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GUIDELINE FOR STABLE CORONARY ARTERY DISEASE

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Guideline for Stable Coronary Artery Disease

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Affiliated at the Brazilian Medical Association

Adress: Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brazil
Phone.: (21) 3478-2700
E-mail: arquivos@cardiol.br
www.arquivosonline.com.br
SciELO: www.scielo.br

Commercial Department
Phone: (11) 3411-5500
e-mail: comercialsp@cardiol.br

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Summary

Guideline for Stable Coronary Artery Disease

Realization

Sociedade Brasileira de Cardiologia

Coordinator of Standards and Guidelines

Álvaro Avezum Junior; Anis Rassi; Carisi Anne Polanczyk; Gilson Soares Feitosa

General Coordinator

Luiz Carlos Bodanese

GECETI President

João Fernando Monteiro Ferreira

Coordinator

Luiz Antonio Machado Cesar

Editor

João Fernando Monteiro Ferreira

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Mailing Address:
Sociedade Brasileira de Cardiologia
Av. Marechal Câmara, 160/330 – Centro – Rio de Janeiro – CEP: 20020-907
e-mail: scb@cardiol.br

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Work Groups

Group 1 - Diagnostic and Risk Stratification

Coordinator: João Fernando Monteiro Ferreira. **Participants:** Antonio Carlos de Sousa, Antonio de Pádua Mansur, Brivaldo Markman, Bruno Caramelli, Claudio Meneghetti, Eduardo Nagib, Ibraim M. F. Pinto, Iran Castro, Jeane M. Tsutsui, Kerginaldo Torres, Raul Dias dos Santos, Romeu Meneghello.

Group 2 – Clinical Treatment

Coordinator: Luis Henrique Gowdak. **Participants:** Andrei Sposito, Caio de Brito Vianna, Cesar Cardoso de Oliveira, Denilson Campos de Albuquerque, Jamil Cherem Schneider, João Fernando Monteiro Ferreira, Luis Henrique W Gowdak, Marcelo Ferraz Sampaio, Otávio Rizzi Coelho, Sergio Tavares Montenegro.

Group 3 - Treatment with Invasive measurements

Coordinator: Dikran Armaganijan. **Participants:** Áurea J. Chaves, Edson Stefanini, Jamil Abdalla Saad, José Klauber Roger Carneiro, Leopoldo Soares Piegas, Luis Alberto Dallan, Luiz Augusto F. Lisboa, Miguel Antonio Moretti, Neuza Helena Lopes, Pedro Lemos, Roberto Botelho, Rodolfo Staico, Vinicius Daher Vaz.

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Names Members	**"Participated in clinical studies and / or experimental trials supported by pharmaceutical or equipment related to the guideline in question"**	**"Has spoken at events or activities sponsored by industry related to the guideline in question"**	**"It was (is) advisory board member or director of a pharmaceutical or equipment"**	**"Committees participated in completion of research sponsored by industry"**	**"Personal or institutional aid received from industry"**	**"Produced scientific papers in journals sponsored by industry"**	**"It shares the industry"**
Andrei Sposito	No	No	No	No	No	No	No
Antônio Carlos Sobral Sousa	Estudo SIGNIFY- Servier	No	No	No	No	No	No
Antonio P. Mansur	No	No	No	No	No	No	No
Áurea J. Chaves	No	No	No	No	No	No	No
Brivaldo Markman	Signify - Ivabradina	No	No	No	No	No	No
Bruno Caramelli	No	No	No	No	No	No	No
Caio de Brito Vianna	No	No	No	No	No	No	No
Carlos Eduardo Rochitte	No	No	No	No	No	No	No
Cesar Cardoso de Oliveira	No	No	No	No	No	No	No
Denilson Campos de Albuquerque	No	No	No	No	No	No	No
Dikran Armaganijan	AstraZeneca, Parexel	No	No	No	No	No	No
Edson Stefanini	No	No	No	No	No	No	No
Eduardo Nagib Gaui	No	AstraZeneca, Daiichi Sankyo	No	No	AstraZeneca, Daiichi Sankyo, Bayer	No	No
Ibraim Masciarelli F. Pinto	No	No	No	No	No	No	No
Iran Castro	No	No	No	No	No	No	No
Jamil Abdalla Saad	No	No	No	No	No	No	No
Jamil Cherem Schneider	No	No	No	No	No	No	No
Jeane Mike Tsutsui	No	No	No	No	No	No	No
José Klauber Roger Carneiro	No	No	No	No	No	No	No
Kerginaldo Paulo Torres	No	No	No	No	No	No	No
Leonardo Sara	No	No	No	No	No	No	No
Leopoldo S. Piegas	No	No	No	Sanofi Aventis, BMS, Boehringer Ingelheim	No	No	No
Luis Alberto Oliveira Dallan	No	No	No	No	No	No	No
Luís Henrique Wolff Gowdak	Servier	Servier	No	Servier	No	Servier, Eurofarma	No

Continuation

Luiz Antonio Machado Cesar	Servier e Astra Zeneca	Servier e Astra Zeneca	Servier e Astra Zeneca	Servier e Astra Zeneca	Servier e Astra Zeneca	Servier e Astra Zeneca	No
Luiz Augusto Ferreira Lisboa	No	No	No	No	No	No	No
Marcelo Ferraz Sampaio	No	No	No	No	No	No	No
Miguel Antonio Moretti	Clarify e Signify - Servier	No	No	No	No	No	No
Neuza Helena Moreira Lopes	No	No	No	No	No	No	No
Otávio Rizzi Coelho	Servier	Servier, Bayer, Astra Zeneca, Biolab, Pfizer	No	No	Bayer e Biolab	No	No
Pedro A. Lemos	Scietch, Boston Scientific	Biosensors	Scietch, Medtronic, Boston Scientific	Scietch, Boston Scientific	No	No	No
Raul Dias dos Santos Filho	Genzyme, Roche, Pfizer e Astra Zeneca	Astra Zeneca, Biolab, Pfizer, Aegerion, Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Novartis, Novo Nordisk , MSD, Genzyme	Astra Zeneca, Bristol Myers Squibb, Boehringer Ingelheim, Novo Nordisk, Biolab, Unilever, Amgen, Aegerion, Sanofi/ Regeneron, Pfizer	Pfizer, Genzyme	Genzyme, Biolab	Novartis, MSD, Bristol Myers Squibb	No
Roberto Vieira Botelho	Abbott Vascular, Astra Zeneca, Sanofi Aventis, Novartis, Daiichi Sankyo, Elixir, CardioMed, The Medicines Company	No	No	No	No	No	No
Rodolfo Staico	No	No	No	No	No	No	No
Romeu Sergio Meneghello	No	No	No	No	No	No	No
Sergio Tavares Montenegro	Servier, Takeda, Boehringer	Servier, Astra Zeneca	No	No	No	No	No
Vincius Daher Vaz	No	No	No	No	No	No	No

Part I - Diagnosis and risk stratification

1. Introduction

This guideline was developed to guide all physicians, particularly cardiologists, to identify adults at high risk of CAD as early as possible and to highlight its most common symptoms.

Cardiovascular disease, including one of its main forms of presentation, CAD, is one of the most important diseases of the 21st century, considering its morbidity and mortality[1]. On the basis of the results of several studies, the prevalence of angina is estimated to be 12%–14% in men and 10%–12% in women aged between 65 and 84 years. In the United States, one in three adults (approximately 81 million people) have some form of cardiovascular disease, including > 10 million people with angina pectoris[2,3].

In Brazil, data from the Informatics Department of the Unified Health System (DATASUS) show that cardiovascular disease represents approximately 30% of the overall causes of death. More than 80,000 hospital admissions occurred in Brazil in February 2014 because of circulatory system diseases[4].

For a better understanding of this scenario, this guideline is divided into five parts: diagnosis, risk stratification, clinical treatment, treatment with invasive techniques, and special situations. The grades and levels of evidence were considered as follows:

Grade of recommendation:

- Class I: conditions for which there is conclusive evidence and, in their absence, general agreement that the procedure is safe and useful/effective;
- Class II: conditions for which there is conflicting evidence and/or divergence of opinion about the safety and useful/effective of the procedure;
- Class IIa: evidence/opinion in favor of the procedure. Approved by most professionals;
- Class IIb: less well established safety and useful/effective, with no predominance of opinion in favor of the procedure;
- Class III: Conditions for which there is evidence and/or consensus that the procedure is not beneficial/no effective and in some cases may be harmful.

Level of Evidence:

- Level A: data derived from multiple large randomized controlled studies and/or robust systematic meta-analyses of randomized clinical trials;
- Level B: data derived from less robust meta-analyses, from a single randomized trial, or from nonrandomized studies (observational);
- Level C: data obtained from consensus opinion of experts.

2. DIAGNOSIS

2.a. Diagnosis of subclinical CAD

The identification of asymptomatic individuals with atherosclerosis and consequently at risk of acute cardiovascular events, including myocardial infarction (MI) and death, is essential for the indication of treatment and measures for secondary prevention.

The estimated risk of atherosclerotic disease can be evaluated by the sum of the individual risks and by the synergistic effect of the risk factors known for cardiovascular disease. Considering the complexity of these interactions, the intuitive assessment of risk often results in the underestimation or overestimation of the cases with increased or decreased risk, respectively. To circumvent this difficulty, several algorithms have been created on the basis of the regression analysis of population studies, and by means of which the evaluation of the overall risk is substantially improved.

2.a.1. Diagnosis in symptomatic patients

In contrast, in patients with symptoms and risk factors, although it seems premature to predict the likelihood of CAD after clinical history assessment and physical examination, authors such as Diamond and Forrester[5] have demonstrated that diagnosis is possible. By combining data from angiographic studies from the 1960s and 1970s, it became evident that clinical examination, pain assessment, age, and gender were significant predictors of CAD. These findings were later confirmed in other studies, including the CASS study, wherein the initial clinical approach involving medical history assessment and physical examination was predictive of CAD[6-9].

Therefore, patients presenting with chest pain should be evaluated on the basis of their clinical history, with a detailed symptom assessment, complete physical examination, and evaluation of associated risk factors. With this information, it is possible to estimate the probability of occurrence of significant CAD and to establish a low, moderate, or high CAD risk. **Grade of recommendation I, Level of evidence B.**

On the basis of Forrester's information and the CASS study, it is possible to estimate the probability of occurrence of CAD after the evaluation of symptoms, gender, and age, as described in Table 1[5,9].

For the assessment of cardiovascular risk, the Brazilian guideline for the prevention of atherosclerosis and the Fifth Brazilian Guideline on Dyslipidemia and Prevention of Atherosclerosis were adopted, which recommend the performance of a risk assessment of atherosclerotic disease[10,11]. The risk assessment is divided in three stages as detailed below and can be consulted in the guidelines listed above:

Table 1 – Pretest probability of coronary atherosclerotic disease in symptomatic patients, according to age and gender (Diamond-Forrester and CASS Data)

Age (years)	Nonanginal chest pain		Atypical Angina		Typical Angina	
	Male	Female	Male	Female	Male	Female
35	3–35	1–19	8–59	2–39	30–88	10–78
45	9–47	2–22	21–70	5–43	51–92	20–79
55	23–59	4–25	25–79	10–47	80–95	38–82
65	49–69	9–29	71–86	20–51	93–97	56–84

- Stage 1: presence of significant atherosclerotic disease or its equivalent;
- Stage 2: application of a risk score;
- Stage 3: identification of aggravating factors.

Of note, the use of biochemical diagnostic tests and/or imaging tests for the detection of subclinical atherosclerosis is not recommended as routine tools for risk stratification, but they can be used on an individual basis in subjects with family history of premature atherosclerotic disease, or those at intermediate risk, based on the risk assessment (**Grade of recommendation IIa, Level of evidence B**). The evaluation of the intima–media thickness (IMT) of the carotid is very controversial and is considered to be of class IIb according to the atherosclerosis guideline we adopted because its ability to predict disease is unclear, and therefore this evaluation is no longer recommended by the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA).

2.b. Diagnosis of Coronary Artery Disease

For an adequate analysis of the research findings on angina, some aspects involved in the clinical assessment of patients with chest pain should be considered, including associated conditions, provoking factors, relieving factors, noninvasive tests used in diagnosis, and risk stratification.

2.b.1. History, physical examination, and differential diagnosis

2.b.1.1. Definition of angina

Angina is a clinical syndrome characterized by pain or discomfort in any of the following body regions: chest, epigastrium, mandible, shoulder, dorsum, or upper limbs. It is typically triggered or aggravated by physical activity or emotional stress and attenuated with the use of nitroglycerin and its derivatives. Angina usually occurs in patients with CAD showing stenosis of at least one epicardial artery. However, it can also occur in patients with valvular heart disease, hypertrophic cardiomyopathy, and uncontrolled hypertension. Patients with normal coronary arteries and myocardial ischemia associated with spasms or endothelial dysfunction may also present with angina. In this respect, changes in the microcirculation, such as those that occur during left ventricular (LV) hypertrophy and syndrome X, can also lead to coronary insufficiency. This observation has attracted attention for years, particularly in women with angina but without obstructions on coronary angiography, and is known as syndrome X. In fact, even without arterial obstruction, both epicardial arteries and those involved in the microcirculation have inadequate flow, which is sufficient to cause myocardial ischemia. This can be diagnosed on exercise electrocardiography (ECG) or myocardial perfusion scintigraphy (MPS). This syndrome is interpreted as a disease of the coronary microcirculation and is caused by endothelial dysfunction or changes in the vascular tone, resulting in decreased oxygen supply at the cellular level. Recently, it has been shown that subjects with this syndrome have atherosclerotic plaques in various segments where coronary obstruction is not present, with a frequency of up to 55%–60% on coronary intravascular ultrasound (IVUS)[12]. It is known that changes in vascular reactivity occur in this condition[13,14], leading to myocardial ischemia, particularly in women, as reported in the WISE study[15]. In addition, this same study revealed that, even in the absence of obstructions, changes in coronary reactivity were a risk factor for future coronary events in these female patients, although the possibility of atherosclerosis in epicardial vessels in the absence of obstruction was not discarded. Another similar condition is the occurrence of low coronary flow[16]. Anatomical abnormalities, e.g., anomalous origins of coronary arteries, can also lead to CAD. Furthermore, a decrease in coronary flow may also occur in the presence of changes in vascular tone known as coronary artery spasms. These spams can alter the degree of obstruction of the vessel lumen and even lead to (or promote) coronary artery occlusion, and consequently to a clinical manifestation of MI, especially because these changes occur in patients with moderate or significant atherosclerotic lesions. When ECG changes occur, this condition is designated Prinzmetal's angina. However, in a few patients, we observe angiographically normal coronary arteries. In addition, many chest pain conditions, or symptoms manifested in other common regions, are identified in other diagnoses, including complications of the esophagus, stomach, lung, mediastinum, pleura, and chest wall. After the diagnosis of heart disease is discarded, the recommendations for the management of these patients are beyond the scope of this guideline.

2.b.1.2. Clinical evaluation of patients with chest pain

a) Clinical history: Clinical examination is one of the most important steps in the evaluation of patients with chest pain, because it helps the doctor estimate the probability of significant CAD with a high degree of accuracy[9]; angiographically, CAD is defined by the presence of stenosis ≥ 70% of the diameter of at least one segment of a major epicardial artery, or stenosis ≥ 50% of the diameter of the left main disease (LMD). Although lesions with a lower degree of stenosis can cause angina, they have a lower prognostic significance[8]. A clinical history with a detailed assessment of symptoms enables physicians to adequately characterize chest pain. Some symptoms should be carefully investigated to determine the likelihood of occurrence of angina:

- Quality: constriction, tightness, heaviness, distress, discomfort, burning, and stabbing;
- Location: precordium, retrosternal region, shoulder, epigastrium, neck, hemithorax, and dorsum;
- Irradiation: upper limbs (right, left, or both), shoulder, mandible, neck, dorsum, and epigastric region;
- Duration: seconds, minutes, hours, or days;
- Provoking factors: physical activity, sexual activity, body position, eating habits, breathing, emotional stress, or spontaneous;
- Relieving factors: rest, sublingual nitrates, analgesics, food, antacids, body position, and apnea;
- Associated symptoms: sweating, nausea, vomiting, pallor, dyspnea, hemoptysis, cough, presyncope, and syncope.

Many symptoms are reported by patients when describing angina, including suffocation, burning, distress, and heaviness. They frequently complain of discomfort but not precordial pain. Angina is rarely reported as stabbing pains and generally has no association with breathing or the decubitus position. Typically, the anginal episode lasts a few minutes. It is generally precipitated by exercise or emotional stress, with frequent improvement or relief at rest. The use of nitroglycerin compounds, such as sublingual nitrate, can relieve angina in approximately 1 min. A sudden, brief, or continuous discomfort, which can last several hours, is rarely angina. Angina usually affects the retrosternal region and radiates to the neck, mandible, epigastrium, and upper limbs. Pain located in the chondrosternal joints rarely has cardiac origin.

Several classification systems have been proposed and the most commonly used divides chest pain into three groups: typical, atypical, and noncardiac[17] (Chart 1). It can also be classified according to its severity (Chart 2). Angina can also be stable or unstable. It is important to diagnose unstable angina because of its close association with acute coronary events. Unstable angina can be divided into three groups according to certain clinical characteristics: at rest, recently emerged, and in development (Chart 3).

b) Physical examination: Physical examination is usually normal in patients with stable angina[18]. However, during the anginal episode, it can provide important clues as to the presence or absence of CAD. When a physical examination is performed during a pain episode, findings such as the third heart sound (S3), fourth heart sound (S4) or gallop, mitral regurgitation, paradoxical splitting of the second heart sound (S2), and bibasilar lung rales are suggestive symptoms and predictors of CAD[19,20]. The occurrence of atherosclerosis in other body regions, including decreased pulse in the lower limbs, arterial hardening, and abdominal aneurysm, increase the likelihood of CAD. Moreover, other findings, including high blood pressure, retinal exudates, and xanthomas, suggest the presence of risk factors for CAD. Muffled heart sounds and facial flushing may indicate diseases of the pericardium and/or pleura adjacent to the heart. Even if the physical examination does not indicate direct or indirect signs of CAD, a complete clinical examination should be carefully performed, especially that of the cardiovascular system, because it can help elucidate other associated conditions, including valvular diseases and hypertrophic cardiomyopathy. Chest wall palpation often reveals the pain location in the patients with musculoskeletal syndromes. However, pain can also occur in patients with typical angina.

2.b.1.3. Differential diagnosis of chest pain: associated conditions, provoking factors, and relieving factors of angina

In all patients, particularly those with typical angina, associated diseases that can precipitate "functional" angina in the absence of significant anatomical coronary obstruction (e.g., myocardial ischemia) should be considered. These diseases

Chart 1 - Clinical classification of chest pain

Typical angina (definitive)	Retrosternal pain or discomfort
	Triggered by exercise or emotional stress
	Relieved with rest or nitroglycerin use
Atypical angina (probable)	Presence of only two of the above factors
Noncardiac chest pain	Presence of only one or none of the above factors

Chart 2 – Canadian Cardiovascular Society Angina Grading Scale

Class I	Everyday physical activity, such as walking and climbing stairs, does not cause angina. Angina occurs with prolonged and intense physical efforts
Class II	Slight limitation of everyday activities. Angina occurs when quickly walking or climbing stairs, walking uphill, walking or climbing stairs after meals, or in the cold or the wind, or while under emotional stress, or only during a few hours after awakening. Angina occurs after walking two level blocks or climbing more than one flight of stairs in normal conditions
Class III	Limitation of everyday activities. Angina occurs after walking one level block or climbing one flight of stairs
Class IV	Inability to carry on any ordinary activity without discomfort ¬— anginal symptoms may be present at rest

Chart 3 – Unstable angina: three main presentations

1. Angina at rest	Usually lasting > 20 min, occurring for approximately 1 week
2. angina that appears	With CCS severity* of at least III and new onset within 2 months
3. angina "in crescendo"	Previously diagnosed angina which occurs more frequently with longer-lasting episodes, or with lower threshold

**Canadian Cardiovascular Society.*

generally cause myocardial ischemia by increasing the oxygen consumption of the myocardium or decreasing the oxygen supply to it (Chart 4)[18-21]. The increased oxygen consumption can be produced during hyperthermia, hyperthyroidism, and cocaine use. Hyperthermia, particularly if accompanied by decreased blood volume due to sweating or loss of other body fluids, can precipitate angina, even in the absence of significant CAD. Hyperthyroidism, and its associated tachycardia and high metabolic rate, can increase oxygen consumption and decrease oxygen supply. It is important to emphasize that older patients may not present clinical signs typical of thyrotoxicosis; therefore, this possibility should always be considered, particularly among older people. Sympathomimetic toxicity, of which cocaine use is the most common, not only increases oxygen consumption but also decreases its supply by simultaneously provoking coronary spasms, which may lead to MI in young patients. Over the long term, cocaine use can lead to angina by causing CAD prematurely[22]. Angina may occur in patients with uncontrolled hypertension owing to increased LV wall stress, decreased coronary flow reserve (ability to increase coronary flow during physiological and pharmacological stress), and increased LV end-diastolic pressure, and the latter can decrease subendocardial myocardial perfusion. These same mechanisms contribute to anginal symptoms in patients with aortic valve stenosis and hypertrophic cardiomyopathy. Moreover, both ventricular and supraventricular sustained tachycardia can increase oxygen consumption. Paroxysmal tachycardia is among the conditions that most often contribute to angina and is usually difficult to diagnose. Conditions that decrease the oxygen supply should also be considered during differential diagnosis or the diagnosis of aggravating diseases in anginal patients. Anemia decreases the oxygen-carrying capacity of the blood and increases cardiac overload. Increased cardiac output usually occurs in anemic patients with hemoglobin levels < 9 g/dL, and ST–T changes (depression or inversion) can occur when hemoglobin levels reach < 7 g/dL. Hypoxemia resulting from pulmonary diseases such as pneumonia, asthma, chronic obstructive pulmonary disease, pulmonary hypertension, interstitial fibrosis, or obstructive sleep apnea can also precipitate angina. Obstructive sleep apnea should be seriously considered in patients with significant nocturnal symptoms.

Conditions associated with increased blood viscosity may increase coronary resistance and consequently decrease coronary artery blood flow, which can precipitate angina in patients with significant coronary artery stenoses.

Chart 4 – Conditions that can cause or exacerbate ischemia by increased consumption or decreased supply of oxygen

Noncardiac causes	Anemia
	Hyperthermia
	Pneumonia
	Asthma
	Chronic obstructive pulmonary disease
	Hypoxemia
	Pulmonary hypertension
	Interstitial pulmonary fibrosis
	Obstructive sleep apnea
	Polycythemia and hyperviscosity
	Leukemia
	Sickle-cell disease
	Thrombocytosis
	Hyperthyroidism
	Sympathomimetic toxicity (for example: cocaine use)
	Hypertension
	Arteriovenous fistula
	Hypergammaglobulinemia
	Anxiety
Cardiac causes	Hypertrophic cardiomyopathy
	Ventricular tachycardia
	Aortic stenosis
	Supraventricular tachycardia
	Dilated cardiomyopathy

Increased blood viscosity is observed in medical conditions, including polycythemia, leukemia, thrombocytosis, and hypergammaglobulinemia. In addition, other diagnoses should be considered during the assessment of the patient's medical history because these associated conditions may be the cause of the symptoms experienced by the patient. To differentiate these diagnoses, it is necessary to evaluate all conditions (Chart 5) and to identify which of these conditions may differ from angina.

2.b.2. Noninvasive tests

The initial evaluation of patients with chest pain or angina includes a detailed analysis of clinical history, physical examination to eliminate noncardiac causes of chest pain, and tests and procedures necessary for the diagnosis and assessment of the severity of CAD.

The requirement for additional tests in stable angina depends on the probability of significant CAD, which in turn depends on the type of pain, gender, comorbidities, and age of patient[6-9]. Factors such as smoking (at least half a pack a day for 5 years or 25 packs per year), total cholesterol levels (TC; > 250 mg/dL), and fasting glucose levels (> 140 mg/dL) can also increase the likelihood of CAD. Other factors, such as family history and hypertension, are not strongly predictive of CAD. After estimating the probability, it can be categorized as low, intermediate, or high according to established criteria: < 10% in low-probability cases, 10%–90% in intermediate-probability cases, and > 90% in high-probability cases[10,11]. In low-probability patients, additional tests are based on the assessment of noncardiac causes of chest pain. In high-probability patients, a diagnostic investigation should be conducted to assess patient's individual risk of having cardiac events (cardiac risk assessment), including fatal or nonfatal MI. In intermediate-probability patients, additional methods are necessary for CAD diagnosis and risk stratification.

With regard to these additional tests, several methods are currently available, including exercise ECG, stress echocardiography, stress MPS, cardiac computed tomography (CCT), cardiac magnetic resonance imaging (CMR), and cine coronary angiography (CA). The choice of each of these methods should be based on the following factors: (1) the patient profile, including physical condition and stress tolerance, resting ECG results (bundle-branch block, permanent pacemaker implantation, and repolarization changes, among others); (2) previous history of CAD (MI and revascularization); (3) patient preferences and occupation, including professions in which individuals require an accurate diagnosis because of potential risks to other people, and when medical assistance is unavailable, such as during acute MI (AMI). Considering that the overall mortality of patients with stable angina varies between 1.2% and 2.4% per year[23-25], a diagnostic method that results in a higher incidence of complications and death would be inappropriate.

2.b.2.1. ECG

ECG has limited importance in chronic CAD because repolarization changes do not necessarily indicate CAD and can be associated with other causes, including LV hypertrophy, electrolyte abnormalities, left bundle-branch block (LBBB), and T-wave changes, among others. Therefore, considering this limitation, a normal ECG does not exclude the possibility of coronary obstruction. However, ECG has diagnostic importance: (1) presence of Qr or QS waves plus negative T wave suggest the diagnosis of previous MI; (2) changes in the ventricular repolarization are suggestive of subepicardial ischemia (negative, sharp, and symmetric T waves) in a specific myocardial region: anteroseptal (V1, V2, V3, V4), anterolateral (V4, V5, V6, DI, and aVL), high lateral (DI and aVL), extensive anterior (V1–V6 in DI, and aVL), inferior (D2, D3, and aVF), and dorsal (V7 and V8 with reciprocal image in V1, V2, and V3); (3) changes in ventricular repolarization are suggestive of subendocardial ischemia (positive, sharp, and symmetrical T waves) in a specific region (anteroseptal, anterolateral, high lateral, extensive anterior, inferior, and dorsal); (4) changes in the ventricular repolarization are suggestive of subendocardial injury (depression of the J point and ST-segment, with superior concavity of this segment in leads exploring the injury) in a specific region (anteroseptal, anterolateral, high lateral, extensive anterior, inferior, and dorsal).

Therefore, ECG is indicated for patients with suspected cardiac cause of chest pain (**Grade of recommendation I, Level of evidence B**) or during an episode of chest pain (**Grade of recommendation I, Level of evidence B**).

Chart 5 – Differential diagnoses in patients with chest pain

Nonischemic cardiovascular	Pulmonary	Gastrointestinal	Thoracic wall	Psychiatry
Aortic dissection	Embolism	Esophagus: esophagitis, spasm and reflux	Costochondritis	Anxiety disorders: hyperventilation
Pericarditis	Pneumothorax	Gallbladder: biliary colic, cholecystitis, cholelithiasis, cholangitis, peptic ulcer	Fibrosis	Panic disorders
	Pneumonia	Pancreatitis	Rib fracture	Primary anxiety
	Pleuritis		Sternoclavicular joint arthritis	Affectivity disorders: depression etc.
			Post herpes zoster neuralgie	Somatic disorders

2.b.2.2. Chest radiography (CR)

Chest radiography is usually the first imaging modality performed in patients with chest pain, with the main purpose of performing a differential diagnosis of angina; it can be diagnosed in patients with pneumothorax, pneumomediastinum, rib fractures, and acute infections. Other conditions that cause acute chest pain with noncardiogenic etiology, including aortic aneurysm, aortic dissections, and pulmonary embolism, can be diagnosed with CR. However, the sensitivity of the method for the diagnosis of these conditions is very low. Therefore, CR is indicated for patients with CAD and signs or symptoms of congestive heart failure (**Grade of recommendation I, Level of evidence B**), patients with signs and symptoms of lung disease (**Grade of recommendation IIa, Level of Evidence B**), and for other conditions (**Grade of recommendation IIb, Level of evidence B**).

2.b.2.3. Exercise treadmill test

Exercise treadmill test (ETT) is a noninvasive method used most frequently in stable angina, aiming to confirm diagnosis, determine prognosis, and define the therapeutics. For ETT interpretation, the clinical responses related to symptoms and functional capacity, and ECG and hemodynamic profiles, need to be considered. The most predictive variables related to the diagnosis of coronary obstruction are ST-segment depression ≥ 1 mm (measured at 0.80 s from the J point), with a horizontal or downsloping pattern, and the presence of anginal pain. For the diagnosis of myocardial ischemia, the test results should be correlated with the pretest probability of CAD. In revascularized patients, particularly those who present ECG with baseline changes in the ST segment, hemodynamic and clinical profiles, and the functional capacity, should be taken into consideration during the test. Imaging tests (scintigraphy, echocardiography, or stress cardiac magnetic resonance imaging) are recommended for these patients for the detection of the presence and location of residual ischemia. Recently, novel analysis criteria, including QT dispersion, have been used in revascularized group for the diagnosis of residual ischemia after revascularization, with some improvment in the sensitivity and specifivity of ETT[26].

Use of ETT for the diagnosis of coronary artery obstruction

Grade of recommendation I, Level of evidence B

Patients with intermediate pretest probability of developing coronary obstruction, according to age, gender, and symptoms, including those with right bundle-branch block or ST-segment depression < 1 mm on ECG.

Grade of recommendation IIa, Level of evidence B

1. Patients with suspected vasospastic angina.
2. Patients subjected to coronary angiography for the assessment of intermediate lesions.
3. Evaluation of asymptomatic patients with more than two risk factors.

Grade of recommendation IIb, Level of evidence B

1. Patients with low or high pretest probability of developing coronary obstruction, according to age, gender, and symptoms.
2. Risk assessment for noncardiac surgery in patients with low cardiovascular risk.

Grade of recommendation III

Patients with baseline ECG abnormalities: pre-excitation syndrome or Wolff–Parkinson–White (WPW) syndrome, pacemaker rhythm, ST-segment depression >1 mm at rest, and complete left bundle-branch block.

2.b.2.4. Echocardiography

Echocardiography is an important test for confirming the diagnosis and evaluating the prognosis in patients with chronic CAD[27,28]. Echocardiography can provide valuable diagnostic aid in elucidating reversible or irreversible segmental wall motion abnormalities in patients with clinical CAD, particularly when the clinical history and ECG are inconclusive. Considering that echocardiography allows a real-time assessment of the LV wall motion, tests using physical or pharmacological stress, whether inotropic or vasodilator, allow the evaluation of the extent and severity of transient changes in LV wall motion. Echocardiography with microbubble-based ultrasound contrast represents a breakthrough in the diagnosis of these patients. These microbubbles are approximately 3 μm in diameter and behave as red blood cells in the bloodstream, and can map the entire tissue perfusion using ultrasound. The microbubbles fill the LV cavity, allowing the accurate evaluation of segmental wall motion abnormalities and, after coronary sinus filling, the evaluation of the intramyocardial blood flow, i.e., myocardial perfusion[29-31].

a) Role of transthoracic echocardiography in the diagnosis of coronary atherosclerosis and its complications: Transthoracic echocardiography is an excellent screening method in patients with CAD during acute events, because segmental wall motion abnormalities occur seconds after coronary occlusion and are reliable markers of previous MI. Although these abnormalities can indicate previous ischemia or infarction rather than acute infarction, they help eliminate other causes of chest pain, e.g., aortic dissection, pericarditis, and massive pulmonary embolism (Chart 6). In the stable patient, the anatomical information is important but not necessary in the routine of all cases. Echocardiography at rest provides a lot of information on the LV function, including the myocardial viability, with important therapeutic and prognostic implications after AMI. The wall motion score is obtained from the echocardiographic division of LV into 16 segments, and values between 1 and 4 are assigned to each segment according to the degree of motility. This finding is valuable in establishing the degree of LV dysfunction, especially because it is better correlated with the total mass involved in the process of ischemic injury compared with the actual ejection fraction (EF), which may be overestimated. A value of "1" indicates a normal contractile movement. Subsequently, hypokinesia, akinesia, and dyskinesia are assigned other

Chart 6 – Recommendations for the use of transthoracic echocardiogram in diagnosing CAD

Recommendations	Class
Initial assessment of LV function	I
Assessment of left ventricular function when there are signs of CHF or change in clinical status or physical examination	I
Suspected complications, such as pseudoaneurysm, aneurysms, and mitral insufficiency	I
Initial assessment of asymptomatic cases with low probability of CAD	III
Routine periodic re-evaluation of stable patients without change in therapy	III

Source: Brazilian Society of Cardiology[28]. CAD: coronary atherosclerotic disease; CHF: congestive heart failure; LV: left ventricle

values. The LV wall motion score index (LVWMSI) is calculated by the sum of each of 16 segments with motion dysfunction. A score between 1 and 1.6 indicates normal or slightly impaired ventricular function, a score between 1.61 and 2.0 indicates moderate stenosis, and a score > 2.0 corresponds to significant stenosis. The complete echocardiographic study, i.e., with color Doppler flow mapping, is critical for assessing complications, such as diastolic dysfunction, mitral regurgitation, interventricular communication, pericarditis, aneurysm, and pseudoaneurysm. It is the method of choice for the differential diagnosis of diseases, including aortic stenosis, hypertrophic cardiomyopathy, and mitral valve prolapse[27-30].

b) Use of stress echocardiography in chronic coronary atherosclerotic disease: Stress echocardiography is a noninvasive method used to evaluate patients with suspected or known obstructive CAD, make the diagnosis and assess the prognosis, assess the impact of revascularization therapies, detect myocardial viability, and aid in therapeutic decisions. Cardiovascular stress causes myocardial ischemia in regions supplied by an artery with a significant degree of stenosis, and this phenomenon is manifested by transient changes in segmental contraction. Two-dimensional echocardiography allows the evaluation of all myocardial segments of LV with high spatial and temporal resolution, making it an ideal strategy for the noninvasive evaluation of myocardial ischemia. The methods available for stress induction include physical exercise (treadmill or stationary bike), transesophageal atrial pacing, and the use of vasodilators (dipyridamole, adenosine), or adrenergic stimulants (dobutamine). Stress echocardiography shows good accuracy in the detection of myocardial ischemia induced in patients with intermediate or high pretest probability, and has greater sensitivity and specificity for the diagnosis of CAD than ETT Dobutamine stress echocardiography and exercise stress echocardiography have similar diagnostic accuracy (83% and 85%, respectively), whereas dipyridamole stress echocardiography seems to have a slightly lower diagnostic accuracy. This difference can be attributed to a lower sensitivity of dipyridamole in identifying patients with one-vessel diseases (38% for dipyridamole stress echocardiography, in contrast with 70% for exercise stress test and 61% for dobutamine stress echocardiography). The addition of atropine to dobutamine in stress echocardiography improves accuracy and decreases the rate of ineffective tests, particularly in patients using beta-blockers[31-34].

c) General Indications of stress echocardiography: The choice of the type of stress to which the patient will be subjected must be based on the aim of the test and associated clinical conditions, considering the specific contraindications of each method[31-33]. Stress echocardiography is indicated to evaluate myocardial ischemia in symptomatic patients, in cases when ETT is not diagnostic, and to evaluate ischemia in patients with a clinical presentation not suggestive of coronary insufficiency and for those with positive or doubtful ETT. In patients with increased clinical suspicion of CAD, stress echocardiography is valuable in the identification of concurrent conditions that may not be efficiently diagnosed with ETT including changes in the ST segment and T wave at rest, LBBB, LV hypertrophy, ventricular pacemaker rhythms, and digitalis therapy. Similarly, stress echocardiography is not recommended for the initial evaluation of asymptomatic patients without CAD. Stress echocardiography may be important in the clinical management of the patient but is not indicated for the routine periodic evaluation of stable patients with unchanged clinical status.

d) **Preoperative evaluation**: According to the recommendations of ACC/AHA and the European Association of Cardiovascular Imaging (EACVI), dobutamine stress echocardiography has become an invaluable tool for risk stratification of preoperative patients with CAD[35,36] (Chart 7). In addition, it is recommended for the evaluation of patients with one or more clinical cardiovascular risk factors and limited ability to perform physical activities. Several studies have demonstrated the importance of this method in preoperative risk stratification in patients subjected to vascular surgery. A normal test shows a negative-predictive value (NPV) between 93% and 100% for cardiovascular events, and patients with negative test results may undergo surgery after other examinations. The detection of segmental contraction abnormalities has a positive-predictive value (PPV) between 7% and 30%, which is similar to the results found using thallium-201 perfusion scintigraphy[37].

2.b.2.5. Radioisotopes

Nuclear cardiology evaluates the heart and focuses on aspects related to myocardial perfusion, cellular integrity, myocardial metabolism, myocardial contractility, and global or segmental ventricular function. The limited availability of equipment and radiotracers (e.g., thallium-201, technetium-99m, isonitrile, and tetrofosmin) can restrict the large-scale use of nuclear methods.

Chart 7 – Recommendations for the use of stress echocardiogram in chronic CAD

Recommendations	Class
Risk stratification of patients with CAD	I
Pharmacological stress echocardiography in assessing myocardial ischemia in patients with typical, stable precordia who cannot undergo the maximum stress test or when the stress test is inconclusive	I
Assessment of myocardial ischemia in asymptomatic individuals with positive or inconclusive stress test	I
Pharmacological stress echocardiography in the preoperative assessment for noncardiac surgery in patients with three or more risk factors for CHD who cannot exercise	I
Assessment of the functional significance of coronary lesions in planning percutaneous transluminal angioplasty or CABG	I
Assessment of myocardial ischemia in the presence of left bundle-branch block or changes which prevent appropriate electrocardiographic analysis of ischemia	I
Pharmacological stress in assessing myocardial viability (hibernating myocardium) for bypass planning	I
Assessment of restenosis after revascularization in patients with recurrence of typical symptoms	IIa
Diagnosis of myocardial ischemia in selected patients with low pretest probability	IIa
Diagnosis of myocardial ischemia in selected patients with high pretest probability	IIIb
Routine replacement of treadmill test in patients for whom ECG analysis is suitable	III
Routine assessment in asymptomatic patients after revascularization	III

Source: Brazilian Society of Cardiology28. CAD: coronary atherosclerotic disease.

Myocardial perfusion studies are important in the diagnosis of ischemic heart disease because this method is noninvasive, virtually free of adverse reactions to the radiotracer, and is easily administered to patients. By using single-photon-emission CT (SPECT), it is possible to diagnose CAD with high sensitivity and specificity. Current ECG synchronization and regional quantification techniques associated with tomographic studies allow the analysis of concomitant data on myocardial perfusion, wall motion, and overall LV function, thereby significantly increasing the diagnostic power of the method. This is particularly important when the method has limitations, as in cases of obstructive disease isolated from the circumflex artery and in patients with multivessel disease, and can increase the sensitivity > 90% in these cases[38,39]. It should be emphasized that the method specificity — usually between 80% and 90%[40] — is affected by underestimations due to bias, because most patients with normal perfusion scintigraphy are not referred to the gold standard coronary angiography examination. Another important aspect about the exam, highlighted in recent publications, is related to false-positive scintigraphy results associated with moderate reversible defects detected in patients who do not present >70% obstructions in CA. In most of these occasions, intracoronary ultrasound examination indicates that even angiographically insignificant injuries cause major changes in the vasodilatory capacity of the coronary circulation and can potentially cause ischemia and infarction. Furthermore, special attention should be given to the detection of artifacts, especially when using tomographic techniques, to minimize problems with attenuations, movements[41], and interference of the intestinal loops. Sensitivity and specificity values are equivalent in scintigraphic studies using tracers labeled with 99mTc or 201Tl. Considering use of lowest doses, best-quality images, and ease of handling, the examinations with tracers labeled with 99mTc are indicated as the first choice for investigations on ischemia[42-44]. Labeling with 201Tl is less used because of its association with increased radiation and is indicated for investigations on ischemia associated with viable myocardium. New SPECT cameras have significantly decreased radiation and image acquisition time[45]. The indications for the use of scintigraphy are shown in Chart 8[46].

2.b.2.6. Coronary angiography

Coronary lesions are significant when there is obstruction of one or more epicardial arteries with at least 70% stenosis and/or that of LMD with at least 50% stenosis, and such obstructions are evaluated and measured using CA, which is a diagnostic test with low rates of complications[47].

Some patients need to undergo invasive tests because it is the most accurate method for the diagnosis of obstructive coronary lesions. In addition, in some unusual cases, nonatherosclerotic causes for angina, including coronary spasm, coronary anomaly, Kawasaki disease, and primary coronary dissection, may exist.

However, in most cases, noninvasive tests are performed first, as already explained. Analysis of the symptoms as an initial diagnostic method may have an important role in special cases, such as in cases with angina, those in which noninvasive tests are contraindicated or their benefits are negligible, those with severe illness, those having physical disabilities that limit the use of noninvasive methods, and those without a suitable patient profile. Invasive tests are also reasonably indicated for patients at high CAD risk, those with noninvasive tests presenting conflicting results, those with poorly diagnosed conditions, or even those whose incapacity can affect the general population, e.g., aircraft

Chart 8 – Recommendations for the use of MPS in diagnosing coronary atherosclerotic disease (CAD)

Class I	MPS is recommended for patients with intermediate or high pretest probability who have no interpretable electrocardiogram **(Level of evidence B)**
	MPS with pharmacological stress is recommended for patients with intermediate or high pretest probability who have no interpretable electrocardiogram, or who are not capable of physical exertion **(Level of evidence B)**
Class IIa	MPS is reasonable for patients with intermediate or high pretest probability who have an interpretable electrocardiogram and are capable of physical exertion **(Level of evidence B)**
Class III	MPS is not recommended as an initial test in patients with low pretest probability who have an interpretable electrocardiogram and are capable of performing physical exertion **(Level of evidence (C)**

MPS: myocardial perfusion scintigraphy; CAD: coronary atherosclerotic disease.

pilots, firefighters, and professional athletes. Other groups require special considerations. Recent studies suggest that women with positive exercise stress test and thallium stress test results are less frequently indicated for additional noninvasive tests than men (4% vs. 20%, respectively) and invasive tests (34% vs. 45%, respectively)[48-50]. The causes of these differences and how they affect diagnosis are uncertain[51,52]. In addition, the assessment of chest pain in older patients may be difficult[48,49,52,53] because complaints of chest pain, fatigue, dyspnea, and comorbidities with angina-mimicking symptoms are common, which results in decreased evaluation of ischemic symptoms with advanced age. The increased frequency of abnormal resting ECG and the difficulty in performing physical activities also limit the results of noninvasive tests. Furthermore, the high prevalence of the disease in this population group decreases the importance of negative results of noninvasive tests. In contrast, the diagnostic CA poses little risk to older patients compared with younger patients. Under these conditions, some authors[54] prefer invasive tests for this population group. Other patients need to undergo CA with ventriculography to determine prognosis, extent of CAD, and degree of LV dysfunction, because these are the main determinants for the long-term results[55-58]. The simplest and most widely used method for assessing the extent of CAD classifies patients as those with one-vessel, two-vessel, and three-vessel disease or as those with LMD lesions[59-61]. The survival time decreases with the involvement of additional vessels, stenosis of the left anterior descending artery (LAD), and LV dysfunction[56,62,63] (Table 2).

Furthermore, patients who are candidates for revascularization with angioplasty or surgery are indicated for CA. Therefore, the assessment of the coronary vasculature is necessary to determine whether this procedure is indicated. This group includes patients with angina, those with clinical evidence of heart failure and those who have experienced cardiac arrest or serious ventricular arrhythmia. In such cases, the performance of CA as a first option is indicated. Most of these cases include chronic anginal symptoms, which are not included in the above categories. It is necessary to decide whether these patients should either undergo revascularization or simply initiate clinical treatment and undergo revascularization in situations of clinical failure. Therefore, it is important to perform CA along with left ventriculography, when revascularization is proposed, aiming to improve survival. CA is effective when the prognosis related to clinical treatment is poor and when the prognosis improves after revascularization with either angioplasty or surgery. Chart 9 shows the recommendations for coronary angiography in patients with CAD.

Table 2 - Complications from cardiac catheterization

Event	Rate n (%)
Death	2 (0.12)
Myocardial Infarction	0
Neurological events	
Transient	2 (0.1)
Persistent	2 (0.1)
Emergency myocardial revascularization	0
Cardiac perforation	0
Arrhythmias requiring cardioversion	5 (0.3)
Vascular complications from surgery	26 (1.6)
Vasovagal reactions	33 (2.1)
Anaphylactic reactions/hypotension	1 (0.1)

Chart 9 – Recommendations for coronary angiography in patients with CAD

Class I	Stable angina (CCS III or IV) despite clinical treatment (B)
	High risk in noninvasive tests, regardless of angina (B)
	Angina and cardiac arrest or severe ventricular arrhythmia survivors (B)
	Angina and symptoms/signs of congestive heart failure (C)
Class IIa	Uncertain diagnosis after noninvasive tests, in which the benefit of an accurate diagnosis outweighs the risks and costs of cinecoronariography (C)
	Inability to undergo noninvasive tests due to physical disability, illness, or obesity (C)
	High-risk occupations requiring an accurate diagnosis (C)
	Patients with inadequate prognostic information after noninvasive tests (C)
Class IIb	Multiple hospitalizations for chest pain, in which a definitive diagnosis is considered necessary (C)
Class III	Significant comorbidities, where the risk of angiogram outweighs the benefits of the procedure (C)
	Stable angina (CCS I or II) that responds to drug treatment and no evidence of ischemia in noninvasive tests (C)
	Preference to avoid revascularization (C)

CAD: coronary atherosclerotic disease. CCS: Canadian Cardiovascular Society.

2.b.2.7. Cardiac computed tomography

Cardiac computed tomography (CT) offers two main modes of examination, which employ different techniques and provide different information: the calcium score (CS) and coronary CTA.

a) CS

The quantification of coronary artery calcification using CS correlates with the total atherosclerotic load[64-66]. The first study on the subject tried to correlate this score with coronary/luminal stenosis and demonstrated that the greater the amount of calcium, the greater was the chance of significant stenosis. However, despite its high sensitivity and NPV, the specificity and PPV were very low[67,68]. These results suggest that, although the absence of coronary calcification indicates a low probability of coronary stenosis on conventional angiography, especially in asymptomatic patients, calcification does not necessarily imply the presence of coronary stenosis[69]. Several subsequent studies with large numbers of patients showed that CS is strongly correlated with the risk of future cardiovascular events, independently of usual risk factors and the presence of myocardial ischemia[69-71]. In a meta-analysis published by AHA/ACC with 27,622 patients without manifestation of cardiovascular disease[69], the presence of any coronary CS more than zero indicated a relative risk of major coronary events equivalent to 4.3 [95% confidence interval (95% CI) = 3.5–5.2]. In contrast, the patients with a CS of zero had a risk of death or infarction of 0.4% in a follow-up of 3–5 years (49 events/11,815 individuals). For CSs between 400 and 1000 and > 1000, the absolute risk of coronary death and AMI were 4.6% and 7.1%, respectively, which corresponded to a relative risk of 7.2 (95% CI = 5.2–9.9, $p < 0.0001$) and 10.8 (95% CI = 4.2–27.7, $p < 0.0001$), respectively, compared with a CS of zero. Patients at intermediate risk owing to the presence of two or more risk factors, or with a Framingham risk score (FRS) > 10% in 10 years, but with CS > 400, had an annual risk of death by CAD or AMI of 2.4%, i.e., these patients were included in the high-risk category[69]. When associated with conventional risk stratification using FRS, CS can change patient classification in all risk categories, particularly those at intermediate risk and those at low risk with a family history of premature CAD (first-degree relatives, men aged < 55 years and women aged <65 years), and this may affect clinical management[72-74]. Recent studies suggest that CS is a superior predictor of cardiovascular events compared with other risk stratification tools, such as C-reactive protein levels and IMT[75].

Despite the low correlation of CS with coronary stenosis, its use in low-risk symptomatic patients is strongly advocated by the National Institute of Health and Clinical Excellence (NICE)[76,77]. These recommendations are based on the high sensitivity and PPV of the method[78]. In contrast, recent studies have shown that, in addition to the inadequate PPV, CS also presents insufficient NPV to safely exclude the presence of significant obstructive disease, particularly in younger patients or in populations with high prevalence of significant CAD. A substudy of CorE64[79,80] examined patients with clinical indication for CA (most were symptomatic) and showed that 19% of the patients with CS equal to zero had at least one lesion with luminal stenosis ≥50%, 15% of the patients had at least one lesion with stenosis ≥ 70% and 13% of calcification-free patients were revascularized by clinical indication. Of note, 20% of the completely occluded vessels showed no signs of calcification in this study. Furthermore, other studies have demonstrated that the absence of coronary calcification cannot safely exclude the presence of significant luminal stenosis in symptomatic patients[81-83]. Among these studies, a substudy of the CONFIRM[84] registry, which included 10,037 symptomatic patients, showed that 3.5% and 1.4% of the patients with CS of zero had coronary stenosis ≥

50% and ≥ 70%, respectively. The sensitivity and NPV of a CS more than zero for the detection of coronary stenosis ≥50% were 89% and 96%, respectively. However, the specificity and PPV were quite low (59% and 29%, respectively). More importantly, in this large study, even in patients with CS of zero, the presence of obstructive CAD ≥ 50% was associated with worse cardiovascular prognosis. Therefore, similar to the recent guidelines established by the European Society of Cardiology[85] and AHA/ACC[86] for stable ischemic coronary syndromes, the present guideline does not generally recommend the use of CS for evaluation of significant obstructive CAD in symptomatic patients.

At present, CS is primarily used as a tool for cardiovascular risk stratification through the detection of subclinical atherosclerosis, particularly in asymptomatic patients at intermediate risk[72,87]. According to the current guidelines for dyslipidemia of the Brazilian Society of Cardiology/Sociedade Brasileira de Cardiologia (SBC), CS is regarded as an aggravating factor that, when present, can reclassify the individual to a higher cardiovascular risk[11].

Grade of recommendation I, Level of evidence A

Asymptomatic patients at intermediate risk using FRS (10%–20% in 10 years) or using the overall risk score (RS) (men: 5%–20%; women: 5%–10% in 10 years).

Grade of recommendation IIa, Level of evidence B

Asymptomatic patients at low risk using FRS (< 10% in 10 years) or using the overall RS (men or women: < 5% in 10 years) and family history of premature CAD.

Grade of recommendation IIB, Level of evidence B

Patients with suspected low-risk acute coronary syndrome (ACS).

Grade of recommendation III, Level of evidence B

1. Asymptomatic patients at high risk using FRS (> 20% in 10 years) or the overall RS (men: > 20%, women: > 10% in 10 years), or with known CAD.
2. Patients monitored for assessment of coronary calcification.
3. Symptomatic patients.

b) Coronary CT angiography (CTA)

CT angiography (CTA) of coronary arteries allows the noninvasive evaluation of the lumen of the coronary arteries. The equipment with 64-detector columns, now widely diffused, can acquire high-quality images and enable the detailed visualization of the lumen of coronary arteries with high diagnostic accuracy, compared with the gold standard cardiac catheterization, in a noninvasive, fast, and safe manner[88-90]. Technological advances have enabled the improvement of image quality associated with decreased volume of infused contrast medium and a dramatic decrease in the radiation doses, further increasing the method safety[91].

To date, several studies have compared the diagnostic accuracy of CTA with > 64-detector columns with that of cardiac catheterization[92,93]. The results of these studies support the idea that coronary CTA, under various circumstances, can correctly and accurately identify patients with and without significant coronary stenosis. In the population groups evaluated (with a mean CAD prevalence of 61%), NPV was 96% and PPV was 93% (64%–100%). Multicenter trials have indicated a diagnostic accuracy >90% and a very low percentage of patients with equivocal results[80,89,94]. In addition, CTA has good performance in the evaluation of individuals with various clinical conditions, those with coronary artery bypass grafting (CABG), and those with stents > 3 mm[95].

Other studies have assessed the prognostic value of CTA in stable patients with suspected CAD and indicated that the presence and extent of significant coronary stenosis (luminal stenosis ≥ 50%) and the presence and extent of nonobstructive atherosclerosis (luminal stenosis < 50%) were independent predictors of increased overall and cardiovascular mortality[96,97]. The dissociation between the ischemia test results and the anatomical data provided with CTA suggests that these two methods evaluate distinct CAD parameters and provide complementary prognostic information[98].

Recent multicenter and prospective studies evaluated the use of coronary CTA in patients with acute chest pain and demonstrated the great importance of this technique in the assessment of patients with suspected acute coronary syndrome with low and intermediate pretest probability, nondiagnostic ECG, and negative myocardial necrosis markers[97,99-101]. These studies based their recommendations on major international guidelines and on the increasing application of the method in thoracic pain units[102].

The main clinical indications of the method for the evaluation of chronic CAD are directed to symptomatic patients at intermediate risk and may be used as an initial assessment tool, particularly in situations when previous ischemia tests are conflicting or inconclusive, when symptoms are persistent and previous ischemia tests are normal or inconclusive, or when other types of inconsistencies between clinical results and previous ischemia test results are observed.

The increasing application of this method has changed the assessment strategies for cardiovascular diseases, because coronary anatomy data, which were obtained using invasive methods, now can be obtained noninvasively.

Grade of recommendation IIa, Level of evidence A

Patients with suspected chronic CAD with the following:

a) previous ischemia tests that are conflicting or inconclusive;
b) continuous symptoms and previous ischemia tests that are normal or inconclusive;
c) discrepancy between clinical results and previous ischemia test results.

Grade of recommendation IIa, Level of evidence B

1. Evaluation of the patency of grafts for myocardial revascularization in symptomatic patients with intermediate pretest probability calculated with Diamond–Forrester criteria.
2. Alternative method to invasive angiography to differentiate between ischemic and nonischemic heart disease.

Grade of recommendation IIb, Level of evidence B

1. Symptomatic patients with intermediate probability of CAD and positive ischemia test results.
2. Symptomatic patients with low probability of CAD (< 10%, using Diamond–Forrester criteria) and negative ischemia test results.
3. Evaluation of intrastent restenosis in symptomatic patients with intermediate pretest probability (10%–50%, using Diamond–Forrester criteria).

Grade of recommendation III, Level of evidence B

1. Symptomatic patients with high probability of CAD (> 50%, using Diamond–Forrester criteria).
2. Initial evaluation of CAD in asymptomatic patients able to perform physical exercises and with interpretable ECG results.
3. Follow-up of asymptomatic patients with coronary atherosclerotic lesions.

2.b.2.8. Cardiovascular magnetic resonance imaging (CMR)

In recent years, CMR has become a reliable diagnostic method for the evaluation of a variety of cardiovascular diseases. It allows the accurate and reproducible assessment of cardiac and vascular anatomy, ventricular function, myocardial perfusion, and tissue characterization, and all this information is available after a single examination[42]. Moreover, it uses neither ionizing radiation nor contrast medium, which have a greater potential for nephrotoxicity. Its diagnostic versatility and accuracy make it a highly attractive method for the evaluation of various heart diseases, but it is primarily indicated for ischemic heart disease in clinical practice.

Magnetic resonance imaging is a process based on capturing the energy released by protons (hydrogen nuclei) subjected to the action of a strong external magnetic field and stimulated by repeated radiofrequency (RF) waves. On the basis of the organization of RF pulses (pulse sequences), it is possible to obtain high-quality images with exquisite anatomical detail and contrast resolution, allowing the investigation of different molecular properties.

CMR is now considered to be the gold standard method for the quantification of ventricular volume, EF, and myocardial mass[103]. This is mainly owing to its ability to visualize the entire cardiac anatomy with high spatial and temporal resolution and to provide enhanced detail of the endocardial and epicardial borders of the left and right ventricles. Furthermore, CMR allows the application of the Simpson's formula without major technical obstacles, making this method extremely accurate for the assessment of global and segmental biventricular functions. With particular regard to ischemic heart disease, CMR can be used for the assessment of myocardial ischemia, myocardial fibrosis/infarction/viability, and for the noninvasive assessment of coronary arteries[103].

a) Myocardial ischemia

The most commonly used techniques for the study of CAD involve direct visualization of the effects of pharmacological stress-induced ischemia on segmental contractility and myocardial perfusion; the former technique shows increased specificity and the latter shows increased sensitivity[104-106]. For the analysis of segmental contractility/myocardial contractile reserve, the positive inotrope dobutamine is generally used, and the drug infusion protocol is identical to that used in stress echocardiogram[107-109]. In this context, myocardial ischemia during the stress test can be defined as a new segmental change caused by dobutamine infusion or the result of a biphasic response, i.e., increased myocardial contractility at low doses and segmental dysfunction at high doses of dobutamine[109]. Dobutamine stress CMR is a well-established technique characterized by good image quality compared with other imaging methods, and high reproducibility of results[110]. It is very effective for the diagnosis of CAD in patients ineligible for echocardiography owing to suboptimal acoustic window[111]. A quantitative evaluation of regional function using CMR has the potential to further improve the diagnostic accuracy of the method, particularly in cases of one-vessel CAD[112,113]. A meta-analysis conducted by Nadalur el al.[114] indicated a sensitivity of 83% and specificity of 86% for the diagnosis of significant coronary lesions in patients at high of CAD risk. This technique has also been tested in specific population groups, including patients with established segmental dysfunction[115] and those with a history of percutaneous coronary intervention (PCI) and stenting. In addition to its diagnostic importance, the evaluation of myocardial ischemia using CMR also has a prognostic importance. A normal dobutamine stress CMR indicates that patients have a low event rate, and this rate increases in the presence of ischemia[116,117]. The presence of segmental dysfunction helps identify patients at risk of AMI and death from cardiac causes[117]. The presence of ischemia assessed by the change in motility on dobutamine stress CMR is an independent predictor of cardiac events [hazard ratio (HR) of 5.42 in 3 years, $p < 0.001$][118,119]. The main limitations of this technique are the difficulty in continuously monitoring ECG and the patient's vital signs during the examination and conditions in which dobutamine infusion is contraindicated.

Another method used to assess ischemia using CMR is through the analysis of myocardial perfusion (first passage of gadolinium through the heart under conditions of stress and/or rest). The protocols for the evaluation of ischemia using myocardial perfusion on CMR are similar to those used in scintigraphy. The vasodilators most commonly used

are adenosine, which directly stimulates A2 receptors, causing arterial vasodilation, and dipyridamole, which inhibits reabsorption and inactivation of adenosine, the latter being the more widely used drug in Brazil[107]. The use of adenosine and dipyridamole is contraindicated in patients with serious lung disease and severe aortic stenosis. In general, a pharmacological stress is performed with intravenous infusion of dipyridamole (0.56 mg/kg body weight) over a period of 4 min. At the peak effect of dipyridamole, approximately 3 min after the completion of infusion, gadolinium (0.05 mmol/kg body weight) is administered, followed by the acquisition of first-pass images of the contrast medium through the myocardium. The perfusion defects observed only in stress, and not at rest, in a noninfarcted area correspond to areas of flow heterogeneity, which are significantly correlated with myocardial areas irrigated by coronary arteries with major obstructions. In other words, perfusion defects correlate with areas of myocardial ischemia.

The diagnostic accuracy of perfusion CMR has been validated extensively using other imaging techniques previously validated for CAD. Single-center studies have demonstrated its high diagnostic accuracy compared with invasive angiography[120] and fractional flow reserve (FFR)[121], superiority or noninferiority compared with SPECT[122,123], and similarity compared with positron emission tomography–computed tomography[124]. Two meta-analyses have evaluated the accuracy of perfusion CMR. In 2007, Nandalur et al.[114] investigated 1,183 patients with CAD and reported a prevalence of 57.4%, and its sensitivity and specificity were 91% and 81%, respectively. In 2010, Hamon et al.[125] investigated 2125 patients using perfusion CMR and reported a sensitivity of 89% and specificity of 80% in the identification of coronary stenosis ≥ 70%.

Recently, the CE-MARC study was published. This prospective study evaluated the accuracy of CMR for the diagnosis of significant coronary stenosis using cardiac catheterization and compared this technique with SPECT[126]. CE-MARC is the largest prospective study investigating these two diagnostic methods in a population at intermediate risk. The authors found that CMR had a higher diagnostic accuracy than SPECT for the detection of stenosis ≥ 70% using catheterization, with an area under the receiver operator characteristic (ROC) curve of 0.89 (95% CI = 0.86–0.91) vs. 0.74 (95% CI = 0.70–0.78), with $p < 0.001$. A similar result was obtained for the diagnosis of stenosis ≥ 50%: the area under the ROC curve was 0.84 (95% CI = 0.81–0.87) for MRI vs. 0.65 (95% CI = 0.65–0.73) for SPECT ($p < 0.001$). This difference in accuracy was mainly because of the higher sensitivity of CMR (86.5% for CMR vs. 66.5% for SPECT), especially because of the higher spatial resolution of the former.

The prognostic ability of myocardial ischemia assessment using CMR has also been largely demonstrated in recent years[118,127,128]. In a large prospective multicenter study, Bodi et al.[129] highlighted the importance of dipyridamole perfusion CMR in the prognostic evaluation of patients with suspected angina. Both the evaluation of perfusion and the induction of segmental dysfunction during dipyridamole infusion were independent factors in determining adverse cardiac events over 308 days. Patients with dipyridamole-induced segmental dysfunction exhibit increased risk of major adverse cardiac events (MACE) and appear to derive increased benefit from revascularization.

The use of CMR for the evaluation of myocardial ischemia is supported by several clinical guidelines and imaging methods, and it is an important tool for the diagnosis and prognosis of patients with known or suspected stable ischemic myocardial disease[86,130,131].

b) Delayed enhancement

The diagnosis and characterization of areas of MI/necrosis/fibrosis using CMR is based on the delayed enhancement technique[132-139]. CMR allows the evaluation not only of the patients with acute-phase MI but also those in the subacute and chronic phases, and this technique is now considered to be the gold standard for the assessment of myocardial viability.

The delayed enhancement technique is based on a T1-weighted, fast gradient-echo pulse sequence, with a prepulse of inversion-recovery and inversion time (IT) adjusted to abolish the signal of a healthy myocardium after infusion of the gadolinium-based contrast agent at 0.02–0.04 mmol/kg. Gadolinium does not penetrate intact cell membranes and therefore has extracellular distribution. In infarcted zones, the ruptured membranes of necrotic myocytes allow the free distribution of gadolinium (there is increased distribution volume)[140,141]. In addition, myocyte necrosis leads to changes in the distribution kinetics of gadolinium, so that this contrast agent leaves the infarcted areas more slowly (delayed washout)[142]. Because of these two factors, the concentration of the contrasting agent 10–20 min after injection is much higher in the necrotic areas than in areas of healthy myocardial tissue[143], making the infarcted areas turn white (high signal intensity) in the delayed-enhanced images. In the case of previous infarctions, fibrosis (but not necrosis) is the underlying pathological mechanism. In such cases, the largest extracellular space observed in fibrotic tissue compared with normal myocardial tissue is responsible for the increased distribution volume and changes in gadolinium kinetics[143].

Several studies have shown that CMR has excellent accuracy in the evaluation of patients with previous MI[132,134,137,144-148]. In this respect, Kim et al.[132] showed an almost exact correlation between values of infarcted mass obtained with CMR and those obtained in the pathological anatomy examination considering acute ($R = 0.99$, $p < 0.001$), subacute ($R = 0.99$; $p < 0.001$), and chronic infarctions ($R = 0.97$, $p < 0.001$). Because of its excellent spatial resolution, CMR allows the detailed characterization not only of large transmural infarctions but also of small subendocardial infarctions[145,146]. This factor is very important because the correct identification of infarctions and the assessment of infarcted areas (expressed as a percentage of the LV mass) have an important prognostic value[147,149]. Kelle et al.[150] demonstrated that the size of the delayed infarcted area using resonance (involving at least six LV segments)

was a stronger predictor of events than the actual LVEF in patients with ischemic cardiomyopathy[150]. In addition, CMR allows the identification of areas of microvascular obstruction (no-reflow phenomenon)[144,147,151], which is a marker of severe myocardial injury and is associated with worse post-MI prognosis[147,151]. Furthermore, recent studies have shown that the characterization of the border regions at the interface between the intact myocardium and the infarcted tissue (gray area) allows the risk stratification of post-MI ventricular arrhythmia and provides important prognostic information in patients with previous MI[152,153].

Using the delayed enhancement technique, it is possible to identify not only the areas of chronic infarction but also the noninfarcted areas, and the relationship between the extent of these two ventricular wall areas is fundamental to establish a possible functional recovery of the myocardium[154]. The evaluation of the transmural extent (transmurality) of the necrotic and/or fibrotic myocardial areas allows the accurate prediction of the probability of recovery of the regional function after percutaneous or surgical revascularization. Kim et al.[148] indicated that the dysfunctional segments whose extent of delayed enhancement was < 50% of the whole segment had a high probability of functional recovery after revascularization and therefore were considered viable. In contrast, only a few segments with an extent of delayed enhancement ≥ 50% (considered as transmural stenosis) showed functional recovery after a revascularization procedure and therefore were not considered viable[148]. Because of the unique ability to visualize the extent of both normal and infarcted tissues, CMR has a high sensitivity and specificity, an accuracy of 72%–77% and positive and NPVs of 66%–85% and 82%–92%, respectively, for assessing the postrevascularization functional recovery of myocardial segments[148,155,156]. Myocardial segments with infarct size < 50% of the wall thickness and with delayed enhancement have a high probability of functional improvement, whereas segments with infarct size > 50% of the wall thickness have a lower probability of recovery. These results are even higher when applied to patients with severe ventricular dysfunction[157] or when analyzing myocardial segments with significant hypokinesia or akinesia[148].

The unique ability of CRM to assess the location and extent of infarcted zones[138], microvascular obstruction[147], peri-infarct zone[152,153], and regional contractility[151,158,159] make this technique an increasingly important tool for both the diagnostic and prognostic evaluation of patients[150,160,161].

c) Coronary artery magnetic resonance angiography

The adequate visualization of coronary arteries using CMR is a great challenge, considering the various variables that affect image quality, including cardiac and respiratory movements, small diameter, and the complexity of the coronary anatomy. Several techniques have been developed to overcome these difficulties[162-167]. Despite a few promising results[168-170], its clinical use currently focuses on the evaluation of congenital anomalies and the course of the coronary arteries[171,172].

Recommendations for MRI

Grade of recommendation I, Level of evidence A

Evaluation of the global left and right ventricular function, volume, and mass

Detection of ischemia.

- Evaluation of myocardial perfusion under stress using vasodilators.
- Evaluation of ventricular contractility under stress using dobutamine.
- Evaluation of acute and chronic MI.
- Detection and quantification of myocardial fibrosis and infarcted mass.
- Evaluation of myocardial viability.

Grade of recommendation I, Level of evidence B

Differentiation of ischemic and nonischemic heart disease.

Coronary artery magnetic resonance angiography.

- Evaluation of congenital anomalies.

Recommendations of MRI

Grade of recommendation IIb, Level of evidence B

Coronary artery magnetic resonance angiography.

- Detection of coronary luminal stenosis.
- Evaluation of graft patency.

3. Cardiovascular risk stratification of CAD

The same strategies and methods used in the diagnosis of CAD also provide information on disease severity, with implications for the performance of complementary invasive methods, including coronary angiography and therapeutic decision-making.

The clinical history involving recent angina, progressive or limiting angina, and heart failure of probable ischemic origin can help identify patients at high risk of developing cardiovascular events.

Moreover, ECG changes indicative of previous infarction or ischemia can help identify patients who are at increased risk compared with those with normal ECG.

With regard to chest X-ray, the cases with radiological findings of cardiomegaly, LV aneurysm, and pulmonary venous congestion are commonly associated with a worse prognosis than those who do not show radiological changes.

The remaining functional tests are also used to assess the risk of patients with CAD, as follows.

Exercise testing for the assessment of prognosis of coronary atherosclerosis

Grade of recommendation I, Level of evidence B

Patients with intermediate or high probability of CAD after initial evaluation; patients with changes in symptoms.

Grade of recommendation IIb, Level of evidence B

Patients with pre-excitation, ST-segment depression > 1 mm in ECG at rest, pacemaker rhythm, and complete left bundle-branch block.

Grade of recommendation IIa, Level of evidence C

Revascularized patients with symptoms suggesting ischemia.

Grade of recommendation III, Level of evidence C

Patients with severe comorbidities (arthritis, amputations, peripheral artery disease, chronic obstructive pulmonary disease, and decreased functional capacity).

In patients with CAD who are able to reach the third stage of the Bruce protocol, the annual mortality rate was approximately 1%, in contrast with those unable to exceed 5 METs, whose annual mortality rate was approximately 5%[36,173].

Other high-risk variables are as follows: ST-segment depression in multiple leads, persistent ST-segment depression in the recovery phase > 5 min, inadequate chronotropic response, decreased systolic blood pressure during exercise or a flat curve, and severe ventricular arrhythmia at low exercise levels in the presence of ST-segment depression or anginal pain. Another strategy for risk stratification of patients with stable angina is the use of mathematical equations (prognostic scores) developed using clinical and ergometric variables[174-176]. The Duke score[177] can also be used: exercise time (in minutes) − 5 × ST-depression (in millimeters) − 4 anginal index (1 for absence of angina, two for presence of angina, and three for angina as the cause of exercise interruption). Values ≥ 5 represent low risk, with annual mortality rate ≤1%. Values between 4 and −10 represent intermediate risk, with annual mortality rate between 1% and 3%. Values less than −10 indicate a high risk of future events.

Echocardiography for the prognostic evaluation of CAD takes into account primarily LV function and the presence or absence of myocardial ischemia induced by physical or pharmacological stress on echocardiography. These two aspects are important for the long-term prognosis, although higher mortality is associated with decreased ventricular ejection fraction. In contrast, a negative result for ischemia is associated with lower risk of cardiovascular events during follow-up. In patients with previous MI, stress echocardiography may be important for assessing the presence, distribution, and severity of myocardial ischemia, with important prognostic implications[27-36]. Echocardiography can also be used to assess the presence of myocardial viability, considering that the myocardial contractile function may be impaired in patients with CAD because of myocardial necrosis or hibernating myocardium. Therefore, in patients with multivessel disease and impaired LV function, the improved segmental myocardial contraction during the administration of low doses of dobutamine is considered indicative of contractile reserve and predictive of improved ventricular function after CABG. In asymptomatic patients subjected to successful CABG, routine evaluation using stress echocardiography is not necessary or indicated. The identification of residual ischemia in asymptomatic patients does not improve disease outcome. However, when symptoms persist or recur after CABG, stress echocardiography may be important to identify graft occlusion, development of new obstructive lesions, and even in locating and assessing the severity of residual ischemia in cases of incomplete revascularization[27-36,178].

The use of myocardial perfusion scintigraphy (MPS) for the assessment of severity, risk stratification, and prognosis aims to identify patients at risk of death and nonfatal MI. Patients at intermediate CAD risk benefit the most from MPS, with an excellent cost–benefit ratio. This technique adequately stratifies the patients and directs them to either conservative or invasive treatments. The most important aspects of MPS or CMR for the analysis of risk stratification and prognosis of CAD are related to the assessment of injury extent and EF. Associated with these two factors, many clinical situations can greatly interfere with risk stratification, including age, diabetes, hypertension, dyslipidemia, LV hypertrophy, cardiac arrhythmia, heart failure, and MI, among others. Several studies have shown that the main scintigraphic or CMR variables that influence patient management are the diagnosis of induced ischemia, location of ischemia and its association with the affected coronary artery, assessment of the extent of ischemia and other stenosed vessels, and determination of the association between ischemia and necrosis. Other important variables in risk stratification are the occurrence of pulmonary thallium uptake during MPS and the transient dilation of LV[41-45].

Noninvasive test results and annual risk of death

High risk (> 3% deaths/year)

- Severe LV dysfunction at rest (EF < 0.35).
- High risk score on ETT (Duke score less than −11).
- Severe LV dysfunction on imaging stress test (EF < 0.35).
- Major perfusion defects during imaging stress test.
- Multiple moderate-size perfusion defects during imaging stress test.
- Major fixed perfusion defects with LV dilatation or increased thallium uptake by the lungs during radionuclide angiography.
- Moderate-size defects with LV dilatation or increased thallium uptake by the lungs during imaging stress test.
- Defects in more than two segments with low heart rate (< 120 bpm) or with low doses of dobutamine (10 μg/kg/min) during stress echocardiography.

- Evidence of extensive ischemia during stress echocardiography.

Moderate risk (1%–3% deaths/year)

- Mild to moderate LV dysfunction at rest (EF 0.49–0.35).
- Intermediate risk on ETT (Duke score between 4 and −10).
- Moderate-size perfusion defects without LV dilatation or thallium uptake by the lungs during imaging stress test.
- Limited perfusion defects involving two segments with dobutamine doses > 10 μg/kg/min during stress echocardiography.

Low risk (< 1% death/year)

- Low risk score on ETT (Duke score > 5).
- Normal test or small-size perfusion defects at rest or on stress-imaging test.
- Normal myocardial contraction or no changes in a restricted myocardial region during stress echocardiography.

3.a. Strategies for the diagnosis and stratification of CAD

As already indicated, both the diagnosis of patients with suspected ischemic heart disease and the risk stratification of CAD can be performed using several strategies. One of these strategies is based on the direct anatomical visualization of coronary lesions using CA. Another strategy is based on the identification of the functional aspects of coronary occlusion using noninvasive techniques. A normal functional examination conducted with an adequate stress protocol has the same prognostic value as the standard cine coronary angiographic evaluation. In such study groups, the free evolution of events is observed in approximately 99% of the cases in the course of 1 year, even when patients have a positive stress test result or detectable CAD on coronary angiography. The adoption of these methods is indicated on the basis of the clinical presentation and the estimated pretest probability of the disease, as shown in Figure 1.

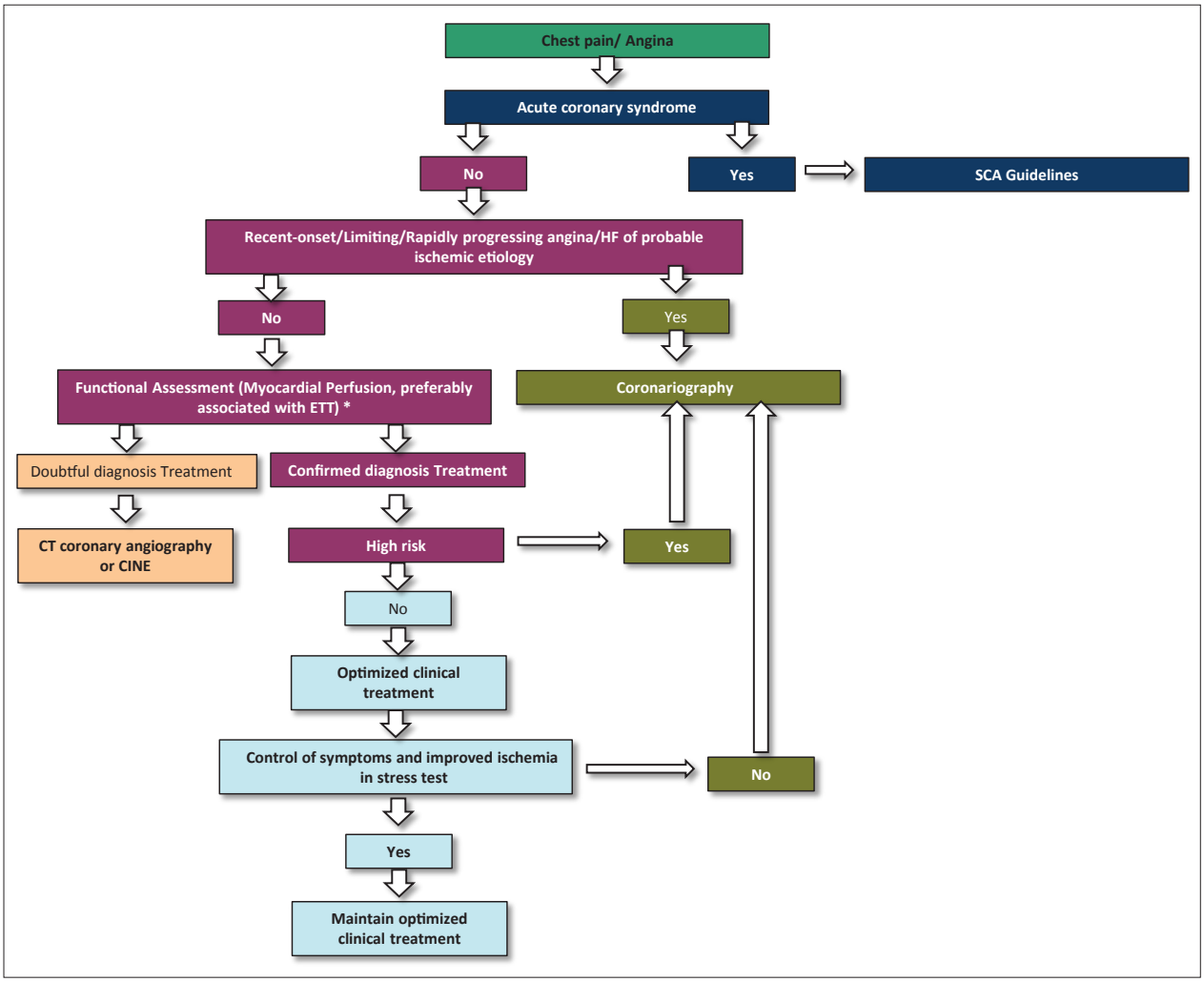

Figure 1 – *Diagnostic algorithm and stratification of CAD. * Optional test. CAD: coronary atherosclerotic disease.*

PART II - DRUG THERAPY

1. Outline

The main goals of treatment of CAD are as follows: (1) prevent MI and decrease mortality; (2) decrease symptoms and the incidence of myocardial ischemia, ensuring a better quality of life.

Several methods are available to achieve these goals, always starting with dietary counseling and physical activity, both of which have been addressed in the 1st Brazilian Guideline for Cardiovascular Prevention[10]; use of therapeutic drugs exclusively marketed in Brazil, which will be addressed in this section; and surgical and interventional therapy, including the novel treatment options under development.

With regard to drug therapy, antiplatelet agents, lipid-lowering drugs (particularly statins), beta-blockers after AMI, and angiotensin I-converting enzyme (ACE) inhibitors help decrease the incidence of MI and increase patient survival. In contrast, nitrates, calcium-channel blockers, and trimetazidine decrease the symptoms and episodes of myocardial ischemia, improving the patient's quality of life. Ivabradine is the most recent antianginal agent and has proven beneficial to patients with ventricular dysfunction and heart rate > 70 bpm, despite the use of beta-blockers. Therefore, it is essential to initiate treatment with medications that can decrease morbidity and mortality and, when necessary, combine them with medications to control angina and decrease myocardial ischemia.

2. Treatment options to decrease the risk of MI and mortality

2.a. Antiplatelet drugs

a) Acetylsalicylic acid (ASA): The antithrombotic effects of ASA are derived from the irreversible inhibition of cyclooxygenase-1, with the consequent blockage of the synthesis of thromboxane A2. In a meta-analysis conducted by the Antithrombotic Trialists' Collaboration[179] on the use of aspirin involving > 350,000 individuals and over 280 randomized trials that compared aspirin with placebo or other antiplatelet agents, approximately 3,000 patients using aspirin developed stable angina, and the risk of cardiovascular events (death, MI, and stroke) decreased by an average of 33% in these patients. In the Physicians' Health Study[180], aspirin at 325 mg administered on alternate days decreased the incidence of MI in an asymptomatic population without any known disease. In the Swedish Angina Pectoris Aspirin Trial (SAPAT) study[181], the addition of aspirin to sotalol at 75 mg/day in patients with chronic CAD decreased the incidence of primary outcomes associated with MI and sudden death by 34%, and the incidence of secondary outcomes by 32%. Therefore, aspirin remains the antiplatelet agent of choice and should always be prescribed, except in rare cases in which it is contraindicated (allergy or intolerance to the drug, active bleeding, hemophilia, and active peptic ulcer) or in cases of high probability of gastrointestinal or genitourinary bleeding. Aspirin is indicated in all patients. **Grade of recommendation I, Level of evidence A.**

b) Thienopyridine derivatives: Ticlopidine and clopidogrel are antagonists of platelet activation mediated by adenosine diphosphate (ADP), an important pathway for platelet aggregation. These drugs decrease the level of circulating fibrinogen and partially block the glycoprotein receptors IIb/IIIa, preventing these receptors from binding to fibrinogen and to the von Willebrand factor. The effects of ticlopidine were superior to those of aspirin for the prevention of cerebral ischemic events in comparative studies involving subjects with previous stroke, although adverse hematological reactions, including neutropenia and thrombocytopenia, were more common and usually regressed with discontinuation of drug use. Thrombocytopenic purpura is a serious complication, and sometimes fatal, but occurs in only 0.029% of the patients. Previous studies that evaluated the effects of ticlopidine included only patients undergoing transluminal coronary angioplasty, with stent implants[182]. However, no previous studies have compared the effects of aspirin with those of ticlopidine in the survival of patients with chronic CAD. The effects of clopidogrel are similar to those of ticlopidine. However, the association between ADP and platelet receptors of glycoprotein IIb/IIIa is selectively and irreversibly inhibited by ticlopidine. Other studies that compared the antiplatelet effects of clopidogrel with those of aspirin included only patients with AMI, stroke, and/or peripheral heart disease[183,184] and did not specifically evaluate patients with chronic CAD. However, in the CAPRIE study[7], although the patients had suffered from MI for < 1 year, they were monitored for > 2 years and started to behave like those with chronic disease and with a previous event. Another study that compared the beneficial effects of clopidogrel and ticlopidine associated with aspirin showed similar results. However, the safety profile of clopidogrel was superior to that of ticlopidine[185]. Clinical trials of novel antiplatelet agents, including prasugrel and ticagrelor, have not yet been completed in patients with stable CAD, and these drugs have no clinical indication yet. Therefore, the use of these drugs for the treatment of chronic CAD is classified as follows.

Clopidogrel

In cases in which aspirin is absolutely contraindicated, and along with aspirin after stent implants, for at least 30 days. **Grade of recommendation I, Level of evidence B.**

Ticlopidine

In cases in which aspirin is absolutely contraindicated, and associated with aspirin after stent implants, for at least 30 days. **Grade of recommendation IIa, Level of evidence B.**

c) **Dipyridamole**: It is a pyrimidine derivative, whose antiplatelet and vasodilator effects are a result of the inhibition of phosphodiesterases, leading to the activation of adenylate cyclase and inhibition of the entry of adenosine into erythrocytes and vascular endothelial cells. When administered orally, in usual doses, dipyridamole can induce myocardial ischemia in patients with stable angina. Individually, dipyridamole does not provide any additional therapeutic benefit and its association with aspirin does not increase the

benefit of the latter. Dipyridamole for the treatment of CAD is no longer indicated. **Grade of recommendation III, Level of evidence B.**

d) **Anticoagulants**: Changes in the fibrinolytic activity in the blood plasma of patients with chronic CAD have motivated the performance of studies on the use oral anticoagulants for the prevention of acute ischemic events. In high-risk patients, the combination of aspirin and warfarin for the prevention of AMI and cardiovascular death was more effective than their individual use[186]. Warfarin increases the incidence of hemorrhagic stroke, and its use should be limited to patients with high thrombotic risk, such as during repeated episodes of stroke or peripheral heart disease. Warfarin can be considered an alternative to aspirin in cases of total intolerance to the latter, as with other antiplatelet agents that are intolerable. The daily dose of warfarin should be guided by the values of the international normalized ratio (INR). In patients with CAD, INR values should be maintained close to 2.0. Furthermore, anticoagulants should be used alone or in combination with aspirin in patients at higher risk.

The drug should be used in combination with aspirin in cases of high thrombotic risk, particularly after MI. **Grade of recommendation I, Level of evidence A.**

As an alternative to total aspirin intolerance. **Grade of recommendation IIa, Level of evidence A.**

For specific situations and in the post-treatment for stents coated with antiproliferative agents, the Brazilian Guidelines of Antiplatelet Agents and Anticoagulants in Cardiology should be consulted[187].

2.b. Secondary prevention: lipid-lowering drugs

Lifestyle change (LC) recommendations involving changes in eating habits and physical activity are indicated for all patients with CAD. Specifically in cases of hypertriglyceridemia, changes in the eating habits are crucial. As indicated in meta-analyses of studies on primary prevention, the decrease in serum cholesterol levels can decrease the incidence of CAD. In clinical trials, the decrease in serum cholesterol levels by 1% led to a 2% decrease in cardiovascular events. Studies on secondary prevention indicated that the decrease in low-density lipoprotein cholesterol levels (LDL-C) with lipid-lowering agents decreased the risk of coronary events in patients with CAD. On the basis of studies included in meta-analyses[188-190], the cholesterol levels recommended by the 1st Brazilian Guideline for Cardiovascular Prevention[10] for patients with CAD are as follows: for high-risk patients, LDL-C < 70 mg/dL and non-HDL-C < 100 mg/dL; for intermediate-risk patients, LDL-C < 100 mg/dL and non-HDL-c < 130 mg/dL. These goals are often achieved with the use of lipid-lowering drugs and LC recommendations (Chart 1).

a) **Statins**: They are the best therapeutic option for the control of serum LDL-C and are the drugs of choice to decrease these levels in adults. Therefore, for proper treatment, the LDL-C target must be achieved. Statins should be suspended when the increase in the aminotransferase levels reaches three times the normal values, if muscle pain occurs, or when the creatine kinase levels are superior to ten times the normal values.

b) **Fibrates**: They are indicated in cases of endogenous hypertriglyceridemia and high hypertriglyceridemia (> 500 mg/dL), and in cases of failure of LC recommendations. Fibrates should be used in the following doses: genfibrozil, 600–1200 mg; bezafibrate, 600 mg/day and 400 mg for the slow-release formulation; etofibrate, 500 mg/day; micronized fenofibrate, 200 mg/day; fenofibrate, 250 mg/day; and ciprofibrate, 100 mg/day.

c) **Ezetimibe**: It impairs cholesterol absorption in the intestinal villi by inhibiting acetyl-CoA cholesterol acyltransferase (ACAT)[191]. Previous studies indicated it can decrease LDL-C and TC up to 20%. The dose recommended is 10 mg and larger doses do not further decrease the cholesterol levels. It has a highly synergistic action when used in combination with lower doses of statins (10 mg in all cases), leading to a decrease in LDL-C of up to 50%–60%[192-195]. The studies cited previously aimed to verify the safety and tolerability of this drug, and the follow-up of patients did not exceed 12 weeks. Although it seems quite safe and effective, a longer follow-up period is needed to consider this drug as a substitute for other lipid-lowering drugs. However, ezetimibe can be an attractive alternative in some situations, as in cases of intolerance to statins, when their levels need to be decreased and thereby they can be combined with ezetimibe, or in cases of intolerance to fibrates and nicotinic acid.

d) **Omega-3 fatty acids**: They are polyunsaturated fats derived from fish and certain plant and nut oils. Fish oil contains both docosahexaenoic (DHA) and eicosapentaenoic acid (EPA). However, vegetable oils contain predominantly alpha-linolenic acid (ALA). At higher doses (4–10 g/day), they decrease triglyceride levels and slightly increase HDL-C but can also increase LDL-C. Previous meta-analyses indicated that these products offer no benefits in decreasing clinical events[196] and therefore are not recommended for cardiovascular prevention.

Chart 1 - Recommendations for pharmacological treatment of dyslipidemias

Recommendation	Class-level of evidence
Statins as first choice medication in primary and secondary prevention	I-A
Use of fibrates in monotherapy or in combination with statins to prevent microvascular diseases in patients with type 2 diabetes	I-A
Ezetimibe or resins in association with statins when LDL-C target is not reached	IIa-C
Niacin in association with statins	III-A
Use of omega-3 fatty acids for cardiovascular prevention	IIII-A

Source: Brazilian Guideline for Cardiovascular Prevention[10]

e) **Resins**: They can be administered with statins when LDL-C are not achieved, despite the use of potent statins in effective doses. However, no previous studies have demonstrated the clinical benefit of this measure. The decrease in LDL-C is dose dependent, ranging between 5% and 30% using doses of 4–24 g/day, and triglyceride levels may increase in subjects with marked hypertriglyceridemia (> 400 mg/dL). In Brazil, only cholestyramine is available. This drug was tested against placebo and caused a 19% decrease in the combined primary outcome involving death from CAD and MI[197].

f) **Niacin**: It is used to decrease triglycerides and increase HDL-C. The Coronary Drug Project[198] study conducted in the 1970s showed that treatment with niacin in its crystalline form can decrease the incidence of cardiovascular events. Treatment with more tolerable formulations, such as the extended forms, can decrease IMT, even in patients on statins, but the association of niacin with statins provided no cardiovascular benefits to patients with the recommended LDL-C[199].

2.c. Blockade of the renin–angiotensin system:

a) ACE inhibitors: The benefits of ACE inhibitors in the treatment of CAD have been corroborated from clinical trials that evaluated asymptomatic patients with decreased EF[200] and patients with ventricular dysfunction after AMI[200,201]. In higher-risk patients, ACE inhibitors helped decrease the number of deaths and clinical events, especially in those with diabetes mellitus[202,203]. The improvement in the hemodynamic profile and subendocardial perfusion as well as the stabilization of atherosclerotic plaques justify the routine use of ACE inhibitors in all patients with CAD, regardless of previous MI, diabetes mellitus, or ventricular dysfunction. The randomized double-blind EUROPA study[204] showed that the ACE inhibitor perindopril decreased combined primary outcomes (cardiovascular death, MI, and cardiac arrest), and secondary outcomes (stroke and worsening of renal function) in patients with CAD (6,110 patients on perindopril vs. 6,108 patients treated with placebo for 4.2 years on average), and in the absence of heart failure and ventricular dysfunction, regardless of other factors, such as peripheral vascular disease. More than 60% of these patients used beta-blockers, 50% of the patients were on statin therapy, and 92% of the patients used antiplatelet agents. The most significant outcome decreased from 10% in the placebo group to 8% in the perindopril-treated group, and 50 patients required treatment for 4 years to prevent one of these events. Therefore, ACE inhibitors are beneficial even for subjects with lower CAD risk. ACE inhibitors are beneficial as a class and should be used routinely in cases of ventricular dysfunction, and/or heart failure, and/or diabetes mellitus. **Grade of recommendation I, Level of evidence A.**

It should be used routinely in all patients with CAD. **Grade of recommendation IIa, Level of evidence B.**

b) **Angiotensin receptor blockers**: They are alternative drugs for patients who do not tolerate ACE inhibitors, considering that no previous studies have been conducted with this class of drugs for the treatment of stable CAD. In other situations, angiotensin receptor blockers provided no additional benefits compared with those of ACE inhibitors, which can decrease infarct sizes.

3. Treatment options to decrease symptoms and myocardial ischemia

a) **Beta-blockers**: Alone or in combination with other antianginal agents, beta-blockers are the drugs of choice in the treatment of stable angina, in addition to the benefits associated with decreased mortality and MI after acute coronary events, situations in which, considering the available therapeutic interventions for infarction, the risk of cardiovascular death and reinfarction is estimated to be approximately 13% according to the COMMIT study[205]. Beta-blockers decrease the heart rate, myocardial contractility, atrioventricular conduction, and ventricular ectopic activity. In addition, they can increase perfusion in ischemic areas by prolonging the diastole duration and vascular resistance in nonischemic areas. Their pharmacological properties, including intrinsic sympathomimetic activity, lipid solubility, and cardioselectivity, help distinguish them. In addition, although all of them are effective, their pharmacological properties must be suitable for the concomitant disease in patients with CAD. Randomized clinical trials that evaluated the effects of beta-blockers for the treatment of CAD in the presence of symptoms or ischemic events have indicated a decrease in the number of angina attacks and in the degree of ischemia, and an increase in exercise tolerance. The Atenolol Silent Ischemic Study (ASSIST)[206] indicated that the incidence of ischemic episodes recorded on a 48-h ECG Holter monitoring after 4 weeks of treatment with atenolol was significantly lower than that in the placebo group. In the atenolol-treated group, there were significantly fewer ischemic episodes, lower incidence of complex ventricular arrhythmias, fewer hospitalizations and MIs, and decreased need for CABG in patients with chronic CAD. The Total Ischemia Burden Bisoprolol Study (TIBBS)[207] compared the effects of bisoprolol with those of nifedipine in patients with silent and/or symptomatic myocardial ischemia. The total number of symptomatic or asymptomatic ischemic episodes using a 48-h ECG Holter monitoring was significantly lower in patients treated with bisoprolol. In the International Multicenter Angina Exercise Study (IMAGE)[208], the effects of metoprolol were compared with those of nifedipine. The number of angina attacks decreased and the exercise time increased for the same ST-segment sloping in the patients treated with both nifedipine and metoprolol. However, the group treated with metoprolol achieved higher ETT levels. Ress et al.[209] compared the effects of monotherapy (atenolol or nifedipine GITS) in patients with stable angina. The number of ischemic episodes was recorded using a 24-h Holter monitoring. The atenolol-treated group had a lower incidence of ischemic events and the combination therapy (atenolol and nifedipine GITS) did not provide additional benefits. Stone et al.[210] compared the anti-ischemic effects of propranolol AP, diltiazem SR, and nifedipine in patients with stable angina. The heart rate and the number of ischemic episodes were recorded using a 24-h Holter monitoring. Propanolol AP was more effective in decreasing

the heart rate and the number of ischemic episodes. Up to one third of the ischemic episodes were symptomatic in patients with stable angina. Davies et al.[211] compared the effects of atenolol with those of amlodipine in decreasing symptomatic and silent myocardial ischemia. The effects of both drugs were similar and satisfactory for the treatment of symptomatic ischemic episodes recorded with Holter monitoring, but atenolol was more effective for decreasing heart rate. During ETT, amlodipine was more effective and significantly delayed the time for the appearance of the same ischemic changes. Combination therapy provided additional benefits.

Beta-blockers are contraindicated in patients with vasospastic angina.

As first-line agent in patients with stable angina without previous MI and/or LV dysfunction. **Grade of recommendation I, Level of evidence B.**

As first-line agent in patients with stable angina with previous MI and/or LV dysfunction even for periods >2 years. **Grade of recommendation I, Level of evidence A.**

For the symptomatic relief in patients with vasospastic angina. **Grade of recommendation III, Level of evidence C.**

b) **Calcium-channel blockers**: They are a heterogeneous class of drugs whose pharmacological effects include smooth muscle relaxation, afterload reduction, negative inotropic effects (in some formulations), and decreased oxygen consumption. Dihydropyridine derivatives (nifedipine and amlodipine, among others), benzodiazepines (diltiazem), and phenylalkylamines (verapamil) are the three major subgroups of calcium-channel blockers that specifically block type L calcium channels. Some pharmacological effects distinguish these three subgroups regarding their vasodilating properties, their ability to decrease both myocardial contractility and the speed of impulse conduction in the atrioventricular node. Verapamil decreases atrioventricular conduction, has a negative inotropic effect, and relaxes vascular smooth muscle, consequently increasing coronary flow and decreasing afterload. Dihydropyridines relax the vascular smooth muscle, have no effects on the speed of atrioventricular conduction, and increase heart rate by reflex mechanisms. Diltiazem has effects similar to those of verapamil, except myocardial depression, which is less intense in this benzodiazepine subgroup. In contrast to beta-blockers, the calcium-channel blockers do not decrease mortality in cases involving MI, although they are quite effective in decreasing myocardial ischemia (both angina pectoris and silent ischemia)[209-216] and in decreasing vasospastic angina[217-218]. In addition, improved anginal symptoms are observed when these drugs are used in combination with beta-blockers[216,219]. The short-duration pharmaceutical preparations have been proscribed for treating stable angina. Unless otherwise specified, the indications below are valid not only for long-acting dihydropyridines but also for diltiazem and verapamil. The use of diltiazem or verapamil associated with beta-blockers should be avoided because of the risk of severe bradycardia and considering that other options are available. In contrast, these drugs are contraindicated in patients with ventricular dysfunction.

As first-line agents for the symptomatic relief in patients with vasospastic angina. **Grade of recommendation IIa, Level of evidence B.**

In patients with symptomatic stable angina on beta-blockers (dihydropyridines). **Grade of recommendation I, Level of evidence B.**

In patients with symptomatic stable angina on beta-blockers (verapamil or diltiazem). **Grade of recommendation III, Level of evidence B.**

In patients with stable angina and contraindications to beta-blockers (preferably verapamil or diltiazem). **Grade of recommendation I, Level of evidence B.**

In patients with symptomatic stable angina (fast-acting dihydropyridines). **Grade of recommendation III, level of evidence: B**

c) Nitrates:

- **Fast-acting nitrates**: Sublingual nitrates or fast-acting sprays exert immediate pharmacological action (between 1 and 3 min after its dissolution), and the vasodilator effects persist for 30–45 min. Symptom relief is a result of venodilation, afterload reduction, and coronary dilation. Fast-acting, short-duration nitrates remain the treatment of choice for angina attacks. When crises occur, the patient should rest in a sitting position, considering the risk of hypotension and/or syncope during orthostasis, and the increased venous return and cardiac output in the lying position. The doses recommended are 5 mg of isosorbide or 10 mg of propatyl nitrate sublingually. Alternatively, fast-acting nitrates can be used prophylactically, before conditions known to cause angina occur, including sexual intercourse and emotional stress, among others[220].

For symptomatic relief of acute angina attacks. **Grade of recommendation I, Level of evidence B.**

- **Long-acting nitrates**: The continued use of long-acting nitrates induces drug tolerance, which can supposedly be circumvented using asymmetric prescriptions to ensure a nitrate-free period of 8–10 h. Although widely used, a worsening of endothelial dysfunction has been reported as a potential complication of the chronic use of long-acting nitrates by activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system, besides increased production of endothelin and superoxide, and increased phosphodiesterase activity, even using asymmetrical prescriptions. Therefore, the common practice of the routine use of long-acting nitrates as first-line agents should be reconsidered because of the current availability of other options[221]. Furthermore, long-acting nitrates should be restricted to patients with angina that cannot be controlled with other antianginal agents. For the treatment of patients with vasospastic angina, nitrates can be associated with calcium-channel blockers for the symptomatic control, if necessary.

As first-line agent in patients with stable angina. **Grade of recommendation III, Level of evidence C.**

As third-line agents in patients with stable angina who are symptomatic even after the associated use of other antianginal agents. **Grade of recommendation IIa, Level of evidence B.**

For the symptomatic relief of patients with vasospastic angina after the use of calcium-channel blockers. **Grade of recommendation IIa, Level of evidence B.**

With regard to protection against cardiovascular events, the ISIS-4[222] and GISSI-3[223] studies indicated that nitrates do not change the mortality 4–6 weeks after MI. An extensive review of the effects of nitrates based on experimental studies on humans[224], particularly involving intravenous nitroglycerin, isosorbide mononitrate, and isosorbide dinitrate, reported that significant endothelial dysfunction, and the stimulation of both the renin–angiotensin–aldosterone and the sympathetic nervous systems, which trigger the release of vasopressors, challenge the prolonged use of long-acting nitrates to treat patients with angina[225-230].

These studies demonstrate that the rapid tolerance acquired with the prolonged use of these drugs is associated with such changes. Therefore, long-acting nitrates should be used orally only in cases of refractory angina. These findings support the use of other antianginal agents, but not nitrate, as a first option for the long-term treatment of angina. Moreover, for patients suffering MI, the single most robust evidence is a nonblinded and randomized Japanese study involving 1700 patients, wherein the oral or transdermal use of nitrates with a follow-up period of at least 60 months resulted in a worst rate of events (death, nonfatal MI, and heart failure) with the use of nitrates in comparison with the control group not treated with nitrates[231], and this trend was observed even in the subgroup with angina. Therefore, considering the existing evidence, this is the most robust evidence for precluding the long-term use of nitrates in patients with angina pectoris.

d) **Trimetazidine**: It is a drug with metabolic and anti-ischemic effects and with no known effects on cardiovascular hemodynamics. Its benefits have been attributed to the following: (1) preservation of intracellular levels of adenosine triphosphate (ATP) and creatine phosphate, with the same residual oxygen[232]; (2) decreased acidosis[225], calcium overload[233], accumulation of ischemia-induced free radicals[234], and (3) preservation of cellular membranes[235]. The administration of this agent has no known effects on the heart rate and blood pressure during rest or physical activity and can be used as monotherapy[236,237] or in combination with other drugs. Several studies showed that combination therapy with beta-blockers or calcium-channel blockers can decrease angina and exercise-induced ischemia[238]. The effects of this combination were superior to those of monotherapy. Trimetazidine can also be used alone, and its beneficial effects were similar to those of monotherapy with beta-blockers or calcium-channel blockers for the treatment of stable chronic angina[238]. A recent retrospective and observational study showed that the use of trimetazidine associated with optimized therapy in patients with heart failure promoted a decrease in the risk of cardiovascular and global mortality[239,240]. A recent meta-analysis[241] reported the decreased number of hospitalizations for cardiovascular causes in patients with LV dysfunction subjected to trimetazidine treatment. Furthermore, a South Korean study reported decreased cardiovascular events (including death in patients after acute coronary events) in patients on trimetazidine compared with those on conventional treatment[242]. Despite their retrospective and observational nature, these studies indicate the possibility of decreasing cardiovascular events with the use of trimetazidine associated with optimize drug therapy. The use of trimetazidine prior to percutaneous or surgical myocardial revascularization decreased the release of markers of periprocedural myocardial necrosis and preserved LV function[243]. Furthermore, the use of trimetazidine as a therapy adjunctive to standard treatment during myocardial revascularization procedures (percutaneous or surgical) led to decreased release of markers of myocardial necrosis, decreased oxidative stress, and improvement of LV function[244-249].

In patients with symptomatic stable angina on beta-blockers alone or in combination with other antianginal agents. **Grade of recommendation IIa, Level of evidence B.**

In patients with stable angina and LV dysfunction associated with optimized medical therapy (OMT). **Grade of recommendation IIa, Level of evidence B.**

In patients with stable angina during myocardial revascularization procedures (percutaneous or surgical). **Grade of recommendation IIa, Level of evidence B.**

e) **Ivabradine**: It is a specific inhibitor of the I_f current in the sinus node (X). This drug specifically decreases the heart rate without affecting blood pressure, myocardial contractility, intracardiac conduction, and ventricular repolarization. Its effects are observed during physical activity and at rest. In noninferiority studies, its antianginal efficacy was similar to that of atenolol and amlodipine[250,251]. The BEAUTIFUL study[252] demonstrated that ivabradine decreases the incidence of MI and the need for revascularization in the subgroup of patients with CAD associated with ventricular dysfunction and resting heart rate ≥ 70 bpm. However, in the overall study population, including individuals with resting heart rate of up to 60 bpm, there was no decrease in the incidence of primary outcomes, including cardiovascular death, hospital admission for AMI, and heart failure. Ivabradine can be used as an alternative in patients who do not tolerate beta-blockers and in patients with diabetes because it does not interfere with glucose metabolism, and also concomitantly with beta-blockers. The main side effects are visual changes, known as phosphenes, which correspond to a bright glare sensation, particularly when moving from a dark to a light environment. However, this effect is reversible over time in most cases or after discontinuing drug use.

In patients with symptomatic stable angina on beta-blockers, either alone or in combination with other antianginal agents, and heart rate > 60 bpm. **Grade of**

recommendation IIa, Level of evidence B.

In patients with symptomatic stable angina who are intolerant to use of beta-blockers in isolation or in combination with other antianginal agents. **Grade of recommendation IIb, Level of evidence B.**

In patients with stable angina, LV dysfunction (LVEF < 40%) and heart rate ≥ 70 bpm under OMT. **Grade of recommendation IIa, Level of evidence B.**

f) **Allopurinol**: It is a xanthine oxidase inhibitor that decreases uric acid levels in subjects with gout and has antianginal properties. In a previous study, a dose of 600 mg/day of allopurinol increased ST-segment depression time and the time for the onset of angina[253,254].

In symptomatic patients with stable angina subjected to antianginal therapy that is maximally tolerated. **Grade of recommendation IIb, Level of evidence B.**

g) **Nicorandil**: It is a derivative of nicotinamide, with a dual mechanism of action. It is a potassium channel activator and — similar to nitrates — a smooth muscle relaxant, causing vasodilation and preload reduction. In addition, this drug decreases the afterload and stimulates the expression of nitric oxide (NO) synthase in the endothelium.

Previous studies reported improvement in exercise tolerance and prolonged time for the onset of ECG changes during ETT. Another study has indicated a reduction in combined events — hospitalizations due to angina, MI, and cardiovascular mortality — with no isolated effects on mortality and myocardial events[255].

h) **Ranolazine**: It is a piperazine derivative. Similar to trimetazidine, it protects patients from ischemia by increasing the metabolism of glucose in relation to fatty acids. However, its major effect appears to be the inhibition of the late sodium current. This current is activated during ischemia, leading to intracellular calcium overload in the ischemic tissue and, consequently, increased ventricular wall stiffness, decreased compliance, and capillary compression. Therefore, inhibition of the sodium current with ranolazine during an ischemic insult improves myocardial function. Its antianginal efficacy was demonstrated using monotherapy and in combination with other anti-ischemic drugs, resulting in increased exercise tolerance, decreased number of ischemic episodes, and decreased nitrate consumption. This drug is metabolized in the liver (through cytochrome CYP3A4); therefore, potential drug combinations with simvastatin, digoxin, diltiazem, and verapamil, among others, should be used with caution. QT-interval prolongation may also occur. Similar to trimetazidine, ranolazine does not decrease major cardiovascular complications[256].

Figures 1 and 2 show the algorithms used to improve understanding of drug treatment options in stable CAD.

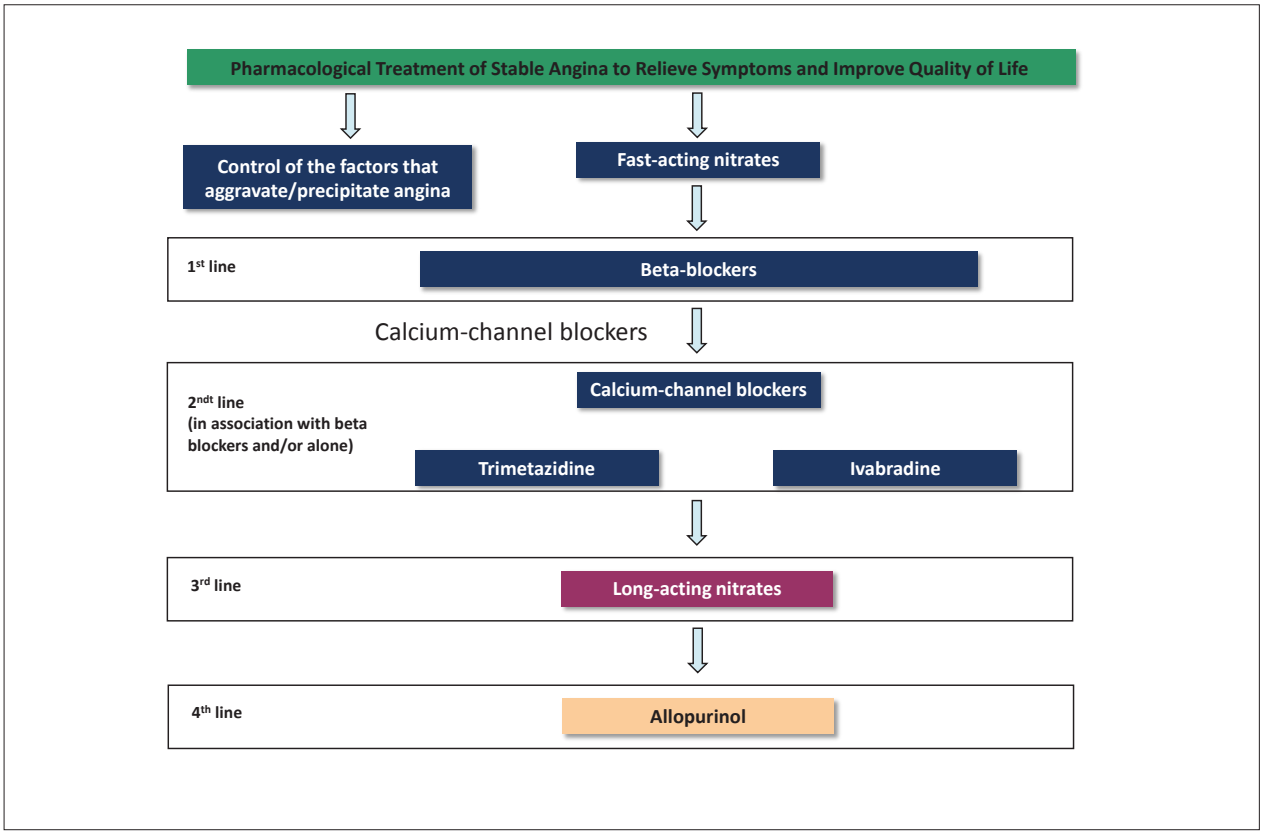

Figure 1 – *Algorithm for use of antianginal medications to relieve symptoms and improve quality of life. Details, degrees of recommendation and level of evidence: see corresponding text.*

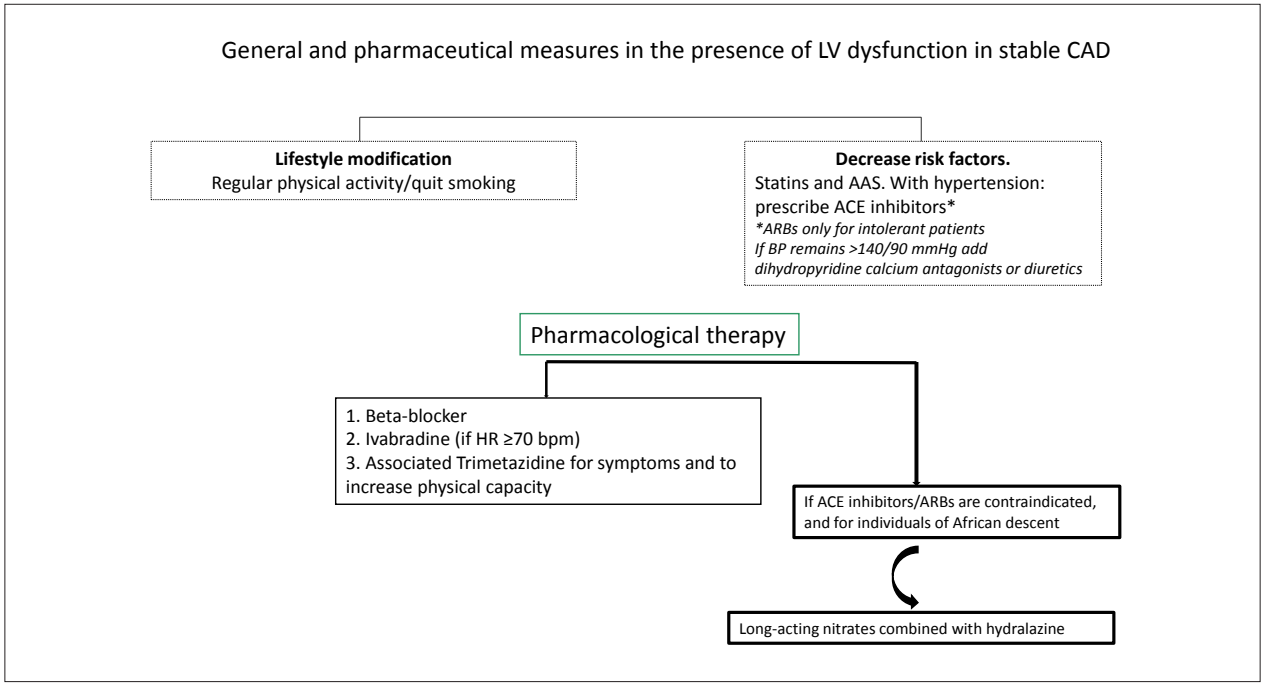

Figure 2 – *Algorithm for reduction of cardiovascular events in the presence of left ventricular dysfunction. Details, degrees of recommendation and level of evidence: see corresponding text. ASA: acetylsalicylic acid; H: hypertension; ACE inhibitors: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blocker I; BP: blood pressure; HR: heart rate.*

Part III - Treatment with invasive measures

1. Treatment with invasive measures

1.a. Coronary artery by-pass surgery

The direct myocardial revascularization using grafts for the coronary arteries from the aorta, or using the native artery itself, revolutionized the treatment of angina pectoris in the 1970s. Since then, numerous studies have been conducted to identify individuals with few limitations in their daily activities from angina pectoris or who are asymptomatic, which could benefit from revascularization, increasing lifespan and extending the period without coronary events. The Myocardial Revascularization Surgery Guideline[257] contemplates the procedures, alternatives, and methods practiced today, and briefly reviews the classical studies, comparing surgical treatment strategies with clinical treatment and PCI[258-261]. Two studies of fundamental importance were conducted in Brazil. The MASS study[262] randomized one-vessel disease patients with stable angina, proximal lesion on the anterior interventricular artery, and normal ventricular function to receive one of three treatments: clinical, surgical, or PCI. The MASS-II study[263] randomized multivessel disease patients using the same experimental design and used stents in most patients with lesions > 70% in the treatment arm subjected to angioplasty. In addition to these studies, a MASS-II substudy[264] indicated the decreased cost of initially treating patients only clinically compared with the other two treatments in the first year of follow-up.

After 10 years of follow-up, the MASS study[265] showed that the patients with multivessel disease subjected to myocardial revascularization had better outcomes than those subjected to PCI or drug therapy for the prevention of new cardiovascular events, with need for additional revascularization, and AMI. However, the long-term mortality rates among the three groups were statistically similar.

Recently, the SYNergy Between Percutaneous Coronary Intervention with TAXus and Cardiac Surgery (SYNTAX) study[266] and FREEDOM study[267] provided new data on the indication of coronary artery by-pass surgery (CABG) to patients with three-vessel CAD and to patients with diabetes.

The multicenter SYNTAX study[266] was conducted in 62 European centers and 23 American centers and compared the surgical and percutaneous strategies of myocardial revascularization in patients with three-vessel CAD or arterial trunk injury. Of a total of 3,075 patients, 1,800 were eligible for both percutaneous and surgical interventions and were randomized into two groups: 903 were subjected to PCI with first-generation Taxus™ drug-eluting stents (DES) and 897 were subjected to CABG. The comparison of noninferiority was assessed using the primary outcomes of major cardiovascular events (MACE), which comprised all-cause mortality, stroke, AMI, and need for additional revascularization. After a 5-year follow up, no difference was observed in the overall mortality (13.9% in the PCI group vs. 11.4% in the CABG group; p = 0.1). However, increased cardiovascular mortality was observed in the PCI group (9.0% vs. 5.3% in the CABG group; p = 0.003). The incidence of cerebrovascular events did not significantly increase in CABG group (3.7% vs. 2.4% in the PCI

group; p = 0.09). The incidence of AMI was significantly higher in the PCI group (9.7% vs. 3.8% in the CABG group, p < 0.001). The need for additional revascularization was significantly higher in the PCI group (25.9% vs. 13.7% in the CABG group; p < 0.001). The MACE rate after a 5-year follow-up was 37.3% and 26.9% in the PCI and CABG groups, respectively. In this study, the CABG procedure proved to be better than PCI in patients with complex coronary anatomy and with intermediate and high Syntax scores. However, PCI results were similar to those of CABG in patients with low-complexity lesions.

The FREEDOM study[267] randomized 1,900 patients with diabetes and multivessel CAD documented angiographically. All patients were referred to myocardial revascularization (angina or evidence of ischemia), CABG with or without extracorporeal circulation, or multivessel PCI using DES and abciximab infusion. The arterial pattern should include patients referred to both revascularization techniques. All patients received OMT. The primary outcome after the 5-year follow-up period, comprising all-cause mortality, nonfatal AMI, or stroke, was observed in 205 patients (26.6%) subjected to PCI with covered stent and in 147 patients (18.7%) subjected to CABG (p = 0.005). The mean Syntax score of the study population was 26, indicating moderate difficulty to treatment with PCI, and using the EuroSCORE, the mean score was 2.7, suggesting low surgical risk. Moreover, in patients with diabetes and advanced CAD, CABG was superior to PCI, with lower rates of death and AMI, but the rate of stroke was higher.

1.a.1. Indication for direct surgical revascularization

Grade of recommendation I[46,268-270]

1 Stenosis ≥ 50% on LMD or an equivalent condition (LAD and Cx in the ostium or before the exit of important branches)[268]. **Level of Evidence A.**

2 Proximal stenosis (> 70%) in the three main arteries with or without involvement of the proximal LAD, particularly in patients with EF < 50% or functional evidence of moderate to severe ischemia[268]. **Level of Evidence B.**

3 Stenosis in two main vessels, with proximal LAD lesion in patients with EF < 50% or functional evidence of moderate to severe ischemia. **Level of Evidence B.**

4 Stenosis in one or two main arteries without involvement of LAD artery but with functional evidence of significant ischemia[270]. **Level of Evidence B.**

5 Disabling angina with the involvement of any arteries, even secondary arteries, after all noninvasive treatment options have been discarded and when treatment with catheter is technically unfeasible. **Level of Evidence B.**

6 Stenoses in one or two arteries without involvement of LAD after an event of resuscitated sudden death or sustained ventricular tachycardia. **Level of Evidence B.**

Grade of recommendation IIa

1. Stenoses of arteries and grafts in operated patients having at least moderate ischemia in functional tests or disabling angina, with stenosis of LAD graft and in situations when treatment with catheter is technical unfeasible. **Level of evidence C.**
2. Performance of left mammary artery grafting in patients with significant stenosis (> 70%) in the proximal LAD and evidence of extensive ischemia, with the aim to improve survival. **Level of Evidence B.**
3. Performance of CABG at the expense of PCI in patients with multivessel CAD and diabetes mellitus, particularly using left mammary artery grafting for the proximal LAD. **Level of Evidence B.**
4. Performance of CABG at the expense of PCI in patients with complex multivessel CAD (e.g., Syntax score > 22) with or without stenosis of the proximal LAD. **Level of Evidence B.**

Grade of recommendation III

1. Asymptomatic patients with normal ventricular function and without extensive areas of ischemia, particularly those without stenosis of the proximal LAD. **Level of evidence C.**
2. Asymptomatic patients without significant anatomical coronary lesions (< 70%, or < 50% of the LMD) or without functional coronary lesions (e.g., FFR > 0.8 or mild ischemia in noninvasive tests). **Level of evidence C.**
3. One or two affected arteries, except the proximal LAD, without any major ischemic area in functional tests or with irrigation of a small area of viable myocardium. **Level of Evidence B.**
4. Moderate lesions (between 50% and 60%) except in LMD, without at least moderate ischemia demonstrable in functional tests.
5. Insignificant lesions (< 50%).

1.a.2. The "Heart Team" concept for the decision to perform myocardial revascularization

Class I[46]

A team composed of a cardiologist, hemodynamicist, and surgeon is recommended to individualize the decision about the best treatment for patients with LMD lesions or complex CAD. **Level of Evidence C**[266].

Class IIa

The calculation of the Syntax and STS scores is suitable for patients with LMD lesions or complex CAD. **Level of Evidence B**[46,266]

1.b. Transmyocardial laser revascularization surgery

a) Use of laser in cardiac muscle.

b) Comparative studies with CO_2 laser.

c) Indication of transmyocardial laser revascularization surgery (TLRS).

d) Future perspectives.

1.b.1. Novel therapeutic approaches — transmyocardial laser revascularization

1.b.1.1. Introduction

Most patients with stable angina can control symptoms using antianginal drugs, PCI, and/or CABG. However, a select group of patients with extensive coronary atherosclerosis and persistence of symptoms despite drug therapy is not eligible for percutaneous or surgical revascularization. In this group, classified as having refractory angina, TLRS and percutaneous myocardial laser revascularization (PMLR) have emerged as therapeutic options.

TLRS, described by Mirhoseini el al.[271] in 1983, was introduced in Brazil by Galantier et al.[272] in 1995 and was performed after lateral anterior thoracotomy without extracorporeal circulation. Most studies have used three types of high-energy lasers (Holmium YAG laser, CO_2 laser, and XeCl excimer laser) capable of creating transmural channels with approximately 1 mm in diameter, from the epicardium to the LV endocardium, distributed in the area of the ischemic myocardium. TLRS can be associated with myocardial revascularization and venous or arterial grafts. At first, the mechanism proposed was that these microchannels would be responsible for the direct perfusion of the ischemic myocardium. However, it was shown that microchannels were occluded by necrotic and scar tissue several weeks after the procedure[273,274]. Other hypotheses intended to explain the mechanism of action involved the emergence of new blood vessels (angiogenesis) and/or denervation of sympathetic epicardial myocardial fibers, although an associated placebo effect cannot be discarded[273,274].

1.b.1.2. Observational studies

Several observational studies have been conducted to evaluate the efficacy and safety of TLRS in patients with refractory angina. Most observational studies have shown decreased angina, improvement in the functional capacity, and increased exercise tolerance. In contrast, the myocardial perfusion imaging results during patient recovery are conflicting. Of note, the surgical mortality varied between 3% and 20% and one-third of the patients had complications associated with the procedure[274,275].

1.b.1.3. Randomized studies

Seven prospective, randomized, and open studies compared TLRS with optical coherence tomography (OCT) available at that time[276-281]. Recently, a systematic review of the Cochrane database reviewed these studies, which involved 1,137 participants, including 559 patients who were randomized for TLRS[282]. This review indicated that none of the studies met all the established quality criteria primarily because they were open studies with great potential for bias in the evaluation of the primary outcome — angina relief.

No significant differences in survival after the 12-month follow-up period were observed between the two groups. Approximately 44% of the patients randomized for TLRS experienced a lowering of at least two angina classes [established by the Canadian Cardiovascular Society (CCS) and New York Heart Association (NYHA)] in contrast to only 15% of the group subjected to OMT (odds ratio (OR) = 4.63, 95% CI: 3.43–6.25). With regard to exercise tolerance, despite the overall improvement at 12 months, no significant differences were observed between the two treatments. Only two studies evaluated the quality of life of patients and both indicated only a slight improvement in the quality of life in the TLRS group when evaluated with the Seattle Angina Questionnaire. Most patients in both treatments experienced improved myocardial perfusion during recovery, but this improvement did not differ significantly between the TLRS and OMT groups in six of the seven studies evaluated.

Furthermore, there was no significant difference in mortality at 12 months (12.2% vs. 11.9% for the TLRS and OMT groups, respectively; OR = 1.12; 95% CI: 0.77–1.63). However, hospital mortality assessed at 30 days was significantly higher in the group subjected to surgery (6.8% vs. 0.8% in the TLRS and OMT groups, respectively; OR = 3.76; 95% CI: 1.63–8.66). A systematic review concluded that the clinical benefits of TLRS do not outweigh the risk of the procedure and that the procedure was associated with increased hospital mortality. Moreover, randomized double-blind studies with sham procedures are needed to avoid evaluation biases in the perception of angina in the clinical group.

Recently, NICE analyzed these randomized trials and highlighted that, although the patients subjected to TLRS achieved better subjective outcomes, including exercise tolerance, angina score, and quality of life, than patients subjected to OMT, these results contradict the increased perioperative morbidity and mortality, indicating an unfavorable risk/benefit ratio. These studies conclude that TLRS alone should not be used in patients with refractory angina[283].

1.b.1.4. CABG associated with laser revascularization

A single prospective, randomized, single-center, and double-blind study compared CABG alone with CABG associated with TLRS in patients with refractory angina. This study involved 263 patients and indicated no significant differences in the relief of angina and exercise tolerance between the two methods in the short term. However, the operative mortality was significantly lower in the group subjected to CABG and TLRS (1.5% vs. 7.6%; $p < 0.05$). After a 5-year follow-up period, although both groups had improved angina relief compared with baseline values, the CABG/TLRS group had a lower angina score (0.4 ± 0.7 vs. 0.7 ± 1.1; $p = 0.05$) and lower proportion of angina III/IV than the group subjected only to CABG [0% (0/68) vs. 10% (6/60), $p = 0.009$]. The survival after 5 years was similar between the two groups (76% vs. 80%; $p = 0.90$). The authors concluded that, in selected patients, CABG associated with TLRS might be superior to isolated CABG in relieving refractory angina[284].

1.b.1.5. PMLR

In 1997, Kim et al.[285] demonstrated the formation of microchannels through the endocardial surface using a system of catheters introduced through the femoral artery puncture. PMLR emerged as an alternative to TLRS with the prospect of maintaining the supposed benefits observed in angina relief but with decreased rates of morbidity and mortality and without the need for thoracotomy. The mechanism of action would be

the same proposed by PMLR (microchannels, microvascular angiogenesis, cardiac denervation, and placebo effect).

Moreover, some observational studies demonstrated the efficacy of PMLR in patients with refractory angina, including a lower angina class, increased exercise tolerance, and improved quality of life, but without the high rates of complications reported in open surgery[286,287].

1.b.1.6. Randomized studies with PMLR

After the encouraging results of these observational studies, other prospective and randomized studies compared PMLR with OCT in patients with refractory angina without therapeutic options. Recently, a meta-analysis evaluated the results of the seven largest randomized studies involving PMLR[288]. Of the 1213 patients evaluated, 651 were allocated to the PMLR group. All studies used Holmium YAG laser and three types of catheter (Eclipse System, Coaxial Cardiogenesis System, and Axcis PMLR) percutaneously, included patients with refractory angina (CCS classes III/IV), and evaluated the improvement in angina class, exercise tolerance, and quality of life during follow-up.

The authors noted that the patients subjected to PMLR showed lower angina class (OR = 2.13, 95% CI: 1.22–3.73), improvement in the quality of life by assessing the difference in the mean deviation (DMD); (DMD = 0.29, 95% CI: 0.05–0.52), perception of disease (DMD = 0.37, 95% CI: 0.14–0.61) and exercise tolerance (DMD = 0.29, 95% CI: 0.05–0.53) compared with patients on OCT. There was no impact on mortality after a 12-month follow-up period. It was concluded that the patients with refractory angina without therapeutic options might benefit from PMLR for decreased anginal symptoms and improved quality of life, without impacting mortality. However, the authors highlighted that not all studies were double blind and that adverse events related to the procedure would need to be assessed because of the heterogeneity of the trials.

Interestingly, in the two largest randomized and double-blind studies involving 439 patients and that used a percutaneous sham procedure in the group randomized for OCT (to avoid the placebo effect of the procedure), no statistically significant difference was observed in any of the clinical outcomes evaluated[289,290]. This suggests that the benefits previously observed with PMLR and TLRS were more associated with a placebo effect of the procedure than with therapy itself (PMLR).

NICE also conducted an analysis of these seven studies involving PMLR[283]. Although they noted some improvement in secondary outcomes (exercise tolerance and anginal symptoms), this study highlighted that little could be concluded in view of the heterogeneity of the studies. Moreover, it emphasized that, although the perioperative mortality was low, the rates of nonfatal complications were high, including MI (7%), ventricular perforation (1%–4%), cardiac tamponade (≤3%), and stroke (2%). Therefore, PMLR may not be as effective in decreasing anginal symptoms and improving the functional capacity and is associated with unacceptable nonfatal complication rates.

1.b.1.7. Conclusion

Over the past 10 years, we have observed a great progress in the TLRS technique, surgical or percutaneous, with encouraging results from a few isolated clinical trials. However, more qualified, randomized, double-blind studies with sham procedures in the control group as well as recent evidence from meta-analyses and systematic reviews do not support the widespread use of this technique.

1. Isolated TLRS.

Class III, Level of Evidence A (meta-analysis and systematic review)

2. TLRS associated with surgical grafts.

Class IIB, Level of Evidence B (one randomized study)

3. PMLR

Class III, Level of Evidence A (meta-analysis and systematic review)

1.c. Catheter revascularization: clinical indications

1.c.1. One-vessel disease patients

Advances in techniques, equipment, stents, and adjuvant therapies have established percutaneous catheter intervention (PCI) as a routine and safe procedure for patients with chronic stable CAD and appropriate and favorable coronary anatomy. In this clinical situation, the mortality risk associated with this procedure is 0.5%[291-293].The effectiveness of PCI compared with drug therapy and CABG has been extensively evaluated.

Technological innovations, including equipment, devices, and adjuvant therapies, have established PCI as a procedure routinely used in patients with stable CAD as long as the anatomy is suitable for the procedure. In this context, the risk of mortality is 0.5%[291-293]. Compared with optimized pharmacological therapy and CABG, the effectiveness of PCI has been extensively evaluated.

The decision for patient revascularization should be based on the presence of significant coronary artery stenosis, the amount of associated ischemia, and on the expected benefit for the prognosis and/or symptoms. Several clinical, anatomical, technical, and environmental factors should be considered and discussed by the medical staff to choose the most appropriate treatment for each case (Chart 1). When technically feasible, with an acceptable rate of risk and good life expectancy, myocardial revascularization using PCI or CABG is indicated in cases of chronic angina that is refractory to optimized pharmacological treatment.

Observational studies of the CASS registry and meta-analysis of seven randomized clinical trials of CABG vs. OMT involving 2649 patients suggested a survival advantage for patients with three-vessel disease (or disease in LMD) subjected to surgery, but no difference was observed in common patients or those with two-vessel disease, except those with involvement of the proximal left anterior artery and another large vessel.

In all, seven large randomized clinical trials involving > 200 subjects on CABG vs. OMT with chronic stable CAD were published in the last 10 years. In general, the study population was selected after angiography and showed at least one significant stenosis in a major epicardial coronary artery in patients with angina, with or without documented myocardial

Chart 1 – Factors considered in deciding the best treatment strategy for stable CAD

Anatomical	*One-vessel/multivessel/LCT CAD, CAD in major vessel, CAD in proximal LAD, TCO, and Syntax score*
Clinical	Age, gender, diabetes mellitus, comorbidities, frailty, ventricular function, drug tolerance, and clinical scores
Technical	Complete/incomplete revascularization after CABG, after PCI, extensive tortuosity, and/or calcification
Environmental	Volume/quality or center/operator, patient preference, local costs, availability, and waiting list

CAD: coronary artery disease; LCT: left coronary trunk; LAD: left anterior descending artery; TCO: Total coronary occlusion; CABG: coronary artery by-pass surgery; PCI: percutaneous coronary intervention.

ischemia, usually with adequate ventricular function and favorable angiographic anatomy without comorbidities, without CAD in LMD, without multivessel diseases, and without prior CABG. The results of these comparative studies demonstrated increased symptom relief and decreased frequency of urgent revascularization in patients subjected to revascularization. However, this strategy had no advantage compared with OMT in decreasing mortality in patients with stable CAD, which opens the possibility of including OMT (or combining OMT with CABG) in the intervention during follow-up. Although the interventional and surgical techniques have been perfected over the past two decades, medical therapy also evolved in the same period. Therefore, OMT can substantially improve the long-term outcomes of patients treated conservatively and those subjected to PCI together with CABG, decreasing the impact of revascularization on survival.

In low-risk stable CAD, after the documentation of ischemia and careful clinical and angiographic selection, the initial OMT strategy is safe and should be the standard method. Cardiologists, interventionists, and surgeons should consider administering OMT for a sufficiently long duration before deciding on revascularization, particularly in cases of high-risk comorbidities, unfavorable anatomy, or patients that are mildly symptomatic or lack extensive ischemia.

When the initial OMT fails and the patient remains symptomatic, or when the area of ischemia is relevant, the options, advantages and limitations of each strategy and advice of the medical staff need to be discussed with each patient.

The implications of revascularization are well known: periprocedural MI, thrombosis, or in-stent restenosis (the latter is decreased compared with second-generation DES) after PCI, as well as perioperative MI, stroke, cognitive impairment, surgical-wound infection, prolonged hospitalization, and rehabilitation after CABG. The potential advantages of an early revascularization strategy (PCI or CABG) include increased symptom relief without increased mortality, decreased drug therapy, fewer hospital visits, and decreased revascularization in the first year, with better quality of life. Nonetheless, the advantages of revascularization compared with OMT for the relief of symptoms are decreased over time. OMT is safer in the short term and as safe as revascularization for up to 5 years in low-risk patients. However, OMT requires larger doses of medications, which can have a direct impact on treatment adherence, side effects, drug interactions, quality of life, and long-term costs.

The results of clinical trials and systematic reviews of PCI vs. OMT can be summarized as follows:

- PCI decreases the incidence of angina[265,294-296];
- PCI does not improve survival of stable patients [297-299];
- PCI increases the risk of MI in the short term[294,298,300,301];
- PCI does not decrease the risk of MI in the long term[294,297-299,301].

Considering the current knowledge, revascularization in one-vessel disease patients with stable CAD is indicated when the goal is to improve prognosis and/or symptoms in certain situations, which can be observed in Chart 2.

Chart 2 – Recommendation contexts for PCI/myocardial revascularization surgery in patients with stable one-vessel CAD [85]

Recommendation (in asymptomatic patients, the decision is guided by the extent of ischemia in stress testing)	Improve prognosis		Improve symptoms	
	Class	Evidence	Class	Evidence
Stenosis > 50% * in LCT	I	A	I	A
Stenosis > 50% * in proximal LAD	I	A	I	A
Stenosis > 50% * in a major vessel	I	C	I	A
Ischemic area in LV > 10% **	I	B	I	B
Stenosis > 50% and limiting angina despite OMT	NA	NA	I	A
Stenosis > 50% related to ischemia/viability > 10% ** and signs of CHF	IIb	B[302,303]	IIa	B

** Documented ischemia or fractional reserve <0.80 flow in angiographic stenoses between 50 and 90%; ** Assessment by noninvasive testing (SPECT, MRI, stress echocardiography). CAD: coronary artery disease; LCT: left coronary trunk; LAD: left anterior descending artery; LV: left ventricle; OMT: best medical treatment; NA: not assessed; CHF: congestive heart failure.*

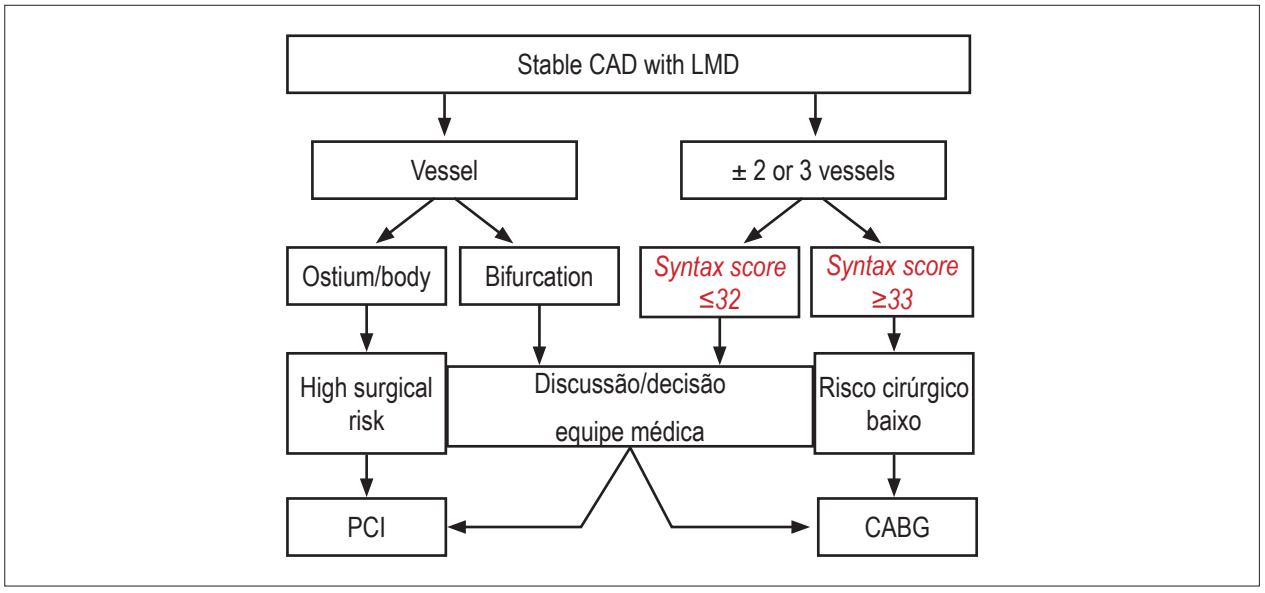

Figura 1 – *PCI or CABG in CAD involving LMD(lesion >50% with evidence of ischemia in functional testing; lesion >70%; or fractional flow reserve <0.80). CAD: coronary artery disease; LMD: left main disease; CABG: coronary artery by-pass surgery; PCI: percutaneous coronary intervention.*

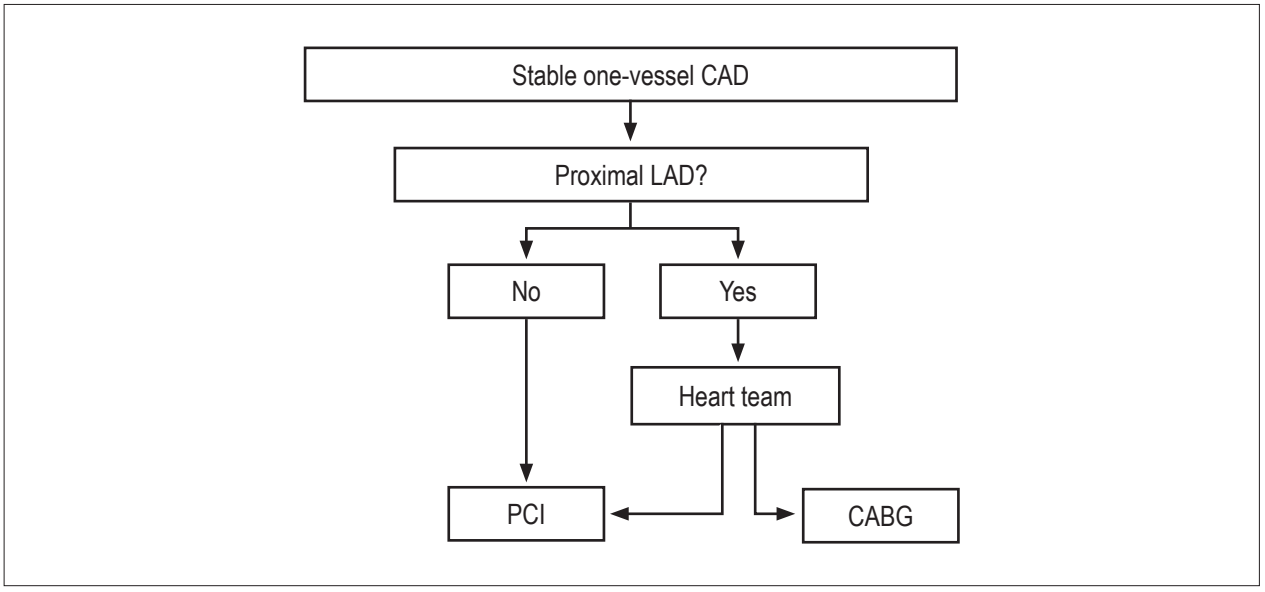

Figura 2 – *PCI or CABG in CAD not involving LMD (lesion >50% with evidence of ischemia in functional testing; lesion > 90%; or fractional flow reserve <0.80). CAD: coronary artery disease; LMD: left main disease; PCI: percutaneous coronary intervention; CABG: coronary artery by-pass surgery.*

Anatomically, the presence of CAD in LMD or proximal LAD is important in making decisions regarding the revascularization strategy, as can be observed in Figures 1 and 2. A cohort study[304] and a meta-analysis[305] conducted in the 1990s suggest that CABG confers a survival advantage in relation to OMT for patients with complications in the proximal LAD. Previous cohort studies, randomized clinical studies[306-312] and meta-analyses[305,313] have shown that PCI and CABG yield similar survival rates in these patients.

The current recommendations for revascularization using PCI in one-vessel CAD may be summarized as follows:

- **For improved survival:**

a) **Class I:** PCI is beneficial to survivors of sudden cardiac death with suspected ischemic ventricular tachycardia, presumably caused by significant stenosis (≥70%) in a major coronary artery (**Level of Evidence C**).

b) **Class IIb:** the benefits of PCI are uncertain in cases of CAD in the proximal LAD (**Level of Evidence B**[294,304,314,315]).

c) Class III: PCI should not be performed with the intent of improving survival in patients with stable CAD and coronary stenosis that is not anatomically or functionally significant (e.g., lesion < 70% in a major coronary artery, FFR > 0.80, and absent or mild ischemia on a noninvasive test), in cases of CAD in the Cx artery or right coronary artery, or in a small area of viable myocardium (**Level of Evidence B**[304,305,316-319]).

- **For improved symptoms:**

a) Class I: PCI is beneficial in patients with significant stenosis (≥ 70%) in a coronary artery susceptible of revascularization and unacceptable angina, despite OMT (**Level of Evidence A**[294-296,320,321]).

b) Class IIa:

i. PCI is acceptable in patients with significant stenosis (≥ 70%) in a coronary artery susceptible to revascularization and unacceptable angina, for which OMT cannot be performed because of contraindications/adverse effects of medications or patient preferences (**Level of Evidence C**).

ii. PCI is acceptable in patients with prior CABG, significant stenosis (≥ 70%) in a coronary artery associated with ischemia and unacceptable angina, despite OMT (**Level of Evidence C**).

c) Class III: PCI should not be performed in patients who do not meet anatomical criteria (lesion ≥ 50% in LMD or ≥ 70% in a major coronary artery) or physiological criteria (e.g., FFR < 0.80) for revascularization (**Level of Evidence C**).

1.c.2. Two-vessel disease patients

1.c.2.1. Intracoronary evaluation of stenosis severity (FFR, intravascular ultrasound, and optical coherence tomography)

When the noninvasive evaluation of ischemia using imaging techniques is contraindicated, inconclusive, or unavailable, the evaluation of FFR during adenosine infusion is particularly beneficial for identifying hemodynamically or functionally significant stenoses that are inducers of ischemia, which can justify the indication for revascularization[291-293].

Previous studies with conventional stent demonstrated that medical treatment provides better results than immediate revascularization in patients with FFR > 0.80[322-324]. Therefore, a patient with stenosis and FFR > 0.80 (with two measurements or during adenosine infusion) should not be revascularized. A recent study known as FFR versus Angiography for Multivessel Evaluation (FAME-2) confirmed that patients with stable CAD and stenoses with FFR ≤ 0.80 benefited from revascularization using PCI compared with OMT, and this benefit was solely the result of the decreased need for urgent revascularization. In contrast, patients without ischemia had excellent results when treated with OMT without revascularization[325]. FFR is already being used clinically to evaluate the efficacy of PCI.

In general, although FFR is not important in lesions angiographically > 90% (almost all these injuries have a FFR ≤ 0.80), FFR can help decide when revascularization is necessary in some unclear clinical conditions, including those of patients with multivessel diseases of heterogeneous presentation. In these patients, the measurement of FFR can change the revascularization strategy (PCI vs. CABG) beyond its scope, according to the functional assessment of stenoses in critical areas of the coronary arteries.

The use of IVUS has been widely investigated in stable CAD in distinct lesion subtypes. In contrast to FFR, IVUS is a diagnostic imaging tool and does not provide a functional assessment of stenosis severity. The cutoff limits of 3.5 or 4.0 mm^2, previously accepted for stenosis in major epicardial arteries, and 6.0 mm^2 for stenoses in LCAT[326], proved to be unreliable and poorly correlated with FFR, and better results are achieved when absolute IVUS measurements are corrected for the reference vessel size. In contrast, considering that the indication for treatment is well established and more information is needed, IVUS is far superior to FFR because the former can perform an anatomical characterization of the lesion in terms of vessel size and plaque composition. It can also control the expansion and position of the stent arm.

Recently, optical coherence tomography (OCT) has been developed as a novel intracoronary image tool with higher resolution (10 mm) and can make a detailed evaluation of surface components, including thickness measurements of the fibrous lipid cap of the plaque[327]. The benefits of OCT in patients with stable CAD and with potential vulnerable plaques have not been well established, and certainly the treatment of severe nonfunctional lesions based solely on the presence of elements of instability is not recommended. On the other hand, its easy image acquisition allows the optimized expansion and placement of the stent and the assessment of its long-term endothelialization[327].

1.c.2.2. Revascularization vs. drug therapy

The goal of revascularization in stable patients is to improve survival and relieve symptoms. The decision to revascularize a patient should be based on the presence of significant obstructive coronary artery stenosis, amount of associated ischemia, and the expected benefits for the prognosis and/or symptoms (Figure 3). Many clinical, anatomical, technical, and environmental factors should be considered and discussed before the benefit of revascularization is anticipated (Chart 3, Figure 3)[86,328-331]. The heterogeneity of these factors makes absolute recommendations unfeasible for the management of each clinical condition. Therefore, for a particular patient in a particular hospital, the clinical assessment should be consensual and not individual, preferably after discussion with the Heart Team of cardiologists (in difficult cases) and also considering the patient's preferences. However, this decision should be individualized, because to many patients, the preferred method is often quite clear. When technically feasible, with an acceptable level of risk and a good life expectancy, revascularization is indicated in patients with angina that is refractory to OMT and chronic stable CAD.

Although contemporary interventional treatments have decreased the risk of restenosis compared with previous techniques (up to 40%), previous meta-analyses did not demonstrate that the introduction of the conventional stent conferred advantage in terms of survival in comparison with balloon angioplasty[291,293,322]. Similarly, the use of covered stents did not have any advantage over conventional stents in terms of survival[323].

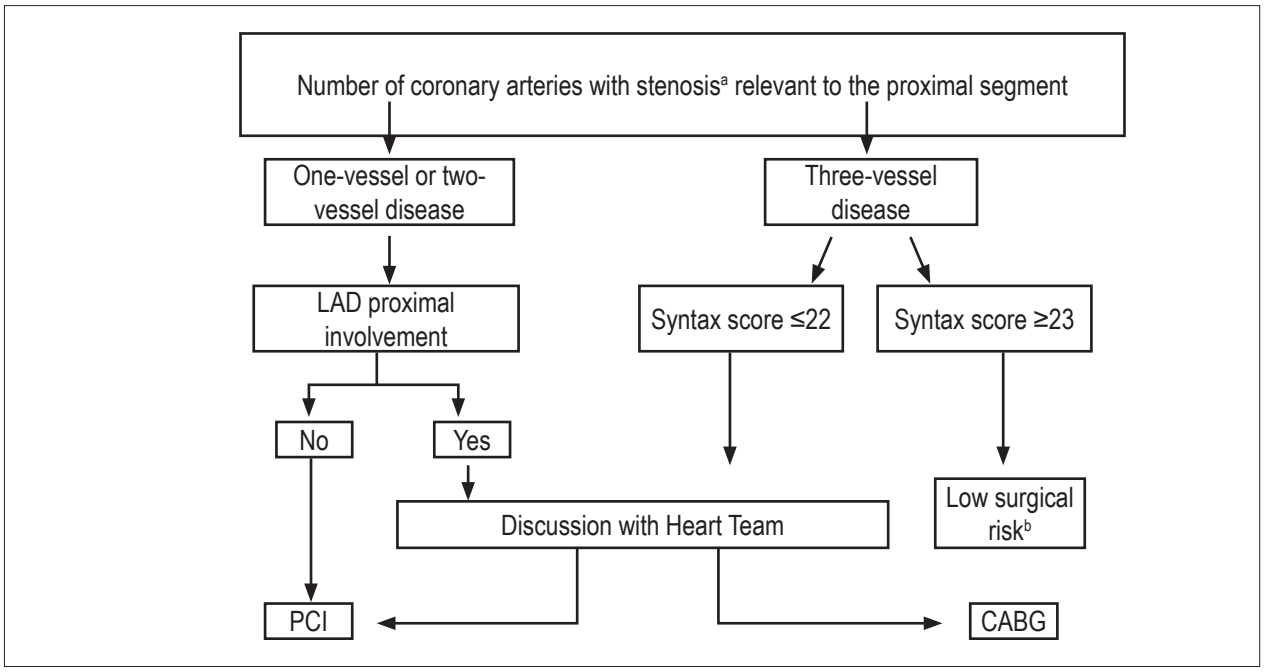

Figure 3 – *PCI or CABG in stable coronary atherosclerosis without involvement of LMD. a ≥ 50% stenosis and evidence of ischemia, lesion > 90%, by two physicians or fractional flow reserve of 0.80; b CABG is the preferred option in most patients, unless they present comorbidities or particularities that merit discussion with the Heart Team. According to local practice (time constraints and workload, for example), direct transfer to CABG may be permitted for low-risk patients, when formal discussion in a multidisciplinary team is not required.*
Adapted from: ESC/EACTS 2010 Guidelines on Myocardial Revascularization. LAD: left anterior descending artery; PCI: percutaneous coronary intervention; CABG: coronary artery by-pass surgery.

Chart 3 – Indication of myocardial revascularization in patients with stable CAD in optimized medical therapy (OMT)

Recommendation[a]	To improve prognosis		To improve symptoms persisting with OMT	
	Class[b]	Level[c]	Class[b]	Level[c]
Heart Team assessment to decide on revascularization is recommended in patients with unprotected left trunk lesions, lesions in two or three arteries, diabetes or other comorbidities	I	C	I	C
Left coronary trunk > 50% diameter stenosis[d]	I	A	I	A
Any lesion > 50% diameter stenosis in the proximal (CHECK) [d]	I	A	I	A
Two-vessel or three-vessel disease with impaired LV function/CHF	I	B	IIa	B
Remaining one-vessel disease (> 50% diameter stenosis[d])	I	C	I	A
Large proven ischemic area (> 10% LV[e])	I	B	I	B
Any significant stenosis with limiting symptoms or symptoms that are unresponsive/intolerant to OMT	NA	NA	I	A
Presence of dyspnea/heart failure with > 10% ischemia/viability[c] caused by a stenosis > 50%	IIb	B[429,430 f]	IIa	B
Absence of limiting symptoms with OMT in lesions other than the left coronary trunk or proximal left anterior interventricular artery, or remaining isolated lesion, or lesions responsible for ischemic area < 10% of myocardial area or with FFR ≥ 0.80	III	A	III	C

Adapted from: ESC/EACTS 2010 Guidelines[172]. OMT: optimal medical therapy; LV: left ventricle; CHF: congestive heart failure; FFR: fractional flow reserve.
[a]in asymptomatic patients, the decision is guided by the degree of ischemia in stress testing;); [b]recommendation class; [c]level of evidence; [d]with documented ischemia or FFR < 0.80 for stenoses with angiographic diameter between 50% and 90%; [e]assessed by noninvasive testing (SPECT, MRI and stress echocardiography[f] supporting the levels of evidence.

1.c.2.3. Revascularization in low-risk groups

With regard to two-vessel disease patients, classical studies that compared CABG with drug treatment indicated increased survival of patients with two-vessel diseases with involvement of the LAD, particularly those with both LV dysfunction and stenosis in the proximal LAD[58,298,301,332-334]. Previous studies that compared the results of CABG with those of PCI using first-generation stents in multivessel-disease patients demonstrated that both interventions yielded similar results regarding late survival and the rate of MI, and the main difference was associated with a larger number of subsequent revascularization procedures in patients subjected to PCI[294,304,316,335-337].

1.c.2.4. PCI vs. clinical treatment

To date, no study could demonstrate that PCI in patients with stable CAD improves the survival rates[58,301,332,333,265,294,316,335-339]. The three most recent studies comparing CABG with OMT are the largest and the most informative and involved contemporary and OMT. Similarly, these three studies indicated no survival advantage with PCI. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial evaluated 2,287 patients and compared PCI and OMT with OMT alone in patients with stable CAD or ischemia and coronary lesions suitable for PCI[294]. The target population of the study comprised patients with chronic angina pectoris (CCS class I–III), stable post-MI, and asymptomatic patients with objective evidence of myocardial ischemia. All patients were diagnosed with CAD using angiography in at least one vessel with indication for PCI (class I or II) according to AHA/ACC. Of these, 30% had one-vessel disease and 39% had two-vessel disease. Patients with stenosis > 80% in one or more vessels encompassing a large myocardial area at risk could participate even in the absence of documented ischemia. The primary outcome of overall death or nonfatal MI did not differ between the two groups during a mean follow-up period of 4.6 years[294]. However, in patients treated invasively, free (angina) time was significantly better in a 3-year follow-up. However, a substudy indicated that patients with ischemia > 10% on stress myocardial perfusion scintigraphy exhibited a higher rate of death or AMI. Moreover, the group subjected to PCI and OMT experienced a significant decrease in ischemia (33% vs. 19%, p = 0.0004) and those with decreased ischemia had a lower unadjusted risk of death or MI, particularly if baseline ischemia was moderate to severe[316].

The Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) study, involving 2,368 patients, assessed whether PCI or CABG (the choice was left to the cardiologist), combined with OMT was better than OMT alone in patients with chronic stable CAD and diabetes mellitus type 2[335]. The target population was patients diagnosed with type 2 diabetes and CAD documented angiographically, whose revascularization was not required for immediate control of severe or unstable angina. Patients with stenosis > 70% showing symptoms of angina were eligible for randomization even without documented ischemia. In contrast, approximately 30% of the patients with a positive stress test were asymptomatic. With regard to the risk factors associated with atherosclerotic burden, 69% of the cases involved two-vessel disease and only 13.2% involved the stenosis of the proximal LAD. The primary outcome of overall mortality and the rate of MI or stroke did not differ between the two treatment strategies in a 5-year follow-up. Patients with more severe disease were selected for CABG instead of PCI and formed a high-risk group, which resulted in increased benefit of early revascularization (decreased MI compared with OMT)[336].

In the FAME-2 study, 888 patients with stable CAD and functionally significant stenosis (FFR ≤ 0.80) were randomly assigned to PCI on the basis of FFR and OMT or OMT alone, and 34.9% of these patients had two-vessel diseases with at least one significant injury in the middle third or the proximal third of LAD[324,325]. The target population of the study were patients who had at least one functionally significant stenosis and, on average, large areas of myocardial ischemia (mean FFR = 0.68), whereas low-risk patients with nonischemic FFR were not randomized but were monitored separately to maintain a record. The study was discontinued prematurely by the Health Safety Monitoring Board owing to a very significant decrease in the rate of hospital readmission and of urgent revascularization in the group with FFR ≤ 0.80 treated with PCI compared with those with FFR ≤ 0.80 treated with OMT. There was no difference in the rates of death or MI between the two strategies. In patients without ischemia (on record), the progress and outcomes were favorable for the group treated with OMT[325].

In summary, a total of seven major randomized revascularization trials vs. medical therapy in stable chronic CAD were published in the last 10 years[265,294,325,335,337-339]. In addition, for low-risk patients with stable CAD, after documentation of ischemia and careful clinical and angiographic screening, the initial OMT strategy is safe and should be the standard approach. Until an adequate duration of OMT is administered, cardiologists and surgeons should be more conservative when making decisions about revascularization, particularly in cases of high-risk comorbidities, unfavorable anatomy, or symptomatic patients without extensive induced ischemia. Previous studies have shown that, despite frequent revascularization procedures, most patients can be treated with OMT alone during these procedures.

However, when the initial OMT procedure fails and the patients remain symptomatic or when the risk of ischemia is relevant, various options need to be discussed, including strengthening of OMT and revascularization. The advantages, limitations, and opinions of the surgeon, clinician, and interventionist should be fully addressed in the discussion with the patient.

The well-known early revascularization complications include periprocedural MI, thrombosis, and late restenosis (nowadays, the latter is greatly decreased with the advent of the second-generation stents) after PCI, as well as perioperative MI, stroke, cognitive impairment, surgical-wound infection, and prolonged hospitalization and rehabilitation after myocardial revascularization. The potential advantages of an early revascularization strategy (PCI or CABG) include greater

relief of symptoms and insignificant increase in mortality, decreased duration of drug therapy, decreased hospitalization, and lower chance of repeated revascularization in the first year, resulting in improved quality of life.

However, the advantage of CABG in relation to OMT with regard to the relief of symptoms is attenuated over time. OMT is safer in the short term and as is safe as CABG considering the mortality rate in low-risk patients in up to 5 years. However, OMT requires more and higher doses of medications, which can have a direct impact on treatment adherence, side effects, drug interactions, quality of life, and long-term costs to patients and the health care system.

The results of the studies that compared myocardial revascularization with OMT confirms that, except for better symptom relief and decreased frequency of urgent revascularization, there is no advantage of CABG in relation to isolated OMT to decrease mortality in patients with angiographically diagnosed stable CAD with a low-risk profile (e.g., two-vessel disease and preserved ventricular function), despite the possibility of OMT during follow-up.

Finally, although interventional and surgical techniques have improved over the past two decades, drug therapy also improved greatly over the same period. As a result, OMT can substantially improve the long-term results of patients treated conservatively, in addition to those subjected to revascularization, decreasing the impact of disease progression on survival and future events, even in revascularized patients. Therefore, for the treatment of chronic stable CAD, OMT is the foundation of treatment whereas myocardial revascularization is the coadjuvant and complementary treatment at some point in disease progression.

1.c.2.5. PCI vs. direct revascularization

During the last two decades, approximately 20 clinical studies that compared PCI with CABG have indicated no difference in the overall survival rate between the two interventions, which is possibly associated with the low CAD risk in the populations evaluated[304,314,340-342]. In contrast, several records matched by propensity scores have consistently demonstrated increased survival rates with CABG, compared with catheter intervention, followed by a decreased need for repeated intervention, although these results are still susceptible to confounding factors[265,343,344].

The relative indications for PCI and CABG in patients with chronic stable CAD have been clearly defined by recent recommendations[86,328-331]. There has been a growing recognition of the importance of the Heart Team staff in defining the consensus about whether, when, and how revascularization should be performed. Figure 3 and Chart 3 show the algorithms recommended to simplify the decision-making process. These guidelines emphasize the importance of OMT for all patients and for both procedures.

In relation to patients with diabetes, even among those with two-vessel disease, the FREEDOM study recently demonstrated a significant reduction in the primary ischemic outcome in a 5-year follow-up for 1900 patients treated with CABG or PCI (16% of the cases involved two-vessel disease)[267], corroborating the results of previous studies that suggested a significant mortality benefit of CABG compared with PCI in patients with diabetes with multivessel disease when both revascularization techniques are technically viable[345], even at the cost of increased risk of nonfatal stroke. In this same study, all patients subjected to PCI received covered stents and glycoprotein inhibitors during the procedure, in addition to dual antiplatelet regimen for at least 1 year, and the control of risk factors was optimized in both groups.

Furthermore, the results of large records matched by propensity scores comparing the results of PCI with those of CABG, are consistent in favor of the use of CABG[346-348]. In fact, in a recent study involving 7235 patients matched for numerous baseline characteristics, the overall survival rates in a 8-year follow-up were 78.0% for CABG and 71.2% for PCI (HR = 0.68; 95% CI = 0.64–0.74, $p < 0.001$]. For anatomical groups, RR was 0.53 ($p < 0.001$) in patients with three-vessel disease involving the proximal LAD, and 0.78 ($p = 0.05$) for patients with two-vessel disease and healthy LAD. A lower risk of death after CABG was observed in all subgroups stratified by different basal risk factors[348].

More recently, Weintraub et al.[349] reported the survival rates of 86,244 patients subjected to CABG (19.7% of the cases involved two-vessel disease) and 103,549 patients subjected to PCI (68.9% involving two-vessel disease) matched for propensity score with two-vessel CAD (53%) or three-vessel CAD. In a 4-year follow-up, increased mortality was observed in the PCI group compared with the CABG group. Despite statistical adjustment, this large record could not eliminate confounding factors, in addition to the fact that the patients in most severe conditions were probably selected to undergo PCI[349].

Considering the above, the need for decision-making on an individual basis is important by assessing risk using scores that are available for both percutaneous and surgical intervention (Syntax score and EuroSCORE), by evaluating the benefits to each patient, and by assessing the cost-benefit ratio and patient preferences to prevent the indiscriminate and improper use of percutaneous interventions. To this end, in addition to common sense, responsibility, and ethics, adequacy criteria related to indication for revascularization are available and have recently been revised to serve as a guideline in the management of patients with chronic stable CAD. Of note, the effect of PCI on the quality of life of patients has not been addressed in the current guidelines, but it deserves attention in the context of chronic CAD and should be considered during the decision to intervene[295,350].

Some comments regarding thrombosis occurring in novel stents need to be made. The risk of thrombosis dramatically increases in patients who prematurely interrupt the double platelet inhibition therapy; the mortality rate associated with stent thrombosis varies between 20% and 45%[351]. Therefore, the ability of the patient to tolerate and respect the period of at least 30 days of treatment with dual platelet inhibition for conventional stents, and 12 months for covered stents, is an important factor when choosing PCI for treatment of patients with stable CAD.

In conclusion, PCI is an alternative to CABG in patients with two-vessel disease when there is appropriate indication for revascularization, as shown in Chart 4. The overall assessment of comorbidities, surgical risk, ischemia, and coronary anatomy is important when choosing the most appropriate method of revascularization for each patient.

1.c.2.6. Appropriate use of revascularization

Adequacy criteria are based on consensus among specialists regarding when the indication for a procedure is appropriate or questionable[352,353]. Coronary revascularization is considered appropriate when the expected benefits in terms of survival and overall status (symptoms, functional status, and/or quality of life) exceed its expected negative consequences[329]. Similarly, indication for revascularization is considered inappropriate when the procedure probably will not improve patient outcome and/or increase patient survival[299,329].

However, this is an important and complex issue because the cost of imaging techniques and revascularization comes under increasing but appropriate scrutiny. In addition, the excessive and inappropriate number of indications for PCI in recent years, without considering the benefit to the patient, can cause complications to the patient. Therefore, stricter guidelines with appropriate indication criteria for intervention in the context of chronic stable CAD are required.

Recently, Chan et al.[352] applied these criteria to patients subjected to PCI in the context of stable angina in the United States and found that 50% of the indications were considered appropriate, 38% were considered questionable, and 12% were inappropriate. Furthermore, Ko et al.[353] observed patients with stable CAD in Ontario, Canada, and found that 68% of the indications for revascularized patients were appropriate, 18% were questionable, and 14% were inappropriate. Among the patients with questionable or inappropriate indications, 86% and 82% were subjected to PCI, respectively[353].

Therefore, PCI is an alternative to CABG for two-vessel disease patients when there is appropriate indication for revascularization, as shown in Chart 4. An overall assessment of comorbidities, surgical risk, ischemia, and coronary anatomy is important when deciding on the most appropriate method of revascularization for each patient.

In conclusion, even in the era of contemporary stents, PCI can be used to decrease the incidence of angina but not the risk of MI in the long term and this risk may even increase in the short term. Furthermore, improved survival compared with optimized drug therapy has not been demonstrated in patients with stable angina. The indications are summarized below.

Indication of PCI in two-vessel disease patients to improve survival:

Recommendation grade IIb, Level of Evidence B

1. Benefit is questionable for two-vessel disease patients with potential involvement of the LAD, with or without symptoms, with normal ventricular function, and without diabetes.
2. Without significant lesions in the LAD combined with a large or moderate myocardial area at risk.

Grade of recommendation I, Level of evidence C.

1. CABG or PCI for improved survival is beneficial to survivors of sudden death caused by ischemia-induced ventricular tachycardia or by significant lesion (> 70%) in at least one major coronary artery.

Grade of recommendation III, Level of evidence C

1. In anatomically and functionally insignificant lesions (< 70% or FFR > 0.08) with or without mild ischemia (on a noninvasive test) involving the Cx artery and the right coronary artery and/or a small viable area.

Chart 4 – Updated appropriateness criteria for coronary revascularization: new or revised recommendations

Revascularization method: Multivessel CAD, angina class ≥III CCS and/or evidence of findings of intermediate to high risk of ischemia in noninvasive testing			
		Appropriateness score PCI	CABG (1–9)
1.	One-vessel or two-vessel disease without proximal involvement of LAD and/or without noninvasive testing	I (3)	I (3)
	Two-vessel disease with proximal stenosis of LAD	A (7)	A (8)
2.	Three-vessel disease with low atherosclerotic load (for example, three focal stenoses, low Syntax score)	A (7)	A (9)
3.	Three-vessel with intermediate to high Syntax score (for example: multiple diffuse lesions, presence of CTO or high score)	U (4)	A (9)
4.	Isolated left coronary trunk lesion	U (6)	A (9)
5.	LMD and additional low-risk disease (for example: additional one-vessel or two-vessel involvement, low Syntax score)	U (5)	A (9)
6.	LMD and additional intermediate to high risk illness (for example: involvement of three vessels, presence of TCO or high Syntax score)	I (3)	A (9)

Source: ACCF/SCAI/STS/AATS/AHA/ASCN/HFSA/SCCT 2012 appropriate use criteria for coronary revascularization focused update.
CAD: coronary atherosclerotic disease. CCS: Canadian Cardiovascular Society; PCI: percutaneous coronary intervention; CABG: coronary artery by-pass surgery; LAD: left anterior descending artery; I: inadequate; A: adequate; TCO: total chronic occlusion; U: uncertain.

Indication of PCI in two-vessel disease patients to improve symptoms

Grade of recommendation I, Level of evidence A.

To improve symptoms, CABG or PCI are beneficial to patients with one or more injured arteries (stenosis > 70%) that are amenable to treatment and to patients with refractory angina, despite optimized drug therapy.

Grade of recommendation IIa, Level of evidence C.

1. CABG or PCI to improve symptoms is reasonable for patients with one or more significant lesions (> 70% diameter) and refractory angina, for whom optimized clinical treatment is not feasible owing to contraindications, side effects, or patient preference.
2. PCI to improve symptoms is reasonable for patients with previous CABG, with one or more significant lesions (> 70% diameter) associated with ischemia and refractory angina, despite optimized drug therapy.

Grade of recommendation III, Level of evidence C.

CABG or PCI to improve symptoms should not be performed in patients who do not meet anatomical criteria (> 50% diameter of LMD or > 70% stenosis in any artery) or physiological criteria (FFR > 0.80) for revascularization.

Grade of recommendation III, Level of evidence B.

PCI with coronary stenting (conventional or covered) should not be performed if the patient will likely not tolerate and/or respect the duration of therapy with dual platelet inhibition required for each type of implanted stent, regardless of the number of affected arteries.

1.c.3. Three-vessel disease patients

When introduced in 1977, PCI was only considered to be suitable to treat patients with single-vessel disease and with noncomplex angiographic characteristics.[354] Since then, there has been great progress in the development of novel devices and in the technical capacity to perform these procedures, with the consequent increase in the number of indications. At present, patients with complex artery diseases are treated routinely, particularly with the use of coronary stents.

With regard to patients with multivessel disease, several studies have compared the results of CABG with those of PCI[355-360]. Many of these evaluations have been limited by the nonrandomized selection of patients, inclusion of less-complex cases, or insufficient statistical power.

The SYNTAX study is the best contemporary analysis of revascularization strategies in multivessel disease patients[361]. In this series, 1,800 patients with significant LMD disease or three-vessel disease were randomized for CABG (n = 897) or PCI (n = 903) with the use of the first-generation SF Taxus®. The primary outcome was MACE comprising death from any cause, MI, stroke, and repeated revascularization. Moreover, this study was responsible for two important contributions to adequate patient revascularization: the angiographic Syntax score and the Heart Team concept. The Syntax score was based on the location, severity, and extent of stenosis, to determine the level of anatomical complexity of CAD. Subsequently, patients were categorized as low score if Syntax score ≤ 22, intermediate score if Syntax score was between 23 and 32, and high score if Syntax score was ≥ 33. With regard to the Heart Team, the revascularization strategy was decided collectively by the cardiac surgeon and the interventional cardiologist.

In the SYNTAX study, 1,096 patients had three-vessel disease. After a 5-year follow-up period, no significant difference in the MACE rate was observed among three-vessel disease patients with low Syntax score (0–22) subjected to PCI or MACE (33.3% vs. 26.8% respectively; p = 0.21)[362]. The patients with intermediate Syntax score (23–32) and randomized for PCI had a significantly higher MACE rate than those subjected to CABG (37.9% vs. 22.6% respectively; p = 0.0008). The performance of PCI became even more unfavorable for patients with high Syntax score (≥ 33), and an increase in MACE rate of 57% was observed in the patients subjected to this strategy (41.9% vs. 24.1%, respectively; p = 0.0005).

At present, CABG is the preferred strategy for three-vessel disease patients with more severe clinical and angiographic characteristics (increased age, low EF, renal dysfunction, peripheral vascular disease, diabetes mellitus, or Syntax score > 22). However, for lower-risk patients, PCI has a safety profile similar to that of CABG and can be considered the initial revascularization strategy for these patients[294,314,315,363]. The choice of treatment on an individual basis is the most relevant factor when choosing the best therapeutic option for these patients. The adherence to the Heart Team concept, detailed clinical evaluation, evaluation of the experience of the operators and the surgical clinic, and respect for patient preferences after giving the necessary recommendations are essential for the achievement of favorable outcomes.

Therefore, ICP has the following indications

Grade of recommendation IIb, Level of evidence B.

Three-vessel disease patients with or without disease in the proximal LAD, with favorable anatomy, Syntax score ≤ 22, and potential for complete revascularization.

Grade of recommendation III, level of evidence A

Three-vessel disease patients with Syntax score > 22 and impossibility of complete revascularization.

1.c.4. Patients with lesions in the LMD

In the last decades, the presence of stenosis > 50% in LM has been indicative of CABG. Only high-surgical-risk patients with disease in LMD were eligible for PCI. Recently, however, PCI for treatment of significant stenoses in the unprotected LMD has become an alternative to surgical treatment, considering that several clinical trials have consistently

demonstrated the feasibility, safety, and effectiveness of PCI with stenting in this context, particularly with DES. Together with the development of percutaneous treatment devices, technical approaches, and adjunct pharmacological treatment, PCI proved to be a less-invasive procedure and has been associated with lower rates of intraprocedural complications and decreased hospitalization[364].

Obstructive disease of LMD can show different degrees of complexity, depending primarily on location, and may involve LMD bifurcation and the origin of the LAD and Cx arteries. Therefore, stenoses of LMD can be classified on the basis of the stenosis of the arterial ostium, body, or bifurcation. Several studies have demonstrated better clinical prognosis of PCI when the LMD bifurcation is unimpaired, and this factor is important when choosing the best strategy and revascularization technique. In general, compared with CABG, PCI in the unprotected LMD has shown high success rates and a similar safety profile in the long-term follow-up but a higher incidence of target lesion revascularization (TLR) at late follow-up (2%–38%), with most of the scientific evidence being derived from retrospective, single-center studies, multicenter studies, nonrandomized comparisons, and prespecified subanalyses of randomized trials. Even so, the percutaneous treatment of the unprotected LMD is already considered in situations of decreased anatomical complexity without significant stenosis of the bifurcation as an alternative approach to surgery[364].

However, before referring a patient for myocardial revascularization, either percutaneous or surgical, it is important to confirm the presence of significant atherosclerotic obstruction, considering that spasm or artifacts generated by the positioning of the guiding catheter or angiographic projection are common and may lead to incorrect conclusions about the degree of LMD stenosis. Therefore, in addition to a detailed clinical evaluation, intracoronary ultrasound (IVUS) is recommended to confirm the presence of significant LMD stenosis. Such assessment is obviously more important in cases of moderate stenosis on coronary angiography and should include the measurement of the minimum diameters and areas as well as the load and distribution of the atherosclerotic plaque. A minimal luminal area (MLA) of > 6 mm^2 indicates safety for nonrevascularization of LMD[365]. In contrast, MLA of 4.8 mm^2 was correlated with FFR <0.80 and AML of 4.1 mm^2 was correlated with FFR < 0.75, indicating functional impairment[366]. A subanalysis of the MAIN-COMPARE study evaluated the use of IVUS to guide PCI in the unprotected LMD. Overall, procedures in 756 patients were guided by IVUS whereas those in 219 patients were guided only by angiography. Using the propensity score, there was a lower (statistically nonsignificant, $p = 0.06$) mortality rate after a 3-year follow-up associated with the use of IVUS. However, when considering the group treated with DES, the mortality rate was significantly lower in those guided by IVUS (4.7% vs. 16.0%; $p = 0.048$)[367].

The impact of PCI and DES in the unprotected LMD lesions has been shown in previous studies. The Left Main Coronary Artery Stenting (LE MANS) registry[368] included 252 patients with LMD lesions treated with nonpharmacological stents (NDES) and DES (36.2%). At 30 days, the rate of MACE + stroke and the mortality rate were 4.8% and 1.5%, respectively. After a mean follow-up period of 3.8 years, the rate of MACE + stroke and the mortality rate were 25.4% and 13.9%, respectively. After a 5-year and 10-year follow-up period, the survival rates were 78.1% and 68.9%, respectively. Importantly, the rates of MACE were significantly lower with DES than with NDES ($p = 0.04$). In the multicenter observational study known as Revascularization for Unprotected Left Main Coronary Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization (MAIN-COMPARE)[357], 2,240 patients with significant unprotected LMD lesions were treated with PCI or CABG (NDES = 318, DES = 784, CABG = 1,138). Patients were subjected to PCI when the anatomy was favorable to stenting and in cases of refusal or high risk during CABG. In patients subjected to PCI, the rate of complications during hospitalization and the mortality rate were 2.7% and 0.8%, respectively. At late follow-up (approximately 3 years), no difference was observed between PCI and CABG in 542 pairs regarding the survival rate (92.2% vs. 92.1%; $p = 0.45$) and mortality-free survival rate + AMI + stroke (90.8% vs. 90.7%; $p = 0.61$), respectively. However, patients subjected to PCI had increased target vessel revascularization (TVR) ($p < 0.001$). In the very late follow-up stage (mean of 5.2 years), after adjustment with propensity score, there was no significant difference in the mortality rate ($p = 0.35$) and death + AMI + stroke ($p = 0.59$) for PCI compared with CABG. However, TVR was higher in the groups subjected to PCI treated with both NDES and DES. Furthermore, a meta-analysis performed by Pandya et al.[369] involving 44 studies and 10,342 patients treated with DES or NPS revealed that the mortality rate, AMI, and new TVR were 8.8%, 4.0%, and 8.0% among those treated with DES and 12.7%, 3.4%, and 16.4% among those treated with NDES, respectively. Considering only nine comparative studies (n = 5,081), the DES group had lower rates of adverse events, mortality rate ($p = 0.01$), MI ($p = 0.03$), and TVR ($p < 0.001$) than the NDES group after a 3-year follow-up period[369]. Therefore, when PCI is indicated for LMD, the latter should be performed preferably with DES.

The prospective, randomized, and multicenter SYNTAX study[370] compared PCI and DES with CABG in complex multivessel disease patients with or without involvement of LMD, and a prespecified subanalysis involving 705 patients evaluated the impact of the two strategies for LMD treatment. The clinical results of a 5-year follow-up indicated similar values for mortality rate (12.8% vs. 14.6%; $p = 0.53$), cardiac death (8.6% vs. 7.2%; $p = 0.46$), MI (8.2% vs. 4.8%; $p = 0.10$), and the composite outcome of death + stroke + AMI (19.0% vs. 20.8%; $p = 0.57$) for the PCI group compared with the CABG group. In contrast, the rates of stroke were significantly lower in the PCI arm (1.5% vs. 4.3%; $p = 0.03$). However, a lower rate of new TVR was observed in the surgical arm (26.7% vs. 15.5%; $p < 0.01$). When the results were stratified by anatomical complexity, comparable or better results for PCI were observed in the subgroups with low (< 23) and intermediate Syntax score (23–32). In this context, the event rates for those treated with PCI compared with those treated with CABG in the low-score subgroup were as follows: total death (7% vs. 11.3%; $p = 0.28$), stroke (1.8% vs. 4.1%; $p = 0.28$), MI (6.2% vs. 3.1%; $p = 0.32$), total death + stroke + AMI (13.9% vs. 15.2%; $p = 0.71$), and TVR (23.0% vs. 20.3%; $p = 0.65$), and the results in the intermediate-score subgroup were as follows: overall death (8.9% vs. 19.3%; $p = 0.04$), stroke (1.0% vs. 3.6% $p = 0.23$), MI (6.0% vs. 4.6%; $p = 0.71$), total death + stroke + AMI (15.7% vs. 24.9%; $p = 0.11$), and

TVR (22.2% vs. 16.6%; p = 0.40). In the high-score subgroup (> 32), the event rates were similar for overall death (20.9% vs. 14.1%; p = 0.11), stroke (1.6% vs. 4.9%; p = 0.13), MI (11.7% vs. 6.1%; p = 0.40), and total death + stroke + AMI (26.1% vs. 22.1%; p = 0.33). However, the rate of TVR was higher in the PCI group than with the CABG group (34.1% vs. 11.6%; p < 0.001). Overall, the SYNTAX study demonstrated that multivessel CAD patients subjected to PCI for treatment of lesions in the unprotected LMD is a worse clinical prognostic factor, particularly when the lesion is accompanied by lesions in two or three other vessels. Similarly, the associated presence of lesions in the right coronary artery (particularly in cases of total occlusion) was found to be a predictor of mortality in the late follow-up of patients subjected to PCI of LMD[371,372].

In addition, the PRE-COMBAT prospective study randomized 600 patients with unprotected LMD lesions subjected to PCI or CABG. After 1 year, the composite outcome of death, AMI, stroke, and ischemia-associated TVR was observed in 8.7% of those from the PCI group compared with 6.7% of those from the CABG group (p < 0.001 for noninferiority). However, this incidence was below the value considered in the calculation of sample size. Consequently, the study lacked statistical power to adequately respond to the tested hypothesis[373].

The angiographic Syntax score proved to be a good discriminator for PCI but not for CABG because it did not include clinical factors considered important for the prognosis of CABG patients already covered in surgical risk scores, including EuroSCORE, Parsonnet, and the score of the Society of Thoracic Surgeons (STS). Accordingly, PCI should not be used in isolation when making clinical decisions. For this reason, the Syntax score II was recently introduced, considering eight variables strongly associated with mortality after a 4-year follow-up in the SYNTAX study. In addition to the original angiographic Syntax score, the other seven variables were age, creatinine levels, LV function, disease of the unprotected LMD, peripheral vascular disease, being of the female gender, and chronic obstructive pulmonary disease. The validation study by Farooq et al.[374] demonstrated the greater predictive power of the Syntax II score than the purely angiographic Syntax score; in theory, the former score could facilitate clinical decision-making for patients with multivessel disease and unprotected LMD.

According to current evidence, the following factors should be considered when choosing the treatment strategy for unprotected LMD:

- Age, gender, risk factors/associated comorbidities, clinical presentation (EuroSCORE, Parsonnet, STS, Syntax II);
- LV function;
- Involvement of the LMD bifurcation;
- Disease extent and anatomical complexity (Syntax);
- Available devices (DES, IVUS);
- Experience/results of the operator/service of PCI;
- Experience/results of the surgeon/service of CABG.

Therefore, the development of both DES and management techniques have supported PCI as a viable alternative to CABG for the treatment of unprotected LMD lesions. Randomized clinical trials involving patients eligible for both PCI and CABG helped elucidate the feasibility, safety, and efficacy of PCI in this setting. At present, it is reasonable to consider PCI for treatment of unprotected LMD lesions in clinically stable patients with the aim of improving survival by following these recommendations:

- **Class IIa, Level of Evidence B**: stable patients with significant stenosis (≥ 50%) in LMD with: (1) anatomical conditions associated with low-risk complications during PCI and high probability of favorable long-term outcome (lesion in the ostium or body of LMD; Syntax score ≤ 22) and (2) clinical characteristics that predict high surgical risk (STS ≥ 5%).
- **Class IIb, Level of Evidence B**: stable patients with significant stenosis (≥ 50%) in LMD with: (1) anatomical conditions associated with low-risk complications during PCI and intermediate/high probability of favorable long-term outcome (lesion in the LMD bifurcation; Syntax score ≤ 33) and (2) clinical characteristics that predict high surgical risk (STS > 2%).

1.d. Novel therapeutic approaches

1.d.1. Gene therapy

a) Gene Therapy

Gene therapy can be defined as a medical intervention in which the transfer of genetic material is used for the modification of somatic cells *in vivo*, allowing the *in situ* expression of the transferred gene with a consequent therapeutic effect[375]. The transfer of therapeutic genes requires the use of a vehicle known as a vector, which carries the gene of interest and guides it to the target cell, thereby facilitating the transfer of genetic material in somatic cells *in vivo*[376]. Basically, there are two groups of gene transfer vectors: viral and nonviral. Among the viral vectors, the most commonly used for the optimization of gene transfer are modified retroviruses and adenoviruses[377].

Until June 2013, 27 gene therapy protocols for CAD (24 protocols for chronic CAD and three for arterial restenosis) had been submitted to the Office of Biotechnology Activities at NIH in the United States, which is responsible for regulating all protocols involving gene manipulation in the country[378].

The growth of knowledge regarding vascular growth and angiogenic cytokines, and the parallel development of more efficient vectors, allowed for the testing of the hypothesis that gene transfer of growth factors could mitigate the damage from myocardial ischemia by stimulating vascular growth, and this strategy became known as therapeutic angiogenesis[379].

Around the late 1990s, Losordo et al.[380], Symes et al.[381], and Rosengart et al.[382], among others, reported the initial results of gene transfer of vascular endothelial growth factor 165 ($VEGF_{165}$) via direct intramyocardial injection in patients with refractory angina. During follow-up, researchers documented a significant decrease in anginal episodes, increased number of normally perfused myocardial segments, and increased Rentrop score (number of collateral vessels) in all patients. No procedure-related adverse effects were observed.

More recently, the first multicenter trial known as Angiogenic Gene Therapy (AGENT)[383] selected 79 patients with symptomatic CAD to receive one of five increasing doses of a viral vector encoding FGF4, or placebo. Although the results of therapeutic

efficacy of ETT were not significantly different between the groups, the analysis of the subgroup with greater initial functional limitation indicated that gene therapy proved effective in increasing exercise tolerance. Subsequent studies such as AGENT-3 and AGENT-4[384] involving > 500 patients in several countries did not replicate the initial results related to increased exercise tolerance after administration of FGF4 in patients with stable angina, and therefore these studies were discontinued. Similar neutral results were obtained in the Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis (VIVA) trial[385]. However, in an evaluation performed 120 days after treatment, the group treated with the highest dose of VEGF showed a significant decrease in angina (functional class improvement) and a favorable tendency of increased performance effort and of decreased anginal episode frequency.

Grade of recommendation: Till date, no recommendation is available for the clinical use of gene therapy, except within the context of experimental clinical research in accordance with current standards.

b) Cell therapy

The transplantation of stem cells and/or progenitor cells may be a therapeutic option for inducing vascular growth (angiogenesis)[386] and/or limiting the postischemic myocyte loss[387] and can therefore decrease or even prevent the onset of heart failure secondary to chronic ischemic heart disease.

In the last decade, the first reports on cell therapy in patients with CAD began to be published. Assmus et al.[388] transplanted, via intracoronary infusion, progenitor cells from bone marrow or peripheral blood in patients who had acute stroke after reperfusion. During the 4-month follow-up, these patients showed increased LVEF, improved regional wall motion in the infarct zone, decreased end-systolic volume, and increased coronary flow reserve in the artery supplying the infarcted region. No adverse events were observed.

The use of cells derived from adult bone marrow for treatment of severe ischemic heart disease associated with heart failure has been proposed in the study conducted by Perin et al.[389] involving 14 patients. Patients were subjected to transendocardial injection guided by electromechanical mapping in viable but ischemic areas (hibernating myocardium). In a 4-month follow-up period, the authors observed functional class improvement, significant reduction of the perfusion defects according to SPECT, and an increase in EF from 20% to 29%.

Stamm et al.[390] proposed the combined use of intramyocardial injections of bone marrow-derived stem cells with the potential to induce angiogenesis using CABG in six post-AMI patients. All patients survived after 3–9 months of follow-up. In addition, increased overall wall motion was observed in four of six patients and increased perfusion of the infarcted area was observed in five of six patients. Gowdak et al.[391] adopted a similar strategy for the treatment of patients with severe and diffuse CAD who were refractory to clinical treatment and ineligible for complete surgical revascularization because of the disease extent. In 21 patients, stem cells and autologous hematopoietic progenitor cells were injected during revascularization surgery in myocardial areas previously identified as viable and ischemic. No adverse events related to the procedure were observed[392]. The analysis of myocardial perfusion in the injected and nonrevascularized segments indicated the reversal of ischemia in these segments and a contractile improvement. A large, randomized, double-blind, and placebo-controlled clinical trial is underway to test the role of cell therapy complementary to incomplete CABG in patients with stable angina[393].

The RENEW study, currently underway, will test the efficacy and safety of the intramyocardial injection of autologous $CD34^+$ cells in patients with angina refractory to OMT and in patients who are ineligible for revascularization procedures[394]. Moreover, the IMPACT-CABG[395] study was recently initiated and will test the safety and efficacy of intramyocardial injection of autologous $CD133^+$ cells in patients subjected to CABG procedure.

Human adult adipose tissue has high plasticity and contains two cell populations with distinct functionalities, which can contribute to neovascularization in ischemic tissues: endothelial cells and mesenchymal cells derived from adipose tissue[396]. Several clinical studies have been initiated to test the angiogenic potential of mesenchymal cells derived from adipose tissue in patients with chronic ischemic heart disease[397], AMI, and cardiac failure[398]. The conclusion of these important clinical trials will help investigate the possibility of using this abundant cell source for the treatment of patients with heart disease.

Furthermore, one of the most recently investigated cell types for the treatment of patients with ischemic cardiomyopathy was obtained via the identification of resident cardiac stem cells with the potential for myocardial regeneration[399]. Numerous preclinical studies have demonstrated the efficacy of these cells for the treatment of post-AMI LV dysfunction[400,401]. In the SCIPIO study[402], resident cardiac stem cells were obtained from the right atrial appendage during the CABG procedure. After isolation, these cells were expanded and injected via intracoronary infusion approximately 4 months after surgery. The assessment of cardiac function using MRI showed a significant increase in LVEF in the treated group from 27.5% (baseline) to 35.1% and 41.2%, 4 and 12 months after cell infusion, respectively, as well as significant reduction in the infarcted area.

Grade of recommendation: Till date, there is no recommendation for the clinical use of cell therapy, except within the context of experimental clinical research in accordance with current standards.

1.d.2. Cell therapy

Stem-cell therapy is a promising alternative for the treatment of ischemic heart disease but it is still in its infancy and many questions remain unanswered. The cell types most frequently studied for the treatment of myocardial ischemia include hematopoietic stem cells[403-406], progenitor endothelial cells[407-411], mesenchymal stem cells[412-415], and marrow-derived mononuclear cells[416,417].

The potential routes of percutaneous administration are intracoronary, transvenous, and transendocardial. The latter is the preferred route because it allows the direct intramyocardial injection and the delivery of cells to ischemic myocardial areas[389,418]. Intraventricular catheter guided by a three-dimensional electromechanical mapping system is often used, and enables the identification of myocardial areas that are viable, hibernating, and infarcted before each cell injection[419,420].

However, the cell type, injection dose, route of delivery, and the optimal period of administration are issues that still need to be addressed. To better understand these variables and optimize the beneficial effects of these therapies, it is important to monitor the presence and the kinetics of the transplanted cells over time and correlate this information with the evaluation of ventricular structure and function.

Several mechanisms may be responsible for the results observed in patients with refractory angina. Previous studies have suggested that stem cells may have the ability to regenerate the myocardium[403,406]. However, more recent studies have shown that only a few of these cells can differentiate into cardiomyocytes[421,422]. The most widely accepted mechanism is that cell therapy increases angiogenesis and improves blood supply to ischemic regions[423-427]. Previous studies suggest that neovascularization can restore and improve microcirculation and consequently myocardial perfusion, help revascularize the hibernating myocardium, and inhibit cardiomyocyte apoptosis[424-430]. The mechanisms involved in myocardial regeneration and angiogenesis include paracrine effects, which can provide the substrates for the process, e.g., VEGF[431].

Some randomized and nonrandomized studies involving relatively few patients were conducted to evaluate the safety and efficacy of percutaneous administration of cell therapy in patients with refractory angina. Taken together, these results suggest that this approach is safe and can improve symptoms[418,432-435]. At present, another randomized trial involving 400 patients is underway and will help elucidate the role of the percutaneous administration of cell therapy for the treatment of refractory stable angina[394].

Recommendation: percutaneous cell therapy for the treatment of refractory stable angina–Class IIb B

2. Decision-making strategies in the treatment of CAD

CAD may progress silently for a long time without symptoms and is the leading cause of death in most countries, including Brazil. Furthermore, this disease requires an active investigation using diagnostic methods and its incidence depends on people's lifestyle. It is important to know these methods and that many individuals will present with acute cases, particularly in emergencies, with chest symptoms and a high mortality risk. The main prognostic indicators of this disease are the number and location of the arterial stenosis, myocardial area at risk, and LV functional status.

Angina pectoris of recent onset or of difficult control with drug therapy, or that is accompanied by heart failure symptoms, has increased risk of coronary events.

Electrocardiographic signs considered strong indicators of ischemia during stress, including early onset (< 4 min) of ST-segment depression ≥ 0.1 mV or > 0.2 mV at any stage of the test, are indicative of increased risk of the occurrence of events. Moreover, after the test, an ST-segment depression > 5 min accompanied by a decrease in systolic pressure indicates a more severe condition.

During cardiac catheterization, the presence of increased LV end-diastolic pressure and increased ventricular volume, with decreased EF, is a sign of poor prognosis. Conversely, the prognosis is better even considering anginal symptoms as long as the ventricular function is preserved. However, the presence of critical stenosis in one, two, or three vessels, primarily involving LAD, can result in mortality rates of 2%, 8%, and 11%, respectively, after a 5-year follow-up period. Furthermore, critical stenosis located in LMD is associated with a mortality rate of 15% per year.

In summary, considering any degree of coronary obstruction, the mortality rate increases when LV function is impaired, and the prognosis is influenced by the myocardial area at risk.

3. Special situations

3.a. Patients with diabetes

Diabetes mellitus is an increasingly prevalent clinical condition associated with an increased risk of cardiovascular complications, particularly late mortality. Insulin resistance, chronic hyperglycemia, and dyslipidemia predispose to complications, such as endothelial dysfunction, systemic inflammation, and prothrombotic state, which are associated with accelerated atherogenesis, which is present in these patients[436]. Coronary revascularization is an important therapeutic intervention because of its impact on symptoms and prognosis. The effective control of cardiovascular risk factors is the central aspect of treatment, and the decision about when and how to revascularize patients with stable angina should be based on the severity of symptoms, ischemic burden, and coronary anatomy[329].

3.a.1. Indications for CABG

The BARI 2D study[335] compared immediate CABG and adjunct OMT vs. isolated OMT in 2,368 patients with type 2 diabetes mellitus with stable CAD and symptoms of mild to moderate intensity. Patients from the immediate CABG group were referred to surgery (CABG) or PCI, according to the complexity of coronary anatomy. A 5-year follow-up indicated no difference between the two strategies in the survival rates (88.3% vs. 87.8%; p = 0.97) or the survival free from major adverse cerebrovascular and cardiovascular events (MACCE) (77.2% vs. 75.9%; p = 0.70). However, MACCE-free survival in the CABG group (n = 763), which included patients with higher angiographic complexity, was higher in the immediate CABG group (77.6% vs. 69.5%; p = 0.01), and this difference was caused by decreased MI. However, the survival rates were similar between the two groups (86.4% vs. 83.6%; p = 0.33). In the PCI group (n = 1,605), there was no difference in the survival rate (89.2% vs. 89.8%; p = 0.48) or MACCE-free survival (77.0% vs. 78.9%; p = 0.15) between the two strategies.

Patient selection for CABG, which involved patient stratification before randomization, was influenced by angiographic factors including three-vessel disease (OR = 4.43), lesion in the left LAD ≥ 70% (OR = 2.86), lesion in the proximal LAD ≥ 50% (OR = 1.78), total occlusion (OR = 2.35), and multiple type-C lesions (OR = 2.06), all with p < 0.005. The absence of prior PCI (OR = 0.45, p < 0.001) and the availability of DES was associated with decreased probability of choosing CABG (OR = 0.60, p = 0.003)[437].

When evaluating quality of life, immediate percutaneous or surgical CABG was associated with improved performance compared with isolated OMT using scores, such as the Duke Activity Status Index (1.32 points, p < 0.001), RAND Energy (1.36 points, p = 0.02), and Self-Rated Health (1.77 points, p = 0.007), but not the Health Distress score (−0.47, p = 0.46). These treatment effects were maintained at the 4-year follow-up[438].

3.a.2. Comparison of revascularization strategies in patients with diabetes with multivessel CAD

A collaborative analysis of individual data from 7,812 patients from 10 randomized clinical trials compared the efficacy of CABG with PCI in patients with and without diabetes with multivessel CAD. PCI was performed with balloon angioplasty in six studies and with conventional stents in the remaining studies. At a mean follow-up of 5.9 years, the mortality rate of patients treated with CABG was similar to that of patients treated with PCI (15% vs. 16%; HR = 0.91; 95% CI: 0.82–1.02; p = 0.12). However, the mortality rate was lower in the CABG patients than in the PCI patients (HR = 0.70, 95% CI: 0.56–0.87) in the subgroup with diabetes, but was similar among CABG and PCI patients in the nondiabetic subgroup (HR = 0.98, 95% CI: 0.86–1.12, p = 0.014 for the interaction)[340].

Both surgical and percutaneous improvements in the treatment of CAD have made results of previous randomized trials outdated. The SYNTAX study compared CABG with PCI using first-generation paclitaxel-eluting stents in 1,800 patients with complex CAD (three-vessel disease or LMD injury). A prespecified subgroup analysis evaluated results of a 5-year follow-up in patients with and without diabetes. In patients with diabetes (n = 452), the MACE rate (46.5% vs. 29.0%; p < 0.001) and repeat revascularization rate (35.3% vs. 14.6%; p < 0.001) significantly increased in the PCI group. However, there was no difference for the combined outcomes of mortality rate, stroke, and MI (23.9% vs. 19.1%, p = 0.26) or its individual components: mortality rate (19.5% vs. 12.9%; p = 0.065), stroke (3.0% vs. 4.7%; p = 0.34), and MI (9.0% vs. 5.4%, p = 0.20)[439].

FREEDOM[267] was the only study specifically designed to compare contemporary PCI and CABG techniques in patients with diabetes with multivessel disease. Most patients (83%) had three-vessel disease and two-thirds had intermediate or high anatomical complexity of lesions (Syntax score >22). Sirolimus-eluting and paclitaxel-eluting stents were used exclusively in 51% and 43% patients in the PCI group, respectively. In this group, the number of treated lesions was 3.5 ± 1.4 and the total length of stents was 26.1 ± 14.2 mm. In the CABG group, left internal thoracic artery grafts were used in 94.4% of the patients and the number of grafts was 2.9 ± 0.8. The primary outcome at a 5-year follow-up (death from any cause, nonfatal MI, or nonfatal stroke) occurred more frequently in the PCI group (26.6% vs. 18.7%; p = 0.005). The advantage of CABG was attributed to the differences in the rates of MI (13.9% vs 6.0%, p < 0.001) and death from any cause (16.3% vs 10.9%, p = 0.049). Stroke was more frequent in the CABG group (2.4% vs 5.2%, p = 0.03) and most of these events occurred within the first 30 days after randomization. The need for repeated revascularization after 1 year was higher in the PCI group (12.6% vs. 4.8%; RR = 2.74; 95% CI: 1.91–3.89; p < 0.001).

More recently, a meta-analysis of the results of the randomized trials that compared PCI with DES vs. CABG in patients with diabetes with multivessel disease (FREEDOM, SYNTAX, CARDIA, and VA CARDS) evaluated 3052 patients (1,539 in the PCI arm and 1,513 in the CABG arm). At a mean follow-up of 4 years, the primary outcome of death, nonfatal MI, or stroke occurred in the PCI arm in 22.5% patients and in the CABG arm in 16.8% patients (RR = 1.34, 95% CI: 1.16–1.54, p < 0.0001). Similar results were obtained for the mortality rate (14% vs. 9.7%; RR = 1.51; 95% CI: 1.09–2.10; p = 0.01), MI (10.3% vs. 5.9%; RR = 1.44; 95% CI: 0.79–2.6; p = 0.23), and need for repeated revascularization (17.4% vs. 8.0%; RR = 1.85; 95% CI: 1.0–3.40; p = 0.05). The risk of stroke was significantly lower with DES (2.3% vs. 3.8%; RR = 0.59; 95% CI: 0.39–0.90; p = 0.01). The sensitivity analysis showed that the superiority of CABG was more evident in the group with high Syntax score (> 33), whereas no significant difference was observed in the groups with low or intermediate score[440].

3.a.3. PCI in patients with diabetes

DES in patients with diabetes is recommended to decrease restenosis and the need for new TVR[441]. No consistent data are available to support the use of one type of DES over another in patients with diabetes. However, in anatomical conditions associated with increased probability of restenosis, including extensive lesions and/or small-diameter vessels, the selection of second-generation DES with increased capacity of inhibition of intimal hyperplasia is recommended.

The dual antiplatelet therapy with aspirin and P2Y12 receptor blocker is an integral component of periprocedural and postprocedural drug regimens. Potential PCI patients should be evaluated before the intervention to determine the risk of bleeding, and they should be guided about the importance of properly using dual antiplatelet therapy. Patients who receive DES should use it for 12 months and those who receive NDES should use it for 1 month[442].

Aspirin and clopidogrel is the combination of oral antiplatelet agents most commonly used in dual antiplatelet therapy in the medical field because of its effectiveness for most patients, low cost, and wide availability. Prasugrel[443] and ticagrelor[444] have yielded increased levels of platelet inhibition, faster onset of action, and decreased ischemic events compared with clopidogrel. However, they are associated with increased risk of bleeding, are more costly, and are approved for use only in patients with acute coronary syndrome.

3.b. Cerebrovascular disease: systematic evaluation of the carotids

Over the past 40 years, the official data for mortality rate in Brazil indicate that cerebrovascular disease is responsible for more deaths than heart disease, a fact that distinguishes Brazil from other countries of the western hemisphere. Data from the Ministry of Health indicate that cerebrovascular disease is the leading cause of death in Brazil and stroke is the leading cause of temporary or permanent neurological disability in adults > 50 years (Table 1).

The data presented herein indicate that, despite the slow decrease in the mortality rate from cerebrovascular disease in

Table 1 – Mortality in men and women due to cardiovascular causes

	Men n (%)	Women n (%)	Total n (%)
Cerebrovascular	126,773 (27%)	119,549 (25.5%)	246,322 (52.5%)
Coronary	128,750 (27.4%)	94,102 (20.1%)	222,852 (47.5%)
Total	255,523 (54.5%)	213,651 (45.5%)	469,174 (100.0%)

Brazil, the magnitude of the disease is of great importance, especially considering other consequences of the disease, including disability, with a high social cost.

Depending on the brain hemisphere affected by stroke, different outcomes are observed. Left-sided occlusions cause aphasia (inability to express or understand speech), alexia (inability to read), agraphia (inability to write), and acalculia (inability to calculate). Right-sided occlusions cause neglect (nonrecognition) of the left side of the body and loss of speech prosody. Apraxia (difficulty in performing previously learned motor tasks, e.g., combing your hair or changing clothes) can occur after lesions in both hemispheres, but mostly on the left. Considering that apraxia is often associated with aphasia, it may be difficult to recognize apraxia in practice.

All patients should be tested for systemic diseases often associated with stroke. The recommended tests include complete blood count, erythrocyte sedimentation rate (ESR), blood glucose, creatinine, homocysteine, fibrinogen, sodium, and coagulogram (PT, APTT, and bleeding time). In patients with risk behavior, VDRL (syphilis) and HIV tests should be performed, considering that these diseases can cause cerebrovascular disease.

When the mechanism of infarction cannot be explained by the history of risk factors presented by the patient and by routine examinations, some special tests should be requested in specialized laboratories, including lupus anticoagulant, antiphospholipid antibodies, D-dimer, protein C, protein S, factor V Leiden, resistance to activated protein C, and antithrombin III. These tests should be performed ideally 2–3 weeks after the acute phase of MI.

A cranial CT scan should be obtained as soon as possible in all patients with stroke to differentiate between infarction and hemorrhage, considering that the clinical distinction of these complications is difficult.

Ischemic strokes appear as hypodense areas (darker on CT) whereas hemorrhagic stroke areas appear as hyperdense areas (clear on CT). However, although CT is always abnormal in hemorrhage cases, it may be normal in the first 24 h of onset of MI. Therefore, we must interpret these findings according to the time of progression of symptoms. When CT is normal, it should be repeated after 24–48 h to confirm infarction. Posterior circulation infarctions (in the brain stem and cerebellum) may be difficult to visualize on CT.

In patients with intracerebral hemorrhage, a hyperdense area surrounded by edema can be observed on CT.

CMR of the skull must be requested when CT is normal, and an early diagnosis is necessary. Diffusion-weighted imaging (DWI) allows a rapid diagnosis (in minutes) and the visualization of hyperdense areas. Other advantages of MRI compared with CT are the ability to detect small lesions, particularly in the posterior fossa, and to differentiate recent from old injuries more easily. Furthermore, MRI does not emit ionizing radiation, and is the examination of choice for the diagnosis of cavernous angioma (cavernomas).

The main disadvantages of MRI are its high cost, lack of availability in many centers in rural regions of Brazil, and the need for complete immobilization. Patients with metal clips for aneurysms or cardiac pacemakers cannot undergo MRI owing to the risk of displacement of these devices by the magnetic field. MR angiography allows the visualization of major brain arteries and may help locate a thrombus or embolus occluding a vessel, as well as the detection of asymptomatic aneurysms.

Despite the recent emergence of MR angiography and CT, conventional angiography, also known as cerebral angiography, remains the diagnostic imaging method of choice for the detection of ruptured aneurysms in patients with meningeal hemorrhage. It should be performed early, preferably on the first day of bleeding, so that the aneurysm can be clamped early. When the first angiography is normal, a second and even a third test should be performed several weeks later with the aim of detecting a possible aneurysm not observed during the first test.

Doppler of the carotid and vertebral arteries should be performed in all patients suspected of atheroma in these arteries as possible sources of cerebral embolism. Transcranial Doppler is a method used for the evaluation of intracranial blood flow. It is an important complementary method for the evaluation of intracranial hemodynamics in cases of cerebrovascular diseases.

The cardiac evaluation using ECG and echocardiography should be considered in patients with suspected embolic sources in the heart or aortic arch. ECG can identify atrial fibrillation as an embolic source or a sequel to infarction of the LV anterior wall. In contrast, echocardiography is essential to discard the possibility of intracardiac thrombus as a potential source of emboli. Transesophageal echocardiography is more sensitive for the visualization of thrombi, especially atrial thrombi.

Vascular imaging should be performed rapidly so that patients with significant arterial stenosis can be properly diagnosed and potentially benefit from a surgical treatment via endarterectomy or angioplasty. Color duplex ultrasonography, CCTA, magnetic resonance angiography, and intra-arterial angiography are generally available in tertiary care hospitals. These tests are low risk, with the exception of intra-arterial angiography, which can precipitate stroke in approximately 1%–3% patients with symptomatic carotid artery disease.

Patients with transient ischemic attack (TIA) need a rapid clinical diagnosis because approximately 10% of these patients

may suffer a stroke within the first 48 h of onset. In addition, the patients with nondisabling stroke and rapid spontaneous clinical recovery are at high risk of recurrent stroke.

Recommendations

Class I

1. Noninvasive imaging tests are recommended for the detection of Extracranial Carotid and Vertebral Artery Disease (ECVD) in patients with symptoms suggestive of neurological impairment of ischemic origin. Level of Evidence C.
2. Color Duplex ultrasonography is the recommended initial examination to detect vascular stenosis when ECVD is suspected. Level of Evidence C.
3. When the overall initial data collected is necessary or focal ischemic neurological signs suggestive of involvement of the carotid and/or vertebral arteries occur, the performance of magnetic resonance angiography or CT angiography is recommended for better diagnosis of arterial stenosis. Level of Evidence C.

Class IIa

In candidates for revascularization in the presence of ECVAD (extracranial carotid and vertebral artery disease), catheter-based angiography may be useful when noninvasive imaging studies are not sufficient for assessment. **Level of Evidence C**.

Stroke is a major cause of morbidity and mortality worldwide. Large differences between countries in incidence, prevalence and mortality have been attributed to changes in risk factors, uncontrolled hypertension, and other risk factors, resulting in more frequent and/or severe strokes in some countries. Stroke is the leading cause of morbidity and disability in the developed world. It is the second leading cause of dementia, the most common cause of epilepsy in the elderly, and a common cause of depression.

It is recommended that all patients with stroke be treated in a unit specialized in treating this type of patient. **Class I, Level of Evidence A**

3.c. Peripheral artery disease

The association of CAD with peripheral artery disease, even in asymptomatic patients, leads to poor prognosis in the postoperative period following CABG, probably because of high atherosclerotic load. Concomitant CAD with extracardiac multivessel involvement has been the focus of attention in recent years due to the significant improvement in the technical aspects of CABG, especially when considering older patients.

In the 1990s, several studies showed peripheral artery disease to be an independent predictor of increased perioperative morbidity and mortality in patients with chronic CAD who underwent CABG. In these patients, hospital mortality was 2.4–3.6 times greater than that of patients in other age groups[445,446].

In the risk score[447], extensive calcification in the ascending aorta and PVI were included among the top 10 independent predictors of poor prognosis in the early and late postoperative periods for patients undergoing CABG. For calcification in the ascending aorta, OR was 2.09 (95% HF = 1.5–2.90; p = 0.0001) and for PVI, OR was 1.75 (95% HF = 1.35–2.28; p = 0.0001).

A study by O'Rourke et al.[448] analyzed data from hospitals in northeast New England, in the United States, including a total of 1,305 CAD patients undergoing multivascular CABG. In the postoperative period, the authors found 2.4 times higher mortality among patients with PVI. Atherothrombosis was indicated as the greatest cause of postoperative complications, in the form of death, stroke, cognitive dysfunction, and multiple organ failure. After 5 years, disease progression was unfavorable in this group of patients; mortality doubled, after adjustments for age and comorbidities in patients with PVI. Furthermore, evolution was more favorable in patients undergoing CABG than in those who underwent percutaneous intervention.

3.d. Patients with previous revascularization

Depending on clinical symptomatology, functional assessment, and anatomical complexity, stable anginal CAD may be best treated by medication, coronary revascularization through angioplasty, or surgery. The main indications for revascularization are the persistence of symptoms, despite OMT and/or prognosis. In recent decades, we have witnessed a breakthrough in all modes of treatment, which has diminished the value of former studies to mere historical value.

There are many well-known adverse effects when ischemia is demonstrated (death, MI, acute coronary syndrome, recurring angina). Although symptomatic patients with no or little evidence of ischemia gain little benefit from revascularization, asymptomatic patients with ischemia clearly benefit from the procedure[317,449].

In patients with recurrent angina after a previous surgery, repeat revascularization will have the greatest impact on the survival of high-risk patients, such as obstruction in LAD and extensive anterior ischemia[450-454]. Patients with ischemia in other areas, such as the internal mammary artery patent to LAD, probably will not gain increased survival by repeating revascularization[455].

Cohort studies comparing angioplasty and surgery among patients with prior surgical revascularization report similar survival rates in the intermediate and long term after the two procedures. Patients who previously underwent surgery and were recommended for new revascularization for ischemia refractive to drug treatment should exhibit factors supporting the new surgical intervention: inability to perform angioplasty in the affected vessel, number of compromised grafts, possibility of using the internal mammary artery, chronically occluded coronary artery, and good distal bed in the native vessel to receive a graft. Among the factors that favor angioplasty over surgery, we highlight the following: limited area of ischemia that causes significant symptoms, a vessel in which it is possible to carry out the intervention, patent internal mammary artery (patent graft), and the patient's comorbidities.

Guidelines

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