

## Pharmacoinvasive strategy for ST – Segment Elevation Myocardial Infarction : Paradigm shift in Indian scenario

Coronary Artery Disease (CAD) is the leading cause of morbidity and mortality in India. It is estimated that, over 65 million people will be affected by CAD by the year 2015<sup>1</sup>. CAD occurs in Indians almost 5 to 10 years earlier, resulting in loss of potentially productive life years<sup>2</sup>. The prevalence rates of CAD in India are increasing in both urban and rural population<sup>3</sup>. Approximately 3-4% Indians in rural areas and 8-10 % in urban areas have CAD<sup>4</sup>. The growth of CAD is also observed in the poor and middle aged Indians which is a reason for concern<sup>5</sup>. ST elevation myocardial infarction (STEMI) is one of the serious complication of CAD, resulting from sudden occlusive thrombus formation in the epicardial coronary arteries<sup>1</sup>. In the CREATE registry over 60% of acute coronary syndrome patients had STEMI, as compared to 40% of patients from developed countries<sup>6</sup>.

Timely reperfusion is the most effective treatment of the STEMI<sup>7</sup>. Early reperfusion results in limiting the amount of myocardial damage which in turns results in better left ventricular function and low mortality<sup>8</sup>. The two ways of achieving reperfusion are either through pharmacological or through mechanical means. Though primary percutaneous coronary intervention (PCI) achieves immediate and sustained patency of infarct related artery (IRA), unavailability and transport delays have restricted PCI to a small proportion of eligible patients<sup>9</sup>. Even in developed nations, like the USA, only 25% of hospitals are capable of primary PCI, and are mostly located in urban areas<sup>10</sup>. Data from Create registry shows that only 9% of patients with STEMI underwent Primary PCI. 6 Primary PCI procedures formed only 17% of total coronary interventions in the year 2013 in India<sup>11</sup>. Tenecteplase (TNK) is a fibrin specific lytic agent with improved patency rates<sup>12</sup>. According to the ACC/AHA guide lines, there is no preference for either thrombolytic therapy or PCI in STEMI if the presentation is less than 3 hours after symptom onset<sup>13</sup>.

Also PCI related delay of more than 60 minutes might negate the potential advantage of primary PCI over immediate thrombolysis in terms of death<sup>14</sup>. Patients can also undergo coronary angiography safely 3 hours after administration of TNK<sup>15</sup>. A pharmacoinvasive strategy, consisting of initial timely fibrinolysis, to open the infarct related artery, followed by early PCI is an alternative approach, particularly in developing countries like India, where catheterisation facilities are limited to major cities<sup>9</sup>.

Guidelines recommend a primary percutaneous coronary intervention (pPCI) as the preferred reperfusion

modality in patients presenting with ST-segment elevation myocardial infarction (STEMI). Because most STEMI patients initially present to hospitals without PCI facilities, performing a pPCI in a timely fashion constitutes a significant logistic challenge in many healthcare systems across the world. Despite concerted efforts to decrease transfer times, PCI related system delays remain substantial in many countries. Because these delays clearly have an unfavorable effect on morbidity and mortality, early fibrinolysis, followed by timely angiography often constitutes a faster reperfusion option in many patients than transfer for standard primary PCI.

Numerous studies tested the combination of fibrinolysis with or without glycoprotein IIb/IIIa inhibition immediately followed by PCI or facilitated PCI as a means to early and sustained reperfusion of the infarct artery. Compared to primary PCI, the facilitated approach results in higher mortality; nonfatal reinfarction; bleeding; and stroke, including hemorrhagic stroke. The caveat is that if primary PCI is not an option, and fibrinolytic therapy is part of the primary reperfusion strategy, a strategy of routine or adjunctive PCI is superior to rescue or selective ischemia-guided PCI with respect to adverse events. This approach is now referred to as a pharmacoinvasive strategy in lieu of the terms facilitative or rescue.

In the Strategic Reperfusion Early After Myocardial infarction (STREAM) study, they explored the strategy of pre-hospital fibrinolysis with bolus tenecteplase given before transport to a PCI-capable hospital, followed by timely coronary angiography, in STEMI patients presenting. The primary endpoint was the composite of death, shock, congestive heart failure and reinfarction. At 30 days, they found that the pharmacoinvasive (PI) approach was associated with a nominally (not statistically significant) lower primary endpoint compared to primary PCI. Because of an excess of bleeding complications in the elderly, including intracranial hemorrhage (ICH), the dose of tenecteplase was reduced by 50% in patients above 75 years of age, after enrolling about 20% of the ultimate study population. After implementing the age-adjusted dose, no more ICH were seen in patients 75 years of age or older assigned to the PI arm, but a small non-significantly increased risk of ICH remained in the total population studied. We also observed a non-significant 1.5% absolute lower incidence of both cardiogenic shock and congestive heart failure in the PI arm. In the CAPTIM study, prehospital fibrinolysis within 3 hours but unable to undergo primary PCI within 1 hour.

In the subset of STEMI patients presenting within two hours of symptom onset was associated with lower 30-day rates of both cardiogenic shock and death, as compared to transfer for primary PCI. A combined analysis of the CAPTIM and WEST studies also suggests a beneficial effect at one year from a PI therapy in patients presenting early after symptom onset. Furthermore, the 5- year data from the French FAST-MI registry suggested that fibrinolysis administered early in the pre-hospital settings resulted in lower mortality than pPCI during long-term follow-up.

A pharmaco-invasive strategy is a safe and effective strategy in patients presenting with STEMI to centres without cath lab facilities. Further randomized studies are needed to compare this strategy with the primary angioplasty strategy not only in centers where primary PCI is not available but also in those centers where primary PCI facilities are available, especially in terms of number of stents saved and number of procedures being avoided. Studies also are required to see whether any particular age group benefits more with pharmaco-invasive strategy and whether the time of presentation has any influence on selecting the type of treatment.

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