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REVIEW

Recent advances in the diagnosis and treatment of acute myocardial infarction

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Abstract

The Third Universal Definition of Myocardial Infarction (MI) requires cardiac myocyte necrosis with an increase and/or a decrease in a patient's plasma of cardiac troponin (cTn) with at least one cTn measurement greater than the 99th percentile of the upper normal reference limit during: (1) symptoms of myocardial ischemia; (2) new significant electrocardiogram (ECG) ST-segment/T-wave changes or left bundle branch block; (3) the development of pathological ECG Q waves; (4) new loss of viable myocardium or regional wall motion abnormality identified by an imaging procedure; or (5) identification of intracoronary thrombus by angiography or autopsy. Myocardial infarction, when diagnosed, is now classified into five types. Detection of a rise and a fall of troponin are essential to the diagnosis of acute MI. However, high sensitivity troponin assays can increase the sensitivity but decrease the specificity of MI diagnosis. The ECG remains a cornerstone in the diagnosis of MI and should be frequently repeated, especially if the initial ECG is not diagnostic of MI.

There have been significant advances in adjunctive pharmacotherapy, procedural techniques and stent technology in the treatment of patients with MIs. The routine use of antiplatelet agents such as clopidogrel, prasugrel or ticagrelor, in addition to aspirin, reduces patient morbidity and mortality. Percutaneous coronary intervention (PCI) in a timely manner is the primary treatment of patients with acute ST segment elevation MI. Drug eluting coronary stents are safe and beneficial with primary coronary intervention. Treatment with direct thrombin inhibitors during PCI is non-inferior to unfractionated heparin and glycoprotein Ⅱb/Ⅲa receptor antagonists and is associated with a significant reduction in bleeding. The intra-coronary use of a glycoprotein Ⅱb/Ⅲa antagonist can reduce infarct size. Pre- and post-conditioning techniques can provide additional cardioprotection. However, the incidence and mortality due to MI continues to be high despite all these recent advances. The initial ten year experience with autologous human bone marrow mononuclear cells (BMCs) in patients with MI showed modest but significant increases in left ventricular (LV) ejection fraction, decreases in LV end-systolic volume and reductions in MI size. These studies established that the intramyocardial or intracoronary administration of stem cells is safe. However, many of these studies consisted of small numbers of patients who were not randomized to BMCs or placebo. The recent LateTime, Time, and Swiss Multicenter Trials in patients

with MI did not demonstrate significant improvement in patient LV ejection fraction with BMCs in comparison with placebo. Possible explanations include the early use of PCI in these patients, heterogeneous BMC populations which died prematurely from patients with chronic ischemic disease, red blood cell contamination which decreases BMC renewal, and heparin which decreases BMC migration. In contrast, cardiac stem cells from the right atrial appendage and ventricular septum and apex in the SCIPIO and CADUCEUS Trials appear to reduce patient MI size and increase viable myocardium. Additional clinical studies with cardiac stem cells are in progress.

Key words: Myocardial necrosis; Type 1-5 myocardial infarctions; Troponin assays; Percutaneous coronary intervention; Fibrinolytic therapy; Thienopyridines; Cardioprotection; Bone marrow stem cells; Cardiac stem cells

Core tip: The Third Universal Definition of myocardial infarction (MI) combines clinical symptoms, cardiac biomarkers and electrocardiogram (ECG) changes. Small amounts of myocardial necrosis may occur with heart failure, renal failure, myocarditis, arrhythmias, pulmonary embolism or uneventful percutaneous or surgical coronary revascularization and should be termed myocardial injury. High sensitivity troponin assays increase the sensitivity but decrease the specificity of MI diagnosis. The ECG remains a cornerstone of MI diagnosis. Primary percutaneous coronary intervention in a timely manner is the primary treatment of patients with acute ST segment elevation MI. Antiplatelet agents (clopidogrel, prasugrel or ticagrelor), in addition to aspirin, reduce patient MI morbidity and mortality. The recent LateTime, Time, and Swiss Multicenter Trials of bone marrow stem cells in MI treatment did not demonstrate significant improvement in patient LV ejection fraction in comparison with placebo. In contrast, cardiac stem cells from the right atrial appendage or ventricular septum/apex in the SCIPIO and CADUCEUS Trials reduced patient MI size and increased viable myocardium. Studies with cardiac stem cells are continuing.

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DEFINITION OF MYOCARDIAL INFARCTION

The Third Universal Definition of myocardial infarction (MI) expert consensus document was published in October 2012 by the global Myocardial Infarction Task Force[1]. The definition of MI requires cardiac myocyte necrosis with an increase and/or a decrease in plasma of cardiac troponin (cTn). At least one cTn measurement should be greater than the 99th percentile normal reference limit during: (1) symptoms of myocardial ischemia; (2) new (or presumably new) significant ECG ST-segment/T-wave changes or left bundle branch block; (3) the development of pathological electrocardiographic (ECG) Q waves; (4) new loss of viable myocardium or regional wall motion abnormality identified by an imaging procedure; or (5) identification of intracoronary thrombus by angiography or autopsy.

Cardiac troponin (I or T) has high myocardial tissue specificity as well as high clinical sensitivity because cTn T and I are essential contractile components of myocardial cells and are expressed almost exclusively in the myocardium. Release of cardiac troponin from the myocardium can result from normal turnover of myocardial cells, myocyte apoptosis, myocyte release of troponin degradation products, increased myocyte wall permeability and bleb formation, or myocyte necrosis[1].

Myocardial necrosis due to myocardial ischemia is defined as myocardial infarction[2]. Detection of a rise and a fall of troponin, expressed in ng/L or pg/mL, is essential to the diagnosis of acute MI[3,4]. Blood samples for the measurement of cTn should be drawn during the initial patient assessment and repeated 3-6 h later. Subsequent additional blood samples are required if further ischemic episodes occur, or when the timing of the initial symptoms onset is unclear[5]. The demonstration of a rise and fall in troponin measurements is extremely important in the differentiation of acute from chronic elevations in cTn concentrations that can be associated with structural heart disease such as patients with left ventricular hypertrophy (LVH), renal failure and heart failure (Table 1)[6].

The ECG remains a cornerstone in the diagnosis of MI and should be acquired and interpreted within 10 min after patient presentation[7]. Since ECG changes of MI can be transient, ECGs should be acquired at 15-30 min intervals, especially if the initial ECG is equivocal. Wide spread and profound ST-T changes are associated with greater degrees of myocardial ischemia. The extent and severity of coronary stenosis, collateral coronary circulation and prior myocardial necrosis impact on the ECG manifestations of myocardial ischemia[8]. Prior ECGs, when available, should be compared with current tracings. Mimickers of ECG changes of MI such as acute pericarditis, LVH, left bundle branch block (LBBB), Brugada syndrome, stress cardiomyopathy, and early repolarization patterns should be considered in the differential diagnosis[9].

Electrocardiographic ST-T wave criteria for the diagnosis of acute myocardial ischemia is listed in Table 2. The J point is used to determine the magnitude of the ST-segment shift. "Contiguous leads" refers to lead groups such as anterior leads (V1-V6), inferior leads

Table 1 Causes of troponin elevation

System	Causes of troponin elevation
Cardiovascular	Acute aortic dissection
	Arrhythmia
	Medical ICU patients
	Hypotension
	Heart failure
	Apical ballooning syndrome
	Cardiac inflammation
	Endocarditis, myocarditis, pericarditis
	Hypertension
	Infiltrative disease
	Amyloidosis, sarcoidosis, hemochromatosis, scleroderma
	Left ventricular hypertrophy
Myocardial injury	Blunt chest trauma
	Cardiac surgeries
	Cardiac procedures
	Ablation, cardioversion, percutaneous intervention
	Chemotherapy
	Hypersensitivity drug reactions
	Envenomation
Respiratory	Acute PE
	ARDS
Infectious/immune	Sepsis/SIRS
	Viral illness
	Thrombotic thrombocytopenic purpura
Gastrointestinal	Severe GI bleeding
Nervous system	Acute stroke
	Ischemic stroke
	Hemorrhagic stroke
	Head trauma
Renal	Chronic kidney disease
Endocrine	Diabetes
	Hypothyroidism
Musculoskeletal	Rhabdomyolysis
Integumentary	Extensive skin burns
Inherited	Neurofibromatosis
	Duchenne muscular dystrophy
	Klippel-Feil syndrome
Others	Endurance exercise
	Environmental exposure
	Carbon monoxide, hydrogen sulfide

GI: Gastrointestinal; ICU: Intensive care unit; PE: Pulmonary embolus; ARDS: Acute respiratory distress syndrome; SIRS: Systemic inflammatory response syndrome.

(Ⅱ, Ⅲ, aVF) or lateral/apical leads (Ⅰ, aVL).

Supplemental leads such as V3R and V4R, in the third and fourth right intercostal spaces, indicate the electrical activity in the free wall of the right ventricle and V7-V9 indicate the electrical activity in the inferobasal left ventricular wall. In patients with inferior and right ventricular infarction, ST segments are often elevated ⩾ 0.05 mV in V3R and V4R. In addition, ST elevation of ⩾ 0.05 mV ST in leads V7-V9 (V7 at the left posterior axillary line, V8 at the left mid-scapular line, and V9 at the left paraspinal border), supports the diagnosis of inferobasal MI due to left circumflex coronary artery occlusion. ST depression in leads V1-V3 also may be suggestive of inferobasal myocardial ischemia (posterior infarction), especially when the terminal T wave is positive[10-12].

Table 2 Electrocardiogram manifestations of acute myocardial ischemia (in absence of left ventricular hypertrophy and left bundle branch block)

ST elevation
New ST elevation at the J point in two contiguous leads with the cut-points:
⩾ 0.1 mV in all leads other than leads V2–V3 where the following cut points apply: ⩾ 0.2 mV in men ⩾ 40 yr; ⩾ 0.25 mV in men < 40 yr, or ⩾ 0.15 mV in women
ST depression and T wave changes
New horizontal or down-sloping ST depression ⩾ 0.05 mV in two contiguous
leads and/or T inversion ⩾ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1

ST segment elevation of > 0.5 mV is observed in lead aVR in acute left main coronary artery (LMCA) obstruction and proximal left anterior descending coronary artery (LAD) obstruction proximal to the first major septal branch. The ST elevation in aVR is more pronounced than in V1 in patients with acute LMCA occlusion. This pattern occurred in 88% of the patients with acute occlusion of LMCA group in one study[10,13]. Types of MI, five types of MI are based on pathological, clinical and prognostic differences (Table 3).

DIFFERENTIATING BETWEEN SPONTANEOUS TYPE 1 AND ISCHEMIC IMBALANCE TYPE 2 MYOCARDIAL INFARCTION

Differentiation between type 2 and type 1 MI is challenging and needs careful clinical assessment. It is very important that the differentiation be made whether the myocardial injury is likely to be due to plaque rupture (type 1 MI), or whether it is due to an imbalance in myocardial oxygen supply or demand (type 2 MI), because the management of these two conditions is very different. While, the treatment of type 1 MI primarily includes antithrombotic therapy and/or revascularization, as clinically appropriate, the management of type 2 MI is more varied because several different mechanisms may be responsible for pathogenesis ischemic imbalance. In critically ill patients or in patients with major (non-cardiac) surgery, biomarker elevation may be caused by the direct toxic effects of endogenous or exogenous high circulating catecholamines, coronary vasospasm and/or endothelial dysfunction or fixed coronary atherosclerosis and demand-supply mismatch (Figure 1). For example, a post-operative patient with hypotension and troponin elevation due to hypovolemia or acute blood loss, requires treatment with intravascular volume replacement, including blood transfusion. In certain instances, troponin elevation due to ischemic demand may unmask severe coronary artery disease (CAD) by increasing myocardial oxygen demand in the presence of fixed coronary stenosis. Consequently once the

Table 3 Third universal classification of myocardial infarction

Type 1: Spontaneous MI Spontaneous MI due to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD, non-obstructive coronary disease or no CAD
Type 2: MI secondary to an ischemic imbalance Myocardial injury with necrosis occurs due to conditions other than CAD that contribute to an imbalance between myocardial oxygen supply and/or demand such as coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachycardia-bradycardia arrhythmias, anemia, respiratory failure, hypotension, and hypertension
Type 3: MI resulting in death when biomarker values are unavailable Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurs before blood samples can be obtained, before cardiac troponins biomarkers rise, or when cardiac biomarkers were not collected
Type 4A: MI related to percutaneous coronary intervention MI associated with PCI is defined by elevation of cTn values greater than five times the 99th percentile upper normal reference limit (URL) in patients with normal baseline values (< 99th percentile URL) or a rise of cTn values by > 20% if the baseline troponins are elevated and are stable or falling. In addition one of the following criterion are required: (1) symptoms suggestive of myocardial ischemia; (2) new ischemic ECG changes or new LBBB; (3) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no coronary flow or coronary embolization; or (4) demonstration with imaging of a new loss of viable myocardium or new regional wall motion abnormality
Type 4B: MI related to stent thrombosis MI associated with stent thrombosis detected by coronary angiography or autopsy in the presence of myocardial ischemia with a rise and/or fall of troponin biomarkers. One troponin measurement should be above the 99th percentile UR
Type 4C: MI related to restenosis MI associated with restenosis defined as ⩾ 50% stenosis or a complex lesion demonstrated at coronary angiography after (1) initial successful stent deployment; or (2) dilatation of a coronary artery stenosis with balloon angioplasty. These coronary angiographic changes should be associated with an increase and/or decrease of cTn values > 99th percentile URL and no other significant obstructive CAD
Type 5: MI related to coronary artery bypass grafting MI associated with CABG is defined by elevation of cardiac troponins greater than ten times the 99th percentile URL in patients with normal baseline cTn values (< 99th percentile URL). In addition, one of the following should be present: (1) new pathological Q waves or new LBBB; or (2) angiographic documented new graft or new native coronary artery occlusion; or (3) new loss of viable myocardium or new regional wall motion abnormality as shown by an imaging modality

Adapted from Thygesen *et al*[14]. MI: Myocardial infarction; CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; cTn: Cardiac troponin; CABG: Coronary artery bypass grafting; LBBB: Left bundle branch block.

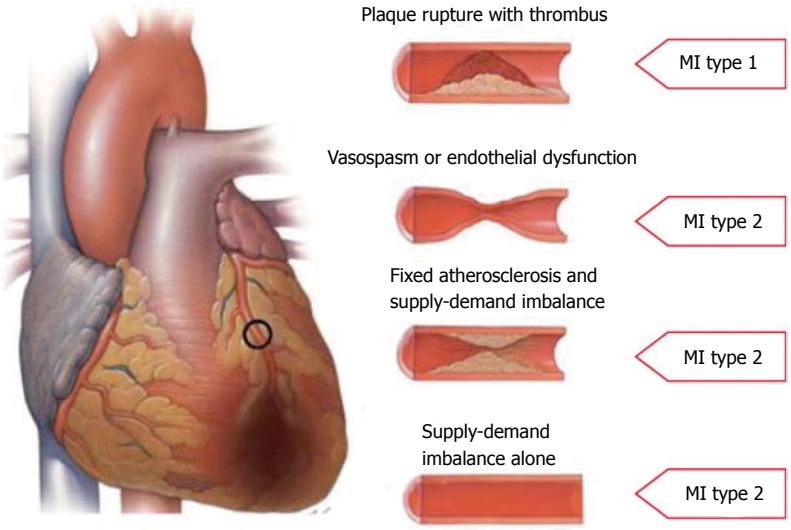

Figure 1 Type 1 and type 2 myocardial infarctions.

patient recovers from the acute illness, a stress test for inducible ischemia or coronary angiography can be helpful.

MYOCARDIAL INFARCTION DUE TO RE-VASCULARIZATION PROCEDURES

The 2007 universal MI definition required the presence of cardiac biomarkers greater than three times the 99th percentile of the upper normal range limit (URL) without requirements for associated ischemic changes or complications from angiographic procedures. This resulted in approximately 15% of patients undergoing PCI being diagnosed with an AMI[15,16]. In the 2012 definition of MI, there is a more strict definition of type 4a MI[1]. Percutaneous coronary intervention related MI is defined by cTn elevation greater than *five times* 99th percentile within 48 h after the procedure with: (1) symptoms suggestive of myocardial ischemia; or

(2) new ischemic ECG changes; or (3) angiographic findings consistent with a procedural complication with loss of a major artery or side coronary artery branch, decreased coronary flow, or coronary embolization; or (4) demonstration of new loss of viable myocardium or new regional wall motion abnormality. The occurrence of procedure-related myocardial cell injury with necrosis can be detected by measurements of cardiac troponin before the procedure, 3-6 h after the procedure and, optionally, re-measurement 12 h thereafter. An increasing cTn can only be interpreted as a procedure-related myocardial injury if the pre-procedural cTn value is $\leqslant 99^{th}$ percentile URL or if the troponin measurements are stable or falling. If the pre-procedural troponin is increased but is either stable or falling, an increase in cTn levels of > 20% is used to characterize a PCI-related MI.

The relationship between troponin increases after revascularization and mortality is controversial. The evidence for the association between biomarkers and mortality has evolved over the last 15 years. Studies have suggested a stronger association with the post-PCI MB fraction of creatine kinase (CK-MB) and subsequent cardiovascular events than with cTn elevation[15,17]. The level of CK-MB measurements varied from three to ten times the URL in these studies. When analyzed in categories of incrementally increasing biomarker elevations, most contemporary PCI studies have reported associations between periprocedural myonecrosis and mortality only for very large patient infarctions[17]. Only pre-procedure cTn elevations are correlated with subsequent mortality[18,19]. Consequently, in patients with baseline troponin elevation prior to PCI, the diagnostic accuracy of using the definition of post-PCI MI is limited.

With the application of the 2007 universal definition of post CABG MI (type 5), 42% to 82% of cardiac surgical patients had cardiac biomarker elevation greater than five times the URL[20], but only 4% to 7% had electrocardiographic evidence required for post-CABG MI[21]. Elevation of cardiac biomarker values after CABG can occur due to myocardial trauma, with dissection of the coronary arteries, manipulation of the heart, inadequate cardiac protection, reperfusion injury, or graft failure. Any increase in cardiac biomarker values > 99^{th} percentile URL is defined as myocardial injury. The new criteria for type 5 MI in patients with CABG requires an increase in biomarkers > 10 × 99^{th} percentile URL from a normal baseline during the first 48 h after surgery, plus new electrocardiographic Q waves or new LBBB, angiographic documentation of new graft or new native coronary artery occlusion, or imaging evidence of new regional wall motion abnormality or new loss of viable myocardium. The 2012 global MI task force emphasized that the threshold for diagnosing MI is more robust for on-pump CABG. The existing criteria for the universal definition of myocardial infarction should be used for diagnosing MI in patients who are more than 48 h after cardiac surgery[1].

The Society for Cardiovascular Angiography and Interventions has published an expert consensus document that defines clinically relevant myocardial infarction after revascularization (Table 4)[14].

REINFARCTION/RECURRENT MI

The term "reinfarction" is used for an acute MI that occurs within 28 d of a MI. If the cTn concentration is elevated, but stable or decreasing at the time of suspected reinfarction, the diagnosis of reinfarction requires a 20% or greater increase in the cTn measurement. If the initial cTn concentration is normal at the time of suspected reinfarction, the criteria for new acute MI apply[1,22].

TROPONIN ELEVATION IN HEART FAILURE

Based on the type of assay used, a range of elevated cTn values, indicative of myocardial injury with necrosis, may be seen in patients with a heart failure (HF) syndrome[23]. In stable heart failure patients, the median concentration of hs-cTnT is 12 ng/L, which is very close to the 99^{th} percentile URL of 14 ng/L for this assay[24]. Hence, using hs-cTn assays, cTn concentrations may be measured in nearly all patients with HF. Many HF patients exceed the 99^{th} percentile URL, especially those patients with severe decompensated HF syndrome[25]. While type 1 MI is an important cause of acutely decompensated heart failure, other mechanism(s) leading to troponin elevation in HF syndromes such as supply-demand inequity (type 2 MI) should be considered. Non-coronary triggers, such as anemia, cellular necrosis, apoptosis, or autophagy in the context of wall stress may cause troponin release in HF, as can the toxic effects of circulating neurohormones, toxins, inflammation, and infiltrative processes. Nonetheless, in patients with HF, troponin elevation independent of its mechanism, is strongly predictive of an adverse outcome and should not be ignored[25].

HIGH SENSITIVITY TROPONIN ASSAYS

Highly sensitive assays for cTnT and cTnI are available and are widely used in many parts of the world, although they are not generally used at the present time in the United States[26]. Two criteria should be met for high sensitivity troponin assays (hs-Tn). First, the coefficient of variation at the 99^{th} percentile value should be $\leqslant$ 10%. Second, the assay should be able to measure cTn concentrations below the 99^{th} percentile in $\geqslant$ 95% of normal individuals[27]. Compared with standard cTn assays, the hs-cTn assays have improved sensitivity and discrimination for MI, particularly in the first 3 to 6 h after symptom onset[28]. These advantages are somewhat offset by a decrease in specificity for MI[28-30] and concerns regarding the broad application of these tests, especially in populations with

Table 4 Proposed definition of clinically relevant myocardial infarction after both percutaneous coronary intervention and coronary artery bypass grafting procedures

In patients with normal baseline CK-MB	The peak CK-MB measured within 48 h of the procedure rises to ≥ 10 × the local laboratory ULN, or to ≥ 5 × ULN with new pathologic Q-waves in ≥ 2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to ≥ 70 × the local laboratory ULN, or ≥ 35 × ULN with new pathologic Q-waves in ≥ 2 contiguous leads or new persistent LBBB
In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level
In patients with elevated CK-MB (or cTn) in whom the biomarker levels have not been shown to be stable or falling	The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension

ULN: Upper limit of normal; MI: Myocardial infarction; cTn: Cardiac troponin.

a low MI prevalence.

There is controversy regarding the metrics that should be used with hs-cTn assays for the diagnosis of AMI. In this regard, attempts have been made to define in these assays the optimal value for relative change or deltas in hs-cTn concentrations. Higher deltas increase specificity while lower ones improve sensitivity. The potential for analytical interferences with hs-cTn assays is greater than with conventional assays. Examples include reductions in hs-cTnT concentrations due to hemolysis and autoantibodies or increases due to heterophilic antibodies[31]. Studies suggest that an absolute increase of hs-cTnT values, *i.e.*, > 7 ng/L over 2 h, is superior to relative percentage changes from the baseline in the diagnosis of MI[32-34].

According to the recent guideline for the management of patients with acute coronary syndromes, blood samples for high-sensitivity cardiac troponin measurements should be obtained at presentation and 3 h after admission[35]. Measurements of hs-cTn should be repeated 6 h after admission in patients in whom the 3 h values are unchanged but in whom the clinical suspicion of MI is still high[36].

Distinguishing between type 1 and type 2 MI is challenging with high sensitivity troponin measurements. As troponin assay sensitivity increases, the frequency of possible type 2 MI increases and the distinction from type 1 MI becomes more complicated. Moreover, the diagnostic accuracy of a baseline measurement of hs-cTn for presence of AMI in patients with renal insufficiency is poor[37]. Nevertheless, elevated hs-cTns have important prognostic implications and patients require additional evaluations because a high cTnT level is associated with all-cause and cardiovascular mortality and with incident heart failure in 3 population based studies[30].

TREATMENT OF ACUTE MYOCARDIAL INFARCTION

The incidence of ST segment myocardial infarction (STEMI) has gradually declined over the past decade. However it still accounts for 25%-40% of all acute coronary syndrome related hospitalizations in the United States[37]. Moreover, the incidence of acute myocardial infarction is increasing in the developing countries[38]. Heart disease is expected to be the leading cause of death in the developing world by the year 2020. With changing dietary and personal habits, the prevalence of smoking, hypertension, diabetes, obesity and metabolic syndrome are increasing in areas of the world with large populations such as India[39], China[40] and South America[41]. Advances made in the area of medical therapy and coronary interventions have resulted in a significant decrease in the mortality rates. Current in-hospital and one year mortality are in the order of 5%-6% and 7%-18% respectively[42,43]. During the course of last three decades, there have been significant advances in our understanding of the pathophysiology and treatment of STEMI. In addition to these scientific advances, substantial progress has been made in the areas of public awareness and guideline driven clinical practice[44]. This has led to a gradual decline in STEMI related mortality and improved patient related outcomes. However, there continues to be significant difference in the 30-d mortality rates based on the geographic region[45], age[46,47], gender[48] and race[49]. In addition, individuals with diabetes and chronic renal insufficiency continue to have high rates of mortality[50-52]. In the recent INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy During Primary PCI for Anterior STEMI) trial[53], diabetics compared to non-diabetics, had higher incidence of stent thrombosis at 30 d (4.3% *vs* 0.8%, P = 0.03) and higher rates of major cardiovascular and cerebrovascular events at 1 year (16.5% *vs* 8.0%, P = 0.04). It has been shown that patients with end-stage renal disease frequently do not receive guideline based therapies. In one registry, it has been shown that only 45% of eligible patients on dialysis received coronary reperfusion therapy, and only 70% of patients received aspirin on admission for coronary syndromes. In-hospital mortality rate from myocardial infarction is 21.3% in those on dialysis and 11.7% in those with renal disease but not on dialysis[54].

Approximately 7% of the eligible patients with myocardial infarctions do not receive reperfusion therapy[55]. There is evidence suggesting that reperfusion therapy offers benefit in the elderly. However, age is

the strongest predictor associated with an individual not receiving reperfusion therapy[56]. Programs that focus on patient education, systematic organization of STEMI programs and standardization of clinical practice result in improved care of all groups of patients and minimize disparities[57,58].

One of the most important components of STEMI management is getting the patients in a time efficient manner to a hospital that is capable of administering reperfusion therapies such as fibrinolytic therapy and primary percutaneous coronary intervention. Although approximately 98% of the United States population is within the reach of 911 based emergency medical service systems, patients with STEMI do not routinely utilize the system[59]. System based delays have been shown to increase STEMI related morbidity and mortality[60-63]. Hence increased community awareness and preparedness is important. In addition, regional STEMI centers with organized protocols, system based time-to-treatment goals and quality improvement programs must be established. Such efforts minimize delays and lower morbidity and mortality in STEMI patients[64,65]. In a study by Sørensen *et al*[66], where 759 consecutive STEMI patients were divided into a group with pre-hospital diagnosis and direct referral to a primary PCI center *vs* a group without pre-hospital diagnosis. Pre-hospital diagnosis and direct referral resulted in shorter system delay (92 min *vs* 153 min, $P < 0.001$).

CORONARY REPERFUSION STRATEGIES

Fibrinolytic therapy (FT) and Primary Percutaneous Coronary Intervention (P-PCI) are the two currently available modalities of reperfusion therapies. Both of these options are extensively studied. P-PCI, when performed in a timely manner at a high patient volume center is superior to FT. However, P-PCI is not universally available[67]. Delays in door-to-balloon times (D2B) are associated with increased mortality[68]. Adherence to D2B goal of < 90 min lowers mortality[69,70]. Although P-PCI is superior to FT, emphasis should be placed on timely administration of some form of reperfusion therapy rather than the mode of treatment[71].

For patients who present to a P-PCI capable hospital, the door to balloon time should not exceed 90 min. When patients present to a hospital that is not capable of P-PCI, factors such as time of onset of symptoms, risk of bleeding, presence of acute heart failure or shock, risk of mechanical complications, time-to-transfer to a P-PCI capable hospital should be taken into consideration. In patients who present within less than 1-2 h of onset of symptoms, immediate FT may be advantageous even if the transfer times are short[72].

ROLE OF PRE-HOSPITAL FIBRINOLYTIC THERAPY

Multiple trials have shown the safety and efficacy of pre-hospital FT[73-76]. This approach reduces the time to treatment by approximately 60 min and decreases mortality by 17%[77]. Similar findings were also seen in the pooled analysis of two other trials[78]. The Swedish and the French (USIC) registries showed that pre-hospital FT can be administered safely and results in reduces mortality[79,80]. At this time, pre-hospital use of FT is not commonly used in the United States but is used frequently in Western Europe and England.

STEMI PATIENTS WITH OUT-OF-HOSPITAL CARDIAC ARREST

Approximately 70% of CAD related deaths present as cardiac arrest prior to presenting to a hospital[81]. Less than a quarter of patients presenting with sudden cardiac arrest have ventricular tachycardia or ventricular fibrillation that can be electrically converted to normal sinus rhythm[82]. Of the 60% patients who are resuscitated by emergency response teams, the median survival rate to hospital discharge is 7.9%[83]. In patients with STEMI who present with sudden cardiac arrest, timely defibrillation and hypothermia have been shown to increase survival. For every minute delay in defibrillation, there is 7% to 10% drop in survival[83,84]. Increasing access to and use of defibrillators in public places has resulted in an increase in the number of patients that are neurologically intact after sudden cardiac arrest[84-86]. In patients with out-of hospital cardiac arrest, hypothermia with temperatures between 32 ℃ to 34 ℃ increases survival. In a study of 77 patients[87], hypothermia (with the core body temperature reduced to 33 degrees C within 2 h after the return of spontaneous circulation and maintained at that temperature for 12 h) compared to normal temperature increased the survival rates 26% to 49% $P = 0.0046$. In another study, survival was shown to be improved with hypothermia[88]. In patients with out-of hospital cardiac arrest in the setting of STEMI, hypothermia should be initiated as soon as possible.

FIBRINOLYTIC THERAPY

When P-PCI is not available, FT is an alternative. It reduced mortality and morbidity when carefully administered within 12 h of symptom onset[89-94]. The usefulness of FT in patients presenting greater than 12 h from the onset of symptoms is not well established[95-98]. Fibrin specific agents such as tenecteplase, retaplase and alteplase are preferred. Tenecteplase is the most fibrin specific. None of the fibrin specific agents are antigenic. Patency rates of the infarct related artery with fibrin specific agents are approximately 85%[99-103]. Streptokinase is a non-fibrin-specific agent and can cause antigenic reactions. Infarct related artery patency rate with streptokinase is 60%-70%[104]. When the delay from first medical contact to primary PCI is > 120 min, FT is indicated if the time of onset of symptoms is < 12 h.

ADJUNCTIVE PHARMACOTHERAPY WITH FIBRINOLYTIC THERAPY

The role of Aspirin and Clopidogrel with fibrinolytic therapy is well established[105-107]. Aspirin and Clopidogrel should be given prior to the administration of fibrinolytic agent. Dual antiplatelelt therapy should be continued for at least one year[107]. The data on using newer antiplatelet agents like Prasugrel and Ticagrelor as an adjunct to thrombolytic therapy for fibrinolysis is not yet well established.

In addition to antiplatelet therapy, the use of adjunctive anticoagulants is supported when fibrinolytic agents are used for STEMI[108]. Unfractionated heparin, Enoxaparin and Fondaparinux can be used. However, low molecular weight heparins (LMWH) should be avoided in patients with impaired renal function (Creatinine Clearance < 30 mL/min)[109].

FAILED FIBRINOLYTIC THERAPY

Ongoing chest pain, lack of > 50% ST segment resolution and the absence of reperfusion arrhythmias at 60-90 min after the administration of fibrinolytics is considered failure of treatment. These parameters predict TIMI flow < 3 in the infarct artery[110]. In patients who don't respond to (FT), "rescue" PCI has been shown to be beneficial. In the Rapid Early Action for Coronary Treatment Trail[111]. The primary components endpoint of death, reinfarction, stroke, or severe HF at 6 mo, was lower among patients randomized to rescue PCI compared to conservative care or repeat fibrinolysis (event-free survival rate: 84.6% *vs* 70.1% *vs* 68.7%, $P = 0.004$). This was due to reduction in reinfarction. There was no significant survival benefit. Minor bleeding was significantly higher among patients randomized to rescue PCI. However, there were no differences in major bleeding among the conservative therapy, repeat fibrinolysis or, rescue PCI groups. Similar findings of improved event free survival were reported in the Middlesbrough Early Revascularization to Limit Infarction trail. However, higher rates of stroke and periprocedural bleeding were associated with rescue PCI[112,113]. In patients with ongoing symptoms, lack of signs reperfusion, significant hypotension, severe CHF, cardiogenic shock, ECG evidence of large area of myocardium at risk, the benefit of early PCI justifies the risk of bleeding. Conservative treatment might be reasonable in a patient with improving symptoms and a limited inferior infarction despite the persistence of ST elevation.

PATIENTS PRESENTING WITH CARDIOGENIC SHOCK

In the SHOCK trial[114], 302 patient with STEMI with shock were randomized to medical stabilization ($n = 150$) group, which included thrombolysis (63% of patients), intra-aortic balloon counterpulsation (86%), and subsequent revascularization (25%), or to an early revascularization group ($n = 152$). The primary endpoint of survival at 1 year was 46.7% for patients in the early revascularization group compared with 33.6% in the initial medical stabilization group (absolute difference in survival, 13.2%; $P < 0.03$). In a prespecified subgroup analyses, only age (< 75 years *vs* ⩾ 75 years) interacted significantly ($P < 0.03$) with treatment. The benefit was seen only in patients younger than 75 years (51.6% survival in early revascularization group *vs* 33.3% in initial medical stabilization group). The benefit of early revascularization was apparent across a wide time window, extending up to 54 h after MI and 18 h after shock onset. Based on this data, STEMI patients who present with acute cardiogenic shock should undergo emergency cardiac catheterization and revascularization. This is especially true for patients younger than 75 years.

ROUTINE EARLY ANGIOGRAPHY AFTER SUCCESSFUL FIBRINOLYTIC THERAPY

In the Grup de Analisis de la Cardiopatia Isquemica Aguda trial[115], 500 patients with STEMI that were treated with recombinant tissue plasminogen activator were randomly assigned to angiography and coronary intervention if indicated within 24 h of thrombolysis, or to an ischemia-guided conservative approach. The primary endpoint of combined rate of death, reinfarction, or revascularization at 12 mo occurred in 9% of the angiography and intervention group compared to 21% in the conservative group ($P = 0.0008$). There was a trend towards reduced rates of death or reinfarction (7% *vs* 12%, $P = 0.07$). There were no differences in major bleeding or vascular complications.

In the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction[116], 1059 high-risk patients who had a STEMI received FT at centers not capable of performing P-PCI were randomized to either standard treatment (including rescue PCI, if required, or delayed angiography) or immediate transfer to another hospital and PCI within 6 h after fibrinolysis. At 30 d, the primary composite endpoint of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock occurred in 11.0% of PCI and in 17.2% of the patients assigned to standard treatment ($P = 0.004$). There was no evidence of increased major bleeding with the early invasive strategy.

In the Norwegian Study on District Treatment of ST-Elevation Myocardial Infarction trial[117] 266 patients with acute STEMI living in rural areas, where the transfer time to P-PCI are greater than 90 min, were initially treated with the combination of tenecteplase, aspirin, enoxaparin, and clopidogrel and were randomized to immediate transfer for P-PCI or to standard man-

agement in the local hospitals with early transfer, only if indicated for rescue or clinical deterioration. The primary outcome of composite of death, reinfarction, stroke, or new ischemia at 12 mo occurred in 21% *vs* 27% in the early invasive group and the conservative treatment group respectively (P = 0.19). Although this study failed to demonstrate a statistically significant difference between the 2 treatment groups in the incidence of the primary composite endpoint, the incidence of death, recurrent MI, or stroke was significantly lower in the immediate-transfer group. The risk reduction was similar to that reported for high-risk patients in the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction.

In a meta-analysis by Borgia *et al*[118] that included 2961 patients from 7 trials, early PCI after successful fibrinolysis reduced the rate of re-infarction (P = 0.003), the combined endpoint death/re-infarction (P = 0.004) and recurrent ischemia (P < 0.001) at 30-d. There was no evidence of an increase in patient major bleeding or stroke.

In the recent Strategic Reperfusion Early After Myocardial Infarction trial[119], 1892 patients with STEMI who presented within 3 h of symptom onset who were unable to undergo primary PCI within 1 h, were randomly assigned to undergo either primary PCI or fibrinolytic therapy with bolus tenecteplase (half dose in patients ⩾ 75 years of age), clopidogrel, and enoxaparin before transport to a P-PCI capable hospital. Emergency coronary angiography was performed only if fibrinolysis failed, which occurred in 36.3% of the patients; otherwise, angiography was performed 6 to 24 h after randomization. The primary composite end point of death, shock, congestive heart failure, or reinfarction within 30 d occurred in 12.4% of the patients in the fibrinolysis group and in 14.3% in the primary PCI group (P = 0.21). In patients who did not undergo primary PCI within one hour of medical contact, pre-hospital fibrinolysis with coronary angiography with a median time = 17 h resulted in effective reperfusion. The incidence of intracranial bleeding was higher with FT when compared to PCI (1.0% *vs* 0.2% P = 0.04).

Based on these studies, in STEMI patient who are treated successfully with FT, cardiac catheterization can be considered as part of a routine pharmacoinvasive or ischemia-guided approach > 24 h after administration of FT. Very early cardiac catheterization and PCI within 2-3 h after the administration of (FT) increases the risk of bleeding. Very early (< 2-3 h) invasive approach should be utilized for patients who require rescue PCI.

FACILITATED PCI

Fibrinolytic agents use as adjunct to primary PCI has been studied. This approach is called facilitated PCI. Full dose or half dose of a fibrinolytic agent is administered with or without glycoprotein Ⅱb/Ⅲa (GP Ⅱb/Ⅲa) inhibitor prior to planned PCI. This approach is based on the assumption that pre PCI pharmacotherapy will facilitate higher and faster rates of reperfusion.

The Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction trail[120] was stopped prematurely because of an increased mortality associated with facilitated PCI. In the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events trial[121], patients were randomized to primary PCI or facilitated PCI with abciximab or facilitated PCI with half-dose reteplase and full-dose abciximab. Although the rates of death, heart failure, and ischemic outcome at 90 d for all three groups were similar, there was increased rate of major bleeding with the facilitated strategies. Because of these findings, facilitated PCI is currently not advised.

PRIMARY PCI

Timely reperfusion with primary PCI (P-PCI) by experienced operators at an experienced center is superior to FT. Compared to FT, P-PCI results in higher rates of infarct related artery patency, higher rates of TIMI 3 flow and lower rates of complications such as recurrent ischemia, reinfarction, emergency repeat revascularization procedures, intracranial hemorrhage (ICH), and death. However, P-PCI is associated with increased rates of access site bleeding complications[122]. In addition, PCI can result in the "no reflow" phenomenon where the myocardial perfusion is inadequate despite restoration of TIMI 3 epicardial flow in the infarct related artery. No reflow phenomenon is due to a combination of endothelial injury, edema, atheroembolization, vasospasm, and myocyte reperfusion injury and inflammation[123]. Occurance of no reflow is associated with with increased mortality[123]. Multiple treatment strategies that included the use of GP Ⅱb/Ⅲa antagonists, nitroprusside, verapamil, adenosine, nicorandil, pexelizumab have not shown promising results[123].

The benefits of P-PCI over FT are time sensitive. Door to balloon (D2B) times greater than 90-120 min can eliminate the benefits of P-PCI over FT[124]. Over the past ten years, there has been a significant reduction in the median D2B times. Although approximately 80% of the United States population lives within one hour from a P-PCI capable hospital, the majority of patients in the rural areas do not have access to such facilities. A significant increase in the number of PCI capable hospitals from 2001 to 2006 result in minimal increase in the overall patient access to such facilities[125,126]. One of the strategies to make P-PCI more accessible is to allow hospitals without onsite cardiac surgery facilities to perform PCI procedures. The Cardiovascular Patient Outcomes Research Team trail[127] showed that primary PCI can be performed safely and rapidly at hospitals without cardiac surgery back-up. Other strategies include bypassing the non PCI hospital and transferring the patients to a primary PCI capable hospital where the care and transfer protocols are standardized. These strategies have been shown to extend P-PCI to more

patients and result in better patient outcomes[127-129].

DELAYED PRESENTATION

In patients presenting more than 12 h after the onset of symptoms, cardiac catheterization and PCI should be considered in the setting of ongoing chest pain, cardiogenic shock, acute severe heart failure, or spontaneous or provoked myocardial ischemia.

In the Occluded Artery Trial[130], 2166 patients with occluded infarct related arteries who presented 3-28 d after myocardial infarction and had ejection fractions less than 50% were randomized to PCI *vs* conservative medical therapy. The 4-year cumulative primary event rate was 17.2% in the PCI group and 15.6% in the medical therapy group (P = 0.20). However, patients with high risk features such as New York Heart Association class Ⅲ-Ⅳ, rest angina, high risk stress test, left main or three vessel diseases were excluded from the trial. The trail showed that routine PCI did not reduce the occurrence of death, reinfarction, or heart failure, and there was a trend toward excess reinfarction during 4 years of follow-up in stable patients with occlusion of the infarct-related artery 3 to 28 d after myocardial infarction. Based on this data, in patients who present more than 12 h after their symptom onset and are clinically stable, routine cardiac catheterization and PCI are not advised.

PCI OF THE NON-INFARCT RELATED ARTERY

In patients presenting with STEMI, multivessel coronary artery disease is frequently seen and is associated with poor outcomes[131]. PCI of a non-infarct related artery prior to discharge from the hospital, at a time that is separate from the index STEMI related PCI, is indicated if there is evidence of spontaneous myocardial ischemia. However, this practice is largely based on non-randomized cohort studies[132-134]. The role of fractional flow reserve (FFR) at the time of STEMI, to evaluate the functional significance of a non-infarct related artery is not well established. In a small study by Ntalianis *et al*[135], FFR was useful in evaluating the functional significance of a non-culprit coronary lesion.

In the recent Preventive Angioplasty in Acute Myocardial Infarction trail[136], 465 patients with acute STEMI who were undergoing primary PCI were randomly assigned to either preventive PCI defined as immediate PCI of any lesion with > 50% stenosis or no preventive PCI. The trial was stopped early by the data safety monitoring board. In an intention to treat analysis, the primary composite endpoint of death from cardiac causes, nonfatal myocardial infarction, or refractory angina occurred in 9% of the preventive PCI arm and 23% of the non-preventive PCI arm, respectively (P = 0.001). It should be noted that the trail excluded patients with concomitant disease in the left anterior descending and left circumflex arteries, patients with > 50% stenosis of the left main artery, patients with prior CABG and patient with a non-culprit artery with a chronic total occlusion.

At this time, PCI of a non-infarct related artery should be performed prior to hospital discharge if the patient has evidence of spontaneous or provocable myocardial ischemia.

PCI TECHNIQUE BASED STRATEGIES

During the past decade, we have seen significant advances in the field of interventional cardiology as it relates to the management of acute myocardial infarction. Some of the frequently debated issues include access site (radial *vs* femoral), routine use of aspiration thrombectomy, and bare-metal *vs* drug eluting stents.

Access site

Transradial PCI had gained widespread acceptance and is now used routinely for elective angioplasty. Major advantages with transradial approach include reductions in bleeding complications and length of hospitalizations and improved quality of life. Given these advantages, transradial PCI during STEMI has been extensively studied. Multiple randomized trials and a large meta-analysis showed that transradial primary PCI is associated with significant reduction in access site complications. In the Radial *vs* femoral access for coronary angiography and intervention in patients with acute coronary syndromes trial[137] 7021 patients with STEMI were randomly assigned to radial *vs* femoral access sites. The primary endpoint of death, myocardial infarction, stroke, or non-CABG-related major bleeding at 30 d occurred in 3.7% and 4.0% of the radial access and femoral access patients respectively (P = 0.5). In a pre-specified subgroup analysis, non-CABG-related major bleeding at 30 d occurred in 24 patients in the radial group compared with 33 patients in the femoral group (P = 0.23). At 30 d, 42 of 3507 patients in the radial group had large hematomas compared with 106 of 3514 in the femoral group (P < 0.0001). In the Radial *vs* Femoral Randomized Investigation in ST Elevation Acute Coronary Syndrome[138,139] trial, 1001 STEMI patients undergoing primary/rescue percutaneous coronary intervention were randomized to the radial or femoral approach. The primary endpoint of cardiac death, stroke, myocardial infarction, target lesion revascularization, and bleeding at 30 d occurred in 13.6% in the radial artery group and 21.0% in the femoral artery group (P = 0.003). Radial access was associated with significantly lower rates of cardiac mortality (5.2% *vs* 9.2%, P = 0.020), bleeding (7.8% *vs* 12.2%, P = 0.026), and shorter hospital stay. In the STEMI-RADIAL trail[103] 2959 patients undergoing primary PCI within 12 h of onset of symptoms were randomized to radial *vs* femoral approach. The primary

endpoint of access site complications and bleeding occurred in 7.2% of the femoral *vs* 1.4% of the radial group (80% relative risk reduction, $P = 0.001$). Radial and femoral approaches are both safe and effective for PCI. Lower rates of local vascular complications may be a reason to use the radial access approach. There is some concern about longer D2B times and increased radiaton exposure with radial artery access. This is mostly limited to low volumes centers and operators[140,141]. Data from the randomized control trials suggests that D2B times and the cumulative radiation dose are minimally increased with radial artery catheterization. The impact of the radial artery approach on patient mortality remains unclear at this time as the reported studies are underpowered to evaluate this end-point.

Adjunctive thrombectomy

A vast majority of patients with STEMI have large thrombus burden. It seems intuitive that thrombectomy may improve epicardial coronary flow, prevent distal embolization, reduce microvascular obstruction and the no-reflow phenomenon. However, trials that have used mechanical thrombectomy have been largely negative without any improvement in myocardial blush grade, final infarct size and overall left ventricular ejection fraction[142-144]. Recently there has been renewed interest in aspiration thrombectomy. In the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study[145], 1071 patients were randomly assigned to the thrombus-aspiration group or the conventional-PCI group before undergoing coronary angiography. The primary end point of myocardial blush grade of 0 or 1 occurred in 17.1% of the patients in the thrombus-aspiration group and in 26.3% in the conventional-PCI group ($P < 0.001$). At one year follow up, cardiac death occurred in 3.6% of the patients in the thrombus aspiration group and 6.7% in the conventional PCI group ($P = 0.020$). In the Impact of Thrombectomy With Export Catheter in Infarct-Related Artery During Primary Percutaneous Coronary Intervention trail[146], 155 STEMI patients were randomly assigned to standard percutaneous coronary intervention PCI ($n = 87$) or aspiration thrombectomy guided PCI ($n = 88$). The primary end points of myocardial blush grade $\geqslant 2$ and the rate of 90-min ST-segment resolution > 70% occurred more frequently in the thrombectomy guided PCI group (88% *vs* 60%, $P = 0.001$; and 64% *vs* 39%, $P = 0.001$). In a meta-analysis conducted by Bavry *et al*[147], total of 30 studies with 6415 patients were included, a weighted mean follow-up of 5.0 mo showed that the morality was 3.2% for the adjunctive thrombectomy group *vs* 3.7% for conventional PCI.

In the recently published TASTE[148] (The Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) trial, aspiration thrombectomy did not show reduction in 30 d mortality. The event rate was 2.8% in the aspiration arm *vs* 3.0% in the routine PCI arm ($P = 0.63$). The recently published TOTAL [A Trial of Routine Aspiration Thrombectomy With Percutaneous Coronary Intervention (PCI) *vs* PCI Alone in Patients With ST-Segment Elevation Myocardial Infarction (STEMI) Undergoing Primary PCI] trial[149] 10732 patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI were randomized to routine upfront manual thrombectomy versus PCI alone. Within 180 d, manual aspiration thrombectomy did not lower the rates of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class Ⅳ heart failure. Stroke within 30 d occurred in 33 patients (0.7%) in the thrombectomy group *vs* 16 patients (0.3%) in the PCI-alone group (HR = 2.06; 95%CI: 1.13-3.75; $P = 0.02$).

The TASTE and the TOTAL Trials suggest that routine use of aspiration thrombectomy may not be beneficial in reducing patient morbidity and mortality.

TYPE OF STENTS IN THE SETTING OF PRIMARY PCI

It is now a routine practice to use coronary stents during primary PCI. Compared to balloon angioplasty, primary PCI with bare metal stents (BMS) has been shown to reduce the rates of reinfarction and target vessel revascularization. However, this does not translate into a reduction in mortality[150]. Drug eluting stents (DES) are currently being used for both elective and primary PCI. DES when compared with BMS significantly reduces restenosis rates and the need for reintervention but does not definitively reduce rates of death[151]. First generation DES such as Taxus and Cypher, when compared to BMS, can increase the risk of very late stent thrombosis[152]. Newer generation DES such as Xience, Promus and Endeavour, when compared to BMS do not increase the risk of acute or late stent thrombosis. Cobalt-chromium based everolimus eluting stents have the lowest reported rates of stent thrombosis[153]. In the Xience or Vision Stents for Management of Angina in the Elderly trail[154], second generation, everolimus eluting DES were safely used in the elderly without increasing the risk of bleeding. Patients who are taking oral anticoagulation and present with a STEMI pose a significant challenge. Triple therapy significantly increases the risk of bleeding. In the What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting trial[155], the group receiving warfarin plus clopidogrel had lower bleeding complications compared with the group receiving warfarin, clopidogrel and aspirin. Although the rate of stent thrombosis was not increased, this trial was not powered to evaluate the risk of stent thrombosis.

Given the advantages of marked reduction in

the rates of restenosis, target vessel and target lesion revascularization and very low rates of late stent thrombosis, second generation DES should be the preferred choice during primary PCI. However, that decision should be made on a case to case basis. Factors such as bleeding risk, other indications for systemic oral anticoagulants, socioeconomic status, compliance, need for surgical procedures during the following one year should be considered. If these factors are a concern, DES implantation should be avoided. There still remain gaps in our understanding of routine use of DES in the elderly and patients who are on oral anticoagulants. Further research is need in these areas.

ADJUNCTIVE PHARMACOTHERAPY BASED STRATEGIES

In recent years, there has been extensive research done in the area of adjunctive pharmaco-therapy. As a result, we now have multiple antithrombotic and anti-platelet agents that have been shown to reduce major adverse cardiac events in the setting of STEMI.

Unfractionated heparin (UFH) is time tested and the most familiar of all the agents. It is used frequently. When titrated to appropriate activated clotting times of 250-300 s, it is an acceptable strategy. Low molecular weight heparins (LMWN) such as Enoxaparin and Fondaparinux are not well studied in the setting of STEMI. In the STEMI Treated With Primary Angioplasty and Intravenous Lovenox or Unfractionated Heparin trial[156] 901 patients were randomized to treatment with enoxaparin (n = 450) or unfractionated heparin (n = 460). The composite primary endpoint of 30-d incidence of death, complication of myocardial infarction, procedure failure, or major bleeding occurred in 126 (28%) patients after anticoagulation with enoxaparin *vs* 155 (34%) patients on unfractionated heparin (P = 0.06). Data from this trail suggests that enoxaparin can be safely and effectively used in patients with STEMI. In the OASIS-6 trial[157] death or reinfarction at 30 d was significantly reduced from 11.2% in the control group to 9.7% patients in the fondaparinux group (P = 0.008). However, fondaparinux was associated with higher rates of catheter thrombosis. At this time, fondaparinux in not used as an anticoagulant in the setting of primary PCI.

The role of Bivalirduin in the setting of STEMI treated with primary PCI was tested in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction trial[158]. Three thousand six hundred and two patients with ST-segment elevation myocardial infarction presenting within 12 h after the onset of symptoms and were undergoing primary PCI, were randomly assigned to treatment with heparin plus a glycoprotein Ⅱb/Ⅲa inhibitor or to treatment with bivalirudin alone. Primary end points of major bleeding and combined adverse clinical events, including death, reinfarction, target-vessel revascularization for ischemia, and stroke within 30 d occurred in 22% of the heparin plus glycoprotein Ⅱb/Ⅲa inhibitor group *vs* 9.2% in the bivalirudin group (P = 0.005). The risk of acute stent thrombosis within 24 h in the bivalirudin group increased, but no significant increase was present by 30 d. This was most likely secondary to a combination of adenosine diphosphate–induced platelet activation before maximal thienopyridine blockade of the platelet P_2Y_{12} receptor or by residual thrombin activity after the discontinuation of bivalirudin. Based on the results from the HORIZONS-AMI trail, it is a reasonable approach to use bivalurudin in patients with STEMI who are undergoing primary PCI. This approach may provide long term survival benefit by lowering the rate of bleeding complications.

ADJUNCTIVE ANTIPLATELET THERAPY

Aspirin

An initial single dose of 325 mg of Aspirin should be administered as early as possible. This should be followed by a maintenance dose of 81 mg once daily. Higher doses of Aspirin for maintenance therapy have shown to increase the risk of bleeding. In the Committee members of the Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Syndromes trial[159] 25086 patients with an acute coronary syndrome who underwent cardiac catheterizatoin were randomized to either double-dose clopidogrel (a 600-mg loading dose on day 1, followed by 150 mg daily for 6 d and 75 mg daily thereafter) or standard-dose clopidogrel (a 300-mg loading dose and 75 mg daily thereafter) and either higher-dose aspirin (300 to 325 mg daily) or lower-dose aspirin (75 to 100 mg daily). The primary outcome of cardiovascular death, myocardial infarction, or stroke at 30 d was not different between higher-dose and lower-dose aspirin (4.2% *vs* 4.4%, P = 0.61) or major bleeding (2.3% *vs* 2.3%, P = 0.90).

Clopidogrel

The importance of at least 12 mo of dual antiplatelet therapy with aspirin and clopidogrel in the setting of ACS with and without PCI has been well established based on the data from the Clopidogrel in Unstable Angina to Prevent Recurrent Event (CURE)[160] and PCI-CURE[161] trials. A 600 mg loading dose of clopidogrel offers rapid platelet inhibition compared to 300 mg dose[162]. In the CURRENT-OASIS 7 trail[159] the primary outcome of cardiovascular death, myocardial infarction, or stroke at 30 d occurred in 4.2% of the double-dose clopidogrel group *vs* 4.4% in the standard-dose clopidogrel (P = 0.30). Major bleeding occurred in 2.5% of the double-dose group and in 2.0% in the standard-dose group patients (P = 0.01). Rates of stent thrombosis was lower in the double dose group (1.6% *vs* 2.3% P = 0.001). Incidence of major bleeding was 2.5% in the double dose group *vs* 2.1%

in the standard dose group (P = 0.001). Clopidogrel 600 mg loading dose followed by 75 mg once daily for at least one year should be considered for all patients with acute coronary syndromes.

One common clinical concern with the use of clopidogrel is the variable therapeutic response. This is secondary to multiple factors such as diabetes, obesity, polymorphisms in enteric ABCB 1 and hepatic cytochrome P450 (CYP450) enzymes (CYP2C19*2) and drug interaction that interferes with the metabolism of clopidogrel. Nearly 30% of patients have a reduced functional allele of CYP2C19*2. This has been shown to be associated with decreased levels of the active metabolite of clopidogrel, suboptimal platelet inhibition and increased rates of major adverse cardiac events and stent thrombosis[162-165]. Based on this data, the United States Food and Drug Administration made changes to clopidogrel's prescribing information noting the potential impact of CYP2C19 genotype on clopidogrel's bioavailability and clinical response. However, in a study by Mega *et al*[166] homozygotes and heterozygotes for loss of functional allele had similar rates of primary efficacy outcomes. At this time routine testing for CYP2C19*2 polymorphisms is not indicated. Further studies are needed to fully understand the clinical risk associated with these polymorphisms and to develop effective treatment strategies.

Proton-pump inhibitors, such as omeprazole, have been shown to interfere with clopidogrel metabolism resulting in decreased antiplatelet effect[167]. However, this does not lead to worse clinical outcomes[168]. At this time there is no strong evidence to avoid concomitant use of PPIs, when clinically indicated, in patients receiving clopidogrel.

Prasugrel

Prasugrel is a thienopyridine class of drug that competiviely antagonizes the P2Y12 receptor. Similar to Clopidogrel, it is also a pro drug that requires biologic conversion to an active metabolites. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel trial[169] 13608 patients with moderate-to-high-risk acute coronary syndromes treated with early invasive approach were randomly assigned to prasugrel, with a 60-mg loading dose and a 10-mg daily maintenance dose, or clopidogrel, with a 300-mg loading dose and a 75-mg daily maintenance dose, for 6 to 15 mo. The primary efficacy end-point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (P < 0.001). There was significant reductions in the rates of myocardial infarction (9.7% for clopidogrel *vs* 7.4% for prasugrel; P < 0.001), urgent target-vessel revascularization (3.7% *vs* 2.5%; P < 0.001), and stent thrombosis (2.4% *vs* 1.1%; P < 0.001). Major bleeding was increased with prasugrel 2.4% in comparison with 1.8% of patients with clopidogrel (P = 0.03). The prasugrel group had higher rates of life-threatening bleeding (1.4% *vs* 0.9%; P = 0.01), including nonfatal bleeding (P = 0.23) and fatal bleeding (0.4% *vs* 0.1%; P = 0.002). While prasugrel significantly reduced the rates of ischemic events and stent thrombosis, it increased the risk of major bleeding and did not reduce mortality. The benefits of prasugrel must be carefully weighed against the increased risk of bleeding. Prasugrel may be a preferred agent in younger, high risk acute coronary syndrome patients with large area of myocardium at risk and low bleeding risk. Prasugrel should not be used in patients with history of prior stroke, transient ischemic attacks, age greater than or equal 75, or body weight less than 60 kg. A lower dose of prasugrel 5 mg once daily has been suggested in patients who are at higher risk for bleeding. However, prasugrel 5 mg/d has not been prospectively studied.

Ticagrelor

Ticagrelor is a cyclopentyl triazolo pyrimidine that acts on the platelet P_2Y_{12} receptor as an antagonist. It does not require conversion to active metabolite and is a reversible agent. In The Study of Platelet Inhibition and Patient Outcomes trail[170] 18624 patients with acute coronary syndromes, were randomized to ticagrelor (180-mg loading dose, followed by 90 mg twice daily) or clopidogrel (300-to-600-mg loading dose, followed by 75 mg daily). Thirty-five percent of the patients had STEMI. Overall, at 12 mo, the composite end-point of death from vascular causes, myocardial infarction, or stroke occurred in 9.8% of patients receiving ticagrelor *vs* 11.7% of patients receiving clopidogrel (P < 0.001). The rate of death from any cause was also reduced with ticagrelor (4.5% *vs* 5.9%, P < 0.001). In addition, there were reductions in the rates of myocardial infarction (5.8% in the ticagrelor group *vs* 6.9% in the clopidogrel group, P = 0.005) and death from vascular causes (4.0% *vs* 5.1%, P = 0.001). There was no difference in the frequency of stroke alone (1.5% *vs* 1.3%, P = 0.22) or the rates of major bleeding (11.6% and 11.2%, P = 0.43). However, ticagrelor was associated with a higher rate of major non CABG related bleeding (4.5% *vs* 3.8%, P = 0.03), including more instances of fatal intracranial bleeding.

In a pre-specified subgroup analysis of the Study of Platelet Inhibition and Patient Outcomes trail, the net benefit of ticagrelor was smaller in the North American cohort. This was attributed to chance alone or alternatively to the frequent use of higher dose of aspirin for maintenance therapy. Based on this observation, the dose of aspirin when used in combination with ticagrelor for maintenance therapy should not exceed 100 mg a day.

When considering adding a second drug to aspirin for dual antiplatelet therapy (DAPT), the decision should be individualized. The anti-ischemic benefits should be carefully weighed against patient comorbidities, risk of bleeding, need for long term treatment with an oral

anticoagulant, cost, compliance, and the possibility of surgical procedures during the following year.

DURATION OF ANTIPLATELET THERAPY

Current guidelines[171] support uninterrupted use of dual antiplatelet therapy for at least one year in post ACS patients regardless of invasive or conservative treatment or the type of stent (BMS *vs* DES). Recently, there has been significant data supporting the discontinuation of dual antiplatelet therapy 3 to 6 mo after a PCI in the setting of acute coronary syndrome.

In the Efficacy of Xience/Promus *vs* Cypher in Reducing Late Loss after Stenting trail[172] 1443 patients undergoing implantation of drug-eluting stents were randomized to receive 6- or 12-mo DAPT. The primary end point of target vessel failure at 12 mo was 4.8% in the 6-mo DAPT group and 4.3% in the 12-mo DAPT group (P = 0.001 for non-inferiority). This study was underpowered for evaluation of death and MI.

In the Prolonging dual antiplatelet treatment after grading stent-induced intimal hyperplasia trial[173] 2013 patients were randomly assigned to receive bare-metal, zotarolimus-eluting, paclitaxel-eluting, or everolimus-eluting stent implantation. At 30 d, patients in each stent group were randomly allocated to receive up to 6 or 24 mo of clopidogrel therapy in addition to aspirin. The primary composite endpoint of death from any cause, myocardial infarction, or cerebrovascular accident at 24 mo was similar.

In the Real Safety and Efficacy of a 3-mo dual antiplatelet Therapy following E-ZES Implantation trail[174], 2117 patients with coronary artery stenosis were randomized to 2 groups according to DAPT duration and stent type: 3-mo DAPT following zotarolimus-eluting stent (E-ZES) implantation *vs* 12-mo DAPT following the other (sirolimus, everolimus DES implantation). The primary composite endpoint of cardiovascular death, myocardial infarction, stent thrombosis, target vessel revascularization, or bleeding at 1 year occurred in 4.7% patients assigned to E-ZES + 3-mo DAPT compared with 4.7% patients assigned to the standard therapy (P = 0.001 for noninferiority).

In the recently published Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus - Eluting Stent in the Real World Clinical Practice trail[175], 3119 patients undergoing PCI using zotarolimus DES were randomly assigned to 3 mo *vs* 12 mo of dual antiplatelet therapy. The primary composite end point of all-cause death, myocardial infarction, stroke, or major bleeding occurred in 6.0% *vs* 5.8%, respectively P = 0.002 for noninferiority.

Although the data from these trials is reassuring and supports the discontinuation of dual anti-platelet therapy at the end of 6 mo, it is important to note that these trial included patients with stable coronary disease and low risk acute coronary syndrome. Caution should be used in extrapolating this data to patients with STEMI. At this time, dual anti-platelet therapy should be continued for at least one year without interruption when tolerated in patients with ACS.

Role of glycoprotein IIb/IIIa receptor antagonists

Role of glycoprotein Ⅱb/Ⅲa (GP Ⅱb/Ⅲa) receptor antagonists in the setting of STEMI was extensively studied prior to routine use of dual antiplatelet therapy. Addition of a GP Ⅱb/Ⅲa receptor antagonist to combination of DAPT plus unfractionated heparin or bivalirudin failed to show benefit[176-178]. However, in a meta-analysis by De Luca[179] where 722 patients with STEMI from seven randomized trials were included, early administration of abciximab compared to late/peri-procedural administration was associated with reduction in mortality (20% *vs* 24.6% P = 0.02), improvement in pre-procedural (TIMI) 3 flow (21.6% *vs* 10.1%, P < 0.0001), post-procedural TIMI 3 flow (90% *vs* 84.8%, P = 0.04), post-procedural myocardial blush grade (52.0% *vs* 43.2%, P = 0.03), ST-segment resolution (58.4% *vs* 43.5%, P < 0.0001) and distal embolization (10.1% *vs* 16.2%, P = 0.02). There was no difference in the rates of major bleeding complications between early and late abciximab administration (3.3% *vs* 2.3%, P = 0.4). Adjunctive use of GP Ⅱb/Ⅲa inhibitors can be considered at the time P-PCI if there is evidence of large thrombus or inadequate response to a P_2Y_{12} antagonist[179,180]. Based on the data from the HORIZONS-AMI[158] and CICERO[181] trials, a GP Ⅱb/Ⅲa receptor antagonist can be used as adjunct to bivalirudin in the presence of large thrombus or for "bail-out use" for procedure related dissection. Similar findings were also confirmed in a recent meta-analysis by Shimada *et al*[182]. In a recent MI trail[183], intra-coronary infusion of abciximab reduced infarct size at 30 d. This approach should be considered on an individual patient basis[182,183].

ROLE OF CARDIOPROTECTION IN STEMI

Despite significant improvements in every area of STEMI management, adverse event rates continue to be high. Although, reperfusion therapy and the adjunctive pharmacotherapy help reestablish coronary flow, restoration of coronary blood flow can cause further injury to cardiac myocytes. This type of injury is called lethal reperfusion injury. In animal models, close to 50% of the final infarct size is due to lethal reperfusion injury[184]. This injury results from oxidative stress[185,186], calcium overload[187,188], inflammation[189] and rapid restoration of pH[189]. Understanding these mechanisms at a cellular level has led to renewed interest in designing treatment strategies that target pathways that mediate lethal reperfusion injury. These strategies mediate their cardioprotective effect by multiple signaling pathways such as reperfusion injury salvage kinase (RISK) group of protective kinases. The cardioprotective signaling pathways inhibit the mitochondrial permeability transition pore and multiple other molecules[190].

PRECONDITIONING

Repeated, brief episodes of coronary occlusion with myocardial ischemia alternating with coronary reperfusion before a prolonged episode of ischemia, is a powerful way to limit infarct size. This is known as ischemic pre-conditioning[191]. However due to the fact that the brief episodes of ischemia need to be applied prior to an ischemic event, this approach has limited value in the setting of STEMI.

POST CONDITIONING

Applying the principles of preconditioning after the ischemic event has been shown to be beneficial in animal models[192,193]. In a small randomized control trial, Staat *et al*[194] showed that post-conditioning by 4 cycles of 1-min coronary angioplasty balloon inflations followed by 1 min of balloon deflation within 1 min of coronary reflow after deployment of a coronary stent reduced infarct size and improved myocardial blush grades. Similar findings have also been noted in other small studies that used different balloon inflation and deflation protocols[195]. A significant limitation of catheter/balloon based post-conditioning is that it is limited to cardiac catheterization laboratories at the time of P-PCI.

Post conditioning by cyclosporine

Cyclosporine has been shown to be cardioprotective by inhibiting the mitochondrial permeability transition pore[196]. In a small randomized study of 58 patients, single bolus of 2.5 milligrams of intravenous cyclosporine, compared to placebo reduced infarct size by 40% as quantified by the degree of plasma creatine-kinase elevation[197]. The cardioprotective effect of cyclosporine appears to be promising.

REMOTE ISCHEMIC CONDITIONING

Transient, repeated episodes of ischemia when applied to an organ distant from the heart have been shown to reduce infarct size[198]. This is called remote ischemic conditioning. One proposed mechanism is the release of a chemical by the distant organ that promotes cardiac conditioning. Another possibility is afferent neural pathway stimulation. In a study by Bøtker *et al*[199], 333 patients with a suspected first STEMI were randomly assigned in a 1:1 ratio to receive P-PCI with or without remote conditioning that consisted of intermittent arm ischemia through four cycles of 5-min inflation and 5-min deflation of a blood-pressure cuff. The patients received remote conditioning during transport to hospital, and P-PCI in hospital. The primary endpoint of myocardial salvage index at 30 d, measured by myocardial perfusion imaging, was significantly improved in the preconditioning group (0.75 in the remote conditioning group *vs* 0.55 in the control group, $P = 0.0333$). Given the ease of use and potential universal applicability of this approach, large-scale trials are underway to study this treatment.

ROLE OF ADENOSINE

Adenosine, by mediating its effects *via* A_1 and A_3 receptors appears to play a key role in promoting a cardioprotective a state. Although the mechanisms are complex, inhibition of the formation of mitochondrial permeability transition pores appears to be a primary mechanism[200]. Intravenous infusion of adenosine in patients with STEMI was tested in the Acute Myocardial Infarction Study of Adenosine Ⅰ trail[201]. Although there was 33% relative reduction in the infarct size, this was mostly limited to individuals with large anterior wall MI. Based on this study, the Acute Myocardial Infarction Study of Adenosine Ⅱ trail[202] randomized 2118 patients to 3-h intravenous infusion of low-dose adenosine (50 μg/kg per minute), high-dose adenosine (70 μg/kg per minute), or placebo before PCI or within 15 min of the initiation of fibrinolysis. There was no difference in the composite endpoint of death, new-onset congestive heart failure, or rehospitalization for congestive heart failure within 6 mo. However, subsequent post-hoc and subgroup analyses showed that there was significant reduction in the infarct size in those who received the high dose and those who received adenosine within 3 h of onset of symptoms[203]. Although the routine use of adenosine is currently not supported, early administration of high dose adenosine may reduce infarct size in patients with anterior wall STEMI with large areas of myocardium at risk.

ROLE OF BETA BLOCKERS

Most of the data on the role of routine use of beta blockers in STEMI either predates or involves thrombolytic therapy. There is very limited data on the cardioprotective benefits of beta blockers in the setting of PPCI. In the recently published Effect of Metoprolol in Cardioprotection during an Acute Myocardial Infarction trail[204], 270 patients with STEMI (Killip Class 2 or less) presenting within 6 h of onset of symptoms were randomized to receive intravenous metoprolol or no metoprolol. The primary endpoint of infarct size by magnetic resonance imaging was smaller after intravenous metoprolol compared with control (25.6 ± 15.3 gm *vs* 32.0 ± 22.2 gm, $P = 0.012$). This trail illustrates that a commonly used inexpensive medication may play a significant role in cardioprotection in the setting of reperfusion by P-PCI for STEMI. Larger clinical trials that are powered to analyze hard clinical endpoints are needed to definitively understand the role of intravenous beta blockers in the setting of P-PCI.

The ideal duration of treatment with beta blockers after a STEMI is not well established. At the present time most patients are treated indefinitely with beta

blockers after a STEMI. This is mostly based on evidence from a large meta-analysis that included 50000 patients and showed a 23% reduction in mortality at a mean follow up of 1.4 years[205]. Lower rates of reperfusion, suboptimal utilization of medical therapy, and short duration of follow up limit this data.

In a recent meta-analysis by Bangalore *et al*[206], that included 21000 patients with mean follow up of 44 mo, the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke in post myocardial infarction patients were not significantly different the group that was treated with β-blockers compared with those who were not. (16.93% *vs* 18.60% respectively, $P = 0.14$). At the present time, the data on duration of therapy with beta blockers after an MI in inconclusive. In patients with preserved left ventricular ejection fraction and without any evidence of arrhythmias and ischemia, beta blockers can most likely be stopped after one year.

ROLE OF ATRIAL NATRIURETIC PEPTIDES

The cardioptotective effects of atrial natriuretic peptides (ANP) was tested in the Human Atrial Natriuretic Peptide and Nicorandil as Adjunts to Reperfusion Treatment trail[207]. Following reperfusion by either PCI or fibrinolytic therapy, 569 patients with STEMI were randomized to receive a continuous infusion of ANP or placebo for 3 d. Compared to placebo, there was 14.7% reduction in infarct size by area under the curve for total creatine kinase. ANP infusion was also associated improved ejection fraction at 6 to 12 mo compared with controls (44.7% *vs* 42.5%). Over a median follow-up time of 2.7 years, cardiac death and rates of hospitalization were also reduced in the ANP group. Further large-scale studies are needed to fully understand the cardioprotective role of ANP.

ROLE OF HYPOTHERMIA

In animal models, moderate hypothermia (28 ℃-32 ℃) offers cardioprotection by altering signaling pathways[208]. The Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients With Acute Myocardial Infarction trail[209] failed to show overall statistically significant reduction in infarct size. However, in patients with large anterior STEMI who were cooled to temperatures of less than 35 ℃ prior to reperfusion there was a reduction in the infarct size (9.3% in treated patients *vs* 18.2% in controls; $P = 0.05$).

The Rapid Cooling by Cold Saline and Endovascular Cooling before Reperfusion in patients with ST-elevation Myocardial Infarction trail[210] randomized 20 patients with STEMI undergoing P-PCI to rapid hypothermia by an endovascular catheter or standard therapy. Temperatures < 35 ℃ were obtained in all hypothermia patients prior to reperfusion. The primary end point of infarct size by cardiac MRI was reduced by 38% in the hypothermia group.

However, in the CHILL-MI[211] trail, hypothermia resulted in only a trend towards reduction in infarct size in patients who presented within 4 h of symptoms onset and were cooled to 33 ℃ large scale randomized trials are needed to determine if hypothermia during or immediately prior to P-PCI will result in significant reductions in infarct size and clinical endpoints.

STEM CELLS IN THE TREATMENT OF ACUTE MYOCARDIAL INFARCTION

Because atherosclerotic coronary vascular disease is the major cause of death in the United States and has recently become a major cause of death throughout the world, stem cell therapy is being investigated in patients with acute myocardial infarction (AMI) to limit myocardial damage and possibly regenerate myocardium[212-214]. Two populations of stem cells have been examined in patients with myocardial infarctions and/or ischemic cardiomyopathies: adult bone marrow mononuclear cells and cardiac stem cells. Adult bone marrow mononuclear cells from bone marrow aspirates contain approximately 0.5%-3% hematopoietic and mesenchymal "progenitor" cells that secrete growth factors and cytokines that can limit myocardial inflammation and infarct size. These cells have limited ability to replicate, do not trans-differentiate into myocytes, but can chemoattract endogenous patient stem cells for repair of cardiac injury. Cardiac stem cells are specific undifferentiated progenitor cells found in the right atrial appendage and the ventricular apices of the heart that have paracrine effects, can chemoattract patient stem cells, and may transdifferentiate into myocytes for cardiac repair.

The initial ten year experience with autologous human bone marrow mononuclear cells (BMCs) in the treatment of patients with AMIs showed significant approximately 2%-3% (range 1.9%-5.4%) increases in left ventricular ejection fraction (LVEF), decreases in left ventricular end-systolic volume of -4.8 mL (range -1.4 to -8.2 mL) and reductions in myocardial infarction size of approximately 5.5% (-1.9% to -9.1%)[213,214]. These studies established that the direct intramyocardial or intracoronary administration of bone marrow mononuclear cells was safe and that significant side effects did not occur with administration of these cells[213-214], see Tables 5 and 6[215-237]. However many of the initial clinical bone marrow cell studies consisted of small numbers of patients and not all the studies randomized patients to treatment with either bone marrow mononuclear cells or placebo (Tables 5 and 6)[215-237].

Since the initial treatment of patients with AMIs with BMCs, major questions have persisted about the use of these cells: what is the optimal cell for AMI treatment; when is the optimal time to inject cells for

treatment; what is the viability of the stem cells prior to injection into patients; what is the best parameter to monitor cardiac patients after stem cell treatment. The LateTIME, the TIME, and the Swiss Myocardial Infarction Trials were multi-center trials that addressed the questions whether adult BMCs limit myocardial damage in comparison with patients treated with placebo and what is the optimal time of cell administration after AMIs.

LATETIME TRIAL

The LateTIME trial was a randomized double blind, placebo-controlled trial designed to determine if delivery of adult BMCs two to 3 wk after primarily anterior wall myocardial infarction would be safe and effective in limiting infarct size and improving left ventricular (LV) function[238]. All patients in this study were successfully treated initially with primary percutaneous coronary intervention (PCI) within a median time of 4 h after the onset of chest pain. Bone marrow mononuclear cells were isolated from bone marrow aspirates in each center with a closed, automated system (Sepax, Biosafe). The Infarct volume and LV global and regional LV function were measured by magnetic resonance imaging (MRI) with gadolinium prior to intracoronary injection and 6 mo after injection. The LVEF prior to intracoronary infusion of cells or placebo in 87 AMI patients averaged 48.7% in the bone marrow cell (BMC) group and 45.3% in the placebo group. 150 × 10^6 autologous BMCs or placebo were infused in 87 patients. The changes between baseline and 6 mo in the BMC group for infarct volume, LVEF, wall motion in the infarct zone, and wall motion in the border zone of the infarction were not statistically different from the placebo group[238].

TIME TRIAL

The TIME Trial was a double-blind, placebo controlled trial that investigated the intracoronary administration of autologous BMCs or placebo in 120 patients three or seven days after primarily anterior AMI[239]. The TIME Trial was based on the REPAIR AMI trial that reported that delivery of BMCs to patients 5 to 7 d after AMI resulted in a 5.1% absolute increase in LVEF[239,240].

All patients had successful coronary reperfusion with coronary angioplasty within a median time of 3-4 h of the onset of ischemic symptoms. The mean LVEF in these patients was $\leqslant$ 45% by echocardiography. The mean time from PCI to bone marrow aspiration and cell processing was 3.3 d in the day 3 group and 7.4 d in the day 7 group. Bone marrow mononuclear cells were isolated in each center with a closed, automated system (Sepax, Biosafe) and the cells or placebo were infused into the coronary arteries within 12 h of aspiration and cell processing. The BMC contained 2.3% CD34 and 1.1% CD34 plus CD131 hematopoietic cells. All patients had baseline cardiac MRIs with gadolinium at day 3 or at day 7 after AMI and the MRIs were repeated at 6 mo after the AMI.

Forty-three patients received BMCs on day 3 and 36 patients received bone marrow cells on day 7 after AMI. Each patient received approximately 147 × 10^6 BMCs within 12 h of aspiration and cell processing. Forty-one patients received a placebo. The median time from bone marrow aspiration to infusion directly into the infarct related coronary artery was 8.3 h. In addition, all patients received heparin during the procedure as well as aspirin and clopidogrel.

The differences between the BMC treatment and the placebo treatment in the 3 d group and in the 7 d group were not significant. When both BMC groups were combined (n = 75) to include patients with MRI measurements at baseline and 6 mo and compared with the combined placebo group (n = 37), LVEF in the BMC group increased from 45.2% at baseline to 48.3% at 6 mo while in the combined placebo group the LVEF increased from 44.5% to 47.8% (P = NS). Moreover, there was no significant difference between the changes in regional wall motion in the infarct zone and the border zone between BMC and placebo groups. Infarct volumes uniformly decreased in both groups but the differences between groups were not statistically significant. No difference was observed in global or regional function in patients stratified by myocardial ischemic time.

SWISS MULTICENTER INTRACORONARY STEM CELL STUDY IN ACUTE MYOCARDIAL INFARCTION TRIAL

The Swiss Study[241] randomized patients with AMIs with LVEF < 45% as measured by ventriculography or echocardiography, who had been successfully treated with PCI of the infarct related artery within a median of 5 h of onset of chest pain, to either the intracoronary administration of 140-160 million autologous BMCs at a median of 6 d after AMI (early group, n = 58) or at a median of 24 d after AMI (late group, n = 49) or to a placebo group (n = 60). Ninety-two percent of the patients had anterior wall infarctions. Bone marrow aspirates were performed only in patients assigned to the BMC treatment. Each 10 mL aspirate was treated with 1000 IU Heparin to prevent clot formation. The BMCs were isolated by density gradient centrifugation at a centralized processing facility and contained 1% to 1.3% $CD34^+$ hematopoietic cells. However, the median percentage of mononuclear cells that exhibit migration capacity was only 29%[241].

Cardiac magnetic resonance imaging with gadolinium was performed on patients at baseline prior to cell infusion and at 4 mo after the injection of BMCs into the infarct-related coronary artery and were compared with MRIs of control patients treated with

Table 5 Bone marrow and circulating progenitor cells in coronary artery disease patients

Ref.	*n*	Randomize	Time post PCI and/or MI	Cell dose	Injection route	Baseline LVEF	LVEF change	Duration	Other findings
Assmus *et al*[215]	92	Yes	2348-2470 d	22 ± 10^6 CPC $205 \pm 110 \times 10^6$ BMC	IC	CPC 39% ± 10% BMC: 41% ± 11%	CPC -0.4% BMC 2.90%	3 mo	Pts with previous MI; ↑ LVEF in BMC but not CPC
Bartunek *et al*[216]	35	Cohort	10 d	$12.6 \pm 2.2 \times 10^6$	IC	45% ± 2.5%	7%	4 mo	↑ LV regional function, perfusion; restenosis ↑
Chen *et al*[217]	69	Yes	18.4 ± 0.5 d	$8\text{-}10 \times 10^9$	IC	49% ± 9%	18%	6 mo	↑ LVEF by ventriculogram ↑ perfusion; ↓ ESV
Erbs *et al*[218]	26	Yes	225 ± 87 d	$69 \pm 14 \times 10^6$	IC	51.7% ± 3.7%	7.20%	3 mo	Pts with chronic CAD occlusion Rxed with CPC; ↓ EF by MRI; infarct size 16%
Ge *et al*[219]	20	Yes	1 d	$39 \pm 22 \times 10^6$	IC	53.8% ± 9.2%	4.80%	6 mo	↑ Perfusion by SPECT
Hendrikx *et al*[220]	20	Yes	217 ± 162 d	$60 \pm 31 \times 10^6$ IM	IM	42.9% ± 10.3%	5%	4 mo	CABG in Pts with previous CAD ↑ Regional but not global LV function; 6/9 with induced ventricular tachycardia
Janssens *et al*[221]	67	Yes	1 d	172×10^6	IC	48.5 ± 7.2	3.30%	4 mo	↓ Infarct size
Kang *et al*[222]	96	Yes	< 14 d AMI; > 14 d OMI	$1\text{-}2 \times 10^9$	IC	52.0 ± 9.9	5.10% AMI	6 mo	G-CSF for 3 d; ↓ ESV and infarct size in AMI; = EF, ESV and infarct size in OMI
Katritsis *et al*[223]	22	Cohort	224 ± 464 d	$2\text{-}4 \times 10^6$	IC	39.7% ± 9.3%	1.60%	4 mo	↑ Regional but not global LV function
Lunde *et al*[224,225]	100	Yes	6 ± 1.3 d	68×10^6 (median) $54\text{-}130 \times 10^6$	IC	41.3 ± 11.0	=	6-12 mo	↑ LVEF in treated and controls; = EDV and infarct size
Meyer *et al*[226]	60	Yes	4.8 ± 1.3	$24.6 \pm 9.4 \times 10^8$	IC	50 ± 10	5.90%	18 ± 6 mo	↑ LVEF by MRI significant at 6 but not 18 mo
Mocini *et al*[227]	36	Cohort	AMI < 6 mo	$292 \pm 232 \times 10^6$ IM	IM	46% ± 6%	5%	3-12 mo	CABG in all; troponin increased
Perin *et al*[228]	20	Cohort	ICM	$25.5 \pm 6.3 \times 10^6$	IM Trans-Endo-cardial	30% ± 6%	5.10%	12 mo	LVEF = Controls; ↑ LV perfusion ↑ Exercise
Ruan *et al*[229]	20	Yes	Approximately 1 d	NR	IC	53.5% ± 5.8%	5.80%	6 mo	↑ LV segmental contraction
Schächinger *et al*[230,231]	204	Yes	3-8 d	2.4×10^8	IC	48.3% ± 9.2%	6%-7%	4-12 mo	↑ EF when Rx > 4 d post MI and when EF ↑ ≤ 48.9; LV perfusion
Strauer *et al*[232]	20	Cohort	5-9 d	$2.8 \pm 2.2 \times 10^7$ IM	IC	57% ± 8%	5%	3 mo	↑ Regional but not global LVEF; ↓ ESV and ↓ Infarct size
Li *et al*[234]	70	Yes	7 ± 5 d	$7.3 \pm 7.3 \times 10^7$	IC	50% ± 8.2%	7%	6 mo	G-CSF for 5 d; ↓ LV ESV, ↓ LV wall motion score

NR: Not recorded or equals no change; CPC: Circulating progenitor cells; BMC: Bone marrow cells; ICM: Ischemic cardiomyopathy; IC: Intracoronary injection; IM: Intramyocardial injection; AMI: Acute myocardial infarction; OMI: Old myocardial infarction; G-CSF: Granulocyte colony stimulating factor; ESV: LV end-systolic volume; SPECT: Single photon emission computer tomography. Adapted from Henning[213].

best medical care. At 4 mo after coronary infusion, there were no significant differences in infarct scar size or LV myocardial wall thickening in patients treated with BMCs at either 5-7 d or 3-4 wk after AMI in comparison with control patients. Moreover, LV function did not significantly improve at 4 mo after the intracoronary infusion of autologous BMCs in either the early or late treated groups in comparison with the placebo group. However, patients with NT-proBNP levels at baseline above 1437 ng/L experienced a greater increase in LVEF of 7.1% in the early group and 9% for the late BMC group. In all cell and placebo treatment groups, LV scar as determined by late gadolinium enhancement on MRI decreased by more than 10 g with a 4%-5% decrease

Table 6 Stem cells in the treatment of patients with acute myocardial infarction

Ref.	*n*	Random-ized	Time post MI	Cell dose	Baseline	LVEF	Duration	Other findings
Strauer *et al*[232]	20	Cohort	8 d	$2.8 \pm 2.2 \times 10^7$	57% ± 8%	5%	3 mo	↑ Regional but not global LVEF ↓ LV ESV and infarct size
Bartunek *et al*[216]	35	Cohort	10 d	$12.6 \pm 2.2 \times 10^6$	45% ± 2.5%	7%	4 mo	↑ LV regional function, ↑ perfusion; ↑↑ restenosis
Li *et al*[234]	70	Yes	6 d	$7.3 \pm 7.3 \times 10^7$	50 ± 8.2	7%	6 mo	↓ LV ESV, LV wall motion score
Janssens *et al*[221]	67	Yes	1 d	172×10^6	48.5 ± 7.2	3.30%	4 mo	↓ Infarct size
Meyer *et al*[226] and Wollert *et al*[237]	60	Yes	4.8 d	24.6×10^8	50.0 ± 10.0	=	6-18 mo	↑ LVEF at 6 but not at 18 mo
Kang *et al*[222]	96	Yes	4 d	$1\text{-}2 \times 10^9$	52.0 ± 9.9	5.1% AMI	6 mo	↓ LV ESV and infarction in acute MI; = ESV and = old MI
Lunde *et al*[224,225]	100	Yes	6 d	68×10^6	41.3 ± 11.0	=	6-12 mo	LVEF ↑ in treated and controls; = EDV and infarct size
Ge *et al*[219]	20	Yes	1 d	4×10^7	53.8 ± 9.2	4.80%	6 mo	↑ LV regional wall perfusion by SPECT
Meluzín *et al*[235,236]	66	Yes	5-9 d	$10^7\text{-}10^8$	42 ± 0.0	3-5	3-12 mo	↑ LVEF 3% @10^7 ↑ LVEF 5%-7% @ 10^8 3-12 mo
Schächinger *et al*[230,231]	204	Yes	3-8 d	2.4×10^8	48.3 ± 9.2	6-7	4-12 mo	↑ EF when Rx > 4 d post MI and when EF < 48.9%; ↑ LV perfusion

Adapted from Henning[213]. MI: Myocardial infarctions; LVEF: Left ventricular ejection fraction.

in the ratio of myocardial scar to myocardial mass.

ASSESSMENT OF LATETIME, TIME, AND SWISS TRIALS

Several variables in these studies contributed to the lack of significant improvement of AMI patients treated with BMCs in comparison with placebo treated patients.

Early percutaneous coronary intervention

Patients with AMIs in the LateTIME, TIME, and Swiss Multicenter Trials were treated with PCI within a median of 4 to 5 h of the onset of chest pain. Thereafter, the patients were treated with American and European Heart Association guided best medical therapy. Consequently, AMI sizes and the extent of LV remodeling in the different trial patients were significantly limited and the differences between BMC treated patients and placebo treated patients were small. Although the initial qualifying LV ejection fractions by echocardiography after PCI in the LateTIME and TIME trial patients were ⩽ 45%, the LVEFs by MRI at the time of BMC injection were greater than 45%. Bone marrow mononuclear cells are much less effective in patients with small myocardial infarctions with near normal LVEFs. In addition, placebo treated patients continue to improve with best medical therapy after AMIs as demonstrated by the control patients in the Bone Marrow Transfer to Enhance ST-elevation Infarct Regeneration (BOOST) trial in which the LVEFs equaled or exceeded the increases in the LVEFs in the BMC treated patients at 18 mo after AMI[242]. In addition, the Valsartan in Acute Myocardial infarction Trial and trials of neuro-hormonal blockade of patients with AMIs have demonstrated that optimal medical therapy can increase LVEF by a mean of 2.7% at 20 mo[243]. Consequently much larger numbers of patients will be required in clinical trials to demonstrate statistically significant differences between BMC treated patients and placebo treated patients who receive PCI early after the onset of AMI and guideline directed optimal medical therapy.

Heterogeneous bone marrow cell populations

Unfractionated adult BMCs contain less than 3% $CD34^+$ and 1% $CD34^+/CD133^+$ hematopoietic progenitor cells and ⩽ 1% $CD105^+$ mesenchymal stem cells in healthy subjects when marrow cells are separated by Ficoll density gradient-based separation. However, both $CD34^+$ endothelial colony number and the mesenchymal cell colony number were significantly decreased amongst subjects that participated in the LateTime and Time Trials[244]. In addition, the marrow aspirates in the LateTIME and TIME Trials were separated by an automated cell process system (Sepax, Biosafe), which recovered only 23.6% of the total nucleated cells[245]. Consequently, the BMCs delivered in the LateTIME and TIME trials contained smaller numbers of $CD34^+$ and $CD105^+$ cells than earlier BMC studies. Moreover, stem cell motility can decline by as much as 68% 72 h after harvest from the bone marrow[246]. In addition, 140-150 × 10^6 unfractionated BMCs may not be the most optimal dose of BMCs for stem cell treatment of patients with AMI. In this regard, BMCs from patients with advanced age and patients with chronic diseases, such as ischemic heart disease or diabetes mellitus, are often functionally impaired, propagate poorly, and have a shortened life span[246-248]. Consequently, BMC colony forming units and cell migration capability must be determined in addition to bone marrow cell number and viability prior to use in the treatment of AMI. Furthermore, BMCs produced only a modest increase in the LVEF of approximately 2%-3% in earlier analyses of stem cell trials

of patients with AMIs or ischemic cardiomyopathies[213,214]. Despite well conducted clinical trials, unfractionated BMCs selectively infused into an infarct related coronary artery have a small therapeutic effect and may not be the most optimal cells for the treatment of patients with AMIs.

Red blood cell contamination of stem cells

Red blood cell contamination of bone marrow mononuclear cells can significantly decrease the migration ability and the efficacy of BMCs. Large numbers of red blood cells in the cell preparations cause reduced BMC viability, decreased colony forming capacity, and are associated with reduced recovery of LVEF in patients with AMIs[249]. In patients in the REPAIR-AMI Trial, contamination of the bone marrow cells with red blood cells prior to infusion into patients with AMI independently predicted reduced recovery of LVEF[249]. Moreover, the addition of red blood cells to BMCs dose-dependently decreased neovascularization in ischemic hind-limbs compared to treatment with BMCs without red blood cells[249]. The mechanism by which red blood cells interfere with bone marrow cell propagation, migration and neovascularization involves a dose-dependent reduction of BMC mitochondrial membrane potential and a decrease in BMC mitochondrial adenosine triphosphate (ATP) production[249]. As a consequence of decreased mitochondrial metabolism and function, stem cell self-renewal and differentiation are decreased.

Heparin decreases stem cell migration

Heparin can bind to the chemoattractant stromal derived factor-1 (SDF-1), which is released from ischemic myocardium, and also bind to its receptor CXCR4 on stem cells and thereby block CXCR4 signaling and stem cell migration to injured myocardium[250]. Heparin, in a dose-dependent manner, can inhibit SDF-1 induced BMC migration and homing of BMCs to areas of myocardial ischemia[250-253]. Incubation of BMCs with 20 U/mL of heparin for 30 min abrogates SDF-1 BMC migration by 84% *in-vitro* and significantly reduces the homing of injected BMCs to injured and infarcted myocardium by 50% in research animals[250]. Decreased migratory capacity of BMCs also correlates with reduced neovascularization and decreased functional capacity in subjects with limb ischemia[251]. In addition, heparin decreases the concentration of vascular endothelial growth factor (VEGF) in ischemic tissue and thereby decreases neovascularization[252]. Heparin also interferes with activation of the cell survival factor Akt (Protein Kinase B) by SDF-1-CXCR4 signaling and in this manner interferes with cell survival and growth. In contrast, the thrombin inhibitor bivalirudin does not interfere with BMC homing or SDF-1/CXCR4 signaling and does not decrease VEGF[252].

Stem cell expulsion from myocardium

Ninety to 97% of unfractionated BMCs leave the myocardium in less than 2 h after injection directly into the myocardium or into the coronary arteries[254,255]. Most of the cells are ejected out of the myocardium through the myocardial injection sites or through the coronary veins and lymphatics into the right heart due to the massaging action of the contracting myocardium. The cells are ultimately lodged in the lungs, liver, spleen and kidneys. In addition, approximately 12% of BMCs are retained in the catheter delivery system after injection[255]. With the intravenous injection of BMCs or other cells for cardiac repair the majority of the cells become entrapped in the lungs. Consequently, fourfold greater numbers of cells are required above that required for intramyocardial or intracoronary injection for repair of myocardial infarctions[256].

Future bone marrow cell studies

The BAMI Trial (The effect of intracoronary reinfusion of bone marrow derived mononuclear cells on all-cause mortality in acute myocardial infarction) is recruiting 3000 patients with LVEFs $\leqslant$ 45% within 7 d of AMIs, who have undergone successful coronary reperfusion therapy, for randomization into treatment with either intracoronary autologous unfractionated bone marrow mononuclear cells or placebo[257]. Hopefully the BAMI Trial will avoid the important variables that have been described in this paper and will provide definitive answers to the questions whether BMCs can significantly decrease patient mortality due to myocardial infarction, substantially reduce infarct size and increase LVEF over three years in comparison with patients treated with best medical therapy.

CARDIAC STEM CELLS

Cardiovascular investigators have sought alternatives to BMCs for cardiac repair in patients with ischemic heart disease. Cardiac stem cells, which are multi-potent progenitor cells, are present in niches in the heart and contribute to the physiological turnover of myocytes and vascular endothelial cells in the heart. The number of cardiac stem cells in the heart is estimated at one cardiac stem cell per 10000 cardiac myocytes[258]. Consequently, endogenous cardiac stem cells are not normally able to reverse heart damage due to myocardial infarctions. The turnover of cardiac myocytes occurs at rates estimated to be 1% to as much as 22% per year and is dependent on the age, sex, and the health of the individual[259,260]. Two major types of autologous cardiac stem cells have been investigated in patients with injured and infarcted myocardium in the SCIPIO and CADUCEUS clinical trials: C-kit + lineage negative cardiac stem cells isolated from right atrial appendages and cardiosphere derived cells (CDCs) grown from right ventricular cardiac muscle biopsies.

C-KIT + STEM CELLS

C-kit is a receptor for stem cell factor, which is released from the ischemic myocardium, and is important

in the chemoattraction of stem cells to apoptotic, injured and necrotic myocardium. C-kit + stem cells have the capacity for self-renewal, clonogenicity and multi-potency[261,262]. These stem cells can express the cardiac transcription factors GATA-4, Nkx2.5 and MEF2 and can differentiate into myogenic, vascular endothelial and smooth muscles cells *in-vitro*[261,262]. In research animals with AMIs, cardiac stem cells can form new myocardium[262].

Autologous C-kit cardiac stem cells from right atrial appendages have recently been used for the treatment of patients with myocardial infarctions and ischemic cardiomyopathies in the open labeled Cardiac Stem Cell Infusion in Patients with Ischemic Cardiomyopathy (SCIPIO) Trial[263-265]. In this trial C-kit positive stem cells were isolated during coronary artery bypass surgery from the right atrial appendages of patients with LVEFs < 40%. The cells were then propagated in the laboratory. Four mo later, a maximum of one million cardiac stem cells were injected directly into the patient's saphenous vein grafts and coronary arteries supplying infarcted myocardium. The two year results of this trial have been presented at the American Heart Association Scientific Sessions in November of 2012 and 2013. In the SCIPIO trial the LVEF, measured by three-dimensional echocardiography and by MRI with gadolinium in patients who received cardiac stem cells, increased in 12 patients in absolute units by 11.9% at 2 years[265]. Left ventricular scar, determined by MRI, decreased by as much as 20.4 g at 2 years (n = 6) and was associated with an increase in viable myocardium of 17.9 g (n = 6) at 2 years[265]. New York Heart Association Functional Class score decreased in these patients by 0.77 at 2 years (n = 13). A left internal mammary graft dissection occurred in one treated patient, which was treated with a graft stent, and a peri-procedural myocardial infarction occurred in a second treated patient[264]. In this study, C-kit cardiac stem cells were proposed to chemoattract patients' native stem cells to areas of myocardial injury and also to transdifferentiate to myocytes for cardiac repair. A Phase 2 trial of safety and efficacy of C-kit cardiac stem cells in a larger group of patients is currently being planned.

CARDIOSPHERE DERIVED CELLS

Percutaneous endomyocardial biopsy specimens of the right ventricular septal wall and apex in patients, when grown in culture, can yield spherical multicellular clusters termed "cardiospheres". Cardiospheres are a mixture of stromal, mesenchymal and hematopoietic progenitor cells that contain cells that express CD 105 (commonly associated with mesenchymal stem cells) and partially express C-kit[266,267]. Cardiosphere derived cells (CDCs), when injected into the border of myocardial infarctions in mice, engraft and increase viable myocardium[268]. The functional benefit of CDCs is predominantly due to the secretion of growth factors and the recruitment of endogenous stem cells to injured and infarcted myocardium for myocyte generation. In this regard, cardiospheres and CDCs secrete the growth factors angiopoietin-2, basic fibroblastic growth factor, hepatocyte growth factor, insulin-like growth factor 1, stromal derived factor-1 and vascular endothelial growth factor which are beneficial in repair of injured myocardium[267,268].

Autologous CDCs have been investigated in the open labeled Cardiosphere-derived Autologous Stem Cells to Reverse Ventricular Dysfunction (CADUCEUS) Trial[269,270]. In this trial, 17 patients, post myocardial infarction with LVEFs of 25%-45%, underwent endo-myocardial biopsies of the right ventricular septum. Cardiosphere derived cells were obtain from cultures of the endomyocardial biopsies and the cells were propagated. In this trial, between 12.5 and 25 million CDCs were then given directly into the infarct related coronary artery of each of the 17 patients 1.5 to 3 mo after their myocardial infarctions. The one year followup of 12 of the 17 patients treated with autologous CDCs and 8 control patients have been reported[270]. Left ventricular scar by MRI significantly decreased by a mean of 11.9 g in CDC-treated patients and by 1.7 g in control patients. Left ventricular viable mass increased by a mean of 22.6 g in treated patients in comparison with 1.8 g in control patients. Left ventricular ejection fractions did not significantly increase but the regional wall function of infarcted segments did increase and correlated with the decrease in LV myocardial scar size[269,270]. Covariate statistical analysis demonstrated that the lower percentage of infused $CD90^+$ cells caused the greatest reductions in scar size in patients with large infarctions. A Phase 2 study of CDCs (ALLSTAR Trial) is currently in progress that involves allogeneic CDCs for the treatment of patients after myocardial infarction.

ASSESSMENT OF THE SCIPIO AND CADUCEUS TRIALS

In the SCIPIO trial 1545 patients were evaluated. Two hundred thirteen patients had LVEFs < 40% and 20 patients were treated with C-kit + stem cells. Twelve of 20 patients had MRI determinations of left ventricular function whereas the control patients did not have MRI determinations of left ventricular function. In the CADUCEUS Trial 436 patients were evaluated and 17 patients received CDCs. Consequently, these trials report a highly selected patient population and the results of these trials cannot be applied to all patients with myocardial infarctions and ischemic cardiomyopathies. Much larger trials are necessary of each of these cell types in patients with myocardial infarctions.

In each of these studies, LV infarction was defined by MRI of delayed enhancement of myocardium in the

region of coronary artery occlusion/reperfusion due to gadolinium that leaked from myocardial capillaries and pooled in the myocardial interstitial spaces and intracellular spaces. In these patients the gadolinium volume of distribution was increased and washout from the myocardium was reduced. However, cardiac stem cells can incorporate into damaged blood vessels, chemoattract endogenous stem cells that can form entirely new blood vessels, and can also secrete angiogenic growth factors that stimulate new blood vessels from preexisting vessels. Consequently, the blood vessels in the damaged myocardium of patients treated with these stem cells were less permeable to gadolinium[271]. Infarct scars can potentially appear smaller on MRI due to less gadolinium leak as well as contracture of the myocardial infarction. Moreover inter-scan variability and intra- and inter-observer variability in infarct measurements and interpreting MRI scans can account for some myocardial changes between pre- and post-stem cell infusion[272]. Rebuttals to these arguments against the use of contrast enhanced MRI in estimating infarct size and myocardial regeneration after stem cell treatment have been published[273]. The rebuttal is based on a porcine myocardial infarction study in which allogeneic CDCs decreased infarct scar size and led to cardiomyocyte hyperplasia on MRI and also on histological examination[273]. Nevertheless, anatomical and histological examinations of myocardial biopsies of infarcted hearts of patients or myocardial autopsy examinations of patients treated with these stem cells are necessary to determine if infarct fibrosis is significantly decreased and if substantial generation of new myocytes occurs. Trials of larger numbers of patients treated with C-kit + cardiac stem cells and cardiosphere derived cells for longer times are warranted to determine the precise mechanisms of action of these stem cells and their clinical benefit.

FUTURE DIRECTIONS

The LateTIME, TIME, Swiss, SCIPO and CAUDUCEUS Trials demonstrate that stem cells can be safely administered to patients with acute myocardial infarctions and ischemic cardiomyopathies and do not have significant adverse effects. Specific bone marrow cell subsets, such as unconditioned or conditioned mesenchymal cells or $CD34^+$ hematopoietic cells, may prove to be more efficacious in myocardial infarction repair than unfractionated BMCs[274,275]. In this regard, bone marrow mesenchymal stem cells or mesenchymal stem cells conditioned with cardiogenic growth factors have been reported to be beneficial in increasing LV function and functional capacity in patients with ischemic cardiomyopathies[275]. In addition, mesenchymal stem cells may enhance the beneficial effects of C-kit cardiac stem cells when these cells are administered together[276]. The large size of mesenchymal stem cells, however, requires that these cells be most safely delivered into the heart by direct myocardial injection rather than intracoronary injection in order to avoid problems of cell clumping and coronary occlusion. Mesenchymal stem cells and also umbilical cord stem cells are reported to be "immunoprivileged" and lack Class II human leukocyte antigens[277,278]. If allogeneic stem cells prove to be safe and effective in limiting myocardial damage and LV remodeling after myocardial infarction in patients, then these cells might become an "off the shelf" product that surpasses the significant limitations of inter-patient variability of unfractionated bone marrow mononuclear cells. Since the functional benefit of stem cells appears to be predominantly due to the secretion of biologically active factors, the ultimate rejection of allogeneic stem cells may not be of major concern if the rejection is delayed long enough to allow these cells to exert their paracrine effects. Nevertheless, stem cell trials must be performed in patients with large myocardial infarctions and LVEFs by MRI less than 40% at the time of stem cell administration because stem cells may not be efficacious in patients with small infarctions and near normal or normal LVEFs. In these studies, substantial stem cell viability, colony forming and migration capabilities must be established prior to infusion in patients.

A major problem with all stem cell trials is the short term engraftment and survival of stem cells in injured and infarcted myocardium. The cells that remain in the myocardium do not survive due to ischemia, inflammation, or anoikis or migrate from the myocardium in one to two weeks[254,255]. Consequently, stem engraftment in the heart must be increased in order to significantly enhance their beneficial effects. Possible treatment options include "conditioning" of the myocardium prior to stem cell delivery or co-delivery of stem cells directly into the myocardium with extracellular matrix molecules, nanofibers, hydrogels, or fibrin glues[213,214,279]. Co-delivery of stem cells with other molecules will require direct intramyocardial cell injection at the time of cardiac surgery or cardiac catheterization which appears to produce the greatest functional benefit[280]. Alternatively, stem cells can be administered in patches that are applied directly to the epicardial surface of the damaged myocardium at the time of cardiac surgery[213,214]. Direct stem cell to myocyte contact and interactions may be crucial in eliciting beneficial myocyte functional effects. In addition, genetic engineering of stem cells must be developed that facilitate the homing of stem cells to ischemic myocardium and the retention of the stem cells within the myocardium after intracoronary or intravenous injection.

A major mechanism of action of stem cells studied to date in myocardial repair is the secretion of growth factors, chemokines, anti-inflammatory cytokines and exosomes or microparticles, which contain proteins, messenger ribonucleic acids and micro-ribonucleic acids. Hypoxic stress appears to increase the paracrine effects of stem cells[281,282]. Biologically active factors from stem cells can suppress inflammatory cytokines and inflammatory cells in the injured myocardium,

improve myocardial metabolism, promote angiogenesis, inhibit myocyte and endothelial cell apoptosis, recruit endogenous progenitor cells to injured myocardium, and possibly stimulate surviving myocytes to re-enter the cell cycle and proliferate. The most efficacious stem cell biologically active factors must be identified, purified, and the pharmacologic effects established in research animals and ultimately in patients with injured myocardium.

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