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Medical therapy post revascularization in chronic stable angina patients–OPTA approach

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Abstract
The prevalence of coronary artery disease (CAD) has been steadily increasing in India. Percutaneous and surgical revascularization with angina treatment is important for the management of CAD. Revascularization may benefit patients with stable ischemic heart disease (SIHD) by preventing death, myocardial infarction (MI), and unstable angina. Beta-blockers, long-acting nitrates, and calcium-channel blockers are considered as the mainstay of pharmacological treatment of restenosis. Timing from successful coronary angioplasty to the onset of recurrent chest pain is the strongest predictor of angiographic outcomes. Patients presenting with pain between 1 and 6 months following percutaneous coronary intervention (PCI) typically had angina secondary to restenosis, and those presenting with pain for more than 6 months after the procedure were likely to have progression of coronary disease in a vessel other than the target vessel. The consensus stresses on repeat angiography to assess the cause for recurrent angina, re-stratify the patients at risk, and promptly initiate appropriate medical therapy in light of the goals of OPTA medical management.

Keywords: coronary artery disease, angina, recurrent angina, revascularization

Introduction
Coronary artery disease (CAD) is a leading cause of mortality and morbidity around the globe. It results from the development of obstructive coronary artery plaques, reducing the oxygen supply to the myocardium. Stable CAD (SCAD) is for the most part characterized by episodes of reversible myocardial demand/supply incongruity, leading to myocardial ischemia or hypoxia, which are usually inducible by exercise, emotion or other stress and are reproducible, which may also be occurring spontaneously. Despite the fact that the prevalence and mortality due to CAD are declining in the developed countries, the same cannot be held true for developing countries. About 4-fold increase in CAD prevalence has been reported in India during the past 40 years [1]. The prevalence of CAD has been steadily increasing, and India is no exception to this. In the last 3 decades, the prevalence of CAD has significantly increased. The prevalence of CAD in urban areas was 2.5%–12.6%, and in rural areas it was 1.4%–4.6%. The projected data show that from 1990 to 2020, there will be a 117% and 105% rise in mortality from CAD in men and women, respectively, in India [2]. Stable angina, which affects a large proportion of individuals in the general population, is associated with major cardiovascular events including myocardial infarction (MI) and cardiac deat [3].
In the absence of Indian guidelines, this article provides consensus of eminent cardiologists from major regions in India to aid in prompt diagnosis and successive treatment of recurrent angina.

Methodology
Zonal level consensus meetings were held at five metro cities of India (Coimbatore, Mumbai, New Delhi, Patna and Chennai) during mid-2019. Fifty-one eminent experts (cardiologists and consulting physicians) from different regions attended a panel meeting. Various aspects of the medical management of stable ischemic heart disease (SIHD), need for revascularization, factors responsible for recurrent angina after percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), diagnostic tests and management of recurrent angina post revascularization were discussed. The consensus of these meetings is discussed in this article.

Review of consensus
Management of chronic stable angina
The goals in treating patients with chronic stable angina are (1) to relieve symptoms, (2) to prevent progression of the atherosclerotic process and reduce risk of MI or sudden cardiac death and (3) to control complicating factors that trigger or

worsen ischemia [3].

Medical management of angina

All patients with established CAD should be prescribed guideline-directed medical therapy (GDMT) to mitigate progression of atherosclerosis and to prevent MI and cardiovascular (CV) death (Table 1). In patients with biomarker-positive acute coronary syndromes (ACS), it is widely accepted that routine revascularization, in addition to GDMT, reduces the short- and long-term rates of death and MI compared with a more conservative approach [4].

In spite of the widespread use of percutaneous and surgical revascularization, medical treatment of angina remains an important modality for the management of CAD. In addition to symptom control with antianginal drugs, medical treatment also involves the identification and treatment of associated conditions, risk factor reduction and lifestyle modification (Table 1) [5].

Table 1: Medical management of angina

Angina relief
Treat associated conditions if any (e.g., anemia)
Short-acting nitrate plus
• Beta-blocker/rate-lowering CCB
• (Beta-blocker if history of MI or LVD)
• Consider CCB-DHP if low heart rate/intolerance/contraindications
• Consider beta-blocker + DHP-CCB if still symptomatic
Add second-line drugs if still symptomatic or contraindications/intolerance to first-line drugs
• Long-acting nitrate
• Ivabradine
• Nicorandil
• Ranolazine
• Trimetazidine
Prevention of further atherosclerosis & CV event prevention
• Control of risk factors
• Lifestyle modification and adaptation
• Antiplatelet (aspirin)
• Statin
• ACEI/ARB if LVD, diabetes, high BP and CKD, consider ACEI for all stable CAD patients
• Beta-blocker if post MI or LVD

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; CV, cardiovascular; DHP, dihydropyridine; LVD, left ventricular dysfunction; MI, myocardial infarction

Requirement of revascularization

Revascularization may benefit patients with SIHD by preventing death, MI and unstable angina and by improving quality of life (QoL). Randomized trial data suggest revascularization is safe and reduces death and/or MI and/or improves QoL, especially when substantial ischemia is present. In the Medicine, Angioplasty or Surgery Study (MASS) II trial, 611 patients with proximal multivessel disease and documented ischemia were randomly assigned to receive CABG, PCI or optimal medical therapy (OMT). The 10-year mortality rates in the 3 groups were 25.1%, 24.9%, and 31.0%, respectively (P = 0.09). The 10-year MI rates were 10.3%, 13.3%, and 20.7%, respectively (P<0.01). The proportion of patients with freedom from angina at 10 years was 64% with CABG, 59% with PCI, and 43% with OMT (P<0.001 [4, 6].

Epidemiology of recurrent angina after percutaneous coronary intervention

Despite a lot of innovations in coronary angioplasty techniques, recurrent angina (RA) after coronary angioplasty is a frequent problem that many cardiologists in everyday clinical practice have to deal with. More than 30% of patients with prior revascularization still report episodes of angina in a 3-year follow-up. The prevalence of RA after PCI is high, and more than one-half of all patients in community practice had at least 1 stress test within 24 months of revascularization. In the Arterial Revascularization Therapies Study (ARTS) trial, angina was still present in 21% of patients 1 year after PCI, while 42% of patients showed either RA or need of repeat revascularization after 5 years. In a large retrospective study from the Mayo Clinic, most of the patients treated with PCI experienced an improvement in episodes of angina although 30% still reported RA and 12% severe RA [7].

Factors responsible for angina in post-revascularization patients

First, a careful rule-out of several non-cardiac causes of chest pain (gastrointestinal, lung, osteoarticular, herpes zoster, anxiety) is necessary to accurately diagnose RA. Cardiac causes of RA are either linked to structural causes (stretch pain, in-stent restenosis, in-stent thrombosis, incomplete revascularization, progression of coronary atherosclerosis) or functional causes (microvascular dysfunction, epicardial coronary spasm), or a combination of both. Stretch-pain is chest pain reported early after PCI, mainly caused by coronary stenting and irritation of nerves in the coronary adventitia; it is usually not associated to ECG anomalies and cardiac troponin elevation although it accounts for several unnecessary coronary angiographic controls. This type of non-ischemic chest pain develops in almost half of all patients undergoing stent implantation and seems to be related to vessel overexpansion caused by the stent in the diseased vessel segment. Other cases of RA are due to incomplete revascularization, as observed in patients with multi-vessel coronary disease treated with PCI according to the Synergy Between percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial results, wherein RA occurred within 30 days after PCI. Data from the ARTS study show that revascularization was incomplete in 30% of patients after PCI. Patients with incomplete revascularization had higher occurrence at 12 months of the combined end point of new coronary events and revascularization (30.6% *vs*. 23.4%), with a 5-fold higher need for CABG (10.0% *vs*. 2.0%) when compared with complete revascularization. Functional causes of RA can be (a) impaired vasodilatation and/or (b) enhanced vasoconstriction (epicardial coronary spasm, microvascular dysfunction, coronary spasm at stent edges). Inappropriate constriction of small coronary vessels is a possible cause of chest pain and a positive exercise stress test early after successful coronary angioplasty [7].

Rationalistic approach: Identification of recurrent angina

A rational diagnostic approach to RA should start from a careful evaluation of chest pain characterization, complete risk stratification and an accurate analysis of prior PCI procedures

(Figure 1). In case of suspected non-cardiac symptoms, an exercise stress test should be performed in order to discriminate 'cardiac' from 'non-cardiac' chest pain and for risk stratification. Negative exercise stress test results should lead towards investigations for 'non-cardiac' chest pain (e.g., gastroscopy, chest X-ray) and positive findings to coronary angiography. Patients complaining of RA with characteristics similar to those prior to PCI may either undergo exercise stress testing or may directly be referred for coronary angiography. Repeat coronary angiography should be performed when typical symptoms occur in patients with higher CV risk profile (worsening angina, arrhythmias, heart failure, diabetes, renal failure and poor compliance to drug therapy), prior high-risk PCI (left main, bifurcations, chronic total occlusion, ostial lesions, 'full metal jacket' stenting, impaired left ventricular function) or incomplete revascularization. Moreover, adenosine stress cardiac magnetic resonance (CMR) may allow accurate detection of non-culprit territory stenosis in patients successfully treated with primary-PCI post ST-segment elevation myocardial infarction (STEMI). In the case of a moderate stenosis on coronary angiography (50%–70%), fractional flow reserve (FFR) measurements can be helpful to decide whether or not a stent implantation is justified. In the absence of flow-limiting stenosis, intracoronary assessment of coronary vasomotion using coronary flow reserve and provocation testing with acetylcholine or ergonovine can reveal functional causes for RA. Intra-coronary flow reserve (CFR) describes the amount of additional blood flow that can be supplied to the heart above baseline blood flow [7].

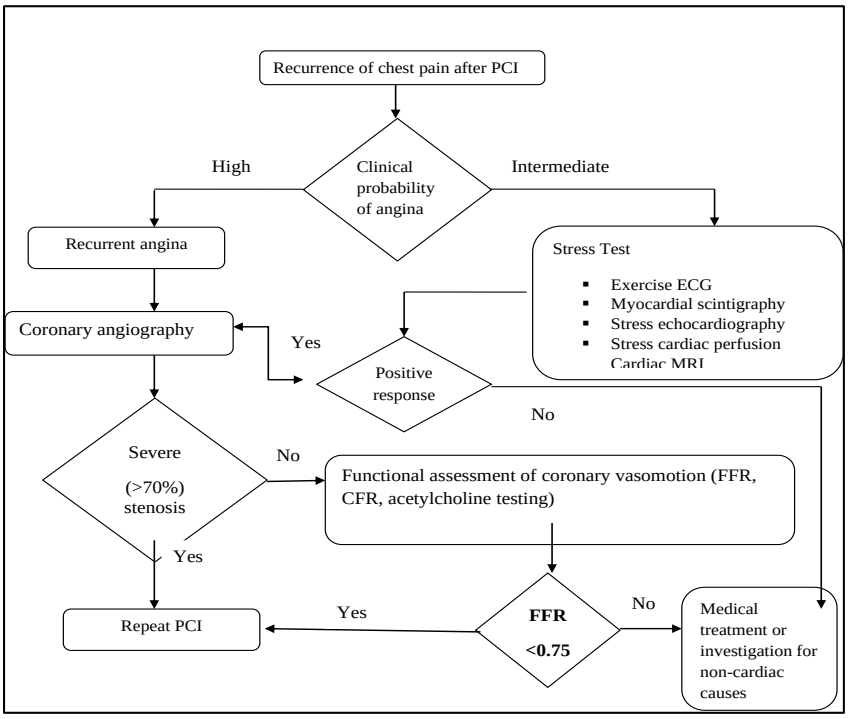

Fig 1: Recurrent angina: Diagnostic and therapeutic strategies

Differences between refractory and recurrent angina

Table 2 lists the differences between refractory angina and RA [8, 9, 10]

Table 2: Difference between refractory and recurrent angina

Angina	Recurrent Angina
Conventionally defined as a chronic condition (≥3 months in duration) Otherwise, defined as occurrence of chest pain due to myocardial ischemia Refractory in a patient with severe CAD who cannot be managed adequately by medical therapy and who are not candidates for revascularization (interventional or surgical).	Recurrent angina, defined as the persistence of chest pain due to myocardial ischemia after revascularization, may be triggered by several causes not necessarily related to revascularization failure.
Precise estimates of the prevalence and incidence of refractory angina are not available. Several sources suggest that this is a large and growing problem.	Highly prevalent condition, occurring in 20% to 60% of patients within 1-year post-PCI.
Characterized by angina caused by coronary insufficiency in the setting of CAD.	Chest pain of coronary origin may recur after PCI due to both structural and functional causes, many of which have a common pathophysiological background, such as endothelial dysfunction.
The presence of reversible myocardial ischemia has been clinically established to be the cause of the symptoms.	The main cause for early readmission was chest pain or other symptoms concerning for angina (38.1% of cases).
Cannot be controlled by a combination of medical therapy,	In addition to mechanical therapies for the treatment of structural disorders,

angioplasty or bypass surgery.	pharmacological therapy should be optimized with the use of antianginal drugs and other compounds that may help treat the pathological conditions behind recurrent angina to maximize the benefit for patients.

CAD, coronary artery disease; PCI, percutaneous coronary intervention

The diagnostic challenges for recurrent angina

Recurrent chest pain after coronary revascularization is always a disappointment to both the patient and the cardiologist. The approach to recurrent chest pain should start with an accurate analysis of the initial procedure. In a patient who had a CABG in the last year and symptoms consistent with angina, one should have a low threshold for early repeat catheterization to determine if an insertion site lesion is present and/or a native vessel can be dilated to resolve symptoms owing to graft failure. It is extremely important, indeed, to identify graft failure as early as possible to allow for PCI as a method to preserve the surgical benefits. Stress tests are often equivocal because of local perfusion abnormalities and/or partial collateral filling of ischemic zones, especially in the context of functionally adequate but anatomically incomplete revascularization [10].

Diagnostic tests for recurrent angina after PCI or CABG

Since many of the tests used to detect ischemia actually test for the presence of coronary reserve, it is reasonable to consider coronary angiography as the gold standard for the diagnosis of coronary restenosis, especially when supplemented by invasive assessment of FFR in cases of intermediate stenosis at angiography (Table 3). Selection of cases for angiography may, however, be challenging. The decision should not only be based on the symptoms of the patient but also on the characteristics of the original procedure. A low threshold for angiography should be present when assessing patients who underwent high-risk procedures such as those involving the left main coronary artery, multiple vessels, proximal branches, bifurcations, multiple stents, or with left ventricular dysfunction, and in those with incomplete revascularization in whom further interventions are considered feasible. Non-invasive modalities aimed at detecting restenosis independently from the assessment of coronary reserve are currently highly investigated. Large-scale application of these techniques, however, is still hampered by some artifacts related to the visualization of the stent itself and relatively high costs. Computed tomography (CT) angiography has been used for evaluating coronary stent patency. Interestingly, magnetic resonance (MR) imagining (MRI)/MR angiography (MRA) could be an extremely powerful tool if it shows to be able to evaluate for coronary anatomy and assess myocardial perfusion reserve at the same time. Contrast echocardiography is highly accessible, non-invasive, non-irradiating, and a relatively low-cost procedure to assess perfusion, while being largely operator-dependent and more difficult to standardize. Positron emission tomography (PET) is considered to be the gold standard for the assessment of perfusion and function. Because of the high maintenance costs, PET is not largely utilized at present and unlikely to be utilized in the near future for this indication. The American Heart Association/American College of Cardiology clinical guidelines for the treatment of chronic stable angina recommend the use of nuclear or echocardiographic stress test for the evaluation of patients with prior revascularization who have a change in clinical status. This recommendation is graded as Class I (condition for which there is evidence or general agreement) but with a level of evidence of C (based primarily on expert consensus). Although exercise electrocardiogram (ECG) testing in unselected patients has great predictive value for cardiac mortality, the use of exercise ECG testing is discouraged because management decisions are often not only based on the presence or absence of ischemia but also on the site and extent of ischemia, therefore favoring the use of stress imaging modalities such as single photon emission computed tomography (SPECT) or echocardiography [10].

Table 3: Investigations for the diagnosis of recurrent angina

Test	Look for	Indicates
Cardiac biomarkers		
Cardiac troponins (troponin T and troponin I) Creatine kinase MB	Elevated levels	Presence of myocardial injury in which case it is ACS and not stable angina and should be treated accordingly[2]
NT-pro BNP	Elevated levels	Important predictor of long -term mortality independent of age, ventricular EF) and conventional risk factors
Cardiac tests		
ECG	Normal/abnormal	Previous signs of CAD and acts as a baseline ECG for the future comparison
Treadmill test	Based on Duke'sprotocol	Diagnoses CAD
ECHO	LVEF and structural abnormalities	Heart failure and structural abnormalities that may be causative or affect prognosis
Angiography	Coronary arterial blocks	Risk stratification rather than diagnosis
FFR/IVUS	Measurements and cut -off values	Assist in decision making for treatment strategies

ACS, acute coronary syndrome; CAD, coronary artery disease; ECG, electrocardiogram; ECHO, echocardiogram; EF, ejection fraction; FFR, fractional flow reserve; IVUS, intravascular ultrasound; LVEF, left ventricular ejection fraction; NT-pro BNP, N-terminal pro b-type natriuretic peptide.

Prognosis questionnaire [2]

There is a need to sensitize clinicians regarding the OPTA goals of medical management like disease control, relief from symptoms, building exercise capacity, and improvement of quality of life, which would assist them in risk stratification and further management of patients. The following questionnaire was designed to help meet these needs [2].

1. Over the past 4 weeks, my day-to-day activities have been_____.

☐ Extremely limited ☐ Moderately limited ☐ Not limited at all

2. Over the past 4 weeks, I have had chest pain/tightness/discomfort/angina _____.

☐ Four or more times per week ☐ Three or less times per week ☐ Not at all

3. Over the past 4 weeks, on average, how many times have you had to take short-acting nitrate for your chest pain, chest tightness, or angina? I have taken nitroglycerin…

☐ Four or more times per week ☐ Three or less times per week ☐ Not at all

4. Over the past 4 weeks, how much has your chest pain, chest tightness, or angina limited your enjoyment of life?

☐ It has extremely limited my enjoyment of life

☐ It has moderately limited my enjoyment of life

☐ It has not limited my enjoyment of life at all

5. If you had to spend the rest of your life with your chest pain, chest tightness, or angina the way it is right now, how would you feel about this?

☐ Not satisfied at all

☐ Somewhat satisfied

☐ Mostly satisfied

Fig 2: Prognosis questionnaire

While establishing the diagnosis of CAD, it is important to estimate the subsequent mortality risk for a patient with CAD because it has significant treatment implications. This estimate of prognosis, termed "risk stratification," is an essential part of defining treatment recommendations for a given patient. Left ventricular function is one of the dominant factors in predicting mortality in persons with CAD. Among patients with CAD, mortality increases as left ventricular function declines. An ejection fraction (EF) of <35% is associated with a mortality rate in excess of 3% per year. Left ventricular function may be assessed by echocardiography, radionuclide studies, or angiographic ventriculography (Figure 3) [11].

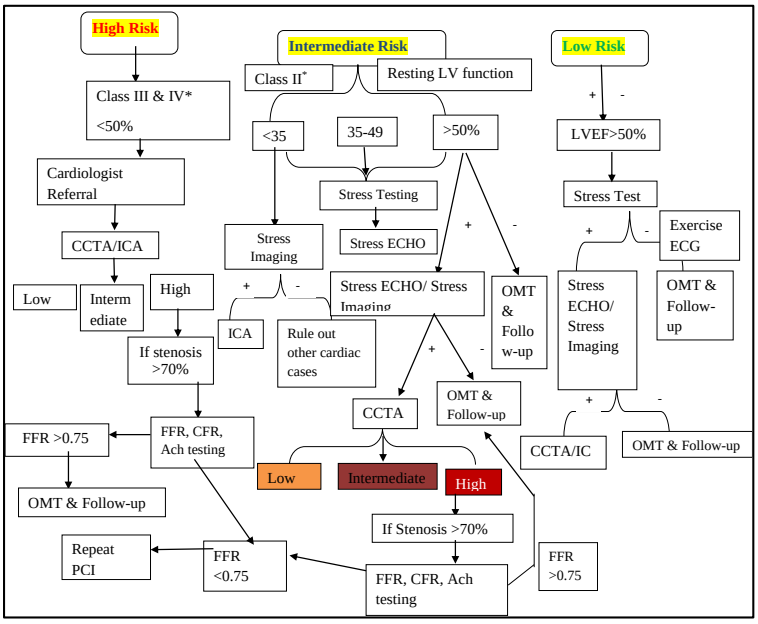

Fig 3: Risk stratification of recurrent angina

Pharmacological options

The management of angina after coronary angioplasty largely depends on the cause of the angina. When restenosis is present or suspected, repeat angiography and repeat intervention are usually warranted. Beta-blockers, long-acting nitrates, and calcium channel blockers (CCBs) are considered the mainstay of treatment. Below are the more commonly used antianginal drugs (Table 4) [10].

Table 4: Anti-anginal drugs and recommended dosage

Commonly used anti-anginal drugs [9]	Recommended dosage
Anti-platelet agents	
Aspirin	81–325 mg daily
Clopidogrel	75 mg daily
Beta-blockers	
Atenolol	25–200 mg daily
Metoprolol	25–200 mg daily
Calcium-channel blockers	
Amlodipine	5–10 mg daily
Diltiazem	60–480 mg daily
Nifedipine XR	30–120 mg daily
Verapamil	80–480 mg daily
Nitroderivatives	
Isosorbide mono-/di-nitrate	10–120 mg daily
Nitroglycerin	0.4–1.2 µg/h
Nicorandil	5–20 mg daily
Ranolazine	1000–2000 mg daily
Trimetazidine	20–70 mg daily

ACE inhibitors and statins should be part of pharmacological treatment in all patients with CAD to improve endothelial dysfunction and improve vascular remodelling. Statin therapy benefit has been shown by several trials, with possible reduction in coronary plaque volumes. Intensive treatment with aspirin, clopidogrel, statins, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, CCBs and nitrates may yield 'encouraging' results, but very high compliance levels obtained in the COURAGE trial (90%–96% at five years) are not easy to obtain in everyday clinical practice [7].

Prognosis: an indicator for follow-up

Timing from successful coronary angioplasty to onset of recurrent chest pain is the strongest predictor of angiographic outcome. Though the most common cause of recurrence of chest pain after initially successful coronary angioplasty is restenosis, other mechanisms may also be responsible. The incidence of new lesion development is higher in the vessels that have undergone instrumented angioplasty, possibly reflecting accelerated atherosclerosis or increased fibrocellular proliferation from intimal injury [12].

Patients presenting with pain between 1 and 6 months following PCI typically had angina secondary to restenosis, and those presenting more than 6 months after the procedure were likely to have progression of coronary disease other than the target vessel.[9] When the chest pain recurred within 4 weeks of angioplasty, 70% of patients had either incomplete revascularization or no significant coronary artery stenosis; when it recurred between 4 and 24 weeks of angioplasty, restenosis was the most common finding (71%); and when it recurred more than 24 weeks after angioplasty, new disease was the most common finding, occurring in 53% of patients. At repeat angiography, 61% of vessels that had had angioplasty and 49% that had not had angioplasty had new lesions. The incidence of new lesion development is higher in the vessels that have instrumented angioplasty. In-stent restenosis after PCI, which is a serious complication, is defined as acute (within 24 hours), sub-acute (>24 hours <30 days), late (>30 days <12 months) and very late (>12 months). The presence of an angiographic confirmation of stent thrombosis (the presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent) is associated with the presence of at least one of the following criteria within a 48-hour window: acute onset of ischemic symptoms at rest, new ischemic electrocardiographic changes that suggest acute ischemia or typical rise and fall in cardiac biomarkers; or in the presence of a histopathological confirmation of stent thrombosis (evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy) [7].

Taking the mentioned scenarios into consideration, clinicians have to exercise their rationale and discretion in advocating a robust follow-up for better anginal free outcomes.

Guideline Recommendations

- Current guidelines do not distinguish between chronic stable anginas (CSA) and RA. Therefore, theoretically, the treatment should be the same [7].
- The AHA/ACC guidelines for the treatment of patients with angina do not distinguish between the different types of angina and no controlled randomized trial was specifically designed to assess efficacy in the subgroup of patients with RA after revascularization [10].
- Current ACC/AHA guidelines recommend a dosage of 325 mg daily of aspirin after coronary stenting. This recommendation is based on consensus rather than direct evidence of a superiority of 325 mg dosage *vs*. lower regimens [10].

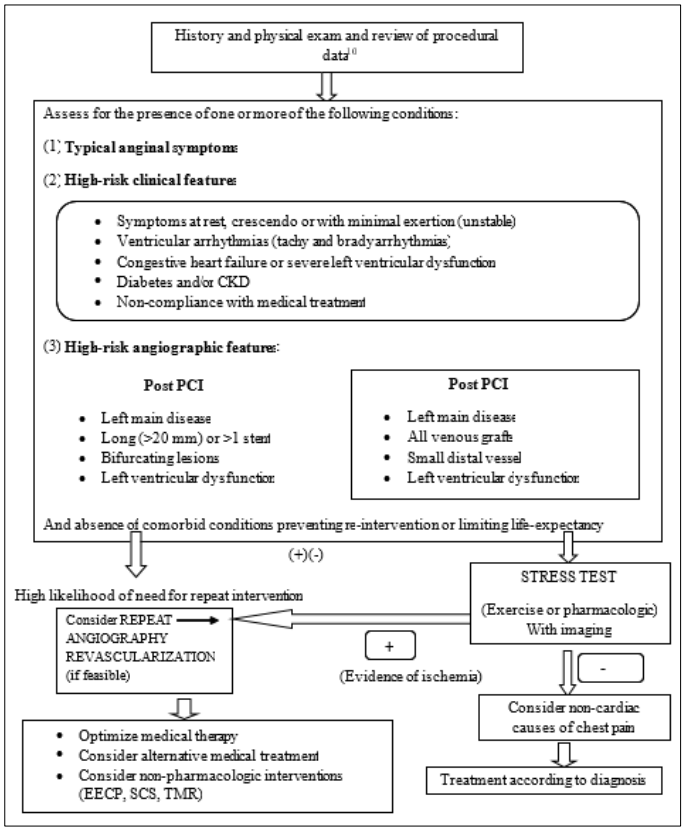

Fig 4: Clinical approach to recurrent angina post revascularization

Ranolazine

Ranolazine, an inhibitor of late I_{Na} current, reduces calcium uptake indirectly via the sodium/calcium exchanger, preserves ionic homeostasis, and reverses ischemia-induced left ventricular dysfunction.[7] Ranolazine was shown to increase the ischemic threshold and to reduce occurrence of angina and the use of nitrates (CARISA,ERICA trials), thereby lowering episodes of recurrent ischemia in the sub-group of patients with CSA by 22% (MERLIN-TIMI36 trial) [13, 14, 15]. Ranolazine therapy prolonged exercise duration and decreased exercise-induced ischemia and angina with quantitative effects equal to or greater than those obtained with atenolol. Unlike atenolol, the anti-ischemic and anti-anginal effects of ranolazine occurred without decreases in blood pressure, heart rate, or rate-pressure product. Among patients with a history of angina before their ACS event (54% of the study MERLIN-TIMI36 trial cohort), there was a significant and sustained beneficial effect of ranolazine relative to placebo across the QoL and disease-specific health status measures – including angina frequency, perceived burden of disease, dyspnea, and overall treatment satisfaction [7].

Trimetazidine

Trimetazidine, an inhibitor of the fatty acid oxidation enzyme, 3-ketoacyl coenzyme A thiolase, reduces the symptoms of demand-induced ischemia, shifting oxidation of free fatty acids, which is energy-consuming compared with glucose oxidation, towards glucose oxidation and better use of the energy supply (TRIMPOL II study) [16].

Another study which aimed at clinical benefits of trimetazidine in patients with RA reported excellent tolerability of the drug and recommended the same for elderly and coronary diabetic patients, especially those with impaired left ventricular function. It was observed that trimetazidine use was associated with longer time to onset of angina (508.1 ± 132.4 *vs*. 433.6 ± 164s, P = 0.031); total duration of exercise was significantly greater than that recorded for patients with placebo plus metoprolol (524.4 ± 131.5 *vs*.466.9 ± 144.8, P = 0.048); and also the mean angina attacks per week were significantly reduced (1.7 ± 2.3 for patients in the trimetazidine group *vs*. 3.1 ± 2.9 in the placebo group) [1].

Conclusion

The anti-anginal management post coronary angioplasty chiefly depends on the cause of the angina. In lieu of a suspected or confirmed restenosis, a repeat angiography with prompt treatment is a must. Despite a multitude of pathophysiological etiologies for RA, evidence in favor of specific diagnosis and intervention in this variant of angina is lacking. Angina recurring or persisting after a successful CABG or multivessel PCI still has affected a large number of patients, both in terms of morbidity and mortality. Despite these diagnostic and management hurdles, there could still be possibilities for interventions leading to symptomatic and prognostic benefits, especially given the recent advancements in medical therapy, percutaneous coronary devices, and cardiac surgery.

Disclosures

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