Resource and infrastructure-appropriate management of ST-segment elevation myocardial infarction in low- and middle-income countries

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WHITE PAPER

Resource and Infrastructure-Appropriate Management of ST-Segment Elevation Myocardial Infarction in Low- and Middle-Income Countries

Endorsed by Indian Council of Medical Research (ICMR), Public Health Foundation of India (PHFI), Population Health Research Institute (PHRI), Latin America Telemedicine Infarct Network (LATIN), Pan-African Society of Cardiology (PASCAR), South Africa Society of Cardiovascular Intervention (SASCI), and STEMI-India Task Force Writing Committee for Management of ST-Elevation MI in LMIC

ABSTRACT: The 143 low- and middle-income countries (LMICs) of the world constitute 80% of the world's population or roughly 5.86 billion people with much variation in geography, culture, literacy, financial resources, access to health care, insurance penetration, and healthcare regulation. Unfortunately, their burden of cardiovascular disease in general and acute ST-segment–elevation myocardial infarction (STEMI) in particular is increasing at an unprecedented rate. Compounding the problem, outcomes remain suboptimal because of a lack of awareness and a severe paucity of resources. Guideline-based treatment has dramatically improved the outcomes of STEMI in high-income countries. However, no such focused recommendations exist for LMICs, and the unique challenges in LMICs make directly implementing Western guidelines unfeasible. Thus, structured solutions tailored to their individual, local needs, and resources are a vital need. With this in mind, a multicountry collaboration of investigators interested in LMIC STEMI care have tried to create a consensus document that extracts transferable elements from Western guidelines and couples them with local realities gathered from expert experience. It outlines general operating principles for LMICs focused best practices and is intended to create the broad outlines of implementable, resource-appropriate paradigms for management of STEMI in LMICs. Although this document is focused primarily on governments and organizations involved with improvement in STEMI care in LMICs, it also provides some specific targeted information for the frontline clinicians to allow standardized care pathways and improved outcomes.

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The burden of cardiovascular disease in general and acute ST-segment–elevation myocardial infarction (STEMI) in particular is increasing at an unprecedented rate in low- and middle-income countries (LMICs*).[1] In addition, their large populations (80% of the world's population or roughly 5.86 billion people in 2014) make this a massive problem compared with that in developed countries. The World Health Organization estimates that 80% of all cardiovascular deaths now occur in LMICs.[2] Accurate estimates of STEMI incidence are challenging in LMICs, but there could be upward of 3 million cases each year.[1] Furthermore, STEMI tends to affect younger working-age people in LMICs more than in high-income countries, with tremendous direct and indirect economic consequences.[3] For instance, the cumulative economic loss from cardiovascular diseases in LMICs between 2011 and 2025 is projected to be approximately $3.76 trillion.[4] The implementation of evidence- and guideline-based treatments has dramatically improved the outcomes of STEMI in high-income countries. However, outcomes remain suboptimal in LMICs, largely as a result of a big implementation gap, a multifactorial and multifaceted issue.

This document is a consensus from a major multicountry collaboration for the management of STEMI in LMICs and is endorsed by multiple organizations involved in healthcare policy, research, and implementation, as well as funding and measuring outcomes health in LMICs. These include the Indian Council of Medical Research, Public Health Foundation of India, Population Health Research Institute in Canada, Latin America Telemedicine Infarct Network, Pan-African Society of Cardiology, and South Africa Society of Cardiovascular Intervention, as well as the STEMI-India initiative. This document takes a deep dive into many of the systems-based issues and lists the group's expert recommendations for addressing and surmounting of them. Every effort has been made to tailor these recommendations to ground realities and to emphasize resource-appropriate paradigms for the management of STEMI in LMICs. One of the difficulties with such a document (covering nearly 143 countries that can be counted as LMICs, [according to the Organisation for Economic Co-operation and Development data], with nearly 5.8 billion people and much variation in geography, culture, literacy, financial resources, access to health care, insurance penetration, governmental control of health care, etc) is that it can cover only general principles. We emphasize that we cannot propose a one-size-fits-all scenario; local jurisdictions have to adapt and find what works best for them. Although clinicians in these countries will undoubtedly relate to many of the issues discussed and, we hope, learn from this document, we believe that the greatest utility of this document will be at a health-policy level. Our document will likely be of great interest for governments and nongovernmental organizations (NGOs) involved in programmatic improvement of STEMI care in LMICs because it lays out the minimum required standard of care needed to support these endeavors in resource-poor settings. In addition, it suggests workable systems of care to which these organizations, depending on their resources, should aspire, because these measures have been shown to reduce long-term mortality and morbidity on a population scale in some LMICs.[5]

*For the 2018 fiscal year, low-income economies are defined as those with a gross national income per capita, calculated with the World Bank Atlas method, of $1005 or less in 2016; lower middle-income economies are those with a gross national income per capita between $1006 and $3955; upper middle-income economies are those with a gross national income per capita between $3956 and $12 235; and high-income economies are those with a gross national income per capita of $12 236 or more (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups). A list of LMICs is available at http://www.oecd.org/dac/financing-sustainable-development/development-finance-standards/DAC-List-of-ODA-Recipients-for-reporting-2020-flows.pdf.

SOME KNOWLEDGE GAPS IN STEMI CARE IN LMICS

As mentioned, the biggest hurdles for STEMI care in LMICs relate to an implementation gap of established therapies and practices. However, there are also some key knowledge gaps, which we discuss briefly here. For instance, much work has been done to understand the impact of traditional and nontraditional risk factors in nonwhite populations, but a lot has yet to be learned. The INTERHEART study noted a higher prevalence of diabetes mellitus among South Asians, with low physical activity scores and lower intake of fresh fruits and vegetables compared with other populations. The overall attributable risk of these risk factors, however, appeared to be similar.[6] There is also pretty clear evidence that the burden of lifestyle risk factors is affected by socioeconomic position within LMICs; studies are needed to understand the best way to address the poverty-health nexus in these settings.[7]

It is also unclear whether medications prescribed in these patients have the same efficacy and safety, and the optimal dosing is also unknown. For instance, although high-dose statins are recommended as a Class I indication in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for all patients with STEMI, the pharmacokinetic profile of statins is not uniform across all races. For instance, a single dose of 20 mg rosuvastatin can result in as much as 26% to 84% higher levels among different Asian subgroups.[8] Even a moderate-intensity statin (pitavastatin 4 mg) resulted in a 19% reduction in the risk of death compared with a low-intensity statin (pitavastatin 1 mg) among Japanese patients with coronary artery disease in the REAL-CAD trial (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in

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Coronary Artery Disease).[9] Similarly, the use of more potent $P2Y_{12}$ receptor antagonists such as ticagrelor and prasugrel is endorsed as a Class I recommendation by both the ACC/AHA and European Society of Cardiology (ESC) guidelines. The 2017 ESC guidelines further indicate that ticagrelor or prasugrel be used preferentially over clopidogrel as a Class I indication. However, clinical pharmacology studies including East Asian subjects have reported that higher exposure to ticagrelor and its active metabolite (AR-C124910XX) can lead to higher levels of inhibition for platelet aggregation compared with whites.[10] In addition, at least 2 prospective trials performed in East Asian populations have demonstrated a concerning safety signal with ticagrelor compared with clopidogrel with no difference in efficacy.[11] Neither trial was powered for efficacy, however, and a mega-trial of the scale of PLATO (Platelet Inhibition and Patient Outcomes) specifically in the concerned patient population(s) would be necessary to make definitive conclusions. In the meantime, it remains unclear whether a different dose of ticagrelor should be recommended in other countries (eg, a small Korean study noted that low-dose/60 mg twice-daily ticagrelor was as effective for adequate platelet inhibition as standard-dose/90 mg twice-daily ticagrelor in Korean patients with acute coronary syndrome) or whether clopidogrel would be as safe, more effective, or both compared with prasugrel and ticagrelor in these patient populations.[12,13]

Another key knowledge gap is related directly to implementation issues. For instance, the STREAM trial (Strategic Reperfusion Early After Myocardial Infarction) demonstrated that a pharmaco-invasive strategy incorporating fibrinolysis first followed by percutaneous coronary intervention (PCI) resulted in outcomes similar to those of primary PCI among patients who could not undergo timely primary PCI. However, all patients in this trial received tenecteplase as part of a pharmaco-invasive strategy. The use of fibrin-specific thrombolytics such as tenecteplase and tissue plasminogen activator can be cost-prohibitive compared with streptokinase in LMICs, but the efficacy of this drug has not been tested specifically in this scenario in randomized, controlled trials.[14] Similarly, patients with STEMI in LMICs frequently present late and have longer ischemic times.[15] Will the resultant longer delay in PCI after the use of fibrinolytic therapy provide the same efficacy as noted in STREAM and TRANSFER-AMI (Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction)? Which is the optimal antiplatelet agent under such a scenario is also unclear. In TREAT (Ticagrelor in Patients With ST Elevation Myocardial Infarction Treated With Pharmacological Thrombolysis), ticagrelor did not reduce cardiovascular events compared with clopidogrel among patients with STEMI receiving fibrinolytic therapy.[16] These and other issues need to be systematically studied as well. Similarly, there are key knowledge gaps in the health services research realm. For instance, an accurate mapping of what proportion of the population can already access existing thrombolytic/PCI centers in a timely fashion would be very helpful to help plan for additional resources[17–20] but is largely lacking. Any recommendation needs to acknowledge such limitations and can provide only a general overview of implementation principles.

SOME IMPLEMENTATION GAPS AND RELATED ISSUES IN LMICS

Perhaps the biggest barrier to uniform STEMI care in LMICs is that regional systems of care for STEMI are virtually nonexistent. A lack of adequate financial, capital, and personnel resources to set up these systems and to administer and maintain them successfully is obviously a big reason for this deficiency in LMICs. Emergency medical services systems are virtually nonexistent, and emergency rooms are ill equipped to handle patients with acute coronary syndrome.[20] Cardiac catheterization laboratories are far too few to serve the large numbers of patients with STEMI. These laboratories are almost always clustered in urban locations, whereas the vast majority of patients still live in rural areas. Poor transportation infrastructure and a lack of adequately trained/equipped paramedics and ambulances make access to these invasive centers difficult. In addition, political and societal support for these endeavors may be challenging or transient. Thus, although many LMICs have transitioned from an infectious disease–predominant cause of population mortality and morbidity to a more Western chronic disease–predominant cause, local and national priorities frequently remain focused on infectious disease programs and systems. A number of social issues compound implementation abilities. An average person in LMICs tends to be less literate and educated than his or her Western counterpart. This results in a significant lack of awareness of the problem and appropriate therapies. When individuals do seek help, the first healthcare providers they encounter may have inappropriate and perhaps dubious credentials and experience and, in general, have less knowledge about these complex issues. Added to this is the lack of insurance coverage for the large majority of the population who are relatively poor, limiting these expensive procedures and costly medications to a small proportion of patients. Compounding this problem is the fact that patients often do not have stable employment that allows sick leave or time off for medical visits.

This document discusses strategies to address STEMI care in LMICs in the context of these implementation issues. Unless otherwise discussed below, we fully support following international STEMI guidelines (AHA/

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ACC, ESC) as best as possible. For this reason, we focus this document almost entirely on reperfusion issues that are uniquely related to STEMI care in LMICs. Indeed, it is our hope that localities with abundant resources and high levels of expertise should approximate the well-known evidence-based recommendations as much as possible.[21,22] Other locations with variable resourcing should maximally use as many of these recommendations as feasible while adhering to the principles of equity.

CHALLENGES RELATED TO DEFINITION AND DIAGNOSIS OF STEMI IN LMICS

The diagnosis of STEMI is well characterized in US and European recommendations. For typical presentations, there is less ambiguity, and efforts should be focused on timely recognition and management. Some additional considerations are discussed below.

1. ST-segment elevation can have multiple other causes, including pericarditis, old STEMI with aneurysm formation, coronary spasm, conduction abnormalities, and early repolarization. Most of the first-point-of-contact centers in LMICs may not have expertise in accurately triaging for these nuanced presentations. Therefore, from a systems perspective, we believe that it would be safer to assume that ST-segment elevation in the setting of appropriate chest pain syndrome is coronary occlusion and to refer to an appropriate higher level of care as soon as possible.
2. It is very likely that there are large numbers of individuals in LMICs with STEMI who do not satisfy STEMI criteria because of uniquely local exigencies or logistic reasons. The reasons may be delayed access to medical services,[23,24] unavailability of ECG, or lack of facilities for laboratory assay of specific cardiac biomarkers. Clinical judgment should be used in these situations. In many ways, this may be low-hanging fruit and an essential first step for governments, NGOs, and policy makers interested in improving STEMI care. Creating an easy access to proven systems of care and connecting as many patients into such networks are likely to improve STEMI outcomes in this scenario.
3. LMICs have limited economic resources and may not be able to use all the elements of the Universal Definition of Myocardial Infarction. The World Health Organization recommends flexible standards in such locations.[25] However, LMICs can make use of the Essential Medicine and Essential Diagnostics List from World Health Organization or modifications by local governments[26] to facilitate better health care, and this could improve diagnosis and treatment.[27] Given that coronary artery disease–related events are the leading cause of morbidity and mortality in the LMICs, a concerted look at and periodic updates of the Essential Medicine and Essential Diagnostics List should maximize the ability to diagnose and treat STEMI and its subsequent care.

COMMUNITY-BASED PATIENT/PHYSICIAN EDUCATION: RECOGNITION OF SYMPTOMS

Early recognition of symptoms suggestive of STEMI and understanding of the need for urgent remediation will help a patient in immediately seeking medical assistance. Unfortunately, our experience while working in LMIC STEMI care informs us that there is meager public awareness of STEMI and symptoms of STEMI in most LMICs. Even when there is awareness, denial and minimal understanding about the "time is muscle" concept (and the need to access medical facilities rapidly) hamper prompt treatment. No amount of excellent in-hospital care can improve national STEMI outcomes unless the patient understands that acute chest pain should prompt rapid access to the healthcare system. Public education programs are thus vitally important to educate patients about the symptoms of an acute STEMI and should be a major focus of governments, physician organizations, NGOs, and others.

PUBLIC AND PATIENT AWARENESS, EDUCATION, AND POSSIBLE ACTION

Inordinate delays in accessing care remain one of the biggest impediments to improving STEMI outcomes. For instance, the mean time from symptom onset to hospital presentation in the CREATE registry (an acute coronary syndrome registry from India) was 360 minutes (ie, 6 hours).[23] Other registries have demonstrated much longer delays in rural areas, even up to 13 hours.[24]

- Public service announcements have been used successfully in both developing countries[28] and LMICs for increasing population awareness of many health topics, for example, infectious diseases, sanitation, and contraception, and a similar campaign of education can help STEMI awareness. This program could emphasize and educate the population about coronary artery disease, symptoms of a heart attack, and the need for early presentation to registered medical practitioner/STEMI-designated hospitals. Social media, the entertainment industry, and community theater can incorporate educational messaging like that currently done for smoking prevention.
- STEMI systems of care should invest in rapid and efficient low-cost transportation options given the lack of such infrastructure at present except in major

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cities. Patients often use public transport or the variably available private transport to reach medical care. This can be expensive or infrequently available, thus introducing unwanted delays in STEMI care. Some systems of care in India and Latin America have such transport facilities as part of their program, which has helped improve outcomes.

- These efforts also need to be socially and culturally appropriate.[29] From a medical anthropological perspective, health-seeking behavior is increasingly recognized as an important tool for understanding people's preferences and decision-making with regard to healthcare options and timing of health seeking across various health conditions. Bhattacharya Chakravarty et al[30] have shown that people do not respond to illness in an ad hoc manner; they use past experiences, accumulated knowledge, contemporary advice, and referral to find the optimum strategy for obtaining the best results within the prevailing circumstances. Once inside the health system, the patient may shop around among the providers until she/he is satisfied with the diagnosis or care received. Thus, it is imperative that people are active, rational decision-makers, particularly for a time-sensitive condition such as STEMI. It is very essential in public health discourses to survey and understand health-seeking behaviors because this helps in aligning public health practice and healthcare and health service delivery models for better health outcomes.
- The facilities available for treatment of heart attacks at local hospitals and other healthcare institutions can be prominently identified and displayed. Benchmarking of quality metrics and regular feedback to these sites are essential, and NGOs can play a prominent role in assisting governmental resources in this area (see below).
- An innovative idea is to encourage use of social media communication tools such as WhatsApp, which has >1.5 billion users (≈20% of the world population) with high penetration in the poorly resourced people and countries. Social media communication tools have found prominent use in developed countries[31] but are also being used in LMICs, for example, in Africa to improve HIV or neonatal care,[32,33] and are generally effective in speeding up communication, consultation, and emergency department discharge. Its use in STEMI is still early but allows local physicians in remote areas to transmit electrocardiographic images to higher-level centers in STEMI systems of care using mobile phones and related applications (apps). A number of studies being done on the use of social media (of which messenger apps such as WhatsApp and WeChat are 1 aspect) in the STEMI[34–36] and non–STEMI cardiovascular care arena indicate that there is wider use of SMART applications in cardiac care in LMICs[37,38] with some improved healthcare measures. There is every reason to believe that this kind of technology enhancer might help in better STEMI care in LMICs. It is thus our recommendation to NGOs and governments to invest in rigorous study of the use of such technologies in the LMICs.
- In this scenario, patients can also carry a copy of their baseline ECG as a photographic image, if they have had one, when possible. This strategy is not without precedence. Patients have routinely taken their own chest x-rays to appointments with them as part of national tuberculosis control strategies. This could be tested in small NGO-funded pilot projects and might become a low-cost option with little downside. As an example, India has the largest user base on WhatsApp (200 million people in 2018); Brazil has 120 million users. WeChat has >1 billion active users each month, and most of them are in China. All these app users, even if illiterate or semiliterate, are taking photos, sharing them, and downloading such content. In addition, WhatsApp content is encrypted, and some healthcare facilities in LMICs are already using it to transmit medical images, including ECGs. Some of the frontline investigators in LMICs believe that this will substitute for investing in a hospital-grade secure transmission network in LMICs. This idea is finding favor with bureaucrats and has increased government interest in LMICs such as India, Brazil, and China. Further targeted investment will allow testing such strategies and perhaps make this idea more universally implementable in LMICs.
- Awareness efforts should also be directed toward prehospital use of soluble/chewable aspirin before transport to an appropriate medical facility, as long as this does not increase time to seeking medical attention.

PHYSICIAN EDUCATION

This is another essential cog in the wheel of STEMI systems. There are several interrelated issues.

- General practitioners in urban areas and community health workers in rural areas are frequently the first providers to see these patients. Many of us routinely working in LMICs have found that these general practitioners may lack awareness of the problem or its treatment options. Accordingly, STEMI endeavors need to emphasize the need for an immediate ECG in patients with suspected STEMI. Most licensed medical practitioners, especially internal medicine and family practice physicians, should try to procure some form of subsidized or low-cost electrocardiography machine, even if fairly basic. Fortunately, many such low-cost local

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options are available in some LMICs. Similarly, primary health and community health centers in rural areas should have the ability to perform timely ECGs. They need to develop the capability and establish protocols to transfer the ECG to a local or remote expert facility for a second opinion if needed to confirm STEMI. The presence of an electrocardiography machine with the primary care physician is estimated to be cost-effective in an LMIC.[39] Widely available smartphone apps such as WhatsApp have been tested for this purpose and may facilitate such interactions.[34]

- All efforts should aim to teach the importance of early reperfusion and constantly re-emphasize the need to rapidly triage STEMI, administer reperfusion therapy if feasible, or transfer to a reperfusion-capable center to avoid delays in reopening the occluded coronary artery.
- Similarly, continuing medical education programs should routinely teach and encourage timely decision-making. Policy makers should encourage participation in low-cost or no-cost educational efforts such as STEMI-India, Africa STEMI Live, Latin America Telemedicine Infarct Network, or an equivalent in their own locales or those sponsored by well-respected local cardiovascular societies.
- Efforts should be directed toward other members of local STEMI teams as well. They too benefit from periodic retraining to keep abreast of the changes. Sponsored by nonprofit organizations or NGOs, this retraining is beneficial, as shown by the experience with the STEMI-India program in which such teams regularly schedule conferences directed specifically to their training and needs.
- From a policy-making perspective, there is also a need to find ways to align complex financial incentives among different providers. This is challenging because the time crunch adds to the complexity. For instance, patients with STEMI may be treated medically or with ineffective fibrinolysis at clinics and nursing homes and transferred to larger centers only after long delays, frequently when the patient is in cardiogenic shock. Another related issue is that physicians in LMICs are not necessarily accustomed to working as part of teams/groups, and a deliberate alignment, as needed for STEMI care, may be a hard goal to accomplish. Government officials and policy makers have to find ways to assign culpability to providers, and perhaps a combination of carrot and stick approaches will be needed.

COST FOR STEMI CARE IN LMICS

In addition to navigating the various layers of health systems, patients come face to face with the dilemmas of costs and payments at a very vulnerable time. Third-party insurance and government-sponsored plans are typically nonexistent/rudimentary in LMICs, and much of the medical cost is paid in cash or cash-equivalent instruments on a point-of-care basis. Even for affluent patients presenting with STEMI, such payments can become a barrier because patients may not have enough liquidity at hand to immediately pay out of pocket for appropriate care.

- We believe that government bodies, NGOs, and other stakeholders should find ways to promote widespread healthcare coverage for conditions such as STEMI. For instance, a national program is now starting to cover (in 2018) the entire population of poor and vulnerable beneficiaries in India.[40] It will cover >500 million people, providing coverage up to $7000 per family per year as a cashless benefits system for secondary and tertiary care hospitalization, including for STEMI. Integrating such options into STEMI systems of care will be optimal. This will allow many patients who are below the poverty line to receive appropriate treatment for STEMI while minimizing their out-of-pocket hospital expenses.[15]
- Coverage for STEMI care should be comprehensive (cover all aspects of care) and tailored to ground realities.
- It should also be equitable, and uniform care should be available across socioeconomic strata. In other words, the system should work for everyone, not just for those who can afford it.
- To support these programs, governments can also consider pursuing minimal essential drug and device pricing. To improve widespread and easy availability, volume negotiations, bulk purchasing, and other locally appropriate and feasible methods could further be pursued. This has been successfully implemented in India, where the cost of stents is now capped at a uniform and affordable price across the country.

EDUCATING FRONTLINE CLINICIANS: GENERAL PRINCIPLES OF TREATING STEMI

Patients in LMICs can present to a variety of medical care facilities with varying resources and expertise (Table 1), and depending on where the health system is accessed, patients should be moved rapidly to a higher level as needed via a coordinated system of care as shown in Figure 1. A thorough initial clinical assessment and rapid action depending on local capabilities are very important in the management of STEMI. The central aim of this assessment should be recognizing and diagnosing an STEMI and then rapidly evaluating

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Table 1. Types of Facilities Where the Patient May Present With Symptoms of Acute STEMI

Level 1 facility: Has a general practitioner–level physician, may or may not have electrocardiography facility and may be able to transmit ECG on mobile or WhatsApp-like platforms, can measure vitals, and has access to basic medicines such as aspirin and oral β-blockers. No thrombolysis facility.
Level 2 facility: Has a general practitioner–level physician, has electrocardiography facility and can transmit ECG on mobile or WhatsApp-like platforms, can measure vitals, and has access to basic medicines such as aspirin, clopidogrel, LMWH, and oral β-blockers. No thrombolysis facility but can develop one with investment and training.
Level 3 facility: Fibrinolysis-capable but non–PCI-capable centers. Has a general practitioner–level or higher-level physician capable of diagnosing STEMI confidently, assessing appropriateness for thrombolysis, and providing therapy. Has access to all necessary medications such as anticoagulation, aspirin, clopidogrel, ACE inhibitors, and oral β-blockers. May have echocardiographic facility.
Level 4 facility: Full-service facility capable of providing care consistent with international standards. Has primary PCI capability that may or may not be 24/7. If PCI is not logistically possible, physicians can rapidly provide thrombolysis, pharmaco-invasive therapy, and full post-MI care.
Level 5 facility: Operational STEMI system of care center of excellence and may be the hub of such system of care. Patient may present directly or via any Level 1–4 facility or arrive via an ambulance service that is part of an STEMI access program. Patients will be managed rapidly with appropriate reperfusion therapy. Has expertise comparable to international standards.

ACE indicates angiotensin-converting enzyme; LMWH, low-molecular-weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

suitability for reperfusion, either thrombolytic therapy or PCI. Each of the levels of facilities should have standardized protocols and pathways for STEMI care, as shown in Figures 2 through 5. These figures can be printed as flash cards and distributed for ready reference in the appropriate centers. There is evidence that providing educational material to remote providers as a part of a multifaceted educational effort is beneficial in improving care and outcomes.[41] We therefore believe that converting the figures depicting management options in this document into freely available flash cards can provide an important educational resource for the nonspecialist, underresourced clinicians who routinely encounter and manage STEMIs in LMICs. However, just providing such educational material is not sufficient, and program managers should create a systematic mechanism of evaluation to see the use of the material and to modify educational content according to feedback and monitoring data.

DEFINITION AND CLINICAL DIAGNOSIS OF STEMI

Acute myocardial infarction or STEMI is well defined in US and European recommendations, and LMICs should generally adopt these definitions. STEMI should be thought of as a clinical condition that includes the following:

- Characteristic chest pain lasting ≥10 minutes. It is often felt as a pressure or heaviness in the central chest that sometimes radiates to the arm, jaw, or throat and is not worse with respiration, changes in position, or local pressure;

and

- Electrocardiographic changes (in the absence of left ventricular hypertrophy and bundle-branch block) that are new onset and persistent ST-segment elevation of 1 mm in >2 contiguous leads or the following in V_2 and V_3: >1.5 mm in women, >2.5 mm in men <40 years of age, and >2.0 mm in men >40 years.
- The initial ECG may occasionally be nondiagnostic. In such situations, particularly if the chest pain and the clinical setting are suspicious for an STEMI, ECGs should be serially obtained (with the same electrode position) at 10-minute intervals for the initial 1 hour. This will minimize the risk of missing an STEMI in such cases.

THERAPEUTIC OPTIONS FOR STEMI

Thrombotic occlusion that completely occludes flow in the coronary artery is the most common cause of STEMI, and rapidly restoring flow (coronary reperfusion) is the primary goal of therapy in STEMI. Coronary reperfusion therapy in the form of either primary PCI or fibrinolysis should be administered as quickly as possible in all eligible patients with acute STEMI (Figure 2). A combined approach, as part of a pharmaco-invasive strategy, is a uniquely attractive option for patients in LMICs because the majority have little to no access to primary PCI facilities, which are concentrated in a few major metropolitan centers. Pharmaco-invasive strategy should thus form an important core of any STEMI systems of care in LMICs. This is one of the most noticeable variances that we propose from Western guidelines, which recommend primary PCI as the best practice. As mentioned, patients who can access primary PCI will still avail that whenever possible, leaving pharmaco-invasive strategy to situations in which efficient and effective primary PCI is not possible. The choice of reperfusion therapy is most often determined by a number of interconnected factors, listed in the Figure 2.

PRIMARY PCI

PCI is the preferred reperfusion option compared with fibrinolysis because it restores coronary flow more completely than fibrinolysis (TIMI [Thrombolysis in Myocardial Infarction] flow grade 3, ie, near-normal perfusion, in 70%–90% of patients) and has a lower risk of intracranial bleeding. Primary PCI also provides immediate

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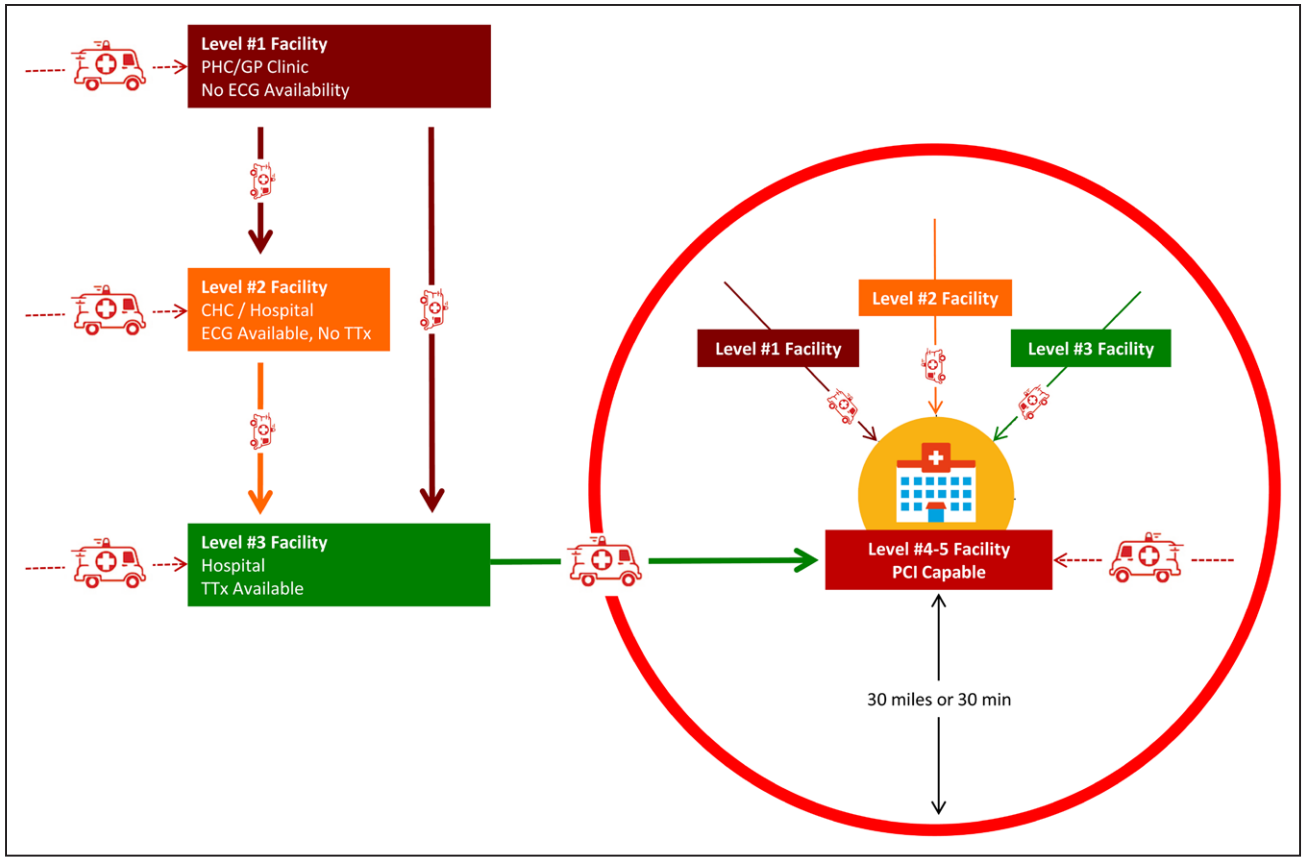

Figure 1. ST-segment–elevation myocardial infarction care model.
CHC indicates community health center; PCI, percutaneous coronary intervention; PHC/GP, primary health center/general practitioner; and TTx, thrombolytic treatment.

assessment of coronary anatomy and hemodynamic data, and it is suitable for most patients with STEMI. It also allows early hospital discharge and rapid identification of patients who will not benefit from reperfusion therapy, including those patients who spontaneously reperfuse the infarct-related coronary artery, coronary vasospasm, and coronary dissection.

There are 3 variations of PCI. When PCI is the reperfusion strategy of first choice instead of fibrinolysis, it is known as primary PCI. PCI done to salvage the myocardium when fibrinolysis fails to restore perfusion is called rescue PCI. PCI performed routinely 3 to 24 hours after fibrinolysis, even when lysis has been apparently successful, is called pharmaco-invasive therapy. Primary PCI is also the preferred option in high-risk patients; these patients include those presenting with heart failure (Killip class 2 or higher), cardiogenic shock, extensive ST-segment elevation, STEMI in the presence of clear new and recent left bundle-branch block, hemodynamic or electric instability, or inferior wall myocardial infarction with left ventricular ejection fraction <0.35. Patients with STEMI at high risk of intracranial hemorrhage should be treated with PCI rather than fibrinolytic therapy. PCI is not recommended in asymptomatic patients >12 hours after the onset of STEMI (if they are electrically and hemodynamically stable).

The limitations of primary PCI include an ≈7% to 8% risk of major bleeding,[42] some of which is related to access site, with femoral access associated with higher bleeding rates compared with radial access.[43] Radial access may be the preferred method of choice for primary PCI, and many centers are now adopting this route in preference over femoral access. With femoral access, vascular complications requiring surgical repair occur in ≈0.4% to 2% of the patients and 0.5% to 13% risk of acute renal failure.

FIBRINOLYSIS

Fibrinolysis remains the most common treatment for reperfusion in LMICs because of the lack of easily and readily available PCI. The benefit of fibrinolysis has been observed in patients treated as late as 6 to 12 hours after the onset of ischemic symptoms, but the most dramatic effects are seen in those who are given the drug within <2 hours of symptom onset. The short-term survival benefit observed with fibrinolysis is maintained over a 10-year follow-up. Better antiplatelet and antithrombotic therapies have resulted in a reduction in reinfarctions after fibrinolysis. Fibrinolysis is the preferred option when PCI therapy is not possible or when it cannot be delivered in a timely fashion. Therefore, fibrinolysis should be recommended to patients

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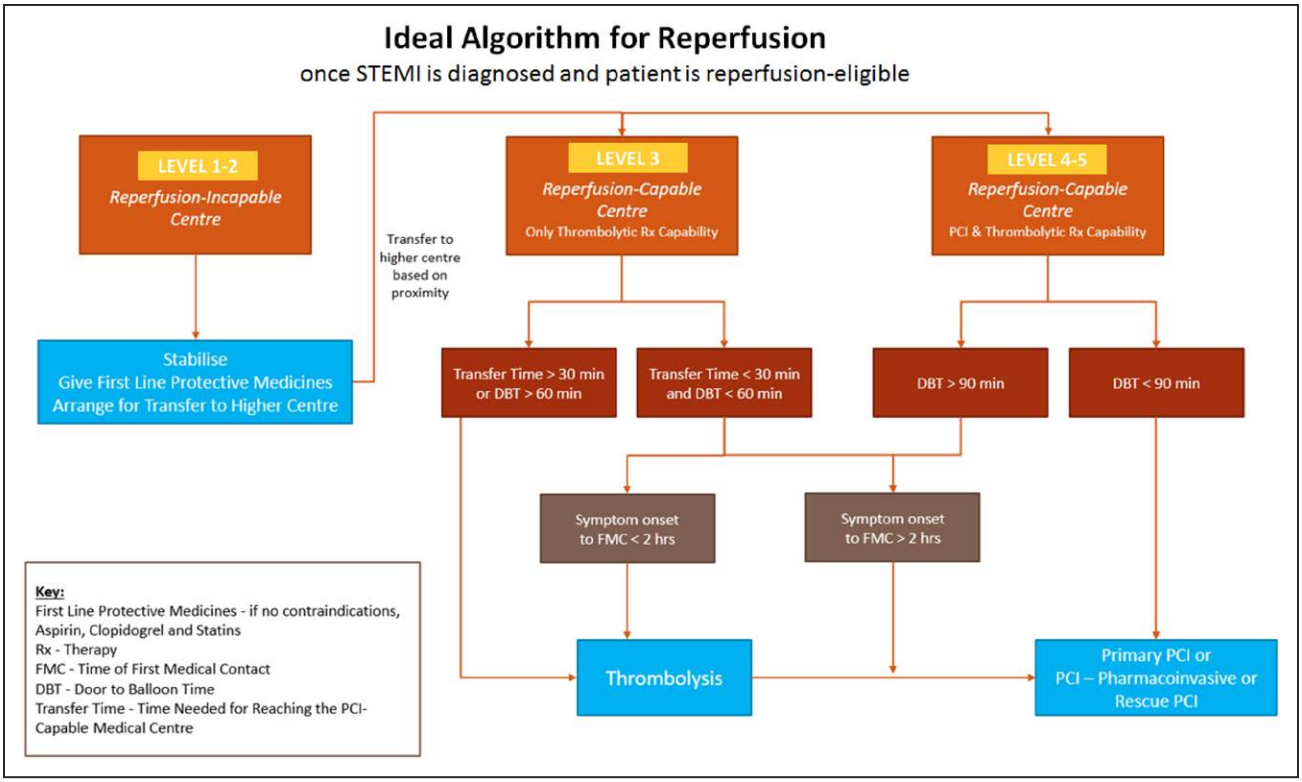

Figure 2. Choice of reperfusion therapy.
PCI indicates percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

with acute STEMI presenting within 12 hours of onset of symptoms when primary PCI cannot be delivered within 120 minutes of presentation (during which time fibrinolysis can be given) or if fibrinolysis can be given >60 minutes before PCI.

Reperfusion achieved in the first hour after onset of symptoms, the so-called golden hour of reperfusion, is associated with the most reduction in mortality.[44] There is a 50% reduction in mortality when reperfusion is achieved with a fibrinolytic administered within 60 to 90 minutes.[45] Prehospital fibrinolytic therapy, in which fibrinolysis is delivered in the ambulance to speed up reperfusion, is commonly used in certain high-income countries with significant benefits. However, this is possible in only a small minority in LMICs, but protocols and logistics should be re-evaluated continually to include this possibility when feasible.

Complications of fibrinolysis include intracranial hemorrhage, resulting in death or disabling stroke in 0.6% to 1.4%, particularly in the elderly. Recent studies[46] have shown reduced intracerebral hemorrhage rates in older patients with a reduction in dose of a fibrin-specific agent used for fibrinolysis. This approach could be considered to at least partially reduce one of the major risks of fibrinolytic therapy. Other limitations include failed reperfusion of the infarct-related artery in 15%; restoration of normal coronary blood flow in only 50%, resulting in reduced myocardial salvage and reduced survival; and reocclusion of the infarct-related artery in 30% of patients, resulting in reinfarction within the subsequent 3 months.

It is important to note that streptokinase is the most common thrombolytic in LMICs because of its widespread availability and low cost (≈30 times less than fibrin-specific agents). It is possible that higher doses may be necessary because of a higher prevalence of anti–streptolysin O antibodies in adult populations in LMICs, particularly for patients who have already undergone fibrinolysis.[14]

PHARMACO-INVASIVE STRATEGY

Although fibrinolysis is successful in a reasonable number of patients and improves outcomes, there is evidence that performing a PCI for residual lesions after thrombolytic therapy further improves outcomes. This practice, called a pharmaco-invasive strategy, can be useful when primary PCI cannot be done within 2 hours of first medical contact or if fibrinolysis can be given >60 minutes earlier than primary PCI, regardless of whether the patient is located in a rural or an urban area. It involves fibrinolysis followed by planned angiography at 3 to 24 hours in hemodynamically stable patients. The CAPTIM trial (Comparison of Angioplasty and Pre-Hospital Fibrinolysis in Acute Myocardial Infarction) and PRAGUE-2 trial (Primary Angioplasty in Patients Transported From Community Hospitals to Specialized PTCA Units With or Without Emergency Fibrinolysis-2)

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suggested that in patients presenting earlier (within 2 hours) mortality with fibrinolysis was either similar to or lower than that with primary PCI.[45] The recent STREAM and STEPP-AMI study (Study Comparing Tenecteplase Facilitated PCI Versus Primary PCI in Indian Patients With Acute Myocardial Infarction) from India[47] reported that a pharmaco-invasive strategy can be implemented in patients with STEMI who are not selected for primary PCI, and the findings suggested that outcomes may be similar to those of PCI at the end of 1 year. It is the opinion of this group that a pharmaco-invasive strategy is the most feasible and thus desirable pathway for STEMI networks in LMICs. However, we recognize that this may not be feasible in many LMIC settings. In such resource-constrained settings, other well-studied options such as triaging only the high-risk patients to angiography/PCI and using noninvasive risk stratification after fibrinolysis (predischarge exercise treadmill test or stress imaging as locally possible) for all other stable low-risk patients might be quite reasonable.

OPERATIONAL STEPS ONCE STEMI IS CONFIRMED

Initial Facility of Presentation and Emergency Medications

The point of first medical contact makes a big difference for patients in LMICs because facilities are variable and most first-contact centers may not be able to provide the necessary therapy expediently (Figures 1 and 3–5). Most LMICs do not have an organized STEMI system of care, and patients often travel and self-present to the nearest medical facilities using private or public transport. Often these are a doctor's consulting room or primary health center, most without an electrocardiography machine (Figure 3). The challenge, then, is to get an ECG, confirm STEMI, and then move the patient to an appropriate facility for reperfusion. An organized STEMI system of care would be the preferred strategy to manage patients with STEMI. Some such models have been in use in LMICs such as India, Indonesia, and Brazil. A strategy for treating these patients, based predominantly on experience from various efforts such as STEMI-India, Africa STEMI, and the Latin America Telemedicine Infarct Network, is discussed below.[15] The operating principle is based on a hub-and-spoke–based structured treatment format (Figure 1): The best feasible initial medical care is provided at the facility of first medical contact, and less resourced centers move the patient to higher-order facilities in a safe and expeditious manner. Figure 1 shows the various ways (and facilities to which) a patient may present and how the management should proceed from that point. Figures 3 through 5 show diagrammatic representations of access point–specific therapies and recommended transfer strategies in LMICs.

It is important that patients rapidly reach appropriate medical facilities. To that extent, those that have the

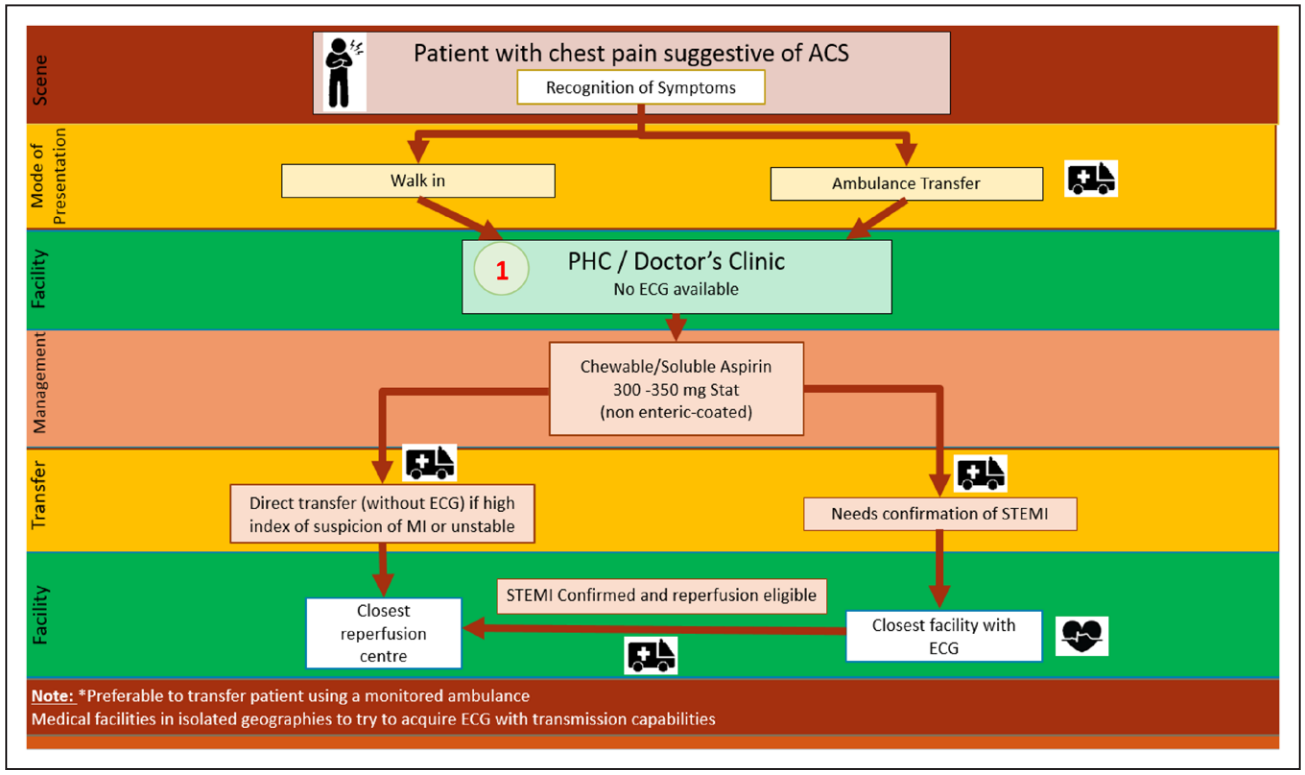

Figure 3. Access point–specific therapeutic pathways for a patient with ST-segment–elevation myocardial infarction (STEMI).
Diagrammatic representation of specific pathways that should be followed in patients presenting to Level I facilities, that is, those with the least capabilities for treatment of STEMI. ACS indicates acute coronary syndrome; CHC, community health center; MI, myocardial infarction; and PHC, primary health center.

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required training and capabilities for the diagnosis/management of STEMI should be prominently identified and appropriately labeled as STEMI accredited centers. This is not unheard of in some LMICs; many major hospitals/facilities already advertise various accreditation achievements (eg, International Standards Organization 9000 or Joint Commission on Accreditation of Healthcare Organizations) prominently on their promotional material and billboard displays. These facilities should be given wide publicity specifically targeting the high-risk groups (eg, patients with diabetes mellitus, hypertension, and known cardiovascular diseases), so that time is not lost in transferring the patient to an appropriate facility. In addition, governmental agencies should invest in upgrading lower-level facilities when feasible.

Listed below is a 5-tiered approach to setting up an STEMI network. Although it might appear superfluous at first glance to Western observers, this format helps readers understand and encompasses the uniquely varied clinical facility landscape in LMICs and is an important component of efficient flow within a hub-and-spoke STEMI system of care. As outlined in Figure 1, this could be condensed down to 3 tiers, but the 5-tier approach is presented first for the sake of clarity.

Level 1 Facility

Patients may self-present to a general practitioner or a primary health center with chest pain (Figure 3). An ECG is usually not available at this medical facility. Any patient with chest pain suggestive of acute coronary syndrome should be given soluble/chewable aspirin and then transported, preferably in an ambulance with monitoring capabilities.

- If the symptoms are highly suggestive of STEMI or hemodynamic/electric instability, then the patient should be transported immediately to the closest reperfusion center (regardless of the distance, if not prohibitively far) for confirmation and definitive treatment. This should be treated like any other life-threatening medical emergency.
- All other patients should be transported by ambulance to the closest facility where an ECG can be done and an STEMI confirmed/ruled out. This could be a reperfusion center, if located close to the clinic. However, because medical facilities with electrocardiography machines are more easily accessible than reperfusion centers, it is better to confirm STEMI before transfer to a reperfusion center, which may be located further away.

Level 2 Facility

- Patients may self-present or be transported by ambulance from another medical facility to a clinic or community health center (Figure 4). These are medical facilities that have electrocardiography equipment and an onsite physician who can interpret tracing. If the facility is part of an STEMI system of care, then remote interpretation of the ECG may be possible. Confirmation of STEMI would be followed by emergency administration of appropriate medications such as aspirin and statin. The patient is then transported by ambulance to the closest reperfusion center.

If the ECG is not confirmatory, an ECG is repeated every 10 to 15 minutes for the first hour, and a point-of-care cardiac biomarker is done if available. If it still remains inconclusive and the symptoms are suggestive of STEMI, then consideration should be given to transfer to a higher-order facility after aspirin and statin are administered. At any stage, confirmation of STEMI should be followed by administration of appropriate medications and immediate transfer to the closest reperfusion center.

Level 3 Facility

Fibrinolysis-Capable Center

A patient with a confirmed diagnosis of STEMI should be transferred from either Level 1 or Level 2 centers to a center equipped to provide thrombolytic therapy (Figure 5). A patient could also directly self-present to a center equipped to provide thrombolytic therapy. It is important to ensure that all patients have received appropriate medications before or concomitant with fibrinolysis.

A fibrinolysis contraindication checklist should be readily available and administered before fibrinolysis. The patient may be immediately shifted from this center to a PCI center, without fibrinolysis, for the following reasons:

- PCI center is within 60 minutes of the fibrinolytic center, and a catheterization laboratory and team are available to perform urgent primary PCI.
- Fibrinolysis is contraindicated.
- The patient is in cardiogenic shock.

Once a decision is made to proceed with fibrinolysis, it is performed per protocol using standard drug choices. A diagnosis of failed or successful fibrinolysis should be made promptly and based on the patient's clinical response and ECG at 90 minutes. All patients should be considered for transfer to the PCI center (Level 4) for final definitive angiography. This transfer will be immediate when lysis cannot be administered expediently, for rescue angioplasty when lysis has failed or 3 to 24 hours after fibrinolysis for pharmaco-invasive therapy even when lysis has apparently been successful.

Level 4 Facility

PCI -Capable Center but Without Consistent 24/7 Support for Primary PCI

This is a uniquely pertinent problem in LMICs where many hospitals with PCI capability may not have the resources to offer it around the clock. The reason could be a limited number of laboratories (often just 1 laboratory in most

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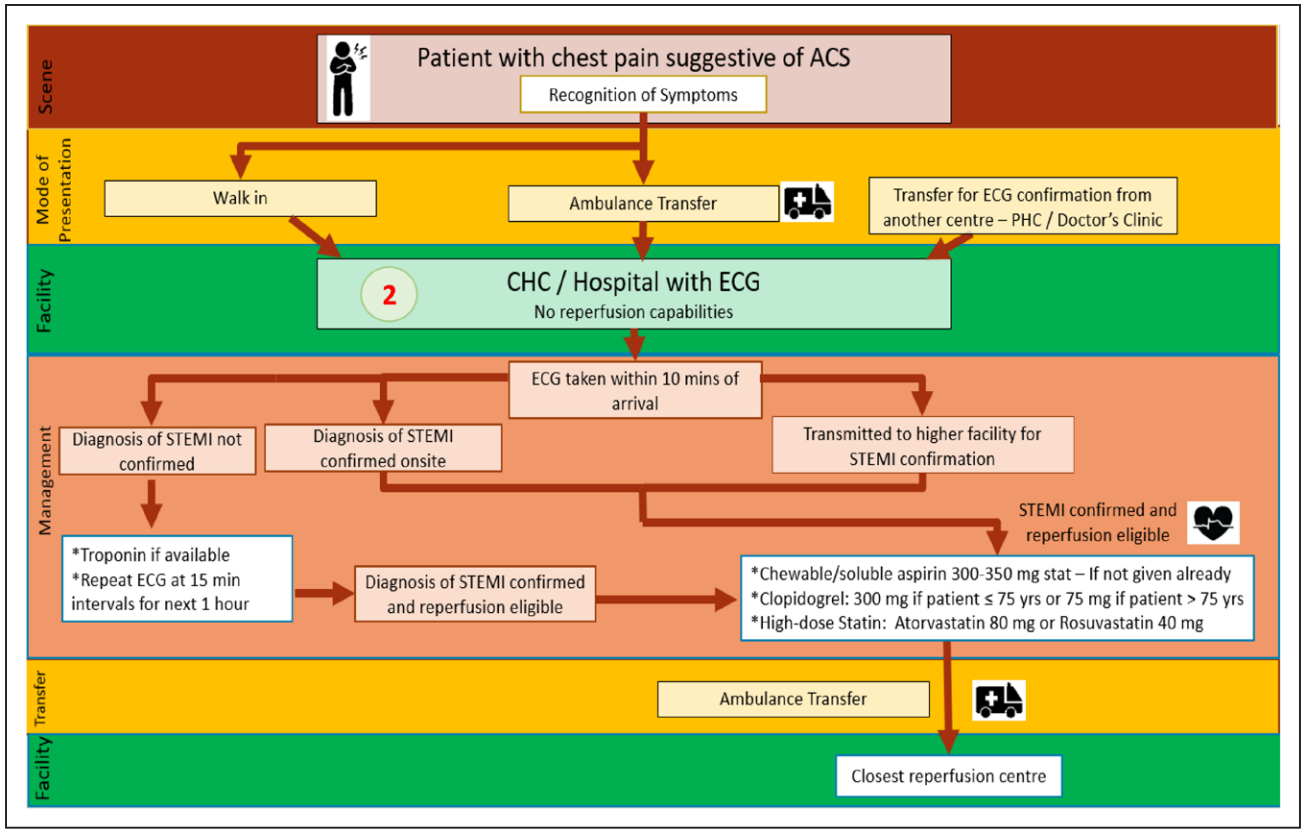

Figure 4. Access point–specific therapeutic pathways for a patient with ST-segment–elevation myocardial infarction (STEMI).
Diagrammatic representation of specific pathways that should be followed in patients presenting to Level 2 facilities, that is, those with somewhat better capabilities for initial treatment for STEMI. The patient may self-present or be transported by ambulance from another medical facility to this facility. ACS indicates acute coronary syndrome; CHC, community health center; and PHC, primary health center.

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places) or very few interventional cardiologists with expertise in PCI. A patient could be transferred or self-present to such a PCI center without knowing the immediate availability of primary PCI (because LMICs lack the "divert" mechanisms available to emergency medical services and hospitals in the developed world), and most hospitals do not have the logistics centers to transfer such patients to other PCI-capable facilities within the adequate door-to-balloon time window or even enough PCI-capable receiving hospitals to accept such a transfer offer. Again, appropriate medications should be administered.

Primary PCI should be performed, when feasible in a timely manner, per standard protocols. A patient may undergo fibrinolysis in a PCI center in certain exceptional circumstances. These include the following:

- Delay in access to catheterization laboratory because it is already occupied
- Cardiologist/catheterization laboratory team unavailable
- Delay in consent for PCI for any reason
- Other logistical limitation to access invasive treatment

The subsequent pathway for these patients who have received fibrinolytics at these centers will be similar to that of patients presenting to Level 3 centers.

Level 5 Facility

Hub Center of STEMI Program With Full Spectrum of Capabilities

This facility is the hub of a formal STEMI care model system and has contractual arrangements with spoke hospitals and ambulance services. It also provides second-opinion facilities for evaluating ECGs transmitted via high-speed lines or via the cloud and, if necessary, provides pathway advice to participating hospitals. A patient with chest pain could activate the STEMI system if operational (Figure 1). Such systems of care have been used with variable levels of success in India, Brazil, and other parts of the world and could be appropriate for adoption with local modifications in LMICs.[15] This is described later in the section on STEMI systems of care.

SPECIFIC OPERATIONAL STEPS FOR THROMBOLYTIC THERAPY

Once a decision is made for thrombolytic therapy, some practical aspects need attention. Before fibrinolytic therapy is started for a patient, it is important to check on the absolute and relative contraindications. Although a number of fibrinolytics are available in LMICs (Table I in the Data Supplement), streptokinase

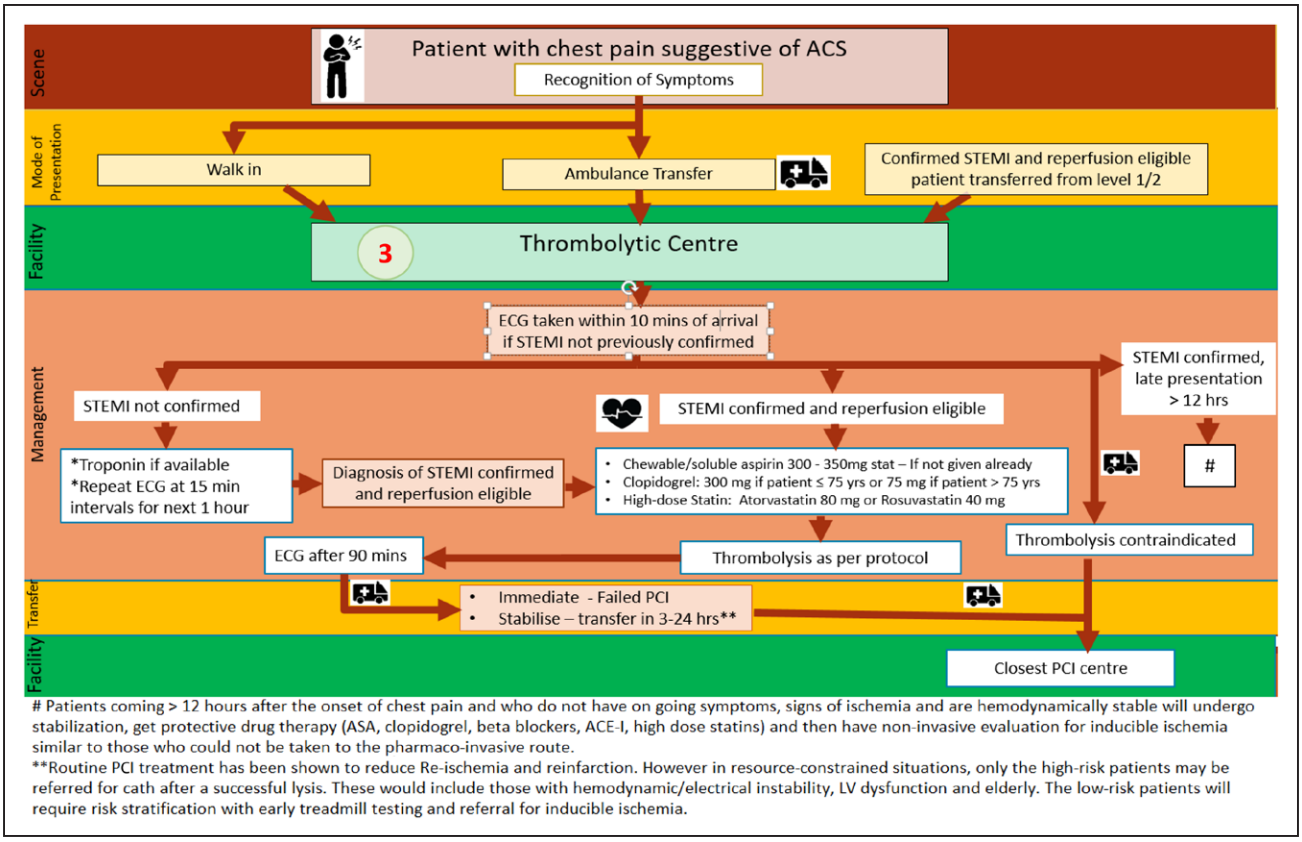

Figure 5. Access point–specific therapeutic pathways for a patient with ST-segment–elevation myocardial infarction (STEMI).
Diagrammatic representation of specific pathways that should be followed in patients presenting to Level 3 facilities, that is, those with capabilities for thrombolytic treatment of STEMI. The patient may self-present or be transported by ambulance from another medical facility. #Patients coming >12 hours after the onset of chest pain who do not have ongoing symptoms or signs of ischemia and are hemodynamically stable will undergo stabilization, receive protective drug therapy (acetylsalicylic acid [ASA], clopidogrel, β-blockers, angiotensin-converting enzyme inhibitor [ACE-I], high-dose statins), and then have noninvasive evaluation for inducible ischemia similar to those who could not be taken to the pharmaco-invasive (PI) route. **Routine pharmaco-invasive treatment has been shown to reduce reischemia and reinfarction. However, in resource-constrained situations, only the high-risk patients may be referred for catheterization after a successful lysis. These would include those with hemodynamic/electric instability, patients with left ventricular (LV) dysfunction, and the elderly. The low-risk patients will require risk stratification with early treadmill testing and referral for inducible ischemia. ACS indicates acute coronary syndrome; and PCI, percutaneous coronary intervention.

remains the most commonly used agent because of cost. It is, however, significantly less effective than newer agents. The improvement in outcomes and the ease of administration (single bolus injection compared with prolonged infusion) of newer agents may be reason enough for governments to consider bulk purchasing and aggressive price negotiation to procure such agents and make them available in at least in their midsized facilities. In a context in which many patients present late, one may expect even greater benefits from fibrin-specific drugs compared with the less specific older agents such as streptokinase. However, as pointed out, streptokinase is significantly cheaper than fibrin-specific agents. Dosing of streptokinase as part of a pharmaco-invasive strategy is a bit unclear. At least 1 study has demonstrated that full-dose streptokinase may be associated with low bleeding rates as part of a pharmaco-invasive strategy compared with fibrin-specific agents, for which half-dose fibrinolytic is typically recommended.[14]

SPECIFIC OPERATIONAL STEPS FOR PRIMARY PCI

Primary PCI comes with some unique features in LMICs that need to be recognized and addressed.

- The relatively smaller number of surgical facilities available compared with PCI centers makes it necessary to permit primary PCI without onsite surgeons standby.
- Because of cost constraints, bare metal stents may be the default stent used in LMICs. Although the short-term results are comparable, drug-eluting stents have better long-term results with comparable or better safety data. Despite the cost, it may be prudent to use drug-eluting stents in certain subsets of patients such as those with smaller vessels (<3.0 mm), longer lesions (>20 mm long), and diabetes mellitus.
- Government policies, which are highly varied even among LMICs, have the ability to significantly affect the pricing of medications and devices.[48,49]

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For instance, in a landmark decision, stents were placed on the National List of Essential Medications in July 2016 by the health ministry of India. Then, in 2017, India's National Pharmaceutical and Pricing Authority made a landmark decision to fix price ceilings for coronary stents (approximately $108 for bare metal stents and $444 for drug-eluting stents), cutting the immediate price by up to 85% in some cases.[50,51]

- To keep costs down and to reduce the need for repeat procedures, for patients presenting with multivessel disease, operators can consider revascularization of both culprit and nonculprit vessels, if hemodynamically stable, during the index procedure itself. Recent evidence from randomized, controlled trials suggests that such an approach (non–infarct-related artery PCI either during the same setting or before hospital discharge) may have better outcomes compared with PCI of only the culprit vessel. Accordingly, this was also upgraded from Class III (harm) to Class IIb (can be considered) in the 2015 update of the STEMI guidelines and to a stronger Class IIa (should be considered) in the 2017 ESC STEMI guidelines.[52]

EFFICIENT STEMI MANAGEMENT IN LMICS: THE STEMI SYSTEM OF CARE MODEL

Although this document outlines best practices that can fit most of the current healthcare settings in LMICs, the committee felt that the most efficient delivery of STEMI care in LMICs will be one in which countries adopt a formal STEMI care model with a clear definition of what needs to be done in differently resourced settings, a common evidence-based format for treatment protocols, and established standards for care, triage, and transfer. Table 2 identifies some of the essential principles for a successful operation. A STEMI care model system is a comprehensive arrangement between hospitals of various levels of medical care capabilities designed to harness strengths of the better-equipped hospitals and to mitigate weakness in the weaker peripheral systems of care. Most commonly arranged as a hub-and-spoke formation, it allows a seamless process of rapid triage, provision of urgent/emergency care, and expeditious transport to designated centers for advanced reperfusion therapies. Appropriately sized groupings of facilities should aim for the highest level of efficiency within these care models and find partners/investments to reach timelines that have been shown to improve outcomes in the developed world.

A number of countries have tried to create their own STEMI systems of care models,[53,54] and each country should adopt one that fits its needs the best. One such protocol, STEMI-India, has generated substantial outcome data that may be generalizable to other LMICs with similar societal and logistical challenges. Some of its principles have been incorporated into our proposed system of care strategies. Extensive data show that it is feasible[5] and effective in improving access to PCI and decreasing reperfusion times[55] with improvements in hard outcomes[15] in a highly cost-effective manner[56] in large populations in rural areas in India. It had great utility with a number needed to treat of 30 to save 1 life, at a cost of Indian Rupee 13643 (US $233) per life-year saved. These measures of efficacy will be of particular interest to policy makers in LMICs, where financial and resource constraints pose a perennial public health challenge.

STEMI systems of care should be cognizant of the widely variable nature of resources and create a protocol to work well within the paucity of primary PCI facilities. Although LMICs recognize the need to increase primary PCI facilities and there has been a steady increase in the number of primary PCIs done in LMICs, only a small minority of patients with STEMI receive this modality of reperfusion.[57] The recent STREAM data[58] and data from the STEPP-AMI study showed that the pharmaco-invasive strategy compared well with primary PCI in overall morbidity and mortality. On the basis of this evidence and the success of the Kovai-Erode pilot study,[55] STEMI management should liberally adopt the

Table 2. Essential Components of an Effective STEMI Care Program in LMICs

Develop a personalized care strategy that targets therapies in a uniquely specific manner, depending on point of access in the healthcare system
Rapid mobilization to a reperfusion center if the point of access is to a center without reperfusion facilities
Fibrinolytic therapy followed by pharmaco-Invasive strategy when patients access facilities that can offer fibrinolysis but cannot provide primary PCI
Primary PCI in centers capable of providing it expeditiously
Create a STEMI system of care and create pools of communities who have a buy in into such hub-and-spoke formations
Introduce performance measures for STEMI care; these should be educational and have no punitive implications
Create an easily accessible, preferably cashless, system of paying for care at any approved STEMI care facility, both public and private; this should eliminate upfront out-of-pocket payments because they are a formidable barrier for accessing the healthcare system for most patients
Have a strong component of program evaluation, agile response to lessons learned from such audits and create incentives for programs that consistently produce above-average STEMI performance measures and outcomes

LMIC indicates low- and middle-income country; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

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dual strategy of combining primary PCI with pharmaco-invasive reperfusion to develop an easily implementable framework for developing a system of care:[59]

- Primary PCI would be performed in patients located close to catheterization laboratories. This option would be available mostly for patients in urban areas with presumed short transportation time (<30 minutes) to the hospitals equipped with 24/7 primary PCI capabilities.
- Patients in rural areas with expected long transportation time (>30 minutes) to PCI-capable hospitals would be treated with the pharmaco-invasive strategy: fibrinolysis followed by catheterization and PCI, if indicated, within 3 to 24 hours of fibrinolysis.

Although it is clear that one cannot recommend a universal model for all LMICs and that each country should adopt models that are congruent with its individual needs, some architectural principles such as moving a patient in a spoke-and-hub pattern that harnesses increasing expertise may be common to many LMICs. The architecture of various STEMI models used in numerous LMIC settings is based on a hub-and-spoke model, with each unit being called an STEMI cluster, but each country would need to create its own specific formats. For instance, each cluster in the STEMI-India model[5] is made up of 1 of 2 types of hub hospitals (those with 24/7 primary PCI facilities [Hub A] and those that have some primary PCI capabilities but offer fibrinolysis at other times when primary PCI is not feasible [Hub B]) and 2 types of spoke hospitals (Spokes C and D) that have fewer facilities but have the ability to access advice and support from the hub hospitals and a contractual arrangement to transfer patients to them.

A hub-and-spoke model is also proposed in this document, but various units in this model are called Levels (from 1–5) to cover a wider spectrum of varying capabilities and to allow applicability to other LMICs.

Countries should adopt their own patterns of STEMI system of care formations consistent with the general outlines described above. Standardized protocols describing the expected care delivery for a patient with STEMI have been designed. Different protocols have been implemented, depending on the setting of care, that is, emergency medical services, rural spoke hospitals, and PCI-capable hub hospitals. However, the care at each of these locations is largely standardized to meet best practices. Protocols are simple and straightforward to eliminate complexity, thus minimizing confusion during emergency care situations. One of the goals of this document, in addition to providing best practice algorithms, is to provide a network of experts who can assist governments and NGOs in setting up and optimizing their STEMI care models. All the authors of this technical document have agreed to be available to make this happen.

SUGGESTED FRAMEWORK FOR A STATEWIDE STEMI PROGRAM

Government Support and Infrastructure Needs

For any STEMI program to be successful, a certain infrastructure has to be in place, and a clear partnership among various key stakeholders has to exist (Table 3):

1. Government participation: Any STEMI program will require the full support and involvement of the government. Social insurance to cover individuals who are poor, an efficient ambulance service, and participation of public hospitals in an STEMI program is crucial to the success of any STEMI program. Furthermore, funding for the program has to be provided by the health budget of governments. Important areas in which the government, in consultation with the other stakeholders, would be involved are the following:
    a. Social insurance scheme/universal health insurance. Some countries or some selected states in some LMICs offer government-run insurance schemes to cover medical expenses to the populations falling below poverty line. This is critical for implementation of an STEMI program and to ensure equitable access to the vulnerable population for emergency care. The STEMI experience from selected states in India and universal national care in Brazil could be useful for understanding the strengths, weaknesses, opportunities, and threats to implementing such programs in diverse settings.
    b. Legislation to accredit STEMI hospitals and to prescribe minimum training requirements, infrastructure requirements, medication stock, and manpower requirements to handle patients with STEMI. Because governments in many LMICs are the main source of insurance for people below the poverty level, they can certainly plan a positive role in enforcing quality care through these measures.
    c. Minimum standards, equipment, and training requirements for ambulance services.
    d. Legislation for emergency medical services, if necessary, to bypass non-STEMI hospitals and transport patients to STEMI accredited hospitals for management.[60] New STEMI hospitals can be regulated so that there is an even distribution of STEMI hospitals. This could be somewhat similar to the Certificate of Need legislation in the United States. This would encourage newer centers in poorly

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Table 3. Systems of Care Priorities for Governmental Organizations Involved in STEMI Care

Understand the problem	Map local trends and resources already available for STEMI care and create projections for needs
	Evaluate their existing resources including emergency medical services (EMS) capabilities
	Obtain ongoing data on primary PCI-capable hospitals within effectively transferable distances
	Map prevalence patterns of patients with STEMI in various administrative units
	Identify stakeholders (general practitioners, cardiologists, EMS personnel, transportation experts, health care–related NGOs, government health department bureaucrats, financial economists and management experts, general public, etc) and involve them in planning and decision-making
Standardize protocols within the system of care environment	Create standardized protocols applicable to various components of the STEMI care chain
	Create best-practices templates for care at the various point-of-access situations
	Fund development of tools for ongoing program evaluation and collection of data on lessons learned
	Facilitate making this a part of a long-term quality improvement program
Create mechanisms for knowledge transfer	Create a mechanism for successful transfer of policies, pathways, and protocols from successful STEMI systems of care
	Plan for an online web-based repository site for hosting seminal best practice documents (translated into an easily readable format and in various regional languages) for easy, and firewall-free access
Identify STEMI centers of excellence	Governments and NGOs should create and fund a mechanism to identify and prominently display a list of hospitals that comply with best practices in STEMI care.
	Widely advertise the importance of timely access to prompt reperfusion for all patients with STEMI
Identify infrastructure improvement needs	Governments and NGOs should find solutions to rapidly transporting sick patients
	Encourage public-private partnerships in creating an efficient EMS system when lacking
	Upgrade emergency care for patients with STEMI in government and public hospitals
Identify low-cost communication infrastructure improvement needs	Encourage the use of social media communication tools and cloud-based resources for transmitting encrypted data for second opinions from expert hub centers
	Governments should create the legal framework to make this acceptable
Modify legislation and healthcare regulations	Modify existing state regulations and enact legislation to facilitate new models for improved implementation of a STEMI system
	Match regulation to allow rapid identification and speedy movement of patients to centers that can ensure the best possible outcomes
Explore and encourage use of SMARTHealth solutions	Explore how various currently available modules such as the SMARThealth program or other platforms that use mobile technology for multifaceted healthcare provider communication, advice, feedback, and decision support tools, can foster guideline-based assessment and care in remote areas
	Invest in developing low-cost eHealth or mHealth solutions to address current limitations or to enhance such currently available modules
	Plan programs that target multiple facets that have been shown to improve LMIC care: mobile decision support tools, distribution of educational materials to frontline healthcare professionals, educational outreach visits, rapid access to higher-level providers for advice, patient and healthcare provider reminders, a system of nonpunitive audit and feedback, and help with case management
	Modify existing state regulations to allow greater NGO participation, either as the primary funder or in a public-private partnership, in facilitating clinical studies that rigorously evaluate such new models for improved implementation of an STEMI system
	Encourage eHealth or mHealth interventions as a mechanism to reduce health outcome inequities and to level the field of opportunities for low-income patients
	Help fund real-world studies targeting these interventions in remote and resource-depleted parts of their populations, including reminders, educational outreach visits, audit and feedback, case management, and distribution of educational materials to healthcare professionals

eHealth indicates electronic health; EMS, emergency medical services; LMIC, low- and middle-income country; mHealth, mobile health; NGO, nongovernmental organization; PCI, percutaneous coronary intervention; SMARTHealth, Systematic Medical Appraisal Referral and Treatment; and STEMI, ST-segment–elevation myocardial infarction.

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served areas and discourage allocation of resources in well-served areas.

2. Dedicated or shared ambulance networks. Most LMICs have fragmented and multiple ambulance services with limited numbers, often inadequate to cover the population at risk. Integrating them is important to optimize resources and access. It is crucial that ambulance services are specifically dedicated or repurposed to deal with some emergent conditions such as STEMI, strokes, or trauma and adopt the models well established in the developed countries. Whereas some LMICs such as those in the Latin America provide such a facility as part of public service, LMICs such as India

have started to venture into the public-private partnership mode.

3. The minimum requirements for the ambulance system would include the following:
   a. Paramedics trained in doing ECGs with a basic ability to read ECGs
   b. Familiarity with emergency protocol for STEMI management
   c. Emergency medications
   d. Electrocardiography equipment, preferably with transmission capability
   e. Multifunctional monitoring device
   f. Automated external defibrillator
4. Technology partners should be harnessed to bring innovation to the recognition, transport, and care of patients with STEMI in LMICs. To be effective in the field, the system of care must allow ECGs with transmission capability and could incorporate ≥1 features and functions as outlined below.
   a. Electrocardiographic recording. Twelve-lead ECGs should be done at the earliest point of contact: home, ambulance, or hospital. The ECG could be transmitted from the device to a handheld device with the on-call cardiologist in the hub hospital for confirmation of STEMI or could be interpreted by at-will cardiologists available on the web for widely disseminated electrocardiographic alert.
   b. Vital signs monitoring. This device could be converted to a multiparameter monitoring device and used for monitoring oxygen saturation, ambulatory blood pressure measurement, and rhythm monitoring of the patient in the smaller spoke hospitals and in the ambulance during transportation. Transmission of data to the destination hospital any time during treatment in the spoke hospital or during transportation is possible. This will help the hospital clearly understand the hemodynamic status of the patient and, if required, advise the doctor or paramedic on management.
   c. The vital signs monitoring device could also become a data-entry device with the capability for real-time data entry. Management protocols and work-flow algorithms that are preloaded on this device guide the paramedic and spoke hospitals on management.

Technology Needs, Data Collection, and Quality Assurance

A robust information technology platform, preferably hosted securely on the cloud for real-time access regardless of device, would enable data collection and sophisticated analytics. Various modules can be adopted to provide level-dependent functionalities so that each facility can easily input relevant data. A dashboard should give the administrator access to analytical and visual representations of various parameters to allow quick data analysis, audit, and quality checks. Audit feedback to hospitals further improves performance and provides motivation for better compliance with the protocol. Ideally, STEMI systems would work on building live registries, analogous to the AHA's Mission Lifeline and the ACC's National Cardiovascular Data Registry's ACTION registries. These provide regular feedback to sites on patient characteristics, process measures, and outcomes achieved and allow benchmarking to local and national data. Closing this feedback loop is vital from a quality standpoint[61] and can serve as a means for accreditation and public reporting, if that is felt to be necessary. Various LMICs have already explored such registries[23,53,62–64]; future efforts should build on these experiences.

Program Evaluation, Outcome Measures, and Quality Improvement in STEMI Care

National STEMI control programs, given the limited resources in these countries, should focus primarily on improving patient outcomes. However, long-term success depends on a working toward a clearly defined slate of target goals and the ability to measure performance metrics; programs should therefore also prospectively build capacity for measuring key performance indicators. These should be individualized in the context of each country and jurisdiction but should, at the minimum, measure STEMI care use rates, document actual reperfusion times, identify choke points in achieving internationally accepted goals for timely reperfusion, and keep a detailed database of region-level outcomes for STEMI care. These should be sufficiently granular to allow rectification in care processes at the grassroots level as needed. Massive nationwide insurance schemes are being deployed in some LMICs,[65,66] and providing such data could become an integral part of provider and facility reimbursement under such coverage.

Other Peri-STEMI Management

A host of other management issues need to be dealt with during the peri-STEMI period to improve short- and long-term outcomes in patients with STEMI. These should also be protocolized to the extent possible. Regular assessment of these metrics should also be part of the feedback loop for participating sites.

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Discharge and Postdischarge Management

Addressing complications of STEMI and planning for discharge and postdischarge management issues are important for better intermediate- and long-term outcomes in patients with STEMI. If patients are part of an STEMI care model, these will likely be done per their protocols. Other centers with lesser capabilities might do well if they can adhere to as many of these principles as possible and connect patients to facilities that can at least initially create a structured plan for the patient. These include evaluation for possible complications, predischarge risk assessment, including left ventricular function and stress testing, measures for secondary prevention, exercise prescription/rehabilitation, and a future follow-up plan. Use of appropriate medications (antiplatelet agents, statins, β-blockers, etc) should be continued and monitored after discharge. Innovations such as polypill with fixed drug combinations may have advantages over single medicines given concomitantly, including increased adherence, reduced pill burden, and greater cost-effectiveness,[67,68] especially in underserved populations,[69] and could be tested in the post–myocardial infarction setting. This might be very important given that delay in initiating secondary prevention medications after discharge is associated with worse outcomes[70] and that loss of follow-up is a major problem in LMICs.

All centers involved in STEMI management should have periodic audit of quality indicators and work toward improving them. These should be regularly communicated to all the healthcare workers and administrators in each of the medical facilities and ambulances services involved in the management of patients with STEMI.

Follow-up should focus on aggressive risk factor modification because this has been shown to reduce morbidity and improve outcomes. In the minimum, this should include the following:

1. Efforts to ensure smoking cessation
2. Adequate ongoing management of diabetes mellitus and hypertension
3. Encouragement of regular physical activity, starting with a postdischarge rehabilitation plan
4. Advice on dietary modification and ensuring a healthy diet

Tobacco use deserves a special mention because it is very prevalent in LMICs (in some countries, up to a half of the men and a fifth of the women consume some form of tobacco according to GATS [Global Adult Tobacco Survey] data) and is one of the foremost causes of cardiovascular death. It is a leading risk factor for STEMI, attenuates the efficacy of STEMI therapies, and adversely affects long-term prognosis. Much of this morbidity is preventable, and suitable governmental actions can definitely curb smoking. For example, after concerted governmental efforts, the prevalence of smoking decreased significantly between 1990 and 2016 among all epidemiological transition-level groups in India[71]; the multicountry GATS data show similar experience across many countries. This success should be further leveraged through targeted efforts, and smoking cessation is a viable opportunity in any LMIC-based STEMI management program. We strongly recommend that governments and NGOs create a systematic tobacco surveillance and management program for patients presenting with STEMI, and discharge planning should include clearly documented efforts toward smoking cessation interventions.

LONG-TERM INVESTMENT FOR PROMOTING EXCELLENCE IN STEMI CARE

This document emphasizes that excellence in STEMI care is an ongoing process rather than a one-time investment, and success or failure is crucially dependent on adequate investments in thought, ideas, time, effort, and resources. This can be done only by extensive involvement of governmental and legislative machinery, along with input from physician experts and NGOs on the front lines of STEMI care. It is thus important to update STEMI programs constantly on the basis of emerging evidence and lessons learned from current implementation efforts. It should be understood that STEMI is increasing in LMICs and affects their working-age population disproportionately compared with Western data, and the morbidity and loss of quality-adjusted life-years can significantly detract from growth in their national economies. The ultimate goal should be the provision of effective evidence-based care efficiently and equitably to the largest number of patients possible in any administrative unit. This might involve targeting resources to normalize care discrepancies and to beef up healthcare facilities in resource-challenged areas catering to large number of patients with STEMI. This should be coupled with meticulous program evaluation, which in turn should dictate future changes to program implementation and evaluation processes.

CONCLUSIONS

The recommendations developed by the ACC/AHA and ESC are based on voluminous published data and are applicable to populations with no resource constraints, the majority of whom can access that level of cardiac care. Unfortunately, the published data from across the LMICs are sparse and do not cover many of the important aspects of STEMI management. Furthermore, many of the published multicenter studies have only a minority of patients from LMICs; therefore, their relevance to this group is not fully established.

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This technical report for LMICs provides a construct to manage patients with STEMI across the LMICs where significant healthcare resource and infrastructure constraints exist. With consistent efforts in these countries to develop a pragmatic and cost-effective STEMI system of care, more accurate diagnosis and management of patients with STEMI should result in better patient outcomes and reduced mortality rates. STEMI management experience gained in both developed countries and LMICs is consistent in highlighting 2 crucial realities. The first is that an organized system of care will produce better outcomes both for patients and for countries than fragmented, individual- or institution-specific methods of treatment. The minutia of the specific system are superseded by the importance of having a workable system of any format. The second is that individuals driving effective STEMI management will need to find creative means of harnessing all available resources, even when they are limited, to deliver quality care to as many as possible.

Thoughtful regulatory policy changes covering large regions like states or administrative territories are likely to improve STEMI care in LMICs far more effectively than depending on individual or local efforts. Such policy needs to be based on local data mapping current limitations in the STEMI care chain and unique local circumstances that can be barriers for optimal delivery of STEMI care. It should also, preferably, tap into processes that have been successfully implemented in various regional domains such as STEMI-India, Latin America Telemedicine Infarct Network, and China.

Finally, some may question the value of systems-based endeavors like these. It could be argued, for example, that money spent on STEMI systems of care in LMICs might be better invested in primary cardiovascular risk prevention, vaccination programs for children, or even non–health-related societal needs. This is a false dichotomy: We do not have to choose between STEMI management and other priorities; rather, efforts can focus on both. Particularly for LMICs to meet the urgent needs of their changing populations, they will need to address many challenges simultaneously.

These STEMI recommendations for LMICs form a consensus document put together by a group of experts working in the STEMI area in diverse countries of the LMICs. It is the first version of what will be a live and periodically updated document. As more evidence from these geographies becomes available, this document will have to be suitably amended to reflect contemporary and contextual realities. Similarly, as infrastructure and medical facilities improve in LMICs, it is possible that these recommendations will promote equity and will be available to the large majority of LMIC population. This document goes over many of the tasks that governments and NGOs could do to help improve reperfusion therapy in LMICs and should be considered areas of investment. A working summary of the essential elements of this document is presented in Tables 2 and 3. Strategies will differ in various jurisdictions, but some kind of minimal essential drug and device mandate should be pursued and widespread availability ensured through volume negotiations, bulk purchasing, and other locally appropriate and feasible methods.

ARTICLE INFORMATION

The Data Supplement, podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.119.041297.

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Disclosures

None.

Supplemental Materials

Data Supplement Table I

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