Review Article

Experts' consensus: pharmaco-invasive therapy for ST-elevation myocardial infarction along with focus on secondary prevention and cardiac rehabilitation in India

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ABSTRACT

In India, patients with acute coronary syndrome (ACS) tend to present with higher percentage of ST-elevation myocardial infarction (STEMI). Numerous existing challenges like patient unawareness, lack of structured STEMI care systems, inadequacy of promptly available facilities and unequipped ambulances for patient transport make it difficult to achieve optimal STEMI treatment. Also, due to socio-economic diversities prevailing in India, a large proportion of the entire population has access to only basic primary healthcare and are unable to afford proper medical facilities. Judicious and timely reperfusion strategy has been the mainstay of STEMI management. Even though, percutaneous coronary intervention (PCI) continues to be the gold standard for treating STEMI worldwide, it is not the ideal strategy in many Indian settings, especially in villages and smaller towns/cities. In such scenarios, pharmaco-invasive approach has proved to be a better reperfusion therapeutic strategy for improving treatment outcomes and subsequently reducing morbidity and mortality. 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 optimization of STEMI treatment approaches. The experts shared their views on the rationale of pharmaco-invasive approach and highlighted the significance of commonly used thrombolytic agents, STEMI treatment protocols, secondary prevention and cardiac rehabilitation.

Keywords: STEMI, Pharmacoinvasive approach, Reperfusion, Cardiovascular disease, PCI, Acute coronary syndrome

INTRODUCTION

Cardiovascular diseases (CVDs) are one of the major causes of mortality worldwide.[1] These diseases have a tendency to influence patients in their most productive years and cause appalling social and economic consequences.[2] It was observed that deaths due to CVDs in India rose from 1.3 million in 1990 to 2.8 million in 2016, with an increase by 34.3% in the crude death rate.[3] Amongst all the CVDs, ST-segment elevation myocardial infarction (STEMI) presents a life-threatening manifestation of coronary artery disease (CAD).[4] It is associated with increased mortality and morbidity and therefore, demands prompt detection and management.[4,5] The presence of economic and geographic diversities impose additional challenge to STEMI management in India.[5] Other challenges involved in developing structured systems of STEMI care in India include inadequate healthcare resources, inadequate infrastructure, lack of trained manpower and many more.[6] Early reperfusion and

appropriate pharmacotherapy are the need of the hour for STEMI.[5] As a reperfusion therapy, primary percutaneous coronary intervention (PPCI) may not be possible always owing to various challenges , initial thrombolysis followed by pharmaco-invasive approach (PI) could be the major strategy in such circumstances.[6] According to evidence, the use of pharmacoinvasive strategy might prove to be a more practical and effective reperfusion treatment intervention in many patients in the low- and middle-income countries facing challenges of timely PCI intervention.[6] Overall, there is an imperative need to identify gaps in current clinical approaches and subsequently improve STEMI outcomes in India.[4]

METHODOLOGY

A total of 5 expert panel meetings involving experts from Cardiology, were conducted in different cities of India namely, Kolkata, Cochin, Noida, Jalandhar and Nagpur. All the experts reviewed evidence on the current scenario of reperfusion strategies in India, the existing need gaps and the importance of pharmaco-invasive therapy in STEMI management. They finally shared their experience and opinions on different aspects of utilizing timely pharmaco-invasive strategies with an emphasis on optimization of STEMI outcomes. 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 on appropriate and systematic treatment approaches for STEMI in the Indian scenario and is prepared according to the experts' suggestions. Every section in this article is followed by consensus points for proper understanding of all the aspects.

EPIDEMIOLOGY

CVDs are the leading cause of death globally with over three quarters of CVD deaths occurring in low- and middle-income countries like India.[7,8] Apart from the high burden CVDs impose, these diseases have an impact on the productive workforce aged 35–65 years.[9] According to the CREATE registry data, India had the maximum burden of acute coronary syndromes (ACS) globally.[10] This prospective registry included more than 20,000 patients, out of which over 60% of them had STEMI.[10] Moreover, there is an estimate of more than 3 million STEMI cases occurring in the country every year.[11] Even though primary PCI is considered to be the gold standard for reperfusion therapy, less than 10% STEMI patients have access to it in India.[8] An analysis of INTERHEART data in South Asians demonstrated a prevalence of 11.7% (n=55/470) of acute MI in Indian patients below the age of 40 years.[12]

STEMI MANAGEMENT IN INDIA: THE IDEAL REPERFUSION STRATEGY

Decreasing the time from symptom to reperfusion and electing the optimum reperfusion strategy are significant challenges in STEMI care.[5] Early reperfusion therapy reduces the occurrence of myocardial damage during an acute event of MI and its consequent mortality.[13] Currently, primary percutaneous coronary intervention (PPCI) is the optimal reperfusion strategy if it can be performed in a timely manner.[13] According to available evidence, pharmacoinvasive approach can prove to be an effective treatment option for the management of STEMI patients in India.[8,14] This strategy is particularly useful in the Indian scenario, where delay in presentation to the hospital from onset of symptoms as well as non-availability of PPCI facilities at first medical contact (FMC) center is a common circumstance.[14]

The use of pharmacoinvasive strategy was supported by a multicenter randomized clinical trial, namely, the STREAM study, which clearly established that there was no statistically significant difference in the rate of primary composite outcome between pharmaco-invasive strategy (PI) and PPCI.[15] Similarly, the pilot Kovai Erode study and the following pilot Tamil Nadu STEMI program have demonstrated the practicability of combining PPCI and PI strategies in systems for optimal care of STEMI patients.[16] Findings from the STEPP-AMI study suggest that a pharmacoinvasive strategy resulted in outcomes similar to those with primary PCI at 2 years, making it a suitable option for Indian settings.[17] STEMI INDIA suggested that STEMI management in India adopt the dual strategy of primary PCI with pharmacoinvasive reperfusion for developing a framework for a system of care, referred to as STEMI INDIA model.[6]

Challenges in STEMI Management

There are several major loopholes at various levels in STEMI care in India.[18] Some of them include lack of dedicated STEMI care systems, lack of instantly available electrocardiogram (ECG) facility at first point of medical contact, lack of patient awareness, lack of physician readiness, lack of equipped ambulance systems network for patient transport.[18] On account of economic diversities present in India, only 20% of the entire population can afford proper medical care either with government supported schemes or private insurance.[5] Also, many regions in India do not have access to PCI facilities or cardiac catheterisation laboratories.[8] In addition, facilities for round-the-clock PCI do not exist in many cath-labs.

Moreover, prolonged transportation time, traffic congestions in metro cities and consequent delayed presentation are major hurdles for access to early reperfusion therapy.[8] The CREATE registry exhibited that the median time from onset of symptoms to hospital arrival was 300 min in STEMI patients and only 5% of those individuals used ambulances with most utilizing private transportation.[5,10] Additionally, monetary issues and getting patient/caretaker consent for performing primary PCI cause delay in getting timely treatment.[5,8] Overall, delay in getting timely STEMI care in India is multifactorial (Figure 1).[5,8]

Figure 1: Reasons for delay in STEMI care.

PHARMACO-INVASIVE APPROACH

Timely intervention for revascularizing the occluded coronary artery is the backbone of treatment for STEMI.[14] This must ideally be achieved as soon as possible in all patients presenting within <12 hours of onset of symptoms.[5,14] The concept of management in this period is "Time is Muscle" since there is maximum opportunity for saving lives by quick initiation of optimal reperfusion therapy.[5] The ensuing benefit from revascularization can extend up to 24 hours, specifically if there is ongoing evidence of coronary ischemia.[14] Even though, PCI is the preferred reperfusion therapy when performed in a timely manner (preferably within 90 min from FMC) and by skilled operators, this strategy is limited in settings with lack of PCI facilities and delay in the first medical contact-to-balloon time for logistic reasons.[19,20]

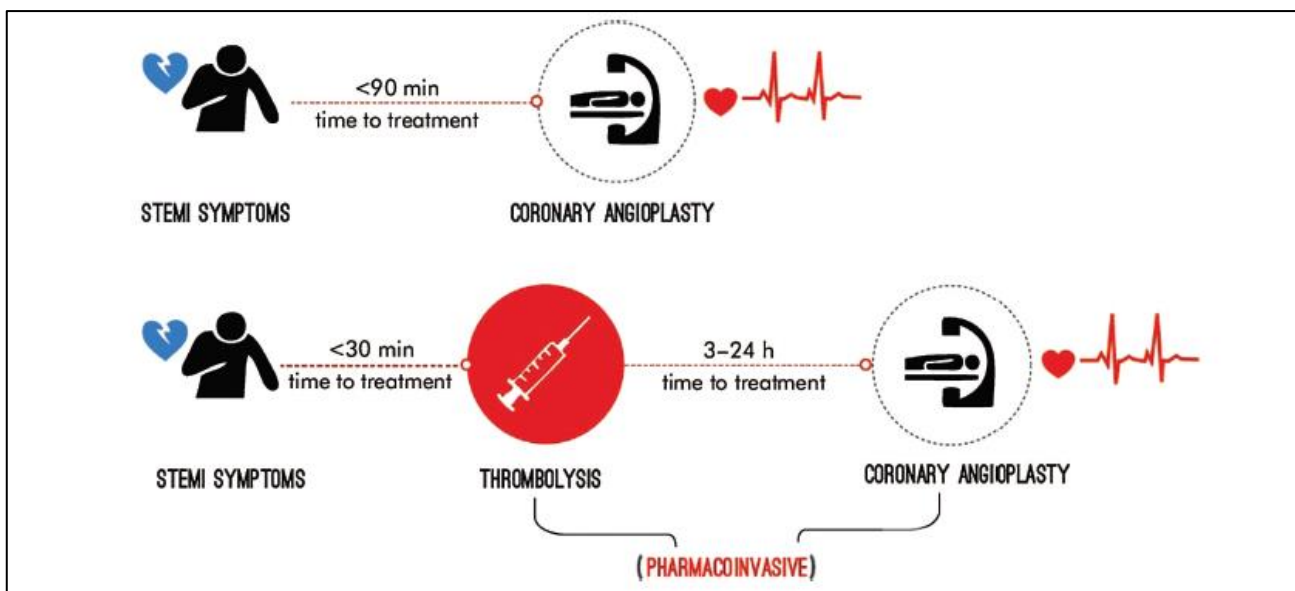
Figure 2: Pharmaco-invasive approach (Adapted from Alexander et al., 2016)[6].
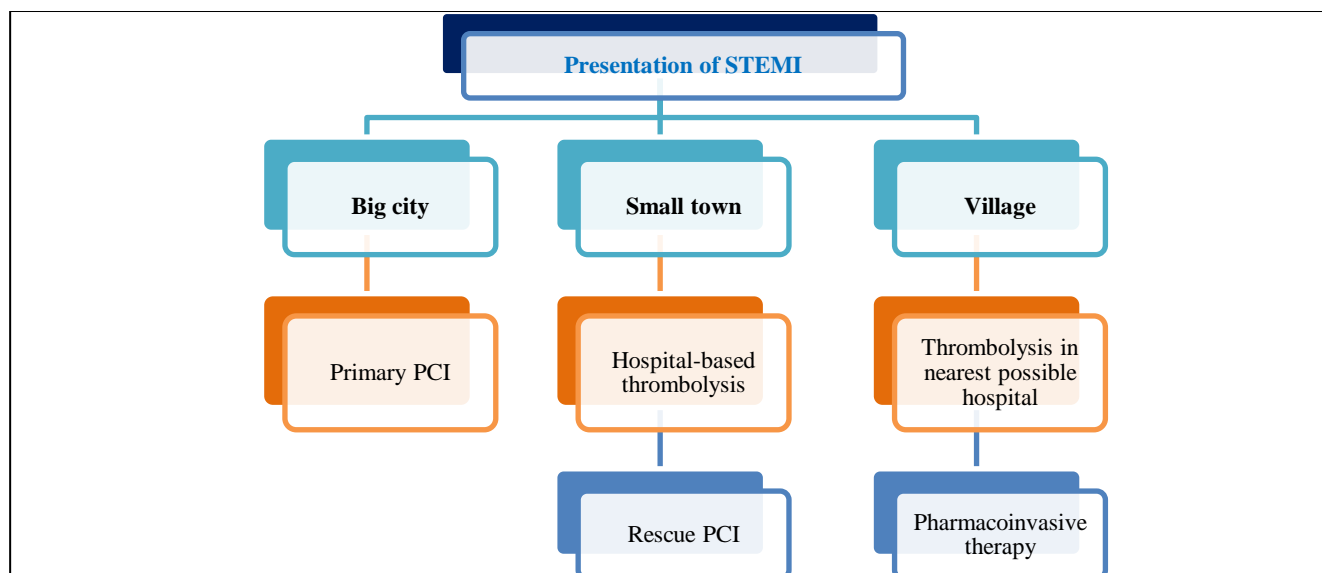
Figure 3. Proposed Triage plan for patients of STEMI in India (Adapted from Guha et al., 2017)[5].

Majority of the clinical evidence with respect to pharmacoinvasive approach suggest that patients present in the time frame of 0-3 hours.[5] Current practice guidelines recommend transferring patients from non-PCI capable hospitals to hospitals offering PPCI services if the FMC-to-device time is kept to less than 120 minutes.[21] When this is not feasible, a pharmacoinvasive strategy followed by transfer to a PCI-capable hospital for either immediate (rescue) PCI for failed thrombolysis cases, or for non-urgent coronary angiography to assess the necessity for additional revascularization within 3–24 hours is an effective alternative strategy.[21] The pharmaco-invasive approach primarily comprises of initial administration of fibrinolytic agents followed by PCI intervention within 3 to 24 hours after the start of fibrinolytic therapy, irrespective of whether fibrinolysis causes successful reperfusion or not (Figure 2).[8] Thrombolysis can be started by a qualified medical person at a centre where facilities of ECG, defibrillator and resuscitation measures are available.[5] PCI performed 3 hours after thrombolysis prevents the early pro-thrombotic phase and decreases the probabilities of re-occlusion.[5]

Thus, pharmaco-invasive therapy could be a better alternative in the Indian context, especially in rural and semi-urban regions where delay in PPCI is expected.[8] Nevertheless, this approach can also be useful in metro and tier-I cities where PCI facilities already exist.[8] Patients referred from smaller non-PCI centres to PCI centres in metro and tier-I cities must be advised to institute lytic therapy at the first medical facility before early transfer to PCI centres.[8] The proposed triage plan for patients of STEMI in India is illustrated in figure 3.[5]

ROLE OF THROMBOLYTICS IN STEMI

Thrombolytic therapy principally restores function to the affected area arising due to blood clot or thrombus and thus, improves clinical outcomes and decreases case fatality.[22,23] Fibrinolytics are preferred thrombolytic agents for treatment of STEMI as they can achieve reperfusion, and improve myocardial function and survival over the short-term and long-term.[8,24] These drugs convert plasminogen to plasmin, which sequentially cleaves fibrin, thus causing clot dissolution and restoration of blood flow to ischemic tissues.[24] Fibrinolytics can restore blood flow efficiently if administered within 12 hours of symptom onset.[24] However, maximum benefit is achieved on prompt administration with least possible delay.[24]

Amongst all the thrombolytics, the third-generation agents like reteplase and tenecteplase bring about a greater angiographic patency rate in patients with acute myocardial infarction.[25] Reteplase is a single-chain, non-glycosylated peptide, fibrin-specific recombinant plasminogen activator derived from t-PA which is mainly designed for bolus thrombolysis in STEMI patients.[26] Bolus administration of reteplase causes rapid reperfusion in significantly shorter time as compared to other fibrinolytics like alteplase, streptokinase and urokinase.[26] It is administered as a double bolus, with each dose consisting of 10 units given over two minutes 30 minutes apart.[27] Thus, it is easy, rapid and safe to administer.[28] A major advantage of reteplase is non-weight-based dosing thus reducing treatment errors which might occur due to dosage errors on visual estimation of the patient's body weight.[26] The choice of thrombolytic (bolus injection or infusion) can be an important factor since continuous intravenous infusion might complicate administration in hospital settings whereas prehospital administration may not be possible.[26] In such circumstances, bolus-injection is convenient and preferable.[26] Furthermore, numerous clinical trials such as RAPID 1, RAPID 2 and INJECT trials established the safety of reteplase.[26,28] An Indian study conducted by Xavier et al. established reteplase to be the safest and most efficacious drug followed by tenecteplase and streptokinase.[29]

Among all the fibrinolytics, tenecteplase is the most fibrin-specific molecule and can be administered as a single bolus intravenous injection.[30] Re-infarction rates have been significantly greater for tenecteplase compared to reteplase.[31]

Unlike these agents, the first generation thrombolytics like streptokinase have several clinical disadvantages like low fibrin specificity, increased risk of allergic reactions, hypotension and short half-life.[29,32] Still, streptokinase is one of the most commonly using thrombolytics in India due to its free availability and minimum cost.[29] Some of the significant differences between thrombolytics are listed in Table 1.[8,26]

Table 1: Comparison of thrombolytic agents.

	Reteplase	Tenecteplase	Alteplase	Streptokinase
Generation	Third	Third	Second	First
Fibrin specificity	Moderate	Very high	High	Non-specific
Can be given by bolus route	Yes	Yes	No	No
Weight-based dosing	No	Yes	Yes	No
Allergic reactions	No	No	No	Yes

NICORANDIL: A POTENTIAL POTASSIUM CHANNEL ACTIVATOR

It has been confirmed that a notable proportion of STEMI patients still have impaired cardiac function and increased cardiovascular mortality regardless of effective reperfusion by PCI.[33] Hence, early administration of agents like nicorandil that attenuate coronary microvascular dysfunction may further improve the prognosis of STEMI.[33]

Nicorandil, a hybrid of an adenosine triphosphate (ATP)-sensitive opener of potassium channel and nitrates, has been established in improving coronary microvascular dysfunction and obstruction through its vasodilatory effect on small coronary arteries.[33] Clinical evidence suggests that nicorandil enables cardiovascular protection through pleiotropic effects including reductions in oxidative injury and systemic inflammation.[34] This in turn significantly improves left ventricular (LV) function, CAD mortality and nonfatal myocardial infarction.[34] It has been observed that reperfusion injury may occur due to reperfusion even after recanalization is achieved, including no-reflow or slow-reflow in which adequate myocardial blood flow cannot be obtained, thus resulting in poor treatment outcomes in the long term and.[35] Overall, nicorandil shows a more pronounced effect on the coronary microcirculation than nitrates, and therefore might be a better alternative for patients with microvascular angina, including those with microvascular spasm.[36] Less than 10 % patients report side-effects after 30 days of treatment with headache being the most common side effect to nicorandil, occurring in approximately one third of patients.[36] Accordingly, the use of nicorandil prior to primary PCI must be strongly considered in STEMI patients.[33]

STATINS, DUAL ANTI-PLATELETS AND OTHER AGENTS

Statins, along with aspirin, are the keystone of secondary prevention treatment in stable CAD and ACS.[37] The European and American guidelines recommend the administration of high-potency statins as early as possible in ACS.[37] It is hypothesized that high-potency statins like atorvastatin and rosuvastatin exert a prompt clinical pleiotropic effect well before the low levels of low-density lipoprotein-cholesterol (LDL-c) can affect plaque progression.[37]

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study was a randomized controlled trial which confirmed a clinical benefit of intensive lipid lowering with atorvastatin 80 mg/day when it was initiated in the initial days after ACS and continued for 16 weeks.[38] Sun et al. established that short-term atorvastatin loading before PCI was well tolerated and revealed beneficial myocardial effects in ACS patients with increasing dose and frequency of statin loading.[39] Similarly, an observational study demonstrated that rosuvastatin 40 mg, initiated early and continued for 12 weeks, was effective in decreasing low-density lipoprotein (LDL) cholesterol and was well -tolerated in Indian patients with acute coronary syndrome and at high risk of cardiovascular disease.[40] In survivors of MI and stroke, statins reduce rates of recurrent CHD, the need for revascularization procedures as well as mortality.[41] According to a nation-wide survey of doctors in India (Wander et al.), high-intensity statin therapy (atorvastatin 40/80 mg or rosuvastatin 20/40 mg) was preferred in post-ACS cases.[42]

Dual antiplatelet therapy (DAPT) is the standard therapy after PCI in ACS patients which aims at preventing stent thrombosis, myocardial infarction, and stroke.[43] Aspirin is an antiplatelet agent which has proven benefits in primary and secondary prevention of CAD.[44]

Current evidence strongly supports the use of dual antiplatelet therapy) for at least one year in patients with ACS after PCI, after which aspirin must be continued indefinitely.[44] Amongst antiplatelet agents used in patients with ACS, ticagrelor is also used frequently.[45] Its unique chemical structure, which is not a prodrug, enables rapid, potent, and consistent inhibition of platelet aggregation.[45] Several pharmacodynamic studies suggest that ticagrelor showed a faster onset/offset of action and more potent inhibition of platelet aggregation than clopidogrel.[45] A recent study by Sawhney et al. (2019) suggested that ticagrelor has been used across various ACS types and in different management strategies in real-world settings in India with lower incidence of clinical events in comparison to data in literature.[46]

OVERCOMING CHALLENGES OF STEMI CARE

Currently, challenges of optimal STEMI care exist at public awareness level, patient level, hospital/physician level and societal levels in India.[18] Certain measures taken at various levels can help overcoming them.

Patient awareness and education

In our country, patients tend to ignore symptoms, self-medicate and consult non-physicians in many instances.[18] To overcome such barriers, systematic patient education and awareness programs are needed on an urgent basis.[18] Many individuals may have atypical presentations of acute coronary syndromes. Four group of patients - elderly, very young, diabetics and women can have atypical symptoms and presentations which must not be missed. People should know that for anyone beyond teenage, an ECG is a compulsory intervention for acute chest pain or discomfort from jaw to umbilicus including upper limbs.[18] Patients with STEMI can be encouraged to carry baseline ECG during transfer to PCI/Non-PCI hospitals.[27] The patient and relatives must be quickly informed about the current condition to build their confidence towards readiness for fibrinolysis/ primary PCI.[27] This helps in patient information, reduction in the anxiety and time for decision as well as avoiding further delay in treatment.[27] Adherence to medications can be promoted by constantly learning from patients and their interactions with the healthcare system.[47]

Education and training of physicians and FMCs

Most importantly, physicians must be well educated with respect to time dependant decision-taking, immediate ECG in patients of suspected AMI and confirmation of STEMI and the pharmaco-invasive concept.[27] Since the general practitioner (GP) provides initial contact with the patient and family commonly, the GP societies need to include a STEMI educational agenda on their scientific deliberations and reinforce their basic training.[48] Moreover, refining the level of care given by paramedics with the help of improved education and training can help minimising treatment delays and providing definitive care.[49]

Standardized protocols and availability of amenities

Emergency STEMI treatment modalities must be made available at subsidized cost to all Indians, probably through medical insurance schemes.[18] Even availability of thrombolytics, especially bolus agents like tenecteplase and reteplase must be made available at subsidized cost to the poor population.[18]

Standardized protocols explaining the expected care delivery for a STEMI patient are available from STEMI India.[11] Various protocols have been implemented depending on the setting of care like emergency medical services, rural spoke hospitals, and PCI-capable hub hospitals.[11] Standardized inter-hospital transfer protocols must be established for permitting routine post-fibrinolysis coronary angiography or PCI within the recommended time frame.[21] Building a healthcare infrastructure (Hub and Spoke Model) like STEMI-INDIA in every state of the country can also be very helpful in assuring appropriate care of STEMI patients.[8] Emergency ambulances, equipped with ECG facilities, trained medical and paramedical personnel to perform ECG and evaluate the suitability for thrombolysis, facilities to monitor rhythm and defibrillator are essential in the Indian settings.[18] In situations where delay in getting STEMI care is likely, a wireless transmission of 12-lead ECGs to an offsite cardiologist should be adopted to save time.[21] Also, coronary care units in hospitals must be equipped with cardio pulmonary resuscitation facility including defibrillators, temporary pacing, mechanical ventilator support and skilled individuals for identifying and initiating treatment for life threatening arrhythmias as well as starting hemodynamic monitoring and respiratory support.[5]

SECONDARY PREVENTION AND CARDIAC REHABILITATION

Secondary prevention and cardiac rehabilitation post STEMI must begin as soon as the patient meets the first medical contact.[5] Secondary prevention mainly involves life style management and drug therapy.[5] Both are complementary to each other. There is no definite secondary preventative drug regimen for MI, due to factors like varying presentations, timing of reperfusion therapy and the range of comorbidities.[50] The commonly used medications for secondary prevention include antiplatelets, anticoagulants, statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor blockers neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists

(MRAs) and beta-blockers.[50] However, according to the PURE study, utilization of secondary preventive drug therapies in South-Asian patients with known CHD or stroke was low, out of which over 80% received none of the effective therapeutic agents.[51]
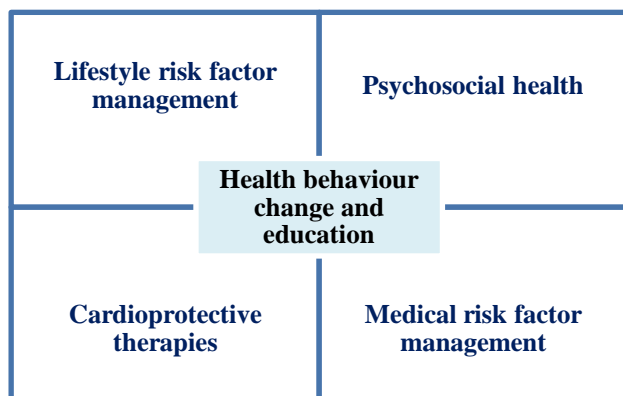

Lifestyle risk factor management	Psychosocial health
Health behaviour change and education	
Cardioprotective therapies	Medical risk factor management

Figure 4: Core components of cardiac rehabilitation- BACPR, NICE guidelines.

Cardiac rehabilitation (CR) is a complex intervention which involves health education, advice on cardiovascular risk reduction, physical activity and stress management.[52] CR has been proved to improve exercise capacity, quality of life and psychological well-being as well as decrease mortality and unplanned hospital admissions.[52] The core components of cardiac rehabilitation recommended by The National Institute for Health and Care Excellence (NICE), Department of Health, British Association for Cardiovascular Prevention and Rehabilitation (BACPR), are illustrated in figure 4.[52]

All patients must be offered a CR program after STEMI which involves structured exercise training, healthy life style advice on diet, regular physical activity, decreased alcohol consumption, smoking cessation and weight management as well as psychosocial counselling.[5] Nevertheless, the use of CR in India is very low due to multiple reasons, including healthcare provider factors.[53] Barriers for CR include low knowledge regarding CR and secondary prevention, non-association with CR institutions and negligence about referrals which are done.[53] The overall system of CR in India needs to be strengthened by training cardiologists to increase their knowledge and awareness of CR, which would subsequently promote greater referral of patients to eventually improve cardiovascular mortality, morbidity and quality of life.[52,53]

Lastly, regular patient follow-ups which include yearly return visits for a physical examination, including the assessment of cardiovascular risk factors, limb symptoms and functional status are an important part of individuals with CVDs.[54] Patients must be guided by health professionals through regular follow-ups and interaction for ensuring long-term adherence to changes in health behaviour.[54]

CONCLUSION

With the ever-increasing incidence of STEMI in India, prompt and appropriate treatment interventions are very critical. Although, primary PCI is considered as the gold standard treatment for reperfusion therapy, it is not feasible in a significant number of patients in the Indian settings due to numerous factors like delay in presentation, affordability and lack of adequate facilities. Hence, pharmacoinvasive approach has emerged to be a very effective reperfusion strategy for the management of STEMI patients. For fibrinolytic therapy, third-generation fibrinolytic agents are proven to have better potential and more clinical advantages over the first-generation agents. To optimize wholesome management, secondary prevention and cardiac rehabilitation must be an integral part of STEMI care. An appropriate healthcare infrastructure, integration of systemic treatment protocols, community education and minimizing transfer delays can ensure optimal STEMI management system for patients in India.

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