Acute ST-segment myocardial infarction—Evolution of treatment strategies

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ABSTRACT

The commonest cause of acute myocardial infarction involves the rupture or erosion of vulnerable atherosclerotic plaques followed by aggregation of platelets and subsequent thrombus formation, leading to partial or complete epicardial coronary arterial occlusion. Over the last 25 years, advancement in therapeutic options for acute myocardial infarction has resulted in substantial improvement in morbidity and mortality. As a result, the absolute risk reduction of in-hospital deaths for patients presenting with STEMI has been on the decline in the last decade. The focus of the treatment for acute myocardial infarction involves achieving epicardial and microvascular patency, prevention of recurrent ischaemic events while balancing the risk of bleeding. This involves antiplatelet and antithrombotic therapies or fibrinolytic agents when timely performance of primary percutaneous coronary intervention is not possible. We review the evolution of treatment strategies for STEMI that has contributed to the improvement in patient outcome.

Keywords: Myocardial Infarction; STEMI; PCI; Coronary Artery Intervention

1. BACKGROUND

Pathophysiology of Acute Myocardial Infarction

The commonest cause of acute myocardial infarction involves the rupture or erosion of vulnerable atherosclerotic plaques followed by aggregation of platelets and subsequent thrombus formation, leading to partial or complete epicardial coronary arterial occlusion [1,2]. Microcirculatory perfusion is compromised by this thrombotic process due to reduced coronary artery blood flow through fixed epicardial stenoses, as well as distal embolisation of thrombus. During the early phase of coronary occlusion, the discrepancy between myocardial oxygen supply and demand results in myocardial ischaemia. If ischaemia persists, myocardial injury becomes irreversible, resulting in myocardial necrosis. This typically extends from the subendocardium towards the subepicardium. Reimer and Jennings [3] first described the concept of “wavefront phenomenon of myocardial death”. The major determinant of final infarct size, transmural necrosis and microvascular damage is the duration of ischaemia. Previous studies have validated the association between increased duration of ischaemia with worse myocardial perfusion and increased mortality rate in patients treated with fibrinolysis [4] and primary percutaneous coronary intervention (primary-PCI) [5]. Therefore, the cornerstone for management of ST-segment elevation myocardial infarction (STEMI) involves:

1) Rapid restoration of epicardial and microvascular blood flow utilising combination of pharmacological and percutaneous intervention;
2) Prevention of recurrent ischaemic events with anti-thrombotic and antiplatelet therapies;
3) Reducing effect of myocardial necrosis;
4) Reducing in-hospital and out-of-hospital complications;
5) Preventing future events.

Over the last 25 years, therapeutic options for treatment of patients with myocardial infarction have improved substantially. As a result, the absolute risk reduction of in-hospital deaths for patients presenting with STEMI has been on the decline in the last decade [6]. We review the evolution of treatment strategies for STEMI that has contributed to the improvement in patient outcome.
2. REPERFUSION FOR STEMI
The main goal is prompt reperfusion of myocardial blood flow which has been shown to reduce mortality [7]. The options include pharmacological reperfusion with fibrinolytic agents and primary-PCI. In major centres with primary-PCI capability, primary-PCI has become the standard of care. However, fibrinolysis remains the most viable treatment option in patients presenting to non-PCI capable hospitals whose transport time to a PCI-capable hospital is greater than 120 minutes [8].

2.1. Fibrinolysis
A major breakthrough leading to considerable improvement in survival after STEMI was heralded by the introduction of fibrinolysis in the 1990’s as a pharmacological reperfusion therapy [9]. The development of fibrinolytic agents has undergone an evolution from non-fibrin specific agents (streptokinase and urokinase) administered via intravenous infusion, to infusions of fibrin-specific agents (tissue plasminogen activator [tPA]), to bolus only fibrin specific agents (rPA, TNK-tPA). The evolution of these fibrinolytic therapies was associated with incremental benefits to outcome. In the seminal GUSTO trial, tPA was first shown to have a mortality advantage over streptokinase [10]. Subsequently, reperfusion with TNK-tPA was associated with greater vessel patency than streptokinase, along with less systemic bleeding but similar mortality benefit as tPA [11]. An important advantage conferred by TNK-tPA has been the ease of bolus administration, however, its use has not translated to further reductions in 30-day or late mortality compared to earlier generation fibrinolytics [11]. Nonetheless, its simpler dosage regimen does allow for wider application outside of hospital, more timely administration and fewer treatment errors. Studies have shown that the earlier administration of fibrinolysis is associated with greater benefit in preservation of left ventricular ejection fraction and reduction in mortality [12-14].

2.2. Failed Fibrinolysis
Up to 40% of patients treated with fibrinolysis fail to achieve restored microvascular flow to the infarct territory. This is defined by the persistence of chest pain and less than 50% reduction in ST-segment elevation at 90 mins after fibrinolysis. The factors associated with failed pharmacological reperfusion include delay to presentation and treatment, infarct location and concomitant therapies [15]. In the case of failed thrombolytic reperfusion, a strong body of evidence supports the role of emergent angiography and rescue PCI rather than re-administration of fibrinolytics [16]. Rescue PCI was shown by Gershlick et al. to be associated with lower rates of death, reinfarction, severe heart failure and stroke 6 months after STEMI compared to conservative therapy and repeated thrombolysis. The rate of event free survival at 6 months among patients treated with rescues PCI was 84.6%, as compared with 70.1% among those receiving conservative therapy and 68.7% among those undergoing repeated thrombolysis (overall P = 0.004) [16]. Subsequently, a meta-analysis showed that rescue PCI was associated with improved clinical outcomes for STEMI patients after failed fibrinolytic therapy but the benefits is associated with increased risk of stroke and minor bleeding compared to conservative strategy [17]. Other studies such as the ASSENT-4 PCI (Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention) have assessed the role of routine emergency PCI after fibrinolysis, (also known as “facilitated PCI”) and found that this approach is associated with an increase in the composite of death, heart failure and shock compared to primary-PCI alone (18.6% vs. 13.4%, P = 0.005) [18]. Similarly, the use of facilitated PCI after administration of half dose r-PA and abciximab (glycoprotein IIb/IIIa inhibitor) was also found not to improve outcome compared to primary PCI with administration of abciximab in the cath lab in the FINESSE (Facilitated Intervention for Enhanced Reperfusion Speed to Stop Events) trial [19].

2.3. Primary Percutaneous Coronary Intervention
Despite the clear benefits of fibrinolytic therapy compared with no reperfusion and its ease of use, there were still issues of both efficacy and safety that limits its use. These issues include:
1) Normalisation of blood flow (as assessed by TIMI flow grade 3) occurs in only 50% - 60% of patients treated with fibrinolysis [10,20]. The clinical benefits of fibrinolytic therapy correlate only with restoration of TIMI grade 3 flow.
2) High incidence (20% - 30%) of early recurrence of ischaemia with 5% - 15% [20,21] of frank fibrinolytic coronary reocclusion and reinfarction in 3% - 5% [22,23] despite initial apparent successful fibrinolysis.
3) bMajor haemorrhagic complications occurring in 2% - 3% of patients with the most serious being intracerebral haemorrhage which occurs in as many as 1% [24].
4) There is a high proportion (20% - 30%) of patients particularly older adults who are not candidates for fibrinolytic therapy because of contraindications such as active internal bleeding, a recent stroke or hypertension [25].

In the early 1990s, it was hypothesised that these problems could be overcome by the use of primary-PCI. Although the implementation of primary-PCI requires more resources and is more difficult to quickly implement than
fibrinolysis studies have shown that when both methods of reperfusion are available, primary-PCI offer better clinical outcomes than fibrinolysis. In a meta-analysis that reviewed 23 randomised trials consisting of 7739 patients, primary-PCI resulted in lower rates of stroke (1% vs. 2%, P = 0.004), early death (7% vs. 9%, P = 0.0002) and non-fatal reinfarction (3% vs. 7%, P < 0.001) compared to fibrinolysis [14]. Nonetheless, these benefits of primary-PCI remain firmly dependent on timely implementation. Traditionally, this has been measured by “door-to-balloon time”, which represents the interval between presentation of the patient to hospital and the achievement of coronary artery patency by balloon angioplasty. Studies have demonstrated that the incremental gains from primary PCI are lost when door-to-balloon time and door-to-needle time (time from hospital arrival to initiation of fibrinolytic therapy) are greater than 60 min and 114 min respectively [17,26,27]. Notably, relative 1 year mortality rates increase by 7.5% for every 30 minute delay in reperfusion [28]. Therefore efficient and effective clinical systems that are able to deliver timely and consistent reperfusion are required to preserve the advantage of primary-PCI over fibrinolysis. As reducing door-to-balloon time is crucial, strategies involving the performance of 12-lead ECG triage and emergency department activation of primary-PCI have been proposed. A study including 349 patients showed that such a strategy reduced the median door-to-balloon time from 98 minutes to 56 minutes, compared to conventional strategy [29]. The key to achieving a balance between transfer for primary-PCI and fibrinolysis in hospitals without invasive services remains a challenge. Current guidelines recommend transfer for primary-PCI if the door-to-balloon time is expected to be less than 90 minutes. When this criterion can be satisfied, the DANAMI-2 study showed that transfer for primary-PCI results in lower rates of recurrent myocardial infarction, unplanned revascularisation and stroke compared to onsite fibrinolysis. However a reduction in mortality was not demonstrated [30].

2.4. In-Lab Strategies during Primary Percutaneous Coronary Intervention

2.4.1. Antithrombotic Therapies

In order to optimally restore myocardial perfusion during primary-PCI, effective antithrombotic therapies are required. Unfractionated heparin (UFH) remains the most common antithrombotic therapy used with an initial intravenous bolus of 70 IU/kg during primary-PCI. Recent studies have shown that low molecular weight heparin (LMWH) is better than UFH during primary-PCI. An open label ATOLL trial randomly assigned 901 STEMI patients to enoxaparin (intravenous bolus of 0.5 mg/kg) or UFH (initial intravenous bolus of 70 - 100 IU without or 50 - 70 IU with glycoprotein Ib/IIa inhibitor) before primary-PCI [31]. There was no significant reduction in the rate of primary outcome of death, complication of MI, procedure failure or major bleeding with enoxaparin (28% vs. 34%; relative risk 0.83, 95% CI 0.68 - 1.01). The secondary end-point of death, recurrent MI or acute coronary syndrome, or urgent revascularisation however occurred significantly less often with enoxaparin (7% vs. 11%; relative risk 0.59, 95% CI 0.38 - 0.91). Furthermore two meta-analyses have concluded that the use of LMWH (generally enoxaparin) compared to UFH leads to lower rates of mortality and major bleeding [32,33].

More recently bivalirudin, a short acting direct thrombin inhibitor, has emerged as alternative and possibly more efficacious antithrombotic therapy during primary-PCI. The HORIZONS AMI trial enrolled 3600 STEMI patients and randomised patients to either bivalirudin (initial bolus of 0.75 mg/kg followed by an intravenous infusion of 1.75 mg/kg per hour that was discontinued after PCI) plus provisional glycoprotein IIb/IIIa inhibitor or to UFH plus planned GP IIb/IIIa prior to primary-PCI. Patients treated with bivalirudin had reduced major bleeding (8.3% vs. 4.9%, P < 0.001). The 30 day cardiac mortality and total mortality were also reduced in the patients treated with bivalirudin (2.1% vs. 3.1%, P = 0.047) [34].

2.4.2. Parenteral Antiplatelet Therapies

Abciximab, a chimeric monoclonal antibody fragment targeting the glycoprotein IIb/IIIa receptor, prevents platelet aggregation by blocking the binding of the GP IIb/IIIa receptor to fibrinogen, thereby inhibiting fibrinogen-platelet bridging. It has been shown to be associated with a reduction in the composite endpoints of death, recurrent myocardial infarction and urgent revascularisation in patients undergoing primary-PCI [35-37]. However in the CADILLAC trial, the clinical benefit of abciximab in stented patients was not confirmed. It was observed that there was no difference in the rate of reinfarction or in left ventricular function at six months [38]. In a meta-analysis, abciximab therapy was associated with significant reductions in mortality at 30 days (2.4% vs. 3.4%, P = 0.047 with placebo) and six to twelve months (4.4% vs. 6.2%, P = 0.01) and in reinfarction at 30 days (1.0% vs. 1.9%, P = 0.03); in addition there was no increase in bleeding. This analysis provides support for the concept that abciximab is beneficial in reducing acute ischemic events during primary PCI with stenting [39]. The intracoronary delivery of abciximab however has not been proven to be superior to intravenous administration in two recent randomised controlled trials [40,41]. Small molecule glycoprotein IIb/IIIa inhibitors (tirofiban and eptifibatide) have not been extensively studied but mechanistic studies have also suggested im-
proved vessel patency [42,43].

2.4.3. Stents
In patients treated with primary-PCI for STEMI, deployment of stents is now routine. The benefit of drug eluting stent (DES) platforms over bare metal stents (BMS) has been examined. In a meta-analysis that included thirteen clinical trials with 7244 STEMI patients, treatment with DES was associated with decreased target vessel revascularisation and myocardial infarction rates [44]. Furthermore, there was no increase in cardiac death or stent thrombosis occurrence with DES [44].

2.4.4. Aspiration Thrombectomy
Another recent development during primary-PCI is aspiration thrombectomy. Thrombus removal using aspiration thrombectomy devices (e.g. EXPORT catheter) has been recognised as a strategy that is associated with better epicardial and myocardial perfusion. This can be explained by less distal embolisation of thrombus ordinarily resulting in microvascular damage. This was first shown by the TAPAS study which randomised 1071 patients to conventional PCI vs. manual thrombus aspiration. Patients treated with thrombus aspiration had lower rates of myocardial blush grade 0 or 1 (17.1 vs. 26.3%, P < 0.001) [45]. In addition to myocardial perfusion measures, a meta-analysis including nine randomised trials with 2417 patients also showed that adjunctive aspiration thrombectomy during primary-PCI is associated with a significant reduction in 30-day mortality [46].

2.4.5. Reducing Bleeding Complications
Patients treated with primary-PCI for STEMI are at increased risk of bleeding complications because they are concurrently managed with multiple antithrombotic and antiplatelet therapies. Bleeding complications have been linked with increased morbidity and mortality [47,48]. Studies have shown that reduction in bleeding complications may lead to improved longer term clinical outcomes, including mortality [49,50]. A number of pharmacologic and procedural strategies can be employed to reduce the risk of bleeding associated with primary-PCI. The two main strategies that have been associated with reduction in bleeding complications and mortality are bivalirudin and radial artery access. Bivalirudin, a direct thrombin inhibitor, as previously discussed was shown in the HORIZONS AMI study to have reduced major bleeding and mortality in STEMI patients treated with primary-PCI.

2.4.6. Radial versus Femoral Artery Access
Important advances have been made in elective PCI with respect to reduced access site bleeding [51] and ultimately post-procedure mortality [52,53], through the advent of radial artery puncture compared to the traditional femoral artery approach. The RIFLE-STEACS (Radial Versus Femoral Randomised Investigation in ST-Elevation Acute Coronary Syndrome) and RIVAL (A Trial of Trans-radial Versus Trans-Femoral Percutaneous Coronary Intervention (PCI) Access Site Approach in Patients With Unstable Angina or Myocardial Infarction Managed With an Invasive Strategy) studies explored the hypothesis that the safety associated with radial artery access may also translate into mortality benefit in STEMI patients. In the latter study, Mehta and colleagues compared the efficacy and bleeding outcomes in patients with STEMI (n = 1958) and non STEMI (n = 5063) separately in those randomised to radial versus femoral arterial access. They found that radial artery access reduced the primary outcome (death/myocardial infarction/stroke/non-coronary artery bypass graft related major bleeding) compared with femoral access in all-comers (3.1% vs. 5.2%; hazard ratio [HR]:0.6; P = 0.026) while also reducing the rates of all-cause mortality at 30 days (1.3% vs. 3.2%; HR 0.39, P = 0.006) and the composite of death, myocardial infarction and stroke (2.7% vs. 4.6%; HR 0.59; P = 0.031) [54]. Interestingly, this effect on mortality outcome was specific for STEMI patients treated with primary PCI (1.4% radial vs. 3.1% femoral; HR: 0.46), as it did not apply to patients in the non-STEMI cohort (3.8% vs. 3.5%, P = 0.49, death/myocardial infarction / stroke (3.4% vs. 2.7%, P = 0.176) or all-cause mortality (1.3% vs. 0.8%, P = 0.082) [54]. Similar results were corroborated in the RIFLE-STEACS study, in which 1001 patients were randomised to radial (n = 500) and femoral (n = 501) approach at 4-high volume centres between January 2009 and July 2011. The primary endpoint was the 30-day rate of net adverse clinical events (NACEs) defined as composite of cardiac death, stroke, myocardial infarction, target lesion revascularisation and bleeding. Radial access in patients with STEMI was associated with lower 30-day NACEs compared to femoral access (13.6% vs. 21%). In addition, radial access was also associated with significantly lower rates of cardiac mortality (5.2% vs. 9.2%), bleeding (7.8% vs. 12.2%, P = 0.026) and shorter hospital stay (P = 0.03) [55]. The results of these two studies highlight the safety, efficacy and benefit of radial arterial access during primary-PCI and herald its use as the preferred option in patients with STEMI, for interventional cardiologists who have adequate experience and expertise in radial approach.

2.5. Oral Pharmacotherapies
The evolution of our focus in modern treatment of STEMI to invasive management is fundamentally enabled by the developments in antiplatelet and antithrombotic therapies. Our improved understanding that plate-
Aspirin has been the mainstay treatment for all patients undergoing either pharmacological or primary-PCI. Therefore, all patients with acute coronary syndromes without contraindications should receive aspirin 150 - 300 mg [56]. The second class of antiplatelet therapy is thienopyridine antagonist of ADP. It has been shown that patients younger than 75 years treated with fibrinolysis randomised to receive clopidogrel (300 mg loading dose and 75 mg daily compared with placebo) achieved improved rates of vessel patency 3 - 5 days later with a non-significant reduction in recurrent myocardial infarction (2.5% vs. 3.6%, P = 0.08) [57]. In addition, among 45,852 patients treated for myocardial infarction, there was a 7% reduction in hospital mortality following the addition of clopidogrel (75mg a day added to aspirin, without loading dose) compared to placebo [58]. The issue of clopidogrel loading dose was recently evaluated in the CURRENT-OASIS 7 trial which assigned 25,086 patients with ACS (29.2% STEMI) to either clopidogrel 600 mg loading dose on day 1 followed by 150 mg daily for 6 days and 75 mg thereafter or clopidogrel 300 mg loading dose followed by 75 mg daily [59]. The rate of primary outcome (cardiovascular death, MI, or stroke at 30 days) was not statistically different (4.2% vs. 4.4%, P = 0.3) between the two groups. Major bleeding occurred significantly more often in patients who received higher clopidogrel dose (2.5% vs. 2%, P = 0.01 in the overall population and 1.6% vs. 1.1%, P = 0.009 in the PCI subgroup). However, the higher dose of clopidogrel was associated with a significant reduction in the secondary outcome of definite stent thrombosis among patients who underwent PCI (0.7% vs. 1.3%, P = 0.0001).

Prasugrel which irreversibly inhibits the P2Y12 receptor at the same site as clopidogrel was recently compared to clopidogrel in the TRITON-TIMI 38 trial of 13,608 moderate to high risk ACS patients undergoing PCI, including 3534 STEMI patients [60]. In patients with STEMI at 15 month follow up, the primary efficacy endpoint of cardiovascular death, nonfatal MI or nonfatal stroke occurred significantly less often in patients treated with prasugrel (9.9% vs. 12.4%; HR 0.81; 95% CI 0.73 - 0.9, P < 0.001), driven primarily by a significant reduction in nonfatal AMI (7.4% vs. 9.7%, P < 0.001). In addition, the rate of definite or probable stent thrombosis was significantly reduced in the prasugrel group (1.6% vs. 2.8%, P < 0.001). However, a subset of patients had increased risk of bleeding, specifically those >75 years old, those <60 kg in weight and those with a history of prior stroke.

Another antiplatelet agent, ticagrelor which blocks the P2Y12 receptor reversibly, has a more rapid onset of action than clopidogrel. Its efficacy in the treatment of STEMI has recently been studied in the PLATO trial. At 12 months, the composite primary endpoint (death from vascular causes, MI, or stroke) occurred significantly less often in patients receiving ticagrelor (9.8% vs. 11.7% with clopidogrel, HR 0.84, 95% CI 0.77 - 0.92, P < 0.001). There was no significant difference in the rates of major bleeding between the two groups (11.6% and 12.2% respectively; P = 0.43), but ticagrelor was associated with a significantly increased risk of major bleeding not related to CABG (4.5% vs. 3.8%, P = 0.03). In addition, the secondary endpoints of the rates of myocardial infarction (5.8% vs. 6.9%, P = 0.005), death from vascular causes (4.0% vs. 5.1%, P = 0.001), and death from any cause (4.5% vs. 5.9%; P < 0.001) were all significantly lower in the ticagrelor group [61].

Taken together, there is compelling evidence for the use of dual therapy with aspirin and complementary antiplatelet agents. The relevant data apply both to the overall management of patients with STEMI and furthermore to the primary PCI setting. Although recent results indicate that prasugrel and ticagrelor may have an advantage over clopidogrel, individual patient criteria relating to the risk of bleeding must be taken into consideration before selecting a regime. Furthermore, the cost and availability of newer agents would also be a consideration.

In summary, the combination of antiplatelet and anti-thrombotic therapies needs to strike a balance between optimising ischaemic outcomes, while reducing bleeding risk.

1) In general, all patients should receive dual antiplatelet agents (aspirin and Clopidogrel, Prasugrel or Ticagrelol) and one antithrombin agent (unfractionated heparin, enoxaparin, bivalirudin or fondaparinux, but not a combination).

2) In patients with increased risk of bleeding and invasive strategy is planned, use of bivalirudin is supported by strong data [34].

3) In patients with increased risk of bleeding and conservative management is planned, fondaparinux is associated with reduced bleeding and mortality [62]. There is evidence to support the additive benefits of combination antiplatelet agents (aspirin, thienopyridines, and glycoprotein IIb/IIIa inhibition).

4) For patients with elevated troponin levels undergoing PCI, abciximab in addition to clopidogrel and aspirin...
3. CONCLUSION

Significant reductions in in-hospital, intermediate and long-term outcomes in patients afflicted with acute myocardial infarction have occurred as a result of the additive benefits of prompt mechanical revascularisation strategies coupled with the administration of up-stream anti-thrombotic and anti-platelet therapies. Newer anti-platelet agents have impacted upon rates of stent thrombosis, however, at the expense of increased bleeding rates. It is likely that a personalised approach to the chronic management of thrombotic and bleeding risk in patients’ post-AMI will yield optimal patient outcomes.

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