REVIEW

New treatment strategies in STEMI

Diana Crețu[1]

Abstract: ST segment elevation myocardial infarction represents the most severe form of acute coronary syndromes and requires immediate therapy. Prompt revascularization with percutaneous coronary intervention within 90 minutes of first presentation or thrombolysis within 12 hours of symptom onset, can prevent or decrease myocardial damage and decrease morbidity and mortality by preventing acute complications. Progress made in coronary angioplasty devices, including manual aspiration catheters and drug-eluting stents and pharmacologic therapy, such as potent antiplatelet and anticoagulant agents, have significantly improved the acute outcome for these patients. The main issue of current pharmacological or interventional therapies remain their inability to obtain in many cases a prompt reperfusion to avoid their irreversible loss of functional cardiomyocytes. The functional recovery of injured myocardium by novel approaches, like cell therapy, tissue engineering or reprogramming of scar tissue resulting in the restoration of the left ventricular function could revolutionise the way we treat patients with acute myocardial infarction.
Keywords: ST segment elevation myocardial infarction, reperfusion, cell therapy, prognosis.

Rezumat: Infarctul miocardic acut cu supradenivelare de segment ST reprezintă cea mai severă formă de sindrom coronarian acut și necesită terapie imediată. Revascularizarea promptă prin angiografie coronariană percutană în primele 90 minute de la prezentare sau terapie trombolitică în primele 12 ore de la debutul simptomelor, poate preveni sau diminua pierderea de țesut miocardic și poate reduce morbiditatea și mortalitatea prin prevenirea complicațiilor acute. Progresele înregistrate în domeniul dispozitivelor de angioplastie coronariană, incluzând catetere de aspirație manuală și stenturi active farmacologic și terapia farmacologică, cu agenți potenți antiplachetari și anticoagulanți, au îmbunătățit semnificativ prognosticul acestor pacienți. Principalul neajuns al terapiilor actuale farmacologice și intervenționale rămâne incapacitatea lor de a obține în unele cazuri o reperfuzie promptă pentru a evita pierderea ireversibilă a cardiomiocitelor funcționale. Recuperarea funcțională a miocardului lezat prin concepte noi, ca terapia celulară, ingineria tisulară sau reprogramarea țesutului cicatriceal, cu restabilirea funcției ventriculare stângi ar putea revoluționa modul în care ne tratăm pacienții cu infarct miocardic acut.
Cuvinte cheie: infarct miocardic acut cu supradenivelare de segment ST, reperfuzie, terapie celulară, prognostic.

INTRODUCTION

STEMI (ST segment elevation myocardial infarction) results primarily from sudden-onset plaque rupture and complete occlusion of a coronary artery[1]. The main goals of treatment in acute myocardial infarction are to limit myocardial damage by restoring myocardial blood flow as quickly as possible and to decrease subsequent remodelling, which can have unfavorable effects on ventricular function and prognosis[1].

REPERFUSION THERAPIES

The prompt reestablishment of antegrade flow is the aim of the therapy for STEMI patients. The earlier and the more complete the reperfusion, the greater the myocardial salvage, which resulting in preservation of left ventricular function, the most important prognostic factor for long-term survival[1].

According to ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation - 2012, for patients with the clinical presentation within 12 hours of symptom onset and with persistent ST-segment elevation or new or presumed new left bundle branch block, early mechanical or pharmacological reperfusion should be performed as early as possible[2]. The reperfusion therapy should be considered if there is clinical and/or electrocardiographic evidence of ongoing ischaemia, even if, according to the patient, symptoms started over 12 hours[2].

[1] University Emergency Hospital, Bucharest, Romania

◤ **Contact address:**
Diana Cretu, MD
Emergency University Hospital of Bucharest
Splaiul Independentei 169, Sector 5, Bucharest, Romania
Tel.: +40 74 002 33 70
Fax: +40 21 601 23 97

Primary percutaneous coronary intervention (PCI) of culprit coronary arteryis preferred to thrombolytic therapywhen the delay from the symptoms onset to reperfusion therapy is shortand when the patient presents to a center with experienced interventional cardiologists andhigh coronary procedures volume[3]. *The National Registry of Myocardial Infarction* (NRMI) showed that mortality was significantly reduced at hospitals with great number of PCI procedures. High PCI volume was found to be an important predictor of mortality benefit compared with thrombolytic therapy[1].

Primary PCI reduced mortality by 25%, reinfarction by 64%, intracranial hemorrhage by 95% and stroke by 53% versus thrombolytic therapy[4]. Primary PCIs provide TIMI 3 flow in the infarct-related artery in over 90% of cases compared with only approximately 50% with thrombolytic therapy[1,4]. PCIs also prevent recurrent ischemia, reinfarction andneed for repeat revascularization procedures by definitively treating the severe stenosis that maybe present even after a successful thrombolysis, resulting in a shorter hospitalization and a faster resumption of usual activities[1,3].

Door-to-balloon (D2B) time for primary coronary angioplasty has been shown to be very important in salvaging ischemic myocardium and improving survival. The randomized comparative trials between primary PCI and thrombolytic therapy showed that D2B time of >90 minutes could eliminate the mortality benefit of primary PCI versus thrombolytic therapy. Although the goal should always be to minimize the D2B time, recent large-scale studies suggest that, longer D2B times, but up to 120 minutes could provide good prognosis, for patients with STEMI presenting initially to hospitals without PCI capability, if are transferred to nearby PCI centersfor primary PCI, even if not receiving thrombolytic therapy at the non-PCI facility centers[1]. Despite substantial improvements in D2B times, evidence that these efforts have translated into reduced mortality rates is lacking[3].

Unfortunately, many patients with STEMI cannot be treated with primary PCI. When it can not be ensured an acceptable D2B time or if there are no nearby PCI centers with high PCI volume or experienced interventional cardiologists, thrombolytic therapy despite its shortcomings is the preferred initial therapy, as some form of reperfusion therapy is better thanconservative treatment[1]. In many cases, thrombolysis alone is associated with high reocclusion rates and reinfarction due to the residual severe stenosis[1].

Delayed PCI of the infarct artery can be performed in patients treated initially with a noninvasive strategy (with fibrinolysis or without reperfusion therapy) who become unstable due to the development of cardiogenic shock, acute severe HF or postinfarction unstable angina or who did demonstrate significant residual ischemia during the hospitalization for STEMI. Delayed PCIs also encompass interventions performed for fibrinolytic failure or infarct artery reocclusion or a part of an invasive strategy for patients after successful thrombolytic therapy[3].

Few studies have examined whether the patients in whom primary PCI is not an option and thrombolysis is administered, should be treated interventionally only if they have spontaneous recurrent ischemia or induced ischemia during subsequent stress test or whether all patients should be transferred to a PCI-capable hospital for routine coronary angiography and angioplasty using stents if necessary[1]. Meta-analyses suggest that routine early PCI following thrombolytic therapy, usually between 2 and 24 hours, confers a significant reduction in the composite endpoint of death, reinfarction and ischemia during the first year after STEMI without an increase in stroke or major bleeding rate[1].

TRANSFER-AMI trial (*The Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction*) showed that, compared with rescue PCI or ischemia-guided delayed coronary angiography, routine PCI within 6 hours after thrombolysis can significantly improve the rate of mortality, reinfarction, recurrent ischemia, new or worsening congestive heart failure or cardiogenic shock within 30 days. The early routine PCI strategy seems to not be associated with an increasing of major bleeding. The TRANSFER-AMI investigators concluded that the transfer to PCI centers should be initiated immediately after fibrinolysis without waiting to see whether reperfusion was successful[1,4].

Thrombolysis ensures successful reperfusion in only 50-60% of patients. Rescue PCI is necessary in patients with ongoing ischemia. The randomized trials showed the benefit of rescue PCI with 35% reduction in mortality rate and 36% reduction in reinfarction rate. The REACT (the Rapid Early Action for Coronary Treatment) trial found that rescue PCI after failed thrombolytic treatment was associated with a statistically significant reduction in the incidence of major adverse cardiac and cerebrovascular events, as compared with either repeated thrombolysis or conservative management[1,4,6].

Facilitated PCI, bridging the pharmacologic therapy and primary PCI, refers to planned immediate PCI following an initial pharmacological regimen, usually

thrombolytic therapy, full-dose or half-dose with or without a glycoprotein IIb/IIIa inhibitor. Because pharmacotherapy may open closed arteries before the procedure, one would expect to see greater benefit by the administration ofthe fibrinolytic agents or glycoprotein IIb/IIIa inhibitors prior to primary PCI[5]. However, despite angiographic benefits, the clinical benefits of „facilitated PCI" have thus far been disappointing. The ASSENT-4 (*The Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction-4*) PCI trial had to be terminated prematurely due to increased mortality in the facilitated PCI group. The FINESSE (*Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events*) trial enrolled patients with STEMI within 6 hours of pain onset with estimated time to cath lab of 1-4 hours. Patients were randomized in a double-blind to either one of the three treatment strategies: primary PCI, facilitated PCI with abciximab alone or facilitated PCI with reteplase plus abciximab[5]. The FINESSE trial demonstrates that, in the setting of ST elevation myocardial infarction, there is no clinical benefit with reteplase plus abciximab or abciximab alone when are adminitrated pre-PCI compared with primary PCI plus abciximab at the time of the procedure, with a significant increase in bleeding complications rate in the facilitated PCI groups[1,4].

Up to one-third of patients with STEMI may not receive reperfusion therapy due to their late presentation[1]. The recanalization of the occluded infarct-related artery at patients presenting beyond the 12-hour window after symptom onset is associated with very low probability for myocardial salvage, but with a theoretical advantage on the improving of the the left ventricular remodeling[1,4].

The OAT (*Occluded Artery Trial*) study enrolled 2166 patients with total occlusion of the infarct-related artery, at 3 to 28 days after myocardial infarction and who presented left ventricular ejection fraction <50% or proximal vessel occlusion[1,7]. Of these patients, 1082 were assigned to routine PCI and stenting with optimal medical therapy and 1084 were assigned to optimal medical therapy alone. The study shown that routine PCI with the mechanical opening of a persistently occluded infarct-related artery at a time too late for myocardial salvage is did not provide mortality or other cardiac benefit during a mean follow-up of 3 years despite the procedural success of PCI and sustained patency[1,7]. A meta-analysis of trials, testing whether late re-canalization of an occluded infarct artery is beneficial, provided results consistent with those from OAT study[2]. Thus, delayed PCI of a totally occluded infarct artery >24 hours after STEMI should not be undertaken in clinically stable patients without evidence of severe ischemia[3]. Additionally, the benefits of routine, non–ischemia-driven PCI of an angiographically significant stenosis in a patent infarct artery beyond 24 hours after STEMI are less well established[3].

PROCEDURAL ASPECTS OF PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Approximately 50% of STEMI patients have significant multivessel disease. Only the infarct-related artery should be treated during the initial intervention. There is no current evidence to support emergency intervention in non-infarct-related lesions[2]. In patients with cardiogenic shock, percutaneous revascularizationof a severe stenosis in a non-culprit artery but supplying a large territory might improve hemodynamic instability and should be considered during the primary PCI[3]. Apart from patients in cardiogenic shock and in patients withcontinuous ischaemia despitethe opening the supposed culprit lesion, performing PCI of non-culprit vessels in the acute setting is generallydiscouraged[2]. In STEMI patients with multivessel disease initially treated for culprit lesion with PCIs (primary or post-thrombolysis) and confirmed the presence of ischaemia in non-infarcted territories, staged revascularizationmay be performed before discharge or in the days to weeks after initial PCI[2]. More trials: CVLPRIT (*CompleteVs. Lesion-only PRImary PCI*) Trial, PRAMI (*Preventive Angioplasty in Myocardial Infarction*) trial, DANAMI-3 (*DANish study of optimal acute treatment of patients withST-elevation Myocardial Infarction 3*) trial, which assess the benefit/risk ratio of treating non-infarct-related lesions, are in progress[2].

Drug-Eluting Stents versus Bare-Metal Stents

Bare-metal stents remain the device of choice during primary PCI[1]. Some concerns still have not been resolved about the long-term safety of drug-eluting stents (DES), especially those of first-generation, in patients with acute STEMI. Observational studies suggested that the drug-eluting stents during primary PCI are associated with higher stent thrombosis risk[1]. An additional issue with the routine use ofDES in STEMI setting is that it is often difficult to determine the ability of patients to comply with or tolerate the prolonged use of dual antiplatelet therapy[2]. DES should not be used when there are financial or social considerations that should limit patientcompliance, in the presence of a elevated bleeding risk, a known need for surgical interventions in the next year or there is an independent indication for long-term anticoagulant therapy[3].

The randomized trials which compared the first-generation drug-eluting and bare-metal stents showed a benefit regarding the need for repeat target vessel revascularization for drug-eluting stents, as compared with bare-metal stents[1,2]. In addition there was no difference in mortality, although the incidence of late stent thrombosis and late reinfarction was higher with drug-eluting stents. The reason for this discrepancy of higher late stent thrombosis without associated higher mortality can be explain through less catastrophic results of late stent thrombosis compared with acute or subacute stent thrombosis[1].

It is unclear whether the newer generations of drug-eluting stents will provide improved outcome versus the first-generation drug-eluting stents in the setting of primary PCI[1]. One randomized trial between a first-generation DES (sirolimus-eluting stents) and a second-generation DES (everolimus-eluting stents) in STEMI patients showed a significant reduction of the major adverse cardiac events at 1 yearand 1-year incidence of stent thrombosis[1]. Although these results are encouraging, longer-term follow-up is necessary to confirm the definite advantage of the second-generation DES during primary PCI[1]. In July 2014, in *Journal of American College of Cardiology,* were published the results of a study, which evaluated stent thrombosis rate up to 3 years in patients with STEMI, enrolled in the SCAAR (*Swedish Coronary Angiography and Angioplasty Registry*), treated with primary PCI with new-generation drug-eluting stents versus bare-metal stents and old-generation drug-eluting stents. The research demonstrated that patients treated with new-generation DES have a lower risk of early and late stent thrombosis than patients treated with BMS and that the risk of very late thrombosis is low and comparable between new-DES and BMS up to 3 years of follow-up, whereas coronary procedures with old-DES is associated with an increased risk of very late stent thrombosis[8].

Distal Protection and Aspiration of Thrombus

One single randomized trial, the TAPAS (*Thrombus Aspirationduring Percutaneous coronary intervention in Acute myocardial infarction*) trial showed an improvement in terms of myocardialreperfusion (ST-segment resolution and myocardial blush) following the routine use of manual thrombus aspiration before PCI. One-year follow-upfound a reduction in mortality rate with thrombus aspiration. In the recent INFUSE-AMI (*Intracoronaryabciximab inFUsion and aSpiration thrombEctomy in patientsundergoing percutaneous coronary intervention for Anterior STsegment elevation Myocardial Infarction*) trial, thrombus aspiration did not affect infarct size. Several large,randomized trials have been initiated to attempt to confirm theresults of TAPAS[2].

Mechanical thrombectomyor embolic protection devices have not been found toprovide similar benefits. The randomized trials have shown no benefit from distal protection during primary PCI. Distal embolic protection devices did not reduce clinical outcome compared with PCI alone (3.1% versus 3.4% mortality rate)[1]. One possible explanation is the presence of multiple side branches in native coronary arteries, which cannot be protected with one distal protection device and may paradoxically have more distal embolization, especially with occlusion devices. Meta-analysis showed that catheter aspiration resulted in significantly lower mortality (2.7% versus 4.4%) whereas mechanical thrombectomy resulted in higher mortality (5.3% versus 2.8%) compared with standard PCI[1].

LV Assist Devices

Intra-aortic balloon counterpulsation (IABP) mechanically augments coronary blood flow, unloads the left ventricle and reduces myocardial oxygen demand[9]. By these favorable hemodynamic effects, IABP has been shown to improve outcomes in patients presenting with STEMI and cardiogenic shock and therefore has been recommended in these patients undergoing reperfusion therapy.1New percutaneous ventricular assist devices have been studied in these patients and have been found to improve hemodynamics compared with IABP but may not confer mortality benefit[1].

It is not clear if STEMI patients without cardiogenic shock may also benefit from IABP therapy[1]. The CRISP AMI (*Counterpulsation to Reduce Infarct Size Pre-PCI Acute Myocardial Infarction*) trial randomized anterior STEMI patients who met high-risk criteria (at least 2 mm ST-segment elevation in 2 contiguous anterior leads or a total elevation of 4 mm or higher in anterior leads) to a routine strategy of IABP prior to PCI, lasting at least 12 hours after PCI, compared with PCI alone; infarct size, expressed as a percentage of left ventricular mass was measured by cardiac magnetic resonance imaging 3 to 5 days after PCI[1,9]. The trial showed that among patients with anterior STEMI without shock, IABC plus primary PCI compared with PCI alone did not result in reduced infarct size; also, there were no significant differences in clinical outcome at 6 months between the two groups[1,9]. The results of this largest randomized trial suggest that IABP should not be routinely used in STEMI patientswithout cardiogenic shock[1,2].

Access site

Due to the intense anticoagulation and antiplatelet therapy during STEMI treatment, bleeding complicationsare common, especially at the vascular access site[1]. Because major bleeding has been associated with increased risk of ischemic complications, alternative access site for primary PCI such as the radial artery may provide a safer approach with reduced bleeding and, consequently, reduced ischemic complications[1]. After almost 20 years of research in the area of transradial PCI, there was a need for a larger, multicenter, prospective, randomized trial[10]. The RIVAL (radial versus femoral access for coronary intervention) trial was the first large, randomized trial comparing the potential benefit of radial access versus femoral access in patients with acute coronary syndrome (ACS), including STEMI patientsundergoing coronary interventions. The study found that there was a significant benefit, including lower composite endpoint of death, recurrent myocardial infarction or stroke and lower major vascular complications for transradial PCI[1,10].

The HORIZONS-AMI (*Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction*) trial also showed that transradial approach resulted in improved event-free survival rate and reduced major bleeding complications versus transfemoral approach.Recent meta-analyses of all randomized trials between transradial and transfemoral approaches in STEMI patients showed a significant reduction in mortality, major adverse cardiac events and access site complications in the transradial group[1].

PHARMACOLOGIC THERAPIES

STEMI is the result of a complete occlusion of amain coronary artery by an acute thrombus. Thrombin has an important role in thrombogenesis being involved both in the conversion of fibrinogen to fibrin and platelet activation and aggregation[11]. The pharmacological agents that aim to inhibit thrombin generation and platelet aggregation are essential in the treatment of ACS and primary PCI. The pharmacotherapy during primary PCI has undergone substantial evolution over the last decade[11]. Pre-procedural antiplatelet and anticoagulant therapy has been the focus of numerous clinical trials and currently there are several options available[11].

ANTIPLATELET THERAPY

Platelets play a major role in the initiation and propagation of the thrombus during STEMI following plaque rupture[1]. Therefore, antiplatelet therapy has been shown to reduce ischemic complications following STEMI[1]. Antiplatelet agents are represented byciclooxigenase inhibitors (aspirin), oral thienopyridine derivatives (clopidogrel and prasugrel) and non-thienopyridine P2Y12 receptor antagonist (ticagrelor and cangrelor) and glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors[11].

Oral antiplatelets agents

Clopidogrel has been shown to be synergistic with aspirin in STEMI patients with thrombolytic therapy alone as well as PCI alone or PCI following thrombolytic therapy[1]. Recent studies suggest that clopidogrel administered with thrombolytic therapy can improve the patency rate of the infarct-related artery and reduce ischemic complications. Pretreatment with clopidogrel significantly increased TIMI flow, prevented infarct-related artery reocclusion and improved survival without an increase in major bleeding versus aspirin alone. But, there is a marked inter-individual variability in its platelet inhibition. Clopidogrel may not be the optimal oral ADP-receptor inhibitor[1].

Therefore, newer ADP-receptor inhibitors, including prasugrel and ticagrelor, have been studied in STEMI patients compared with clopidogrel and were approved by the FDA for clinical use in 2009 and 2011, respectively. The patients presenting with STEMI would benefit more from these agents following primary PCI versus clopidogrel[1].

Prasugrel is a third-generation thienopyridine with improved pharmacodynamics and less inter-individual variability when compared with clopidogrel[1]. It achieves greater inhibition of platelet aggregation than clopidogrel[1,3]. The TRITON-TIMI 38 (*Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38*) trial showed that the treatment with prasugrel is associated with a significant reduction in major ischemic complications, in patients presenting with acute coronary syndromes and treated primarily with stent implantation, with a significant reduction in stent thrombosis rate. This benefit, however, came at the expense of significantly increased bleeding risk[1,3]. Prasugrel should be avoided in patients with a history of stroke or transient ischemic attack, in patients older than 75 years or patients with body weight less than 60 kg[3]. Young patients with diabetes mellitus or large areas of myocardium at risk, who are at low bleeding risk have the greatest benefit from the treatment with prasugrel[3].

Ticagrelor is a nonthienopyridine, reversible, direct actingP2Y12 receptor inhibitor, that does not need

conversion to active metabolite[1,3]. The PLATO (*Platelet Inhibition and Patient Outcomes*) study,which compared ticagrelor (loading dose of 180 mg, then 90 mg twice daily) with clopidogrel (loading doseof 300 mg or 600 mg, followed by maintenance dose of 75 mg daily), showed a significant reduction in ischemic complications, including cardiac mortality, at the patients treated with ticagrelor versus clopidogrel[1,3]. The trial also included patients treated conservatively without revascularization and demonstratedsimilar benefit whether the patients were treated conservatively or interventionally. As one-third of STEMI patients doesn't receive either mechanical or pharmacologic reperfusion therapy, it is important the finding that ticagrelor improves survival at the "medically managed" patients. There was no increased bleeding risk with ticagrelor therapy versus clopidogrel[1]. Ticagrelormay also be associated with asymptomatic bradycardia in the firstweek of therapy[2]. Ticagrelor may also cause transient dyspnea at the onset of therapy,which is not associated with morphological or functional lung abnormalities and which rarely result in discontinuation of the therapy[2]. InPLATO study, patients presenting dyspnea had a mortality benefit of ticagrelor consistent with the overall trial population.

Glycoprotein IIb/IIIa inhibitors (GP IIb/IIIa Inhibitors)

A growing number of evidence suggest that the adjunctive use of GP IIb/IIIa inhibitors, in particular abciximab, is associated with improved tissue reperfusion, recovery of left ventricular function and clinical outcomes in the setting of primary PCI. By directly targeting the receptor on the activated cell surface, GP IIb/IIIa inhibitors act by preventing distal embolization of platelet aggregates and inhibiting activated platelets from interacting with the endothelium[12]. A recent compresensive meta-analysis demonstrated a significant reduction in mortality at 30 days in patients treated with abciximab and primary PCI. The benefit was maintained at 1 year of follow-up. A second meta-analysis suggests that a reduction in mortality and recurrent MI may extend to 3 years, with a fivefold greater benefit in patients with diabetes mellitus. There is current data to suggest that eptifibatide is non-inferior to abciximab in this setting[12].

The optimal timing of GP IIb/IIIa inhibitors administration is under continued investigation. The restoration of optimal epicardial flow prior to PCI has been shown to be associated with better clinical outcomes. It has been shown that pre-PCI TIMI grade 3 flow of the infarct-related artery is an important positive predictor of improved survival. Behind the potential clinical benefit of "open artery", improved flow allows a better visualization of the culprit lesion, facilitate PCI and improve microvascular perfusion. In the TITAN-TIMI 34 (*Time to Integrilin Therapy in Acute Myocardial Infarction 34*) trial, early initiation of eptifibatide in the emergency room was shown to improve pre-PCI vessel patency compared with lateeptifibatide administration, in the cardiac catheterization laboratory[1,12].

In the HORIZONS-AMI trial which showed overall benefit of bivalirudin during primary PCI, it found an unanticipated increasing of the acute stent thrombosis rate in the bivalirudin group compared withunfractionated heparin and GP IIb/IIIa inhibitors group[1]. Therefore, GP IIb/IIIa inhibitors therapy seems toprovide protection against acute stent thrombosis, although prolonged infusion may cause bleeding complications[1]. But novel regimens, such as shorter duration of infusion or bolus only with concomitant potent oral antiplatelet therapy, may reduce the bleeding risk.1Recent studies showed that prehospital administration, in the ambulance, of high-dose bolus tirofiban in addition to aspirin, heparin, and clopidogrel was associated with a significantly lower residual ST-segment deviation versus placebo, resulting in a strong trend for decreased mortality at 30 days (2.2% versus 4.1%) and 1 year (3.7% versus 5.8%)[1].

Recent studies suggest that intracoronary bolus administration of these agents rather than the traditional intravenous route may provide greater benefit especially in high-risk patients[1]. The current guidelines recommend the use of GP IIb/IIIa inhibitors only in high risk conditions (patients with high risk acute coronary syndroms, patients with high thrombotic load and with no increased risk of bleeding)[11].

GP IIb/IIIa inhibitors have been shown to be beneficial in STEMI patients, especially when these patients were not pretreated with oral antiplatelet agents.1The most of these trials with GP IIb/IIIa inhibitors dates from the period in which the aggressive antiplatelet therapy was not routinely used[11]. Over the last decade, the use of GP IIb/IIIa inhibitors has significantlydecreased[11].

ANTICOAGULANT THERAPY

Parenteral anticoagulants are represented byindirect thrombin inhibitors (unfractionated heparin and enoxaparin) and direct thrombin inhibitors (bivalirudin)[11]. In the OASIS 6 trial,use of fondaparinuxin the context of primary PCI was associated with potentialharm and

is therefore not recommended[2]. There are very few studies comparing bivalirudin directly with unfractionated heparin in acute coronary syndroms. In majority of the studies, the comparison was between bivalirudin and unfractionated heparin plus GP IIb/IIIa inhibitors[11].

At the patients with stable angina and low-risk acute coronary syndrome, bivalirudin has been shown to provide effective anticoagulation during angioplasty with reduced bleeding complications compared with other options[1].

The role of bivalirudin versus unfractionated heparin and glycoprotein IIb/IIIa inhibitor therapy inpatients undergoing primary PCI, was evaluated inthe HORIZONS-AMI trial. The results of study showed a significant net clinical benefit, including significantly reduced cardiac mortality (1.8% vs. 2.9%, p=0.03) and markedly reduced bleeding complications in those patients randomized to bivalirudin therapy. The benefits were maintained up to 3 years following the initial procedure[1,15]. The favorable effect of bivalirudin in cardiac mortality, even at three years, cannot probably be explained only by decrease in hemorrhagic complications[11,15]. Other mechanismssuggestedto berelated to this benefit are:amelioration of reperfusion damage, reduction of inflammation and apoptosis process, resulting in decreasing infarct size and improvement myocardial function[11]. One unexplained adverse outcome was the significantly higher acute stent thrombosis rate in bivalirudin group versus heparin plus glycoprotein IIb/IIIa inhibitor group[15-17]. From the HORIZONS AMI trial, clinical practice has substantially changed.

The EUROMAX (*European Ambulance Acute Coronary Syndrome Angiography*) trial evaluated bivalirudin administrated early in the ambulance, during transport for primary PCI, versus unfractionated heparin and optional use of GP IIb/IIIa inhibitors in 2218 STEMI patients. After a follow-up period of 30 days, use of bivalirudin has been shown to reduce significantly major bleeding events (2.6% versus. 6.0%, p<0.001), without a significant influence on mortality rate (2.9% versus. 3.1%) or reinfarction (1.7% versus. 0.9%)[11,17].

Contrary the results of previous trials, the HEAT-PPCI trial, which enrroled 1829 STEMI patients, found that compared with bivalirudin, the use of unfractionated heparin was associated with a significant decreasing of major cardiovascular events (all-cause mortality, stroke, reinfarction and target vessel revascularization) (5.7% versus. 8.7%, p=0.01); additionally, there was no significant difference between two groups (3.5% versus. 3.1%, p= 0.59) regarding major bleeding complications[11].

NAPLES III (*Novel Approaches in Preventing and Limiting Events*) trial and BRAVE 4 (Efficacy study of combined prasugrel and bivalirudin versus clopidogrel and heparin in myocardial infarction) trial are two trials presented at the ACC 2014. In these studies, was observed no difference in the rate of bleeding events at the patients treated with bivalirudin compared to those treated with unfractionated heparin, supporting the unexpected results of the HEAT PPCI trial[18,19].

In conclusion, medical literature available at this moment comparing bivalirudin with unfractionated heparin provides discordant results. The mortality benefit conferred by bivalirudin in HORIZONS AMI trial was not found in EUROMAX trial. Given the results of the HEAT PPCI, NAPLES III and BRAVES trials, the use of bivalirudin as the preferred antithrombotic drug in primary PCI should be reconsidereduntil further evidence is available[11].

After an ACS, patients remain at risk for recurrent cardiovascular events despite standard medical therapy, including long-term antiplatelet therapy with aspirin and an adenosine diphosphate–receptor inhibitor. This risk may be related in part to excess thrombin generation that persists beyond the acute phase in such patients. As a result, there has been interest in evaluating the role of oral anticoagulants after an acute coronary syndrome[21].

The recent ATLAS ACS 2–TIMI 51 (*Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51*) trial tested the addition of rivaroxaban, a factor Xa antagonist, to aspirin and clopidogrel following ACS. In that trial, a low dose of rivaroxaban (2.5 mg twice daily) reduced the composite primary endpoint of all-cause and cardiovascular death, myocardial infarction and stroke. Additionally, stent thrombosis was reduced by one third. The study demonstrated a threefold increasein major bleeding and intracranial hemorrhage.Importantly, the high dose of rivaroxaban (5 mg twice daily) was not associated with similar benefits but with a important increase in the risk of bleeding[2,21]. In the APPRAISE-2 (*the Apixaban for Prevention of Acute Ischemic and Safety Events*) trial, apixaban, another factor Xa antagonist, failed to find similar benefits of adding a high dose of apixaban to the antiplatelet therapy in a very-high-risk ACS population[2,22]. In conclusion, the role of novel anticoagulants in combination with dual

antiplatelet therapy in secondary prevention of STEMI remains under discussion[2].

TERAPEUTHIC HYPOTHERMIA

Many patients with STEMI experience out-of-hospital cardiac arrest as their initial presentation. Some patients which are successfully resuscitated, present permanent hypoxic/anoxic neurologic injury despite successful reperfusion therapy. For these patients, mild therapeutic hypothermia has been shown to improve neurologic recovery[1]. Combining systemic mild therapeutic hypothermia with an invasive interventional approach to the successfully resuscitated STEMI patientmakes good sense if it can be logistically performed[23]. Mild hypothermia not only improves neurological function, but also post-resuscitation myocardial function.Likewise, it is possible that reperfusing an acutely occluded coronary artery not only salvages myocardium, but the resultant improved left ventricular function may help an injured brain[23].

A large number ofregistry data, observational studies and experimental animal work does provide some support for a positive influence of therapeutic hypothermia.In a meta-analysis, the number needed to treat (NNT) to achieve a good neurological outcome at discharge was only 6[24]. Based on these observations, hypothermia was included in the international guidelines on postresuscitation care. Although induced hypothermia seems safe, the evidence for its efficacy is relatively weak and, thus, there is a need for further randomized trial to confirm the true benefit and ideal temperature range[1].

CELL THERAPY

Despite early thrombolysis and subsequently percutanoeus coronary interventions, which have improved significantly the prognostic of the patients with STEMI, today less than 50% of patients suffering ongoing myocardial necrosis achieve adequate epicardial and microvascular reperfusion before irreversible damage of the infarcted myocardial tissue. As a result, a high proportion of survivors after a acute myocardial infarction are at risk of developing permanent LV systolic dysfunction and congestive heart failure due to LV remodeling, which unfavourablyaffects mortality and morbidity[23]. 12-month mortality for patients with STEMI and LV dysfunction still exceeds 10%[25].

There isa constant interest for the searching of therapies which to limit infarctsize, which can be an adjuvant to early reperfusion strategies. In the past decade, a large number of human trials have studied the safety and efficacy of various stem cell populations(adult stem and precursor cells) for cardiacregeneration in the post-STEMI setting[23]. Main features of the selected adult stem cell populations are represented by theirability to migrate, to proliferate and theirpotential to transdifferentiate into various mature cell types[27].

In the first clinical trials, different cytokines like erythropoietin (EPO) or granulocytecolony stimulating factor (G-CSF) were employed to mobilize resident progenitor cells[27]. Nowadays, the clinical studies used adult stem cells derived from different sources like bone marrow derived stem cells (BMCs), adipose tissue derived cells (ADRCs) or cardiactissue derived stem cells (CPCs), which are transplantated direct intracoronary orintramyocardial[24]. The first two cell types, BMCs and ADRCs, act in a paracrine way for improving cardiac function whereas CDCsseem to have some capacity to transdifferentiate intocardiomyocytes[27].

Bone marrow derived stem cells (BMCs)

The bone marrow is an easily accessible, renewable, autologous source for adult stem cells.The BMCs are represented by different subpopulations like bone marrow hematopoietic stem cells- BM-HSCs, bone marrow mesenchymal stromal cells- BM-MSCs, bone marrow endothelial progenitor cells- BM-EPCs or side population cells. BM-HSCs present some receptors on their surface such as CD133, CD34 or CD117 (c-KIT), whereas BM-MSCs have surface receptors like CD105, CD73 and CD90. BM-EPCs have embryonic angioblastic properties which confer them the ability to repair the damaged endothelium[27].

Multiple clinical trials with various results used BM-HSCs, BM-MSCs and BM-EPCs[25,27]. Arecently published meta-analysis, based on the results of 50 studies conducted between 2003 and 2011, found that, compared withthe standard treatment, BMCs transplantation improvedthe left ventricular systolic function and decreased the infarct size both in acute myocardial infarction and in chronicischemic heart disease[27].

TOPCARE-AMI AMI (*the transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction*) and BOOST (*Bone marrow transfer to enhance ST-elevation infarct regeneration*), two trials analyzing BMCs transplantationfor cardiac repair, have recently publishedtheir five year follow-up results[25,27].

Of the 59 subjects included in TOPCARE-AMI, 29 receiving BMCs and 30 subjects receiving circulating mononuclear cells. It has to be mentioned that from the trial design lacks a placebo-controlled treatment group.

Cells were administrated intracoronary, in the infarct-related artery, at 4.9+/-1.5 days after STEMI. At a mean follow-up of 4 months, LVEF improved from 49+/-10% to 57+/-10% (p<0.001) in the BMCs group and from 51+/-10% to 59+/-10% (p<0.001) in the group receiving circulating progenitor cells. The resultsof the study at 5 years confirmed a persistence of thebeneficial effects on LV function, with a improvement of LVEF with 11% (P <0.001)[25].

The BOOST trial enrroled 60 patients. The BMCs were delivered in the infarct-related artery at 4.8+/-1.3 days after STEMI. In the BOOST trial, the control group received postinfarction conventional medical therapy, but no cells. At six months, mean LVEF improved by 6.7% in the cell therapy group and by 0.7% in the control group (P=0.04). This increasing of LVEF was attribuited to improved regional systolic wall motion in infarct area[26]. But, 5-year follow-up data showed a increase a LV volumes and a decrease in LVEF in both groups, without significant difference in mortality rate between two groups. Subgroups analysis suggested that the patients with larger infactions have the most benefits from cell therapy in terms of LV dimensions and LVEF[25,26].

The REPAIR-AMI (*the Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction*) trial, as the largest double-blind, placebocontrolledtrial, included 204 patients which were randomized to intracoronary injection of bone marrow mononuclear cells (BM-HSCs, BM-MSCs or BM-EPCs) versus placebo 3-7 days after successful primary PCI in STEMI. At 4-month follow-up, LVEF improved by5.5+-7.3 % in the BMCs group and by 3.0+/-6.5% in the placebo group (p=0.01), but 2-year follow-updata found no ameliorated LVEF in the BMCs treated group compared tothe placebo treated group[25].

The CELLWAVE study used extracorporal shock wave therapy performed prior to cell therapy for induction of therapeutic neovascularization and improvement of homing of bone marrow progenitor cells in patients following anterior myocardial infarction. Shock waves can induce expression of some growth factorssuch as stromal cellderived factor 1 (SDF-1) and vascular endothelial growth factor (VEGF) in the injured myocardial tissue and can direct autologous bone marrow mononuclear cells which are injected intracoronary 24 hours following shock wave therapyto ischemic myocardium. The shock wave BMC group showed an increase in LVEF of 3.2% after four months whereas the shockwave placebo infusion group only presented a 1% improvement (p=0.02)[28].

In conclusion, clinical trials have shown that BMCs transplantation is safe and feasible but outcomes in terms of efficacy are not consistent and in someresearch only transient.

Adipose tissue derived regenerative cells (ADRCs)

The human lipoaspirates,harvested in relatively large quantities by liposuction, contain multipotent cells with a differentiation potential beyond that of the adipocytic lineage. These ADRCs have manyproperties similar with BM-MSCs. Adipose tissue contains up to 2.500 times more MSC-like cells than freshly isolated bone marrow[27].

The APOLLO trial is a randomized, double-blind, placebo-controlled, phase I/IIa studydesigned to assess the safety and efficacy of intracoronary transplantation of ADRCs in 14 patients in the acute phase of a large ST-segment elevation acute myocardial infarction (STEMI). At six months, SPECT analysis demonstrated a significant reduction in infarct size and an improvement of LVEF by 4% in ADRC-treated patients (from 52.1% to 56.1%), whereas in the placebo group LVEF deteriorated by 1.7% (from 52.0% to 50.3%), resulting in an absolute difference between the treatment groups of 5.7% (p=0.114)[26,27,30].

The ongoing ADVANCE study is a multicenter, prospective,randomized, placebo-controlled phase IIb/III clinical trial that willevaluate the safety and efficacy of an intracoronary administration of two dosesof ADRCs in up to 375 patients with STEMI. This study wasinitiated in May 2011 and the results have not yet been published[27].

Cardiac derived stem cells (CPCs)

Current clinical studies also use some cell populations, derived directly from thehuman adult heart, heart tissue having its own rezervoir of progenitor cell. CDCs are a naturalcomposite of stromal, mesenchymal and progenitor cellswhich exhibit distinct surface receptors[26,27]. There are two main CDCs populations that have described, the c-kit+ population and cardiosphere derived cells. Safetyand efficacy of CDCs transplantation has been demonstrated inmany preclinical studies. CDCs has been shown to be superior to BM-MSCs or ADRCsin terms of recovery of ischemic tissue, anti-remodelling effects and functional benefits[27].

In the CADUCEUS (*Cardiosphere-Derived autologous stem cells to reverse ventricular dysfunction*)trial, in 17 patients at 2-3 months after acute myocardial infarction, CDCsharvested fromright ventricular endomyocardial biopsieswere administrated by intracoronary transplantation into the infarct related artery.

The results were compared with eight patients who receivedstandard medical treatment. The trial showed not only that scar size was reduced on cardiac magnetic resonance imaging at six months in CDCs group, but also that the amount of viable heart mass and regional contractility were also improved, with a LVEF significantly improved at 12 months compared with control patients.But the study could not be done in a blinded manner because of ethical considerations related to right ventricular biopsy on the controls patients[26,27,32].

C-kit positive populationwere first described in 2003. These cardiac stem cellsare able of differentiating into cardiomyocytes, vascular smooth muscle cells and endothelial cells[27]. The SCIPIO trial is a first-in-human phase 1, randomized, open-label trial, which used c-KIT-positive CDCs, in patients with left ventricular dysfunction (LVEF <40%) following an acute myocardial infarction. In the trial, the cells were collected from the patient's right atrial appendage, isolated and expanded at the time of coronary bypass surgery and then re-infused to repair an infarction, at 3-4 months after surgery. In the 18 patients treated with the CDCs infusion, the average LVEF,assessed by echocardiography, increased from 29.0% before infusion to 36.0% (p <0.001) four months after the procedure. During that period, LVEF improved only from 29.2% to 29.4% in 13 control patients. There was no difference in adverse event rate between two groups[26,27,33].

Mobilization of progenitor cells

Another strategy for cardiac regeneration is the mobilization from the bone marrow of some progenitor cells by administration of growth factors or cytokines[27].

Erytropoietin is a hormone that controls erythropoiesis and is known to rise capacity of the blood to carry oxigen. Hypoxic ischemic cardiomyocytes and vascular endothelial cells exhibit surface receptors for erytropoietin. A meta-analysis based on 13 randomized trials involving 1564 patients demonstrated that erythropoietin therapy did not improve left ventricular ejection fraction, did not influence infarct sizeor risk of stent thrombosis, did not decrease the risk of heart failure or all-cause mortality rate[29].

Granulocyte colony stimulating factor (G-CSF) is secreted by monocytes, fibroblasts and endothelial cells. Two meta-analyses analyzing the role of G-CSF in cardiac repair after myocardial infarction demonstrated no any functional benefit from G-CSF administration[27].

In conclusion, from over 1300 subjects randomized in these studies, there is sufficient evidence to conclude that stem cell therapy after STEMI is safe, while the efficacy of this intervention for improving outcomes is less clear[26]. Recent meta-analyses have highlighted the importance of both timing of cell delivery, as well as the type, quantity and mobility of delivered cells as determinants of response[26].

The optimal timing of cell delivery after myocardial infarctionis potentially one of the main issues in terms of cell homing andsurvival[26]. Myocardial infarction is a condition associated with a significant inflammatory response.Administration ofunprotected cells into this unfriendly environment can results in cell death. It is possible that transplanted stem cellseven to be involved in the inflammation cascade and not in the formation of newvessels and cardiac repair. The optimal time for stem cell transplantation seems to be within the first monthfollowing a myocardial infarction[27]. It seems that higher doses of CD34+ cells which are more potent in terms of their migratory capacity, offer the best hope for preserving cardiac function following STEMI[26].

FUTURE DIRECTIONS

The ideal antithrombotic agent has yet to be found. The best combination of antiplatelet and anticoagulant agents that results in lower thrombotic complications without increasing the risk of bleeding complications is currently unknown. Some patients continue to experience adverse ischaemic events despite the treatment with aspirin, a P2Y12-receptor antagonist and new anticoagulants, because platelets can remain activated and an excess thrombin generation seem to persist via pathways not inhibited by these agents. Emerging antithrombotic therapies include thromboxane-receptor inhibitors (picotamide, ridogrel, ramatroban, NCX 4016- a nitric oxide- releasing aspirin derivative, Si8886/terutroban, EV077- a combined TXA2 synthase inhibitor and thromboxane-receptor inhibitor), intravenous P2Y12 antagonists (cangrelor), oral PAR-1 antagonists (vorapaxar/SCH530348, atopaxar/E5555). But, at the present time, none of these agents appear to be suitable for replacing aspirin in patients with coronary arteries disease[34].

Intracoronary transplantation of alternative cell with "true"regenerative propertiesor a reprogrammingof scar tissue back into functional myocardium are promisingapproaches. Subsequent research should lead to a better understanding of how cells can be made to differentiate *in vitro* into a phenotype that may improve cardiac repair[26].

Abbreviations:

STEMI	ST segment elevation myocardial infarction
PCI	percutanenous coronary intervention
DES	drug-eluting stents
ACS	acute coronary syndrome
LV	left ventricle
LVEF	left ventricular ejection fraction.

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