Introduction
ST elevation myocardial infarction (STEMI) commonly results from disruption of a vulnerable plaque with superimposed thrombus formation resulting in acute occlusion of the infarct related artery (IRA) which culminates into acute myocardial necrosis. Quick and sustained opening of infarct related artery with good TIMI Grade III flow coupled with good myocardial tissue perfusion is the cornerstone of treatment of STEMI. If the microcirculation is patent, opening of IRA transforms into myocardial tissue perfusion. However, if there is microvascular dysfunction with slow or no flow, opening of the IRA will not produce myocardial tissue perfusion and additional pharmacotherapy has to be utilized to improve it as shown in Fig.1.

The major advances in pharmacological treatment are outlined in Table -1

Achievement of quick myocardial reperfusion
Currently, myocardial reperfusion can be achieved in STEMI in a spell of 2-3 minutes and this indeed is a major achievement. A conjoined triple therapy is utilized for pharmacological reperfusion targeting all the 3 components of the clot, i.e. fibrin, platelet and thrombin.

1. The fibrin is targeted by bolus fibrinolytic therapy with TNK-tPA (0.53mg/kg by IV push) which takes 1/2 to 1 minute.

2. The platelets are targeted with aspirin 325 mg orally followed by 75-160 mg/day and

Table 1 : Newer aspects in pharmacological treatment of STEMI
• Achievement of quick myocardial reperfusion.
• Emerging prospects for circumventing the limitations of clopidogrel with newer antiplatelet agents.
• Prevention of bleeding: A new focus in ACS care.
• Increasing role of LMWH in STEMI and emerging role of factor Xa inhibitors.
• Improved outcome of post-fibrinolytic therapy induced hemorrhagic stroke with activated recombinant factor VII a.
STEMI: Newer Aspects in Pharmacological Treatment

Table 2: Pharmacological reperfusion in STEMI

- TNK-tPA 0.53 mg/kg IV push.
- Aspirin 325 mg orally followed by 75-160 mg/day plus clopidogrel 300 mg as a bolus dose followed by 75 mg/day.
- Enoxaparin 30 mg IV bolus followed by 1 mg/kg subcutaneously twice a day.

clopidogrel 300 mg orally followed by 75 mg/day, which takes another one minute.

3. The thrombin is targeted by LMWH (Enoxaparin) 30 mg IV bolus followed by 1 mg/kg subcutaneously twice a day.

The current pharmacological reperfusion is summarized in Table 2.

The above pharmacological regime allowed reperfusion to be achieved within 2 hours of onset of STEMI in 50% of patients. If the reperfusion is achieved in the 1st hour, the golden hour, the infarction may even be aborted.

Emerging prospects for circumventing the limitation of clopidogrel

After the CLARITY TIMI 38 and COMMIT trial, clopidogrel in conjunction with aspirin has become an integral part of therapy for STEMI. Although it provides definite benefit but several limitations of clopidogrel has erupted out which are shown in Table 3.

a. Slow onset of maximal inhibition of platelet aggregation

Clopidogrel is a pro drug and is converted to an active metabolite by a complex mechanism. Therefore the onset and peak is delayed (Fig. 2). Prasugrel, a new P₂Y₁₂ receptor antagonist, has a faster onset and earlier peak action (Fig. 2).

Table 3: Limitations of clopidogrel

- Slow onset of maximal inhibition of platelet aggregation.
- Irreversible platelet inhibition with slow recovery of function.
- Inter individual and intra-individual variability in therapeutic response.
- Increased rate of bleeding.

It is therefore likely that prasugrel may provide better benefit in STEMI compared to clopidogrel. The TRITON-TIMI 38 trial is ongoing in patient with ACS undergoing PCI (both STEMI or NSTEMI) which is comparing prasugrel in a head to head fashion with clopidogrel. The primary end point is a composite of CV death, MI and stroke.

AZD 6140 is another new P₂Y₁₂ receptor antagonist. It is a direct acting drug and therefore has quick onset and quick offset action. The PLATO trial which is enrolling 16000 patients of ACS is in progress and will compare in a head to head fashion AZD 6140 with clopidogrel. Cangrelor is the first parenteral P₂Y₁₂ receptor antagonist with a fast onset of action. It is more potent and has a quick offset action also. It is being compared in a head to head fashion with clopidogrel in an ongoing Champion PCI trial.

b. Irreversible platelet inhibition with slow recovery of platelet function

Clopidogrel is an irreversible antiplatelet agent and if a patient of ACS on aspirin plus clopidogrel needs an emergency CABG, then even if clopidogrel is stopped before CABG, there is increased bleeding with increased peri-operative morbidity and mortality. However, with the new antiplatelet agent like AZD 6140 which has a quick onset and quick offset action, the issue may be resolved in future.
c. **Inter-individual and intra-individual variability in therapeutic response to clopidogrel** (Fig. 3)

Some patients of STEMI despite intake of adequate dosage of clopidogrel continue to get ischemic events and stent thrombosis and an important reason believed to be responsible for this is the inter-individual or intra-individual variability in therapeutic response to clopidogrel. The newer agents like prasugrel, AZD 6140 and cangrelor which are more potent and provide additional antiplatelet effect even on top of clopidogrel may provide solution to this but at present there is no data available on this.

**Prevention of bleeding: A new focus in ACS care**

The ACUITY trial clearly showed that patient with bleeding has a statistically significant higher mortality. Therefore prevention of bleeding has emerged as a new focus in ACS care and attempt are being made to provide antithrombotic treatment with minimal or no bleeding.

**Increasing role of LMWH enoxaparin and emerging role of Xa inhibitor fondaparinux in STEMI.**

After the EXTRACT TIMI-25 trial, enoxaparin has become an integral part of therapy of STEMI. The trial showed a statistically significant reduction in the primary end point of death or Re-MI at 30 days by 17% and also a statistically significant (Fig. 4) reduction in the secondary end point of death, MI and urgent revascularization by 19% with enoxaparin as compared to UFH. No doubt, enoxaparin is associated with slight increase in bleeding (not intracranial hemorrhage) compared to UFH but when we consider efficacy plus safety, the balance hits in favor of enoxaparin.

Fondaparinux is a factor Xa inhibitor and has been tested head to head with UFH in OASIS-6 trial in STEMI patients and OASIS-5 trial in NSTEMI patients. The combined analysis of both the trials has shown that fondaparinux has same efficacy but less bleeding compared to UFH (Fig. 5).

**Post fibrinolytic intracranial hemorrhage**

Fibrinolytic therapy is associated with intracranial hemorrhage in 0.6 to 1.4% of patients and this is associated with higher morbidity and mortality. Of late, there has been exciting results with recombinant activated factor VIIa in intracranial hemorrhage. It limits amount of bleeding, reduces risk of death and improves survivor’s functional outcome at 90 days (Fig. 6)

**Effect of reperfusion strategies on mortality of AMI**

The effects of various reperfusion strategies on mortality are seen in (Fig. 7).

The only strategies associated with decreased mortality in STEMI are early pharmacological
Both modalities, pharmacological reperfusion or primary PCI, if carried out in the first 3 hours, produce equivalent results. However after 3 hrs to 12 hours, primary PCI is distinctly superior to pharmacological reperfusion and is the modality of choice. However because of logistic concerns and financial constraints, primary PCI is being carried out only in 5% of STEMI patients throughout the globe. If patient has cardiogenic shock, primary PCI is the modality of choice irrespective of the time of presentation.

The CAPTIM trial\textsuperscript{11} (Fig. 8) showed a very interesting data. There was a slightly lower mortality with thrombolysis than with PCI in the first 2 hours of myocardial infarction in this trial. In
a meta analysis\(^4\) of 23 randomized trials comparing pharmacological reperfusion with primary PCI there was a slightly better results with primary PCI. However the point to remember is early reperfusion and early reperfusion should be the goal.

Thus treatment of STEMI has witnessed several newer facets in its pharmacological treatment.

References