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Management of Acute Coronary Syndrome in the Light of Recent Trials

KK Sethi, Vivek Prakash

Abstract: The spectrum of acute coronary syndrome (ACS) constitutes unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI). Disruption of plaque is now considered to be the common pathophysiological substrate of ACS. Patients with NSTEMI, defined as those with an elevated biomarker of necrosis, CB-MB or troponin, have a worse long-term prognosis than those with unstable angina. Beyond just a positive versus negative test results, there is a linear relationship between the level of troponin T or I in the blood and subsequent risk of death—the higher the troponin, higher the mortality risk. Patient presenting with persistent ST segment elevation are candidates for reperfusion therapy (either pharmacological if in the first two hours or catheter based) to restore flow in the occluded epicardial infarct-related artery. ACS patients presenting without ST segment elevation are not candidates for pharmacological reperfusion but should receive anti ischemic therapy, often followed by PCI. Meta analysis of recent randomized trials in over 8,000 NSTE–ACS patients treated in the era of potent antiplatelets therapy and coronary stents shows that early invasive therapy decreases mortality by 25% at a mean of 2 years of follow-up, compared with a more conservative approach. Early invasive therapy also decreases nonfatal myocardial infarction by 17% and recurrent unstable angina requiring rehospitalization by 31%.

INTRODUCTION

Patients with ischemic discomfort present with or without ST-segment elevation on the electrocardiogram (ECG). The majority of patients with ST-segment elevation ultimately develop a Q-wave acute myocardial infarction (QWMI), whereas a minority develop a non-Q wave myocardial infarction (NQMI). Patients who present without ST segment elevation are either experiencing unstable angina or a non-ST segment elevation myocardial infarction (NSTEMI). The distinction between these two diagnosis is ultimately made based on the presence or absence of a cardiac biomarker detected in the blood. Most patients with NSTEMI do not evolve a Q wave on the 12-lead ECG. Only a minority of NSTEMI patients develop a Q wave MI and are later diagnosed as Q wave MI. The spectrum of clinical conditions ranging from unstable angina to Q wave MI constitutes the acute coronary syndromes[1] (Fig. 7.1).

Disruption of plaques is now considered to be the common pathophysiological substrate of the acute coronary syndrome (ACS).[2] Characteristically, such complete occlusive thrombi lead to a large zone of necrosis involving the full or nearly full thickness of the ventricular wall in the

myocardial bed subtended by the affected coronary artery and typically produce ST elevation on the ECG. In about 25 percent of patients presenting with ST elevation, no Q waves develop, but other abnormalities of the QRS complex are frequently seen such as diminution in R wave height and notching or splintering of the QRS.

Patients presenting with persistent ST segment elevation are candidates for reperfusion therapy (either pharmacological or catheter based) to restore flow in the occluded epicardial infarct-related artery. ACS patients presenting without ST segment elevation are not candidates for pharmacological reperfusion but should receive anti-ischemic therapy, often followed by PCI. Antithrombin therapy and antiplatelet therapy should be administered to all patients with ACS regardless of the presence or absence of ST segment elevation.

Many new markers have been shown to be independent predictors of an adverse prognosis. troponin is a marker for myocardial necrosis, high-sensitive C reactive protein (hs-CRP) and CD 40 ligand are markers of vascular inflammation, creatinine clearance (CrCl) and micro-albuminuria are markers of vascular damage, HbA_{1C} and blood glucose are markers of diabetes and accelerated atherosclerosis.

Creatine Kinase-MB and the Troponins

Patients with NSTEMI, defined as those with an elevated biomarker of necrosis, CK-MB or troponin, have a worse long-term prognosis than those with unstable angina. Beyond just a positive versus negative test result, there is a linear relationship between the level of troponin T or I in the blood and subsequent risk of death- the higher the troponin, the higher the mortality risk. Similar results have been obtained using a bedside rapid assay for troponin T, in which time to positivity is a semi-quantitative measure of serum troponin T and related to increased mortality. Thus troponin T and troponin I are useful not only in diagnosing infarction but also in risk assessment and in targeting therapies to high-risk patients.

C-reactive Protein

High sensitive C-reactive protein (CRP) directly participates in myocardial injury of acute myocardial infarction (AMI). High CRP levels in the acute phase strongly indicate poor early clinical outcome of the patients with AMI. In AMI,[3] the peak plasma value of CRP can also be used to estimate the risk of cardiac rupture as well as short and long-term prognosis. Estimation of CRP levels in acute phase may provide valuable information on left ventricular (LV) function and exercise capacity and can help in long-term risk stratification after AMI.[4] According to AHA/CDC recommendations, CRP levels are classified as: low hs-CRP < 1 mg/dl; average 1-3 mg/dl; and high CRP > 3 mg/dl. Higher CRP levels in patients with AMI indicate an increased risk of subsequent coronary events because CRP is associated with inflammation of coronary vessels. It is reasonable to suggest that high CRP levels are associated with adverse outcome as a result of coronary instability. Several large-scale prospective studies have shown the inflammatory marker-high sensitivity CRP (hs-CRP) to be a potent predictor of future MI, stroke and peripheral vascular occlusion among apparently healthy men and women, as well as among high-risk smokers and the elderly. Levels of hs-CRP are also elevated among those with acute coronary syndromes at high-risk for recurrent events and among post-MI patients at high-risk for recurrent instability.[5] These effects are independent of other risk factors and appear to add to the predictive value of lipid screening in terms of risk prediction. However, there remains much confusion as to when it may be appropriate to measure CRP levels, and what to do about them when they are found to be elevated. The association of elevated CRP and poor prognosis in patients with acute coronary syndrome is independent of other serum markers of myocardial cell injury and necrosis like cardiac troponin and CK-MB. Suleiman, et al[6] showed that plasma CRP level obtained within 12 to 24 hours of symptom onset is an independent marker of 30 days mortality and the development of heart failure in patients with AMI. CRP levels may be related

to inflammatory processes associated with infarct expansion and post-infarction ventricular remodeling. Anzai, et al, showed that cardiac rupture, LV aneurysm formation, and one-year cardiac mortality were associated with an elevation of serum CRP early after AMI. Berton, et al,[4] showed that first day hs-CRP is a strong independent predictor of both heart failure progression and depressed LV ejection fraction in AMI. In contrast to above studies, Kimura, et al showed that elevated CRP immediately after onset of AMI is associated with less myocardial damage and better LV function in reperfused anterior AMI. They have suggested that two mechanisms may account for the myocardial protective effect associated with the elevation of CRP. First, silent myocardial ischemia, which is frequently associated with unstable angina, and in which CRP levels may increase greatly, may exert an ischemic preconditioning effect on the myocardium. Second, inflammation induces expression of angiogenic growth factors associated with reduced infarct size, and endogenous production of nitrous oxide protects the myocardium from ischemic reperfusion injury.

Among patients with negative troponin I at baseline, who had an overall 14 days mortality of only 1.5%, CRP was able to discriminate a high and a low-risk group: mortality for patients with an elevated CRP was 5.8% versus 0.4% for patients without an elevated CRP. When using both CRP and Troponin mortality could be stratified from 0.4% for patients with both markers negative, to 4.7% if either of the two was positive, to 9.1% if both were positive[7] as shown in Figure 7.2.

CD 40 Ligand

Another emerging and important marker is CD 40 ligand (CD40L), a member of the tumor necrosis factor- alpha family of proteins. CD40L is expressed on the surface of platelets when platelets are activated and is subsequently cleaved, generating a soluble hydrolytic fragment termed CD40L. It has been found to be both prothrombotic and proinflammatory and to have a role in atherosclerotic lesion progression. CD40L has been correlated with the degree of platelet activation, as measured by platelet monocyte aggregates and thus is a novel marker of platelet activation. Studies have found that increasing levels of CD40L are associated with increased rate of death, MI and recurrent ischemic events, independent of troponin and CRP in patients with ACS.[8,9]

Other inflammatory markers have offered consistent evidence of an association between systemic inflammation and recurrent adverse events, including serum amyloid A, monocyte chemoattractant protein-1 (MCP-1) and interleukin-6 (IL-6).

B-type Natriuretic Peptide

B-type natriuretic peptide (BNP) is a neurohormone that is synthesized in ventricular myocardium and released in response to increased wall stress. It has many actions including natriuresis, vasodilation, inhibition of sympathetic nerve activity, and inhibition of the renin-angiotensin-aldosterone system. BNP has been shown to provide prognostic information in patients with acute coronary syndrome (ACS).[10] Current knowledge indicates that NT-pro-BNP may be a more sensitive and an effective prognostic tool in these patients.[11,12] On multivariate analysis, NT-pro-BNP was found to be as predictive of mortality and morbidity as the gold standard of low EF. Using the multivariate regression analysis, NT-pro-BNP emerged as the only predictor of absence of adverse events at 30 days follow-up after the acute event and this relation was equally strong across the entire spectrum of AMI patients.[13] The interpretation of early natriuretic peptide measurement in ACS patients can be difficult since levels of BNP and NT-proBNP vary according to index diagnosis and rise continuously during the first 24 hours after the onset of ischemia. Concentrations increase very rapidly and steeply during the first day after the onset of myocardial ischemia, making the comparison of concentrations difficult. Recent studies have provided information on the sampling times that provide the best predictive value

for NT-proBNP in patients presenting with AMI. Measuring NT-proBNP in STEMI, Talwar, et al declared that samples collected between 72 and 120 hours provided maximal prognostic value. However, it has lately been shown that NTproBNP is a strong predictor of mortality irrespective of sampling time, even up to 4 weeks after the index event.

Myeloperoxidase

Myeloperoxidase (MPO) is a hemoprotein expressed by polymorphonuclear neutrophils that possesses potent inflammatory properties and that promotes oxidation of lipoproteins in vascular atheroma. One case-control study found an association of MPO levels with the presence of angiographically documented CAD, independent of other risk factors and of WBC count. In patients with UA/NSTEMI, MPO serum levels were associated with increased risk for subsequent death or MI, independent of other risk factors and other cardiac markers. Elevations of MPO have been seen throughout the coronary vasculature in patients with UA/NSTEMI. Thus MPO may be both a marker of inflammation, and its presence also suggests a direct role of neutrophil activation in the pathophysiology of vascular inflammation and ACS.

Creatinine

Another simple tool for risk stratification is the use of creatinine or calculation of creatinine clearance, or both. Several studies have found elevated creatinine to be associated with an adverse prognosis, and the risk appears to be independent of other standard risk factors such as troponin elevation. This factor may also play a role in decreased drug clearance in which dosages of medications such as LMWH need to be altered.

Glucose

Adverse outcomes have been seen among diabetic patients with acute MI with elevated admission glucose values compared with patients without hyperglycemia. Studies have found that this association exists even in patients without a prior diagnosis of diabetes. In addition, this association was seen in patients with both STEMI and UA/NSTEMI and was independent of other baseline factors. A similar association of poor glycemic control, as measured by HbA1c, has been seen in other studies.

TIMI Risk Score

It has seven independent risk factors:

1. Age older than 65 years
2. More than 3 risk factor for CAD
3. Documented CAD at catheterization (> 50% stenosis)
4. ST deviation greater than 0.5 mm
5. More than two episodes of angina in the last 24 hours.
6. Aspirin within the prior week
7. Elevated cardiac markers.

This scoring system was used to stratify the risk for patients across a 10-fold gradient of risk, from 4.7 to 40.9 percent.[14] More important, this risk score has been found to predict the response to several of the therapies used in UA/NSTEMI: patients with higher TIMI risk score had significant reduction in events when treated with enoxaparin compared with UFH; with a GP IIb/IIIa inhibitor compared with placebo, and with an invasive versus conservative strategy.

With the ever growing number of new cardiac markers it is expected that these comprehensive risk scores can be expanded to include these new markers as they become more widely available in clinical practice.

MANAGEMENT

The ACC/AHA guidelines suggest an approach to the immediate management of patients with possible ACS that integrates information from the history, physical examination, 12 lead ECG, and initial cardiac marker tests to assign patients to 4 categories: non-cardiac diagnosis, chronic stable angina, possible ACS and definite ACS (Fig. 7.3).

Rational Approach for STEMI

Clearly, patients with contraindication to thrombolytic therapy or in cardiogenic shock should be considered for primary PCI. In situations where facility of PCI is not readily available (in rural or remote areas, or at odd hours of day) or where transit time is significantly higher, thrombolytic therapy at point of first medical contact (if feasible, pre-hospital) should be given. Based on the Boersma's equation and its proposed modification, the following rationale can be drawn.

Patients Presenting within 2 Hours from Onset of Symptoms

These patients are the ideal candidates for pre-hospital administration of thrombolytic therapy. Primary PCI should be considered only if patient reaches hospital within this time frame without thrombolysis. However, a large registry data showed that only 8% of patients actually receive primary PCI within 2 hours of symptom onset due to combination of delays in patient presentation and those inherent to interventional strategy.

Patients Presenting between 2-6 Hours from the Onset of Symptoms

The effect of thrombolytic therapy weans off with time as the aging thrombi become more resistant to lysis. In comparison, primary PCI is far less time dependent in achieving reperfusion and salvaging ischemic myocardium. Given this superiority of PCI over thrombolytic therapy, patients presenting between 2 to 6 hours from the onset of symptoms should be considered for PCI even if it involves transfer to another hospital. The controversy of initiating thrombolysis for patients who are being shifted to other institutions for PCI is a subject of ongoing trials. Recent report from the National Cardiovascular Data Registry of American College of Cardiology highlighted the need of thrombolysis in patients who require transport to other institutions for PCI. Patients transferred on thrombolytic therapy had lower rate of mortality post-PCI (3.2% *vs* 5.8%, $p<0.0001$) perhaps due to lesser rate of occluded infarct-related artery prior to PCI (24.7% *vs* 49.2%, $p < 0.0001$) in comparison to patients transferred without thrombolytic therapy. However, large scale randomized trials are needed to support this contention.

Patients Presenting beyond 6 Hours from the Onset of Symptoms

Little myocardial salvage is expected beyond 6 hours, especially if the chest pain and ST segment elevation has settled. These patients have only modest benefit from thrombolytic therapy and are not candidates for pre-hospital thrombolysis. These patients may be considered for coronary angiography and revascularization to achieve patent infarct-related coronary artery (open artery hypothesis), though the merits of this approach are still contentious.

Concept of Pre-hospital Thrombolysis

It is widely acknowledged that the key factor in the successful treatment of AMI by thrombolytic therapy is the time elapsed between the onset of symptoms and initiation of therapy. A meta-analysis of 22 trials, including more than 50,000 patients, showed maximal effectiveness of thrombolytic therapy within the first hour of symptom onset (the golden hour), whereas the benefit was reduced by nearly 50% in the subsequent hour (the Boersma's curve). An estimated 65, 37, 26 and 29 lives are saved per 1000 patients when treated with thrombolytic therapy within

0-1, 1-2, 2-3 and 3-6 hours respectively.[15] If the patients of AMI can be identified and treated very early after the onset of symptoms, the infarction process can essentially be aborted.

The European Task Force Report[16] recommends that thrombolytic treatment should be administered by the first qualified person evaluating the patient whether this is before or after the hospital admission. Ideally a medical professional should administer thrombolytic therapy in the pre-hospital scenario. Due to technological advances in acquisition and transmission of 12-lead electrocardiogram to a referral center, initiation of thrombolysis by paramedic personnel is being increasingly employed. At present, pre-hospital thrombolysis is advised to be initiated in a fully equipped ambulance of the emergency medical services (EMS) en-route to the hospital.

Various factors need to be considered regarding the choice of agent for pre-hospital thrombolytic therapy. These include ease of drug administration, its efficacy, potential for adverse reactions, cost, and storage. Streptokinase (first generation thrombolytic agent) is not an ideal option for a paramedic-initiated pre-hospital thrombolysis. It has to be administered as an infusion and carries risk of allergic reactions and hypotension. Similarly, anistreplase (APSAC) though given as a bolus injection, has similar risks of allergic reactions. Alteplase [tissue-type plasminogen activator (t-PA), a second generation thrombolytic agent] has high safety and efficacy profile, but need for administration as an infusion makes it less attractive in the pre-hospital setting. New third generation thrombolytic agents which are predominantly derivatives of alteplase include: reteplase (recombinant plasminogen activator, r-PA), tenecteplase (TNK-mutant of alteplase), and lanoteplase (novel plasminogen activator, n-PA). Reteplase has a great potential for pre-hospital administration. The advantages of this drug in the pre-hospital treatment are manifold. It is administered as a bolus injection. Since early reoccclusion of the infarct-related artery had been observed with single bolus administration, it is currently given as double boluses of 10 U each, 30 min apart. The drug-dosing pattern is standard irrespective of the body weight of the patient making its use simple in the pre-hospital scenario.[16] An additional advantage of this drug may be its role in facilitating percutaneous coronary intervention (PCI). Since the first bolus is given in the pre-hospital setting, the hospital staff has a choice of the treatment regime to follow; a second dose of reteplase or PCI once the patient arrives in the hospital. If the patient is still not in the hospital within 30 min, the other bolus can be given. This concept is being tested in the Pre-hospital Administration of Thrombolytic Therapy with Urgent Culprit Artery Revascularization (PATCAR) pilot study. Presently, it appears that reteplase may be considered as the 'drug of choice' for pre-hospital administration. Another thrombolytic agent, tenecteplase, has relative long plasma half-life that allows for a single bolus application. Lanoteplase has plasma half-life 10 times that of alteplase and therefore can be administered as single bolus. But higher incidence of hemorrhagic stroke has been reported with this drug. Thus, the third generation thrombolytic agents are likely to replace current thrombolytic therapy regime in near future. Reteplase and tenecteplase are ideal agents to be used in setting of pre-hospital administration. However, a much higher cost and non-availability remain major issues in the developing countries.

Aborted Infarction—"The Ultimate Myocardial Salvage"

The expression "aborted infarction" was first used to describe the patients treated very early in the Myocardial Infarction and Triage Intervention (MITI) trial. It was found that 40% of all patients treated within 3 hours of onset of symptoms had no evidence of infarction as measured by thallium scan at 30 days follow-up. Minimal infarct size of less than 10% was noted in additional 35% patients.[17] The key factor influencing these results was the early treatment through pre-hospital triage and not necessarily pre-hospital administration of thrombolytic therapy. Few recent reports have focused on the impact of pre-hospital thrombolysis on the incidence of aborted infarction. Aborted infarction was defined on the basis of ECG criteria (subsiding of cumulative ST segment elevation and depression to <50% of the level at presentation), together with a rise of creatine kinase less than twice the upper limit of normal. As

expected, the median time-to-treatment was shorter by approximately one hour in the pre-hospital group compared to in-hospital group (97 min *v*s 153 min, $p < 0.05$). Pre-hospital thrombolysis was associated with a four-fold increase of aborted infarction compared with in-hospital therapy (17.1% *v*s 4.5%, $p < 0.05$).[18,19]

ACS without ST Segment Elevation— "The Role of Early Intervention"

During the past 15 years, there have been important advances in both percutaneous coronary intervention (PCI) and the pharmacotherapy of acute coronary syndromes without ST segment elevation. Several carefully designed, randomized clinical trials have evaluated prospectively two contrasting strategies for managing these syndromes (a routine early invasive strategy and selectively invasive strategy) and their effect on short- and long-term clinical outcomes.[20-22]

A total of thirteen studies were initially identified; three studies (TIME IIIB, MATE, VANQWISH trial),[23-25] were excluded for being noncontemporary (i.e. before the era of enhanced antiplatelet therapy and coronary stents), 2 studies (Swift and Danami Trial)[26-28] were excluded because fibrinolytic agents were used and 1 study (TIME trial)[29] was excluded because patients had chronic stable angina. In all, there were 7 studies with 8,375 total patients that were included for analysis (Table 7.1).[29-36] Follow-up ranged from one month (ISAR-COOL) to 60 months (RITA-3),[35] and 4 of the 7 studies have reported outcomes beyond one year. The weighted mean follow-up was 23.7 months. Completeness of follow-up ranged from 98.8 to 100%. All participants received aspirin and either unfractionated or low-molecular-weight heparin. Glycoprotein IIb/IIIa inhibitors were available during PCI in all trials except for VINO, and during medical stabilization in TACTICS-TIMI-18 and ISAR-COOL. Thienopyridines were used as an adjunct to PCI in all trials.

Invasively treated patients were directed to catheterization laboratories and, depending on coronary anatomy, continued medical therapy or underwent revascularization. Conservatively treated patients were generally managed with antiplatelet and antithrombin agents, and only directed to catheterization laboratories if there were persistent anginal symptoms despite maximal medical therapy, if there were hemodynamic or electrical instability, or if a large ischemic burden was shown on predischarge stress testing. A notable exception to this approach was the ISAR-COOL trial in which diagnostic catheterization was performed early (i.e. within 6 hours) or delayed (i.e. within 3-5 days). Over the mean follow-up of 23.7 months, 71.1% of invasively treated patients eventually underwent revascularization by PCI or CABG, compared with 46.4 of conservatively treated patients.

Meta-analysis of 7 contemporary randomized trials in over 8,000 NSTEMI-ACS patients treated in the era of potent antiplatelet therapy and coronary stents shows that early invasive therapy decreases mortality by 25% at a mean of 2 years of follow-up, compared with a more conservative approach. Early invasive therapy also decreases nonfatal myocardial infarction by 17% and recurrent unstable angina requiring rehospitalization by 31% (Table 7.2).

Trials that performed very early invasive therapy (median of 9.3 hours) did not show an improvement in long-term survival compared with trials that performed later angiography (median of 30.4 hours). The ISAR-COOL trial was the only trial in which both study arms underwent invasive therapy, and this study found that very early angiography (median of 2.4 hours) was superior to delayed angiography (median of 86 hours); however, it is also possible that delaying invasive therapy for nearly 4 days with continuous glycoprotein IIb/IIIa inhibition could have been harmful.

The goal in the management of NSTEMI-ACS should be to perform early invasive therapy within 48 hours. This view is also supported by recent insight from the CRUSADE registry, in which a delay of invasive therapy of 46 hours was not associated with increased adverse events, compared with a delay of only 23 hours.

All trials reported nonfatal myocardial infarction as separate events, except for TIMI-18, which reported fatal and nonfatal myocardial infarction as a composite event. The cumulative incidence of nonfatal myocardial infarctions was 7.6% among recipients of early invasive therapy compared with 9.1% among conservatively treated patients over a weighted mean follow-up of 23.7 months (RR = 0.83, 95% CI-0.72 to 0.96, P = 0.012). The ICTUS trial documented a high incidence of post procedural myocardial infarction, although this study used the lowest threshold for defining and highest frequency of sampling for these events. Although this definition is consistent with the current consensus document of the joint European Society of Cardiology/American College of Cardiology, it is in contradistinction to the other trials, which generally only sampled blood once after PCI and defined a post procedural myocardial infarction as a createnine kinase-MB > 1.5 to 5 times the upper limit of normal (Table 7.3).

Analysis of noncontemporary trials performed before the era of potent antiplatelet therapies and coronary stents showed that early invasive therapy was associated with harm.[5] Glycoprotein IIb/IIIa inhibitors and stents enhance the safety of PCI by decreasing major adverse cardiac events, including myocardial infarction and death.[28-30] Early invasive therapy in the management of NSTE-ACS provides a durable survival advantage without increasing early adverse events. This approach also reduces nonfatal myocardial infarction and recurrent unstable angina requiring rehospitalization.

Role of GP IIb/IIIa Inhibition in ACS Patients

The overall benefit of early GP IIb/IIIa inhibition in UA./NSTEMI can be increased when it is applied to appropriate risk stratified patient. This has been seen most dramatically in patient with elevated troponin valves. These patients are at a two to three fold higher risk of subsequent cardiac complications, including mortality. Elevated markers have been shown to correlate with a higher rate of thrombus at angiography and worse TIMI flow grade in the culprit artery, as well as worse myocardial perfusion. It has further been observed that a greater antithrombotic effects is observed in these groups; for example, the degree of resolution of thrombus after 24 hours of therapy with abiciximab in the CAPTURE trial was greater in those who were troponin T positive vs negative. Clinical benefits have followed the same pattern. The reduction in death or MI at 6 months in the capture trial was 70% in those who were troponin T positive vs no significant benefit for those who were trop T negative. These findings have been duplicated with tirofiban vs heparin in the PRISM trial. Identical findings of a 50-70% reduction in death or MI was seen in the Paragon B and prism–plus troponin substudies.[38,39] Thus, four independent trials confirmed the very large benefit of GP IIb/IIIa inhibition in troponin positive patients. The benefit of GP IIb/IIIa inhibition was seen in those with a TIMI risk score of 4 or higher, regardless of whether they had PCI or not.[39] Thus in ACS, the benefit of GP IIb/IIIa inhibition appears to relate to the patients risk and not necessarily to the treatment strategy used.

As an Adjunctive Therapy to PCI

The principle goal of reperfusion therapy is preservation of contractile function by myocardial salvage. Optimization of both large vessel patency and microvascular perfusion is pivotal to this goal. Modern interventional techniques are highly successful in restoring large vessel patency. To improve distal circulation, additional measures need to be taken. GP IIb/IIIa blockade is highly promising for this end. GP IIb/IIIa blockade appears to prevent distal embolization of platelet aggregates from the treated plaque.[40,41] Moreover, abciximab, because of its ability to block not only GP IIb/IIIa but also vitronectin receptors and Mac-I can interfere with heterotypic platelet and leukocyte interactions that limit micro vascular reflow. The role of GP IIb/IIIa receptor blockade in optimizing microvascular reperfusion could be confirmed clinically in ISAR-2 The study demonstrated that in acute myocardial infarction abciximab has important effects beyond the maintenance of large-vessel patency. It improves the coronary perfusion at the level of the

distal vascular bed and concomitantly enhances the restoration to left ventricular function in the infarct area. These findings are consistent with the results of the ADMIRAL trial which found better TIMI flow grades after PCI in the abciximab treated group compared with the placebo group, as well as higher global LV function ejection fractions. Meta-analysis of the four randomized clinical trials using abciximab as an adjunct to PCI in acute myocardial infarction, RAPPORT, ISAR-2, ADMIRAL, and CADILLAC, reveals a reduction in the composite of death, reinfarction and re-intervention during 30 days and 6 months follow-up. This benefit is particularly large if abciximab is administered upstream, as suggested by ADMIRAL, and may be negligible in low risk settings, as suggested by analysis of the stent grouping CADILLAC. In TITAN-TIMI 34 trial,[42] eptifibatide used in the emergency department before primary PCI for STEMI yielded superior pre-PCI TIMI frame counts, reflecting epicardial flow, and superior TIMI myocardial perfusion compared with a strategy of initiating eptifibatide in the Cardiac Catheterization Laboratory without an increase in bleeding risk.

Role of Bivalirudin in ACS

Bivalirudin effectively inhibits thrombus, and thrombin mediated platelet activation. It is potent, highly specific and reversible inhibitor of thrombus. It inhibits both circulatory and clot bound thrombus. It has half life of 25 minutes and onset of action in 2 minutes at bolus and 15-19 minutes at infusion dose. It has been tested during PCI and found to have a trend toward superior outcome compares with UFH and outcomes similar to those with the combination of UFH plus a GP IIb/IIIa inhibitor. In REPLACE-2 randomized trial;[43] Bivalirudin and provisional Glycoprotein IIb/IIIa blockade was compared with Heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention. The study revealed Bivalirudin with provisional GP IIb/IIa blockade is statistically not inferior to heparin plus planned GP IIb/IIIa blockade during contemporary PCI with regard to suppression of acute ischemic end points and is associated with less bleeding. In ACUITY Trial-Bivalirudin was used in high risk ACS without STEMI, having TIMI risk score 3-7, new or dynamic ST segment depression, elevation of cardiac enzymes (Trop.T) or CPK-MB at the time of presentation. This study revealed statistically significant less bleeding complication in bivalirudin group compared to UFH/exonaparin plus GP IIb/IIIa blocker group (ACC.2006, Scientific Session, March 12, 2006, Atlanta, GA).

ABBREVIATIONS AND ACRONYMS

CABG	Coronary artery bybass grafting.
CI	Confidence interval.
FRISC-II	Fragmin and fast revascularization during instability in coronary disease.
ICTUS	Invasive versus conservative treatment in unstable coronary syndromes investigators.
ISAR-COOL	Intracoronary stenting. With antithrombotic regimen cooling off.
NSTE-ACS	Non-ST segment elevation acute coronary syndrome.
PCI	Percutaneous coronary invervention.
RITA-3	Randomized intervention trial of unstable angina.
RR	Risk ratio.
TACTICS TIMI-18	Treat angina with aggrastat and determine the cost of therapy. With an invasive or conservative. Strategy-thrombolysis in myocardial infarction.
TRUCS	Treatment of refractory unstable angina in geographically isolated areas without cardiac surgery.
VINO	Value of first day coronary angiography/angioplasty in evlolving non-ST segment elevation myocardial infarction.

TITAN-TIMI 34	Time to integrilin therapy in
TRIAL	Acute myocardial Infarction.
PATCAR	Pre-hospital administration of thrombolytic therapy with urgent culprit artery revascularization pilot study.
ACS	Acute coronary syndrome.
h-CRP	High sensitive reactive protein.
t-PA	Tissue type plasminogen activator.
r-PA	Recombinent plasminogen activator.
n-PA	Novel plasminogen activator.
MITI trial	Myocardial infarction and triage intervention.
CRUSADE	Can rapid risk stratification of unstable angina. Patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines) registry.
REPLACE-2	Randomized evaluation in PCI linking angiomax to reduced clinical events.
TIMI III B	Thrombolysis in myocardial ischemia.
MATE	Medicine vs angiography in thrombolytic exclusion trial.
SWIFT	Should we intervene following thrombolysis ?
DANAMI	Danish multicenter randomized study to invasive vs conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction.
TIME	Outcome of elderly patient with chronic symptomatic CAD with an invasive vs optimized medical treatment strategy.
ADMIRAL	Abciximab before direct angioplasty and stenting in myocardial infarction.
CADILLAC	Controlled abciximab and device investigation to lower late angioplasty complications.
RAPPORT	Reopro and primary PTCA organization and randomized trial
ISAR-2	Intracoronary stenting and antithrombotic regimen.
PARAGON B	Platelet IIb/IIIa antagonists for reduction of acute coronary syndrome events in a global organization network.
PRISM	Platelet receptor inhibition in ischemic syndrome management.
PRISM-PLUS	Platelet receptor inhibition for ischemic syndrome management in patients limited by unstable signs and symptoms.
REPLACE-2	Randomized evaluation in PCI linking angiomax to reduced clinical events.
VANQWISH	Veterans affairs non-Q-wave infarction strategies in hospital.
CAPTURE	Chimeric 7E3 antiplatelet therapy in unstable angina refractory to standard treatment.

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