

## Perspective

### Prevalence of ST-Segment Elevation Myocardial Infarction (STEMI) in Pakistan and the Role of Primary Percutaneous Coronary Intervention (PPCI)

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#### Abstract:

There are various strategies used for treating ST-segment elevated myocardial infarction (STEMI). Among those approaches, Primary percutaneous coronary intervention (PPCI) is the current treatment of choice for STEMI as it reperfuses the ischaemic cardiac tissue with fewer reported adverse events and a better survival rate. Although thrombolytic therapy is still used for STEMI in approximation, the benefits of PPCI outweigh thrombolytic therapy as thrombolytic therapy is associated with higher bleeding events and higher morbidity. The barriers in implementing a PPCI program and regional differences arise due to limited technologies, lack of proper training of first responders, lack of public awareness, and transport facilities and finances. Therefore, treatment varies between different regions of countries and even between different countries, including Pakistan. PPCI should be used in a timely manner as delayed use of this intervention can significantly reduce the benefits. We lack a coordinated approach to the delivery of this system in Pakistan; mainly, the paramedical staff is not fully familiarised and trained for making a definite diagnosis and lacks referral portals. We need a comprehensive approach and program to identify factors that cause a delay in providing PPCI to STEMI patients and to eliminate the factors responsible for the delay. This will help in improving the survival rate morbidity in STEMI patients.

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#### Introduction:

ST-elevation myocardial infarction (STEMI) is a type of severe heart attack. It happens due to the blockage of one of the major coronary arteries of the heart. The coronary arteries supply nutrients and oxygen-rich blood to the cardiac muscle. STEMI can be detected on the 12-lead ECG<sup>1</sup>. According to the WHO, a heart attack is still a leading cause of death globally<sup>2</sup>. It has a high prevalence in both the developed and the developing world<sup>3</sup>. 17.9 million people died from cardiovascular diseases in 2016, representing 31% of all global deaths<sup>4</sup>. Out of these deaths, 85% are due to myocardial infarction and stroke. The South Asians have been shown to experience their first myocardial infarction almost ten years earlier than the rest of the world<sup>5</sup>. Pakistan is a developing South Asian country, and 67.5% of its population is living in a rural area and

have the most significant burden of heart disease<sup>6</sup>. A study showed that more than 30% of the people affected by this disease in Pakistan are over the age of 45 years. The most populated province of Pakistan, Punjab, accounts for more than 45% cases of the entire population of Pakistan<sup>7</sup>.

There are two primary treatment methods for STEMI. The preferred & well-established (in the developed world) is the primary percutaneous coronary intervention (PPCI). The other method is fibrinolysis (treatment with clot-busting drugs). The PPCI is more effective, and it has higher vessel patency rates in the culprit's vessel and has favourable outcomes at three years of follow-up<sup>8</sup>. The PPCI further reduces the overall short-term mortality by STEMI, non-fatal re-infarction, and stroke.

**Discussion:****Primary Percutaneous Coronary Intervention**

PPCI is an emerging strategy to restore blood flow in a blocked & stenosed coronary artery in developing countries. The vascular access is made through a peripheral artery for this intervention. There are two approaches: Trans radial and trans femoral, frequently used in clinical practice. There are advantages and disadvantages to both approaches. The transfemoral approach is made through the groin, and it has a long history of use. However, it can cause urinary retention, back pain, haemorrhage, aneurysm and requires extended bed rest following the procedure. The retroperitoneal bleeding and pseudoaneurysm are potentially severe complications. The radial route is the preferred approach because of lesser access site bleeding and lesser rest period following the procedure. However, it can be technically challenging. This is due to the small calibre of the radial artery compared to the femoral artery and due to vascular spasm<sup>9</sup>. Elective PCI in angina does not prevent the occurrence of acute myocardial infarction or improves survival, according to a meta-analysis<sup>10</sup>. The PPCI restores normal flow in more than 90% of patients and ensures long-lasting reperfusion. The delay in this interventional procedure and timely perfusion causes loss of mortality benefit<sup>11</sup>. The PPCI leads to higher mortality benefits in younger individuals as compared to older individuals<sup>12</sup>. The SYNTAX (Synergy Between PCI With Taxus and CABG) score is also used to assess which intervention should be used. A lower SYNTAX score suggests a Primary Percutaneous Coronary Interventional procedure to be used for revascularization. Coronary artery bypass surgery (CABG) can be appropriate when the SYNTAX score is very high<sup>13</sup>.

**Fibrinolysis**

Fibrinolysis is a strategy used to treat any acute episode of ST-segment elevation myocardial infarction. Fibrinolysis is based on the principle that the thrombus occluding the coronary artery leading to infarction, and necrosis of the myocardium should be resolved by the dissolution of the thrombus. This can be achieved by using fibrinolytic agents. The thrombus is formed by the conversion of fibrinogen into fibrin. After the formation of the primary platelet plug, the conversion of fibrinogen into fibrin is carried out by clotting cascade.

The secondary plug formed by this process is more stable than the primary platelet plug. When a thrombus occludes the coronary artery, the blood flow to the myocardium of the heart is compromised. This is the leading cause of the development of STEMI. The fibrin component of the blood clot can be dissolved by the fibrinolytic agents. The fibrin is broken down by the fibrinolytic agents, thus restoring the coronary blood flow. As a result, coronary blood flow is re-established again. The various fibrinolytic agents have been used clinically over the years. The most common fibrinolytic agents are streptokinase, Alteplase, Reteplase, and Tenecteplase. One of the limitations associated with the use of fibrinolytic agents in the treatment of STEMI is the time-lapse that must be considered while prescribing fibrinolytic agents to the patients. The fibrinolytic agents must be administered within 12 hours from the onset of an episode of STEMI. Fibrinolytic therapy with fibrinolytic agents has proved beneficial in various clinical trials and case studies. There are different ways of administration of these drugs to the patients. Alteplase is given through as intravenous infusion. The Reteplase is given as a double bolus intravenous injection. The use of fibrinolytic agents in the treatment of STEMI is not without risks; for example, the administration of streptokinase has the risk of development of hypersensitivity reaction for an autoimmune reaction. The streptokinase is derived from *Streptococcus* bacteria. The foreign antigenic nature of streptokinase may trigger an adverse immune response.

**Incidence and Prevalence Worldwide, and Pakistan:**

According to the WHO, cardiovascular disease is the number 1 cause of death globally. It is highly prevalent in developed and as well as in developing countries. 17.9 million people died from cardiovascular diseases in 2016, representing 31% of all the global deaths, as shown in figure 1<sup>14</sup>. Out of these, 85% of deaths are due to heart attack and stroke. Among these deaths, 75% were in low, middle-income countries. In the United States, 2744248 resident deaths were registered in 2016<sup>15</sup>. The cardiovascular diseases were reported to be the number one cause of mortality in the United States, and the second common cause of mortality was cancer. In 2017 Pakistan, the reported deaths due to CVDs

were 29.1%. The most common cause of premature death was ischemic heart disease, and it ranked second in 2017, as shown in figure 2<sup>16</sup>. According to WHO data, reported deaths in Pakistan in the lower-middle-income group was 19% due to CVDs, and mortality was higher in females as compared to males (age-standardised death rate per 100,000) as shown in figure 3. Non-communicable diseases accounted for 50% of the total deaths in the population proportion between 30 and 70 years<sup>16</sup>. The probability of premature deaths between ages 30 and 70 years from the four major communicable diseases is 21% (cancer, CVDs, diabetes, and chronic respiratory diseases), as shown in figure 4.

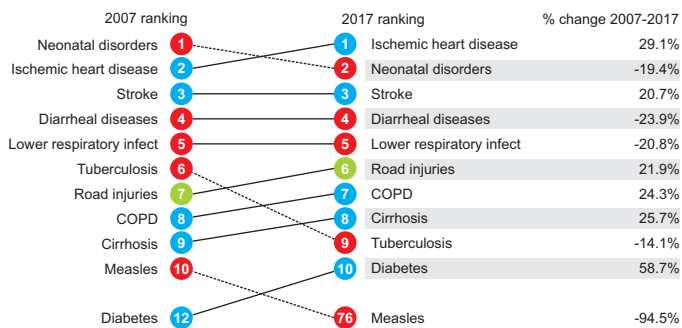


Figure 1: Top ten causes of death in 2017

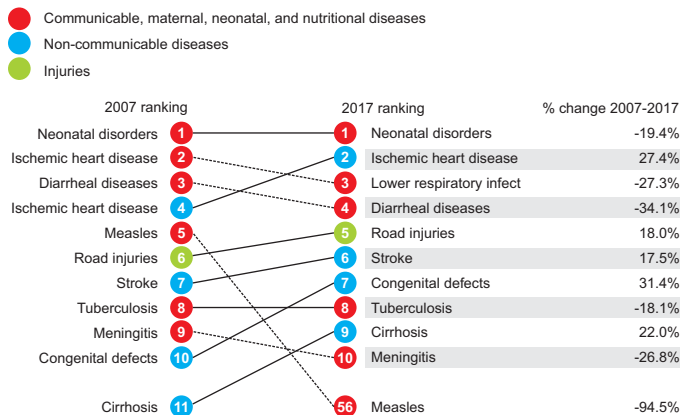


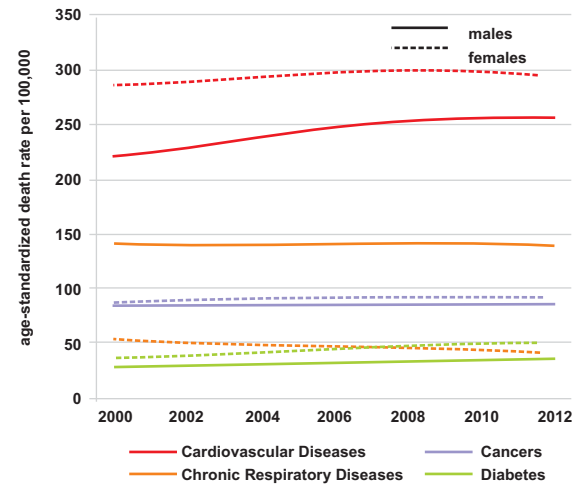
Figure 2: Most common premature death (ischemic heart disease at 27.4%)

The prevalence of cardiovascular diseases in Pakistan shows no reported figures, but a study in Karachi showed alarming results. The Prevalence of CVDs in the age above 40 years is 1 in 4 men and 1 in 3 women. The figures in other parts of Pakistan are likely found to be similar. The STEMI related deaths affect the socioeconomic status of the individual and affect the whole family. The age distribution of MI is most common in 41-60 years, followed by the age group

## Pakistan

Total population: 179 000 000  
 Income Group: Lower middle

### Age-standardized death rates\*



Percentage of population living in urban areas: 36.2%  
 Population proportion between ages 30 and 70 years: 32.8%

### Proportional mortality (% of total deaths, all ages, both sexes)\*

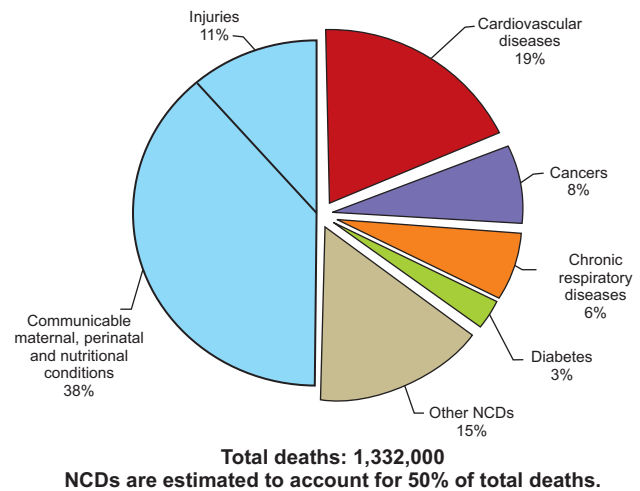


Figure 3: WHO data of heart diseases mortality in Pakistan

above 60 years. The prevalence of cardiovascular diseases in Punjab, Pakistan: A cross-sectional study data reported that CVDs are a severe problem for both genders and affected 17.5% of the studied population.<sup>16</sup> The studied mortality trends in the last 2-3 decades show that a drop in mortality rate in developed countries is due to patient education, early diagnosis, access to primary percutaneous coronary intervention and post-MI care, and lack of these facilities in developing countries lead to rising death rates. The incidence of STEMI has been prevalent among ischaemic cardio-

## Premature mortality due to NCDs\*

The probability of dying between ages 30 and 70 years from the 4 main NCDs is 21%

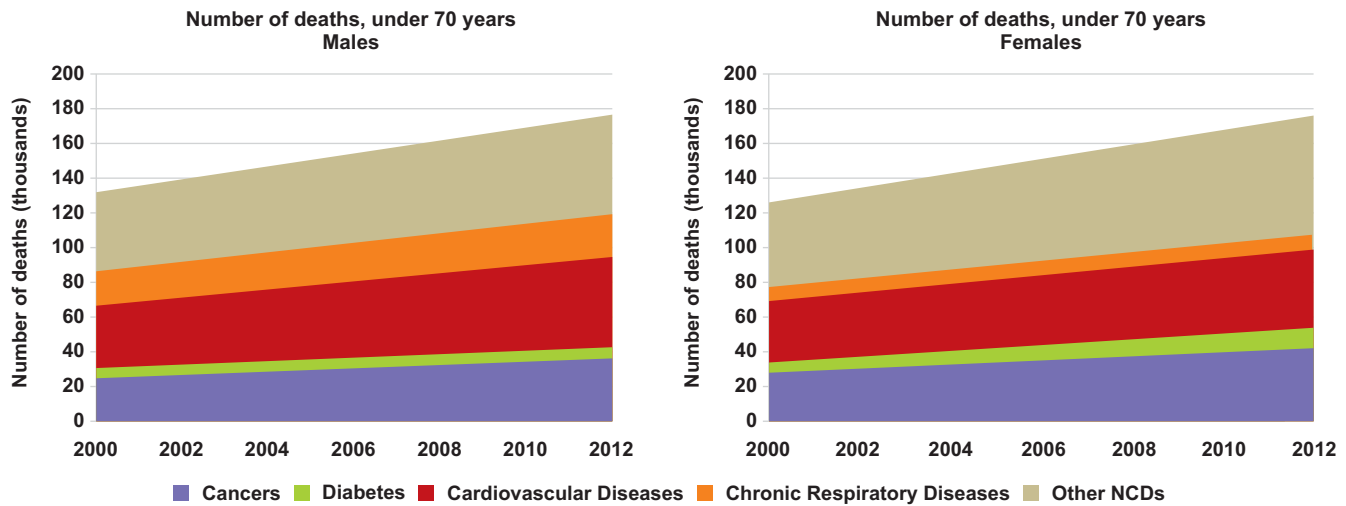


Figure 4: Comparison of mortality of cardiovascular diseases with other NCDs

vascular diseases in the world. Ischaemic heart disease is a significant contributor to mortality and morbidity across the globe. When we compare other chronic diseases with ischaemic heart diseases, the prevalence of ischaemic heart disease is more remarkable than other conditions in both developed and developing countries. Ischaemic heart disease is the leading cause of death in the United States of America, followed by cancer and trauma. Like other countries in the world, Pakistan also faces an alarming situation regarding ischaemic heart diseases. Acute coronary syndrome is the term used to include various ischaemic heart conditions like non-ST-elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), and unstable angina. According to the World Health Organisation, 29% of mortality is caused by cardiovascular diseases. As far as the statistics of the United States regarding CVD deaths are concerned, almost 665,000 people die from CVD each year. The percentage of STEMI among all cardiovascular diseases is 20%. That is, the complement of myocardial infarction is almost 50 times more significant in the Asian population as compared to the European population<sup>17</sup>. In Pakistan alone, a vast number of deaths are contributed by STEMI. Overall statistics of STEMI mortality in Pakistan are not available, yet several studies suggest that STEMI is causing numerous deaths each year<sup>18</sup>.

### STEMI treatment programs

STEMI treatment program consists of reperfusion

strategies like thrombolytic (TL) therapy and primary percutaneous coronary intervention (PPCI). But in comparison to TL therapy, there is strong evidence that PPCI has improved outcomes in decreasing overall short-term death, stroke, and non-fatal re-infarction. The development of the streptokinase from its discovery to its current use proved to be an essential milestone in the STEMI program. The STEMI and other ACS-Spectrum carry much higher death rates. Stable CAD carries about 1% mortality per year. Most of these deaths are preventable (evidence support PPCI for STEMI and early coronary intervention with unstable Coronary Syndromes). Success in the STEMI program depends upon the door-to-balloon time (D2BT); it is the time from hospital arrival to the first device used in the PPCI procedure that crosses the lesions. The recommended cut-off value in the international guidelines for the door to balloon time (DTBT) is 90 minutes<sup>19</sup>. There are five essential elements in the STEMI program. They consist of early diagnosis, fast transfer to a PPCI centre, or fibrinolysis, post-MI care, and secondary prevention. There are several challenges to running a successful STEMI program in Pakistan. These include distance to PPCI centre, delay in diagnosis and journey time, variable standards among urban PPCI providers, quality controls, skilled staff, patient factors, education and awareness, economic and social barriers, limited financial resources, IT backup for ease of transfer and recording of PPCI activity,

population burden. We need to develop a national program that can be affordable, deliverable and adaptable to local needs. We may not reach the international gold standards, but we need a concerted effort to upgrade logistics and infrastructure to run a successful STEMI program.

### **PPCI vs fibrinolysis**

Fibrinolytic therapy (thrombolytic therapy) for STEMI activates plasminogen to form plasmin, which then lyses acute blood clots by cleaving the fibrin cross-links causing thrombus breakdown<sup>21</sup>. In contrast, Primary Percutaneous Coronary Intervention (PPCI), also known as coronary angioplasty, is a procedure used to treat the narrowed coronary arteries of the heart by placing a stent to open them. The PPCI is more effective ST-segment resolution compared to thrombolysis<sup>20</sup>. Although fibrinolytic therapy significantly lowered STEMI deaths; it is no longer the best treatment available compared to PPCI nowadays. The thrombolytic therapy only restores <50% Culprit vessel patency and has high bleeding risk<sup>22</sup> as compared to fibrinolysis, nearly 95-100% patency rate PPCI<sup>23</sup>.

To establish a PPCI program, an advanced set-up is required. It is a relatively expensive procedure and needs a highly skilled team of 4-6 persons round the clock<sup>24</sup>. The fibrinolysis is cheap, readily available, requires less equipped to set up and no need of a highly skilled team. The PPCI also decreases the rate of overall death, stroke and non-fatal re-infarction.

### **The current situation in Pakistan**

As South-East Asia faces a cardiovascular epidemic, a study conducted in 2008 suggested that favourable outcomes can be achieved at a tertiary care teaching Hospital (National Institute of Cardiovascular Diseases Karachi, Pakistan)<sup>25</sup>. The reported in-hospital mortality was 5.3%. The mean door to balloon time was 98.4 minutes. Procedural success was achieved in 98.2% of cases<sup>26</sup>. A comparative study was conducted at the Punjab Institute of Cardiology in Lahore. The procedural success of the primary percutaneous coronary intervention was less prevalent, and the mortality rate was more in females as compared to males. The outcomes of PPCI reported were more adverse in females as compared to males<sup>19</sup>. The results of a meta-analysis conducted in 2019 compared PPCI vs CABG

mortality in older individuals. PPCI was associated with a lower rate of early stroke but caused higher mortality with advancing age as compared to patients who underwent CABG<sup>20</sup>. A study conducted in Kulsoom International Hospital, Islamabad, demonstrated that favourable outcomes could be achieved in MI patients with PPCI when the average door to balloon time was 35 min. A study conducted at the Pakistan Institute of Medical Sciences (PIMS) in 2013, Islamabad, concluded that PPCI was technically successful in all patients. There is one reported death three months after PPCI. A study conducted at the National Institute of Cardiovascular Diseases, Karachi, from 2017 to 2018 reported positive outcome after PPCI. The mortality rate was 6.3% after six months of PPCI<sup>21</sup>. Therefore different studies conducted in different cities of Pakistan showed that PPCI has an overall positive outcome in patients having cardiovascular diseases, but its effects on mortality depend on various conditions, including door to balloon time, comorbidities etc.

### **Objectives of the PPCI program:**

Due to STEMI mortality in Pakistan, the PPCI program is being developed to reduce the mortality rate of STEMI. The main objective of the PPCI program is to reduce mortality from STEMI as soon as possible<sup>22</sup>. The PPCI program is an effective way to limit the incidence and prevalence of STEMI. The second objective of the PPCI program is to replace fibrinolysis therapy with the primary percutaneous coronary intervention (PPCI) as it is more effective compared to thrombolysis due to achieving higher patency rates in culprit's vessel and favourable clinical outcomes at three years of follow-up<sup>23</sup>. The DANAMI-2 and PRAGUE-1 & 2 trials (and the ensuing meta-analysis by Keeley et al.) provide strong evidence in favour of the PPCI program<sup>27</sup>.

### **PPCI models:**

Worldwide, numerous models for the PPCI program have been implemented depending on the healthcare infrastructure. All these models have been tested and evaluated for their effectiveness. Hub and Spoke model is one of the most widely accepted models of the PPCI program.

### **Hub and Spoke Model:**

This is the most prevalent and popular model for the implementation of a PPCI program. The basic princi-

ple of the hub and spoke model is centralised dissemination of services working in coordination with peripheral centres to decrease the mortality resulting from coronary heart diseases. The central hub, as the name shows, consists of type A hospitals. These centres provide the utmost care and specialised staff 24/7. The accident and emergency teams are also available 24/7 to manage any emergency.

Facilities like PPCI, intensive care units, Cath labs, ITU, and operation theatres are available. The centres are specialised to respond to an emergency call in less than 150 minutes. All these facilities make Hub a Central point of dissemination of services across the state. The admission criteria for admitting patients into the hub hospitals is well-defined. These hubs are working in coordination with smaller hospitals and care centres. These care centres are labelled as Type B centres. The type B centres (spoke centres) are working on a smaller scale as compared to the Hub hospitals. The primary medical facilities are available in spoke centres all the time. It confers its services to the patients that are outside the PPCI transfer zones. Primary and immediate care is given to the patients. The centres are specialised in the diagnosis and treatment of STEMI. These centres provide early intensive pharmacotherapy. Local protocol for initiation of treatment and care are carefully followed.

The facilities for arranging a transfer to the hub are available. The success of the hub and spoke model lies in the effectiveness of the IT infrastructure. Communication between the hub and spoke centres is essential. The coordinated communication involves the sharing of patient information like history, lab investigations, angiograms, echocardiograms, and ECGs. Spoke centres also report previously failed thrombolysis cases. The spoke centres keep that record of the patients, and this data is compiled in the national database. An additional advantage of Hub hospitals is the research area working for the betterment of health care.

### **PPCI in Europe and UK:**

The importance of PPCI is emphasised in Europe and the United Kingdoms. The total population of the UK is 66 million<sup>28</sup>. The European society of cardiology recommends that there should be a state-of-the-art PPCI centre for 0.6 million to 1 million people<sup>29</sup>. This

number is expected to decrease in future as the importance of the PPCI program is increasing day by day. The number of PPCI centres is determined by the PPCI rate per million population. Healthcare policies are being modified to accomplish the goal of a straightforward approach to a PPCI centre for each individual.

### **Hurdles in PPCI**

Fibrinolytic therapy is associated with more haemorrhagic episodes, recurrent MIs and ischaemia as compared to primary percutaneous coronary intervention. The PPCI has shown promising results in STEMI patients, but the lack of a coordinated approach to the delivery of this service is a significant barrier in the process of delivering Primary PCI for STEMI. Inadequately trained paramedics at some referring hospitals is a significant barrier in providing PPCI service. The geographical barriers cause a major hurdle, as patients may have to travel a long distance. The lack of transport facilities can lead to adverse events. Direct transport of patients with STEMI to cardiac catheterisation labs can help in reducing the door to balloon time may result in better clinical outcomes. As PPCI has become recommended nowadays for reperfusion STEMI patients, significant changes in its delivery system are required necessary to implement a PPCI program. The financial costs of PPCI can be expensive and hence is a major barrier, especially in a developing country such as Pakistan. The lack of public awareness in our community will be a significant cause of prolonged ischaemic time and very likely to result in poor clinical outcomes. Hence a concerted effort by media would be required for public awareness and education. The low availability of experienced PPCI centres and PPCI teams is still a big hurdle to overcome for the treatment of STEMI. However, the Pakistan Cardiac Society can help to sort this out.

### **Current Scenario and Real-World Issues in Pakistan:**

Only about 10% of STEMI patients or less get standard gold treatment (PPCI). Almost 70% of STEMI patients are treated with fibrinolysis. The remaining 20% fail to receive even any treatment<sup>29</sup>. There are several reasons for not receiving any treatment, which includes or late diagnosis, late presentation and affordability to have PPCI. The lack of facilities in rural areas a long distance

away from the major cities having PPCI centres is a worldwide issue. There is no proper training of the first responders (Ambulance crew & paramedics). Therefore, it may not be realistic to achieve a significant majority of patients. Therefore, a comprehensive training program will be required for the ambulance crew (1122) and paramedics.

### Stakeholders and Their Role

Prehospital management (PHM) improves clinical outcomes in ST-elevation myocardial infarction (STEMI) by reducing reperfusion delay. This is the responsibility of the stakeholders<sup>30</sup>. If all stakeholders perform their tasks, the STEMI mortality and morbidity can be significantly reduced.

There are the following stakeholders in the PPCI program:

- Government (Provincial & Federal)
- Ambulance services
- Pakistan Cardiac Society
- CARE Providers (Government & Private Hospitals)
- Citizens

The government must make plans, policies and provide resources involving the Pakistan Cardiac Society and the Provincial Governments. The Pakistan Cardiac Society will have a central role to keep checks on the care providers. It should also ensure quality, protocols and policies, and raise awareness in the medical community and public. It should also have control over the adequate training program for the cardiologists to provide a high-quality PPCI service measured by the clinical outcomes.

The role of the ambulance services is pivotal in providing a uniform quality PPCI program. In the Punjab province, there is already a footprint in the form of 1122 available. There are other NGOs led ambulance services (Eidhi & Chhippa) also available in various cities. They can also be trained and included in the implementation of the PPCI program.

### Conclusion:

Cardiovascular disease is the leading cause of worldwide mortality. PPCI is an emerging strategy to establish normal blood flow in the stenosed vessel of the heart. Ischaemic heart disease is highly prevalent in both

developed and developing countries. Although there is no reported figure related to mortality data in Pakistan, the reported mortality rate of available research studies is alarming. Pharmacological therapy, such as thrombolytic therapy used within 12 hours of the patient presentation, shows some adverse events in STEMI patients (i.e., stroke and infarcts). PPCI shows promising results in STEMI patients when this approach is used timely, keeping in view the ECG findings and ongoing ischaemia. The procedural success rate of PPCI is higher in patients having cardiovascular diseases, and we need an architectural STEMI treatment program that helps in providing prompt treatment to STEMI patients. PPCI program suffices the need for an effective mechanism for disseminating channelised care to patients afflicted with STEMI. Hub and Spoke model is of practical significance. It ensures the provision of emergency and OPD services to all. The coordinated effort of stakeholders and policymakers is an index to the success of the STEMI program.

### Salient Points:

- 1- Cardiovascular disease is the leading cause of mortality worldwide.
- 2- Due to greater bleeding tendencies with the use of fibrinolytic agents, PPCI is the preferred treatment to reperfuse the ischaemic heart tissue.
- 3- Early diagnosis of STEMI and prompt transfer of these patients to PPCI centre is necessary to reduce mortality associated with myocardial infarction.
- 4- Hub and spoke model is the popular model that centralised dissemination of services by working in coordination with peripheral centres to decrease the mortality resulting from coronary heart diseases.
- 5- Geographical barriers, inexperienced first responders, financial costs, lack of PPCI centres and public awareness are the hurdles that are encountered in proper implementation of program. These factors should be addressed to decrease the door to balloon time for better clinical outcomes in these patients.

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