Interventional Cardiology

The efficacy and safety of combination glycoprotein IIbIIIa inhibitors and reduced-dose thrombolytic therapy–facilitated percutaneous coronary intervention for ST-elevation myocardial infarction: A meta-analysis of randomized clinical trials

Mohamad C.N. Sinno, MD, Sanjaya Khanal, MD, FACC, Mouaz H. Al-Mallah, MD, Muhammad Arida, MD, and W. Douglas Weaver, MD Detroit, MI

Objective We reviewed the literature and performed a meta-analysis comparing the safety and efficacy of adjunctive use of reduced-dose thrombolytics and glycoprotein (Gp) IIbIIIa inhibitors to the sole use of Gp IIbIIIa inhibitors before percutaneous coronary intervention (PCI) in patients presenting with acute ST-segment elevation myocardial infarction (STEMI).

Background Early reperfusion in STEMI is associated with improved outcomes. The use of reduced-dose thrombolytic and Gp IIbIIIa inhibitors combination before PCI in the setting of acute STEMI remains controversial.

Methods We performed a literature search and identified randomized trials comparing the use of combination therapy–facilitated PCI versus PCI done with Gp IIbIIIa inhibitor alone. Included studies were reviewed to determine Thrombolysis in Myocardial Infarction (TIMI)-3 flow at baseline, major bleeding, 30-day mortality, TIMI-3 flow after PCI, and 30-day reinfarction. We performed a random-effect model meta-analysis. We quantified heterogeneity between studies with $I^2$. A value $>50\%$ represents substantial heterogeneity.

Results We identified 4 clinical trials randomizing 725 patients; 424 patients were pretreated with combination therapy before PCI, and 301 patients had Gp IIbIIIa inhibitor alone during PCI. Combination therapy–facilitated PCI was associated with a 2-fold increase in TIMI-3 flow upon arrival to the catheterization laboratory compared with the sole use of upstream Gp IIbIIIa inhibitors (192/390 patients [49\%] versus 60/284 [21\%; relative risk [RR], 2.2; $P<.00001$). However, post-PCI TIMI-3 flow was similar between the 2 groups (279/319 patients [87\%] versus 188/212 [88\%]; RR, 0.99; $P=.85$). Major bleeding events significantly increased in the combination therapy group (40/420 patients [9.5\%] versus 14/299 [4.7\%; RR, 2.2; $P=.007$). The 30-day mortality (15/424 patients [3.5\%] versus 5/301 [1.7\%; RR, 1.47; $P=.46$) and 30-day reinfarction rate (5/424 patients [1.1\%] versus 3/301 [1.0\%; RR, 0.96; $P=.96$) were similar in the 2 treatment groups.

Conclusions Awaiting the results of the ongoing clinical trials, the current cumulative evidence does not support the routine use of combination of reduced-dose thrombolytic and Gp IIbIIIa inhibitor therapy–facilitated PCI for the treatment of STEMI. (Am Heart J 2007;153:579-86.)

The primary goal of therapy for acute ST-segment elevation myocardial infarction (STEMI) is early, rapid, complete, and sustained restoration of infarct-related artery (IRA) blood flow. Irrespective of whether a mechanical versus pharmacological strategy is used, Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the culprit artery within 90 minutes of presentation has been shown to correlate with improved 30-day and long-term survival in patients with acute STEMI.

Primary percutaneous coronary intervention (PCI) is currently the preferred approach to reperfusion therapy when delivered expeditiously in centers with documented expertise and outcomes. Time to treatment,
however, remains an important determinant of clinical outcome in patients with acute STEMI.

Despite the better outcomes, primary PCI has not become the treatment of choice for most patients with STEMI because of logistical issues and the limited availability of institutions that can offer this treatment modality in a timely and efficient manner. In the current US practice, only 4.2% of transferred patients with acute STEMI were treated within 90 minutes in the National Registry of Myocardial Infarction 3/4 registry. The idea of prehospital ambulance triage of patients with STEMI to PCI hospitals has been suggested to decrease inherent time delay that ensues when these patients are seen in non-PCI hospitals. Nallamothu et al obtained PCI status of hospitals from the American Hospital Association annual survey and established the location of the population from the 2000 US census and found that 79% of the adult population lived within 60 minutes of a PCI hospital. Among those with non-PCI hospitals as the closest facility, the additional time to arrive to a PCI hospital was 30 minutes. However, with the variability of the emergency medical system in the United States, getting electrocardiograms in the ambulance for patients with chest pain and training paramedics to interpret these electrocardiograms is the major issue. Pharmacological therapy, however, can be carried out expeditiously and without site-specific variations in outcome in patients with STEMI. Therefore, it is logical to think that initial early pharmacological therapy followed by PCI may deliver both expediency and efficacy that is desired in treating myocardial infarction (MI) patients.

PCI, the range of initial pharmacotherapy encompasses thrombolytic and glycoprotein (Gp) IIb/IIIa inhibitors. The use of Gp IIb/IIIa inhibitors has been shown to improve short-term outcomes in most studies of primary PCI. However, full-dose fibrinolysis-facilitated PCI has recently been shown to result in worse outcome than primary PCI alone. The results with combination of reduced-dose thrombolytic and Gp IIb/IIIa inhibitors before PCI in patients with MI are however not clear. A recent meta-analysis comparing primary and multiple regimens of thrombolytic-facilitated PCI for STEMI showed a higher TIMI grade 3 flow on initial angiography, but this translated into higher major bleeding events, increased mortality, nonfatal reinfarction, urgent target revascularization, and stroke compared with primary PCI alone. This study, however, does not provide guidance about the common practice of the use of reduced-dose fibrinolytic and Gp IIb/IIIa inhibitors before PCI in patients with acute STEMI. We performed a meta-analysis of randomized clinical trials testing the safety and efficacy of combination therapy (reduced-dose thrombolytic + Gp IIb/IIIa inhibitors)–facilitated PCI versus PCI performed only with Gp IIb/IIIa inhibitors.

### Methods

#### Study objectives and design

Our primary aim was to compare simultaneous administration of Gp IIb/IIIa inhibitors and reduced-dose fibrinolytics before PCI to primary PCI done with Gp IIb/IIIa inhibitors in patients with STEMI. ST-segment elevation myocardial infarction was defined according to the inclusion criteria of the trials concerned.

#### Search strategy

All randomized, controlled trials comparing facilitated PCI to primary angioplasty were identified using a 2-level search...
Tenecteplase, Eptifibatide

Reteplase, Abciximab

Reteplase, Abciximab

Alteplase, Abciximab

<table>
<thead>
<tr>
<th>Agents</th>
<th>Trial eight %</th>
<th>Angiographic End Points</th>
<th>Combined Clinical End Point (Time to Follow up)</th>
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<td>20</td>
<td>TIMI 3 flow grade</td>
<td>Death, Reinfarction or new CHF</td>
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<td>10</td>
<td>TIMI 3 flow grade</td>
<td>ACE= Death, Reinfarction, TVR, Stroke and major Bleeding</td>
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Strategy. First, we searched public domain databases including MEDLINE (from 1966 to December 14, 2005), the Cochrane Central Register of Controlled Trials (second quarter 2005), Database of Abstracts of Reviews of Effects (second quarter 2005), Cochrane Database of Systematic Reviews (second quarter 2005), EMBASE (from 1980 to 2005 week 6), and BIOSIS Previews (from 1969 to 2005 week 8). We used the following key words: acute MI; ST elevation; primary angioplasty; thrombolytics including the following individual medications: streptokinase, alteplase, r-TPA, and TNK; and Gp IIbIIIa inhibitors including the following individual medications: abciximab, tirofiban, and eptifibatide. In addition, relevant studies were identified through a hand search of secondary sources including references of initially identified articles and proceedings from national cardiology meetings at the American Heart Association, American College of Cardiology, European College of Cardiology and Transcatheter Therapeutics from 2001 through 2005. The search was performed without any language restrictions. When an abstract from a meeting and a full article referred to the same trial, only the full article was included in the analysis. When there were multiple reports from the same trial, we used the most complete and/or recently reported data.

Study selection and data extraction

We restricted our meta-analysis to trials that performed a randomized comparison between simultaneous administration of Gp IIbIIIa inhibitors and reduced-dose fibrinolytics and sole use of Gp IIbIIIa inhibitor before PCI in STEMI. A randomized controlled trial was defined according to the National Library of Medicine criteria (http://www.nlm.nih.gov/mesh/pubtypes2001.html). To be included in the meta-analysis, the trials should have randomized patients within 12 hours of symptom onset to either Gp IIbIIIa inhibitors or combination therapy (thrombolytic + Gp IIbIIIa inhibitor) followed by preplanned angiography and angioplasty if indicated. We excluded trials where postfacilitation angiography was not done. We also excluded trials that compared facilitated PCI with thrombolytic therapy alone. Symptom-driven angioplasty trials were also excluded. Outcome data had to be available on culprit artery patency evaluated on admission by TIMI flow grades, bleeding, and mortality. Two authors (M.S., M.M.) independently reviewed abstracts or complete articles. Only 4 nonoverlapping studies met the inclusion criteria. Two reviewers performed independent data extraction; all discrepancies were identified and resolved by consensus or, as needed, with a third investigator and confirmed by consensus.

End points and definitions

The primary angiographic end point was TIMI flow grade 3 on the first angiogram, which defined open culprit artery on admission. The TIMI grade 3 flow was also assessed after PCI. The clinical end points were all-cause mortality, reinfarction rate, and major bleeding events at 30 days follow-up.

Statistical analysis

The meta-analyses were performed by computing relative risks (RRs) using random-effects model. Quantitative analyses were performed on an intention-to-treat basis and were confined to data derived from the period of follow-up. Relative risk for all-cause mortality, TIMI-3 flow, and major bleeding were calculated along with 95% confidence intervals (CIs). Between study heterogeneity was analyzed by means of $I^2 = [(Q - df) / Q] \times 100$, where $Q$ is the $y^2$ statistic, and $df$ is its degrees of freedom. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered substantial heterogeneity. Publication bias was assessed graphically using a funnel plot. All analyses were performed with RevMan Analyses Version 4.2.7 (2004 the Cochrane Collaboration).

Results

Trial patient characteristics and study design

Of the 1427 potentially relevant articles initially identified, 126 full-text articles were reviewed. Four trials were identified with a design including randomization to combination therapy (reduced-dose thrombolytic + Gp IIbIIIa inhibitors) versus upstream Gp IIbIIIa inhibitors alone for PCI. The trial names, acronyms, patient characteristics, and details of the study groups are shown in Table 1.

Enrollment criteria of chest pain (<6 or <12 hours) with ST elevation or new left bundle-branch block on the electrocardiogram were used in all the trials (Table 1). Trial design was broadly similar in all studies; however, there were some differences regarding the type and dose of thrombolytic and/or Gp IIbIIIa inhibitors used. The same-dose regimen was used throughout the 3 trials that used abciximab in both arms of the study—0.25 mg/kg IV bolus followed by 12 hour infusion at 0.125 mg kg$^{-1}$ min$^{-1}$. Eptifibatide was used in the ADdressing the Value of Facilitated ANgioplasty after Combination therapy or Eptifibatide monotherapy in acute Myocardial Infarction (ADVANCE-MI) trial with 2 boluses of 180 mg/kg IV 10 minutes apart, then 2.0 mg kg$^{-1}$ min$^{-1}$ infusion.
Alteplase used in the Asia-Pacific Acute Myocardial Infarction Trial (APAMIT) was 15 mg of standard bolus followed by a reduced dose of 35 mg over 60 minutes. The ADVANCE-MI study group used half dose of tenecteplase, whereas reteplase was used in the remaining 2 trials. The Strategies for Patency Enhancement in the Emergency Department (SPEED) study group tested multiple doses of reteplase, but we included the 5 U + 5 U dose regimen in our analysis because it was associated with a better safety profile and was confirmed as the better dose in phase B of the trial. The same 5 U + 5 U dose of reteplase was used in the Bavarian Reperfusion Alternatives Evaluation (BRAVE) trial as well. The 4 trials randomized 725 patients. Four hundred twenty-four patients were initially randomized to the combination therapy–facilitated PCI group, and the rest (301) were randomized to the Gp IIbIIIa inhibitor–facilitated PCI. There were 92% (390/424) assigned to the combination therapy–facilitated PCI group and 94% (284/301) in Gp IIbIIIa inhibitor group that had postfacilitation angiography. We decided to include the APAMIT trial despite being labeled as a rescue angioplasty trial because all the patients in both groups had angiography and only those patients with TIMI-3 flow post reduced-dose alteplase did not have angioplasty.
the ADVANCE-MI trial, the results were analyzed both in the “as randomized” and “as treated” fashion. We included the data from the former group to reduce bias and maintain an intention-to-treat analysis.

Clinical outcomes and angiographic end points
All 4 trials reported 30-day mortality, 30-day major bleeding events, and TIMI-3 flow upon arrival to the catheterization laboratory. Patients who received combination therapy more often had patent arteries upon arrival on the catheterization laboratory (RR, 2.18; 95% CI, 1.70-2.81; P < .00001; I^2 = 0%). However, that did not affect the procedural success rate because the postprocedural TIMI-3 flow rate was similar between the 2 groups in 3 trials (RR, 0.99; 95% CI, 0.86-1.14; P = .85; I^2 = 81.7%). The postprocedural TIMI-3 flow was not reported in the ADVANCE-MI trial.

The increased original vessel patency (TIMI-3 flow on presentation) was not associated with increased survival. Each of the 4 trials reported all-cause mortality. The 30-day all-cause mortality was the same in patients randomized to either treatment group with no heterogeneity between the different trials (RR, 1.47; 95% CI, 0.52-4.14; P = .46; I^2 = 0). The incidence of 30-day reinfarction was similar between the 2 groups (RR, 0.96; 95% CI, 0.23-4.02; P = .96; I^2 = 0).

The safety of this approach was also assessed. Combination therapy–facilitated PCI was associated...
with increased major bleeding as reported by all the included trials except in the APAMIT trial (RR, 2.15; 95% CI, 1.17-3.94; \( P = .01; I^2 = 0 \)).

Because small trials are more prone to be affected by publication bias, we constructed funnel plots for both angiographic and clinical end points that exhibited a fairly symmetrical distribution and convergence toward the pooled effect when the weight of the trials increased, suggesting that publication or selection bias was unlikely (Figures 1-5).

Discussion

Time-to-treatment remains an important determinant of clinical outcome in acute MI care, regardless of the methodology used to establish adequate blood flow in the IRAs. Mortality benefit of primary PCI is lost for patients with door to balloon times exceeding 2 hours (cannon et al) compared with patients treated with thrombolysis. The attendant delay for primary PCI may limit its clinical benefit over early use of thrombolysis, especially when patients present within 3 hours after the onset of symptoms.16,17 Thrombolysis has been compared to primary PCI in multiple studies. These investigations demonstrate that PCI-treated patients experience lower short-term mortality rates, less nonfatal reinfarctions, and less hemorrhagic strokes than those treated with fibrinolysis alone when performed in a timely and efficient manner.5,18 To take advantage of early therapy of thrombolysis and the more definite therapy of PCI, a facilitated approach has been advocated where patients initially receive thrombolysis while waiting for the definitive primary PCI. However, full-dose fibrinolysis-facilitated PCI has recently been shown to be associated with higher mortality, nonfatal reinfarctions, and urgent target vessel revascularization compared with primary PCI alone for patients with STEMI.10

Gp IIbIIIa inhibitors have been shown to reduce event rates when used in the setting of primary PCI.8,9,19-24 Moreover, the early use of Gp IIbIIIa inhibitors improved outcomes in a recent meta-analysis that included 931 STEMI patients.25 Therefore, in addition to aspirin, heparin, and clopidogrel, Gp IIbIIIa inhibitors have been considered standard of care during primary PCI.

Combination of full-dose thrombolysis with full-dose Gp IIbIIIa inhibitors results in prohibitively high risk of bleeding complications.26 A reduced-dose combination therefore may offer the benefit of earlier reperfusion without increasing bleeding risks. A reduction of recurrent MI has been demonstrated in patients treated with half-dose tenecteplase with abiciximab when compared to full-dose tenecteplase in patients with STEMI.26 Although the mortality rate at 30 days was the same between the 2 groups, the combination therapy group experienced fewer recurrent MIs. It is possible that Gp IIb/IIIa inhibitors improve flow in the infarct artery and prevent the prothrombotic milieu that occurs after the thrombolytic wears off. Because administration of half-dose thrombolysis may be safer than full-dose in patients undergoing primary PCI, many hospitals advocate administration of reduced-dose thrombolytic and Gp IIbIIIa inhibitor during the delay in performing PCI. However, the safety and efficacy of the combination of these 2 classes of drugs before PCI have not yet been validated in a large randomized, blinded, placebo controlled trial.

The major finding of our meta-analysis is the demonstration of a “facilitating” effect of reduced-dose fibrinolytic combined with Gp IIbIIIa inhibitors by improving preprocedure TIMI-3 flow of the IRA. The TIMI flow on initial angiography has been shown to be a major determinant of survival in primary PCI27 and a valid end
point for mortality in thrombolytic trials. However, in spite of improved preprocedural TIMI-3 flow, postprocedural flow was similar compared with patients undergoing primary PCI alone. Moreover, the combination therapy–facilitated PCI was also associated with unfavorable trends for mortality and significant increase in major bleeding events. The reasons for neutral to worse outcomes in the facilitated arm despite improved preprocedural TIMI-3 flow in this analysis may be the same factors that worsen outcomes in patients undergoing facilitation with full-dose thrombolytics. The possible explanations may be suboptimal antithrombotic/antiplatelet therapy, treatment delay, and increased bleeding complications in the facilitated group compared with patients undergoing primary PCI alone. The addition of fibrinolytic before PCI has been shown to increase nonbleeding adverse clinical events in spite of improved initial TIMI-3 flow. Therefore, whether hemorrhagic transformation of the infarcted muscle and increased infarct size occurs in the setting of reperfused arteries has to be entertained. It has been demonstrated that the bleeding risk is proportionately increased with increasing doses of antithrombins (heparin and low-molecular-weight heparin). The studies described mostly used standard dose antithrombin therapy. It is possible that bleeding may be reduced if lower antithrombin doses are lowered in the facilitated therapy group. The current meta-analysis has a number of limitations, including inevitable clinical heterogeneity between trials and an overall sample size of only 725 patients, which is statistically adequate to compare TIMI grade 3 flow (power of 97%) but insufficient for clinical outcomes like mortality. Sensitivity analyses were also performed, and comparable results were obtained with a random effect model or when the largest study was excluded from the meta-analysis. Our analyses were also limited to short-term outcomes, whereas some Gp IIbIIIa inhibitor studies have often demonstrated increased survival benefit with longer follow-up. In spite of the various limitations, however, the individual trials were in most cases underpowered, and the combined analysis allows more robust conclusions. Whether combination of reduced-dose thrombolytic and Gp IIbIIIa inhibitor–facilitated PCI will result in better outcomes compared with primary PCI with Gp IIbIIIa inhibitor only will be finally be determined by ongoing randomized studies like the Facilitated Intervention with Enhanced reperfusion Speed to Stop Events trial. Until the results of these studies are available, our analysis suggests that reduced-dose thrombolytic and Gp IIb/IIIa inhibitor combination–facilitated PCI does not offer an advantage over primary PCI done with Gp IIbIIIa inhibitors only.

Contrary to the previous quantitative review of randomized trials on the comparison of primary and facilitated PCIs for STEMI, where the authors grouped all modalities of facilitation (Gp IIbIIIa alone, thrombolytic therapy alone, and simultaneous Gp IIbIIIa inhibitor with thrombolytic therapy) in one arm and primary PCI in the other; our meta-analysis was dedicated to compare combination therapy (Gp IIbIIIa inhibitors and thrombolytics) to Gp IIbIIIa inhibitors alone before PCI. Besides, in the previous quantitative review, a discrepancy in the definition of primary PCI is to be noted. Some patients received no treatment before angiography, “classical primary PCI,” and others received inhibitors of Gp IIbIIIa. Thus, in the final analysis, some patients who received Gp IIbIIIa inhibitors in the primary intervention group were compared with the subset of patients who received the same treatment modality in the facilitated intervention group.

In conclusion, similar to the results of thrombolytic–facilitated PCI studies, facilitation of PCI with combination of reduced-dose thrombolytics and Gp IIbIIIa inhibitors does not result in improved clinical outcome in spite of better TIMI-3 flow in the infarct artery on presentation. This approach, therefore, cannot be recommended currently except in clinical trial settings.

References


12. ADVANCE AMI Investigators. Facilitated percutaneous coronary intervention for acute ST-segment elevation myocardial infarction: results from the prematurely terminated ADdressing the Value of facilitated ANgioplasty after Combination therapy or Eptifibatide monotherapy in acute Myocardial Infarction (ADVANCE MI) trial. Am Heart J 2005;150:116·22.


