

What has changed in the management of chronic ischaemic heart disease? The new European Society of Cardiology Guidelines 2024

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KEYWORDS

Guideline;
Chronic coronary syndrome;
revascularization;
angina and/or ischaemia in
the absence of obstructive
coronary artery disease
(ANOCA/INOCA)

The 2024 ESC Guidelines for the management of chronic coronary syndromes expand the concept of CCS (chronic coronary syndrome), adopting a broader vision that includes structural and functional alterations throughout the coronary tree. A significant update concerns the stratification of coronary artery disease risk, with a central role played by the integration of cardiovascular risk factors. In the choice of diagnostic test, coronary computed axial tomography remains the ‘gatekeeper’ to exclude the disease in low-risk patients. Non-invasive functional tests are preferred in intermediate-high-risk patients, while coronary angiography is recommended for high-risk patients. There is renewed interest in angina and/or ischaemia in the absence of obstructive coronary artery disease (ANOCA/INOCA) patients, in whom the persistence of symptoms requires a complete invasive functional assessment to identify the specific endotype and personalize treatment. The therapeutic approach is characterized by a holistic vision of the patient. The role of aspirin in primary prevention is emphasized. In secondary prevention, revascularization remains essential, especially in patients with ejection fraction > 35% and high anatomical or ischaemic risk. Bypass is preferred in diabetics and patients with complex coronary anatomy, while percutaneous coronary intervention represents a valid alternative, supported by the aid of intracoronary imaging. Increased use of colchicine and semaglutide is recommended.

Introduction

Ischaemic heart disease is among the main causes of mortality and morbidity in the world, and the management of its various manifestations continues to represent an important focus of scientific research.¹

In recent decades, the paradigm of obstructive epicardial coronary artery disease as a cause of myocardial ischaemia has been integrated with scientific evidence that supports the existence of a more complex scenario in which, in addition to organic alterations, mainly on an

atherosclerotic basis, also functional ones involving the epicardial district and/or the microcirculation, play a significant role as determinants of cardiac ischaemia even in the absence of obstructive coronary artery disease.²

Already in 2019, the guidelines of the European Society of Cardiology (ESC) replaced the term ‘stable angina’ with that of ‘chronic coronary syndrome’, to underline the progressive nature of pathology with a heterogeneous spectrum of clinical manifestations.³

The new 2024 ESC guidelines for the diagnosis and treatment of chronic coronary syndrome (CCS) reflect this paradigm shift and address the management of patients with CCS in the context of the different clinical manifestations of coronary artery disease, which

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includes disease of the epicardial vessels, medium-sized vessels, and microcirculation, including both anatomical alterations and functional disorders.⁴ To this end, the indications previously covered by two different ESC guidelines are unified and updated: those of 2019 for the diagnosis and treatment of CCS and those of 2018 on myocardial revascularization.

Furthermore, the stratification of the risk of coronary artery disease is revisited and a new 'risk map' is developed aimed at choosing the most appropriate second-level diagnostic test.

During diagnostic coronary angiography, a complete angiographic examination is recommended that systematically includes the functional study of intermediate epicardial stenoses, in order to guide any revascularization intervention and the characterization of the specific endotype responsible for the clinical phenotype of the disease.

Finally, the new ESC guidelines of 2024 address the therapeutic strategies for the management of patients with CCS using a 'personalized medicine' approach, based on the setting of a therapy aimed at the precise physiopathological mechanism underlying the clinical manifestations of coronary artery disease.

Stratification of the probability of obstructive coronary artery disease

A novel element of the latest guidelines on the diagnosis and treatment of CCS is represented by the use of a diagnostic work-up that includes the estimation of the probability of the risk of obstructive coronary artery disease based on the integration of the clinical evaluation and the presence of cardiovascular risk factors. Following this evaluation, the most accurate diagnostic test for the estimated pre-test probability is performed.⁴

In the past, systems for estimating the risk of obstructive coronary artery disease based on the Diamond-Forrester approach have been used, which integrated the variables of sex, age, and characteristics of the angina symptom in a model based on autopsy data of prevalence of atherosclerotic coronary artery disease in the subject with the clinical profile of the patient examined.⁵

However, the use of highly effective pharmacological therapies and cardiovascular prevention programmes has led to a significant reduction in the prevalence of obstructive coronary artery disease in Western countries in recent decades, making old risk estimation models inaccurate, especially in the low-risk group of patients where the probability of obstructive coronary artery disease was frequently overestimated.⁶ The new ESC guidelines therefore propose the incorporation of cardiovascular risk factors (smoking habits, arterial hypertension, diabetes, obesity, and family history of cardiovascular disease) in the assessment of the patient's pre-test probability, providing a model that allows the risk to be stratified into very low ($\leq 5\%$), low (5-15%), moderate (15-50%), high (50-85%), and very high ($>85\%$) (Figure 1). The advantage of this approach, especially if integrated with the calculation of the 'calcium score' (CS), lies in its accuracy up to three times higher than previous systems in reclassifying patients with 'low' risk to 'very low', with a potentially significant saving of resources and reduction in the rate of inappropriate coronary angiography.⁴

It should be remembered, however, that the model proposed by the ESC 2024 guidelines does not include some risk factors or comorbidities that are associated with an increased probability of developing coronary artery disease, such as familial hypercholesterolaemia, renal failure, systemic inflammatory diseases, or lower limb arterial disease, which must nevertheless be considered.⁴ Furthermore, it is necessary to weigh the risk of obstructive coronary disease estimated by the results obtained from the clinical examination and any instrumental tests, such as the electrocardiogram and echocardiogram.⁴ A further limitation of the proposed approach is that it does not allow for stratification of the risk of coronary artery disease linked to functional pathology of the epicardial vessels or the microcirculation. For this group of individuals, a careful anamnesis and the clinician's experience remain the main tools available before invasive angiographic examination.

Selecting the most appropriate diagnostic test

Once the pre-test probability of coronary artery disease has been estimated, the guidelines provide recommendations on the choice of the most accurate diagnostic test to which the patient should be directed to confirm or exclude the presence of obstructive coronary artery disease. An important innovation in this field lies in the indications provided for patients with low risk (between 5% and 15%). In this group of individuals, the use of coronary computed axial tomography (CT) with CS calculation is recommended, as previous studies have documented that a CS of 0 allows to exclude the presence of obstructive epicardial disease with a high level of accuracy (negative predictive value of 95%) and to reclassify these patients from low to 'very low' risk, so it is not necessary to continue with the execution of second-level diagnostic tests but only with the control of cardiovascular risk factors without a significant increase in future events.^{4,7} In patients with moderate risk (between 15% and 50%), the probability of obstructive coronary disease justifies the execution of a second-level test, which can be, at the choice of the clinician and based on the availability of the centre, an anatomical test (coronary CT) or an imaging stress test (stress echocardiogram, stress magnetic resonance imaging, or stress scintigraphy). Since in these subjects, the prevalence of significant epicardial disease is around 20%, and considering the intermediate predictive value of both types of method in this prevalence range, it is also permitted, for example, if the coronary CT reveals the presence of an intermediate stenosis' a step-wise use of an anatomical test followed by a functional test (or vice versa) to accurately establish whether coronary artery disease is functionally significant, i.e. whether it causes myocardial ischaemia.⁴

In contrast, in subjects with high risk (between 50% and 85%), it is recommended in Class I to perform an imaging stress test because the high positive predictive value of these tests allows identifying with a good degree of accuracy patients with possible obstructive coronary artery disease to be referred to coronary angiography, as well as to stratify the risk of future cardiovascular

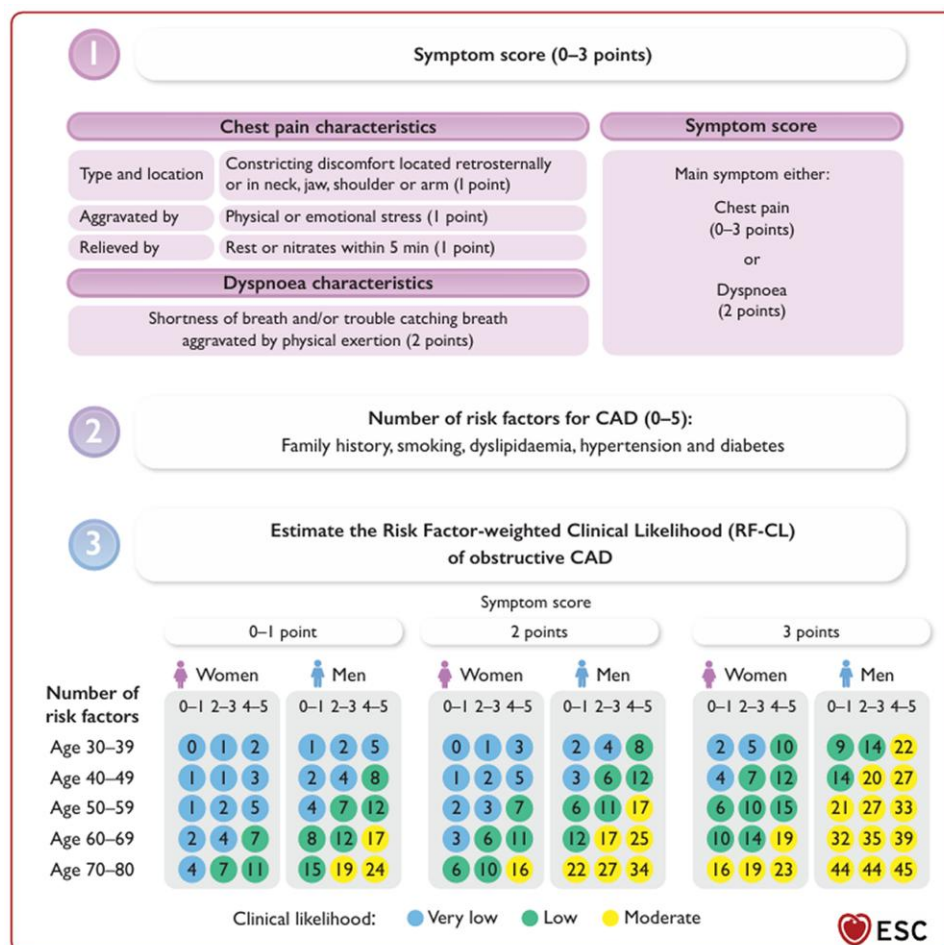


Figure 1 Probability stratification for obstructive coronary artery disease

events based on the degree of ischaemia inducible during stress.⁴ In this context, it is worth remembering the recent evidence emerging from studies with stress echocardiography that have documented the independent prognostic role of reduced coronary reserve values as a predictor of future cardiovascular events.⁸ Therefore, the new guidelines recommend in Class IIb to perform the study of coronary reserve if the stress echocardiogram is the selected ischaemia test.⁴

Finally, in patients with very high risk (>85%), or with refractory angina symptoms despite optimized medical therapy, an invasive angiographic examination is recommended, in light of the high probability of obstructive coronary artery disease. It is essential to reiterate that angiography should very often be accompanied by a functional assessment. In this context, the use of techniques such as fractional flow reserve and instantaneous wave-free ratio for the haemodynamic characterization of epicardial stenoses remains recommended in Class IA. In patients without haemodynamically significant stenosis, the new guidelines introduce and strengthen the concept of angina and/or ischaemia in the absence of obstructive coronary artery disease (ANOCA/INOCA): in this subgroup of patients, for the first time, the functional study of the microcirculation and epicardial vessels is recommended with Class I, level of evidence B. This recommendation is

supported by some trials and observational studies that have shown how the optimization of medical therapy guided by the results of invasive functional studies offers significant benefits both in terms of prognosis and symptoms in this specific population.⁹

Treatment of CCS

Important innovations have also been presented in the field of treatment of CCS. By renewing the two fundamental objectives of treatment (improving the prognosis and quality of life of patients), the new guidelines emphasize the importance of a patient-centred approach, which is not limited to considering only clinical aspects, but also includes psychological, social, and cultural dimensions. Patient education plays a crucial role: understanding the nature of the disease, the importance of risk factor modification, and the positive role of a healthy lifestyle are key elements for effective management, supported by a multidisciplinary team that promotes integrated and shared treatment.

The treatment of CCS is based on four main pillars: lifestyle modifications, antianginal therapy to relieve symptoms, drugs aimed at preventing cardiovascular events, and myocardial revascularization. Lifestyle

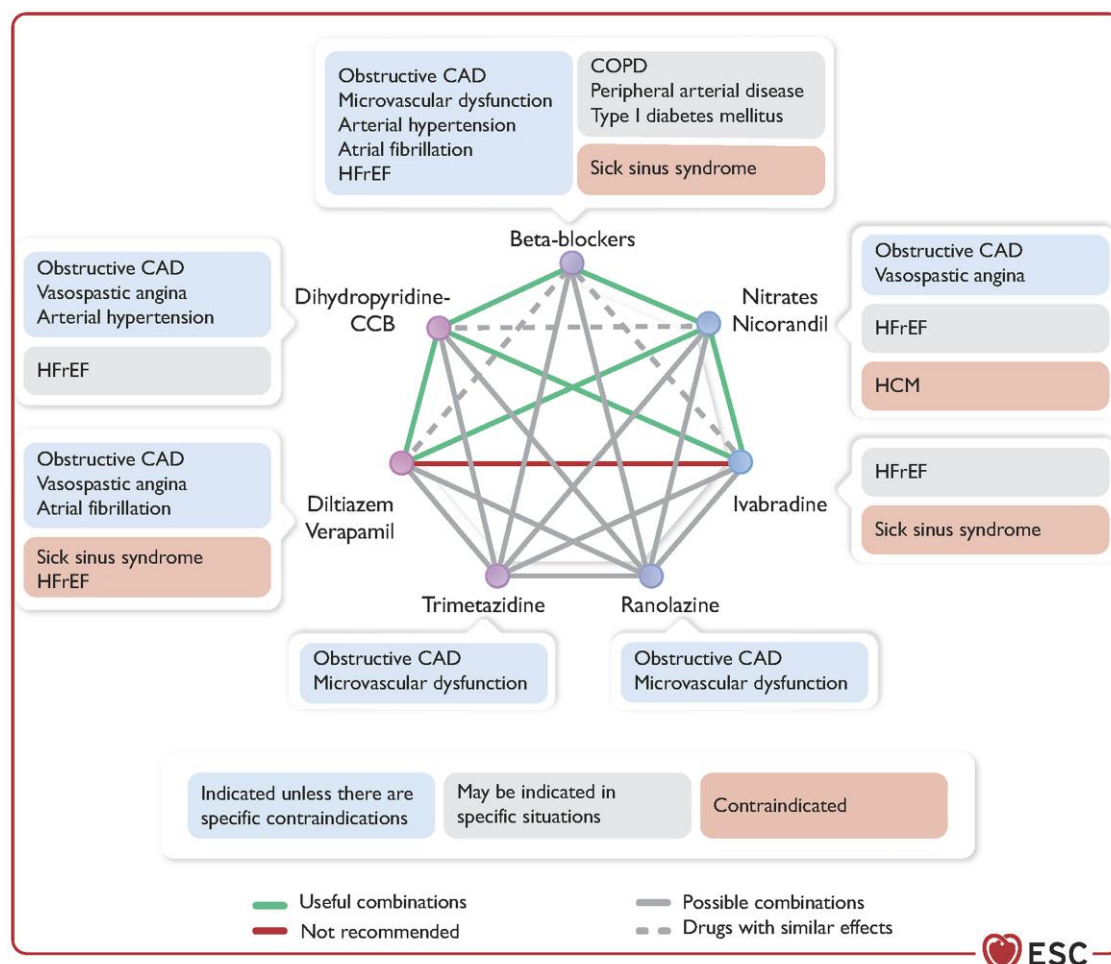


Figure 2 Antianginal therapy in chronic coronary syndromes. HFrEF, heart failure reduced ejection fraction.

modifications remain essential to slow the progression of atherosclerosis and prevent cardiovascular events. The Mediterranean diet, regular physical activity, and smoking cessation (including e-cigarettes) are confirmed as effective measures to reduce cardiovascular mortality. Furthermore, controlling blood pressure, blood glucose in diabetic patients, and LDL cholesterol levels remain fundamental objectives. For patients at high cardiovascular risk, the guidelines set a target for LDL cholesterol of <55 mg/dL, to be achieved with high-intensity statins and, if necessary, lipid-lowering drugs such as PCSK9 inhibitors. The management of angina involves the use of six categories of drugs: beta-blockers, non-dihydropyridine calcium inhibitors, dihydropyridine calcium inhibitors, nitrates/nicorandil, trimetazidine, ranolazine, and ivabradine. For the first time, the guidelines do not identify a first and a second line of antianginal drugs but propose a 'diamond' approach by putting all antianginal drugs on the same level and recommending the choice based on the mechanism of ischaemia and comorbidities, as previously proposed¹⁰ (Figure 2).

Prevention of cardiovascular events through the use of drugs has seen important updates. In primary prevention, aspirin has acquired a Class IB recommendation in

patients with evidence of coronary artery disease, but without a history of myocardial infarction or revascularization. Furthermore, clopidogrel has been indicated, for the first time, as a valid alternative to aspirin in patients who are intolerant or have possible side effects (Class IA).⁴ In secondary prevention, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel remains the standard for post-percutaneous coronary intervention (PCI) patients for at least 6 months. However, in patients at high bleeding risk and low ischaemic risk, a reduction of DAPT to 1-3 months is recommended, followed by monotherapy with a single antiplatelet (Class IA). Recent studies support this strategy, demonstrating that personalized treatment can reduce bleeding risk without reducing the benefit in terms of future cardiovascular events.¹¹

In parallel, drugs such as colchicine and semaglutide have acquired an increasingly important role. Colchicine, at a daily dose of 0.5 mg, has been shown to reduce major cardiovascular events in patients with stable atherosclerotic disease,¹² earning a Class IIa recommendation (level of evidence A). Semaglutide, on the other hand, is effective in reducing cardiovascular events¹³ in non-diabetic, obese, or overweight patients, earning a Class IIa recommendation (level of evidence B).

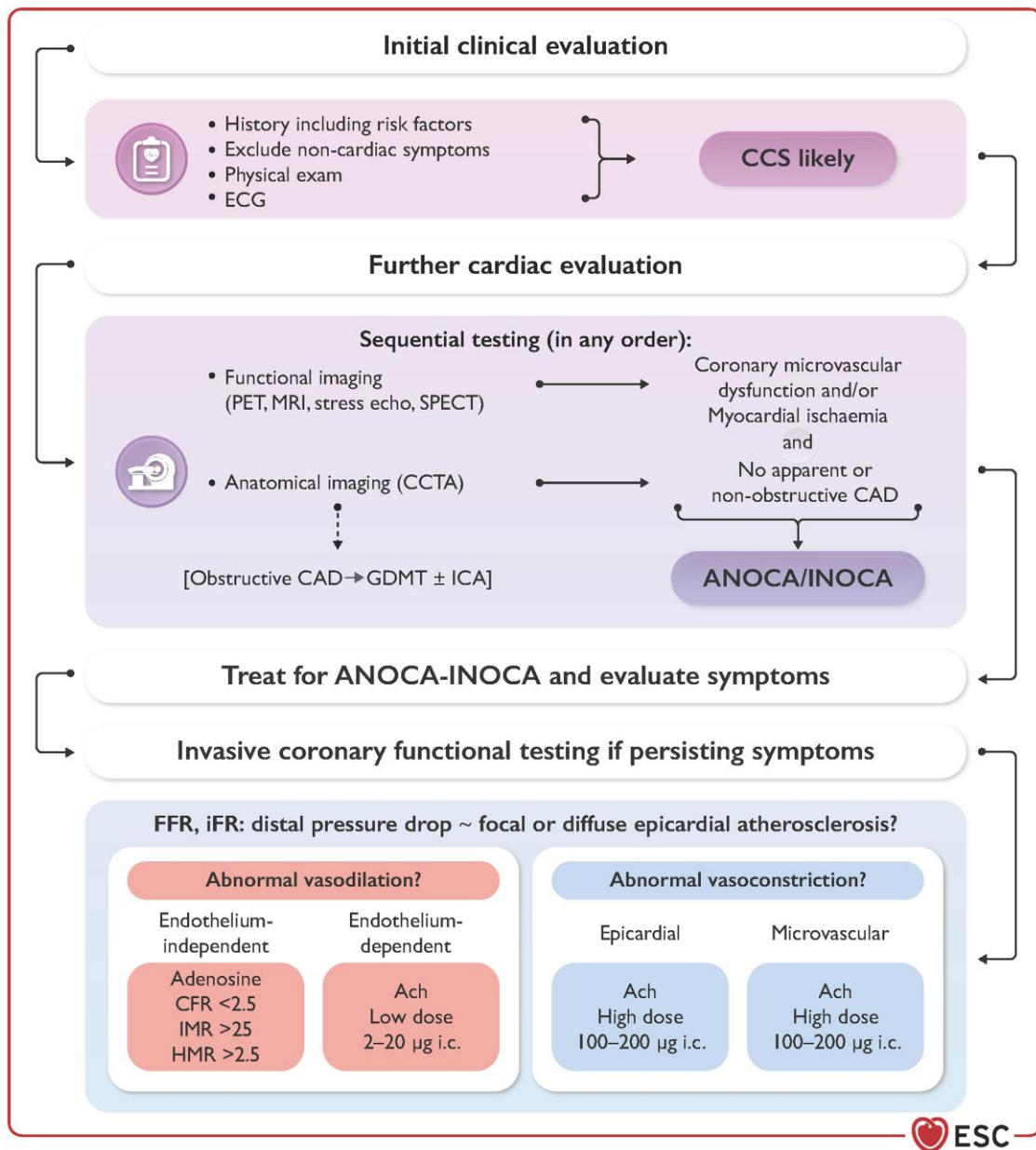


Figure 3 Diagnostic-therapeutic algorithm in ANOCA/INOCA patients (angina/ischæmia in the absence of obstructive coronary artery disease).

Indications for myocardial revascularization

Myocardial revascularization has a proven crucial role in the management of CCS. The new guidelines renew the prognostic indications, recommending invasive treatment for patients with ejection fraction (EF) > 35%, in the presence of high-risk coronary artery disease and/or evidence of extensive myocardial ischaemia (>10% left ventricular ischaemia).

In particular, revascularization is indicated in the following cases:

- significant stenosis ($\geq 50\%$) of the left main (Class IA)
- multi-vessel disease with stenosis $\geq 70\%$ (Class IA)
- single- or two-vessel disease involving the proximal segment of the anterior descending artery (Class IB).

In these circumstances, revascularization has been shown to reduce the risk of spontaneous infarction and cardiovascular mortality, with a consequent improvement in long-term prognosis.¹⁴ In patients with reduced EF (<35%), however, the available data are less robust. The therapeutic decision should therefore be made by a multidisciplinary team, considering the patient's comorbidities and individual preferences (Class IC).

With regard to the type of revascularization to be used, coronary artery bypass grafting (CABG) is generally preferred, especially in diabetic patients, with high anatomical complexity, reduced EF, and low surgical risk. In cases of left main stenosis with complex coronary anatomy (SYNTAX > 22), CABG is the

recommended therapeutic choice, while PCI is considered equivalent in cases with less complex anatomy (SYNTAX < 22, Class IA).

Although the ORBITA II study¹⁵ has shown that myocardial revascularization can be effective even in symptomatic patients not treated with antianginal drugs, the guidelines suggest favouring revascularization only when pharmacological therapy is ineffective (Class IA).

A further innovation introduced by the guidelines is the adoption of intracoronary imaging techniques, such as intravascular ultrasonography and optical coherence tomography, which allow guiding PCI in highly complex situations, such as the treatment of the left main, coronary bifurcations, or long lesions.⁴

The patient with ANOCA/INOCA as mentioned in the previous paragraphs, the new CCS 2024 guidelines place greater attention, both in the diagnostic and therapeutic phase, on the subgroup of patients who do not present obstructive epicardial disease. In particular, they introduce the concept of INOCA/ANOCA by focusing on the patient's symptoms rather than on the sole evidence of ischaemia. For the first time, in patients with non-obstructive coronary artery disease who are persistently symptomatic despite optimal medical therapy, a complete invasive functional study is recommended to characterize the pathophysiological mechanism and define the endotype (Recommendation 1B). Reduced coronary reserve (coronary flow reserve < 2.5, with thermodilution or Doppler methods) can be caused by (i) reduced metabolic dilation of the microcirculation in response to increased myocardial oxygen consumption [in this case microvascular resistance during adenosine testing is elevated [index of microcirculatory resistance (IMR) > 25 with thermodilution or hyperemic microvascular resistance (hMR) > 2.5 with Doppler]]; (ii) high myocardial flow at rest probably caused by reduced metabolic oxygen utilization (in this case, IMR and hMR are normal). In addition to the two aforementioned endotypes, INOCA/ANOCA can be caused by two other endotypes: epicardial spasm or microvascular spasm, the diagnosis of which is based on the acetylcholine test (Figure 3).

Conclusions

In conclusion, the ESC 2024 guidelines for the diagnosis and treatment of CCS offer a holistic and personalized approach in the management of patients with CCS, revisiting the risk stratification of probability of coronary artery disease, underlining the importance of a complete angiographic study and a personalized medicine approach aimed at setting up a specific pharmacological therapy for the precise pathophysiological mechanism of the disease.

Funding

No funding provided.

Conflict of interest: none declared.

Data availability

No new data were generated or analysed in support of this research.

Disclaimer

This paper was originally published in the Italian language as 'Cosa è cambiato nella gestione della cardiopatia ischemica cronica? Le nuove Linee Guida ESC 2024', in the Volume degli Atti del Congresso "Conoscere e Cuare il Cuore 2025", published by Centro per la Lotta contro l'Infarto for distribution at the CCC Conference. This paper was translated by Dr. Mario Albertucci, representative of the CLI Foundation, and republished with permission.

References

1. Timmis A, Vardas P, Townsend N, Torbica A, Katus H, De Smedt D *et al.* European Society of Cardiology: cardiovascular disease statistics 2021: executive summary. *Eur Heart J Qual Care Clin Outcomes* 2022;**8**:377-382.
2. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV *et al.* Low diagnostic yield of elective coronary angiography. *N Engl J Med* 2010;**362**:886-895.
3. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U *et al.* 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87-165.
4. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J *et al.* 2024 ESC guidelines for the management of chronic coronary syndromes. *Eur Heart J* 2024;**45**:3415-3537.
5. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med* 1979;**300**:1350-1358.
6. Jarez-Orozco LE, Saraste A, Capodanno D, Prescott E, Ballo H, Bax JJ *et al.* Impact of a decreasing pre-test probability on the performance of diagnostic tests for coronary artery disease. *Eur Heart J Cardiovasc Imaging* 2019;**20**:1198-1207.
7. Agha AM, Pacor J, Grandhi GR, Mszar R, Khan SU, Parikh R *et al.* The prognostic value of CAC zero among individuals presenting with chest pain: a meta-analysis. *JACC Cardiovasc Imaging* 2022;**15**:1745-1757.
8. Ciampi Q, Zagatina A, Cortigiani L, Gaibazzi N, Borguezan Daros C, Zhuravskaya N *et al.* Functional, anatomical, and prognostic correlates of coronary flow velocity reserve during stress echocardiography. *J Am Coll Cardiol* 2019;**74**:2278-2291.
9. Ford T, Stanley B, Sidik N, Good R, Rocchiccioli P, McEntegart M *et al.* 1-year outcomes of angina management guided by invasive coronary function testing (CorMicA). *JACC Cardiovasc Interv* 2020;**13**:33-45.
10. Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP *et al.* Expert consensus document: a 'diamond' approach to personalized treatment of angina. *Nat Rev Cardiol* 2018;**15**:120-132.
11. Costa F, Montalto C, Branca M, Hong SJ, Watanabe H, Franzone A *et al.* Dual antiplatelet therapy duration after percutaneous coronary intervention in high bleeding risk: a meta-analysis of randomized trials. *Eur Heart J* 2023;**44**:954-968.
12. Andreis A, Imazio M, Piroli F, Avondo S, Casula M, Paneva E *et al.* Efficacy and safety of colchicine for the prevention of major cardiovascular and cerebrovascular events in patients with coronary artery disease: a systematic review and meta-analysis on 12 869 patients. *Eur J Prev Cardiol* 2022;**28**:1916-1925.
13. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S *et al.* Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;**389**:2221-2232.
14. Navarese EP, Lansky AJ, Kereiakes DJ, Kubica J, Gurbel PA, Gorog DA *et al.* Cardiac mortality in patients randomised to elective coronary revascularisation plus medical therapy or medical therapy alone: a systematic review and meta-analysis. *Eur Heart J* 2021;**42**:4638-4651.
15. Rajkumar CA, Foley MJ, Ahmed-Jushuf F, Nowbar AN, Simader FA, Davies JR *et al.* A placebo-controlled trial of percutaneous coronary intervention for stable angina. *N Engl J Med* 2023;**389**:2319-2330.