Evaluation of Infarct-Related Coronary Artery Patency and Microcirculatory Function After Facilitated Percutaneous Primary Coronary Angioplasty

The FINESSE-ANGIO (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events–Angiographic) Study

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Objectives The FINESSE-ANGIO (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events–Angiographic) study evaluated acute treatment effects on infarct-related artery (IRA) patency and angiographic correlates of coronary microcirculatory function.

Background The FINESSE trial evaluated the effects on clinical outcomes of primary percutaneous coronary intervention (PCI) facilitated with pre–catheterization laboratory administration of abciximab with half-dose reteplase (combination-facilitated group), abciximab alone (abciximab-facilitated group), or with abciximab administered immediately before the procedure (primary PCI).

Methods The FINESSE-ANGIO substudy compared the effects of the 3 treatment strategies on patency (TIMI [Thrombolysis In Myocardial Infarction] flow grade 2/3) of the IRA at basal coronary angiography. The secondary efficacy end points were corrected TIMI frame count, percentage of patients achieving TIMI flow grade 3, and the percentage achieving myocardial blush grade 2/3 of the IRA at post-PCI angiography. All angiographies were evaluated at a central core laboratory.

Results Of the 2,452 FINESSE patients, 637 were included in the FINESSE-ANGIO substudy. Patients in the combination-facilitated group exhibited significantly higher rates of baseline IRA patency compared with the abciximab-facilitated and the primary PCI groups (76.1% vs. 43.7% and 32.7%, respectively; p < 0.0001 for both; p = 0.025 abciximab-facilitated vs. primary PCI). There were no significant differences in the post-PCI corrected TIMI frame count (17.1 ± 15.8, 17.4 ± 17.3, and 15.8 ± 14.1) or the rates of post-PCI TIMI flow grade 3 (79.8%, 77.7%, and 76.6%), myocardial blush grade 2/3 (85.6%, 79.5%, and 86.4%), respectively.

Conclusions Pre–catheterization laboratory administration of abciximab alone and especially in combination with half-dose reteplase resulted in higher rates of IRA patency at baseline coronary angiography compared with no pre-treatment. However, post-procedural angiographic and microcirculatory variables were unaffected by facilitation therapy. (J Am Coll Cardiol Intv 2010;3:1284–91)
It is well established that any delay in reperfusion therapy during ST-segment elevation myocardial infarction (STEMI) can limit the effect of either thrombolysis (1–3) or primary percutaneous coronary intervention (PCI) (4–6). In addition, even successful recanalization of the infarct-related artery (IRA) may not result in reperfusion of the coronary microcirculation, that is, of the myocardium, due to mechanisms that are still not completely understood but include embolization of thrombotic material from the treated lesion, adhesion of platelets and leukocytes to the injured endothelium, and inflammation and acute myocardial ischemia (7).

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Previous studies have shown that early administration of abciximab, a glycoprotein (GP) IIb/IIIa inhibitor, enhances IRA patency (8–11). Angiographic studies in patients with STEMI (12) have shown that the combination of a GP IIb/IIIa blocker and fibrinolytic agent increases the IRA TIMI (Thrombolysis In Myocardial Infarction) flow grade 3 at 60 and 90 min compared with fibrinolytic therapy alone. Other reports revealed improved microcirculatory perfusion as assessed by myocardial blush grade (MBG and ST-segment resolution) (13,14).

The FINESSE (Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events) study was designed to evaluate the effects on clinical outcomes at 90 days after the immediate administration of abciximab in conjunction with half-dose reteplase or abciximab alone before PCI, compared with primary PCI with post-angiography abciximab administration in the catheterization laboratory in patients with STEMI with an expected delay to angioplasty of at least 60 min (15). No significant reduction in the 90-day primary ischemic end point was seen with either facilitated approach, although nonsignificant favorable trends with facilitation therapy were seen for some patient subgroups (16).

This FINESSE-ANGIO study is a substudy of FINESSE designed to evaluate the acute effects of the 3 aforementioned treatments on IRA patency and angiographic correlates of coronary microcirculatory function.

**Methods**

**Study design.** The FINESSE-ANGIO study’s patients included FINESSE participants from 6 countries (Italy, France, United Kingdom, Spain, the Netherlands, and Poland). Eligibility criteria for FINESSE-ANGIO mirror those for FINESSE (16). Internal review boards of all institutions approved the study. All patients provided additional written informed consent.

The FINESSE study’s patients were randomly assigned in a 1:1:1 ratio to receive half-dose reteplase plus abciximab (combination-facilitated PCI), abciximab alone (abciximab-facilitated PCI), or placebo immediately following randomization with abciximab administered in the catheterization laboratory after angiography in this group (primary PCI). Heparin was limited to 40 U/kg with a target activated clotting time of 200 to 250 s.

**Study procedures.** Stent implantation at the IRA lesion site was strongly encouraged, but devices to trap embolic materials and prevent clot embolization or techniques to aspirate the intracoronary thrombus were discouraged. After stent implantation, drugs such as adenosine or calcium-antagonists that improve the contrast runoff of the epicardial vessels were permitted.

**Study end points.** The primary efficacy end point was the percentage of patients achieving TIMI flow grade 2/3 of the IRA at first angiography. Secondary efficacy end points included: 1) the percentage of patients achieving TIMI flow grade 3 flow of the IRA; 2)
corrected TIMI frame count (cTFC (17); and 3) the percentage of patients achieving MBG 2 to 3. All pre-PCI TIMI flow, cTFC, and MBG assessments were to be done before wiring the lesion or passing any device. We also evaluated the primary and secondary clinical end points from the overall FINESSE study in the angiographic substudy population (16).

Angiographic analysis. The quantitative coronary angiography (QCA) analysis for TIMI flow, cTFC, and MBG was performed offline by the Rome Heart Research of the Foundation “Centro per la Lotta Contro l’Infarto,” Rome, Italy, with a computer-assisted system using an automated edge-detection algorithm (MEDIS, Cardiovascular Angiography Analysis System II, Pie Medical Data, Maastricht, the Netherlands) by observers blinded to treatment assignment. The QCA analysis of the IRA was performed on basal, pre-intervention and post-intervention angiograms using 2 orthogonal views. Procedural guidelines for angiographic images included reproduction of baseline views, extended cine runs for antegrade and collateral flow and MBG assessment, and use of intracoronary nitroglycerin.

Statistical analysis. The sample size was estimated assuming a 20% pre-intervention TIMI flow grade 3 rate in the IRA without pre-angiography use of abciximab (8,11). An approach based on the pre-PCI use of upstream abciximab would lead to a projected pre-intervention TIMI flow grade 3 rate of 30% and for combination-facilitated PCI patients, 60%.

A sample size of 626 patients was needed to obtain a 90% chance of detecting an absolute difference of 30% in the primary efficacy variable between the abciximab-facilitated and combination-facilitated PCI groups, and an absolute difference of 20% between primary and abciximab-facilitated PCI groups, with 80% power and a 2-sided alpha error of 5%.

The primary efficacy variable and all other noncontinuous angiographic variables were analyzed using the chi-square test or the Fisher exact test. The cTFC and other continuous variables were analyzed using an analysis of variance or the Mann-Whitney U test. Bonferroni correction was applied for multiple comparisons. A p value of <0.05 was considered significant. Analyses were performed with SAS software (version 8.02, SAS Institute Inc., Cary, North Carolina).

Results

Of the 2,452 FINESSE patients enrolled between August 2002 and December 2006, 637 were included in the FINESSE-ANGIO substudy (213 in the combination-facilitated, 222 in the abciximab-facilitated, and 202 in the primary PCI groups). The overall median time from qualifying electrocardiogram to first study-drug administration was 41 min; the median time from first study-drug administration to first angiography was 55 min.

Analyzable pre-PCI TIMI flow grade, cTFC, and MBG were obtained in 99.5%, 96.7%, and 97.8% of patients, respectively. Analyzable post-PCI TIMI flow grade, cTFC, and MBG were available in 97.0%, 85.5%, and 91.2%, respectively.

Baseline characteristics. Baseline clinical characteristics and initial treatments received were similar across groups (Table 1). The times from symptom onset to the start of reperfusion therapy in the combination-facilitated, abciximab-facilitated, and primary PCI groups were 3.5 ± 1.4 h, 3.5 ± 1.5 h, and 3.5 ± 1.6 h, respectively (p = NS for all). Concomitant medication use in the first 24 h following randomization was similar across groups, as was stenting, whereas embolic protection device use was rare. Median infarct size estimated by creatine kinase curve analyses for anterior MIs, stratified by treatment group were 1,756 IU/l, 1,753 IU/l, and 1,865 IU/l for the combination-facilitated, abciximab-facilitated, and primary PCI groups, respectively. Angiographic QCA parameters were comparable across groups, except for a statistically higher pre-procedural minimal lumen diameter and a smaller stenosis diameter in the combination-facilitated versus the primary PCI groups (Table 2). At hospital discharge, use of angiotensin-converting enzyme inhibitors and beta-blockers was very common and equal across groups. Demographics in this angiographic substudy were very similar to those for FINESSE patients not in the substudy, except a higher percentage of substudy patients had hypercholesterolemia (37.7% vs. 31.8%), used angiotensin-converting enzyme inhibitors at baseline (81.2% vs. 77.3%), and were currently smoking (49.5% vs. 41.4%; all p < 0.05).

Primary end point. The combination-facilitated group demonstrated significantly higher rates of pre-procedural IRA patency compared with the abciximab-facilitated and the primary PCI groups (76.1% vs. 43.7% and 32.7%, respectively; p < 0.0001 for both; abciximab-facilitated vs. primary PCI, p = 0.025) (Fig. 1).

Improvement in vessel patency in the abciximab-facilitated group compared with the primary PCI group was due to a significant increase in TIMI flow grade 2 rate whereas TIMI flow grade 3 rate was similar in these groups; the higher patency in the combination-facilitated group was driven mainly by greater TIMI flow grade 3 rate (Table 3). A completely occluded IRA (TIMI flow grade 0) at baseline angiography was found in 19.7% in the combination-facilitated, 46.4% in the abciximab-facilitated, and 59.9% in the primary-PCI groups (p < 0.0001 among all groups). The investigator-reported TIMI rates and the core laboratory rates were not distinctly dissimilar, with a kappa coefficient showing an inter-rater agreement of 0.479, supporting the need for a core laboratory to ensure consistency in large clinical studies.

Secondary end points. Although pre-procedural secondary end point results differed significantly among all groups, post-procedural end point results were similar. TIMI flow...
grade 3 following PCI was observed in 79.8%, 77.7%, and 76.6% (p = 0.6); MBG 2 to 3 was present in 85.6%, 79.5%, and 86.4% (p = 0.7); and cTFC was 17.1 ± 15.8, 17.4 ± 17.3, and 15.8 ± 14.1 (p = 0.3) in the combination-facilitated, abciximab-facilitated, and primary-PCI groups, respectively (Fig. 2).

**Other efficacy outcomes.** In the FINESSE-ANGIO subpopulation, the FINESSE 90-day primary composite end point occurred in 6.6% of the combination-facilitated–PCI group, 5.4% of the abciximab-facilitated–PCI group, and 5.9% of the primary-PCI group (hazard ratio for the combination-facilitated vs. the primary-PCI group: 1.18;
95% confidence interval: 0.58 to 1.35). Complications of MI occurred in 3.7%, 4.0%, and 4.0% of patients in the 3 groups, respectively, with no significant differences. The individual components of the FINESSE primary end point did not differ significantly among groups; the respective rates were 2.8%, 1.3%, and 2.0% for all-cause mortality; 2.8%, 2.7%, and 2.5% for cardiogenic shock; 0.9%, 1.3%, and 1.5% for rehospitalization or emergency department visit for congestive heart failure; and no ventricular fibrillation occurred 48 h after randomization.

Correlation of TIMI flow grade before PCI with outcome independent of treatment. To explore the effect of pre-PCI TIMI flow grade status on outcome independent of treatment, we pooled all treatment groups (Table 4). As expected, TIMI flow grade before PCI was inversely correlated with adverse outcomes.

Discussion

The FINESSE-ANGIO substudy represents 1 of the largest, most rigorous efforts to clarify the effect of periprocedural antithrombotic therapy for primary angioplasty. In this sub-study, we analyzed angiographic data from 637 patients enrolled in the randomized, double-blind FINESSE study. Our main finding is that, in patients presenting with STEMI and having an expected delay of >1 h before angiography, early treatment with abciximab alone or abciximab plus half-dose reteplase resulted in higher IRA patency rates at baseline coronary angiography compared with no pre-treatment before angiography. However, post-procedural angiographic and microcirculatory variables were not affected by facilitation therapy, when compared with standard treatment using abciximab immediately before intervention. These data bring into question the value of pharmacological pre-treatment and pre-procedural versus post-procedural angiographic assessments both as predictors of outcomes and parameters of effective reperfusion.

Previous randomized trials investigated the benefits of the early administration of GP IIb/IIIa inhibitors in patients undergoing primary PCI (18–23). As the adjunctive use of GP IIb/IIIa inhibitors, mostly abciximab, has been shown in both meta-analyses and prospective single studies to reduce mortality among patients undergoing primary PCI (24–26), further benefits by earlier drug administration were expected in terms of improved pre-procedural recanalization and myocardial reperfusion (27).

In our substudy, facilitation with abciximab alone had a relatively modest effect on the pre-procedural IRA patency, with only a slight increase in TIMI flow grade 2 rate and no effect on TIMI flow grade 3 rate. Moreover, compared with standard administration before intervention, earlier treatment using abciximab in the emergency department or the spoke hospital did not significantly improve any post-PCI variables considered to represent better myocardial reperfusion, which is deemed responsible for the beneficial effects of abciximab (28,29). The patency rates observed in this study do, however, correlate with the degree of ST-segment resolution (>70%) previously reported in the overall trial at 60 to 90 min following randomization, where the combination-facilitated group had a significantly higher rate (43.9%) than the abciximab-facilitated (33.1%, p = 0.01) or the primary PCI (31%, p = 0.003) groups (17).

A possible reason for these negative findings is the long delay (>3 h) between symptom onset and start of abciximab in

### Table 3. TIMI Flow Grade Comparisons

<table>
<thead>
<tr>
<th>Variables</th>
<th>Primary PCI (n = 202)</th>
<th>Abciximab-Facilitated PCI (n = 222)</th>
<th>Combination-Facilitated PCI (n = 213)</th>
<th>Prim PCI vs. Abcix Facilitated</th>
<th>Prim PCI vs. Combo Facilitated</th>
<th>Abcix-Facil. vs. Combo Facilitated</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI flow grade 0, %</td>
<td>59.9</td>
<td>46.4</td>
<td>19.7</td>
<td>0.007</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMI flow grade 1, %</td>
<td>7.4</td>
<td>9.9</td>
<td>4.2</td>
<td>NS</td>
<td>NS</td>
<td>0.04</td>
</tr>
<tr>
<td>TIMI flow grade 2, %</td>
<td>14.4</td>
<td>24.8</td>
<td>29.1</td>
<td>0.099</td>
<td>&lt;0.0001</td>
<td>NS</td>
</tr>
<tr>
<td>TIMI flow grade 3, %</td>
<td>18.3</td>
<td>18.9</td>
<td>47.0</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abcix = abciximab; combo = combination; PCI = percutaneous coronary intervention; prim = primary; NS = not significant; TIMI = Thrombolysis In Myocardial Infarction.
the FINESSE study, which is possibly too long for an antiplatelet agent to show significant benefit. As shown in an analysis of in-ambulance use of abciximab in the Bologna STEMI network, earlier administration of abciximab (2-h median time from symptom onset to administration) may result in an improved outcome (30). The presence of a significant time interval between facilitation and PCI is another possible reason. In the FINESSE study, although the bolus of abciximab was administered early, the infusion was not started until after PCI, unlike the steady infusion started directly after the abciximab bolus in the EUROTRANSFER registry. This difference in approach may have diminished pre-intervention TIMI flow grade 3 rates and myocardial salvage (31–33). A much more effective method of achieving early patency of the IRA is fibrinolytic therapy using a fibrin-specific agent able to improve TIMI flow grade after 60 to 90 min. However, previous attempts to reopen the IRA using a fibrinolytic agent upstream of PCI were completely negative, possibly due to platelet activation by fibrinolytic therapy thereby promoting rethrombosis and increasing the risk of early ischemic events, as shown in the PACT (Plasminogen Activator-Angioplasty Compatibility Trial) (34) and the ASSENT-IV PCI (Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction): randomized trial (35).

The antiplatelet/fibrinolytic cocktail with abciximab and half-dose reteplase tested in FINESSE exploited the powerful fibrinolytic effect of reteplase without initiating subsequent hemostatic activation by combining it with a powerful antiplatelet agent. Preliminary data from both TIMI 14 (Thrombolysis In Myocardial Infarction Trial, Phase 14) and SPEED (Strategy for Patency Enhancement in the Emergency Department Group) studies were highly encouraging, showing TIMI flow grade 3 of 60% to 70% at 60 to 90 min in the IRA (13,14). In terms of clinical efficacy, this strategy proved only partially effective in FINESSE. As expected, the pro-ischemic events typically associated with fibrinolytic therapy were ameliorated with concomitant abciximab use, although only a modest trend toward a reduction of STEMI complications and no reduction in mortality was seen, possibly due to an increased risk of bleeding (16). The FINESSE-ANGIO data confirm that this combination-facilitated therapy is able to provide a high rate of patency in the IRA during transportation of the patient to the catheterization laboratory, with 47% of patients achieving TIMI flow grade 3 and another 29% achieving TIMI flow grade 2. This effect may have provided better hemodynamic status and a more expedited PCI procedure in high-risk patients, such as those with large myocardial infarctions, resulting

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**Table 4. Effect of Pre-PCI TIMI Flow Grade on Efficacy Outcomes:**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Primary End Point</th>
<th>90-Day Mortality</th>
<th>1-Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI flow grade missing</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>TIMI flow grade 0</td>
<td>7.5%</td>
<td>3.8%</td>
<td>4.5%</td>
</tr>
<tr>
<td>TIMI flow grade 1</td>
<td>7.0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>TIMI flow grade 2</td>
<td>6.8%</td>
<td>0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>TIMI flow grade 3</td>
<td>2.8%</td>
<td>1.7%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1 and 3.
in smaller infarct size as shown by area under the curve analysis of creatine kinase release (16,36).

However, no advantage in terms of post-procedural myocardial perfusion indexes was observed with combination-facilitation compared with facilitation with abciximab alone. One should keep in mind that the control treatment, that is, abciximab immediately before PCI, has itself been shown to improve myocardial perfusion indexes (13,14) and thus earlier upstream reperfusion therapy may not offer further improvement. Thus, although combination therapy has been highly effective in recanalizing the IRA before intervention without the risk of rebound ischemia associated with fibrinolytic treatment, this improvement in pre-procedural flow was not associated with better post-procedural flow and provided only marginal improvement in myocardial salvage. Also with regard to combination-facilitated therapy, the delay in drug delivery in the FINESSE study may have decreased the likelihood of myocardial salvage. In a recent post hoc analysis of the FINESSE study, clinical benefit appeared to be restricted to higher risk patients enrolled within 4 h of symptom onset at sites without PCI capabilities requiring transfer. In these patients, first door-to-balloon times were longer and the greatest benefit of increased early reperfusion from combination therapy might be expected (37).

Our findings may contrast those reported by Stone et al. (33) and Brodie et al. (38) supporting the prognostic role of pre-procedural flow in primary angioplasty. Besides the PACT (34) and ASSENT-IV PCI studies (35), other studies of pre-procedural reperfusion therapy (39,40) have failed to show improvement in post-PCI clinical outcomes despite a significantly higher initial patency rate (41). Thus, in primary PCI, pharmacologically enhanced pre-procedural patency may not equate to spontaneous patency due to mechanisms not yet understood. These data are supported by the pooled analysis (Table 4) similarly demonstrating that higher pre-PCI TIMI flow grades were associated with better clinical outcomes overall.

Conclusions

Primary PCI preceded by pre-catheterization treatment with abciximab alone, and especially with abciximab plus half-dose reteplase, resulted in higher IRA patency rates at baseline coronary angiography compared with standard primary PCI. However, post-procedural patency and angiographic indexes of myocardial reperfusion were not improved by facilitation strategies compared with abciximab administered immediately before intervention. In patients in this substudy, early reperfusion did not improve clinical outcomes. Whether clinical benefit correlated with pharmacologically induced or improved pre-PCI myocardial reperfusion may be restricted to higher-risk subsets (36,37) remains to be determined by future prospective studies.

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