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JACC STATE-OF-THE-ART REVIEW

Optimizing Management of Stable Angina

A Patient-Centered Approach Integrating Revascularization, Medical Therapy, and Lifestyle Interventions

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ABSTRACT

Angina pectoris may arise from obstructive coronary artery disease (CAD) or in the absence of significant CAD (ischemia with nonobstructed coronary arteries [INOCA]). Therapeutic strategies for patients with angina and obstructive CAD focus on reducing cardiovascular events and relieving symptoms, whereas in INOCA the focus shifts toward managing functional alterations of the coronary circulation. In obstructive CAD, coronary revascularization might improve angina status, although a significant percentage of patients present angina persistence or recurrence, suggesting the presence of functional mechanisms along with epicardial CAD. In patients with INOCA, performing a precise endotype diagnosis is crucial to allow a tailored therapy targeted toward the specific pathogenic mechanism. In this expert opinion paper, we review the evidence for the management of angina, highlighting the complementary role of coronary revascularization, optimal medical therapy, and lifestyle interventions and underscoring the importance of a personalized approach that targets the underlying pathobiology. (J Am Coll Cardiol 2024;84:744-760) © 2024 by the American College of Cardiology Foundation.

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HIGHLIGHTS

- Angina pectoris may arise from obstructive CAD or in the absence of significant CAD.
- Functional mechanisms may be involved in determining angina both in obstructive CAD and in ischemia with nonobstructed coronary arteries.
- Revascularization and medical therapy play complementary roles in achieving optimal outcomes for patients with angina.
- Management of angina is shifting toward a more personalized approach, moving away from the traditional one-size-fits-all strategy.

Angina pectoris is the most common symptom of ischemic heart disease (IHD), affecting >100 million people worldwide.[1] The primary mechanism underlying angina is a mismatch between myocardial oxygen demand and supply, originating from the presence of an obstructive epicardial coronary artery disease (CAD) or even in the absence of significant epicardial CAD (ischemia with nonobstructed coronary arteries [INOCA]).[2]

Obstructive CAD is characterized by significant coronary artery stenosis, typically defined as an angiographic reduction in the luminal diameter of 50% or more, although this threshold may vary, particularly when evaluating the left main (LM) coronary artery or incorporating functional assessments such as fractional flow reserve (FFR) or instantaneous wave-free ratio.[3] However, up to 50% of patients undergoing coronary angiography for angina or myocardial ischemia may have unobstructed coronary arteries. INOCA encompasses a heterogeneous group of disorders, including coronary microvascular dysfunction (CMD) and vasospastic angina (VSA), where ischemia occurs without significant epicardial stenoses seen on coronary angiography.[4]

Distinguishing between obstructive CAD and INOCA represents a significant clinical challenge because they may present with similar symptoms, yet each necessitates distinct diagnostic approaches and therapeutic strategies. At the same time, both require the same intensive interventions on risk factors, especially when obstructive CAD and functional disorders coexist within the same patient. For obstructive CAD, treatment involves a combination of lifestyle modifications promoting a healthy diet and regular physical exercise, cardiovascular (CV) prevention targeting traditional and emerging risk factors, and symptom control; revascularization procedures should be reserved for specific subsets of patients.[5] In INOCA, the focus shifts toward the management of multiple functional alterations of coronary circulation encompassing both epicardial arteries and microcirculation, along with risk factor control and secondary preventive measures.[6]

This review offers a comprehensive analysis of the current landscape of antianginal therapy for stable IHD, with a specific focus on the most recent evidence regarding the management of obstructive CAD and INOCA. In addition, it provides a patient-centered, evidence-based approach to patients presenting with angina symptoms, highlighting the importance of tailoring treatments based on individual patient mechanisms of disease.

TREATMENT STRATEGIES FOR OBSTRUCTIVE CAD

The primary objectives of therapeutic strategies in angina with obstructive CAD are 2-fold: to reduce the risk of CV events, and to alleviate angina symptoms and exercise-induced ischemia. Historically, flow-limiting atherosclerotic obstructions were considered to be the primary cause of angina and major determinants of future CV risk. Consequently, revascularization procedures, such as coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI), were regarded as fundamental treatments.[7] However, over the past 2 decades, a growing body of evidence has challenged this approach, at least in part. Indeed, even if myocardial revascularization does improve the prognosis of patients with LM disease, and CABG

ABBREVIATIONS AND ACRONYMS

ACh = acetylcholine
BP = blood pressure
CABG = coronary artery bypass grafting
CAD = coronary artery disease
CCB = calcium-channel blocker
CFR = coronary flow reserve
CMD = coronary microvascular dysfunction
CV = cardiovascular
FFR = fractional flow reserve
HR = heart rate
IHD = ischemic heart disease
IMR = index of microvascular resistance
INOCA = ischemia with nonobstructed coronary arteries
LAD = left anterior descending artery
LM = left main
LV = left ventricle
LVEF = left ventricular ejection fraction
MI = myocardial infarction
MVA = microvascular angina
OMT = optimal medical therapy
PCI = percutaneous coronary intervention
QoL = quality of life
RCT = randomized controlled trial
VSA = vasospastic angina

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 RCTs Comparing Coronary Revascularization Plus OMT vs OMT Alone in Chronic Coronary Syndromes

Trial Name	First Author (Publication Year)	No. of Subjects and Inclusion Criteria	Exclusion Criteria	Design	Principal Findings
Cardiovascular events reduction					
COURAGE	Boden[15] (2007)	2,287 patients with ≥70% coronary stenosis and evidence of myocardial ischemia or ≥80% coronary stenosis with angina	• Persistent CCS Class IV angina • A markedly positive stress test • Refractory HF or CS, LVEF <30% • Recent revascularization (<6 mo) • Coronary anatomy not suitable for PCI	• Randomization to either PCI with OMT (n = 1,149) or OMT alone (n = 1,138) • Primary endpoint: death from any cause and nonfatal MI during a median follow-up of 4.6 y	• No significant difference in the cumulative primary-event rates (PCI 19.0% vs OMT: 18.5%; HR: 1.05, 95% CI: 0.87-1.27; $P = 0.62$) • Similar rates of the composite of death, MI, and stroke (20.0% vs 19.5%; HR: 1.05; 95% CI: 0.87-1.27; $P = 0.62$), hospitalization for ACS (12.4% vs 11.8%; HR: 1.07; 95% CI: 0.84-1.37; $P = 0.56$), and MI (13.2% vs 12.3%; HR: 1.13; 95% CI: 0.89-1.43; $P = 0.33$) between the 2 groups
BARI 2D	Frye[16] (2009)	2,368 patients with both T2DM and CAD (≥50% coronary stenosis and a positive stress test or ≥70% coronary stenosis and angina)	• Need of immediate revascularization • LM coronary disease • Creatinine level >2.0 mg/dL or $Hb1_{Ac}$ level >13.0% • Class III or IV HF or hepatic dysfunction • Recent PCI or CABG (<12 mo)	• Randomization to either prompt PCI or CABG with OMT or OMT alone and to either insulin-sensitization or insulin-provision therapy • Primary endpoint: rate of death and a composite of death, MI, and stroke	• At 5 y, no significant difference in survival between the 2 groups (88.3% in the revascularization group vs 87.8% in the medical-therapy group; $P = 0.97$) • In the CABG stratum, lower rate of MACE in the revascularization group (22.4%) vs the medical-therapy group (30.5%; $P = 0.01$; $P = 0.002$ for interaction between stratum and study groups).
FAME 2	Xaplanteris[18] (2018)	888 patients with stable angina and at least 1 coronary stenosis ≥50% eligible for PCI and with FFR ≤0.80	• CABG as the preferred treatment • LM coronary disease • Recent ACS (<1 wk) • Previous CABG • Contraindication to DAPT, LVEF <30%, or planned need for concomitant valvular or aortic surgery	• Randomization to either FFR-guided PCI plus medical therapy (n = 447) or to medical therapy alone (n = 441) • Primary endpoint: composite of death, MI, and urgent revascularization	• At 5 y, lower rate of the primary endpoint in the PCI group compared with the medical-therapy group (13.9% vs 27.0%; HR: 0.46; 95% CI: 0.34-0.63; $P < 0.001$) • No difference between the 2 groups in the rates of death (5.1% and 5.2%; HR: 0.98; 95% CI: 0.55-1.75) or MI (8.1% and 12.0%; HR: 0.66; 95% CI: 0.43-1.00)
ISCHEMIA	Maron[19] (2020)	5,179 patients with moderate to severe ischemia on stress imaging or severe ischemia on nonimaging exercise tolerance testing	• eGFR <30 mL/min/1.73 m^2 • Recent ACS (within the previous 2 months) • Unprotected LM stenosis ≥50% • NYHA functional class III or IV HF or LVEF <35% • Unacceptable angina despite the use of medical therapy at maximum acceptable doses	• Randomization to an initial invasive strategy (angiography and revascularization by PCI or CABG) and OMT or to an initial conservative strategy of OMT alone and angiography if medical therapy failed • Primary endpoint: composite of CV death, MI, and hospitalization for UA, HF, and resuscitated cardiac arrest	• Over a median 3.2 y of follow-up, 318 events occurred in the invasive-strategy group and 352 in the conservative-strategy group • At 6 mo, the cumulative event rate was 5.3% in the invasive-strategy group and 3.4% in the conservative-strategy group (difference: 1.9 percentage points; 95% CI: 0.8-3.0) • At 5 y, the cumulative event rates were 16.4% and 18.2%, respectively (difference: −1.8 percentage points; 95% CI: −4.7 to 1.0)

Continued on the next page

demonstrated an improvement in prognosis for diabetic patients with 3-vessel disease[8] and in patients with reduced left ventricular ejection fraction (LVEF),[9] the role of PCI in patients with reduced LVEF remains controversial.[10-13] Importantly, data from randomized controlled trials (RCTs) have suggested that a strategy of coronary revascularization plus optimal medical therapy (OMT) might not always confer additional benefits compared with OMT alone in the remaining patients with chronic coronary syndrome[5] (Table 1).

ROLE OF REVASCULARIZATION IN CARDIOVASCULAR EVENT REDUCTION. In 2007, the landmark COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial was the first RCT to assess the long-term clinical outcomes of OMT with and without the addition of PCI. In that trial, 2,287 patients were randomized to either PCI with OMT or OMT alone. The addition of PCI to OMT did not result in a significant improvement in the primary outcome of death or myocardial infarction (MI) over an average follow-up period of 4.6 years, nor did it improve

TABLE 1 Continued

Trial Name	First Author (Publication Year)	No. of Subjects and Inclusion Criteria	Exclusion Criteria	Design	Principal Findings
Symptoms relief and quality of life					
COURAGE	Weintraub[23] (2008)	2,287 patients with ≥70% coronary stenosis and evidence of myocardial ischemia or ≥0% coronary stenosis with angina	• Persistent CCS Class IV angina • A markedly positive stress test • Refractory HF or CS, LVEF <30% • Recent revascularization (<6 mo) • Coronary anatomy not suitable for PCI	• Randomization to either PCI with OMT (n = 1,149) or OMT alone (n = 1,138) • Angina-specific health status (SAQ scores) and overall physical and mental function (RAND-36 scores) were assessed at baseline and 1, 3, 6, and 12 mo	• At baseline, 22% of the patients were free of angina • At 3 months, 53% of the patients in the PCI group and 42% in the OMT-alone group were angina free ($P < 0.001$) • The benefit from PCI was incremental for 6 to 24 mo, and patients with more severe angina had a greater benefit from PCI. Similar incremental benefits were seen in some but not all RAND-36 domains • By 36 mo, there was no significant difference in health status between the treatment groups
FAME 2	Xaplanteris[18] (2018)	888 patients with stable angina and at least 1 coronary stenosis ≥50% eligible for PCI and with FFR ≤0.80	• CABG as the preferred treatment • LM coronary disease • Recent ACS (<1 wk) • Previous CABG • Contraindication to DAPT, LVEF <30%, or planned need for concomitant valvular or aortic surgery	• Randomization to either FFR-guided PCI plus medical therapy (n = 447) or to medical therapy alone (n = 441) • Angina was classified according to the CCS functional classification	• Lower percentage of patients with angina of CCS grade II, III, or IV in the PCI group vs the medical-therapy group at all time points during the first 3 y of follow-up • This difference was no longer significant at 5 y
ISCHEMIA	Spertus[24] (2020)	5,179 patients with moderate/severe ischemia on stress imaging or severe ischemia on nonimaging exercise tolerance testing	eGFR <30 mL/min/1.73 m^2 • Recent ACS (within the previous 2 months) • Unprotected LM stenosis ≥50% • NYHA functional class III or IV HF or LVEF <35% • Unacceptable angina despite the use of medical therapy at maximum acceptable doses	• Randomization to an initial invasive strategy (angiography and revascularization by PCI or CABG) and OMT or to an initial conservative strategy of OMT alone and angiography if medical therapy failed • Primary outcome: SAQ summary score	• At baseline, 35% of the patients were free of angina • SAQ summary scores increased in both treatment groups, with increases at 3, 12, and 36 mo that were, respectively, 4.1 points (95% CI: 3.2-5.0), 4.2 points (95% CI: 3.3-5.1), and 2.9 points (95% CI: 2.2-3.7) higher with the invasive strategy than with the conservative strategy • Differences were larger among participants who had more frequent angina at baseline (8.5 vs 0.1 points at 3 mo and 5.3 vs 1.2 points at 36 mo among participants with daily or weekly angina compared with no angina)
ORBITA	Al-Lamee[26] (2018)	200 patients with angina or equivalent symptoms and at least 1 coronary stenosis ≥70% suitable for PCI	• Coronary stenosis ≥50% in a nontarget vessel • ACS • Previous CABG • LM coronary disease • CTO • Severe valvular disease or severe LV systolic impairment • Moderate to severe pulmonary hypertension	• After enrollment: 6 wks of medication optimization • Randomization 1:1 to undergo either PCI or a placebo procedure • Primary endpoint: difference in exercise time increment between groups at 6-wk follow-up	• No significant difference in the primary endpoint between the 2 groups (PCI minus placebo 16.6 s; 95% CI: −8.9 to 42.0 s; $P = 0.200$)
ORBITA-2	Rajkumar[28] (2023)	301 patients with angina or angina equivalent, at least 1 severe coronary stenosis, and evidence of ischemia	• Recent ACS (<6 mo) • Previous CABG • LM coronary disease • CTO • Severe valvular disease • LVEF ≤35%	• Stop all antianginal medications, and 2-wk symptom assessment phase before randomization • Randomization 1:1 to undergo either PCI (n = 151) or a placebo procedure (n = 150) • Primary endpoint: angina symptom score (range 0-79, with higher scores indicating worse health status with respect to angina), at 12-wk follow-up	• The mean angina symptom score was 2.9 in the PCI group and 5.6 in the placebo group (OR: 2.21; 95% CI: 1.41-3.47; $P < 0.001$)

Inclusion criteria for **Table 1**: only RCTs directly comparing coronary revascularization plus OMT vs OMT alone, focusing on mortality, cardiovascular outcomes, and quality of life, published within the past 20 years.

ACS = acute coronary syndrome; BARI 2D = Second Bypass Angioplasty Revascularization Intervention in Diabetics; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; CS = cardiogenic shock; CTO = chronic total occlusion; CV = cardiovascular; DAPT = dual antiplatelet therapy; eGFR = estimated glomerular filtration rate; FAME 2 = Fractional Flow Reserve Versus Angiography for Multivessel Evaluation; FFR = fractional flow reserve; HF = heart failure; ISCHEMIA = International Study of Comparative Health Effectiveness With Medical and Invasive Approaches; LM = left main; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; MI = myocardial infarction; OMT = optimal medical therapy; ORBITA = Objective Randomized Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SAQ = Seattle Angina Questionnaire; T2DM = type 2 diabetes mellitus; UA = unstable angina.

overall survival over a median 11.9-year follow-up. However, the COURAGE trial does not fully represent contemporary clinical practices, because it used bare-metal stents and did not include CABG as a revascularization option.[14]

Subsequent RCTs aimed to address these shortcomings. The BARI 2D (Second Bypass Angioplasty Revascularization Intervention in Diabetics) trial included 2,368 patients with both type 2 diabetes and stable IHD who were randomized to either revascularization (PCI or CABG) plus OMT or OMT alone. The study found no significant difference in the rates of death and major CV events between the 2 groups.[15] However, in line with the FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, which specifically focused on patients with diabetes, a distinct benefit of CABG over PCI was noted concerning the composite outcome of death, MI, and stroke.[8]

The FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) 2 trial aimed to evaluate whether FFR-guided PCI would be superior to OMT. In that study, 888 patients with angiographically and hemodynamically (FFR ≤0.80) significant stenoses were randomly assigned to either FFR-guided PCI plus OMT or OMT alone. After 5 years of follow-up, FFR-guided PCI plus OMT was associated with a significantly lower incidence of the primary composite endpoint of death, MI, or urgent revascularization compared with OMT alone, which was entirely driven by urgent revascularization, a soft endpoint that is prone to bias in an unblinded study.[16,17]

More recently, the ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) trial randomized 5,179 patients with moderate or severe inducible ischemia at noninvasive stress testing to an initial invasive strategy (revascularization with third-generation drug-eluting stent or CABG) and OMT or to an initial conservative strategy of OMT alone. Over a median follow-up of 3.2 years, an initial invasive strategy showed no benefits on the primary (CV death, MI, resuscitated sudden cardiac death, or hospitalization for unstable angina or heart failure) or secondary (CV death or MI) endpoints. No incremental benefit was observed in the diabetic subset according to the revascularization strategy (PCI or CABG).[18] Furthermore, at an extended follow-up of 5.7 years, there was no difference in all-cause mortality with an initial invasive strategy compared with an initial conservative strategy, but there was lower risk of CV mortality and higher risk of non-CV mortality with an initial invasive strategy.[19]

Finally, a meta-analysis including 7 RCTs, totaling 10,043 patients with stable angina and evidence of moderate-to-severe ischemia, showed that PCI plus OMT was not associated with any benefits in terms of mortality, CV death, or MI compared to OMT alone.[20] Similarly, a recent meta-analysis, which included the ISCHEMIA trial and 9 other RCTs, involving a total of 12,125 patients, showed that PCI, when added to OMT, did not reduce all-cause mortality, CV mortality, or MI compared with OMT alone. However, it was associated with improved anginal symptoms and a lower risk of revascularization.[21] Conversely, a meta-analysis involving 19,806 stable CAD patients from 25 RCTs found that elective coronary revascularization plus OMT reduced cardiac mortality, but not all-cause mortality, compared with OMT alone.[22] However, that meta-analysis included outdated studies from the 1970s that do not reflect current medical practices, and nearly one-third of the RCTs in the analysis did not report on cardiac death, potentially affecting the reliability of the findings.[23]

ROLE OF REVASCULARIZATION AND OPTIMAL MEDICAL THERAPY FOR SYMPTOMS RELIEF. In the COURAGE trial, both the PCI plus OMT group and the OMT alone group showed significant improvements in angina status and overall quality of life (QoL) over a 6-month period. Although the improvement was more pronounced in the PCI group for up to 2 years, patients with less frequent angina (weekly or monthly) experienced only a marginal improvement in the Seattle Angina Questionnaire (SAQ) summary score, <5 points and not significantly greater after 6 months.[24]

Similarly, in the ISCHEMIA trial, SAQ summary scores increased in both treatment groups over a 36-month follow-up, with a difference of 2.9 points (95% CI: 2.2-3.7 points) favoring the invasive strategy over the conservative strategy. The most significant improvement with the invasive strategy was observed in patients with symptom-limiting angina (weekly to daily), and this improvement persisted throughout the 3 years of follow-up. Nevertheless, it is worth noting that the mean between-group difference in SAQ total score was small (5.3 points at 36 months), which raises some concerns about whether these statistical differences could be considered as clinically meaningful.[25] Furthermore, OMT failed to avoid the need for an invasive strategy in around one-third of cases, as 25% to 30% of patients randomized to the conservative group crossed over to coronary angiography owing to inadequate

angina control or an ischemic event.[18] However, when examining the results of unblinded trials, an important concern is that the perceived benefits of coronary revascularization on angina symptoms might be influenced by a placebo effect.[26]

To overcome the possible placebo effect derived from a PCI procedure, the ORBITA (Objective Randomized Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) was the first blinded, placebo-controlled trial that randomized 200 patients with ischemic symptoms and severe (≥70%) single-vessel stenoses to undergo either PCI or a placebo procedure. Before randomization, all patients underwent a 6-week period of medication optimization with guideline-directed antianginal medications. When evaluated at the 6-week follow-up, no statistically difference was found in the primary endpoint of exercise time improvement between the 2 groups.[27] However, the intensive antianginal treatment with uptitration and intensification of therapy might have influenced the results, contributing to the minimal additional benefit of PCI on treadmill exercise time, symptoms, and QoL.[28]

To assess the net and true effect of PCI on angina symptoms without the influence of medical therapy and placebo effect, the ORBITA-2 trial randomized 301 symptomatic patients with at least 1 severe coronary stenosis and noninvasive evidence of ischemia to either PCI or a placebo procedure. Patients discontinued all antianginal medications and underwent a 2-week symptom assessment phase before randomization. The primary endpoint was the angina symptom score, calculated daily based on the number of angina episodes, number of prescribed antianginal medications, and clinical events. After a 12-week follow-up period, PCI resulted in a lower angina symptom score compared with the placebo procedure, indicating an improved health status.[29] Despite the potential of PCI for effective symptom relief and improved QoL compared with OMT alone, persistence or recurrence of angina after PCI represents an important issue. Indeed, evidence from the ORBITA and ORBITA-2 trials showed that a significant proportion of patients (61% in ORBITA and 59% in ORBITA-2) continued to experience angina despite undergoing effective revascularization while receiving OMT.[26,29] Furthermore, previous trials demonstrated a 20% to 30% chance of angina recurrence within the first year after PCI, increasing to approximately 40% within 3 years.[30,31] Because repeated coronary angiography often excludes in-stent restenosis or residual obstructive CAD, other factors, such as CMD or VSA, are likely to coexist with CAD and influence anginal symptoms and QoL.[32,33] Finally, the recent ORBITA-STAR trial demonstrated that a higher similarity score from symptom replication during ischemic stimulus (low-pressure balloon inflation across coronary stenosis) was a strong predictor of symptom improvement post-PCI, suggesting that this approach could identify patients who would benefit most from PCI.[34]

REAL-WORLD APPLICATION OF RCT FINDINGS. According to available evidence and clinical guidelines, OMT should represent the initial treatment strategy for patients with stable angina. OMT is often an effective option for these patients, even if revascularization may result in a greater improvement in angina and QoL compared with OMT alone. Myocardial revascularization should be considered as an adjunct to OMT, particularly in patients who remain symptomatic despite guideline-recommended OMT or in whom revascularization has a proven prognostic benefit (eg, LM or 3-vessel disease, severely reduced LVEF).[11-13] Benefits and risks of available therapeutic strategies should be discussed with the patient, because treatment decisions might vary among patients according to treatment expectations, levels of physical activity and QoL, and willingness to undertake medical therapy intensification. Furthermore, several issues should be considered and balanced when informing the patient's choice.

First, it is essential to clarify what OMT encompasses. Indeed, the concept of OMT has often been broad and not well defined, leading to ambiguities in its application and failing to reflect its dynamic nature. OMT should not be regarded as a static or singular treatment regimen but rather as a dynamic framework that integrates the latest advancements in pharmacotherapy and lifestyle interventions. These interventions aim to reduce CV risk and improve symptoms or QoL, and should be tailored to the specific needs of each patient. Accordingly, OMT should include not only antianginal drugs but also pharmacologic secondary prevention measures targeting blood pressure (BP) control, lipid management, glycemic control, and thrombotic risk reduction.[35]

Second, the adherence to medical therapy is crucial to get the benefits deriving from OMT and often represents an important issue in real-world clinical practice. RCTs have used rigorous OMT protocols that combine multiple antianginal medications, along with lifestyle changes and strict risk factor control.[14,18,27] In the ORBITA trial, 97.5% of patients were taking at least 2 antianginal drugs and 73% at least 3.[28] Rigorous application of such comprehensive regimens may explain the benefit of OMT in these studies, although their use in clinical practice may be

challenging, with obstacles such as managing side-effects, securing patient adherence, and accommodating individual patient preferences. This challenge is underscored by the underutilization of OMT in clinical practice, with up to 50% of patients undergoing elective coronary angiography receiving only 1 or no antianginal medications, highlighting a gap between evidence-based recommendations for OMT and their application in real-world care.[28,36-38]

Third, the real benefit of PCI in preventing the occurrence of CV events may often be overestimated by both clinicians and patients, because most of severe flow-limiting plaques remain quiescent and do not cause CV events. In the ISCHEMIA trial, there were only 66 sudden cardiac deaths among 5,179 patients (1.3% incidence) during a median 3.2-year follow-up period, and no increase in deaths was observed in conservatively managed patients.[39] These data should reassure patients and clinicians, suggesting that there is no need to rush to revascularization before first considering an adequate trial of medical therapy. At the same time, OMT may reduce the pathobiological risk of the plaque destabilization, regardless of whether a plaque includes a severe flow-limiting obstruction. This notion is particularly relevant when we consider the effects of revascularization, which is directed at ischemia-producing severe arterial narrowing but does not treat areas of adjacent plaque which may remain at risk of destabilization. Preventive PCI of vulnerable plaques detected at intravascular imaging has been suggested to possibly lower CV events.[40,41] However, the real benefit of this approach is still debated, and further evidence is needed before this strategy could be recommended in routine clinical practice. Moreover, since the initiation of key RCTs, novel therapies have emerged that can now be considered part of OMT. These include potent lipid-lowering drugs (eg, proprotein convertase subtilisin/kexin type 9 inhibitors and icosapent ethyl),[42-44] agents for thrombotic risk reduction (eg, low-dose rivaroxaban),[45] and new diabetes treatments (eg, sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists).[46,47] These therapeutic advances have the potential to further reduce the risk of CV events, regardless of whether patients undergo revascularization or not.

Fourth, the risks of procedural MI should be discussed with the patient, along with the risk of stent thrombosis (0.5% per year) and restenosis (1%-2% per year) and further revascularization procedures, the need for dual antiplatelet therapy, and the associated risk of bleeding. The patient should be informed that there is a 30% to 60% chance that PCI could not relieve symptoms and angina may persist. In this regard, at the time of coronary angiography, a complete invasive assessment with the combined use of FFR, coronary flow reserve (CFR), and index of microvascular resistance (IMR) may allow the identification of the specific coronary pathophysiology by means of a comprehensive assessment of epicardial and microvascular function, potentially informing on the eventual benefit of revascularization in terms of ischemia reduction and on the precise mechanism underlying ischemia thus requiring a tailored OMT.[48] This highlights the complementary nature of these approaches, because a combination of PCI and OMT may often be required for comprehensive management based on individual patient needs.

Finally, systemic economic considerations should be considered in situations where clinical effectiveness of 2 interventions is similar but costs differ. An analysis of the ORBITA trial demonstrated that PCI compared with placebo when added to OMT was not cost-effective even in a health care system where costs of PCI are relatively low, as in the publicly funded UK National Health Service; this issue may probably be even more relevant in privately funded health care systems.[49] These findings support, on a cost-effectiveness basis, the strategy of antianginal medication as first line, as advised by international guidelines.[11-13] Indeed, in clinical practice, non-PCI patients might need additional visits to maintain antianginal therapy levels like those in ORBITA. However, even when notional costs of such additional visits are added, the magnitude of the difference between the incremental cost-effectiveness ratio and the cost-effectiveness threshold suggests that the non-PCI approach remains economically advantageous.[42] At the same time, it is possible that the relatively short 6-week clinical follow-up of the ORBITA trial may have underestimated the longer-term clinical benefits of PCI.

TAILORING ANTIANGINAL MEDICAL THERAPY. OMT represents a cornerstone in managing angina, because the majority of patients will require OMT regardless of PCI. Therefore, selecting the most effective antianginal regimen is crucial to achieve the expected clinical benefit, minimize side-effects, and enhance medication adherence. Effectively managing symptoms often requires use of multiple antiischemic drugs that work together to enhance or complement each other's effects (**Table 2**). European guidelines recommend starting with first-line treatments such as β-blockers and calcium-channel blockers (CCBs). When first-line therapies are contraindicated, poorly tolerated, or insufficient for symptom control, the use

TABLE 2 Summary of Drugs, Dosages, and Indications for Managing Angina in Chronic Coronary Syndrome Patients

Class of Drugs	Dosage	Indications for Use
β-blockers	• Atenolol (50-200 mg once daily) • Bisoprolol (5-10 mg once daily) • Carvedilol (3.125-25 mg twice daily) • Metoprolol tartrate (25-100 mg twice daily) • Nebivolol (5-10 mg once daily)	• They should be preferred in patients with elevated BP and/or HR, history of AF, HCM, HF (especially HFrEF), or history of ACS • In patients with diabetes mellitus, vasodilating β-blockers, such as carvedilol and nebivolol, should be preferred as they could improve insulin sensitivity • They should not be combined with nondihydropyridine CCBs (risk of bradycardia, AV block, and hypotension) • They should not be abruptly discontinued because up-regulation of β-adrenoceptors could lead to severe tachycardia and vasoconstriction • They are contraindicated in VSA because they can precipitate α-mediated vasospasm
CCBs	Dihydropyridine: • Amlodipine (5-10 mg orally once daily) Nondihydropyridine: • Diltiazem (30-90 mg 4 times daily for immediate-release formulations; 120-480 mg once daily for extended-release formulations) • Verapamil (40-160 mg 3 times daily for immediate-release formulations; 120-480 mg once daily for extended-release formulations)	• Nondihydropyridine CCBs should be preferred in patients with elevated HR, BP, or history of AF, whereas they should be avoided in those with low HR • Dihydropyridine CCBs should be preferred in patients with low HR or elevated BP and avoided in those with elevated HR, AF or low BP, and in combination with ivabradine • First choice for VSA
Ivabradine	• 5-7.5 mg orally twice daily	• It should be used only in patients in sinus rhythm with HR ≥70 beats/min • It provides additional benefits when used in combination with other antianginal drugs, especially β-blockers, owing to synergistic effects
Nitrates	• Nitroglycerine (5-20 mg daily for transdermal patch; 6.5-15 mg twice daily for prolonged-release tablets) • Isosorbide mononitrate (5-10 mg once daily) • Isosorbide dinitrate (10-40 mg twice daily)	• They should be titrated at the lowest possible dose to control symptoms • They should be avoided in patients with elevated HR and are contraindicated in patients with obstructive HCM, severe aortic or mitral stenosis, or constrictive pericarditis, and in combination with PDE-5 inhibitor
Ranolazine	• 375 mg up to 750 mg twice daily	• It should be preferred in patients with low BP or HR because of its neutral hemodynamic profile • It should be the preferred in patients with diabetes mellitus • Its use is contraindicated in patients with severe hepatic or renal impairment because of the risk of QT interval prolongation
Nicorandil	• 10-30 mg twice daily	• Its concomitant use with aspirin might increase the risk of gastrointestinal ulcers, perforations, and hemorrhage
Trimetazidine	• 20 mg twice daily (35 mg once daily for modified-release formulations)	• It should be preferred in patients with low BP or HR because it does not exert hemodynamic effects (it does not affect oxygen demand but improves the metabolic efficiency of the ischemic myocytes) • Its use is not recommended in patients with Parkinson disease, parkinsonism, and other related movement disorders, or in patients with severe renal impairment

AF = atrial fibrillation; AV = atrioventricular; BP = blood pressure; CCB = calcium channel blocker; CCS = chronic coronary syndromes; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; PDE-5 = phosphodiesterase-5; VSA = vasospastic angina.

of second-line agents such as long-acting nitrates, ranolazine, ivabradine, nicorandil, and trimetazidine is suggested.[11,50] Conversely, U.S. guidelines recommend initiating with either β-blockers, CCBs, or long-acting nitrates, with the addition of a second antianginal agent from a different class or ranolazine if symptoms persist. Notably, U.S. guidelines do not recommend adding ivabradine to standard antianginal therapy in patients with normal left ventricular (LV) function owing to its potentially harmful effects.[13,51] However, this traditional categorization of antianginal medications into first- and second-line choices has been questioned in recent years. Modern antianginal medications, despite being labeled as second-line treatments, are now supported by more current evidence-based clinical research than the older, traditionally preferred, first-line medications.[52-54] Furthermore, no head-to-head comparisons between these treatments are available that demonstrate superiority of one over another in terms of antianginal effects. Therefore, the selection of antianginal medications should be tailored on a range of patient-specific factors including heart rate (HR), BP, LV dysfunction, heart failure, and any comorbidities.[55]

In patients with an elevated HR (>70 beats/min), β-blockers and nondihydropyridine CCBs should be preferred. Ivabradine can be added to β-blockers if the HR remains elevated, but its combination with nondihydropyridine CCBs is contraindicated.[51,56] Combining β-blockers with nondihydropyridine CCBs also is not recommended owing to the risk of

high-degree atrioventricular block. Vasodilators, such as dihydropyridine CCBs and nitrates, should be avoided because they may further increase HR.

For patients with a low HR (ie, <50-55 beats/min), HR-slowing medications should not be used. Instead, dihydropyridine CCBs, nitrates, or nicorandil should be preferred because they can potentially raise the HR through a sympathetic response, with ranolazine and trimetazidine as additional options.

In case of hypertension, β-blockers and dihydropyridine CCBs should be favored, with BP ideally maintained above 130/80 mm Hg to avoid the risk of overlowering, which is especially detrimental in patients with CAD and diabetes.[57,58]

For patients with low BP (eg, systolic BP below 100-110 mm Hg), medications that significantly lower BP, such as CCBs, nitrates, and β-blockers, should be avoided because they might impair coronary perfusion. Instead, the use of ranolazine or trimetazidine should be preferred.

Patients with LV dysfunction or HF benefit significantly from β-blockers; their use has been demonstrated not only to reduce angina, but also to decrease CV morbidity and mortality, likely owing to their heart-rate-lowering effect.[59,60] The addition of ivabradine, if HR remains high, or trimetazidine could potentially offer additional prognostic benefits.[61,62] Nondihydropyridine CCBs should be used with caution owing to potential exacerbation of LV dysfunction.

In patients with atrial fibrillation, which can worsen angina symptoms owing to increased HR, β-blockers and nondihydropyridine CCBs are recommended, and the addition of ranolazine might be useful.[63,64] Ivabradine is not effective for atrial fibrillation and may raise the risk of the arrhythmia.[65] Similarly, dihydropyridine CCBs, nitrates, and nicorandil should not be used, because they can further increase HR.

For patients with diabetes mellitus, ranolazine is recommended as the preferred treatment because it has been demonstrated to improve glycemic control and reduce angina incidence in these patients.[66] Although β-blockers have traditionally been avoided owing to their potential to worsen glycemic control, carvedilol and nebivolol have been demonstrated to improve insulin sensitivity.[67]

Patients with chronic kidney disease are at increased risk of CAD, and their treatment options are limited owing to their exclusion from many RCTs. Ranolazine and trimetazidine, which undergo hepatic metabolism and are primarily excreted by the kidney, are not recommended for those with significant renal impairment (eg, glomerular filtration rate <30 mL/min/1.73 m^2).[68] Other antianginal medications, however, do not have any contraindications for their use.

In patients with chronic obstructive pulmonary disease, β-blockers, especially those selective for β1-receptors, such as bisoprolol, are generally safe and may even confer benefits despite traditional concerns about their respiratory effects.[69] However, β-blockers are contraindicated in asthmatic patients or those with reactive airway disease, and nondihydropyridine CCBs or ivabradine should be preferred. In case of concomitant pulmonary hypertension with right ventricular dysfunction, nondihydropyridine CCBs and nonselective β-blockers are not recommended.

In patients with severe peripheral artery disease, often co-occurring with chronic stable angina, β-blockers and vasodilators (eg, nondihydropyridine CCBs and nitrates) should be avoided or used with caution, and other antianginal drugs (eg, ranolazine, ivabradine, and trimetazidine) should be preferred.

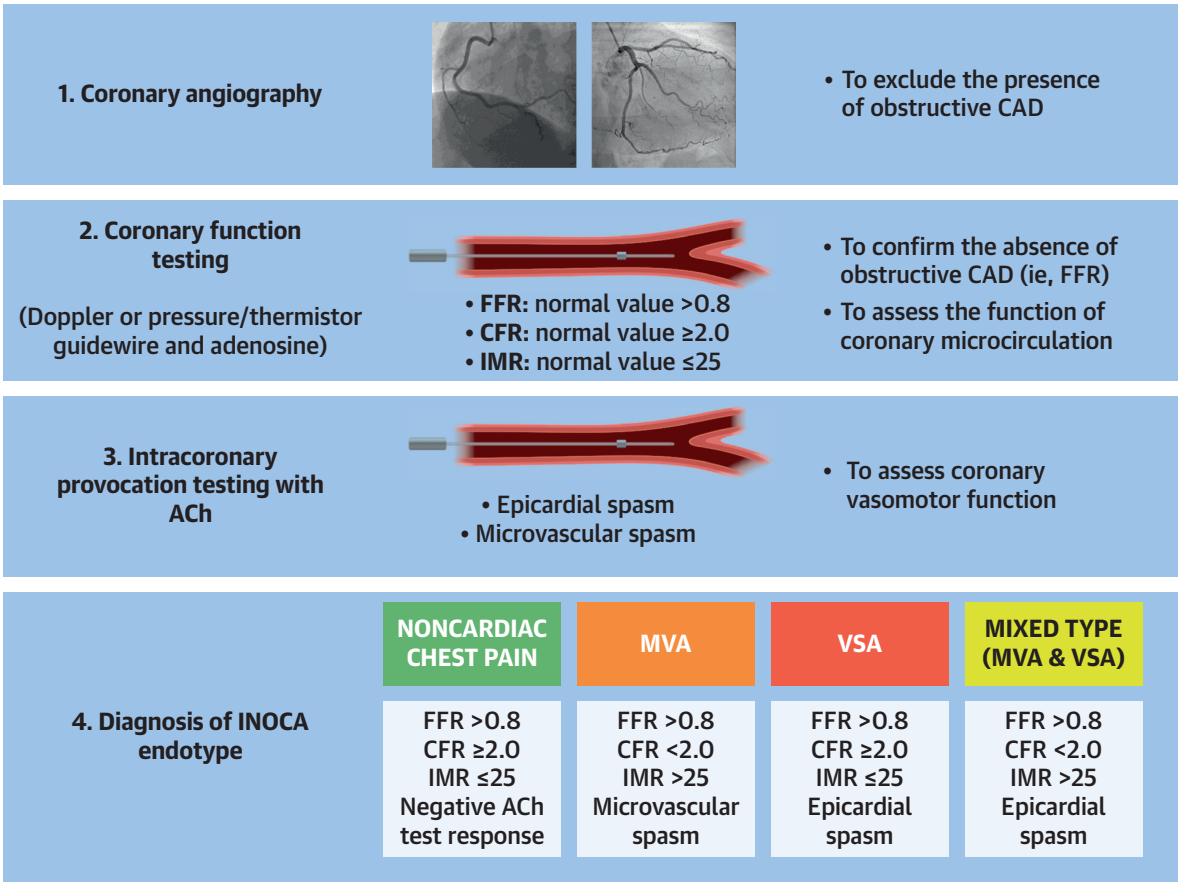
Of importance, a key aspect of correct management is the routine evaluation of therapy effectiveness at 2- to 3-month intervals. During these assessments, therapy should be uptitrated if symptoms are not adequately controlled or if first-line agents cannot be tolerated.[11] Persistence of symptoms with only 1 or 2 antianginal medications, especially at low doses, should not automatically be deemed a sufficient trial of OMT, unless the patient experiences unacceptable side-effects, cannot tolerate increased dosages, or other agents cannot be effectively introduced.[35]

Another crucial aspect of successful treatment is ensuring the patient's adherence to the prescribed regimen. To this aim, effective patient education about the benefits, risks, and management of side-effects is essential. Regular follow-up appointments help assess treatment efficacy and reinforce adherence by addressing potential obstacles like forgetfulness or financial constraints. Simplifying the regimen with strategies such as prescribing long-acting or combination medications can also significantly improve compliance by reducing the complexity and frequency of dosing.[70]

ANTIANGINAL THERAPY IN INOCA

INOCA patients are at increased risk of CV events and experience a notable decline in QoL compared with healthy subjects.[70-74] Microvascular angina (MVA) is the clinical manifestation of CMD, which may originate from structural changes that reduce CFR, functional abnormalities that impair dilation in response to increased myocardial oxygen demand,

FIGURE 1 Invasive Diagnostic Workflow for Assessment of Ischemia With Nonobstructed Coronary Arteries (INOCA)



Step-by-step diagnostic workflow in patients with symptoms and/or signs of myocardial ischemia but no obstructive coronary artery disease (CAD). The process begins with coronary angiography to exclude the presence of obstructive CAD. Subsequent coronary function testing confirms the absence of obstructive CAD (fractional flow reserve [FFR] normal value >0.8) and assesses the presence of coronary microvascular dysfunction (coronary flow reserve [CFR] normal value ≥2.0 and index of microvascular resistance [IMR] normal value ≤25). Intracoronary provocation testing with acetylcholine [ACh] is then performed to evaluate coronary vasomotor function and identify potential epicardial or microvascular spasms. The final diagnostic output categorizes patients into specific INOCA endotypes based on test results: noncardiac chest pain, microvascular angina (MVA), vasospastic angina (VSA), and mixed type (MVA and VSA), facilitating targeted treatment strategies.

microvascular spasms, or a combination of them.[75] VSA, on the other hand, results from transient obstructions in the epicardial coronary arteries due to spasms that transiently diminish blood flow, leading to myocardial ischemia.[76] A comprehensive invasive functional assessment can categorize INOCA patients into distinct subgroups (endotypes) based on CFR, IMR, and response to acetylcholine (ACh) provocation testing (**Figure 1**).[77-79] The endotypes include MVA (evidence of CMD defined as CFR <2.0, IMR ≥25, or microvascular spasm), VSA (CFR ≥2.0, IMR <25, and epicardial spasm), and mixed type (both evidence of CMD and epicardial spasm).[4,80,81]

The landmark CorMicA (Coronary Microvascular Angina) trial, a randomized, controlled, blinded clinical trial of stratified medicine in patients with angina, demonstrated that a strategy of invasive coronary function testing linked to medical therapy tailored to the patient's specific endotype leads to a significant improvement in health-related QoL compared with standard management.[82,83] No disease-modifying therapies have been specifically designed for INOCA yet. Nevertheless, the diagnosis of the specific INOCA endotype is critical for providing personalized treatment and enhancing prognosis.[11,50,84]

Traditional CV risk factors, including hypertension, dyslipidemia, smoking, and diabetes, play a substantial role in the development of both coronary microvascular and vasospastic dysfunction, as well as the structural remodeling of coronary microcirculation. Therefore, it is crucial to systematically identify and effectively manage these risk factors to prevent disease progression and alleviate symptoms. The selection of the most appropriate medications should be tailored to the predominant endotype.[4]

CCBs have been demonstrated to be effective for both VSA and MVA related to microvascular spasm, with expert consensus recommending them as the first-line treatment for vasomotor disorders.[4] Especially in patients with VSA, CCBs have been demonstrated to effectively suppress anginal attacks and reduce the rate of CV events.[85-88]

Long-acting nitrates may reduce anginal episodes in VSA, but they have not shown prognostic benefits and could aggravate symptoms in MVA owing to potential steal syndrome effects or reduced nitrate responsiveness in the microcirculation.[89,90] Similarly, short-acting nitrates may usually offer only partial relief for acute angina episodes.[91]

In case of MVA due to an abnormal CFR and/or an increased IMR, β-blockers, CCBs, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may all be beneficial. β-blockers are first-line therapy for CMD with effort-induced angina, especially when increased adrenergic activity is evident, because they can prolong diastolic filling time and lower metabolic demand.[11,92,93] However, they may exacerbate VSA and are not recommended for these patients.[94] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been shown to restore endothelial function and improve coronary blood flow in hypertensive patients with MVA, improving CFR and alleviating angina, particularly in women.[95,96] Statins also offer benefits by reducing angina episodes and rate of CV events in VSA as well as enhancing endothelial function and CFR in CMD, likely owing to their anti-inflammatory and antioxidant properties.[97]

Ranolazine has been demonstrated to be effective in alleviating angina in MVA patients with significantly reduced CFR due to an impaired vasodilation.[98] Ivabradine might improve persistent anginal symptoms in selected MVA patients, but its role is still controversial and barely investigated.[99] Nicorandil could mitigate exercise-induced ischemia in CMD patients, indicating a direct vasodilator effect on coronary microvasculature.[100] Fasudil, a selective rho-kinase inhibitor currently available only in Japan and China, has been demonstrated to prevent coronary spasm and ischemia in VSA and MVA due to microvascular spasm and reduce microvascular resistance in those with increased IMR.[101-103]

Genetic dysregulation of endothelin-1 has been demonstrated to be possibly implicated in CMD, because endothelin-1 is a potent vasoconstrictor acting on endothelin-A receptors.[104] The PRIZE (Precision Medicine With Zibotentan in Microvascular Angina) trial aims to evaluate whether the add-on treatment with potent and selective oral endothelin-A receptor antagonists can improve exercise tolerance in patients with MVA and impaired exercise capacity.[105]

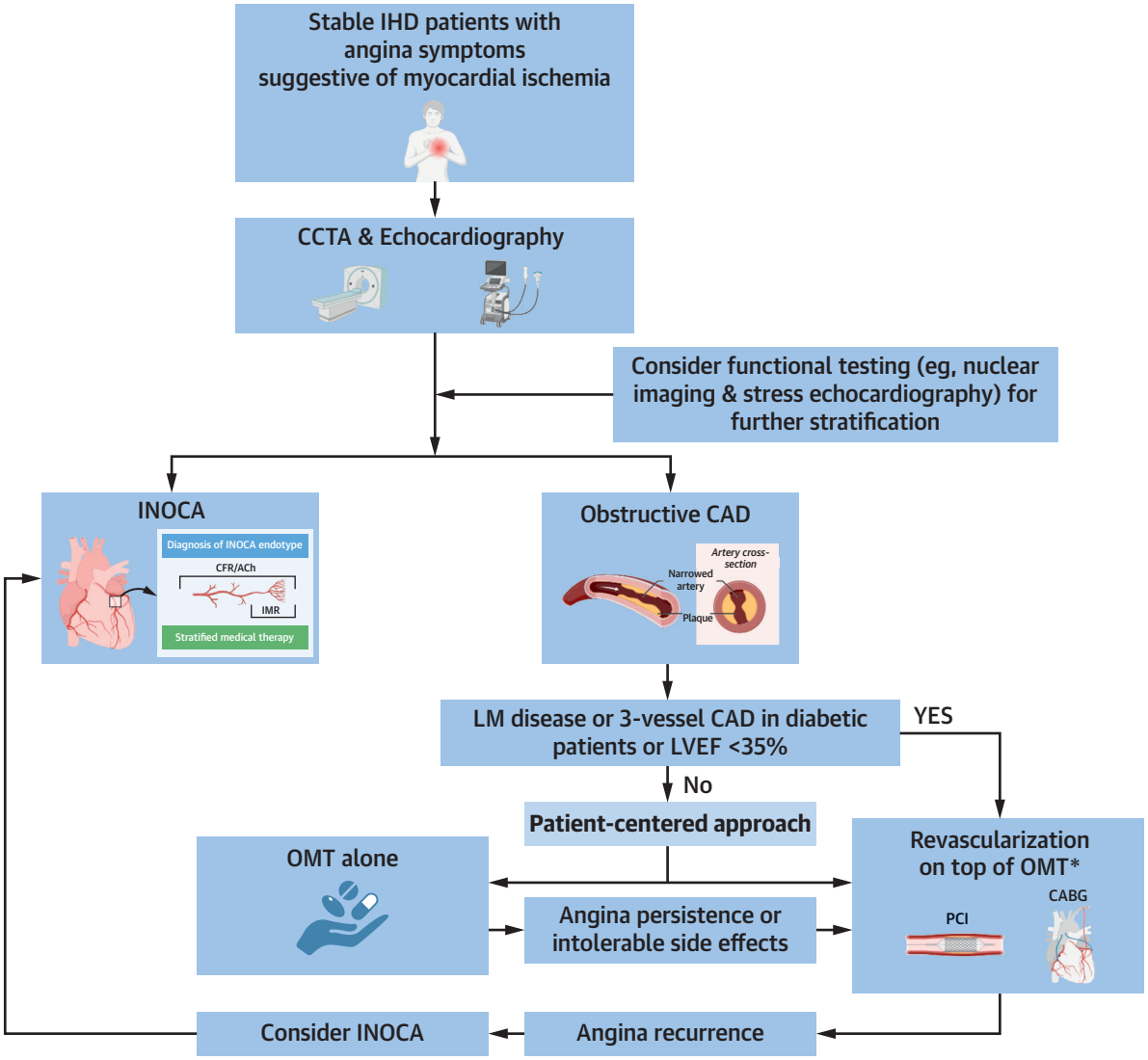
Finally, "sensitive heart syndrome" refers to a condition where individuals experience intense chest pain not linked to structural heart disease but originating from factors such as hyperalgesia, allodynia, noncardiac causes (eg, gastroesophageal reflux, musculoskeletal issues), and psychologic factors (eg, stress, anxiety). Effective management typically requires a multidisciplinary approach, including pain management, psychologic support, and lifestyle modifications.[106,107]

COMPREHENSIVE MANAGEMENT OF PATIENTS PRESENTING WITH ANGINA

Comprehensive management of patients presenting with stable angina is summarized in the **Central Illustration**. For all patients, the achievement of optimal CV risk factor control through lifestyle intervention (diet, exercise, and smoking cessation) and guideline-directed pharmacologic secondary prevention targeting hypertension, dyslipidemia, and diabetes is essential to reduce CV events and improve prognosis.[108-111]

Patients should initially undergo coronary computed tomographic angiography (CCTA) to rule out the presence of LM disease or extensive 3-vessel CAD in diabetic patients. Echocardiography should be performed to detect any severe LV dysfunction caused by obstructive CAD (LVEF <35%) or any other cardiac condition that may cause symptoms (eg, valvular heart disease, cardiomyopathies). Other imaging modalities, such as nuclear stress testing (eg, cardiac single photon emission computed tomography with myocardial perfusion imaging) and stress echocardiography, can provide additional physiologic information and assist with risk stratification, offering valuable insights into myocardial perfusion and function, and assessing the severity and extent of myocardial ischemia. In patients with extensive 3-vessel disease and diabetes or severe LV dysfunction, a strategy of revascularization (with CABG

CENTRAL ILLUSTRATION **Comprehensive Decision Algorithm for Managing Stable Angina**

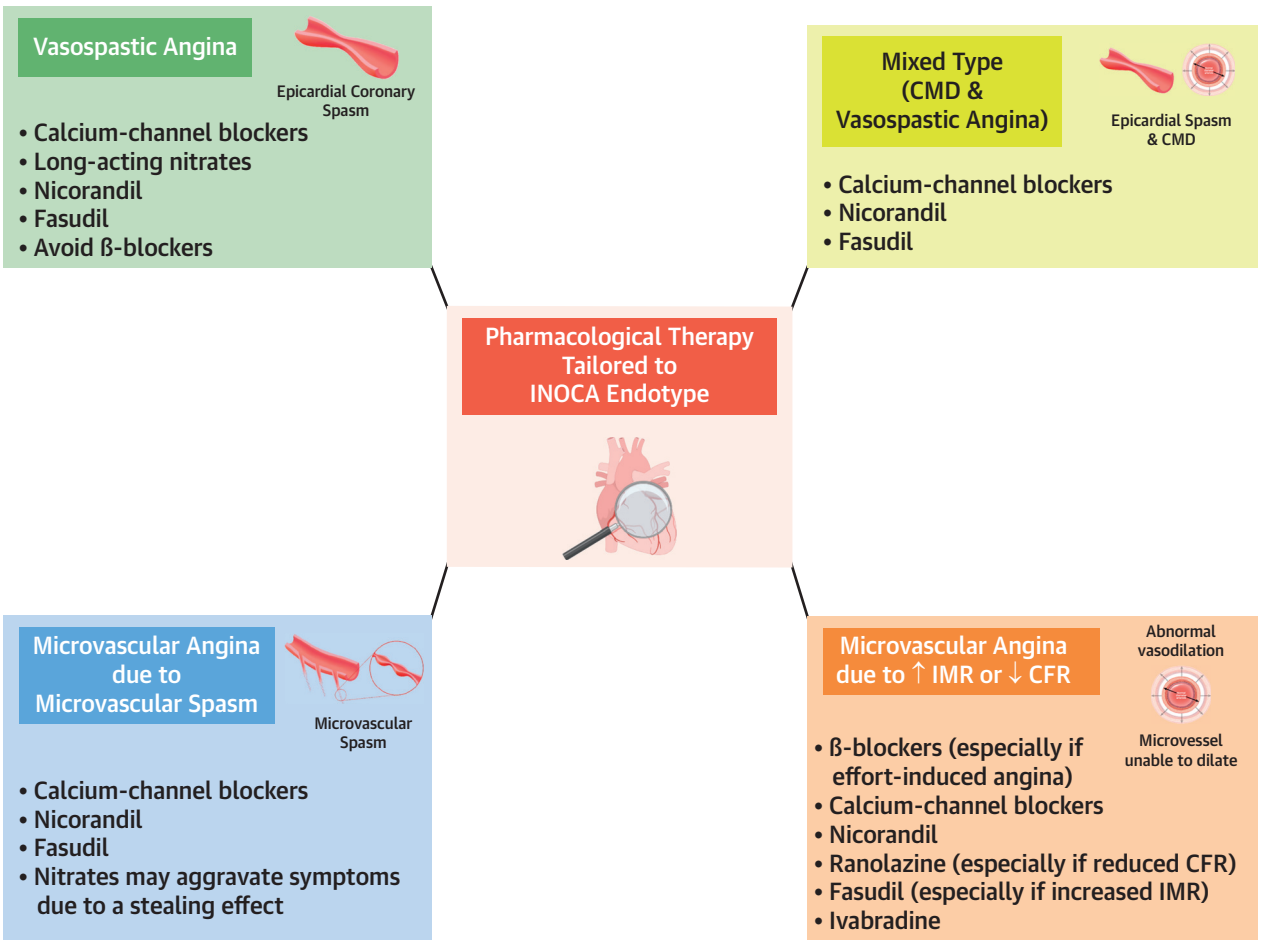


Montone RA, et al. J Am Coll Cardiol. 2024;84(8):744-760.

The initial assessment with coronary computed tomographic angiography (CCTA) and echocardiography categorizes patients into 2 primary pathways: those with obstructive coronary artery disease (CAD) and those with ischemia with nonobstructed coronary arteries (INOCA). Further functional testing, such as nuclear imaging or stress echocardiography, can help to refine risk stratification and guide treatment choices. For patients with obstructive CAD exhibiting 3-vessel disease and diabetes, left main (LM) disease, or severe left ventricular (LV) dysfunction, myocardial revascularization is recommended.* For all other patients, treatment options are outlined between optimal medical therapy (OMT) alone and coronary revascularization in conjunction with OMT, emphasizing a patient-centered approach. In cases of INOCA, treatment should be personalized based on the specific endotype. The figure also highlights decision nodes based on symptom persistence or recurrence, directing further diagnostic or therapeutic measures. *Current evidence does not support recommending PCI over CABG in obstructive CAD exhibiting 3-vessel disease and diabetes, LM disease, or severe LV dysfunction. ACh = acetylcholine; CABG = coronary artery bypass grafting; CFR = coronary flow reserve; IHD = ischemic heart disease; IMR = index of microvascular resistance; LVEF = left ventricle ejection fraction; PCI = percutaneous coronary intervention.

preferred over PCI) on top of OMT might be considered even in the absence of symptoms, and it should be implemented in patients with LM disease in the absence of contraindications. For all other patients with obstructive CAD, an initial trial of empiric antianginal treatment is an important initial step recommended by current clinical guidelines.[11-13] Nevertheless, a significant percentage of patients

FIGURE 2 **Pharmacologic Therapy Tailored to the Specific Endotype of Ischemia With Nonobstructed Coronary Arteries (INOCA)**



After diagnosing the specific ischemia with nonobstructed coronary arteries (INOCA) endotype, tailored medical therapy can be initiated. For vasospastic angina, calcium channel blockers are the first-line treatment, followed by long-acting nitrates, nicorandil, and fasudil; β-blockers are contraindicated. For microvascular angina caused by microvascular spasms, calcium channel blockers are preferred, followed by nicorandil and fasudil, with nitrates contraindicated. In cases of microvascular angina due to reduced coronary flow reserve (CFR) or increased index of microvascular resistance (IMR), both β-blockers and calcium channel blockers are effective, supplemented by nicorandil, ranolazine (particularly if CFR is reduced), fasudil (particularly if IMR is elevated), and ivabradine. For the mixed type, calcium channel blockers are recommended first, followed by nicorandil and fasudil. See the text for more details. CMD = coronary microvascular dysfunction.

(up to 30% in clinical trials) receiving OMT may require a referral for revascularization because of inadequate symptom control.[112] In those patients, the choice of a strategy of coronary revascularization plus OMT should be based on a personalized patient-centered approach stemming from the considerations reported above, considering in particular QoL and angina severity.[113] The choice between revascularization modalities (PCI or CABG) should be made individually based on patients' characteristics. The decision-making process should be collaborative, involving a health care team that includes both treating and referring clinicians alongside the patient and their family. It is important to emphasize that coronary revascularization plus OMT or OMT alone treatment options should not be seen as competing alternatives but rather as complementary strategies working together to enhance patient-centered outcomes. Although this patient-centered approach is ideal, its practical implementation can be challenging. Nonetheless, recognizing the importance of this approach, along with its inherent challenges, is crucial to stimulate significant improvements in informed consent and patient engagement practices. This might include enhancing training for health care providers in communication skills and developing

supportive tools and resources that could help reduce the gap between current practice and the ideal scenario of fully informed decision making.

Finally, for patients without evidence of obstructive CAD on CCTA, or in case of angina recurrence after revascularization, nonobstructive causes of angina, such as CMD and VSA, should be investigated.[31] The diagnosis of the INOCA endotype should be performed with the use of coronary angiography and functional tests, and pharmacologic therapy tailored to the specific endotype should be initiated (**Figure 2**).[4]

CONCLUSIONS AND FUTURE DIRECTIONS

The management of stable angina is shifting toward a more tailored, patient-centered approach, moving away from the traditional one-size-fits-all strategy. Future research is essential to integrate innovative diagnostics and personalized medicine, aiming to customize treatment plans according to the specific needs and characteristics of each patient. An integrated care model that encompasses medical treatments, lifestyle changes, and procedural interventions is crucial for a comprehensive strategy in managing these patients. This evolving patient-centric paradigm represents a significant advancement in angina management, combining the best of OMT and revascularization to ensure the most effective and safe treatment for each individual.

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