

## Management of Acute ST-Elevation Myocardial Infarction: Reperfusion Options

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### Abstract

Primary percutaneous coronary intervention and thrombolysis remain therapies of choice for patients presenting with ST-segment elevation myocardial infarction (STEMI). Clinical outcome in the management of acute STEMI is dependent on myocardial reperfusion time and reperfusion strategies. Optimisation of these strategies should take into consideration logistical limitations of the local medical systems and the various patient profiles. We review the reperfusion strategies and its history in Singapore, comparing its clinical application with that in some developed Western countries.

Ann Acad Med Singapore 2010;39:927-33

**Key words:** Acute Myocardial Infarction, Primary Percutaneous Coronary Intervention, ST-segment Elevation Myocardial Infarction, Thrombolysis

### Introduction

Cardiovascular disease is a leading cause of death globally. More than 920,000 myocardial infarctions (MI) are diagnosed annually in the United States.<sup>1</sup> Of these, about 500,000 ST-elevation myocardial infarctions (STEMI) are estimated to occur each year.<sup>2</sup> More than 6000 MI were diagnosed in Singapore in 2007, of which around 2000 were STEMI (Singapore Myocardial Infarction Registry). Comprehensive management of STEMI is a complex healthcare problem, requiring expensive hospital-based infrastructure and highly trained medical personnel. Outcomes are dependent on the patient's immediate environment, pre-hospital access and transportation, and in-hospital care. The time from the onset of symptoms to the reperfusion of the infarct related artery, often measured in minutes, is crucial to the clinical outcome of the patient.

In providing options for myocardial reperfusion, hospitals may be divided into those with primary percutaneous coronary intervention (PCI) capability and those without. In the United States, approximately 60% to 70% of patients were presented to the hospitals without PCI capability. The National Registry of Myocardial Infarctions-3 and -4

(NRMI-3,-4) and the GRACE (Global Registry of Acute Coronary Events) registry show that only a small proportion of patients who are transferred to specialised hospitals for primary PCI, achieve door to balloon times recommended by the American College of Cardiology (ACC)/American Heart Association (AHA).<sup>3,4</sup> This is unlike in Singapore where transport and access issues are easier to solve, as travel time by ambulance is shorter and public institutions are generally all PCI-capable.

The goal of this paper is to review reperfusion options in STEMI in order to optimise management based on efficacy, safety and logistical limitations of potential treatments.

### Percutaneous Coronary Interventions

Primary PCI within 90 minutes of first medical encounter is recommended as a treatment of choice for patients presenting to hospitals with PCI capability.<sup>5</sup> Multiple randomised clinical trials have demonstrated superiority of primary PCI over fibrinolytics in STEMI within this window period.<sup>6-10</sup>

Primary PCI using bare metal stents (BMS) is an

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established choice for treatment of STEMI. Data regarding drug eluting stents (DES) in the setting of acute STEMI are limited. Initially, DES was shown to be superior to BMS during the first year of follow-up.<sup>11,12</sup> However, long-term follow-up showed increased rates of reocclusions, especially beyond a 2-year period.<sup>13</sup> Meta-analysis of 8 randomised trials comparing sirolimus and paclitaxel drug eluting stents to bare metal stents showed an overall benefit of drug eluting stents.<sup>14</sup> Drug eluting stents significantly decreased the need for reintervention over the 12 to 24 months follow up. However, the risks of myocardial infarction, death or overall risk thrombosis were not different between the types of stents. The Rotterdam registry of 505 patients presenting with acute myocardial infarction showed that the benefit of DES over BMS was not apparent after 3 years.<sup>13</sup> Long-term follow-up data were recently presented at the American College of Cardiology meeting in Atlanta, GA. The 5-year follow-up of PASSION (Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation) trial showed no significant difference in the combined end point of cardiac death, recurrent myocardial infarction or target lesion revascularisation.<sup>15</sup> The rates of major adverse cardiac events were also not statistically different. However, the results of the DEDICATION (Drug Elution and Distal Protection in ST Elevation Myocardial Infarction) trial, which was also presented at the American College of Cardiology 2010 Scientific Session/i2 summit, showed an increased risk of cardiac death in patients treated with DES at a 3-year follow-up period.<sup>15</sup> Thus, further studies on long-term comparison between DES and BMS in STEMI are needed.

At the same time, new generations of soluble stents and pro-healing stents are currently being developed. The Nanyang Technological University (NTU) in Singapore has been working on soluble stents for more than 6 years. A potential benefit of these stents is the possibility of prolonged drug release during the dissolution of the stent and the absence of foreign material remaining in the vessel. This may improve healing and decrease the long-term risk of reocclusion either via endothelial proliferation or thrombus formation, especially in cases where endothelialisation is prolonged. Other benefits could be increased probability of a repeat successful PCI on the same segment and the ability to connect bypass grafts to the previously stented artery. However, these possible benefits have yet to be shown in prospective randomised clinical trials. Recently, registry studies on the use of endothelial progenitor cell (EPC) capture stent (Genous Bio-Engineered R Stent) during primary PCI in Singapore have been published.<sup>16,17</sup> This novel stent is coated with immobilised antibodies (to CD34 antigen) on its stent struts. This is to allow capturing of circulating EPCs to promote rapid endothelialisation

and healing. The stent has been compared to sirolimus-eluting bioabsorbable polymer-coated stent and bare metal stent in STEMI.<sup>18</sup> These studies showed that it is safe and is associated with the low rates of target vessel revascularisation and no late stent thrombosis.

Primary PCI in the setting of acute STEMI has a lower rate of short-term death, non-fatal reinfarctions and strokes when compared to thrombolytic therapy.<sup>19,20</sup> There are several clinical scenarios that primary PCI will be particularly advantageous. Patients, below the age of 75, presenting with acute MI complicated by cardiogenic shock have lower mortality rates between 6 months and 1 year if treated invasively.<sup>8</sup> In addition, patients experiencing severe congestive heart failure (CHF), pulmonary edema, haemodynamic or electrical instabilities should also undergo primary PCI.<sup>2</sup> Lastly, primary PCI is the treatment of choice for patients presenting with STEMI who are ineligible for fibrinolytic therapy. However, in clinical practice, even though primary PCI appears to be the treatment of choice, thrombolytic therapy is still frequently used to treat patients presenting with acute myocardial infarction.<sup>21,22</sup>

### Adjunctive Medications during PCI

Anticoagulation therapy in patients undergoing PCI is usually administered in the form of unfractionated heparin (UFH). For patients who initially receive low molecular weight heparin (LMWH) upfront, no additional doses are usually needed during PCI.<sup>5</sup> Fondaparinux, a factor Xa inhibitor, is sometimes started in patients prior to PCI. However, there is no evidence that fondaparinux is superior to UFH as it does not lower mortality or decrease the amount of bleeding complications in patients undergoing PCI. In addition, patients undergoing primary PCI have an increased risk of guiding catheter thrombosis.<sup>23</sup> It is recommended that additional anticoagulant with anti-factor IIa activity should be added if fondaparinux is used.<sup>5</sup> Fondaparinux, however, is not routinely used in Singapore.

Instead, the direct thrombin inhibitor bivalirudin has emerged as a new anticoagulant of choice for PCI. The HORIZON trial (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) found that, when compared to a combination of UFH and glycoprotein IIb/IIIa inhibitors, bivalirudin reduced the composite endpoint of death, MI, target vessel revascularisation, stroke, and major bleeding for 30 days. This was primarily due to a reduction in major bleeding.<sup>24</sup> The composite end point of death, major adverse cardiac events, reinfarction, stroke or target vessel revascularisation and bleeding were significantly reduced at 1-year follow-up.<sup>25</sup>

Glycoprotein (GP) IIb/IIIa inhibitors are often used to inhibit platelet aggregation during primary PCI. Several

studies showed better vessel patency, clinical outcomes and improvement of left ventricular function with these adjuvant agents.<sup>26,27</sup> Currently, there are 3 glycoprotein IIb/IIIa inhibitors in use: abciximab, eptifibatide and tirofiban. Abciximab is a human murine chimeric monoclonal antibody fragment that inhibits the GP IIb/IIIa receptor. Eptifibatide is a heptapeptide inhibitor of the receptor and tirofiban is a synthetic nonpeptide GP IIb/IIIa antagonist. Abciximab was evaluated in the RAPPORT (ReoPro And Primary PTCA Organization and Randomized Trial) and the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials, showing reduction in incidence of death, reinfarction, target vessel revascularisation and composite endpoint of death, disabling stroke, ischaemia-related target vessel revascularisation and myocardial infarction.<sup>28,29</sup> Some of the benefits were seen as long as 6 months after the procedure. Eptifibatide was shown to be non-inferior to abciximab.<sup>30</sup> The non-inferiority of tirofiban as compared to abciximab was shown in the MULTISTRATEGY (Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study) trial.<sup>31</sup>

### Alternatives to Primary PCI

Treating majority of patients with primary PCI would be an ideal strategy in an ideal situation. However, there are multiple constraints that limit the routine use of primary PCI. The availability of PCI-capable facilities is one of the limiting factors. Appropriate timing is another limitation. One of the studies from the United States recently showed that less than 75% of patients brought to the hospital with PCI capability achieved the ACC/AHA recommended door to balloon time of less than 90 minutes.<sup>32</sup> Delays are more substantial in patients who have to be transferred from the community hospital to specialised centres for PCI. The NRMP-3 and 4 registries showed that only 4% of patients were achieving optimal timing in such circumstances.<sup>3</sup> However, in Singapore, the median door-to-balloon time was considerably shorter.<sup>33,34</sup> This may be largely due to a smaller country size, an efficient transport system and the proximity of the population to the hospitals. Fibrinolysis was a default reperfusion strategy for STEMI previously. With the advent of primary PCI, it has become almost obsolete especially in PCI-capable centres. However, in some centres in the US and in Europe, the fibrinolytic strategy is still being used. The ACC/AHA guidelines do not state a preference between primary PCI and fibrinolysis in STEMI patients presenting within the first 3 hours.<sup>5</sup> As the time delay in door-to-balloon time increases, the mortality benefits of PCI over fibrinolysis declines.<sup>35</sup> In fact, several studies recently showed that early administration

of thrombolytics is not inferior to primary PCI, especially when patients had to be transferred to the PCI-capable facilities.<sup>36-38</sup> In a recent study analysing data from national and/or regional registries in 30 countries in Europe, primary PCI was the dominant reperfusion strategy in 16 countries, whilst thrombolytic therapy was the dominant reperfusion option in 8 countries.<sup>39</sup> The use of a primary PCI strategy varied between 5% and 92% (of all STEMI patients) and the use of thrombolytic therapy occurred between 0 and 55%. They found that significantly less reperfusion therapy was used in those countries where thrombolytic therapy was the dominant strategy. Considering all consecutive STEMI patients, the in-hospital mortality varied between 4.2% and 13.5%. The in-hospital mortality rate for patients treated by thrombolytic therapy was between 3.5% and 14% and for patients treated by primary PCI, it was between 2.7% and 8%.<sup>39</sup>

### Contraindication to Fibrinolysis and Selection of Thrombolytics

All fibrinolytic drugs have similar risks of bleeding complications including that of intracranial haemorrhage which is between 0.5% and 1.5%.<sup>40-43</sup> Thrombolytic therapy is absolutely contraindicated for people who have a known intracranial mass, arteriovenous malformation, history of intracranial haemorrhage, history of stroke within 3 months (except acute ischaemic stroke within 3 hours) or significant head or facial trauma within 3 months. Active bleeding diathesis or suspected aortic dissections are also absolute contraindications.<sup>2</sup> Relative contraindications to thrombolysis include severe uncontrolled hypertension, ischaemic stroke within 3 months, prolonged cardiopulmonary resuscitation, major surgery within 3 weeks, internal bleeding within 1 month, non-compressible vascular puncture, pregnancy, active peptic ulcer disease or current use of anticoagulants.

Several fibrinolytic agents currently being used differ with respect to fibrin affinity, fibrin specificity, method of administration (bolus vs infusion), allergic reactions and multiple other parameters. However, the majority of fibrinolytic agents have approximately the same success rates.<sup>44-48</sup> The choice should be based on the physician's prior experience, availability of the agent in the local market, allergies of the patient and a previous history of streptokinase/anistreplase administration. Recent use of streptokinase, for instance, will elicit neutralising antibody response to the agent and render its repeat use less effective.

Patients who undergo reperfusion with thrombolytic therapy should receive anticoagulation therapy for at least 48 hours.<sup>5</sup> As there may be heparin induced thrombocytopenia, LMWH or fondaparinux may be used. A 4-day treatment

with LMWH was found to have a lower incidence of 90-day reinfarctions, mortality and readmission for unstable angina when compared to UFH.<sup>49</sup>

Bleeding complication is one of the most common and feared problems of fibrinolysis. The risk of bleeding increases as doctors simultaneously use multiple agents to reduce thrombus formation and platelet aggregation. Every effort should be made for the proper choice and adjustment of each component of treatment in order to decrease potentially life-threatening complications.

One of the more common sources of error is weight estimation. Very often, patients are not familiar with their exact weight and visual estimation of the body weight may lead to substantial errors.<sup>50,51</sup> Using a simple weight scale would be a cost-effective method of decreasing this error. There are, however, several fibrinolytic agents which do not require any weight adjustment. For instance, both reteplase and tenecteplase may be administered as boluses, which make both agents more convenient to use.

### Facilitated PCI

Since fibrinolysis for reperfusion in STEMI does not achieve uniform success, patients who failed the initial fibrinolytic approach are usually sent for PCI. Patients who showed signs of severe heart failure, pulmonary edema, haemodynamic or electrical instabilities should undergo PCI as soon as possible. In addition, patients with failed fibrinolysis as reflected by persistent symptoms or absence of resolution of ST-segment elevation by more than 50% at 90 minutes should undergo rescue PCI as well.<sup>2,5</sup>

Facilitated PCI is a strategy of performing planned PCI on patients after pharmacologic reperfusion therapy. It has the potential to combine the best aspects of thrombolysis and primary angioplasty. However, several recent trials evaluating this strategy suggested a lack of incremental benefits and instead, there was an increase in mortality with a higher rate of bleeding complications. For example, the Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention for Acute Myocardial Infarction (ASSENT-4 PCI) trial was prematurely terminated due to increased in-hospital mortality in the facilitated PCI group versus standard PCI group.<sup>52</sup> Repeat target vessel revascularisation and re-infarction were also reported more often in the facilitated-PCI arm. On the contrary, the Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long term follow-up (ADMIRAL) trial showed that early administration of abciximab improved the success rate of stenting procedures, rate of coronary patency at 6 months, left ventricular ejection fraction and clinical outcomes.<sup>53</sup> The Facilitated Intervention with

Enhanced Reperfusion Speed to Stop Events (FINESSE) trial showed no difference in outcomes with respect to the combination of all-cause mortality, readmission for heart failure, ventricular fibrillation and cardiogenic shock when the strategy of facilitated PCI was compared to the regular approach. There was also a statistically significant increase of 3.2% of major and minor bleeding.<sup>54</sup> However, subgroup analysis of high-risk patients with thrombolysis in myocardial infarction (TIMI) score of  $\geq 3$  and symptom to randomisation site of  $\leq 4$  hours showed a significantly better 1-year survival and 90-day composite outcome of death, ventricular fibrillation after 48 hours, cardiogenic shock, and congestive heart failure.<sup>55</sup>

### Improving Reperfusion Times

In a large European study, the time reported for: (i) symptom onset to the first medical contact was between 60 and 210 minutes, (ii) first medical contact to needle time for thrombolytics was between 30 and 110 minutes, and (iii) first medical contact to balloon time for primary PCI was between 60 and 177 minutes.<sup>39</sup> There are several ways to improve the time from the initial patient contact to reperfusion. For example, in the National University Heart Centre, Singapore at the National University Hospital and in the National Heart Center, Singapore, implementations of simple and inexpensive operational measures resulted in shorter door-to-balloon time.<sup>33,34</sup> These result in better clinical outcome.<sup>56</sup> Another promising model involves training care providers (paramedics and nurses) to perform 12-lead electrocardiograms (ECGs) outside the hospitals in order to identify STEMI earlier. Several studies showed significant improvement in initial contact to reperfusion times with the employment of this model.<sup>57,58</sup> Performing a pre-hospital 12-lead ECG results in more patients undergoing fibrinolysis and interventions. This, in turn, leads to a statistically significant improvement of in-hospital mortality, compared to the patients who receive ECGs upon arrival in the hospital.<sup>2</sup>

### Changes in Reperfusion Strategies over Time in Singapore

Indeed, the choice of reperfusion therapy in the treatment of acute STEMI in Singapore closely parallels the development in the international community. Thrombolytic therapy was first introduced in Singapore in the 1980s. It was rapidly replaced by PCI as the preferred reperfusion modality in our public institutions in the mid 1990s. By 2001, both the 2 public tertiary heart centres were offering 24-hour primary PCI with nearly 100% of patients with STEMI receiving this type of treatment. Pre-hospital electrocardiogram recording by ambulance paramedics to



diagnose STEMI in the field is being piloted in Singapore to further shorten the symptom onset to reperfusion time.

## Conclusions

Primary PCI remain the cornerstones in early treatment of STEMI. Primary PCI is the treatment of choice if it can be achieved within 90 minutes from the first medical encounter. It is also the preferred method of treatment in patients whose STEMI is complicated by cardiogenic shock, severe congestive heart failure, pulmonary oedema and haemodynamic or electric instability. However, in some of the patients, primary PCI may not be achieved within the ACC/AHA recommended time. Multiple logistic and financial constraints limit its use for the majority of STEMI patients in many countries. Fibrinolysis is an alternative treatment modality. The best opportunity for decreasing morbidity and mortality lies within the first hour after the development of symptoms. Organised networks involving emergency and cardiology departments are being developed worldwide in order to facilitate optimal timing and treatment.

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