Recent Advances in the Management of Acute Myocardial Infarction

HM Mardikar*, NV Deshpande*, Parag Admane**

Abstract

Recently the reperfusion therapy in the form of Primary Percutaneous Coronary Intervention (PPCI) has become the gold standard for the treatment of Acute Myocardial Infarction. In spite of rapid revascularization either with PPCI or thrombolytic therapy, the significant number of patients develops decreased left ventricular function leading to heart failure which can increase long term mortality and morbidity. The number of strategies are being evolved and evaluated to reduce this post infarct heart failure. They are being developed at the level of optimizing the outcomes of PPCI, protection against the reperfusion injury, and novel therapies like cardiac repair and regeneration and sonothrombolysis. Thrombus aspiration using simple aspiration catheters during PPCI are getting established as a useful adjunct tool to reduce distal embolisation and consequently improving myocardial salvage. The newer antiplatelet drugs like Prasugrel and Ticagrelor may replace the Clopidogrel to reduce ischemic complications. The reduction in reperfusion injury using drugs has shown mixed results. The newer modalities like cardiac repair and regeneration using stem cell therapy looks promising but are yet to be established.

Reperfusion therapy with either fibrinolytic agents or Primary Coronary Angioplasty is the gold standard treatment of Acute Myocardial Infarction. Rapid achievement of reperfusion saves the myocardium at risk of ischemic injury. Despite advances in the reperfusion therapy there is substantial myocardial damage which may lead to heart failure. Indeed the Global Registry of Acute Coronary Events (GRACE) suggests that rates of heart failure are about 18% in either ST elevation myocardial infarction or non ST elevation myocardial infarction.1 Primary percutaneous coronary intervention (PPCI) has become the treatment of choice for acute myocardial infarction (AMI) although there remains the same uncertainty about its net effect on the risk of heart failure as with thrombolytic therapy. The Which Early ST-elevation Myocardial Infarction Therapy (WEST) trial 2 reported that the rates of heart failure at 30 days were higher in those assigned to primary PCI (18%) than in those who received contemporary pharmacotherapy (15%) or fibrinolysis combined with early PCI (14.4%). Thus myocardial damage leads to decreased left ventricular performance and increases heart failure after AMI in spite of timely reperfusion. The overall incidence of heart failure after acute myocardial infarction is almost 25%.3 Suboptimal myocardial salvage despite quick reperfusion therapy is a matter of current research and multiple strategies are being tested to minimize myocardial loss.

Recent advances to improve the outcomes of Acute Myocardial Infarction

- Strategies during PCI
  - Device based strategies
  - Distal protection devices
  - Thrombectomy devices
  - Simple aspiration catheters
  - Pharmacologic therapy Intracoronary/Intravenous
    - Streptokinase, Tenecteplase
    - Abciximab, Eptifibatide, Tirofiban
    - Adenosine
  - Remote ischemic preconditioning
    - Postconditioning
    - Cyclosporine
    - Erythropoietin

- Cardioprotection against myocardial reperfusion injury

- Novel therapies
  - Cardiac repair or regeneration with stem cell therapy
  - Sonothrombolysis

![Fig. 1: New Cardioprotective Strategies for Reducing Lethal Reperfusion Injury](image)

Impaired myocardial perfusion is not uncommon following primary PCI and results in a larger infarct size and increased mortality.4 A number of device-based or pharmacologic strategies have been studied to reduce the final infarct size. The device-based strategies are simple aspiration catheters, thrombectomy devices and distal protection devices. The pharmacologic therapies that are recently being investigated and established are intracoronary or intravenous administration of fibrinolytic or Gp IIb/IIIa inhibitors or administration of new oral antiplatelet drugs.5 Repair of infarcted myocardium with stem cell therapy is an additional modality which has produced mixed results so far. Following review will discusses the recent advances in the management of AMI (Figure 1).

Optimising the Outcomes of PPCI

Coronary thrombosis leading to acute coronary occlusion is the cause of Acute ST Elevation Myocardial infarction. Acute coronary thrombosis is caused primarily by the rupture of a coronary atherosclerotic plaque or by plaque erosion. After rupture of the fibrous cap covering the atherosclerotic plaque,
fragments of the lipid-rich core are exposed to the arterial lumen. This highly thrombogenic material causes platelet aggregation within the lipid core and on the ruptured fibrous cap, forming a mural thrombus consisting mainly of platelets, resulting in early coronary obstruction.\(^6\) Optimal management of the coronary thrombus is the key in achieving good result of PPCI. Following are the approaches to improve the outcomes of PPCI.

**Thrombus aspiration during PPCI**

Thrombus identified at the time of angiography has been associated with an increased risk of acute complications after PCI and affecting the outcome. The distal embolization of thrombus leads to no reflow phenomenon, suboptimal myocardial salvage leading to larger infarct size and ultimately reduced survival.\(^7\) Distal protection devices, thrombectomy devices and thrombus aspiration catheters have been used to improve the outcome of PCI. They have reduced distal embolization and resulted in enhanced TIMI grade 3 flow, enhanced myocardial blush and more complete ST-segment resolution. The meta-analysis of the clinical trials investigating these devices showed that the simple aspiration catheters were more effective than the mechanical thrombectomy devices or distal protection devices. The thrombus aspiration catheters have been able to reduce one year mortality and reduced the combined end point of any death, myocardial infarction or target vessel revascularization (\(P=0.011\)).\(^8\)

The results of Thrombus Aspiration Compared to Balloon Angioplasty (TAPAS)\(^9\) trial have been reported in which 1071 patients with STEMI with symptom onset within 12 hours were randomized before angiography to a simple aspiration catheter before PCI or to primary PCI alone. Adjunctive aspiration resulted in enhanced rates of normal angiographic myocardial perfusion (blush) and ST-segment resolution. At 30 days, mortality tended to be less in patients treated with thrombus aspiration (2.1% versus 4.0%; \(P=0.07\)), a trend that became significant at 1 year (\(P=0.04\)).\(^9\)

Recently the AngiJet Rheolytic Thrombectomy before Direct Infarct Artery Stenting in Patients Undergoing Primary PCI for Acute Myocardial Infarction (JETSTENT)\(^10\) trial investigated whether rheolytic thrombectomy (RT) before direct infarct artery stenting as compared to direct stenting (DS) alone to improve the results of myocardial reperfusion and clinical outcome in patients with acute myocardial infarction. The ST-segment resolution was more frequent in the RT arm as compared to the DS alone arm: 85.8% and 78.8%, respectively (\(p = 0.043\)). Although the primary efficacy end points were not met, the results of this study support the use of RT before infarct artery stenting in patients with AMI and evidence of coronary thrombus.\(^10\)

**Intracoronary Gp IIb/IIIa inhibitors**

Intracoronary administration of drugs increases local drug concentration several fold. The increased concentration of Gp IIb/IIIa inhibitors like Abciximab, Eptifibatide, Tirofiban are shown to improve the outcomes of PCI safely and efficaciously in terms of reduction in infarct size, peri-procedural MI and improved TIMI flow.\(^11\) The greatest benefits of Abciximab was observed with an anterior MI, those with impaired myocardial perfusion after the procedure, and those whose symptom-to-balloon time was \(>4\) hours when the clot may have been more organized and resistant to systemic therapy.\(^12\) The systemic administration of tirofiban at referring hospital or in the pre-hospital phase in Ongoing Tirofiban in Myocardial Infarction Evaluation study (On-TIME 2)\(^13\) study was also associated with improved clinical outcomes.

Recently the use of intracoronary versus intravenous Abciximab during PPCI was evaluated by CICERO (The Comparison of Intracoronary Versus Intravenous Abciximab Administration during Emergency Reperfusion of ST-Segment Elevation Myocardial Infarction) Trial. 534 patients of ST-segment elevation myocardial infarction undergoing PPCI with thrombus aspiration within 12 hours of symptom onset were randomized to either intracoronary or intravenous bolus of abciximab (0.25 mg/kg). No difference was noted in ST resolution between the intracoronary versus intravenous Abciximab groups. However, intracoronary administration was associated with improved myocardial perfusion assessed by myocardial blush grade and a smaller enzymatic infarct size.\(^14\)

Similarly, in the Intracoronary Eptifibatide (ICE) Trial, the intracoronary bolus administration of eptifibatide during PCI in patients with acute coronary syndromes resulted in higher local platelet glycoprotein IIb/IIIa receptor occupancy, which was associated with improved microvascular perfusion demonstrated by an improved corrected TIMI Frame Count.\(^15\) Whether delayed but localized intracoronary pharmacotherapy would be superior to early systemic administration of GPIIb/IIIa inhibitors is not yet known. It also is not known whether intracoronary therapy over and above the early systemic therapy would result in improved clinical outcomes without increased adverse events, including major bleeds. Larger randomized multicenter trials using rigorous clinical end points such as death and MI are required to further substantiate the clinical benefits of this mode of drug delivery.\(^11\)

**Adenosine**

Intracoronary administration of vasodilators such as adenosine during and after PPCI has been shown to improve flow in the infarct-related coronary artery and myocardial perfusion, and/or to reduce infarct size, but large prospective randomized trials with hard clinical outcomes are missing.\(^16\) High-dose i.v. infusion of adenosine was also associated with a reduction in infarct size, but clinical outcomes were not significantly improved.\(^17\) In ADenosine Administration during and after Primary percutaneous coronary intervention in acute myocardial infarction Trial (ADAPT), though the rate of complete ST resolution was considerably higher, administration of intracoronary adenosine after thrombus aspiration and after stenting of the infarct-related artery did not result in improved myocardial perfusion.\(^18\)

**New oral anti-platelet drugs for AMI**

Intense platelet activation and increased risk of thrombosis are the hallmarks of AMI. In patients with STEMI undergoing PPCI, stents reduce restenosis, but do not lower ischemic endpoints; while anti-platelet therapy lowers ischemic endpoints, but not restenosis. As a result, research is focusing on different combinations of anti-platelet therapy to complement PCI. Recently two new oral anti-platelet agents Ticagrelor and Prasugrel are added to list.

The investigational anti-platelet agent Ticagrelor was superior to clopidogrel in a subset of almost 8500 patients with STEMI undergoing PPCI in the Platelet Inhibition and Patient Outcomes (PLATO)\(^19\) trial. Ticagrelor, unlike the thienopyridines Clopidogrel and Prasugrel, is not a pro-drug and therefore has a faster onset of action with less variability than the thienopyridines. It causes stronger platelet inhibition, particularly in the early phase, and it is reversible, which maybe an advantage in reducing bleeding. The ticagrelor group suffered fewer cardiovascular events, with the primary end point of MI, stroke, or vascular death being significantly reduced by 15% with ticagrelor compared to clopidogrel (hazard ratio 0.85; \(p=0.02\)), without any increase in major bleeding complications.
Definite stent thrombosis was significantly lower among the STEMI patients receiving ticagrelor compared to those receiving Clopidogrel.

In TRITON-TIMI 38 trial\(^{20}\) 3534 participants presenting with STEMI were randomly assigned either prasugrel 60 mg loading, 10 mg maintenance \(n=1769\) or clopidogrel 300 mg loading, 75 mg maintenance \(n=1765\). The primary endpoint (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) was reduced significantly by Prasugrel at 30 days and at 15 months. The incidence of stent thrombosis was also reduced. Although bleeding was also similar between the Prasugrel and clopidogrel treatments, major bleeding after coronary-artery bypass grafting was significantly higher with prasugrel \((p=0.0033)\).

**Cardioprotection Against Myocardial Reperfusion Injury**

The restoration of blood flow to ischemic myocardium sometimes leads to myocardial injury termed as reperfusion injury which can be more detrimental than ischemia itself and paradoxically reduce the advantage of early restoration of blood flow.\(^{21}\) This type of injury is called as *Ischemic–Reperfusion* injury. The ischemic–reperfusion injury is lethal for the cardiac myocytes which were viable earlier and increases the infarct size. Studies in animal model suggest that lethal reperfusion injury accounts for up to fifty percent of the final size of myocardial infarct.\(^{22}\)

The reperfusion injury can take the form of\(^{21}\)

- Myocardial stunning (transient LV dysfunction occurring after restoration of blood supply),
- No reflow phenomenon (inability to restore blood supply at micro-vascular level even after opening of epicardial infarct related artery),
- Reperfusion arrhythmia
- Lethal reperfusion injury leading to extension of infarct.

The mediators of reperfusion injury are oxidative stress,\(^{23}\) calcium paradox\(^{24}\) and pH paradox.\(^{25}\) Restoration of blood supply brings the additional oxygen to the site of injury adding to the oxidative stress. Intracellular and mitochondrial calcium overload causes hypercontracture of the heart cells and opening of mitochondrial Permeability Transition Pores (PTP). Opening the channel collapses the mitochondrial membrane potential and uncouples oxidative phosphorylation, resulting in ATP depletion and cell death.\(^{26}\) During myocardial ischemia, the mitochondrial PTP remains closed, only to open within the first few minutes after myocardial reperfusion in response to mitochondrial Ca\(^{2+}\) overload, oxidative stress, restoration of a physiologic pH, and ATP depletion. Another important mediator of reperfusion injury is Reperfusion Injury Salvage Kinase (RISK) pathway; these are group of protein kinases which are activated during reperfusion injury. It mediates a form of programmed cell survival.\(^{27}\) The drugs which target these pathways are cyclosporine, erythropoietin, statins, glucagon-like peptide 1 and atrial natriuretic peptides. The new strategies for protection against reperfusion injury are Ischemic conditioning, targeting the RISK pathway, targeting mitochondrial PTP (Figure 1).

**Remote ischemic preconditioning**

Reduction in infarct size applying brief repeated episodes of non-lethal ischemia and reperfusion to the canine heart before prolonged lethal ischemia provided the first evidence that the myocardium possesses innate cyto-protective mechanisms (Murry and co-workers, 1986).\(^{28}\) They showed that exposure of the circumflex coronary artery territory to brief periods of ischemia (four cycles of 5 min of ischemia followed by reperfusion) before 40 min of complete ischemia substantially reduced the extent of infarction after restoration of blood flow. However, using ischemic preconditioning in clinical setting is the biggest challenge as the onset of acute coronary occlusion cannot be predicted and patients present only after coronary occlusion with STEMI. To overcome these issues, the idea of applying the cardio-protective stimulus to an organ or tissue remote from the ischemic region i.e. remote ischemic preconditioning was first conceived by Pryzklenk et al.\(^{29}\)

The ischemic conditioning can be defined as preconditioning when performed before reperfusion and post-conditioning when performed after reperfusion. In clinical practice the remote ischemic preconditioning is carried out with brief occlusion of blood flow to either upper or lower limb by periodically inflating and releasing the blood pressure cuff. The remote ischemic preconditioning is believed to activate changes in intracellular kinase and mitochondria that are cardio-protective. In addition transient limb ischemia releases a low molecular weight (<15 kDa), hydrophobic, circulating factor that induces protection against myocardial ischemia and reperfusion injury. This needs opioid-receptor activation and is independent of local neurogenic activity\(^{30}\) (Figure 2). In a trial by Nielsen et al,\(^{31}\) remote ischemic conditioning was performed in patients with STEMI en route to hospital for PPCI using 4 cycles of 5-min blood pressure cuff inflation-deflation. The primary endpoint was myocardial salvage index at 30 days after PPCI, measured by myocardial perfusion imaging as the proportion of the area at risk salvaged by treatment. It was observed that remote ischemic conditioning before hospital admission increases myocardial salvage, and has a favourable safety profile.

The ischemic post-conditioning is carried out by transient balloon occlusion of the infarct related artery. The remote ischemic post-conditioning is carried out by transient occlusion of other than the infarct related coronary artery. The cardio-protective effects of ischemic post-conditioning in patients treated with PPCI were evaluated using Magnetic Resonance by Lonberg et al. One hundred eighteen patients with STEMI undergoing PPCI were randomly assigned to have either conventional PPCI or PPCI with post-conditioning. Post-conditioning was performed immediately after opening of infarct related artery with 4 balloon occlusions, each lasting 30 seconds, followed by 30 seconds of reperfusion. Use of post-conditioning resulted in 19% relative reduction in infarct size.\(^{32}\)

**Pharmacological agents to Minimize Reperfusion Injury**

Cyclosporin inhibits opening of mitochondrial PTP and protects myocardium from reperfusion injury. Animal studies...
proof of concept human study, Mewton et al. used intravenous cyclosporine to reperfusion reduces myocardial infarct size by almost 50%. In patients with acute myocardial infarction, cyclosporine was associated with reduction in infarct size. Almost half of the patients were studied using cardiac MRI at 5 days and 6 months which showed that cyclosporine treated patients had persistent benefit at 6 months with smaller infarct size and no detrimental effect on LV remodelling.

Pharmacologic agents like erythropoietin are postulated to reduce infarct size by activating RISK pathway. However, studies using erythropoietin showed no benefit on erythropoietin on infarct size, ejection fraction or LV remodelling. Rather, a higher incidence of adverse effects was observed in patients treated with erythropoietin. Other agents which activate RISK pathway include glucagon like peptide 1 and Atorvastatin.

Cardiac Repair and Regeneration

A number of human tissues like skin, gut, liver and skeletal muscles have tremendous regenerative capacity. However, human heart has only a limited capacity to regenerate and the networks that govern this process are ill defined. Thus, ischemic injury to myocardium leads to formation of scar as myocardium. Studies in metazoans like newt and zebrafish indicate that myocardial regeneration and scar formation are inversely related. Although human heart shows a cellular turnover, it is very slow at 1% cell turnover per year, which is grossly inadequate for myocardial regeneration following ischemic injury. On this background multiple strategies for myocardial regeneration are being tested. Different cell populations have been studied for cardiac regeneration and repair including bone marrow derived cell, skeletal myoblasts, embryonic stem cells, resident cardiac progenitor stem cells, adipose tissue derived cells and umbilical cord derived cells so far. The ideal stem cell should be clonogenic i.e. it is capable of forming colony of cells derived from single cell and all those cells should have the same genetic constitution and pluripotent. The commonly used cell populations in human trials are bone marrow cell, circulating progenitor cells and granulocyte colony stimulation factor mobilised cells (Figure 3).

The mechanism by which these cells improve the cardiac performance is as follows:
- Originally it was thought that injected cells trans-
- differentiate into cardiac phenotype but subsequent studies failed to support these initial observations. The fusion of injected cells with cardiomyocyte was thought to be responsible for trans-differentiation.
- Another possible mechanism was improved vascularisation in injured area by physical incorporation of injected cells into new capillaries or in peri-vascular area.
- The injected cells secrete the paracrine factors that exert cardio-protective effect, recruit resident cardiac progenitor cells and alter the mechanical properties of myocardial scar tissue.

The cell delivery routes available are intravenous infusion, intracoronary injection and intra-myocardial injection. The intravenous infusion is easiest however significant number of cells is trapped in lungs, liver and spleen and only small number of cells reach myocardium. Intracoronary injection is most often sought in clinical practice because of the advantage of direct delivery of cells at the site of requirement. But the important limitation of this route is that cells cannot be delivered to occluded infarct related artery. The cells may also fail to reach the target area due to micro-vascular obstruction with patent epicardial artery.

Clinical Applications of Stem Cell Therapy

More than fifteen clinical trials have been conducted in studying the bone marrow cell infusion in AMI. The cells have been injected through infarct-related artery between one to eighteen days after PPCI. The infusion of cell was safe in short term and mid- term follow up. There was no increased incidence of ventricular tachycardia or micro-reinfarctions. However, some patients had aggravation of coronary atherosclerosis leading to increased coronary event and an increased risk of in-stent restenosis due to neointimal hyperplasia was noted. The clinical trials showed mixed results some showing improvement in ejection fraction, reduction in infarct size and even improved cardiovascular outcomes. Major trials like BOOST, REPAIR-AMI and TOPCARE-AMI have produced mixed results in terms of therapeutic benefit. MRI in the BOOST and the ASTAMI study revealed that bone marrow cell transfer neither improved LV ejection fraction nor decreased the infarct size. However, in the largest study the REAPIR-AMI study the mean (SD) absolute improvement in LVEF on LV angiography at 4 months was 5.5 % in the bone marrow cell group as compared to 3.0 % in the placebo group (p < 0.01). A sub-group analysis showed that patients with impaired baseline LVEF (< 48.9 %) and patients receiving cell transplantation more than four days after infarction derived most benefit.

The Transplantation of Progenitor Cells And Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI) trial investigated both safety, feasibility, and potential effects on parameters of myocardial function of intracoronary infusion of either circulating progenitor cells (CPC) or bone marrow-derived progenitor cells (BMC in patients with acute myocardial infarction (AMI). Contrast-enhanced magnetic resonance imaging after one year revealed an increased EF (p < 0.001), reduced infarct size (p < 0.001), and absence of reactive hypertrophy, suggesting functional regeneration of the infarcted ventricles. 5 years follow-up analysis of patients treated with intracoronary infusion of CPC or BMC after AMI demonstrates an excellent clinical long-term safety profile, excludes the induction of intra-myocardial calcification, and documents sustained improvement of cardiac function as evidenced by persistently normal NT-proBNP serum levels demonstrating absence of overt heart failure.

Recently, the effect of bone marrow cell transfection over...
LV remodelling after AMI was studied in REPAIR-AMI and BONAMI trial. The REPAIR AMI trial investigated the effect of intracoronary administration of bone marrow-derived mononuclear cells (BMC) within 7 days after successful reperfusion therapy for AMI, on early (within 4 months) LV remodelling processes assessed by quantitative LV angiography. The study showed that intracoronary infusion of BMC is associated with a significant improvement in LV remodelling parameters within the first 4 months after AMI compared with optimal standard therapy alone, including acute revascularization and secondary preventive therapy. The BONAMI trial has also revealed that the Intracoronary acute revascularization and secondary preventive therapy.

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Sono-thrombolysis

The use of Ultrasonic waves along with the fibrinolytic agent, described as Sono-thrombolysis, has been shown to improve the outcomes of patients with Strokes. The application of Ultrasonic waves can either be done through intravascular route or trans-cutaneous route. The trans-cutaneous route is more advantageous as it can be made available universally. Recently two studies have shown the benefit of Sono-thrombolysis in AMI. In the first observational study, 25 patients with ST-elevation AMI were subjected to thrombolytic therapy and sono-thrombolysis. Thrombolysis in Myocardial Infarction (TIMI) grade 2 to 3 flow was achieved in 84% of these patients. In another multicenter study randomized 400 patients to tenecteplase alone or to tenecteplase and sono-thrombolysis. There was no difference in the arterial patency rate of TIMI grade flow between the 2 groups. However, ST-segment resolution was better in patients who received tenecteplase and sono-thrombolysis compared with those who received tenecteplase alone. The exact mechanism of benefit of sono-thrombolysis is not known, however the nitric oxide release by vibrating endothelial cells and opening of collateral channels have been contemplated.

Conclusion

Treatment approach of AMI is evolving rapidly with the development of newer strategies during and after PCI. Thrombus aspiration using simple aspiration catheters during PPCI has emerged as a useful adjunct tool to reduce distal embolization and consequently improving myocardial salvage. More complicated thrombectomy devices like rheolytic thrombectomy are useful but may not offer major advantage over aspiration catheters. Use of GP IIb/IIIa inhibitors by intracoronary route has been shown to be safe and does offer some advantage over intravenous route in selected patients. Stronger antiplatelet drugs like Prasugrel and Ticagrelor seem to have added advantage in preventing acute, sub-acute and chronic ischemic complications and are likely to replace clopidogrel. Reperfusion injury is recognized as a major obstacle and various strategies to address this have been tried in last few years including remote ischemic preconditioning, ischemic post-conditioning and use of pharmacologic agents like cyclosporine with mixed results. Cardiac regeneration is another area giving hope to millions of patients with damaged myocardium due to STEMI. However, the results of the recent trials are inadequate for recommending this strategy as routine in clinical practice. Ongoing research in the area of myocardial regeneration using different types of stem cells is promising and is likely to open a new window of opportunity for the patients of AMI. Preliminary studies of Sono-thrombolysis as adjunctive therapy have shown promising results for improving outcomes. This therapy can be exciting in view of its cost effectiveness and wide applicability in Indian Scenario. Larger multicenter studies will be needed to establish role of sono-thrombolysis in management of AMI.

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