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Review Article

Consensus statement on cardiovascular risk stratification and aggressive management of chronic coronary syndromes

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ABSTRACT

Cardiovascular diseases (CVDs) are responsible for 17.5 million deaths globally, and India is more susceptible to coronary artery disease (CAD) than its western counterparts because of certain challenges such as suboptimal management, increased healthcare costs, and physicians undermining the extent of limitation in angina patients. All of these could be resolved by employing strategies starting with accurate diagnosis to timely implementation of aggressive management techniques to contain morbidity and mortality. Pan India, experts from the field of cardiology came together in order to discuss risk stratification and aggressive management of chronic coronary syndromes (CCS). The expert consensus laid down a path of recommendations considering the prevailing healthcare service infrastructure, local evidence-based studies and key international guidelines. With the wide diversity in terms of geographical distribution in India and the risk factors presented across various divisions of the population, risk stratification is necessary for prompt identification and subsequent management of CCS. In this consensus, various risk stratification techniques such as risk stratification based on ventricular function, electrocardiogram (ECG), stress echocardiography (ECHO), the Duke treadmill score (DTS), and myocardial perfusion imaging (MPI) were discussed. After risk stratification, the consensus focused on aggressive management of CVDs with therapeutic optimization for various types of patient profiles such as revascularization for stable angina and angina with comorbidities (diabetes and renal failure), apart from emphasis on various medications and their roles in ameliorating disease symptoms.

Keywords: Risk assessment, Coronary risk factors, Cardiovascular disease, Coronary disease, Cardiac prevention, Management approaches

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death globally, with an estimated 17.9 million deaths from CVDs in 2019. Over three quarters of CVD deaths occur in low- and middle-income countries like India.[1] India is a large and socioeconomically diverse country with increasing cardiovascular burden with high mortality rates and premature coronary heart disease (CHD). While the proportions of years of life lost (YLLs) in 1990 and 2010 due to CVD were 5.1% and 9.8%, respectively, the YLLs from CHD doubled from 3.3% to 6.7% from 1990 to 2010 in India.[2] Due to the high prevalence of risk factors, Indians are more susceptible to coronary artery disease

(CAD) than their western counterparts.[3] The occurrence of angina, which is the manifestation of chronic coronary syndrome is associated with reduced quality of life (QoL) and increased resource utilization. Angina, although common, is also a very subjective symptom.[4] In the absence of obstructive CAD, angina has a 1.5-fold higher mortality rate. QoL too is significantly affected as >40% of these patients need rehospitalization for chest pain and 30% undergo repeat coronary angiography. Angina and myocardial ischemia without obstructive CAD are common, but often neglected because of the assumption of a benign course.[5] Unresolved issues in angina management such as increased healthcare costs, suboptimal management, and physicians' underestimation of the extent of angina and their impact on patients' lives can be tackled with proper diagnosis strategy. Moreover, there is a need for the development and implementation of appropriate guidelines and tools to provide help in the management of patients with CCS.[6]

Experts from the field of cardiology across India came together to discuss various aspects of cardiovascular risk stratification and aggressive management of chronic coronary syndromes (CCS) in the Indian context. They laid down a path of recommendations for risk stratification considering the prevailing healthcare service infrastructure and based on evidence-based studies from India, and key international guidelines.

A total of 24 studies published from 2003 to 2020, majority of them published in 2018, were reviewed to gather old and new evidence and prepare a consensus review.

IDENTIFICATION OF AT-RISK PATIENTS

Risk stratification enables identification of high-risk patients for CV death and myocardial infarction (MI), thereby promoting adoption of measures to optimize medical therapy. The 2019 ESC guidelines categorize patients as high-event risk, intermediate-event risk, and low-event risk based on annual estimated CV mortality rates of >3%, ≥1%-<3%, and <1%, respectively.[7,8]

Risk stratification based on age and gender

The interpretation of noninvasive diagnostic testing for CAD is less reliable in women compared to men, especially in those below 55 years, where the prevalence of CAD is low. Women with noncardiac chest pain are twice as likely to develop a CHD event in 7 years and are 4 times more prone to re-hospitalization and recurrent angiograms in the next 180 days.[9] Women have atypical chest pain that is often misleading with higher chance of being false positive. Traditional diagnostic methods are not optimal for women and they should be treated more aggressively for their risk factors.[9]

Risk stratification by clinical presentation and severity (with or without co-morbidities)

While angina is diagnosed based on history and other typical symptoms, there have been reported cases of overdiagnosis in primary care. Tables 1 and 2 can be utilized to avoid overdiagnosis.

Table 1: Risk stratification by clinical presentation and severity.

Factors		Score
Precipitating factor	Always on exertion, relieved by rest	3
	Emotional stress/exposure to cold/after meal	1
	Nothing in particular/unpredictable	0
	Breathing in/out	-1
Location of pain	Front of chest/neck/shoulders/jaw/arms/epigastric	1
	Right-side/sub-mammary/very localized	0
Type of pain	Constricting/cramping/heavy/tight/burning/dull ache	1
	Stabbing/sharp	0
	Reproducible by manual pressure on chest wall	-1
Duration of pain	<15 minutes	1
	Few seconds only	0
	>15 minutes or hour	-1
Total chest pain score		**4**

Table 2: Risk stratification based on comorbidities.

Risk factors	Yes/No
Diabetes mellitus	Yes/No
Cholesterol >6.47 mmol/l	Yes/No
Current smoker or recent ex-smoker	Yes/No
Family history of a first-degree relative with coronary disease <60 years	Yes/No
Hypertension	Yes/No

Continued.

Risk factors	Yes/No
Past history of IHD[#]?	Yes/No
[#]If Yes, refer to cardiology clinic if suspected of a cardiac origin	

IHD-ischemic heart disease.

As high as 50%–60% of patients with CAD also have diabetes. In certain Indian subpopulations, prevalence of the traditional risk factors like obesity, dyslipidemia, and hypertension is low, which merits further evaluation. The chest pain symptom scoring has resulted in improved discrimination of chest pain by general physicians (GPs) and has improved referral quality, with shorter patient wait times. These benefits were achieved without using additional financial resources and without the time or capital expense of training GPs.[10]

Event risk stratification based on ventricular function

The strongest predictor of long-term survival in CCS is left ventricular (LV) function. In patients with stable coronary artery disease (SCAD), as left ventricular ejection fraction (LVEF) declines, mortality increases. Echocardiography (ECHO) to assess LV function is necessary for all patients at baseline. The 12-year survival rates of patients with ejection fraction (EF) ≥50%, 35%–49%, and <35% were 73%, 54%, and 21%, respectively ($p<0.0001$) in the coronary artery surgery study (CASS). To avoid missing obstructed vessels causing ischemia in such patients, stress imaging should be employed instead of exercise electrocardiography.[7]

Electrocardiography versus stress echocardiography in event risk stratification

Combining multiple predictors into one measure, the Duke treadmill score (DTS) provides clinical information by incorporating stress-induced angina, exercise duration, and exercise-induced ST changes. DTS is an indicator for multivessel obstructive disease and mortality in both high- and low-risk groups. For risk stratification of patients with an intermediate DTS, myocardial perfusion imaging (MPI) is useful.[11] The more negative is the DTS, the poorer is the outcome. Stress electrocardiogram (ECG) is diagnostic; however, if there are abnormalities on resting ECG, then there is no value for stress ECG. While exercise ECG could provide additional data, sub-classification of risk into grades of Duke's scores could be accomplished by stress ECHO. Stress ECHO also can assess both short- and long-term prognosis in all subsets of patients by examining both resting and stress LV function at one sitting.[12] Stress ECHO is a better investigation than stress ECG, and it can be performed in an outpatient department. The sensitivity of stress ECHO is 90% even for single vessel disease.

Stress perfusion scintigraphy versus stress cardiac magnetic resonance imaging in event risk stratification

Myocardial perfusion single photon emission-computed tomography (MPSPECT) is helpful in many clinical situations and useful in identification of suspected artifacts, risk stratification of patients with known or suspected CAD, assessment of myocardial viability, in distinguishing ischemic cardiomyopathy from non-ischemic cardiomyopathy, and in enhanced detection of multivessel disease. Multivariate analysis has shown an independent association between adverse cardiac outcomes and abnormal dobutamine stress cardiac magnetic resonance (CMR) and >99% event-free survival in patients with no evidence of ischemia over a 36-month follow-up. Assuming that the biological principles are the same for stress ECHO and stress MPSPECT, as they are for stress CMR, new wall motion abnormalities (≥3 segments in the 17-segment model) induced by stress or stress-induced reversible perfusion deficits >10% (≥2 segments) in the LV myocardium should be regarded as indicating a high-event risk situation. Nevertheless, there are as yet no data providing proof that this distinction can be made by CMR in the same way as with MPSPECT.7 CMR is preferred to assess the viability of myocardium.

Event risk stratification based on coronary computed tomography angiography

Coronary computed tomography (CCTA) has a specificity of 96% and sensitivity of 89% for the detection of CHD. The SCOT-HEART investigators reported that the addition of CCTA to standard clinical care helped to clarify the diagnosis of angina due to CHD. This reduced the need for further stress testing, increased the use of invasive coronary angiography, and changed treatment regimens that might be associated with a reduction in fatal and non-fatal MI. The strategy of utilizing CCTA was associated with 38% reduction in CHD death and non-fatal MI.[13]

Schulman-Marcus et al studied the effect of early revascularization on 5-year survival in patients with stable CAD and categorized as having low-, intermediate-, or high-risk CAD based on CCTA findings. In high-risk CAD, revascularization was associated with reduced mortality at 1 year and 5 years. For intermediate-risk CAD, revascularization was associated with lower mortality at 1 year, but not 5 years. For low-risk CAD, there was no benefit at either 1 year or 5 years.[14]

Effectiveness of invasive coronary angiography in patients with stable ischemic heart disease

As per the American College of Cardiology (ACC) and American Heart Association (AHA) guidelines, for patients with stable ischemic heart disease (SIHD), a pre-test assessment of risk should be made to segregate them to low (<10%), intermediate (10% -90%) and high (>90%) risk categories to guide the decision for further evaluation to detect CAD. Invasive coronary angiography (ICA),

despite being the standard for CAD detection, is usually recommended for high-risk patients or those with significant ischemic burden as indicated by stress testing. For the intermediate-risk patient, coronary angiography is probably overused and is of low-yield. Moreover, improved diagnostic accuracy may be obtained from stress imaging compared with history alone, thereby enabling avoidance of ICA.[15]

Stress tests, coronary CT angiography, and invasive coronary angiography are preferred in low, intermediate, and high-risk patients, respectively. In patients unwilling to undergo coronary artery bypass grafting (CABG), stress perfusion study is an additional investigative tool to demonstrate the large areas at ischemic risk. Risk stratification identifies patients at high-event risk who can benefit from revascularization beyond symptom amelioration, as a guide for the healthcare team to understand the disease and refer to a cardiologist in a timely manner.[16]

THERAPEUTIC APPROACH

The aim of the management of CCS is to reduce symptoms and improve prognosis, which encompasses lifestyle modification, control of CAD risk factors, evidence-based pharmacological therapy, and patient education. According to ESC/EACTS guidelines, indications for revascularization of SCAD are as follows:[7] (1) a heart team approach to revascularization was recommended in patients with unprotected left main, 2–3 vessel disease, diabetes or comorbidities, (2) left main >50% diameter stenosis, (3) any proximal LAD >50% diameter stenosis, (4) 2–3 vessel disease with impaired LV function/ congestive heart failure (CHF), (5) single remaining vessel (>50% diameter stenosis), (6) proven large area of ischemia (>10% LV), (7) any significant stenosis with limiting symptoms or symptoms non-responsive or intolerant to optimal medical treatment (OMT), (8) dyspnea/cardiac heart failure with >10% ischemia/viability supplied by stenosis >50%, (9) no limiting symptoms with OMT in vessel other than left main or proximal LAD or single remaining vessel or vessel subtending area of ischemia <10% of myocardium or with fractional flow reserve (FFR) ≥0.80.

Angina risk factor reduction

Medical and surgical therapies coupled with intensive risk factor management via pharmacotherapy could prevent symptoms by stabilizing or reducing atherosclerotic burden, which is the underlying cause of the symptoms. Dietary modifications coupled with hypolipidemic drugs are used to treat patients with CAD including those with chronic stable angina. Statins must be given even with mild elevation in low-density lipoprotein (LDL) cholesterol (e.g., >100 mg/dl and <130 mg/dl). The primary goal is to reduce LDL-C to <70 mg/dl (<1.8 mmol/l). The additional goal is to reduce blood pressure to <130/80 mmHg apart from normalizing glycated hemoglobin (HbA1c) in diabetic and hypertensive patients to reduce the risk of future coronary events. A medical evaluation including an exercise stress test is generally indicated for patients with angina prior to a regular physical activity program.[17] The goals of pharmacological treatment include: (1) alleviation of symptoms, extending exercise duration, and improvement in QoL, (2) improvement in prognosis and prevention of CV events by reducing acute coronary thrombosis incidence and slowing atherosclerotic progression and ventricular dysfunction.[18]

Ferrari et al have described guideline-recommended drug therapies for the alleviation of chronic stable angina. As per ESC and ACC guideline recommendations, the antianginal drugs showing symptomatic relief include short- and long-acting nitrates; non-selective and cardioselective (with preserved EF and reduced EF) β-blockers; calcium channel blockers (CCBs); and second-line drugs such as ivabradine, nicorandil, ranolazine, and trimetazidine, but the outcome benefits are well seen with cardioselective β-blockers (with reduced EF) and in second-line drugs like nicorandil. The additive or synergistic effects of two or more of anti-ischemic drugs in tailor-made combinations can control symptoms effectively.[19]

Efficacy of revascularization for chronic stable angina

Percutaneous coronary interventions

Percutaneous coronary interventions (PCIs), such as balloon angioplasty and stent implantation, and CABG surgery are the two routinely available modalities for revascularization in patients with CAD. Nevertheless, the advantages and disadvantages of PCI in the treatment of CAD must be weighed. While PCIs involve low level of procedure-related mortality and reduced hospitalization, thereby early return to activity, these interventions are unsuitable for some patients in whom there is a significant risk of restenosis. Furthermore, there is a risk of coronary occlusion during percutaneous transluminal angioplasty.[20]

The diamond approach for treatment of CAD with comorbidities

Diamond approach is a possible framework for individualized therapy using the established antianginal drugs (Table 3).[19]

Table 3: Possible combinations of classes of antianginal drugs for specific comorbidities.

Comorbidity	Preferred	All possible	Co-administered	Contraindicated or caution needed
High HR ≥70 BPM	BB VER*DILT IVAB	-	TRIM*RAN	DHP NITR*NIC
Bradycardia	-	DHP*NIC*NITR TRIM*RAN	-	BB VER*DILT IVAB
Hypertension	BB DHP*VER DILT*NITR NIC	-	TRIM*RAN IVAB	None
Hypotension	-	TRIM*RAN*IVAB	-	BB*VER DILT*DHP NITR*NIC
Left ventricular dysfunction	BB	-	TRIM IVAB*RAN NITR	DHP VER*DILT NIC
Heart failure	BB*IVAB	-	TRIM*NITR RAN	DHP VER*DILT NIC
Atrial fibrillation	BB VER*DILT	-	TRIM*RAN	DHP NITR*NIC IVAB

BB, β-blockers; BPM, beats per minute; DHP, dihydropyridine calcium-channel blockers; DILT, diltiazem; HR, heart rate; IVAB, ivabradine; NIC, nicorandil; NITR, nitrates; RAN, ranolazine; TRIM, trimetazidine; VER, verapamil.

Recommendations for diabetes mellitus in chronic coronary syndromes

Diabetes mellitus (DM) can increase CAD risk by 2-fold, and control of risk factors is necessary for CVD prevention. Systolic BP in patients with diabetes should be targeted to ≤130 mmHg, if tolerated, but not <120 mmHg, and diastolic BP should be targeted to <80 mmHg, but not <70 mmHg. Initial hypertension treatment should consist of a combination of a renin-angiotensin system (RAS) blockers with CCBs or thiazide/thiazide-like diuretics. Angiotensin-converting enzyme (ACE) inhibitors reduce albuminuria and the appearance or progression of diabetic nephropathy more effectively than other drug classes.

Recommendations for DM in CCS are as follows: (1) risk factor (BP, LDL-C, and HbA1c) control to targets is recommended in patients with chronic kidney disease (CKD) and DM, (2) in asymptomatic patients with DM, periodic resting ECG is recommended for detection of conduction abnormalities, atrial fibrillation (AF), and silent MI, (3) ACE inhibitor (ACEI) treatment is recommended in CCS patients with diabetes for event prevention, (4) the sodium-glucose co-transporter 2 inhibitors empagliflozin, canagliflozin, or dapagliflozin are recommended in patients with diabetes and CVD, (5) a glucagon-like peptide-1 (GLP-1) receptor agonist (liraglutide or semaglutide) is recommended in patients with diabetes and CVD, (6) in asymptomatic adults (age 40>years) with diabetes, functional imaging or CCTA may be considered for advanced cardiovascular risk assessment.

CAD patients with diabetes are considered to be at very high risk; consequently, LDL-C should be lowered to <1.8 mmol/l (<70 mg/dl) or reduced by ≥50% if the baseline LDL-C is between 1.8 and 3.5 mmol/l (70 and 135 mg/dl). Routine use of CTA in asymptomatic patients with diabetes is not recommended.[20] GLP-1 agonists and sodium-glucose transport protein 2 (SGLT2) inhibitors have cardiac benefits and are preferred in DM.

Recommendations for CKD in chronic coronary syndromes

The proportion of patients undergoing PCI and having concomitant CKD has been increasing, and CAD is highly prevalent in patients with CKD. Improved outcomes are seen with risk-factor control (lipids, BP, and glucose). Patients with CKD rarely receive invasive management for CAD treatment compared to those without. Limited data on hemodialysis make generalizable treatment recommendations difficult. Risk factors are controlled to target values; special attention is paid to potential dose adjustments of renally excreted drugs in CCS; the use of iodinated contrast agents is minimized in patients with severe CKD and preserved urine production to prevent further deterioration.[8]

PHARMACOLOGICAL INTERVENTION

OMT as the primary treatment modality for patients with SCAD was recommended by all the standard guidelines (2014 ACC/AHA guideline and 2019 European Society of Cardiology [ESC] guideline). OMT delays atherosclerosis and coronary thrombosis progression. Initial medical therapy has been considered to be safe and effective over PCI.[8,21,22] Beta-blockers, CCBs, and nitrates are the first line of medical management.

Role of statins in the management of CAD[23]

Statins are known to reduce cardiovascular events and mortality in patients with CAD or at high risk of CVD as evidenced by many studies. Statins have pleiotropic effects such as improved endothelial function, reduced inflammation, and thrombus formation. They have been shown to reduce overall major adverse cardiac events. Reduction of the risk of the composite primary endpoint of death, MI, cardiac arrest, and recurrent ischemia by 16% has been observed with 80 mg atorvastatin in patients with acute coronary syndrome.

Role of ACE inhibitors in the management of CAD

Studies have shown that administration of ACE inhibitors (ACEIs) after acute MI improves ventricular function and survival. In the Cooperative Northern Scandinavian Enalapril Survival Study, patients who had an MI exhibited 40% reduction in 6-month mortality after receiving enalapril. Radioligand inhibitor binding studies demonstrate that quinaprilat, the active metabolite of quinapril, has the highest ACE-binding affinity in both tissue and plasma. The rank of potency in tissue among ACEIs is as follows: quinaprilat =benazeprilat >ramiprilat >perindoprilat >lisinopril >enalaprilat >fosinopril >captopril. Trandolapril significantly decreased the level of ACE activity and the size of the atherosclerotic lesions. Although all the agents lowered blood pressure, only quinapril produced a significant improvement in endothelial function. In the Acute Infarction Ramipril Efficacy trial, MI patients receiving ramipril had a 27% decrease in mortality. In the Trandolapril Cardiac Evaluation study, trandolapril increased survival by 27%.[24]

Role of angiotensin receptor blockers in the management of CAD[25]

Role of angiotensin receptor blockers (ARBs) reduce mortality and morbidity in left ventricular systolic dysfunction (LVSD) patients in the settings of chronic heart failure, MI, and also in diabetes accompanied by proteinuria or CKD. In ACEI-intolerant patients, the addition of ARBs to standard treatment reduces the combined endpoints of cardiovascular mortality, nonfatal MI, and stroke. ACEIs and ARBs are preferred antihypertensives. General recommendations for the management of patients with CCS and symptomatic heart failure due to ischemic cardiomyopathy and LVSD: An ARB is recommended as an alternative in patients with persistent symptoms despite OMT with ACE inhibitions or angiotensin II receptor neprilysin inhibitor.

Role of nitrates in the management of CAD[26]

Nitrates display several hemodynamic effects, usually vasodilation of capacitance veins and conductance arteries. Nitric oxide-mediated dilation of capacitance vessels reduces ventricular preload, resulting in myocardial oxygen demand reduction.[26]

Role of trimetazidine in the management of CAD

Trimetazidine has similar antianginal efficacy to propranolol. Improvement in effort-induced myocardial ischemia is seen with trimetazidine combined with beta-blockade.[7]

Role of beta-blockers and CCBs in the management of CAD

Beta-blockers and CCBs are the first line of medical therapy in all angina patients.

Role of ivabradine in the management of CAD

Ivabradine selectively inhibits the sinus node I(f) pacemaking current, thus reducing the myocardial oxygen demand with intact inotropism and blood pressure. Approved by European Medicines Agency, ivabradine is given for chronic stable angina in beta-blocker-intolerant/inadequately controlled patients and in whom heart rate exceeded 60 bpm. Adding ivabradine 7.5 mg twice daily to atenolol resulted in good control of heart rate and anginal symptoms.[7]

Role of ranolazine in the management of CAD

Ranolazine (500–2000 mg/day) reduced angina and increased exercise capacity, keeping heart rate/blood pressure intact. Type 2 Diabetes Evaluation of Ranolazine in Subjects with Chronic Stable Angina (TERISA) study reported reduced episodes of stable angina in 949 diabetics taking ranolazine, who were already receiving one or two antianginal drugs. The benefits were more prominent in patients with higher HbA1c levels. Ranolazine increases QTc, and caution must be exercised in patients with QT prolongation or on QT-prolonging drugs.[7]

Role of nicorandil in the management of CAD[7]

It can be used for the prevention and long-term treatment of angina and can as well be added after beta-blockers and CCBs. In the prospective impact of Nicorandil in Angina (IONA) study, over a mean of 1.6 years in 5126 patients with SCAD, CV events were reduced by 14% (relative risk 0.86; p=0.027). Long-term use of oral nicorandil may stabilize coronary plaque in patients with stable angina.

Nicorandil is preferred in microvascular angina, slow flow phenomenon.

CONCLUSION

Indians are more prone to angina and other related CVDs, and the reach of cardiologist is minimal. This scenario promotes the importance of risk stratification of patients for appropriate management. The dynamic process of management of coronary syndromes begins with cardiovascular risk stratification, clinical evaluation of the cardiac symptoms (new or recurrent), grading the risk, and providing aggressive tailor-made therapeutic regimen to ameliorate symptoms. This consensus was an attempt to understand the current evidences and practices of risk stratification and management. Patients at a higher risk could benefit from early revascularization combined with OMT to improve long-term prognosis; nevertheless, the prognostic benefits of revascularization need newer studies for further clarification.

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