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Consensus statement on evolving terminology in angina and its impact on Indian clinical practice

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Abstract
Coronary artery disease (CAD) is one of the major cardiovascular diseases affecting the global human population. Patients with known cardiovascular disease who have not had a recent acute event are often referred to as having stable coronary artery disease (CAD). However, the concept of 'stable' CAD is misleading due to the continuing risks of cardiovascular events over the long term. The recent 2019 European Society of Cardiology guidelines have changed the clinical terminology of 'stable' CAD to 'chronic coronary syndrome' (CCS). Apart from terminology, the guidelines provided new recommendations on how to manage continuing risk of ischemic events. An eminent group of consulting physicians and cardiologists from India collaborated in order to discuss and understand evolving terminologies in angina and their impact on Indian clinical practice. Extensive literature review, discussions, and feedback from the cardiologists led to the development of a consensus statement for Indian clinical practice. The terminology of CCS was found to be more apt for the Indian context. A careful history and clinical examination followed by investigations can ensure early and accurate diagnosis of CCS. The management of CCS should include combination of medical therapy and revascularization based on the need, severity of disease, and patient acceptability.

Keywords: chronic coronary syndrome, stable coronary artery disease, major adverse cardiovascular events, Indian perspective

Introduction

Coronary artery disease (CAD) is the leading cause of disability and mortality worldwide as well as one of the top 5 causes of death in the Indian population [1]. Globally, more than 7 million deaths are attributable to CAD annually [2]. In India, the prevalence of CAD has increased from 1.1% to about 7.5% in the urban population and from 2.1% to 3.7% in the rural population over the past three decades [3]. Moreover, CAD tends to occur at a younger age in Indians with a reported incidence of 12%-16% [2, 4]. About 52% of cardiovascular disease (CVD)-related deaths in India occur below the age of 50 years, and about 25% of acute myocardial infarction (AMI) occurs under the age of 40 years [4]. Stable CAD is condition characterized by chronic stable angina. It is generally triggered by a reversible mismatch between myocardial oxygen demand and supply, resulting in myocardial ischemia or hypoxia [5]. The underlying mechanisms of stable CAD may include atherogenesis and plaque formation in epicardial arteries, spasm of normal or plaque containing arteries, or micro-vascular or left ventricular (LV) dysfunction due to prior acute myocardial necrosis or ischemic cardiomyopathy.[2]
Stable CAD encompasses a diverse spectrum of patients, including [5]

- Patients with recurrent, transient episodes of ischemia induced by oxygen supply–demand
- Imbalance in the presence of established coronary artery stenosis (i.e., stable angina and silent ischemia), and
- Patients who have stabilized after an acute coronary syndrome (ACS)-a phase that is often asymptomatic

The Prospective Observational Longitudinal Registry of Patients with stable coronary artery disease (CLARIFY) is an international, cohort study conducted in stable CAD outpatients (n = 32,703) demonstrated a high prevalence and poor control of cardiovascular risk factors in Indian patients. Compared to the rest of the world, Indian patients were significantly younger, were more likely to have diabetes and angina, and had greater mean heart rate and lower high density lipoprotein (HDL) cholesterol [6].

How 'stable' is stable CAD?

CAD progression is dynamic and unpredictable and can unexpectedly result in major adverse cardiovascular events (MACE) such as MI, stroke, and CVDs [5]. Despite adherence to current guideline-recommended secondary prevention therapies, patients with stable CAD remain at high risk of MACE. Obstructive as well as non-obstructive lesions can lead to MACE and other clinically significant cardiovascular events such as unstable angina. The complex interplay between prothrombotic factors (such as inflammatory state, lesion size, plaque burden

and vasoconstriction) and antithrombotic factors determine the risk of thrombosis at the site of plaque rupture [7].

Depending on clinical variables that affect the risk, the probability of MACE within 5 years of the onset of apparently stable angina has been reported to be up to 35% [7]. In the REACH registry, patients with stable atherosclerosis had a 12.2% risk of MACE (CV death, MI, or stroke) over 4 years even if they had no prior ischemic events [8]. In the large-scale national Swedish registry study, 18.3% of patients with MI had recurrent MI, stroke, or cardiovascular death in the first 365 days after the index event. The cumulative probability of a subsequent event in the stable post-MI population was 20.0% after 36 months of follow-up [9].

Until 2013, the European Society of Cardiology (ESC) guidelines referred to the terminology 'stable CAD'.[5] In 2019, the ESC guidelines updated their terminology from 'stable CAD' to 'chronic coronary syndromes (CCS)' heralding a new era in the management of CAD [10]. The word 'stable' was perhaps a misnomer and suggested that these patients had a low risk of events. However, the change to CCS reflects the reality that patients with CAD are at continuing risk of MI and stroke [11]. This consensus statement aims to understand the evolving terminologies in stable CAD from different guidelines and relevance of the change in terminology to CCS from the Indian perspective.

Multiple meetings were held across India to develop the consensus statement These meetings were attended by eminent experts from the field of cardiology. The panel discussed the following topics:

1. Do the six clinical scenarios described in the guidelines adequately capture the various presentations of Indian patients with CCS?
2. Invasive tests are primarily recommended for patients at high pretest probability of having disease, functional tests are recommended for patients in the middle ranges, and coronary computed tomography angiography (CCTA) is recommended for patients in whom CAD is unlikely. Is this commonly followed in your clinical practice?
3. The American Heart Association (AHA)/American College of Cardiology (ACC) uses the terminology stable ischemic heart disease (SIHD). What does this mean for you and your patients?
4. The 2016 National Institute for Health and Care Excellence (NICE) guidelines have positioned CCTA as the first test for all stable chest pain patients without confirmed CAD. Is this applicable to Indian practice?
5. What should be the universally accepted terminology?
6. Which guidelines are more appropriate for Indian patients in the diagnosis and management of angina?

Extensive literature review, discussions, and feedback from the cardiologists led to the development of consensus statements on definition, diagnosis, and management of CCS with focus on Indian clinical practice.

Evolving definition of stable CAD

The 2016 NICE guidelines defined stable angina as a chronic medical condition with a low but appreciable incidence of acute coronary events and increased mortality. The aim of management is to stop or minimize symptoms and to improve quality of life and long-term morbidity as well as mortality [12].

The 2019 ESC guidelines have been revised to focus on CCS instead of stable CAD. This change highlights the fact that the clinical presentations of CAD can be categorized as either acute coronary syndromes (ACS) or CCS. CAD is a dynamic process characterized by atherosclerotic plaque accumulation in the epicardial arteries that can be modified by lifestyle, pharmacological therapies, and revascularization, resulting in disease stabilization or regression. Although the disease can have long, stable periods, it can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion. The six most frequently encountered clinical scenarios in patients with suspected or established CCS are illustrated in Table 1 [10].

Table 1: The six clinical scenarios most frequently encountered in patients with CCS

(i) Patients with suspected CAD and 'stable' anginal symptoms, and/or dyspnea
(ii) Patients with new onset of HF or LV dysfunction and suspected CAD
(iii) Asymptomatic and symptomatic patients with stabilized symptoms <1 year after initial diagnosis or revascularization;
(iv) Asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization
(v) Patients with angina and suspected vasospastic or microvascular disease;
(vi) asymptomatic subjects in whom CAD is detected at screening

CAD, coronary artery disease; CCS, chronic coronary syndrome; HF, heart failure; LV, left ventricular.

SIHD refers to patients with known or suspected SIHD who have no recent or acute changes in their symptomatic status, indicating no active thrombotic process is underway [13]. The 2014 AHA/ACC guidelines apply to adult patients with stable, known or suspected ischemic heart disease (IHD), including those with new-onset chest pain (i.e., low-risk unstable angina) or stable pain syndromes [14]. The 2020 state-of-the-art review by ACC defined stable angina as symptoms that may be ascribed to myocardial ischemia but lacks the duration and severity that may be associated with AMI. Therefore, stable angina, can be typically managed in the outpatient setting [15].

In the Indian scenario, risk factors such as diabetes, hypertension, dyslipidemia, smoking/tobacco use are known to have a higher prevalence, resulting in higher CAD cases [16]. According to estimates, 60% of global heart cases were reported to occur in India by 2020 [7]. Most of these patients are likely to develop SIHD and present clinically as stable angina resulting in missed diagnosis. The 2018 Indian Consensus on OPtimal Treatment of Angina (OPTA) has, therefore, highlighted the importance of accurate and early diagnosis for optimum management of chronic stable angina [16].

Consensus Statement 1

Evolving terminology of CAD

- Patients with chronic CAD are not necessarily stable
- The old terminology, "chronic stable angina" gave a false impression that the patient is stable
- Angina patients are at higher risk of developing MACE

despite receiving guideline-recommended therapy
- Presence of comorbidities such as diabetes, obesity, dyslipidemia, metabolic syndrome, hypertension, and renal diseases increases the risk of adverse outcomes
- The terminology of CCS is more apt for the Indian context
- The six clinical scenarios described in the 2019 ESC guidelines adequately capture the various presentations of Indian patients with CCS
- New heart failure (HF) and suspected CAD
- Suspected CAD and 'stable' anginal symptoms, and/or dyspnea
- Stabilized symptoms for less than a year post ACS or PCI
- Stabilized symptoms for more than a year post initial diagnosis
- Patients with angina and suspected microvascular disease
- Asymptomatic CAD detected at screening

Assessment and Diagnosis

The diagnosis and subsequent management of CAD represents a major challenge to the healthcare systems [17]. An assessment of the pretest probability (PTP) of CAD is made on the basis of clinical history, examination and basic tests such as the electrocardiography (ECG) [18]. The 2013 ESC guidelines have recommended exercise ECG as the initial test to establish a diagnosis of stable CAD in patients with symptoms of angina and intermediate PTP (15%-65%) [5].

The 2019 ESC guidelines have recommended a careful evaluation of patient history, including the characterization of anginal symptoms, evaluation of risk factors and manifestations of CVD, as well as proper physical examination and basic testing for the diagnosis and management of CCS. A new phrase 'clinical likelihood of CAD' was introduced that utilizes various risk factors of CAD as PTP modifiers. The factors which increase clinical likelihood of CAD include presence of CVD risk factors (family history of CVD, dyslipidemia, diabetes, hypertension, smoking, and other lifestyle factors), resting ECG changes (Q-wave or ST-segment/ T-wave changes), LV dysfunction suggestive of CAD, abnormal exercise ECG and coronary calcium by CT. The factors that decrease likelihood of CAD include normal exercise ECG and no coronary calcium by CT (Agaston score=0). The optimal use of these factors in improving PTP assessment has not yet been established. However, they should be considered in addition to the PTP based on sex, age, and the nature of symptoms to determine the overall clinical likelihood of obstructive CAD [10].

Non-invasive testing is most beneficial in patients with PTP >15%. In patients with PTPs of CAD in the range 5%-15%, testing for diagnosis may be considered after assessing the overall clinical likelihood based on the modifiers of PTPs (age, sex, and nature of symptoms). Patients with a PTP $\leq$5% have low probability of CAD, and diagnostic testing should be performed only for compelling reasons [10].

The past 2 decades have witnessed a rapid expansion in the number of different non-invasive imaging modalities used for the assessment of stable CAD [18]. In addition to invasive coronary angiography (ICA), a variety of non-invasive testing methods such as single proton emission computed tomography (SPECT), myocardial perfusion imaging (MPI), CCTA and coronary computed tomography with fractional flow reserve (FFRCT) have been advocated to provide an anatomic and/or functional evaluation of coronary artery [19]. Dobutamine stress echo cardiography (DSE) is a tool that aids in identification of obstructive epicardial CAD, detection of viable myocardium, and assessment of the efficacy of anti-ischemic medical therapy in patients with known CAD [20].

The 2012 American College of Cardiology Foundation (ACCF)/AHA guidelines for the diagnosis and management of patients with SIHD [21] and 2013 ESC guidelines on the management of stable CAD [5] rely on pre-test likelihood and offer a multiplicity of functional imaging tests as the first-line diagnostic tool. The 2016 NICE guidelines have positioned CCTA as the first test for all stable chest pain patients without confirmed CAD. Interestingly, they discard the previous emphasis on calculation of pretest likelihood recommended in the 2012 edition of the guidelines [22].

CCTA has been clinically used for exclusion of significant coronary stenoses in patients with a probability of CAD [23]. In a systematic review by Yin *et al* the pooled sensitivity and specificity of CCTA for CAD were 98% (95% confidence intervals [CIs]: 95%–99%) and 84% (95% CIs: 81%–87%), respectively [24]. However, coronary calcification is an important diagnostic concern affecting the accuracy of CCTA [23]. Increased coronary calcifications have shown to lower the predictive negative value of 64-slice CT angiography due to increased likelihood of false positive stenosis [25]. Moreover, the diagnostic performance of 64-slice CT angiography was found to be significantly reduced in diabetic patients than in non-diabetics with similar clinical characteristics [26].

According to the 2019 ESC guidelines, CCTA is the preferred test in patients with lower range of clinical likelihood of CAD, no previous diagnosis of CAD, and characteristics associated with a high likelihood of good image quality. CCTA is recommended for diagnosing CAD in symptomatic patients, in whom obstructive CAD cannot be excluded by clinical assessment alone. Invasive angiography, as an alternative test is recommended to diagnose CAD in patients with a) high clinical likelihood and severe symptoms refractory to medical therapy, b) typical angina at a low level of exercise, and c) clinical evaluation that indicates high event risk [10].

From an Indian context, the basic first-line testing in patients with suspected stable CAD includes standard laboratory biochemical testing, a resting ECG, resting echocardiography, and chest X-ray, in selected patients. Exercise ECG testing is preferred in patients with a PTP of 15%-65% (based on symptoms, age, and sex) as it is more relevant to their activities than pharmacological testing. An invasive coronary angiogram is indicated in significantly symptomatic patients and patients with high risk features on non-invasive testing [2]. CCTA can be considered as an alternative to stress imaging techniques in certain patients.[16]

Assessment of event risk

Due to major impact on therapy decisions, the assessment of event risk is recommended in every patient being evaluated for suspected CAD or with newly diagnosed CAD. All patients should undergo cardiovascular event risk stratification using clinical evaluation, the assessment of LV function by resting echocardiography, and, in the majority of cases, non-invasive assessment of ischemia or coronary anatomy [27]. The occurrence

of ST segment depression at a low workload combined with exertional symptoms (angina or dyspnea), low exercise capacity, complex ventricular ectopy, or arrhythmias and abnormal BP response are markers of a high risk of cardiac mortality [28-31].
Echocardiographic assessment of global longitudinal strain provides incremental information to left ventricular ejection fraction (LVEF) and may be considered when LVEF is >35% [10].
In patients with established CCS, the risk of annual cardiac mortality is used to describe the event risk. A high event risk is defined as a cardiac mortality rate >3% per year, and a low event risk is defined as a cardiac mortality rate <1% per year.[10] The coronary artery calcium (CAC) score is an independent marker of risk for cardiac events, cardiac mortality, and all-cause mortality. A CAC score of 0 indicates very low risk of future coronary events and >400 Agatston score indicates an increased probability of myocardial ischemia [32].

Consensus Statement 2
Assessment and diagnosis of CCS

- A careful history and clinical examination followed by investigations ensures early and accurate diagnosis of CCS.
- There are various tests available for the diagnosis of CAD including ECG, SPECT, magnetic resonance imaging (MRI), positron emission tomography (PET), exercise ECG, exercise stress ECG and SPECT, dobutamine stress ECG and MRI, and vasodilator stress echocardiography.
- Invasive tests are primarily recommended in patients at high PTP of having CAD, functional tests are recommended in patients in the middle ranges, and CT angiography is recommended for patients in whom CAD is unlikely.
- CCTA has the highest sensitivity and specificity. It is preferred in the following patient profiles:
- CCS with low clinical likelihood of CAD
- Middle-aged women with low Ca^{2+} scores
- Patients with atypical symptoms having a history of coronary artery bypass grafting
- Although guidelines recommend CCTA as an initial choice of investigation, it is not routinely used in India due to high cost.

Management
The overall management strategy for stable CAD includes lifestyle changes, pharmacological management and prevention of cardiovascular events, various revascularization techniques, and management considerations for special groups such as women, elderly, and patients with renal dysfunction and diabetes [2]. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, optimal medical therapy included the promotion of medication adherence, behavioral counseling, and support for managing lifestyle risk factors delivered by nurse case managers [33]. Achievement of optimal management may be best accomplished via a multidisciplinary team approach that can provide tailored and flexible support to patients.

Lifestyle management
The recommendations on lifestyle management and risk factor modifications for CCS/stable CAD include: [2, 10]

- Pharmacological and behavioral strategies that can help patients quit smoking. Passive smoking should be avoided
- Diet high in vegetables, fruits, and whole grains. Saturated fat should be limited to <10% of total intake. Alcohol should be limited to <100 g/week or 15 g/day
- Moderate physical activity of 30-60 minutes on most days or even irregular activity can be beneficial
- Attainment of body mass index (BMI) <22.9 kg/m [2] and waist circumference (WC) of 90 cm in men and 80 cm in women to minimize cardiovascular risk
- Statin therapy to achieve optimal low-density lipoprotein cholesterol (LDL-C) goal <70 mg/dL for all stable CAD patients
- Attainment of systolic blood pressure (SBP)/diastolic blood pressure (DBP) goal of 140/90 mmHg with medical management by patients with hypertension
- Glycosylated hemoglobin (HbA1c) <7% for patients stable CAD patients and diabetes. In asymptomatic diabetics (age >40 years), functional imaging or CCTA may be considered for advanced cardiovascular risk assessment. Treatment for stable CAD patients with diabetes should include oral antidiabetics with established cardiovascular safety/benefits such as metformin, gliclazide, gliptins, and sodium-glucose co-transporter 2 (SGLT2) inhibitors

Pharmacological treatment
The aims of pharmacological management for stable CAD and CCS are to [2, 10]

- Reduce angina symptoms and exercise-induced ischemia
- Avert cardiovascular angina episodes
- Prevent cardiovascular events

Anti-ischemic drugs
Beta-blockers and calcium channel blockers
Beta-adrenergic blockers or calcium channel blockers (CCBs) are recommended as the first choice for the treatment of stable angina [10, 34]. Results of a network meta-analysis involving 46 studies and 71 treatment comparisons supported the initial combination of a beta-blocker and a CCB. Moreover, the meta-analysis suggested that several second-line add-on anti-ischemic drugs (long-acting nitrates, ranolazine, trimetazidine, and, to a lesser extent, ivabradine) may prove beneficial in combination with a beta-blocker or a CCB as first-line therapy [34]. Irrespective of the initial strategy, response to initial antianginal therapy should be reassessed after 2-4 weeks of treatment initiation.

Long-acting nitrates
When initial therapy with a beta-blocker or non-dihydropyridine (non-DHP) CCB is contraindicated, poorly tolerated, or in sufficient to control symptoms, long-acting nitrate formulations (e.g. nitroglycerin, isosorbide dinitrate, and isosorbide mononitrate) should be considered as second-line therapy for angina relief [10].

Ranolazine
Ranolazine is a selective inhibitor of the late inward sodium current [35]. The 2013 ESC guidelines recommend ranolazine as a second-line treatment for stable angina as it is devoid of any effects on heart rate, blood pressure, and tolerance [5]. However, there is a lack of evidence to support its use in patients with CCS

following percutaneous coronary intervention (PCI) with in complete revascularization. Additionally, ranolazine increases QTc and should therefore be used carefully in patients with QT prolongation or patients on QT-prolonging drugs [10].

Trimetazidine

Trimetazidine is a novel metabolic modulator having a hemodynamically neutral side effect profile [2, 10]. It has been evaluated in diverse patient populations such as those with stable angina, post-MI, pre, post PCI, and heart failure and has been found to have excellent safety and tolerability profile without any known drug interactions [36]. In a recent systematic review and meta-analysis of patients with AMI, adjunctive trimetazidine treatment was associated with a significant reduction in MACE (odds ratio [OR] = 0.33, 95% CI = 0.15–0.74; p = 0.007) [37]. As per 2019 ESC guidelines, in subjects with low baseline heart rate and low BP, ranolazine or trimetazidine may be considered as a first-line drugs to reduce angina frequency and improve exercise tolerance [10].

Ivabradine

In the Morbidity-Mortality Evaluation of the I_f inhibitor ivabradine in patients with coronary artery disease and left ventricular dysfunction (BEAUTIFUL) trial, ivabradine decreased the rate of hospital admission for fatal and non-fatal MI (hazards ratio [HR] 0.64, 95% CI 0.49-0.84, p = 0.001)and coronary revascularization (HR: 0.70, 95% CI 0.52-0.93, p=0.016) in a subgroup of patients with heart rate $\geq$70 bpm [38]. The 2019 ESC guidelines have supported the use of ivabradine as a second-line drug in patients with CCS [10].

Nicorandil

Nicorandil is a nitrate derivative of nicotinamide, with antianginal effects similar to those of nitrates or beta-blockers. The 2019 ESC guidelines recommend the use of nicorandil as a second-line drug in patients with CCS [10]. In the placebo-controlled Impact Of Nicorandil in Angina (IONA) trial (n = 5126), nicorandil significantly reduced the composite of coronary heart disease (CHD) death, non-fatal MI, or unplanned hospital admission for suspected anginal symptoms in patients with CCS [39].

Traditional versus OPTA Approach

In most cases of angina, more than one drug may be needed for optimal control of symptoms. Moreover, individuals with angina tend to have several associated comorbidities. In the traditional approach, second-choice anti-anginal medications are reserved for patients with contraindications to first-choice agents who do not tolerate them or who remain symptomatic despite treatment. Opposed to traditional approach, the OPTA approach is based on individualization of therapy, taking into consideration the pathophysiology of angina and the associated comorbidities [16].

Event prevention

The measures to stop myocardial ischemia and CVD-related deaths chiefly focus on decreasing the occurrence of acute thrombotic events and preventing ventricular dysfunction.

Anti-platelet drugs

Anti-platelet drugs reduce platelet accumulation and prevent the development of thrombus.[2] The 2019 ESC guidelines recommend aspirin 75-100 mg daily in patients with a previous history of MI or revascularization. The treatment options for dual antithrombotic therapy in combination with aspirin 75-100 mg daily in patients who have a high or moderate risk of ischemic events and who do not have a high bleeding risk include clopidogrel, prasugrel, rivaroxaban, and ticagrelor.[10] In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) study, 27, 395 participants with stable atherosclerotic vascular disease were randomly assigned to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). The primary outcome of cardiovascular death, stroke, or myocardial infarction occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (4.1% vs. 5.4%; hazard ratio (HR) 0.76; 95% CI, 0.66 to 0.86; p<0.001). However, major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group than in aspirin-alone group (3.1% vs. 1.9%; HR, 1.70; 95% CI, 1.40-2.05; p<0.001). No significant difference was found in intracranial or fatal bleeding between these two groups. There were 3.4% deaths in the rivaroxaban-plus-aspirin group compared to 4.1% in the aspirin-alone group (HR, 0.82; 95% CI, 0.71-0.96; p = 0.01). [40]

Statins

Dyslipidemia is considered as one of the critical risk factors for CVD [2]. The 2019 ESC guidelines recommend statins for all patients with CCS. Combination with ezetimibe is recommended if a patient's goal is not achieved with the maximum tolerated dose of statin. Moreover, combination with a proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor is recommended in patients at very high risk who do not achieve their goal on the maximum tolerated dose of statin and ezetimibe [10].

Renin-angiotensin-aldosterone system modulators

Angiotensin-converting enzyme (ACE) inhibitors should be the first choice across the spectrum of cardiometabolic risk reduction [2]. It is appropriate to consider ACE inhibitors for the treatment of stable chronic angina, particularly in patients with coexisting hypertension, LVEF $\leq$ 40%, diabetes, or chronic kidney disease (CKD), unless contraindicated [16]. Angiotensin-receptor blockers (ARBs) can be considered as an alternative therapy for patients with stable CAD when ACE inhibitors are not tolerated [2]. The 2019 ESC guidelines recommend ACE inhibitors in patients with CCS at very high risk for cardiovascular events [10].

Revascularization

Previous guidelines have indicated revascularization mainly in patients with CCS who receive guideline-recommended optimal medical therapy (OMT) and continue to be symptomatic, and/or in whom revascularization may ameliorate prognosis [41]. Invasive functional assessment must be used to evaluate stenoses before revascularization, unless very high grade (>90% diameter stenosis) [10].

The role of PCI in the management of stable CAD remains controversial. A meta-analysis of 12 randomized clinical trials

comparing revascularization with PCI to OMT in patients with stable CAD (n = 7,182) demonstrated no significant improvement in mortality (risk ratio [RR], 0.85), cardiac death (RR, 0.71), nonfatal myocardial infarction (RR, 0.93), or repeat revascularization (RR, 0.93) with PCI. The trials included were Angioplasty Compared to Medicine (ACME 1 and 2), Atorvastatin versus Revascularization Treatment (AVERT), Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D), COURAGE, Medicine, Angioplasty, or Surgery Study (MASS 1 and 2), and Randomized Intervention Treatment of Angina (RITA-2). However, there was a significantly improved outcome with PCI compared with OMT (RR, 1.20) [42].
In stable CAD, prognostic benefit has been found to be dependent on the extent of myocardium subject to ischaemia.[10] In a large registry of 9,016 patients with SIHD and high-risk coronary anatomy (3 vessel disease with ≥70% stenosis in all 3 epicardial vessels or left main disease with ≥50% stenosis), coronary revascularization was associated with improved all-cause death/MI as well as longer survival compared with selection for conservative management (inverse probability weighted HR [IPW-HR] 0.62). The findings indicated that coronary anatomical profile should be considered when contemplating treatment for SIHD [43].
In the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA), 5179 patients with moderate or severe ischemia were randomly assigned to an initial invasive strategy (angiography and revascularization when feasible) and medical therapy or to an initial conservative strategy of medical therapy alone and angiography if medical therapy failed. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. Over a median of 3.2 years, 318 primary outcome events occurred in the invasive-strategy group versus 352 events in the conservative-strategy group. At 6 months, the cumulative event rate was 5.3% in the invasive-strategy group and 3.4% in the conservative-strategy group. At 5 years, the cumulative event rate was 16.4% and 18.2%, respectively (difference, −1.8 percentage points; 95% CI, −4.7 to 1.0). The study concluded that there was no evidence that the initial invasive strategy reduced the risk of ischemic cardiovascular events or death from any cause in patients with coronary disease and moderate or severe ischemia [44].
One of the challenges in the evaluation of patients with stable angina is ascertaining the need/appropriateness for revascularization to improve MACE-free survival. Although clinical practice guidelines list certain anatomic characteristics (e.g., left main, triple-vessel disease, or multivessel CHD including the proximal left anterior descending coronary artery) as high-risk criteria, the ISCHEMIA trial indicates that only left main disease remains undisputed for prompting revascularization in this context. The minimum requirement for evaluating patients with stable angina, therefore, is the exclusion of left main CAD, which may be performed, as in the ISCHEMIA trial, using CT coronary angiography [15].

Consensus Statement 3

Management of CCS

- CCS is a dynamic process. It needs to be managed with a combination of medical therapy and revascularization process based on the need, severity of disease, and patient acceptability
- Patients should be stratified into low, intermediate, and high risk. Early and aggressive treatment should be initiated accordingly
- Aggressive evaluation and intervention are not recommended in totally asymptomatic patients
- The management of CSA or CCS in India focuses on 4 areas including lifestyle modification. Various classes of medications can help in achieving these objectives.
- Controlling lipid levels (LDL level: 55-80 mg) [preferred agents include statins, ezetimibe, PCSK9 inhibitors]
- Controlling BP at <130/80 mm Hg [preferred agents include ACE inhibitors, ARBs, beta blockers, CCBs, and diuretics]
- Controlling blood glucose (HbA1c <6.5%) [preferred agents include metformin, SGLT2 inhibitors, glucagon-like peptide-1 agonists, gliptins, pioglitazone, and insulin]
- Preventing thrombosis [preferred agents include aspirin, dual antiplatelet therapy, and rivaroxaban]

Pharmacotherapy

- Antianginals like nitrates, beta blockers, and CCBs are preferred
- Trimetazidine, ranolazine, nicorandil, and ivabradine are indicated when the patients are intolerant to 1st line drugs or have contraindications to it
- OPTA approach provides guidance on the use of antianginals depending on the indications/contraindications and salient features of the drug
- In patients with CCS at high/moderate ischemic risk but low bleeding risk with multi vessel CAD or history of MI, rivaroxaban can be used

Revascularization

- The survival benefit of revascularization is bigger when the total myocardium at ischemic risk is larger.

Conclusion

CAD is a dynamic disease process that can have long, stable periods, but can become unstable at any time. The latter can occur due to an acute atherothrombotic event triggered by plaque rupture or erosion. The frequent use of the term “stable” implies that the complex pathological process that underpins angina remains dormant, which in most circumstances is far from reality. Stable angina patients are at higher risk of MACE despite receiving guideline-recommended therapy. The change in the terminology from “stable” angina to “CCS” helps in risk stratification and rules out any confusion regarding stability of the disease.
The terminology “CCS” is also apt from an Indian context considering the alarming prevalence of CAD and its association with comorbidities such as diabetes, obesity, dyslipidemia, and CKD. Careful history, physical examination, and investigations can ensure early and accurate diagnosis of CCS. Invasive tests are primarily recommended in patients with high PTP of CAD. It is necessary to segment patients into high-risk, intermediate-risk, and low-risk categories. CCS patients need to be managed with a combination of medical therapy and revascularization based on

the severity of disease and patient acceptability. OMT is a good initial option for the low-risk group and in patients who are not willing to undergo revascularization. Aggressive management is indicated in the high-risk category patients.

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