"Robust evidence can be summarized in easy-to-follow directions to manage an individual with a given clinical condition in the best possible way.

A critical appraisal of the new chronic coronary syndromes guidelines from the European Society of Cardiology

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In 2019, the European Society of Cardiology released five new guidelines, including a new guideline on the diagnosis and management of patients with stable coronary artery disease (CAD), which by the way, got a new terminology. In this article, I will not only comment on the strengths of the document highlighting the new/revised concepts, but also humbly point out a few areas that will deserve a careful review in the next guideline focusing on those topics that have seen the most significant number of changes, namely the diagnosis and the medical treatment of patients with CAD.

First things first: what's in a title?

The first thing to be noted is that a new terminology was adopted to refer to stable angina or chronic coronary artery disease. Look carefully, and you will now read "2019 ESC guidelines for the diagnosis and management of **chronic coronary syndromes**"[1] as opposed to the previous "2013 ESC guidelines on the management of **stable coronary artery disease**."[2] With the new terminology, the authors of the guideline correctly acknowledge the dynamic nature of the CAD process, in which even after long periods of apparent stability, a plaque may rupture or erode, leading to an acute atherothrombotic event.[3] Therefore, they considered that the usually long natural history of a patient with CAD would be best categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS).

After being used for so long in the medical literature, it seemed that an embedded link was created between the term "coronary artery disease" and "atherosclerotic plaque," thus excluding nonobstructive CAD as a cause for angina or myocardial ischemia.[4] By adopting the term "syndrome," the authors made a statement about the multifactorial origin of angina or myocardial ischemia beyond the simplified (and wrong!) view focusing only on finding a coronary obstruction.

As we are now dealing with a "syndrome," six different clinical scenarios were presented within the framework of patients with suspected or confirmed CCS, each one deserving its section on diagnosis and treatment. In an attempt to easily direct the reader, the subsets of patients as proposed by the new guidelines are as follows:

1. Patients with suspected CAD and "stable" anginal symptoms or dyspnea (which appears for the first time as a symptom possibly related to CAD – we'll talk about this in the next section).

2. Patients with new-onset heart failure (HF) or left ventricular (LV) dysfunction and suspected CAD.

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3. Asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS or patients with a recent revascularization.
4. Asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization.
5. Patients with angina and suspected vasospastic or microvascular disease.
6. Asymptomatic subjects in whom CAD was detected at screening.

In patients with a recent (<1 year) diagnosis of CCS or revascularization, for instance, they proposed specific time points for initial and subsequent follow-up for medical visits and risk score restratification that is different from those patients with a long-standing diagnosis of CCS.

Assessing the patient with suspected obstructive CAD: what would Heberden say now?

The classic description of angina pectoris (or at least "typical angina") as first described by Heberden more than 200 years ago still guides[5] the clinical suspicion for the diagnosis of myocardial ischemia. However, in the new guidelines, shortness of breath or dyspnea has been added as an accompanying symptom to angina, along with less-specific symptoms, such as fatigue or faintness, nausea, burning, restlessness, or a sense of impending doom. As other conditions may cause shortness of breath, the attending physician should be especially careful when dyspnea is the sole presenting symptom in order to avoid an unnecessary array of tests to rule out obstructive CAD.

Another tool added in the initial assessment of a patient with suspected obstructive CAD is the new pretest probability (PTP) based on age, sex, and the nature of symptoms (including dyspnea). Previously, data used to generate the PTP tables no longer reflect the current prevalence of obstructive CAD, which is lower than disclosed in the last document. The present PTP is approximately one-third of that predicted by the model used in the previous version of the guidelines, which will substantially decrease the proportion of patients in whom diagnostic testing would be recommended.[6] The authors went on to add more new terms, such as "likelihood-modifying factors" to the PTP to yield a "clinical likelihood of obstructive CAD." Patients with concomitant cardiovascular risk factors, resting ECG changes, left ventricular dysfunction attributable to CAD, or coronary calcification by computed tomography will have a higher clinical likelihood of obstructive CAD. The reader ought to keep in mind, however, that the outlined new PTP table and its modifiers must be used only for the diagnosis of obstructive CAD.

What's new in the diagnosis of a symptomatic patient with suspected obstructive CAD?

In the past, the guidelines were extremely detailed in providing several diagnostic pathways to assess a symptomatic patient with suspected obstructive CAD. Unfortunately, very often and despite all the hard work, a less experienced practitioner would find those pathways not very "user-friendly." Coming from the era of "multiple arrows" in complex diagrams, the authors of the new guidelines proposed a more straightforward algorithm for the confirmation or exclusion of significant obstructive CAD. To achieve that, they performed a thorough review of the diagnostic accuracy of all available noninvasive methods, trying to comparatively determine their ability to "rule in" or "rule out" obstructive CAD.[7]

After their review was complete, they offered three options to decide how to begin the workup of a symptomatic patient with a more straightforward diagram: noninvasive testing, coronary computed tomography angiography (CTA), or invasive coronary angiography. Clinical conditions, such as the severity of angina symptoms or the unresponsiveness to medical therapy, the low or high clinical likelihood of obstructive CAD, left venticular dysfunction suggestive of CAD, all coupled with local expertise and availability, will determine the best route to follow. *Figure 1* shows the new proposed diagnostic pathway for obstructive CAD. The reader must bear in mind that through each path, both functional and anatomical information should be gathered to inform an appropriate diagnostic and therapeutic strategy.

It was just a matter of time for CTA to claim a more prominent role in the diagnosis of obstructive CAD.[8] Indeed, in the new guidelines, CTA can already be recommended as the initial test for diagnosing CAD in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone (class I) or as an alternative to invasive angiography if another noninvasive test is equivocal or nondiagnostic (class IIa). If coronary CTA shows CAD of uncertain functional significance, functional imaging for myocardial ischemia is recommended (class I).

The just presented (and yet unpublished at the time of this writing) results of the ISCHEMIA trial[9] were not incorporated into the new guidelines. We must wait to see how the updated version of the guidelines will deal with the results of that trial, mainly focusing on the interplay between the quantitative noninvasive assessment of myocardial ischemia and the need for invasive coronary angiography to alter prognosis.

A final comment on this topic: if the reader looks closely at the *figure* below, he/she will not see a place for exercise testing without imaging for the diagnosis of obstructive CAD. After Bruce published a specific exercise testing protocol in the early 1960s, allowing for the detection of underlying CAD,[10] there has always been a role for the treadmill test in the diagnostic workup of a patient with suspected CAD. Nevertheless, due to the low diagnostic accuracy of the exercise testing to rule in or rule out obstructive CAD in face of other diagnostic methods, exercise testing was "downgraded"

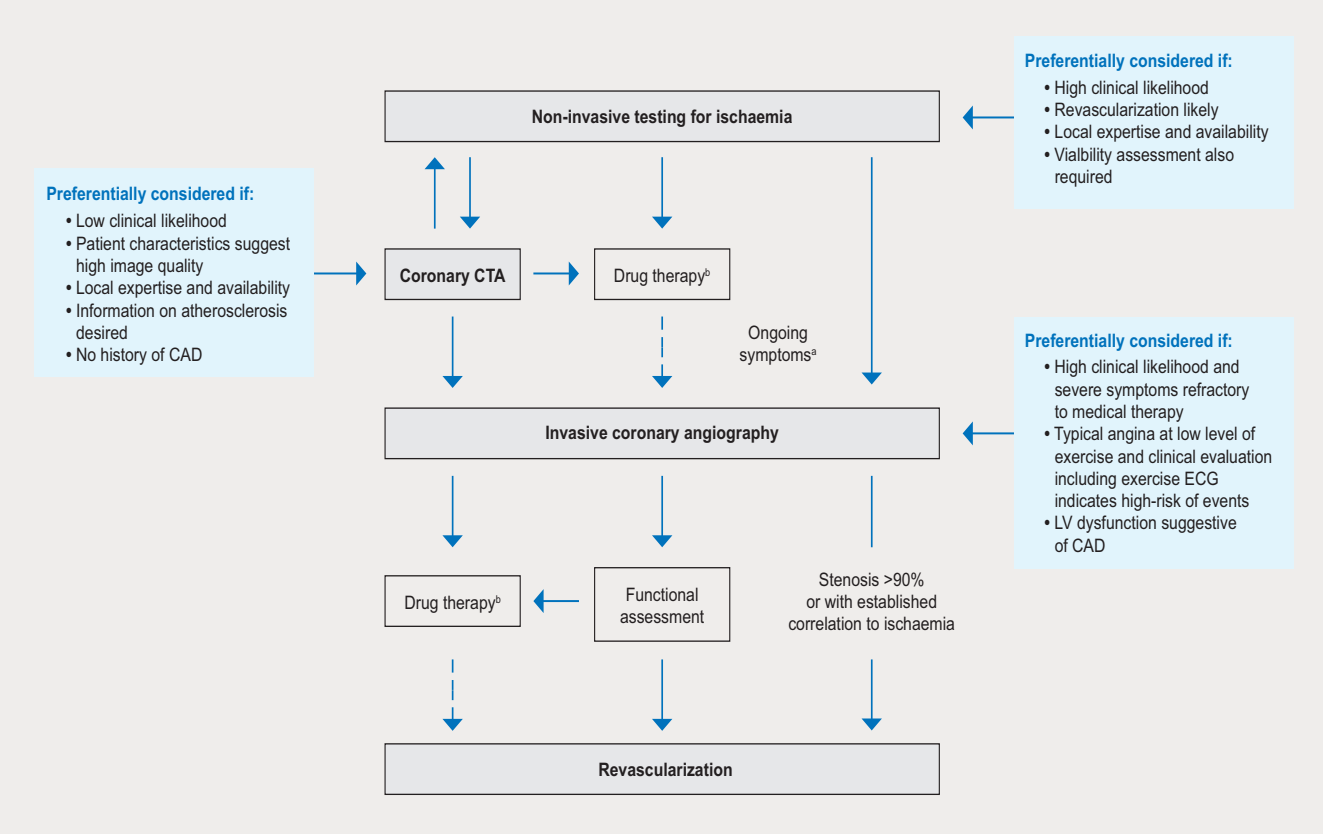

Figure 1. *New diagnostic pathway proposed by the ESC in symptomatic patients with suspected obstructive CAD.* [a]*Consider microvascular angina.* [b]*Antianginal medications and/or risk-factor modification.*

Modified from reference 1: *Knuuti J et al.* Eur Heart J. *2020;41(3):407-477. © 2019, The European Society of Cardiology.*

from class I in the previous document to class IIb in the new one for diagnostic purposes, although it remains a valuable tool to assess exercise tolerance, symptoms, arrhythmias, and blood pressure response in patients with suspected CAD.

Healthy lifestyle behaviors: maybe being clearer gets you there!

Although recognized as an essential part of the management of patients with CCS, perhaps in the past healthy lifestyle behaviors did not get the attention deserved. In the new document, however, lifestyle management got a more extensive section dedicated to proven measures aimed at reducing cardiovascular risk factors (and, therefore, reducing the risk of cardiovascular events and mortality), as well as improving quality of life. The usual lifestyle recommendations for patients with CCS include adopting a healthy diet and regularly performing physical activity to keep up a healthy weight and to stop smoking. For the latter, a new mnemonic process was created – the five A's – to help us remember how to approach the smoker patient: Ask (about smoking), Advise (to quit), Assess (readiness to quit), Assist (with smoking cessation), and Arrange (follow-up).

Interesting enough, all recommendations for lifestyle management received a class I with levels of evidence alternating between A and B, including cognitive-behavioral and psychological interventions, a multidisciplinary health care approach, and an annual influenza vaccination.

Pharmacological treatment for symptom control: let me try again

The objectives of pharmacological therapy in patients with CCS remained unchanged: to reduce symptoms and exercise-induced ischemia, and to prevent cardiovascular events. In the preamble of this section in the guidelines, the authors did an excellent job outlining the general rules governing the choice of an anti-ischemic strategy for patients with symptomatic CCS, briefly summarized below:

- Definition of optimal medical therapy based on effective symptom control and risk reduction in a patient satisfactorily adherent and exhibiting good tolerability to the chosen drugs.
- Acceptance of the fact that optimal medical therapy cannot be defined a priori, and that the choice of drug therapy must consider the patient's characteristics and preferences.
- The initial anti-ischemic medical strategy usually consists of one or two antianginal drugs, as necessary.
- The individual patient's profile and comorbidities, and potential drug interactions with coadministered therapies should direct the attending physician to establish the best strategy for each patient.

• There is no evidence that any antianginal drugs, alone or in combination, reduce clinical events.
• No randomized clinical trial has compared the use of β-blockers or calcium channel blockers as the first choice to an alternative strategy using an initial prescription of other anti-ischemic drugs.
• The response to initial antianginal therapy should be reassessed 2 to 4 weeks after treatment initiation.

After a promising introduction to the medical treatment for symptom relief, the authors described all the available drugs, reviewing the evidence to justify their use in patients complaining of angina or poor exercise tolerance. And then comes a suggested strategy for long-term anti-ischemic drug therapy in patients with CCS and specific baseline characteristics. The authors decided to change from the "first-line, second-line" approach proposed in the previous guideline to a new "step-wise" strategy according with five different clinical scenarios: standard therapy, patients with a heart rate above 80 bpm, or below 50 bpm, and patients with left ventricular dysfunction or low blood pressure. For each situation, a "step-by-step" preferential sequence of drug therapy was provided – and that's when the authors missed the opportunity to fully comply with their opening statements on optimal medical therapy for patients with symptomatic CCS.

My concerns on the issue will refer to the original presentation of the CCS guidelines during the 2019 ESC Congress in Paris, followed by its publication in the European Heart Journal[1] since a corrigendum was later published.[11]

Here, my concerns are about the original strategy for optimal symptom relief:
• After the authors admitted that there was a lack of randomized clinical trials comparing the efficacy of any anti-anginal therapy, β-blockers and calcium channel blockers were kept as the "first-step" standard treatment with a class IA recommendation.
• The addition of a second-line drug was recommended as the third step, although several second-line add-on anti-ischemic drugs (long-acting nitrates, ranolazine, trimetazidine, and ivabradine) may prove beneficial in combination with a β-blocker or a CCB as first-line therapy.
• In patients with a heart rate higher than 80 bpm who remain symptomatic with a combination of a β-blocker and a non-dihydropyridine calcium channel blockers, ivabradine was recommended as a third step. The authors failed to consider that, following a report published in 2014 by the European Medicines Agency, the use of ivabradine combined with moderate CYP3A4 inhibitors with heart rate–reducing properties, such as diltiazem or verapamil was contraindicated. Since then, this recommendation was incorporated on the product's label.
• In patients with left ventricular dysfunction or heart failure who remain symptomatic on a maximally tolerated dose of β-blockers, the second step was the addition of long-acting nitrates or ivabradine. In the SHIFT trial, adding ivabradine to optimally treated heart failure patients led to a 26% reduction in the risk of mortality from heart failure.[12]
• And, finally, maybe the most debatable strategy proposed in the new guidelines is that for symptomatic patients with low blood pressure. In this challenging clinical scenario, the proposed approach consists of a sequence of low-dose blood pressure–lowering agents, such as β-blockers, non-dihydropyridine calcium channel blockers, and long-acting nitrates. As a third step, should the symptoms still be uncontrolled, then non-blood pressure–lowering agents ought to be added, such as ivabradine, ranolazine, or trimetazidine. That was a somewhat surprising proposal as recent data have shown that there is a "J-shaped" curve relationship between blood pressure and the incidence of angina, so that for a diastolic blood pressure <70 mm Hg, there is an increase in the frequency/severity of angina.[13] Not only may symptoms get worse, but, below a certain level of blood pressure (<120/70 mm Hg), there is an increment in the risk of cardiovascular events, including cardiovascular death or myocardial infarction.[14]

Probably because some voices may have risen to call the authors' attention to the inconsistencies or inadequacies of the proposed strategy, a corrigendum was published 3 months after the original paper to clarify the second and third step rows in the original figure. Here are the changes made to the original flowchart for medical treatment:
• In standard therapy, the combination of a β-blocker or any calcium channel blocker with a second-line drug may be considered as a first step.
• Ivabradine should not be combined with nondihydropyridine calcium channel blockers, a significant change from the original proposal.
• In patients with low blood pressure, now they allow switching to non-blood pressure–lowering agents as a second step.

The authors of the guidelines should be praised for the quick action, most likely as a response to queries they must have received after the original publication of the guidelines. Yet, despite the effort for providing an easy-to-follow figure to serve as a reference, they still leave the strategy open, so are the practitioners who will eventually decide their approach adapted to each patient's characteristics and preferences. They go even further, saying that the adopted strategy "does not necessarily follow the steps indicated in the figure."

One alternative approach to tailor the treatment of patients with angina could have been the adoption of the model proposed by Ferrari et al called "the diamond approach."[15] In that model, the main characteristics of the patient (heart rate, blood pressure), associated cardiovascular diseases (heart failure, atrial fibrillation), comorbidities (diabetes, peripheral artery disease, COPD), and underlying mechanism for ischemia/

angina (fixed stenotic lesion, vasospasm, microvascular dysfunction) were all combined in a colorful graphic representation in which the reader could easily find the preferred, possible, or contraindicated drugs. One key aspect of such an image is the incorporation of the pathophysiology of myocardial ischemia in the decision-making process for medical therapy, which was missing in the guidelines.

Finally, a small, but relevant change from the 2013 to 2019 guidelines is the "upgrade" of trimetazidine from class IIb to class IIa, certainly more consistent with all the robust evidence regarding its antianginal efficacy, at least comparable to other antianginal drugs.[16,17]

Pharmacological treatment for risk reduction: new kids on the block

The 2019 guidelines benefited from the latest, gathered evidence regarding cardiovascular protection in patients with CCS, specifically in the field of antithrombotic therapy, lipid-lowering therapy, and the management of diabetes mellitus.

Briefly, there are new recommendations for:

- Preferential use of a non-vitamin K oral anticoagulant in patients with atrial fibrillation and an indication for oral anticoagulation (CHA2DS2-VASc score ≥2 in men and ≥3 in women) (class I).
- Adding a second antithrombotic drug (clopidogrel, prasugrel, ticagrelor, or rivaroxaban) to aspirin for long-term secondary prevention in patients with a high risk of ischemic events and without a high bleeding risk (class IIa); the choice of the second drug will be determined by the clinical scenario (post-myocardial infarction, post-percutaneous coronary intervention, multivessel CAD).
- Aggressive lipid-lowering strategy consisting of statins, statins+ezetimibe, or statins+ezetimibe+PCSK9 inhibitor (class I) as needed until the target for low-density lipoprotein cholesterol levels are achieved.
- Using a sodium glucose cotransporter 2 inhibitor (empagliflozin, canagliflozin, or dapagliflozin) or glucagon-like peptide receptor agonist (liraglutide or semaglutide) in patients with diabetes and cardiovascular disease (class I).

Final thoughts

According to the Merriam-Webster Dictionary, a guideline is "a line by which one is guided, such as an indication or outline of policy or conduct." With this concept in mind, every year, thousands of physicians all around the world eagerly await the release of the new guidelines in anticipation that the most recently available data has been gathered so that robust evidence can be summarized in easy-to-follow directions to manage an individual with a given clinical condition in the best possible way. Regardless of where we practice medicine, guidelines coming from both sides of the Atlantic are a significant reference for cardiologists, even though a few countries may have their local guidelines. To produce such a document may prove to be a Herculean effort, a time-demanding task, subject to disagreements among authors and criticisms by readers. So, I would like to once again compliment the numerous authors of the new guidelines on chronic coronary syndromes, hoping that my observations on what could be improved in a future version will not detract from the overall contribution these new guidelines have made. ■

References

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* 2020;41(3):407-477.
2. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease. *Eur Heart J.* 2013;34:2949-3003.
3. Libby P, Pasterkamp G, Crea F, Jang IK. Reassessing the mechanisms of acute coronary syndromes. *Circ Res.* 2019;124:150-160.
4. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. *Circulation.* 2017;135:1075-1092.
5. Khan IA, Mehta NJ. Initial historical descriptions of the angina pectoris. *J Emerg Med.* 2002;22:295-298.
6. Juarez-Orozco LE, Saraste A, Capodanno D, 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. Knuuti J, Ballo H, Juarez-Orozco LE, et al. The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability. *Eur Heart J.* 2018;39:3322-3330.
8. Kelion AD, Nicol ED. The rationale for the primacy of coronary CT angiography in the National Institute for Health and Care Excellence (NICE) guideline (CG95) for the investigation of chest pain of recent onset. *J Cardiovasc Comput Tomogr.* 2018;12:516-522.
9. Maron DJ, Hochman JS, O"Brien SM, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: rationale and design. *Am Heart J.* 2018;201:124-135.
10. Bruce RA, Blackmon JR, Jones JW, Strait G. Exercising testing in adult normal subjects and cardiac patients. *Pediatrics.* 1963;32(suppl):742-756.
11. Corrigendum. *Eur Heart J.* 2019;ehz825.
12. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet.* 2010; 376:875-885.
13. Peri-Okonny PA, Patel KK, Jones PG, et al. Low diastolic blood pressure is associated with angina in patients with chronic coronary artery disease. *J Am Coll Cardiol.* 2018;72:1227-1232.
14. Vidal-Petiot E, Greenlaw N, Ford I, et al. Relationships between components of blood pressure and cardiovascular events in patients with stable coronary artery disease and hypertension. *Hypertension.* 2018;71:168-176.
15. Ferrari R, Camici PG, Crea F, et al. Expert consensus document: a "diamond" approach to personalized treatment of angina. *Nat Rev Cardiol.* 2018;15:120-132.
16. Zhao Y, Peng L, Luo Y, et al. Trimetazidine improves exercise tolerance in patients with ischemic heart disease: a meta-analysis. *Herz.* 2016;41:514-522.
17. Peng S, Zhao M, Wan J, Fang Q, Fang D, Li K. The efficacy of trimetazidine on stable angina pectoris: a meta-analysis of randomized clinical trials. *Int J Cardiol.* 2014;177:780-785.

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