, beta blocker and mineralocorticoid receptor antagonist (MRA), sacubitril / valsartan is recommended as a replacement for ACE inhibitor to further reduce the risk of HF hospitalization and death in outpatients.337 Aldosterone blockade with spironolactone or eplerenone is recommended for use in post-MI patients who are already receiving therapeutic doses of ACE inhibitors and beta blockers and have LVEF <35%, or diabetes or SI-HF. Caution should be exercised when using MRA in patients with impaired renal function [estimated GFR (eGFR) <45 mL / min / 1.73 m2] and in those with serum potassium> _5.0 mmol / L.

The combination of anti-ischemic drugs and drugs that affect the prognosis and survival in practice are insufficiently used both in the world [110] and in the part of Serbia - Timok region. Doses are not titrated to achieve optimal effects of pharmacological therapy [112]. The analysis of the treatment of DE NOVO coronary heart disease in consecutive 101 pts is presented from the clinical practice of the Dr. Bastać Practice. At the first examination, patients, previously treated or understood as stable angina pectoris, had pharmacological therapy by the attending physician or cardiologist (only 26% had a definitive diagnosis of coronary heart disease by exercise ECG test) attached to TABLE 6.

Table 6. Analysis of prescribed drugs for the treatment of suspected chronic coronary syndrome (CCS) in the Practice "Dr Bastać" on the 101st consecutive patient in 2017

Antiischemic drugs		Drugs that act on the prognosis of coronary heart disease
I lines	II lines	
65% beta blockers (also have hypertension)	**36% long-acting nitrates** molsidomin is not prescribed	**48% acetyl salicylic acid** (ASA) **9% Clopidogrel**
31% Ant CA (due to hypertension)	**16% trimetazidine**	**23% statin**
20% Ntg sublinvally as needed	Not prescribed: ranolazine, ivabradine, nicorandil	**61% ACE inhibitors** (also have hypertension) **65% beta blockers** (also have hypertension)

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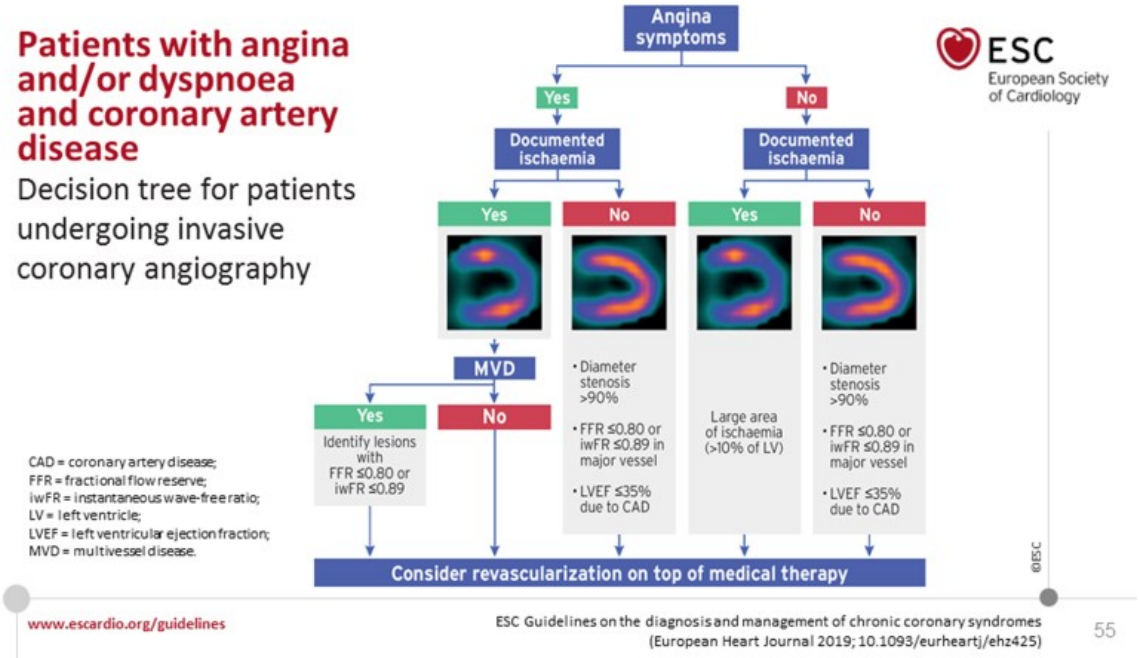
MYOCARDIAL REVASCULARIZATION (MR). The role of coronary myocardial revascularization (MR) in the treatment of chronic coronary syndromes SCENARIO 1. Figure 5

FIGURE 5. The role of coronary myocardial revascularization (RM) in the treatment of chronic coronary syndromes SCENARIO 1



Retrieved from https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Chronic-Coronary-Syndromes

In patients with CCS, optimal medical therapy (lifestyle change, risk factor reduction and pharmacological-drug therapy, do not equate medical and drug therapy) -OMT is key to reducing symptoms, stopping the progression of atherosclerosis and preventing atherothrombotic events. Myocardial revascularization (RM) plays a central role in the management of the most severe forms of CCS as a last resort, but always as an adjunct to optimal medical therapy (OMT), without its elimination. The goals of MR are to alleviate symptoms in patients with angina and / or to improve the prognosis. These recommendations suggest that revascularization in patients with AP and significant stenosis is often second-line therapy when OMT has not been successful. Myocardial revascularization: PCI or CABG can effectively alleviate angina, reduce the use of antianginal drugs, and improve exercise ability and quality of life in a small number of selected patients compared to the OMT-only strategy. Revascularization with 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 adverse CV events including AMI and cardiovascular death.

Numerous meta-analyzes comparing MR strategy by PCI with initial OMT in patients with CCS show either no benefit [126, 127] or myocardial revascularization provides a modest benefit [128, 129,] in terms of survival or lower incidence of AMI and SI. In this regard, previous ESC guidelines from 2013 [4] identified specific subgroups of patients (based on coronary anatomy, size of myocardial ischemia zone, risk factors, cardiac status, etc.) in whom MR may improve prognosis, indicating that in other subgroups it has no effect. FIGURE 5 summarizes the practical approach to MR indications in CCS according to the presence or absence of symptoms and documented myocardial ischemia by noninvasive functional imaging tests. However, the risk-benefit relationship in an individual case should always be evaluated and the MR is considered only if the expected benefit outweighs the potential risk. Also, the aspect of joint team decision-making is crucial, with complete information given to the patient about the expected advantages and disadvantages of the two strategies, including the risk of bleeding associated with DAPT in cases of revascularization via PCI.

A detailed discussion of the best choice between PCI or CABG revascularization modalities for an individual patient on the HEART team was published in the 2018 ESC guidelines for myocardial revascularization [131].
The role of MR has been placed in the context of recent evidence relating to the prognostic role of percutaneous coronary interventions (PCI) or coronary artery bypass grafting or native a. mammario internal and other arteries (CABG) in this low-risk population. MR is now reserved for patients where there is strong evidence to improve prognosis based on evidence of regional ischemia by visual noninvasive tests - perfusion imaging or assessment of FFR and iwFR [131]. The typical constellation is in a patient with a large area of myocardial ischemia corresponding to left main stenosis (left main stenosis> 50%) and multivessel disease that always involves stenosis ≥70% of the proximal anterior-descending branch of the left coronary artery (LAD). There is unequivocal evidence that percutaneous coronary revascularization (PCI) in acute coronary syndromes with ST-segment elevation reduces mortality relative to fibrinolysis, and both relative to those where no reperfusion has been performed.

In other forms of CAD -chronic coronary syndromes (CCS), the role of PCI revascularization is controversial in terms of mortality reduction [132, 133]. A recent meta-analysis of 46 studies in 37,757 individuals examined the PCI benefit of various categories of coronary patients, including true stable angina without a recent heart attack. In stable angina pectoris, the chronic coronary syndrome PCI categories did not reduce overall mortality (RR, 0.98, p = 0.11]), cardiac death (RR, 0.89, p = 0.33), or myocardial infarction (RR, 0.96; P = 0.54). PCI prevents death, cardiac death, and AMI primarily in patients with unstable AP. For patients with stable CAD, PCI shows no effects on any of these outcomes. [132-134]. However, it is now becoming evident that OMT is still underused in recent studies [132]. Mohee K. et al show that OMT is still suboptimal in patients before PCI and becomes optimal only after PCI due to increased compliance. [132]. Argument: OMT is the definitive therapy for patients with stable coronary heart disease and low risk of CV events (mortality <1% per year).

COURAGE STUDIES [16,60,133,134]. (Boden WE et al., Published in NEJM 2007) - initial PCI with a stent does not reduce the risk of death, AMI and hospitalization and has no advantage in stable AP according to OMT on 2287 randomized pts with known significant stable CAD and proven myocardial ischemia who were only on OMT OR OMT + PCI. Between 1999 and 2004, a COURAGE (Clinical Outcomes Utilization Revascularization and Aggressive Drug Evaluation) study randomized 2287 pts with objective evidence of ischemia and proximal angiographic CAD (≥ 70% visual visual stenosis) to OMT with or without PCI. The aim and design of the study was to test the strategy of routine, anatomically-indicated PCI, if necessary, for the failure of the initial OMT. Follow-up of 2.5 to 7 years (median 4.6 g) showed that death or AMI occurred with the same frequency in both subgroups (PCI + OMT vs OMT = 1.05, p = 0.62). After 4.6 years of follow-up, there was no statistically significant difference between the groups for cumulative mortality and nonfatal myocardial infarction -18.5% vs 19%, as well as for stroke and hospitalization due to new unstable AP. Important: COURAGE study patients had marked symptoms at enrollment and had significant comorbidities, a high prevalence of objectively established ischemia, and extensive angiographic coronary heart disease, and were in the population where clinical benefit from PCI was expected.

Subgroup analysis reveals consistency among clinically relevant subgroups. There is no difference only OMT versus OMT + PCI in terms of multidisciplinary disease, low EF, class III-IV angina and the presence of Diabetes Mellitus. By comparison, there was no difference in hospitalization for ACS either. The main result of the study showed that PCI as an initial strategy in patients with stable AP CCS does not reduce death, AMI and other major events (MACE) when OMT is added. Patients with PCI had less angina in the first and 3rd year, but not in the 5th year of follow-up. As initially expected, revascularization was more common in OMT in 16.5% of the first year of follow-up alone. The efficacy of OMT in stable AP where the optimal dose of beta-blocker is a central component is similar to the effect of percutaneous coronary intervention (PCI) with a stent (Boden and Courage, 2007). [133,134].
Comparison between PCI and OMT (Braunwald s Heart disease, 2015- Morow D, Boden WE) [135]. n-) in terms of earlier techniques balloon angioplasty vs medical therapy, belongs to history, now in the era of new PCI techniques and new optimal drug therapy. In 16 studies of about 9000 pts, PCI vs OMT, the invasive strategy did not provide a reduction in mortality

or AMI, but only a reduction in AP severity and a better quality of life- QoL.

META-ANALYSIS OF VINDECKER et al. Reports reduction in death and AMI by revascularization versus OMT only in patients with CCS when CABG revascularization or next-generation drug-coated stent (DES) was performed, as opposed to balloon angioplasty, metal BMS stents, and old earlier DES [129].
FAME 2 [130]: Statistically significant risk reduction with PCI + OMT versus OMT alone, discontinued after 7 months, but had significant limitations, was not randomized, and was not a double-blind controlled study. Nevertheless, Xaplanteris P. I et al. Indicate a potentially broader prognostic impact of the revascularization strategy when targeted with a functional invasive assessment of coronary stenosis via FFR or iwFR. A five-year follow-up of the FAME 2 study confirmed clinical benefit in a subset of patients specifically treated with PCI targeting only ischemia-producing stenoses (i.e., FFR <0.80) plus OMT, which yielded significantly lower rates of emergency revascularization and lower rates of spontaneous AMI [130] but without a clear effect on mortality.

ORBITA A new ORBITA study (a randomized, controlled, double-blind study) comparing OMT or angioplasty with an anatomically significant coronary stenosis (PCI) stent in stable angina, with a false invasive procedure (shame) in the control group, found no advantage of PCI in significantly improving functional capacity. [125]. The study highlights a significant placebo component on clinical effects and warns us of the pitfalls of interpreting end-points that are subject to bias in the absence of false control. However, the results of the ORBITA study cannot provide definitive guidance due to the limited size of the study, the short observation time to treatment crossover, and insufficient strength to assess clinical outcomes.

ISCHEMIA The largest international randomized double-blind controlled follow-up study ISCHEMIA [137-139] recruited patients with stable CAD with moderate or severe ischemia on a stress test and aimed to assess whether there were differences in clinical outcomes - mortality and CV morbidity in patients. with stable chronic coronary heart disease (SCAD) between the invasive strategy + OMT and OMT alone. Out of a total of 8518 recruited patients, 5179 were randomly selected by randomization and were still randomized by type of treatment: Invasive PCI with stent plus medical therapy (n = 2588) versus only medical therapy (n = 2591). Coronary CT angiography was performed in most participants and was examined by the baseline laboratory to rule out main stable stenosis ≥ 50%. Randomized participants had a mean age of 64 years, with 1168 women (22.6%) and 2122 diabetes (41.0%)). Among the 3909 participants randomized after the functional imaging stress test for ischemia, the assessment of the severity of ischemia in 3901 participants was as follows: severe 1748 (44.8%), moderate 1600 (41.0%) and mild 317 (8.1%); 79.0% had multivessel CAD (n = 2679 of 3390) and anterior descending branch (LAD) proximal stenosis 46.8%. During an average of 3.3 years of follow-up, there was no significant statistical difference between primary outcomes: death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, cardiac arrest -13.3% in the invasive strategy versus 15.5% in the medical treatment group. (p = 0.34). The key secondary outcome was death from cardiovascular causes or myocardial infarction: 11.7% in the routine invasive group versus 13.9% of the OMT group (p = 0.21). Total mortality (cardiovascular and all other causes): 6.4% in the routine invasive group versus 6.5% in the OMT group (p = 0.67). Periprocedural AMI: 2.98%. The invasive versus conservative relationship to mortality was similar regardless of the degree of ischemia (p value for interaction = 0.23), which is also true for AMI. (p value for interaction = 0.15). Among patients with stable CAD and moderate to severe ischemia on a noninvasive visualization stress test, routine invasive treatment showed a reduction in major adverse outcomes compared with OMT. There is no benefit from invasive PCI therapy in terms of a complex end result: Overall, CV mortality, and nonfatal myocardial infarction.
The ACC / AHA American Guide to Chronic CAD [140] discourages the use of PCI or CABG for single-vessel or double-vessel CAD without significant proximal LAD involvement in the absence of unacceptable AP after adequate guidance-guided OMT, especially if noninvasive tests show a small area of exacerbated viable ischemia or reduced EF.

CLINICAL SCENARIO 2.
Patients with new-onset heart failure or left ventricular dysfunction and suspected coronary artery disease
CAD is the most common cause of chronic heart failure (HSI) in Europe. Most studies provide evidence to support recommendations for the

study of pts with ischemic cardiomyopathy (CMP) - the pathophysiological basis of ischemic CMP is systolic dysfunction EF <40%, although patients with CCS may also have HSI with preserved EF. Patients with symptomatic HF should be diagnosed according to the 2016 ESC HF Guide [141]. In addition to standard medical history, physical examination, ECG and chest radiography, Doppler echocardiography should be included in the image to evaluate the evidence of diagnosis of ischemic cardiomyopathy with HF with: a) reduced EF; b) mid-range EF; C) preserved EF with focal or diffuse echocardiographic signs of left and / or right ventricular systolic dysfunction, evidence of diastolic dysfunction, compensatory hypertrophy, valve function (ischemic mitral regurgitation) and evidence of secondary pulmonary hypertension [1]. In addition to routine hematological and biochemical analyzes, it is especially important to assess renal function, potassium, and sodium initially and during pharmacotherapy titration.

Measurement of serum natriuretic peptide levels serves to rule out HF if NT-proBNP levels are normal. The degree of increase in GNP titer is used to estimate the severity of HF [142]. The basic treatment in the NYHA II-III class is antianginal or antischemic therapy with drugs that affect the prognosis and prevention of events. BBs are also an essential component in the relief of anginal attacks and event prevention as well as mortality reduction in HF (Class I level A) [142-149]. Amlodipine may be included as an anti-ischemic drug, in those who do not tolerate BB I the only calcium antagonist is considered safe in HIS (Class IIb level B recommendation) [150-151]. Short-acting nitrates by sublingual or transcutaneous patches are also recommended. Patients with symptomatic HF should be treated according to the 2016 ESC Guide to HF [141], with an emphasis on adding to the standard therapy the newer drug angiotensin receptor-neprilysin inhibitor (sacubitril-valsartan) [141]. Doses of drugs: diuretics [152], ACEI, BB, spironolactone or eplerenone possibly and ivabradine should be gradually increased to avoid hypotension, bradycardia, azotemia hyperkalemia. ACEIs are crucial (CLASS I, LE A) in asymptomatic left ventricular dysfunction after myocardial infarction and in symptomatic HF for symptom relief and reduction of morbidity and mortality [153].

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Implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) [154] can provide improvement in symptoms and improve survival [154]. Myocardial revascularization should be considered in suitable patients with ischemic HF based on symptoms, coronary anatomy, and evidence of current ischemia and myocardial viability by imaging tests in akinesia-cicatricial zones, through a multidisciplinary team. Myocardial revascularization is recommended when anginal discomfort and / or dyspnoea persist despite optimal antiaginal therapy (CLASS I, level of evidence A).

THE GROUP OF PATIENTS WITH LONG-TERM Dg CHRONIC CORONARY SYNDROMES INCLUDE:
CLINICAL SCENARIO 3. ASYMPTOMATIC AND SYMPTOMATIC PATIENTS WITH STABILIZED SYMPTOMS UP TO 1 YEAR LAST AFTER ACS OR CORONARY REVASCULARIZATION.
CLINICAL SCENARIO 4: THE SAME ONLY AFTER A YEAR)

Common to both groups, clinical scenarios 3 and 4 are lifelong treatment and follow-up [1]. The clinical course may be favorable for a longer period. However, patients with CCS may develop various CV complications: episode de novo ACS, complications due to therapeutic procedures due to CAD or due to interactions with comorbidities. The risk of complications also exists in asymptomatic patients, so the risk assessment must be applied to both symptomatic and asymptomatic patients. Therefore, a risk based on biomarkers in 2017 was developed and validated [155].

CLINICAL SCENARIO 3
ASYMPTOMATIC AND SYMPTOMATIC PATIENTS WITHIN 1 YEAR OF ACS OR REVASCULARIZATION

After revascularization or stabilization of ACS within one year, the patient must be closely monitored due to the increased risk of complications and the need to adjust pharmacological treatment [35]. It is recommended to have at least two visits to the doctor in the first year of follow-up, while those with systolic LC dysfunction before revascularization or after ACS should report for cardiac examination 8-12 weeks after ACS or revascularization. Cardiac function can be improved by recovering from stunning or hibernating myocardium by revascularization based on the results of the ADVISE II study by invasively assessing whether epicardial coronary stenosis is the cause of ischemia by iwFR [52,53]. However, exacerbations can occur

due to concomitant CV disorders (valvular diseases, infections, arrhythmias, etc.) and these disorders need to be identified and treated. Non-invasive post-revascularization assessment may be considered to rule out residual ischemia or to document a reference ischemia finding to plan treatment intensification and further periodic follow-up [1].

CLINICAL SCENARIO 4.
ASYMPTOMATIC AND SYMPTOMATIC PATIENTS MORE THAN 1 YEAR LAST OF ACS OR REVASCULARIZATION.

Once a year, the patient needs to be evaluated by a cardiologist, even when the patient is without problems. The recommendation is an annual clinical examination and assessment of adherence to pharmacotherapy and non-pharmacological measures with the determination of risk profiles through risk scores. Laboratory analyzes: lipid profile, renal function, blood count and cardiac biomarkers should be performed every two years [1, 45]. An elevated marker of hsCRP inflammation is associated with an increased risk of adverse events. Von Willebrandt factor, interleukin-6 and NTpro BNP are predictors of outcome [25]. Other biomarkers for pts with CCS also have prognostic significance: heart rate, hemoglobin, leukocyte count [156]. Multiple biomarker scores showed prognostic significance: combining: hsCRP, fibrin degrading products, and heat shock protein 70; [157]. For patients with an exacerbated risk score during follow-up, it is warranted to intensify therapy and diagnostic re-evaluation, although risk-guided therapy has not yet been shown to improve prognosis. A 12-channel ECG should be part of each follow-up to record heart rate and rhythm and to detect changes suggestive of symptomatic myocardial ischemia / infarction and to evaluate PR, QRS, and QT intervals. It would be useful to echocardiographically assess systolic and diastolic LV function, valve status, heart size, and volume in apparently (seemingly) asymptomatic patients at 3 to 5 years of age. [1,52,53]. In case of unexplained reduction of left ventricular systolic function, especially regional, it would be useful to do an image of coronary anat 55 Asymptomatic, silent ischemia should also be sought in seemingly asymptomatic patients through periodic stress imaging tests [1, 52].

CLINICAL SCENARIO 5.
PATIENTS WITH ANGINA PEKTORIS AND SUSPECT VASOPASTIC OR MICROVASCULAR DISEASE.

Angina without obstructive disease in the epicardial coronary arteries (INOCA). In clinical practice, there is a discrepancy between the findings concerning coronary anatomy, the presence of symptoms and the results of non-invasive tests often occur [13]. These patients deserve attention because APs with nonobstructive CAD are associated with an increased risk of adverse clinical events [14,15]. The low diagnostic contribution of ICA can be explained by the presence of: (1) mild stenosis or diffuse coronary narrowing, with underestimated functional significance; (2) microcirculation disorders; (3) dynamic epicardial vessel stenosis caused by coronary spasm or intramyocardial bridges that are not apparent during CTA or ICA. Intracoronary pressure measurements are useful in resolving the first case. At diagnostic processing, patients with angina and / or myocardial ischemia who have coronary stenoses with nonischemic FFR or ivFR values may also be referred to as non-obstructive diseases of the epicardial coronary arteries. The presence of clearly defined anginal symptoms and pathological findings of non-invasive tests in patients with normal coronary epicardial arteries should lead to suspicion of a non-obstructive cause of ischemia. Often and mainly as a result of persistence of symptoms, patients with angina and without obstructive CAD undergo multiple diagnostic tests, including repeated coronary CTA or ICA, which contribute to increased health care costs [158]. It is important to emphasize that in everyday practice, there is often a significant discrepancy between the findings of coronary anatomy, the presence of symptoms, and the results of noninvasive tests. Diagnostic pathways investigating microcirculatory or vasomotor coronary disorders are often not performed, so a definitive, evidence-based diagnosis is rarely made. Due to that, patient anxiety and depression are not uncommon in this clinical population. [159]. A 2018 randomized controlled trial of CorMicA found in patients with nonobstructive coronary heart disease, through customized treatment guided by the results of an intracoronary trial: coronary flow reserve (CFR), microcirculatory resistance, and acetylcholine test resulted in a significant reduction in anginal symptoms compared with treatment [160].

Microvascular angina

Patients with microvascular angina typically have chest pain on exertion, a positive ischemia test, either exercise ECG test or noninvasive

imaging tests, without obstructive CAD or with mild to moderate stenosis (40-60%) of the epicardial coronary arteries, which is detected by IC CTA and these stenoses are considered functionally insignificant. The microvascular origin of angina is usually suspected after the exclusion of obstructive coronary epicardial stenosis, during the diagnostic processing of patients with proven myocardial ischemia on the exercise ECG test. Regional abnormalities of wall movement rarely develop during exercise or stress in patients with microvascular angina. Some patients may have a mixed form of microvascular + vasospotic angina, with occasional episodes at rest, especially associated with exposure to cold. Secondary microvascular angina, without obstructive CAD, may be due to cardiac or systemic conditions, including those that cause LV hypertrophy (such as hypertrophic cardiomyopathy, aortic stenosis, and hypertensive heart disease) [161] or inflammation (such as myocarditis or vasculitis).) [162]. Risk stratification in microvascular AP is quite complex. The presence of microcirculatory dysfunction in patients with CCS entails a worse prognosis than originally thought, based on the latest evidence based on monitoring patients with objective microcirculation disorders proven by invasive or noninvasive techniques. [163-167]. Microcirculation dysfunction precedes the development of epicardial coronary lesions, especially in women, and is associated with impairment and adverse outcome events. Among diabetic patients undergoing diagnostic processing, those without obstructive epicardial disease but with abnormal coronary flow reserve (CFR) have a similarly poor long-term prognosis as those with obstructive epicardial disease [165]. In patients with significant CAD with significant stenosis at FFR ≤ 0.80, the presence of abnormal CFR <2.0 is associated with additional exacerbation and a significant number of adverse events especially when the microcirculatory resistance index (IMR) is also abnormal [166].

The possibility of microcirculatory origin of angina should be considered in patients with clear angina, abnormal non-invasive functional tests, and coronary arteries that are either normal or with mild stenosis, which are considered functionally insignificant on ICA or CTA. One of the challenges in performing a comprehensive assessment of microvascular function is to test the two main mechanisms of dysfunction separately:

1. Weakened microcirculatory conductivity (or increased microcirculatory resistance)
and
2. Arteriolar dysregulation. [168-170].

However, it should be clarified which of these two pathways is critical to the choice of pharmacological treatment to minimize the symptoms of these patients. [160]. Weakened or disturbed microcirculatory conduction can be diagnosed by measuring coronary flow reserve (CFR) or minimal microcirculatory resistance. CFR can be measured by noninvasive transthoracic color and pulsed Doppler echocardiography [visualization and measurement of basal flow rate and with vasodilatation test with adenosine or dipyridamole] [171] as well as magnetic resonance imaging (myocardial perfusion index is less available or PET). Microcirculatory resistance can be measured in a catheterization laboratory by combining intracoronary pressure with thermodilution-based data (to calculate IMR) or Doppler flow rates (to calculate hyperemic microvascular resistance or HMR) [172,173]. The decision on abnormal microcirculation is made when the value of the microcirculatory resistance index is greater than 25 units (IMR> 25 J) or CFR <2.0. In contrast, the diagnosis of arteriolar dysregulation requires assessment of endothelial function in coronary microcirculation by selective intracoronary infusion of acetylcholine. Acetylcholine is an endothelium-dependent vasodilator that acts directly on arteriole smooth muscle cells and causes paradoxical arteriolar vasoconstriction — microvascular spasm of dysfunctional vascular endothelium or abnormal smooth muscle cell function [174]. This arteriolar response to acetylcholine causes anginal symptoms with or without concomitant ischemic ECG changes and a decrease in coronary blood flow velocities if simultaneous Doppler measurements are performed. Peripheral pulse tonometry during reactive hyperemia may also reveal abnormal systemic endothelial function in patients with AP and non-obstructive CAD [175].

Vasospastic angina

Vasospastic angina should be suspected in patients with AP when the symptoms occur mainly at rest, with maintained tolerance to exertion. The likelihood of vasospastic angina increases when the attacks follow a circadian pattern, with multiple episodes at night and in the early morning hours. Patients are often younger and have fewer CV risk factors than patients who have AP on exertion, except that

they are most often cigarette smokers [176]. Coronary vasospasm is also suspected in patients with transient coronary stents and persistent AP. [177-178]. The diagnosis of vasospastic AP is based on the detection of transient ischemic changes in depression or elevation of the ST segment during an angina attack (usually at rest rest AP). Patients with Prinzmetal's AP represent a special subgroup where resting AP is accompanied by transient ST-segment elevation [176-179]. This ST elevation on the ECG correlates with proximal occlusion by vasospasm. As most vasospastic AP attacks are self-limiting, it is difficult to register without multi-day ambulatory Holter monitoring by 12-channel recording. The appearance of ST-segment changes at normal pulse supports the probability of myocardial ischemia caused by spasm. In patients with suspected vasospastic AP and documented ECG changes, coronary CTA or ICA is important to rule out the presence of fixed coronary stenosis. Angiographic documentation of coronary spasm requires the use of a provocation test in a catheterization laboratory. Due to the low sensitivity of the hyperventilation test and the cold water test, intracoronary administration of acetylcholine or ergonovine during ICA are preferred provocative tests. [176-179]. 176. Both pharmacological agents are safe, provided that they are selectively inserted into the left or right coronary arteries and that activated spasm is easily controlled by intracoronary nitrates. A small percentage of patients may develop ventricular tachycardia / ventricular fibrillation or bradyarrhythmia during a provocative test (3.2 and 2.7%, respectively), similar to that during spontaneous spasm attacks (7%) [180]. Intravenous administration of ergonovine for non-invasive tests is contraindicated due to the risk of causing long-term spasm in multiple coronary arteries, which can be very difficult to stop and can be fatal.

A provocative test for coronary spasm is considered positive when it causes: (1) anginal symptoms, (2) ischemic ECG changes, and (3) severe vasoconstriction of the epicardial coronary artery. If the test fails to run all three components, this should be considered ambiguous [176]. The development of AP in response to acetylcholine injections in the absence of angiographically evident spasm, with or without concomitant ECG changes in the ST segment, may indicate microvascular spasm and is often seen in patients with microvascular AP [179]. In patients with epicardial or microcirculatory vasomotor disorders, CCB and long-acting nitrates (LANs) are the treatment of choice, in addition to controlling CV risk factors and lifestyle changes. Nifedipine has been shown to be effective in reducing coronary spasm associated with stent implantation. In all patients with vasospastic angina, optimal control of risk factors should be achieved, especially smoking cessation and aspirin use. Exclude drugs that may be narrow vasospasm - cocaine or amphetamine abuse. Chronic preventive treatment of vasospastic angina is mainly based on higher doses of calcium antagonists. Average doses of these drugs verapamil or diltiazem from 240 to 360 mg / day or nifedipine from 40 to 60 mg usually prevent spasm in about 90% of patients. Sometimes high doses of calcium antagonists must be given to prevent spasms: up to 960 mg a day of Verapamil or Diltiazem or up to 100 mg / day of Nifedipine. Long-acting nitrates should be added to some patients. Beta-blockers should be avoided, as they may increase spasm because by blocking the beta-dilating effects, vasoconstriction by unblocked alpha receptors predominates. About 10% of patients are refractory to this treatment, so the addition of guanethidine or clonidine may rarely be indicated. Stent implantation at the site of spasm and without stenosis, as well as surgical or chemical sympathectomy, are extreme measures.

CLINICAL SCENARIO 6. ASYMPTOMATIC PERSONS IN WHICH CAD WAS DETECTED AT SCREENING.

In an effort to reduce the high incidence of coronary sudden death in asymptomatic adults, numerous studies of risk factors and risk indicators, as well as stress tests, are often performed as screening tests. The European guidelines for CVD prevention in 2016 in clinical practice focused in detail on these issues. [15]. In general, the use of a risk assessment system such as ESC SCORE is recommended. People with a family history of premature CAD should be screened for familial hypercholesterolemia. Coronary calcium score, ABI index, and Color Doppler echosonography of the carotid arteries in plaque detection may provide useful information on atherosclerotic risk in selected patients. Routine use of biomarkers or imaging tests for CAD is not recommended. New biomarkers have an increasing predictive value compared to classical ones, but the net improvement in reclassification risk is still only modest (7.18%) compared, for example, with the coronary calcium score, which has a net

improvement in reclassification of 66%. Only persons at high risk of events should be considered for further non-invasive or invasive examination. There are no data on how to treat asymptomatic subjects with a positive CAD test outside the recommendations outlined in these guidelines. However, the principles of risk stratification, as described above for symptomatic patients, also apply to these individuals. It is important to know that there is no data that showed an improved prognosis after appropriate care based on new biomarkers. It is important to note that cancer patients and those undergoing treatment for cancer, chronic inflammatory and systemic autoimmune diseases deserve a more intensive risk evaluation. People whose occupations include public safety (eg pilots or truck or bus drivers, workers) or professional athletes are usually periodically tested to assess the ECG with a TFO test and assess possible heart disease, including CAD, although there is insufficient data to justify this. However, these evaluations can be performed for medical-legal reasons. The threshold for performing a visualization stress test for CAD in such persons is lower than in the average patient.

REFRACTORY ANGINA PEKTORIS (RAP)

RAP as a form of chronic coronary syndrome (CCS) is defined as a chronic condition caused by clinically established reversible ischemia in the presence of CAD, which cannot be adequately controlled by a combination of medical therapy, angioplasty with stenting (PCI) or surgical coronary revascularization (CABG) [1]: The following treatment options are considered:

1- Forced external counterpulsation (EECP) should be considered to alleviate and minimize discomfort in patients with AP Refractory to optimal pharmacological therapy and revascularization strategy

2-Transcutaneous electrical nerve stimulation (TENS) can be used to alleviate the symptoms of refractory AP on optimal pharmacotherapy and revascularization strategy

3-Spinal cord stimulation (SCS) can be used to alleviate the symptoms of refractory angina to optimal pharmacol Th and revascularizа strategy

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4-Transmyocardial revascularization (TMR) is not indicated in patients with symptoms of refractory angina on optimal pharmacological Th and revascularization strategy

FUTURE PERSPECTIVES OF CHRONIC CORONARY SYNDROMES CCS - Quote from Brownwald's textbook of cardiology, authors David Morrow, J. J. A. De Lemos and William Boden [135]:

Our understanding of CHRONIC CORONARY SYNDROMES (CCS), both as a cause, optimal approach and treatment, is constantly evolving.

1. Complex and probably heterogeneous causes of myocardial ischemia require continuous multidisciplinary research through experimental studies in genetics, molecular biology, biochemistry, morphological and functional aspects of coronary circulation, and pathological morphology and pathophysiology of myocardial ischemia, which should then be confirmed in clinical studies with sufficient statistical power to generate new guidelines for more precise and simpler diagnosis and effective therapy of CCS. Today, we are confronted with the essential data that challenge the paradigm that Ischemic CAD requires critical coronary atherosclerosis of the subepicardial coronary artery or other structural heart disease that results in a dramatic increase in oxygen consumption. Preclinical, translational and clinical epidemiological data demonstrate abnormalities in coronary artery function, which can lead to myocardial ischemia in the absence of atherosclerotic obstruction.

2. However, so far, the treatments proposed for this important syndrome-CHRONIC CORONARY SYNDROME have proved insufficient. Additional insight into the pathobiology of ischemia could lead to new directions in treatment.

3. An initial approach to targeted secondary-preventive therapy and coronary revascularization, when necessary, is the best approach for most patients with CCS. There are subgroups of patients with high-risk indicators for whom coronary myocardial revascularization should be logical. However, clinical controversy and doubt remains as to whether such patients, including those with moderate or severe ischemia on a noninvasive test, should be routinely subjected to coronary myocardial revascularization in the absence of symptoms of refractory to optimal preventive and pharmacological therapy (OMT).

4.. Definitive evidence for the care of patients with stable CCS and other consequences of ischemia, especially left ventricular dysfunction and mitral ischemic regurgitation, remains incomplete. In our opinion, complete myocardial revascularization, usually surgical -CABG, remains a reasonable option for patients with multivessel CAD, LC dysfunction, and viable myocardium, especially when there is objective evidence of ischemia. However, some recent studies call this view into question. Despite our

good experience with CCS, there are no answers to important questions [135].

FUTURE PERSPECTIVES OF CHRONIC CORONARY SYNDROME CCS - quote from Braunald's textbook of cardiology, authors David Morrow and William Boden [181]: Our understanding of CCS, as a cause, optimal approach and treatment, is constantly evolving.

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CONCLUSION:

Careful and studious evaluation of the anamnesis, including characterization of anginal symptoms and assessment of risk factors and manifestations of cardiovascular diseases, as well as appropriate physical examination and basic supplementary, basic examination is essential for the diagnosis of chronic coronary syndromes. If obstructive coronary artery disease (mean pre-test probability) cannot be ruled out by clinical evaluation alone, noninvasive diagnostic functional imaging tests with physical or pharmacological loading or anatomical imaging should be used as the initial test to exclude or diagnose chronic coronary syndromes (clinical scenario 1). via coronary CT angiography. The selection of the initial non-invasive diagnostic test is based on the probability test for obstructive coronary heart disease (PTP), its clinical probability, characteristics and test availability. An anatomical and functional evaluation should be performed to decide on revascularization. Either non-invasive or invasive functional evaluation is required to assess the size of myocardial ischemia associated with angiographic coronary artery stenosis, except for very high-grade stenosis (> 90% of diameter stenosis). The risk assessment for adverse events and mortality serves to determine for which patients with CCS the prognostic benefit of revascularization is predicted.

Assessment of left ventricular function by echocardiography is a mandatory part of risk stratification. Patients at high risk of adverse events undergo invasive examination to consider revascularization, even when asymptomatic. The application of a healthy lifestyle reduces the risk of subsequent CV events and mortality and is always included in the program of appropriate measures and therapy of secondary prevention. Clinicians should advise and encourage the necessary lifestyle changes at each clinical encounter with patients. Cognitive-behavioral psychological interventions such as supporting patients to set realistic goals, self-control, planning to implement change, coping with difficult situations, adapting to the environment, and

including social support are effective behavioral change interventions.

Multidisciplinary teams can support patients to change to a healthy lifestyle and guide them to avoid risk and risky behavior. Anti-ischemic treatment must be tailored to the individual patient based on comorbidity, concomitant therapy, expected tolerance and adherence to therapy, but also the patient's preference. The choice of anti-ischemic drugs for the treatment of CCS should be adjusted to heart rate, blood pressure and left ventricular function. Beta-blockers and / or calcium antagonists remain first-line drugs in patients with CCS. Antithrombotic therapy is a key part of secondary prevention in patients with CCS and requires careful consideration. Long-term (and after 12 months) dual antiplatelet therapy (DAPT) with aspirin or any P2I12 inhibitor should be considered in patients with previous myocardial infarction, with or without revascularization, who are at high risk of ischemic events and low risk of severe or fatal bleeding. or rivaroxaban with very low doses, unless they have an indication for oral anticoagulant therapy (OAK) such as the presence of atrial fibrillation (AF). Statins are recommended for all patients with CCS, regardless of the level of LDL cholesterol. ACE inhibitors (or ARBs) are recommended in the presence of heart failure (SI), diabetes, or hypertension and should be considered in all high-risk patients. Proton pump inhibitors are recommended in patients receiving aspirin or a combination of antithrombotic therapies that are at high risk for gastrointestinal bleeding. Efforts should be made to explain to patients the importance of taking prescribed medication regularly, based on evidence that regular adherence to treatment prevents adverse events, relieves the patient of pain, and improves quality of life. Repeated therapeutic education of patients is essential for every clinical encounter. Patients with a long-term diagnosis of CCS should visit a doctor periodically to assess possible changes in risk status, adhere to treatment goals, and develop comorbidities. Repeated physical or pharmacological stress tests, preferably imaging stress tests, or invasive coronary angiography with functional testing in case of worsening symptoms and / or increased risk status are recommended. Assessment of the function and dimensions of the heart cavities, myocardium and valves, as well as a functional test to rule out significant asymptomatic (silent) myocardial ischemia, should be considered every 3–5 years in asymptomatic patients with a long-term diagnosis of CCS. Assessment of coronary vasomotor function should be considered in patients without obstructive coronary disease or with minor epicardial coronary disease who have objective evidence of myocardial ischemia. Objectives of treatment of chronic coronary symptoms (CCS): improving prognosis, ie. reducing mortality by reducing the risk of progression of atherosclerosis and preventing acute coronary events and sudden death; and minimizing symptoms while improving quality of life. Efforts should be made to explain to patients the importance of evidence-based guidelines and guidelines for adherence to treatment.

All patients with stable coronary heart disease need lifestyle changes, risk factor reduction and pharmacological therapy, but all patients with coronary artery stenosis do not benefit from revascularization, which depends on the size of the ischemia and the anatomical involvement of the coronary arteries. Optimal medical therapy is the definitive therapy for patients with stable coronary heart disease and low risk of cardiovascular events. Revascularization and optimal medical therapy should be considered as complementary rather than competitive treatments.

In high-risk CCS patients with mortality> 3% per year or AP refractory to OMT, evidence of physical or pharmacological stress ischemia is required, preferably stress echocardiography to determine the size of ischemia on the stress echo test and anatomical assessment to determine coronary artery disease. to indicate revascularization leading to clinical benefit.

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