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Evolving Management Paradigm for Stable Ischemic Heart Disease Patients:

JACC Review Topic of the Week

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Abstract

Management of stable coronary artery disease (CAD) has been based on the assumption that flow-limiting atherosclerotic obstructions are the proximate cause of angina and myocardial ischemia

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in most patients and represent an important target for revascularization. However, the role of revascularization in reducing long-term cardiac events in these patients has been limited mainly to those with left main disease, 3-vessel disease with diabetes, or decreased ejection fraction. Mounting evidence indicates that nonepicardial coronary causes of angina and ischemia, including coronary microvascular dysfunction, vasospastic disorders, and derangements of myocardial metabolism, are more prevalent than flow-limiting stenoses, raising concerns that many important causes other than epicardial CAD are neither considered nor probed diagnostically. There is a need for a more inclusive management paradigm that uncouples the singular association between epicardial CAD and revascularization and better aligns diagnostic approaches that tailor treatment to the underlying mechanisms and precipitants of angina and ischemia in contemporary clinical practice.

Keywords

coronary microvascular dysfunction; epicardial coronary artery disease; myocardial ischemia; percutaneous coronary intervention; revascularization; stable angina

Since the advent of coronary angiography more than 60 years ago, stable coronary artery disease (CAD) management has been based on the plausible assumption that “significant” flow-limiting atherosclerotic obstructions of epicardial coronary arteries are the proximate cause of angina and myocardial ischemia in most cases. This belief, supported by anatomic and physiologic evidence that obstructive coronary stenoses can result in regional ischemia and may, in the acute setting, cause acute myocardial infarction (MI), has profoundly influenced our approach to CAD management. In acute MI patients, either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) can restore coronary flow and improve event-free survival.[1,2] There is also a prevalent belief that epicardial coronary stenosis remains the dominant cause or sine qua non of stable angina and ischemia. While, indeed, revascularization may reduce incident cardiac events in high-risk subsets with stable CAD (eg, left main disease, 3-vessel CAD with diabetes, and decreased ejection fraction), evidence from multiple randomized controlled trials (RCTs) has shown that revascularization of epicardial coronary obstructions, particularly with the use of PCI, does not reduce mortality or morbidity compared with guideline-directed medical therapy (GDMT) in the great majority of stable CAD patients.[3,4]

While revascularization of epicardial stenoses provides better symptom relief and improved quality of life compared with GDMT, recurrence of angina ranges between 20% and 30% within a year after successful PCI[5] and up to 40% within 3 years,[6] frequently leading to subsequent coronary angiography and repeated PCI. However, because repeat angiography often reveals no evidence of in-stent restenosis or residual coronary obstruction, it is essential to consider *nonobstructive* causes of angina. Thus, an often-unforeseen consequence of focusing disproportionately on epicardial coronary obstruction is that other pathogenetically important causes of angina and ischemia may not be considered. These causes include epicardial or microvascular coronary vasospasm, coronary microvascular dysfunction (CMD), and derangements of myocardial energy or metabolism.[7]

Accordingly, there is a need for a new, more broadly inclusive, management paradigm for patients with stable angina that uncouples the often-singular association between obstructive CAD and revascularization. Because there are many other potential pathogenetic mechanisms responsible for angina and ischemia, it is essential to identify diagnostic and therapeutic approaches to better tailor appropriate treatment of both obstructive and nonobstructive causes of myocardial ischemia. In so doing, a more pathogenetically directed approach to diagnosing and treating angina and ischemia would more likely align pharmacologic and procedural interventions as complementary and synergistic for a broader population of stable CAD patients.

LESSONS LEARNED FROM RECENT COMPARATIVE EFFECTIVENESS TRIALS

Earlier RCTs[3,4] showed no incremental benefit of revascularization in reducing mortality, MI, and repeated revascularization when added to GDMT, which included multifaceted pharmacologic secondary prevention and lifestyle intervention. Those studies, however, had limitations, eg, inclusion of low-risk subjects, those with mild to moderate baseline ischemia, use of bare-metal or first-generation drug-eluting stents, and lack of blinding before diagnostic coronary angiography, that may have resulted in exclusion of subjects with severe angiographic obstructive disease. The ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) randomized patients with moderate-to-severe inducible ischemia to an initial invasive strategy with revascularization (third-generation drug-eluting stents or CABG) plus GDMT vs an initial conservative strategy of GDMT alone.[8] It found no benefit of an invasive approach on the primary endpoint (cardiovascular death, MI, resuscitated sudden cardiac death, or hospitalization for unstable angina or heart failure) or secondary endpoint (cardiovascular death or MI). The invasive strategy did result in a statistically significant quality of life improvement, although the overall effect was modest and concentrated mainly in the ~20% of patients with weekly to daily angina.[9]

In addition, a meta-analysis of GDMT with or without PCI in patients with stable CAD (10 RCTs comprising 12,125 patients, including ISCHEMIA)[10] confirmed that PCI did not reduce mortality or MI vs GDMT alone, though the invasive strategy was associated with fewer follow-up revascularizations and improved anginal symptoms.

To evaluate potential bias in unblinded trials, the efficacy of PCI for the treatment of angina was studied in a placebo-controlled trial, which showed no incremental improvement in treadmill walking time, angina relief, or quality of life with PCI + GDMT vs a placebo procedure + GDMT.[11] While limited by the small sample size and short follow-up, this study raises the issue of whether the observed salutary effect on angina relief attributed to PCI in earlier unblinded trials was due, at least in part, to a placebo effect.[12]

Finally, we should recognize that managing patients with stable angina must include informed and well considered decision making involving the patient, family, and physician. Both invasive and conservative approaches may be appropriate and should not be viewed

as competing treatment approaches but rather as complementary and potentially additive strategies to enhance optimal patient-centered outcomes.[13,14]

WHY REVASCULARIZATION MAY NOT BE A THERAPEUTIC SOLUTION IN MANY STABLE ANGINA PATIENTS

In contrast to type 1 MI, for which prompt revascularization is indicated,[1,2] revascularization has not been shown to reduce cardiac events in most stable CAD patients.[3,4,8,15] Because atherosclerosis is fundamentally a systemic vascular and inflammatory condition affecting epicardial arteries and coronary microcirculation as well as other vascular beds, appropriate GDMT management of ischemia and atherosclerosis must include lifestyle modification (diet, exercise, tobacco cessation), intensive risk factor control, and multifaceted pharmacologic secondary prevention (targeting hypertension, dyslipidemia, diabetes, and perhaps inflammation), and, when angina is present, effective symptom control.[16,17]

Important observational data from recent large registries indicate that self-reported angina may improve or resolve over time with medical therapy in most stable CAD patients,[18] and subsequent revascularization may be needed in only a minority of patients (~5%) during 5-year follow-up.[19] Because angina may relapse or remit over time and coronary plaques may become quiescent, an appropriate assessment of angina requires careful follow-up and systematic ascertainment of patient-reported symptoms and quality of life. Thus, a sufficient time horizon (3–6 months) is often required for an empiric course of GDMT to be adequately evaluated and efficacy assessed.[20,21] Finally, difficulty in achieving optimal GDMT should not necessarily represent justification to refer patients for revascularization, particularly if a sufficient empiric trial has not been implemented[19–22] or if symptoms are infrequent and mild. Instead, effective GDMT can be achieved by an iterative process that entails collaboration with patients, along with education and counseling, toward a goal of largely patient-directed self-care.[23–25]

Nevertheless, ensuring that patients are treated optimally with both lifestyle intervention and multifaceted pharmacologic secondary prevention is time and labor intensive, and many cardiologists to whom patients are referred for specific diagnostic testing, including invasive angiography and revascularization, may lack resources to oversee the intensification of medical therapy personally. Therefore, more inclusive and coordinated team-management strategies incorporating physician extenders (nurse practitioners, physician assistants, pharmacists) are needed to facilitate optimization of GDMT and improve patient care.[23] Using standardized care pathways and management algorithms may further enhance the use of these proven approaches.[24,25] Finally, implementation of GDMT likewise remains suboptimal in patients undergoing revascularization,[26–28] and such therapies must be similarly prioritized to reduce incident events following revascularization.

IMPORTANCE OF DIAGNOSING ANGINA AND ISCHEMIA ACCORDING TO THE UNDERLYING PATHOGENETIC CAUSE(S)

Essential insights on the need for a more encompassing view of the many causes and precipitants of angina and ischemia derive from the SCOT-HEART (Scottish Computed Tomography of the Heart) trial.[29] There, most patients with known or suspected stable CAD did not have flow-limiting stenoses, indicating that the vast majority (approximately 4 in 5 individuals) had underlying causes of angina and ischemia not attributed to epicardial stenoses (Figure 1). For this reason, a purely anatomic diagnostic approach using invasive coronary angiography or coronary computed tomography angiography (CCTA) may fail to diagnose microvascular and/or vasospastic angina as treatable causes of angina, leaving many patients in whom no obstructive coronary lesions are identified and thence falsely reassured that ischemia is not present. Often such patients are discharged from cardiology, at which point myriad potential (and costly) noncardiac causes are probed rather than pursuing a more diligent evaluation of nonepicardial coronary causes of angina.

This is particularly important for women, because most patients with ischemia and no obstructive coronary arteries (INOCA) are female.[30] Heart disease in women is underrecognized and undertreated, particularly INOCA, where failure to account for microvascular and vasospastic angina within the primarily noninvasive anatomic imaging strategy may result in misdiagnosis.[31] Certain stakeholder organizations have recognized that using CCTA as the primary diagnostic testing strategy in angina patients may help only in diagnosing obstructive epicardial CAD, which is not the most common cause of angina and is even less common in women than men.[32]

Indeed, a large observational study of almost 400,000 angina patients undergoing elective coronary angiography found that, among those with a positive noninvasive stress test, only 41% had obstructive CAD,[33] indicating a need to embrace a more inclusive management approach that includes many other pathophysiologic mechanisms, including CMD and coronary vasospasm (epicardial and/or microvascular).[34–36] Similarly, the 2019 European Society of Cardiology guidelines on chronic coronary syndromes showed that, among patients with typical angina in the most common age range for detecting stable CAD (50–59 years), 68% of men and 87% of women did not have obstructive coronary stenoses,[37] and the CorMicA (Coronary Microvascular Angina) trial[36] and others[34] revealed that approximately 45% of patients presenting with angina or ischemia did not have CAD at angiography. Yet nearly 90% of these patients demonstrated objective evidence of coronary vasomotor dysfunction,[38] including 81% with CMD. Thus, in a sizable proportion of suspected stable CAD patients, CMD or epicardial vasoconstriction can contribute to angina, and because functional mechanisms may coexist with obstructive CAD, these ischemia precipitants are not necessarily mutually exclusive and may often occur in the same patient.[39]Accordingly, a complete medical evaluation of stable angina patients should characterize the natural history, cardiovascular risk factors, physical examination, and pharmacotherapy (including treatment response, medication intolerance, and adherence). Treadmill exercise testing remains useful to assess functional capacity, response to the physiologic stress of exercise, and limiting symptoms and features of inducible ischemia

(notably symptoms and electrocardiographic changes). The response to treatment can be diagnostically informative, and the initial management plan should include antianginal drug therapy, such as short-acting nitrates and either a beta-blocker or a calcium-channel blocker. This initial approach complements referral for CCTA because heart rate control (target 60 beats/min) is required for optimal imaging.

HOW TO DIAGNOSE AND MANAGE VASOSPASM, MICROVASCULAR DYSFUNCTION, AND OTHER CAUSES OF MYOCARDIAL ISCHEMIA

Both the 2021 AHA/ACC chest pain guideline[40] and the 2019 European Society of Cardiology chronic coronary syndromes guideline[37] delineate the 3 different mechanisms of stable angina (obstructive CAD, coronary vasospasm, and CMD). However, a fundamental limitation is the lack of a standard diagnostic evaluation for all patients with suspected angina. Although anginal chest discomfort is “the alarm system of the heart” and often the cardinal symptom of myocardial ischemia, it does not provide specificity on its cause. Therefore, it is critical not only to rule in or rule out obstructive CAD but also to establish the cause of myocardial ischemia and to prove or disprove the ischemic origin of symptoms. Such a diagnostic evaluation that comprehensively assesses anatomic and functional coronary alterations would help to confirm or exclude the diagnosis of myocardial ischemia and determine the precipitating cause whenever possible.

Myocardial perfusion imaging using positron emission tomography or cardiovascular magnetic resonance imaging is useful for diagnosing CMD.[41] These noninvasive imaging techniques provide quantitative and qualitative information on inducible myocardial ischemia. Dynamic first-pass vasodilator stress/rest positron emission tomography uses radiotracers (eg, ^{82}Rb, ^{13}N-ammonia, ^{15}O-H_2O) and quantifies absolute myocardial blood flow.[42] Advances with stress cardiovascular magnetic imaging include fully automatic pixelwise quantitative mapping of myocardial perfusion.[43,44] This method generates pixel-encoded maps of myocardial blood flow (mL/min per g tissue) during vasodilator stress and at rest. Postprocessing software gives accurate measurements for both regional and global stress and resting myocardial blood flow and myocardial perfusion reserve (the ratio of stress to rest myocardial blood flow). A myocardial perfusion reserve <2.0, in the absence of obstructive CAD, is widely accepted as the CMD threshold associated with adverse outcomes.[41]

An algorithm for practical assessment of the multiple causes of angina and ischemia is proposed in the Central Illustration. It outlines a pragmatic approach stemming from current international guideline recommendations and results of landmark studies.[3,8,29] It supports an initial evidence-based approach, including lifestyle interventions and pharmacologic secondary prevention with GDMT, to achieve and maintain multiple cardiovascular treatment targets for blood pressure, lipids, and glycemic levels as per the current U.S.[40] and European guidelines.[37] This algorithm endorses selective functional or anatomic imaging to identify high-risk subsets of stable CAD patients for whom revascularization is more appropriate than medical therapy alone.

If noninvasive studies identify a very low angina threshold and/or a large area of ischemic myocardium at risk during noninvasive stress testing, CCTA or invasive coronary angiography is appropriate to exclude left main and/or high-grade multivessel CAD. In all other chronic stable angina patients, an initial trial of empiric antianginal treatment is an important initial step and up-titrating dosages or adding agents for symptom control, as needed, is advocated.[21,22] Stable CAD patients with angina should receive at least 2 antianginal drug classes and adjusted over 3 to 6 months before referral for revascularization, particularly if anginal symptoms are mild or infrequent (Figure 2).

In those with persistent or recurrent ischemic symptoms despite intensive symptomatic treatment, coronary angiography is indicated to identify patients with flow-limiting stenoses who might benefit from myocardial revascularization. In patients without obstructive stenosis, the functional assessment of coronary circulation, including acetylcholine testing for spasm, coronary flow reserve, and microvascular resistance, should be considered to guide subsequent pharmacologic treatment. This algorithm allows tailoring of the diagnostic workup to the clinical situation (Central Illustration) and places less emphasis on CCTA, which, as currently used, is unable to detect functional coronary alterations (endothelial dysfunction or vasospasm) responsible for ischemia. In SCOT-HEART,[29] nonfatal MI at 5 years was lower in the CCTA-guided group than in the standard care group, but there was no effect on mortality. Secondary prevention therapy, including aspirin and statins, was higher in the CCTA-guided group, further implying that disclosure of atherosclerosis resulted in linked therapy.

Ideally, the above-proposed diagnostic evaluation should be performed in all stable angina patients in whom obstructive CAD has been excluded, but, from a practical standpoint, many centers will not have access to such sophisticated testing modalities or may lack the skill or expertise to undertake such evaluations, and there are potential cost-effectiveness concerns that need to be considered as well. Therefore, we advocate additional diagnostic testing, described above, only after obstructive CAD has been excluded and only if symptoms do not improve (or if they worsen) despite appropriate antianginal therapy of at least 2 drug classes.[21]

WHY WE NEED A PARADIGM SHIFT IN OUR APPROACH TO ANGINA AND ISCHEMIA

Cardiologists should reappraise their thinking of angina and prioritize the following: 1) angina may be due to obstructive CAD and/or INOCA; 2) most patients presenting with chronic angina do not have epicardial coronary obstructions; 3) if CCTA is the initial diagnostic test and obstructive coronary stenoses are excluded, subsequent testing should include stress perfusion imaging, positron emission tomography, and/or invasive functional coronary angiography with pharmacologic testing to detect coronary microvascular or vasospastic mechanisms that may require more targeted therapy; and 4) most INOCA patients are women, and a diagnostic strategy with a singular focus on defining epicardial coronary obstructions may be inadequate.

Of interest, a comprehensive noninvasive diagnostic approach that contemplates both anatomic and functional issues may be provided by multimodality imaging such as PET/CCTA or “dynamic” CCTA and could be viewed as a noninvasive “one-stop shop” model to diagnose angina and suspected CAD, both obstructive and nonobstructive.[45] Ongoing RCTs will determine whether dynamic CCTA fulfills this promise.

PHARMACOLOGIC MANAGEMENT TARGETING THE PRECIPITANTS OF ANGINA AND ISCHEMIA

A reduction of coronary/myocardial flow reserve may reflect ischemia due to epicardial stenoses, impaired microvascular function, or both, even in the same patient, as noted above. In this setting, drugs that reduce myocardial oxygen consumption (beta-blockers, nondihydropyridine calcium-channel blockers, or ivabradine) or optimize myocardial oxygen utilization (ranolazine or trimetazidine) are likely the best option. Their combination can also be considered (Figure 2). Alternatively, ischemia can also be caused by epicardial or microvascular spasm. In this setting, vasodilators (calcium-channel blockers, nitrates, or nicorandil) are most appropriate, and their combination can also be considered. Thus, to the extent possible, it is highly desirable to tailor pharmacologic therapies to the underlying causes and precipitants of ischemia.

CONCLUSIONS: WHERE DO WE GO FROM HERE?

The time has come for a paradigm shift in managing stable CAD patients. First, we need to expand our current scientific thinking about the many causes and mechanisms of both angina and myocardial ischemia and uncouple the narrow association of ischemia with obstructive epicardial disease[46] as the guiding approach to management. Both angina and ischemia have many causes, but obstructive epicardial disease may or may not be the underlying pathogenetic mechanism (Central Illustration, Figure 2). Therefore, our nomenclature should reflect the actual causes of ischemia and angina beyond the currently used terms “coronary” and “disease,” both of which connote epicardial coronary obstruction and are perhaps too narrowly restrictive. A more inclusive and descriptive nomenclature might be considered, such as “acute and chronic myocardial ischemic syndromes.”[47]

Second, we must embrace a more enlightened management approach. Assessments of ischemia that do not delineate abnormal coronary angiographic findings should not necessarily shift diagnostic and therapeutic considerations to noncardiac causes of angina but rather to exploring nonepicardial coronary causes (eg, CMD and vasospastic disorders). We must remain mindful that the evaluation and treatment of angina and ischemia need to be tailored to the individual patient and that adoption of available diagnostic tools required for personalized approaches in clinical practice remains challenging.

Third, we must invest in developing newer management strategies and health care delivery models that may better align with treatments proven to benefit patients and society.[48–52] Proven secondary prevention strategies and lifestyle interventions in contemporary GDMT continue to be underutilized, particularly in the United States, where as few as 40% to 50% of eligible CAD subjects are treated according to established clinical practice

guidelines, including those who have been revascularized.[26,49,51] A recent Viewpoint[52] addressing the new coronary artery revascularization recommendations[53] underscoresthe critical importance of concomitant preventive therapies in enhancing event-free survival and improving outcomes in stable CAD patients who had undergone CABG or PCI. In this way, perhaps we can rebalance patient management in a way that does not view procedural and pharmacologic interventions as competing treatments but rather as complementary and additive therapeutic approaches best suited to achieving optimal clinical outcomes and symptom relief for our patients.

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ABBREVIATIONS AND ACRONYMS

CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCTA	coronary computed tomography angiography
CMD	coronary microvascular dysfunction

GDMT	guideline-directed medical therapy
INOCA	ischemia and no obstructive coronary arteries
MI	myocardial infarction
PCI	percutaneous coronary Intervention
RCT	randomized controlled trial

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HIGHLIGHTS

- Several mechanisms other than obstructive coronary artery disease may cause myocardial ischemia.
- A conservative approach to management, including noninvasive testing, lifestyle interventions, and goal-directed multifaceted medical therapy, is evidence based and often effective in patients with stable angina.
- Pharmacologic and procedural approaches to stable ischemic heart disease are complementary, and integrating these can optimize outcomes.

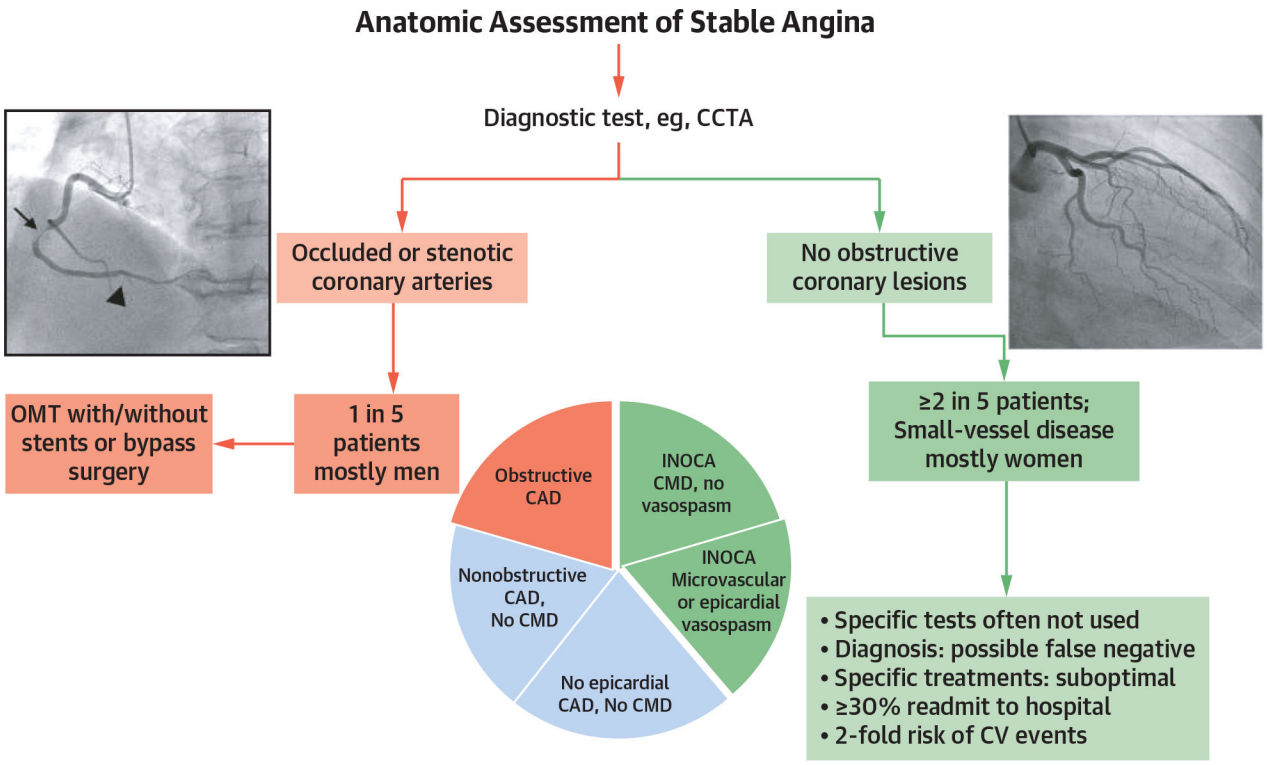


FIGURE 1. Clinical Assessment of Myocardial Ischemia and CAD

In SCOT-HEART,[33] most patients with suspected stable coronary artery disease (CAD) did not have epicardial coronary obstructions, with the vast majority (~4 in 5) having angina and/or ischemia not due to epicardial stenoses. CCTA = coronary computed tomography angiography; CMD = coronary microvascular dysfunction; CV = cardiovascular; INOCA = ischemia with no obstructive coronary arteries; MI = myocardial infarction; OMT = optimal medical therapy.

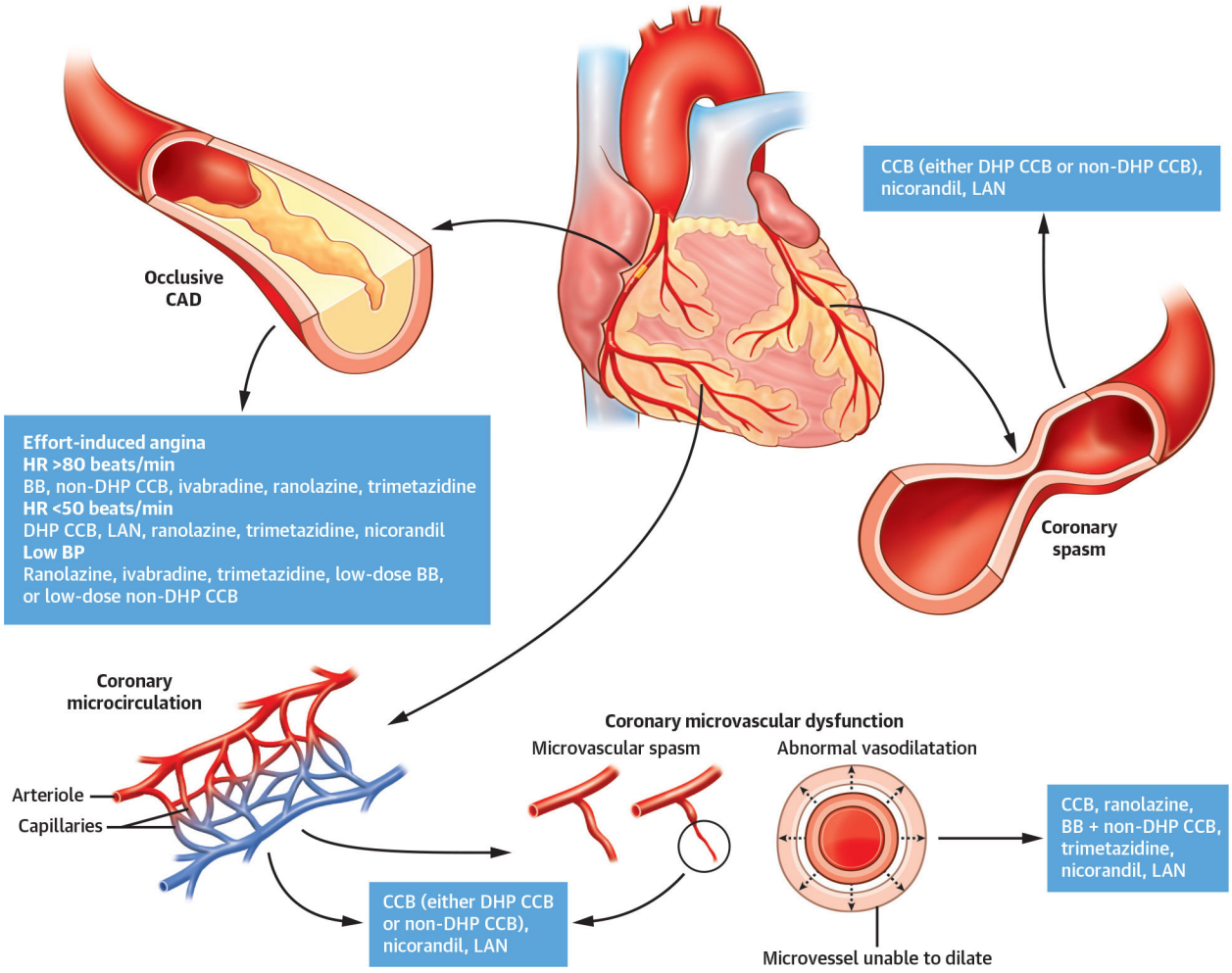
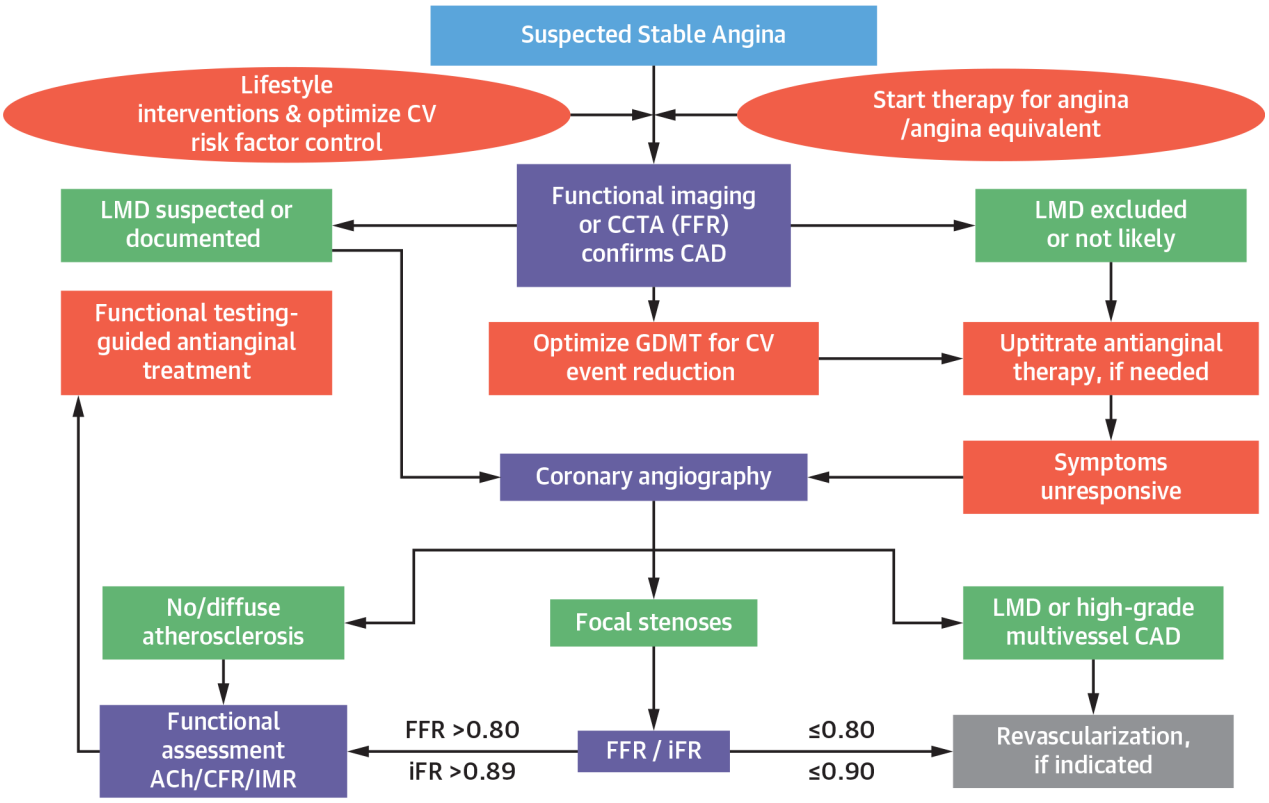


FIGURE 2. Antianginal Treatment Directed to the Mechanism Responsible for Ischemia

For exertional angina, antianginal drugs that reduce myocardial oxygen consumption (ie, beta-blockers [BBs], nondihydropyridine calcium-channel blockers [CCBs], or ivabradine) are most efficacious, whereas for variable threshold angina or coronary microvascular dysfunction, agents that improve myocardial oxygen utilization (ie, ranolazine or trimetazidine) are suitable treatment options. CCBs are the preferred option for epicardial or microvascular spasm, but nitrates and nicorandil may also be appropriate. BP = blood pressure; CAD = coronary artery disease; DHP = dihydropyridine; HR = heart rate; LAN = long-acting nitrate.



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CENTRAL ILLUSTRATION. Management Algorithm for Obstructive and Nonobstructive Coronary Causes of Angina

A more inclusive management paradigm for stable coronary artery disease (CAD) patients that addresses the many pathogenetic mechanisms responsible for angina and ischemia is necessary to identify diagnostic and therapeutic approaches that would better tailor the appropriate treatment of obstructive and nonobstructive causes of myocardial ischemia to the underlying ischemia precipitants. Such an approach seeks to promote both evidence-based pharmacologic secondary prevention and procedural interventions as complementary and potentially additive treatments to optimize the management of stable angina patients. ACh = acetylcholine; CCTA = coronary computed tomography angiography; CFR = coronary flow reserve; CV = cardiovascular; FFR = fractional flow reserve (a hyperemic pressure ratio);GDMT = guideline-directed medical therapy; iFR = instantaneous free wave ratio; IMR = index of microvascular resistance; LMD = left main disease.