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Consensus on evolving usage of anti-anginals: Benefits beyond anginas

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Abstract
Cardiovascular diseases (CVDs) became the leading cause of mortality in India, at the turn of the century. This transition is largely because of the increase in CVD risk factors in India. Ischaemic heart disease is the leading cause of disease burden in India. Traditional anti-anginal drugs, classified as first line and second line give symptom relief and decreased the frequency of angina, however none prevents myocardial ischemia or death caused by coronary disease in patients being treated specifically for chronic stable angina. The Diamond approach is more acceptable as it provides an individualized approach to angina treatment, which takes into consideration the patient, their comorbidities, and the underlying mechanism of disease. The second line drugs such as nicorandil, ranolazine, trimetazidine are equally effective in relieving symptoms and can be considered as the standard of care. Also, the diagnosis of microvascular coronary dysfunction is a challenge which is most of times the underlying cause of angina. Invasive techniques are required for the diagnosis of microvascular angina or vasospastic angina. Therefore, classical and novel anti-anginal medications such as nicorandil should be carefully selected and customized to individual patients. The purpose of this consensus article is to highlight the clinical perspectives of Indian cardiologists at identifying and addressing the need gaps currently existing in India for the management of angina patients and the need for the personalized treatment options.

Keywords: cardiovascular disease, stable angina, microvascular angina, vasospastic angina, nicorandil, vasodilators

Introduction
The burden of cardiovascular diseases (CVD) is increasing in India, and according to 2016 data it varied strikingly between states of India [1]. CVD cases increased in India from 25·7 million in 1990 to 54·5 million in 2016. CVD contributed 28·1% of total deaths in 2016 [1]. One in 4 deaths in India are now because of CVDs with ischemic heart disease and stroke responsible for >80% of this burden [3]. The traditional approach used for the management of angina, i.e. first- or second-line drugs have not shown much impact on reduction in cardiovascular mortality or the rate of myocardial infarction [3]. According to clinical trials second line anti-angina drugs are equally effective. Alternative mechanistic-based approach to drug selection based on individual patient is the need of the hour [3]. Some agents, in addition to having antianginal effects, have properties that could be useful depending on the comorbidities present and the mechanisms of angina [5]. Last few years have observed an exponential rise in the use of anti-anginal agents beyond angina and the long-term outcome of their use has been established [5]. It is important to have an tailored or personalized approach for the management of acute coronary syndrome (ACS) or chronic coronary syndrome (CCS) patients with different co-morbidities [4]. Nicorandil, one such anti-anginal agents have confirmed possible beneficial effects after an MI, reduced mortality and efficiently used in treatment line of ACS patients presenting with comorbidities [3]. Management of primary microvascular angina can be challenging but pharmacological treatments such as nicorandil have been found to be effective with satisfactory control of symptoms [6]. Overall, there is an imperative need to identify gaps in current clinical approaches and subsequently improve ACS and CCS outcomes in India.

Methodology
The experts' group meeting was conducted including cardiologists from major cities of India. The main purpose of the meeting was to understand the challenges faced in the management of Indian cardiac patients and the need for the personalized treatment options. The two main objectives of this focussed group meeting was –

- Developing the "Best fit medication" for various ACS and CCS profiles
- Developing a checklist for the optimal management of anginal patients

The experts shared their experience and opinions on the pharmacological use of anti-anginal drugs in various case

profiles. All the group opinions were collated into one document and the consensus was finalized after approval by all panel members.

This consensus article provides a summary of evidence-based literature and individualized approach to angina treatment in Indian scenario and also taking into consideration the patient, their comorbidities, and the underlying mechanism of disease. Every section in this article is followed by consensus points for proper understanding of all the aspects.

Chronic stable angina

Chronic stable angina occurs either due to decreased supply or increased demand for myocardial oxygen or combination of both [7]. Decrease supply in oxygen can be either due to epicardial coronary artery disease (CAD) among which the two major causes are atherosclerosis and vasospasm or microvascular CAD [7]. Microvascular CAD can be due to endothelial dysfunction, vasospasm, inflammation, post percutaneous coronary intervention (PCI) or post coronary artery bypass grafting (CABG) [8, 9]. Angina can also result because of increase in myocardial oxygen supply leading to left ventricular hypertrophy with factors such as hypertension, aortic stenosis or right ventricular hypertrophy due to pulmonary hypertension or any other cause [10, 11].

Management of angina

Traditional approach of angina management includes first line and second line agents. Sublingual or short-acting nitro-glycerine, beta-blockers, and calcium channel blockers are the first-choice therapy. Ivabradine, nicorandil, ranolazine, and trimetazidine are second choice for patients who have contraindications to the first-choice drugs, or who fail to tolerate them, or who remain asymptomatic [12].

Drawbacks of the traditional approach [12]

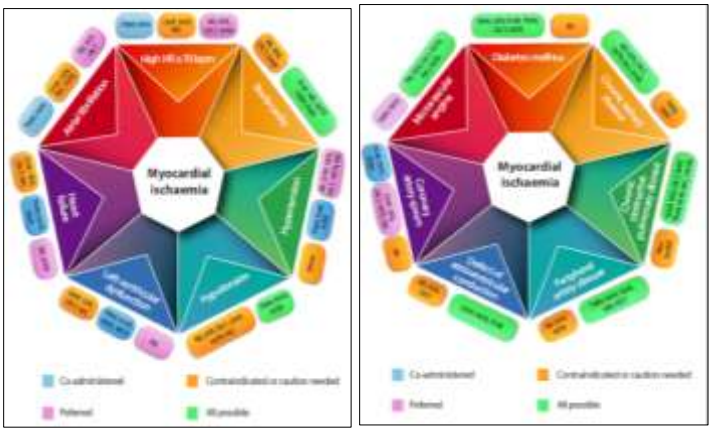
- The ESC experts suggest the chronic use of beta-blockers in patients with documented large areas of ischaemia and ventricular dysfunction
- AHA/ACC guidelines, beta-blockers are suggested as chronic treatment for all patients with CAD independently from the ventricular dysfunction or not
- The first line drugs provide symptomatic relief, with no benefits on hard outcomes
- There are no head-to-head comparisons between 1st & 2nd line treatments
- Guidelines do not provide an indication of the best possible combination where double/triple therapy is required

Although there are minor differences, the common approach of the ESC, NICE, and AHA/ACC guidelines is the classification of drugs into the first and second line [12].

ESC 2019 guidelines on chronic coronary syndrome [13]

- Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-CCB is contraindicated, poorly tolerated, or inadequate to control angina symptoms
- Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates
- In selected patients, the combination of a beta-blocker or a CCB with second-line drugs (ranolazine, nicorandil, ivabradine, and trimetazidine) may be considered for first-line treatment according to heart rate, BP, and tolerance

On the basis of this, a personalized treatment approach, "Diamond approach" has been proposed for the management of angina [4]. Newer antianginal drugs, which are classified as second choice, have more evidence-based clinical data that are more contemporary to support their use than is available for the traditional first-choice drugs [4]. Diamond approach leaves treating physicians free to choose the most appropriate drugs, according to a patient's needs. It is a very flexible approach and allows the use of all available drugs. A combination of two or more of anti-ischaemic drugs with additive or synergistic effects is often needed to control symptoms effectively according to the diamond approach as shown in figure 1 and 2 [4].



BB: β-blockers; DHP: Dihydropyridine calcium-channel blockers; DILT: Diltiazem; HR: Heart rate; IVAB: Ivabradine; NIC: Nicorandil; NITR: Nitrates; RAN: Ranolazine; TRIM: Trimetazidine; VER: Verapamil.

Adapted from: Ferrari R, Camici PG, Crea F, Danchin N, Fox K, Maggioni AP, *et al*. Expert consensus document: A'diamond'approach to personalized treatment of angina. Nature Reviews Cardiology. 2018 Feb; 15(2):120.

Fig 1 and 2: Combinations of two or more antianginal drugs according to different comorbidities[4]

Consensus statement 1

- The first/ second line therapy approach for the treatment of ACS or ischemia are not supported by much of large randomized trials but are more on conventional basis. The burden of epicardial and microvascular disease has increased their usage
- The drugs should not be classified as first-line or second line drugs
- All the drugs should be individualized as per the comorbidities and as per the presenting phenotype of angina. These drugs should be given equal importance
- Newer drugs such as nicorandil, ranolazine, trimetazidine have equal efficacy in relieving symptoms and improving functional capacity
- B-blockers are the mainstay after MI of LV dysfunction unless contraindicated, but do not improve outcome instable angina and do not have mortality benefit. In such patients' drugs such as nicorandil or trimetazidine should be the choice
- If patient affordability is not an issue, nitrate with nicorandil depending upon threshold of the patient in terms of tolerance can be therapy of choice.
- Some experts prefer to use combination of traditional and modern approach while some start with a traditional approach and depending upon co-morbidities clinician can decide on customized approach

Challenges faced in Indian scenario

- Indian population displays a higher trend of presenting with atypical symptoms of angina, which may result in a missed diagnosis [13]
- Due to scarce resources, healthcare affordability and delivery, and other logistical difficulties, the optimal treatment may not be available to the Indian population[13]
- Cost affordability for the diagnostic tests and medications is yet another challenge [14]
- Rural areas lack of facilities, health insurance schemes and public awareness [15]
- STEMI programs are not much implemented in India as they have been in the developed countries [15]

Stable coronary artery disease

Stable coronary artery disease is classified either as atherosclerotic CAD, microvascular CAD or they may be combined. Up to 40% of patients with signs and symptoms of ischaemia undergoing coronary angiography do not have obstructive atherosclerosis. Following exclusion of non-coronary causes of chest pain, the presence of coronary vascular dysfunction, ischaemia on stress testing, and chest pain persisting at 1 year of follow-up identify a subgroup at higher risk for adverse clinical outcomes [16].

Pathophysiological studies have documented frequent coronary endothelial and non-endothelial coronary dysfunction in patients with signs and symptoms of ischaemia despite the lack of obstructive atherosclerosis [16].

Patients with angina have non-flow limiting (non-obstructive) epicardial coronary artery disease (CAD) [17]. Angina may persist in patients following technically successful percutaneous coronary intervention (PCI) [18]. Huqi *et al*. demonstrated that 29% of patients still had an abnormal exercise stress test result after one month of PCI [17]. One third of patients present with a persistent positive stress test result after one month of PCI [17].

Advances in interventional diagnostic techniques enable new insights into coronary microvascular function in patients with stable CAD [18].

Consensus statement 2

- Myocardial perfusion is not merely governed by epicardial stenosis, several other factors also play a very important role such as
- Endothelial dysfunction
- Patency of microvasculature
- Collateral formation
- LV hypertrophy
- Whenever you evaluate a CAD patient consider both epicardial and microvascular components
- Many times, the microvascular component is ignored. This condition is mostly prevalent in patients such as diabetes who have both epicardial and microvascular component
- Microvascular angina is seen in patients without revascularization, post revascularization such as post PCI, post CABG or MI post lytic and even in microvascular spasm.

Microvascular angina

Microvascular angina (MVA), is caused by abnormalities of the coronary microcirculation. The pathogenetic mechanisms of MVA are heterogeneous and may involve both structural and functional alterations of coronary microcirculation, and functional abnormalities may variably involve an impairment of coronary microvascular dilatation and an increased microvascular constrictor activity [6].

MVA is characterized by effort chest pain and evidence of myocardial ischemia with a non-invasive stress test, although the coronary arteries can appear normal or near normal by angiography [19]. MVA patients are often neglected due to the assumption of a good prognosis. The prevalence of MVA is estimated to be up to 30% of stable angina patients with non-obstructive coronary arteries. MVA predominantly affect women [19]. Approximately 10% to 25% of women with ACS have a "normal" or non-obstructive CAD using coronary angiography [19]. Amongst which 19% of women are presented with acute coronary syndrome, 30% of women presenting with unstable angina, 9.1% of women with non-ST-elevation myocardial infarction, and 10% of women with ST-elevation myocardial infarction [19].

Symptoms of patients with MVA are often indistinguishable from those with obstructive CAD. Nonetheless, normal or non-obstructive CAD coronary angiography often leads to the misdiagnosis of "non-cardiac" chest pain; therefore, MVA patients remain untreated. Hence, correct diagnosis is mandatory to minimize the risk of false-negative results [19].

Challenges in microvascular angina [13]

- The clinical diagnosis of microvascular angina remains difficult
- Lack of a standardized definition and diagnostic criteria has made evaluation of treatment strategies for microvascular

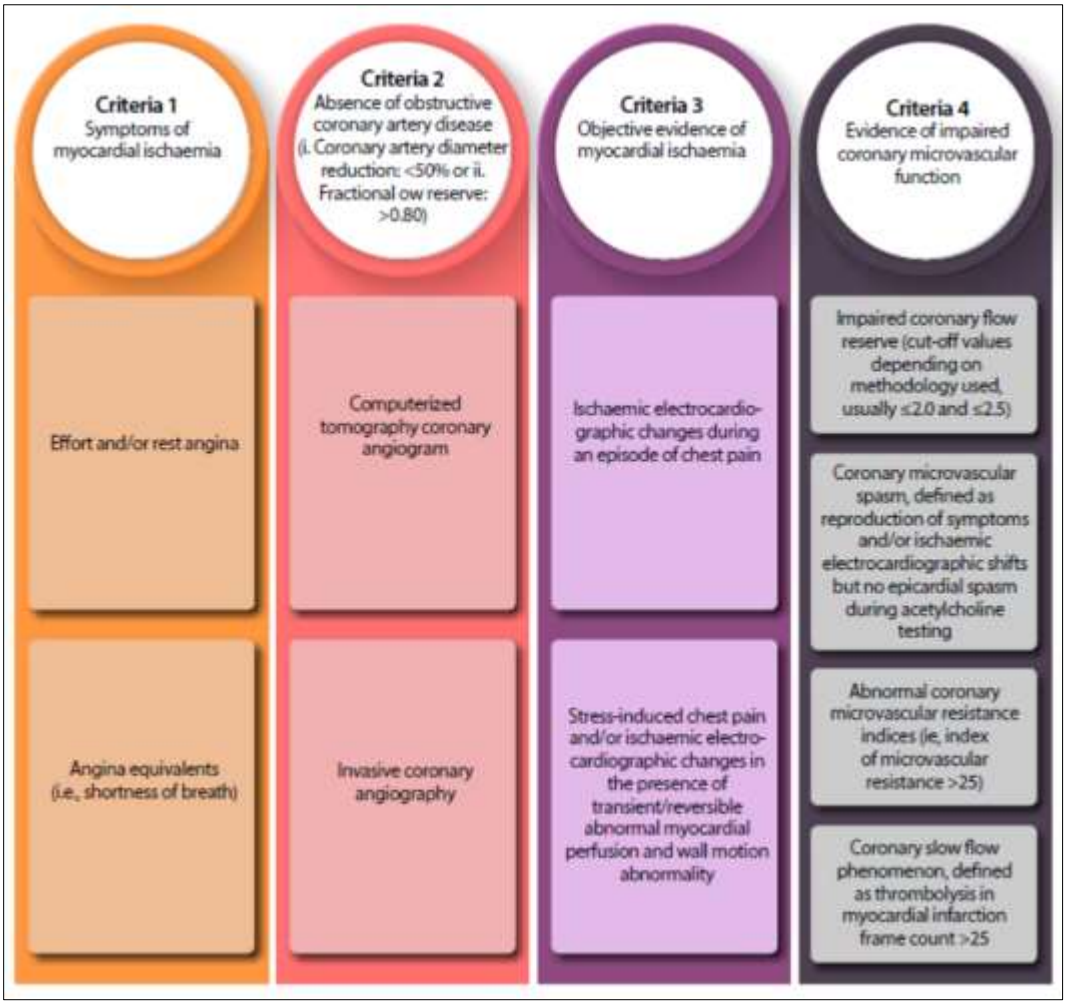
angina challenging

- The current approach is to use traditional antianginal and risk-reduction therapies targeted at epicardial CAD
- However, this seems not to be effective in the management of coronary microvascular dysfunction, particularly those treatments suggested as being first choice by the guideline

Diagnosis of microvascular angina

The diagnostic criteria for MVA is proposed by the COVADIS study group (Coronary Vasomotor Disorders) as given in table 1. This includes the signs and symptoms of myocardial ischemia, reduced coronary flow reserve (CFR) or microvascular spasm, and documented myocardial ischemia, which is not triggered by obstructive CAD but by functional or structural abnormalities at the site of the coronary microcirculation (Table 1).[20] Definitive microvascular angina is diagnosed when all 4 criteria are present. Suspected microvascular angina is diagnosed if criteria 1 and 2 are present, but only objective evidence for ischemia (criterion 3) or impaired coronary microvascular function (criterion 4) are documented [20].

In large number of patients with MVA, the imaging modalities such as stress thallium will give negative results, despite the occurrence of ischemia. This is contrary to what is seen in obstructive CAD, myocardial ischemia does not follow a regional pattern in MVA and ischemia may be in many cases limited to the subendocardium [20]. In such cases the diagnosis can be done with help of fractional flow reserve (FFR) and Coronary flow reserve (CFR).



Adapted from Kaski JC, Crea F, Gersh BJ, Camici PG. Reappraisal of ischemic heart disease: fundamental role of coronary microvascular dysfunction in the pathogenesis of angina pectoris. Circulation. 2018 Oct 2; 138(14):1463-80.

Fig 1: Clinical Criteria for Suspecting Microvascular Angina

Decision making in CSA: Based on FFR and CFR

Fractional flow reserve (FFR) is an invasive measure of the physiological significance of an epicardial coronary stenosis. Since coronary angiography is often insufficient in guiding percutaneous coronary intervention (PCI), FFR has gained wide acceptance for estimating whether a coronary lesion may cause myocardial ischemia [21].

A lesion with an FFR ≤0.80 is generally judged ischemia prone, whereas it is accepted that a lesion with an FFR >0.80 is unlikely to produce myocardial ischemia [21].

Coronary flow reserve (CFR) denotes the myocardial reserve vasodilator capacity, defined as the ratio of maximal hyperemic

coronary blood flow (CBF) to resting CBF. CFR less than 2 is used to distinguish coronary lesions that are likely to trigger myocardial ischemia [21].

Positron emission tomography (PET) myocardial perfusion imaging (MPI) has high diagnostic accuracy and prognostic value. PET-MPI is also used to quantitatively evaluate regional myocardial blood flow (MBF). This technique also allows the calculation of the coronary flow reserve (CFR)/myocardial flow reserve (MFR) [22].

The interpretation of CSA based on CFR by PET and FFR is given in the figure 3

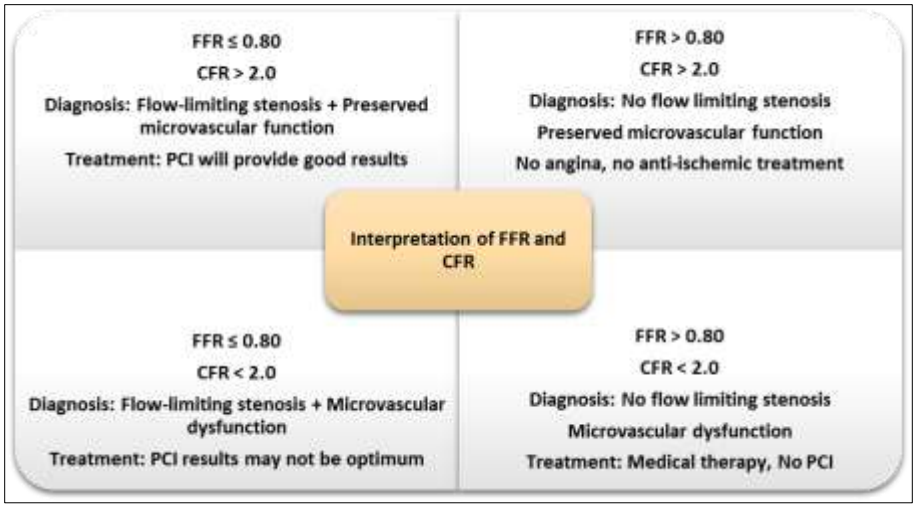


Fig 3: Decision making based on FFR and CFR[21]

FFR: Fractional flow reserve, CFR: Coronary flow reserve (ml/g/min), PCI: Percutaneous coronary intervention

Consensus statement 3

- Symptoms do not make the diagnosis of microvascular angina, they may be same as epicardial atherosclerotic angina
- If the patient has normal angiogram and history of angina, it may be microvascular angina
- But for confirming microvascular angina, invasive methods might require and coronary flow results are mandatory
- Cardiologist needs to rule out coronary lesion before suspecting microvascular and vasospastic angina
- If affordability is not an issue, FFR and CFR should be performed for the confirmation of microvascular angina, with the help of a nuclear cardiologist
- FFR and CFR gives a clear picture whether patient has microvascular angina or epicardial stenosis or both, which will help in the further management

Treatment of microvascular angina

The mode of action of most conventional antianginal agents involves haemodynamic changes, such as a reduction in systemic vascular resistance or coronary vasodilatation or negative inotropism, which improve the imbalance in myocardial oxygen supply and demand. Recently, new drugs based on novel mechanisms of action have emerged such as ranolazine, trimetazidine, nicorandil, ivabradine as highlighted in Table 2 [23].

Table 2: Treatment of angina

Drugs	Improvement in total exercise time	Improvement in time to onset of ST segment depression	Decrease in frequency of anginal episodes	Reduced revascularisation	Prevention of MI	Improvement in survival	Other effects
Drugs with haemodynamic effects							
β-blockers	+	+	+	-	-	-	
Calcium channel antagonists	+	+	+	+	-	-	Prevent atherosclerosis progression
Nitrates	+	+	+	-	-	-	Antiplatelet activity
Drugs with metabolic effects							
Ranolazine	+	+	+	NA	NA	NA	
Trimetazidine	+	+	+	NA	NA	NA	
Ivabradine	+	+	+	NA	NA	NA	
Nicorandil	+	+	+	NA	+	+	Improvement in myocardial perfusion
Fasudil	−	+	−	NA	NA	NA	

Adapted from: Ben-Dor I, Battler A. Treatment of stable angina. Heart. 2007 Jul 1; 93(7):868-74.

All patients with MVA should receive optimal risk factor control. If symptoms are not well controlled, addition of traditional (β-blockers or CCB) and non-traditional anti-ischaemic drugs (Ranolazine, Xanthines, ACE-I, Ivabradine, Nicorandil) is recommended. In patients with enhanced pain perception, drugs which modulate pain perception are indicated [16].

Mortality benefits of Anti-anginal drugs

- Mortality benefit is limited to those with recent myocardial infarction or severe systolic left-ventricular dysfunction [13]
- None of the antianginal drugs (with the possible exception of nicorandil) have been proven to reduce cardiovascular mortality or myocardial infarction, despite the fact that they are equally effective in treating symptoms [13]

Vasospastic angina

The presence of normal or near normal coronary arteriograms often leads the managing physician to make a diagnosis of noncardiac chest pain. Cardiac mechanisms such as increased coronary artery vasomotion (i.e., epicardial or microvascular coronary spasm or both) can be responsible for the occurrence of anginal symptoms in these patients [24].

If a patient has chest pain at particularly at rest, ST segment elevation, which disappears after consumption of nitrates, epicardial coronary spasm is suspected. Angiographic assessment via the intracoronary acetylcholine-provocation test (ACh test) is the standard method for diagnosing epicardial CAS in nonobstructive CAD. Acetylcholine induces spasm and ECG shows ST elevation and when nitrates are given the spasm disappears, this confirms the diagnosis of epicardial coronary spasm [21, 25].

Increased lactate production in the coronary circulation is a definitive sign of microvascular spasm, and it is possible to compare plasma lactate levels in the aortic root and the coronary sinus to assess the occurrence of myocardial ischemia during CAG [25].

In microvascular spasm, the epicardial coronary artery will be normal and upon injecting intracoronary acetylcholine, induces microvascular spasm and ECG shows ST segment depression. But the microvascular spasm is documented when there is increased lactate in the coronary sinus in coronary artery, with ST segment elevation and absence of epicardial coronary spasm [25].

ACOVA (Abnormal COronary VAsomotion in patients with stable angina and unobstructed coronary arteries) study [24]

- ACOVA study determined the prevalence of epicardial and microvascular coronary spasm in patients with anginal symptoms, despite angiographically normal coronary arteries. Nearly 50% of patients undergoing diagnostic angiography for assessment of stable angina had angiographically normal or near normal coronary arteriograms.
- The ACH test triggered epicardial or microvascular coronary spasm in nearly two-thirds of these patients. Coronary spasm was seen in 62% patients. Of which 45% patients had epicardial coronary spasm, and 55% had microvascular spasm. Also, 52% of the patients with microvascular spasm had <25% epicardial constriction during ACH-provocation
- The study suggests that abnormal coronary vasomotion plays a pathogenic role in this setting and that the ACH test might be useful to identify patients with cardiac symptoms, despite normal coronaries
- The high prevalence of microvascular spasm in the study suggests an important role of coronary microvascular dysfunction also as a possible cause of exercise-induced angina in patients with chest pain and unobstructed coronary arteries

Treatment of vasospastic angina (VSA) [3, 26]

- Calcium channel blocker is the first line treatment due to a vasodilation effect in the coronary vasculature and it alleviates symptoms in 90% of patients
- Long-acting calcium antagonist is recommended to be given at night as the episodes of vasospasm are more frequent at midnight and early in the morning. A high dose of long-acting calcium antagonists like diltiazem, amlodipine, nifedipine, or verapamil are recommended, and titration should be done on an individual basis with an adequate response and minimal side effects
- Two-calcium antagonist (dihydropyridine and non-dihydropyridine) can be effective in patients with poor response to one agent
- Long-acting nitrates are also effective in preventing vasospastic events, but chronic use is associated with tolerance
- Nicorandil also suppress vasospastic attacks and successfully treat vasospastic angina
- The use of beta-blockers, especially those with nonselective adrenoceptor blocking effects, should be avoided because these drugs can aggravate the symptoms

Angina with LV dysfunction

Left ventricular (LV) function is a powerful prognostic predictor in patients with coronary artery disease (CAD). The increasing number of patients with CAD and ischemic LV dysfunction is a major clinical problem [27]. Clinical evidence has suggested survival benefit in such patients if they are revascularized when myocardial viability is detected on imaging tests [27].

A meta-analysis included 3,088 patients examining late survival with revascularization versus medical therapy after myocardial viability testing in patients with severe coronary artery disease (CAD) and left ventricular (LV) dysfunction. In patients with viability, revascularization was associated with 79.6% reduction in annual mortality (16% vs. 3.2%, $p < 0.0001$) compared with medical treatment. Patients with viability showed a direct relationship between severity of LV dysfunction and magnitude of benefit with revascularization ($p < 0.001$) [27]

For the prediction of recovery of regional function after revascularization, fluorodeoxyglucose positron emission tomography (FDG PET) has the highest sensitivity followed by the other nuclear imaging techniques. A relatively low sensitivity was observed for dobutamine echocardiography. Conversely, specificity was highest for dobutamine echocardiography and lower for the nuclear imaging techniques [28].

Nicorandil – A novel Anti-Anginal

Nicorandil is a balanced vasodilator, which affects both venous and arterial beds. Its chemical structure consists of a nicotinamide derivative combined with nitrate moiety. Overall, nicorandil is similarly effective for angina prophylaxis to long-acting nitrates and other conventional anti-anginal drugs, however it does not cause tolerance and offers added prognostic benefit [29].

Nicorandil has key benefits as compared to other anti-anginal drugs [3]

- Balanced vasodilator with dual mechanisms of action
- Improves myocardial salvage
- Prevents of ischaemic reperfusion injury
- More "balanced" vasodilatation than nitrates
- Rapidly absorbed via GIT
- Well tolerated with a satisfactory safety profile
- Reduces mortality rate following hospital discharge

Nicorandil causes arterial and venous dilatations, which reduces afterload and coronary arterial tone and reduce preload and coronary venous tone, respectively. This helps in thereby decreasing myocardial ischaemia. Nicorandil provides benefits beyond anti-anginal effects (Figure 4) [29, 30] Nicorandil shows myocaridal and cardio protective actions [30].

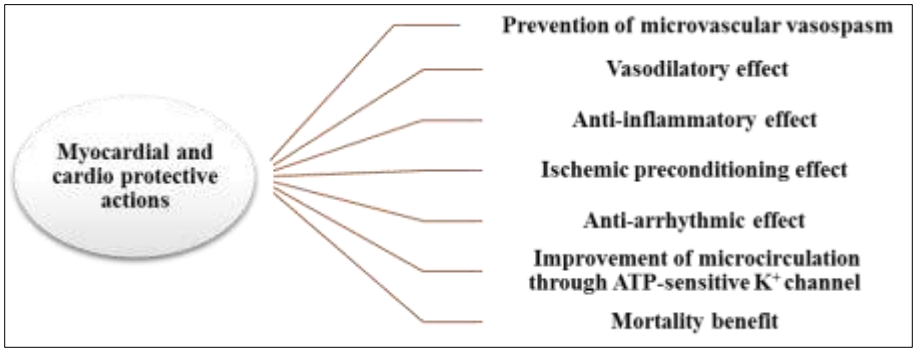


Fig 4: Myocardial and cardioprotection by Nicorndil

Pooled analysis of clinical trials has shown that nicorandil is well tolerated up to >3 years in duration. As compared to other anti-anginal drugs the overall incidence of adverse events did not differ between the two treatment groups. Adverse effects are usually observed during the initial phase of treatment and decreases during the treatment periods. A lower starting dosage appears to reduce discontinuation of nicorandil treatment for headache, and progressive titration is recommended [30].

Clinical evidence for Nicorandil

In patients undergoing PCI, intravenous administration of 6 mg nicorandil immediately before surgery had beneficial effects [31]. Nicorandil significantly decreased the incidence of post-procedural slow coronary flow (SCF) phenomenon in both the ACS and non-ACS groups. (4.3 vs. 26.2% and 4.4 vs. 14.2%, respectively). The corrected TIMI frame count (cTFC) was significantly lower in both ACS and non-ACS patients in the nicorandil group than in those in the control group (11.7 ± 5.8 vs. 14.9 ± 9.8 and 10.2 ± 5.5 vs. 12.1 ± 6.3, respectively). The rate of target vessel revascularization (TVR) was significantly lower in the nicorandil group than in the control group in ACS patients [31].

Nicorandil shows cardioprotective effects in patients undergoing CABG surgery with cardiopulmonary bypass (CPB) [32]. The nicorandil group showed lower concentrations of serum troponin T (TnT) as compared to placebo (p = 0.012). Thus, the study suggests administering nicorandil in patients undergoing CABG surgery when the possibility of severe myocardial damage is suspected before the procedure (ie, for patients with a history of extensive myocardial infarction and those with poor preoperative ventricular function) [32].

Nicorandil enhances the myocardial protective effect of cold hyperkalaemic cardioplegia

in cardiac surgery patients [33]. The T_{arrest} after cardioplegia administration was significantly faster in nicorandil group in both mitral valve replacement (MVR) and CABG patients (P<0.05), but $T_{recovery}$ did not differ significantly. The incidence of postoperative serum CK-MB >75 IU L^{-1} in MVR patients was significantly lower in the nicorandil group than in placebo patients (P<0.05). However, in CABG patients there was no such significant difference. The incidence of dysrhythmias requiring intervention after aortic cross-clamp removal was also less in nicorandil group [33].

The OACIS study (The Osaka acute coronary insufficiency study) demonstrated that the oral administration of nicorandil is associated with reduced incidence of death in the setting of secondary prevention after acute myocardial infarction (AMI) [34]. All-cause mortality rate was 43% lower in nicorandil group compared without nicorandil (2.4% vs. 4.2%, stratified log-rank test: p = 0.0358). Nicorandil treatment was associated with a nearly 50% reduction in all-cause death after discharge (Hazard ratio 0.495, 95% CI: 0.254 - 0.966, p = 0.0393). Oral nicorandil reduced incidence of death for all patients, especially in patients with ages <75 years, male gender and hypertension [34].

Nicorandil has a more pronounced effect on the coronary microcirculation than nitrates, and therefore is a better option for patients with microvascular angina, including those with microvascular spasm [29].

Thus, nicorandil is an important pharmacological agent for management of chronic stable angina triggered by obstructive atherosclerotic coronary artery disease, as well as microvascular angina and epicardial coronary artery spasm [29].

Consensus statement 4

- Nicorandil is a good option in microvascular Angina. Nicorandil shows good response in slow flow.
- Many drugs do not have documented results for the same role as of nicorandil and this assurance needs to be given to patients and about the use of anti-anginal plays an important role
- Nicorandil acts on both preload and afterload, hence particularly useful in refractory angina. Arterial and vasodilator effect of nicorandil scores over nitrates
- Nicorandil should be used more in Indian Angina Patients. It should be much higher up in treatment as it has got benefits in mortality and microvascular dilatation
- Nicorandil being a Japanese molecule, due to global body politics enough justice is not done with them is molecule which it deserves
- In heart failure patients nicorandil IV does not produce any reflex tachycardia and produces a good degree of vasodilation
- Intravenous nicorandil is preferred by many experts before PCI and intracoronary Nicorandil is sometimes given before stenting to check if flow is good
- Oral Nicorandil is given for 1 month to all patients post STEMI

Importance of cold chain management

In India, the healthcare logistical scenario is diverse. It has varied geographical landscape ranging from glaciers to deserts and urban to rural areas with significant variation in temperatures [35]. Proper methods of storage and preservation of drugs are of great importance for maintenance of their potency. Depending on the product's composition, it may expire long before its expiration date if it has not been stored and handled properly [36]. The quality of the drug depends on the stability, efficacy, unchanged form and safety of the drug [36].

Nicorandil is stable in solid state in extreme dry condition, but degrades when exposed to moisture even if only for short period at low humidity levels and at room temperature.34 Nicorandil is unstable in humid conditions, and under the compressive pressure exerted by punching operations and therefore, the development of a stable nicorandil preparation is desired [37] It needs to be stored in refrigerator for its stability [37]

Under unstable conditions, nicorandil partially loses its potency and its ability to produce vasodilation [38]. Hence, it is important to maintain various factors influencing hydrolysis such as the percentage of moisture to which the product is exposed, temperature and storage period [37].

New formulation technologies are used for the preparation and new approaches such as nanoparticle formulation, transdermal preparation or mouth dissolving tablet are being developed for a stable nicorandil preparation [37].

Consensus statement 5

- Cold chain maintenance is a big challenge in developing countries like India.
- If pharmaceutical companies and distributors take care of this, then patients can be given all the important benefits of nicorandil
- If cold chain is maintained and economics is not an issue, then nicorandil can be placed above nitrates in the upcoming guidelines
- Also, the physician has an important role to play in the maintenance of the drug and patient education during the prescription is of utmost importance

Best Fit' Anti-Anginal drug/drug combinations in CCS profiles in Indian Scenarios

Based on the discussion the expert panel were of the opinion that following drugs or combinations can be used in different case profiles.

Table 3

Patient profile	Treatment line		Follow-up treatment line
	Monotherapy	Combinational therapy	
Patient with LV dysfunction with a medical history of COPD	Cardio selective beta blocker (Bisoprolol, nebivolol) With LV dysfunction patient's amlodipine is preferred LV dysfunction with history of COPD: Ivabradine and Carvedilol can be used	Nitrates and Nicorandil Non-selective beta-blockers are contraindicated	
CSA patients with diabetes	Beta blockers	Nitrates Ivabradine not to be added unless there is LV dysfunction.	Nicorandil
Patient with vasospastic angina and comorbid hypertension	Nitrates and Nifedipine (Sublingual) Nicorandil Beta-blockers are contraindicated	Calcium channel blockers such as diltiazem or verapamil ACE inhibitors can also be given	
Patients with suspected CAD and stable angina symptoms and or dyspnoea	Nitrates	Metabolic modifiers or beta-blockers	
Patients with new onset of HF or LV dysfunction	Beta blockers	Nicorandil and metabolic manipulators can be added if required.	
Asymptomatic subjects in whom CAD is detected in screening	Anti- anginal like a metabolic modulator if the patient has a positive treadmill	Anti-platelet with high dose statin should be started	

Table 4: Best Fit' Anti-Anginal drug/drug combinations in ACS profiles in Indian Scenarios

Patient profile	Treatment line		Follow-up treatment line
	Monotherapy	Combinational therapy	
MI	Beta blocker		If the symptoms persist, IV drip of Nicorandil or Nitroglycerine along with Ivabradine can be used if intervention is not possible
In STEMI patient undergoing PCI	Beta blocker	Nicorandil along with adenosine or diltiazem in no flow or slow flow cases Trimetazidine	After 3-4 months the dose can be optimized
After PCI	Beta blocker should be continued		If there is persistent angina after 2 weeks then nitrate or ranolazine can be added
STEMI patients undergoing Thrombolysis	Nitrate/Nicorandil	One metabolic manipulator such as ranolazine or trimetazidine Beta-blockers are contraindicated	
Angina Patients with diabetes and HF	Beta blocker- start low and up titrate	Nicorandil and metabolic modulators like Ranolazine and Trimetazidine	Coronary anatomy should be checked
Elderly with Angina	Beta blockers with closed monitoring in low doses. (They can have increased issues of conduction)	Nicorandil and metabolic modulators like Ranolazine/ Trimetazidine can be used Caution should be exercised with nitrate use, it can lead to postural hypotension.	
Patients with angina and suspected vasospastic or microvascular disease	Nicorandil	Calcium channel blockers such as verapamil, diltiazem Nitrates can be used Beta-blockers are contraindicated	
Asymptomatic and symptomatic patients less than 1 year	Beta- blockers	Nicorandil (If patient is still having chest pain)	
Asymptomatic and symptomatic patients more than 1 year	Continue Beta blocker	Nitrate and then metabolic modulators if not suspecting MVA. Nicorandil or metabolic modulators if suspecting MVA.	
Patient with ACS and concomitant CKD	Nicorandil (As dose modification is not required) Nitroglycerine can be used	Beta blockers to be used as most CKD patients have LV dysfunction Ranolazine and trimetazidine are contraindicated	

Key points from experts' consensus

- Step wise approach for coronary artery disease is not relevant in India.
- Symptomatic relief should be achieved as soon as possible
- As people are not ready to have intervention in most cases, 1st line and 2nd line drugs are given together most times
- Long acting nitrates have the side effects of tolerance and its role is not that high and nicorandil is slowly replacing it
- Stability of nicorandil is the only issue, hence, that has to be taken care
- In case of intervention nicorandil score over most of other anti-anginal drugs
- Due to comorbid conditions, in most patient profiles polytherapy needs to be given
- First line and second line drugs remain but nicorandil can jump start into first line of treatment

Conclusion

Patients with chronic stable angina can have several comorbidities, and cardiac ischaemic pain might result from various underlying pathophysiologies. Several new drugs with a different mechanism of action (ranolazine, trimetazidine, nicorandil, ivabradine) provide new treatment options. Nicorandil in addition to their antianginal effect, have auxiliary properties that could be useful, depending on comorbidities and the mechanisms of the chronic stable angina.

The consensus approach for the treatment of angina is mixture of traditional and diamond approach, more towards an individualised tailored treatment depending on the comorbidities and underlying mechanism.

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Disclosure

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