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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, CANADA

Scientific Update™

# Recent Advances in GP IIb/IIIa Inhibition: The Clinical Implications

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**A Satellite Symposium presented at the 74th Scientific Sessions of the American Heart Association**
Anaheim, California, November 11-14, 2001

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**For the past several years, the glycoprotein (GP) IIb/IIIa inhibitors have become an important therapy for patients with acute coronary syndrome and those undergoing percutaneous coronary intervention (PCI). One of the key studies that led to the widespread use of these agents was the Enhanced Suppression of the Platelet Receptor GP IIb/IIIa using Integrilin Therapy (ESPRIT) trial. In this trial, treatment of patients undergoing PCI with the GP IIb/IIIa inhibitor eptifibatide was accompanied by a reduction in ischemic complications at 48 hours and this benefit was preserved at 30 days and 6 months. In this report, the latest results of the 1-year follow-up of patients of the ESPRIT trial, as well as other new data regarding the use of GP IIb/IIIa inhibitors in patients undergoing PCI and patients with acute coronary syndrome, will be discussed.**

## Glycoprotein IIb/IIIa inhibitors in percutaneous coronary intervention: new data

The ESPRIT trial was a randomized placebo-controlled trial designed to evaluate the safety and efficacy of a high dose of the GP IIb/IIIa inhibitor eptifibatide as an adjunct to non-urgent PCI, in the setting of contemporary practice, including coronary stenting and the use of thienopyridine therapy.[1] In this trial, 2064 patients were recruited from 92 centres in the United States and Canada. Pre-treatment with ticlopidine or clopidogrel was permitted on the day of procedure, but not beforehand. Patients were randomized to receive either high dose (two 180 µg/kg boluses 10 minutes apart, and as a continuous infusion of 2.0 µg/kg/min, 180/2/180, continued for 18 to 24 hours) or placebo. All patients received concomitant aspirin and weight-adjusted heparin (initial bolus of 60 U/kg with a target-activated clotting time of 200 to 300 seconds). Bailout open-label use of eptifibatide, in case of complications of PCI in the placebo group, was permitted. The primary composite endpoint was death, myocardial infarction (MI), need for urgent target vessel revascularization (TVR), or crossover to GP IIb/IIIa inhibitor therapy for thrombosis within 48 hours. The key secondary endpoint was the composite of death, MI, or urgent TVR at 30 days.

The trial was terminated early because of efficacy. The 48-hour, 30-day and the 6-month results have already been published.[2,3] In brief, the primary endpoint was reduced by a relative 37%, from 10.5% (108 of 1024 patients on placebo [95% CI, 8.7-12.4%]) to 6.6% (69 of 1040 [5.1-8.1%]) with treatment (p=0.0015). The key 30-day secondary endpoint was also reduced by a relative 35%, from 10.5% (107 of 1024 patients on placebo [8.6-12.3%]) to 6.8% (71 of 1040 patients on eptifibatide [5.3-8.4%]; p=0.0034).[3] These adjunctive benefits of GP IIb/IIIa inhibition were maintained at 6 months.[2] By 6 months, the composite end point of death or MI had occurred in 7.5% of eptifibatide-treated patients and in 11.5% of placebo-treated patients (hazard ratio, 0.63; 95% CI 0.47-0.84; p=0.002). The composite endpoint of death, MI, or TVR was 14.2% in eptifibatide-treated patients versus 18.3% in placebo-treated patients (hazard ratio, 0.75, 95% CI, 0.60-0.93; p=0.008). Six-month mortality in the eptifibatide group was 0.8% versus 1.4% in the placebo group (hazard ratio, 0.56, 95% CI, 0.24-1.34; p=0.19) and TVR occurred in 8.6% of the eptifibatide group versus 9.4% of the placebo group (hazard ratio, 0.91, 95% CI, 0.68-1.22; p=0.51).

The one-year follow-up data of ESPRIT was presented at the recent scientific sessions of the American Heart Association. Data on the one-year composite endpoint and the individual endpoint are shown in Figure 1 and 2, respectively. The results of this study were recently published.[4] At one year, death and MI were still reduced in the eptifibatide-treated patients by a



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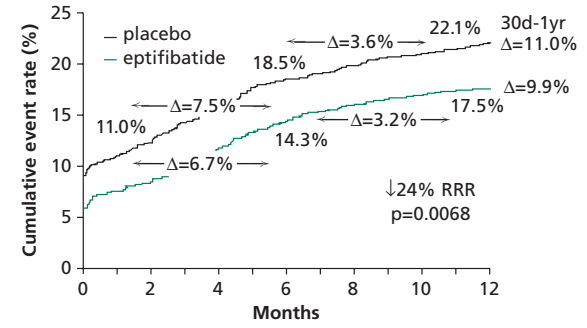
**Figure 1: Data on the one-year composite endpoint**

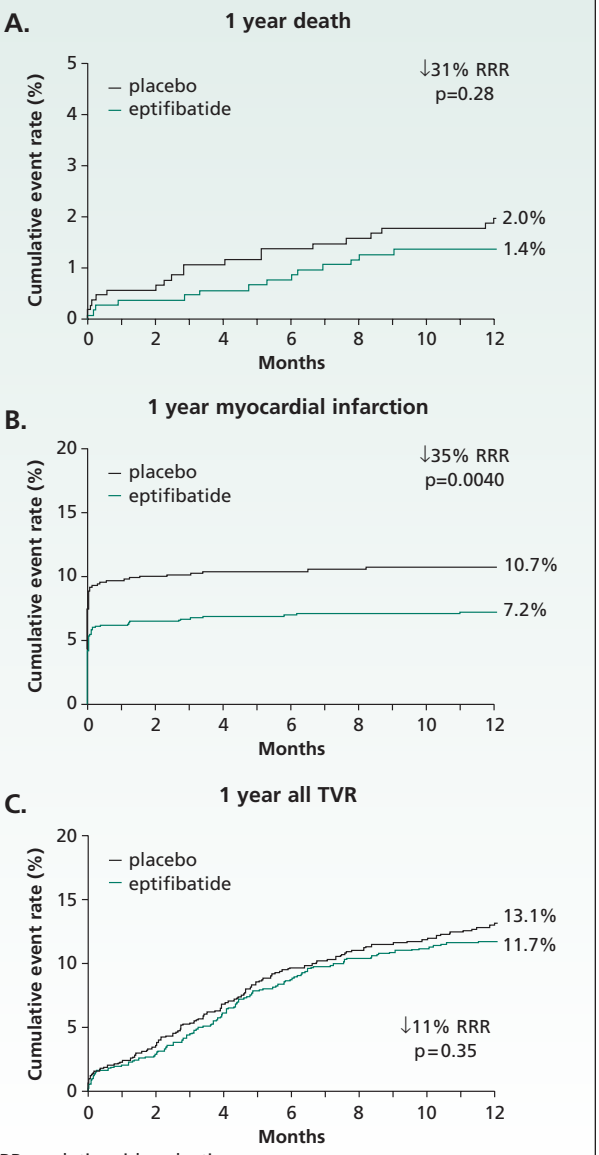



RRR = relative risk reduction

relative 37% (p=0.001), while the triple endpoint of death, MI and TVR was reduced by 24% (p=0.0068) (Figure 1). Among individual components of these composite endpoints (Figure 2A-C), MI was significantly reduced by 35% (p=0.004), whereas the differences in death (31% reduction, p=0.28) and TVR (11% reduction, p=0.35) were not significant. However, on inspection of the Kaplan-Meir curves, the curves for death and TVR appeared to continue to separate at one year, whereas the curves for MI appeared to have become parallel. Patients with elevated post-procedure CK-MB had a higher one-year mortality (2.1%) than patients without elevated CK-MB (1.3%). Patients with diabetes had a higher one-year event rate of death and MI, but the effect of eptifibatide therapy was similar in patients with or without diabetes (event rate, placebo non-diabetic 13.4%; eptifibatide non-diabetic 8.1%; placebo diabetic 12%; eptifibatide diabetic 6.9%).

The one-year results of the ESPRIT trial therefore indicate that in patients who undergo non-urgent PCI with coronary stents, adjunctive therapy with eptifibatide reduces the event rate of death, MI and TVR, the benefit demonstrated earlier at 48 hours, 30 days, and 6 months is sustained at one year. This sustained benefit is driven mostly by a reduction of death and TVR, and is consistent between diabetics and non-diabetics. It is noteworthy that in ESPRIT, the mortality reduction of 31% at one year from eptifibatide is similar to the 28% reduction at one year reported in a recent meta-analysis of EPIC, EPILOG, EPISTENT and ISAR-2.[5] In these studies, abciximab was administered as a bolus followed by a 12-hour infusion post-PCI. In the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial, total costs for baseline hospital stay and cumulative one-year cost, including the cost of abciximab (approximately US$1350 per treatment), were increased by $1350 and $932, respectively, in the stent + abciximab group, compared to the stent + placebo group. The increase in total costs of baseline hospitalization with eptifibatide in ESPRIT was less than $300, substantially less than abciximab in EPISTENT, mostly due to the lower acquisition cost of eptifibatide (approximately $450 per treatment in the U.S.). There have been no head-to-head trials

**Figure 2: Data on the individual endpoints at one year.**




RRR = relative risk reduction

comparing eptifibatide with other GP IIb/IIIa inhibitors, which would be ideal in light of the initial results of TARGET demonstrating that abciximab was superior to tirofiban, at least with the dosing regimen employed. However, on the basis of the efficacy data from ESPRIT and the potential for cost savings, eptifibatide can be considered an attractive alternative to abciximab in patients undergoing non-urgent PCI.

Combination therapy with a GP IIb/IIIa inhibitor and a low-molecular-weight heparin (LMWH) is a promising strategy for management of patients undergoing PCI. Although a great number of patients undergoing PCI in contemporary practice receive a GP IIb/IIIa inhibitor, the use of LMWH in the setting of

PCI is still very low, despite the increasing use of these agents in non-ST-segment elevation (NSTE) acute coronary syndrome (ACS). There may be several reasons for the reluctance to use LMWH at the time of PCI. All large trials with GP IIb/IIIa inhibitors in the setting of PCI were performed with unfractionated heparin (UFH). Furthermore, interventionalists are reluctant to use a LMWH because of the inability to monitor anticoagulation with conventional methods used to monitor the activity of UFH. The use of LMWH in PCI, with or without GP IIb/IIIa inhibitors, has not been vigorously studied. However, several registries have demonstrated encouraging results. For example, the NICE-4 study enrolled 817 patients undergoing PCI.[6] All patients were treated with the LMWH enoxaparin 0.75 mg/kg IV, and abciximab. Preliminary results have shown that the rates of clinical and safety outcomes are low and comparable to those from randomized trials such as EPILOG[7] and EPISTENT.[8]

The Coronary Revascularization Utilizing Integrilin and single-Bolus Enoxaparin (CRUISE) trial evaluated the therapeutic potential with a combination of a GP IIb/IIIa inhibitor and a reduced dose of LMWH in patients undergoing PCI. In CRUISE, 261 patients undergoing PCI treated with epifibatide (the same dosing regimen as in ESPRIT) and aspirin (pre-treatment with clopidogrel was encouraged) were randomized to receive either UFH (60 U/kg IV bolus) or enoxaparin (0.75 mg/kg IV bolus). Outcomes included bleeding events (Landenfeld Bleeding Index, major bleeding according to TIMI criteria) and ischemic complications (death, MI, urgent TVR).

The results of CRUISE were also presented at the recent American Heart Association scientific sessions. In the efficacy assessment, the rates of combined death, MI and urgent TVR at 48 hours were similar in patients treated with eptifibatide + LMWH and those treated with eptifibatide + UHF (8.5% versus 7.6%, p=0.82); a similar trend was observed at 30 days (10.1% in LMWH versus 7.6% in UFH for the combined endpoint, p=0.51). Likewise, no significant differences in MI or urgent TVR were observed either at 48 hours or 30 days. In the safety assessment, the incidence of major or minor bleeding was equally low in both treatment groups. The frequency for reaching a pre-defined mean bleeding index (LMWH versus UFH, 0.9% versus 1.1%, p=0.14), TIMI major bleeding (2.5% versus 1.8%, p=0.68), and TIMI major + minor bleeding (4.1% versus 10.5%, p=0.08) was similar in the two groups. The use of closure devices was also similar (42.1% versus 33.8%). These preliminary results of CRUISE therefore indicate that in patients undergoing non-urgent PCI, the use of the GP IIb/IIIa inhibitor eptifibatide, in conjunction with a LMWH, does not produce excessive bleeding and appears to be equally efficacious compared to combination with UFH.

## GP IIb/IIIa inhibitors in ST-segment elevation MI: new data

Blockade of platelet aggregation with GP IIb/IIIa inhibitors may lead to reduction in adverse outcomes in patients with ST-segment elevation MI (STEMI), because platelet-rich thrombi are major components of *completely* occlusive clots implicated in the pathophysiology of STEMI. Accordingly, several potential therapeutic applications of GP IIb/IIIa inhibitors in patients with STEMI are currently under active investigations, in the context of both pharmacologic and interventional treatment strategies.

One attractive strategy is to combine a GP IIb/Iia inhibitor and a reduced dose of a fibrinolytic agent. This approach may be more effective than fibrinolysis alone as it targets both the platelet-rich and fibrin-rich components of the occlusive thrombus. The Integrilin and Tenecteplase for Acute Myocardial Infarction (INTEGRITI) trial was designed to evaluate the angiographic efficacy of combined therapy with eptifibatide and a reduced dose of tenecteplase (TNK-tPA). The protocol of the INTEGRITI study is summarized in Figure 3A and 3B. The dose-finding protocol was divided to two parts. In Part 1, patients were randomized to 2 doses of TNK-tPA (0.25 and 0.375 mg/kg, or 50 and 75%, respectively, of the dose used in monotherapy), plus fixed dose of eptifibatide (180 µg/kg bolus, followed by a

**Figure 3: Protocol of the INTEGRITI Study**

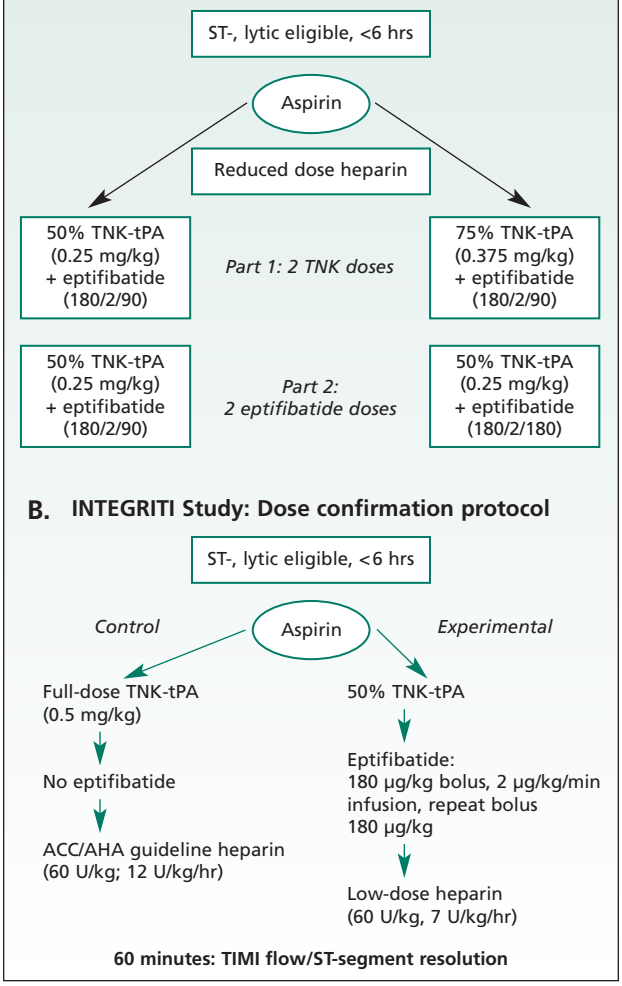


**Figure 4: Part 2: Angiographic results of the dose confirmation studies**

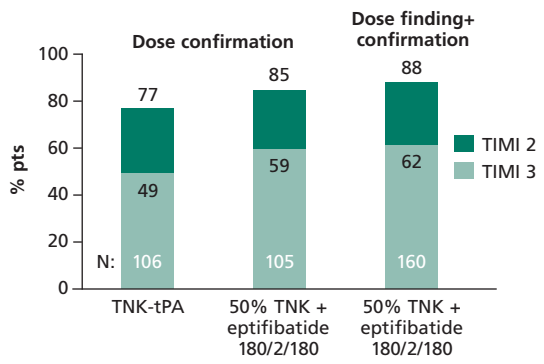



**Table 1: Pilot and dose-ranging studies of GP IIb/IIIa inhibitors and thrombolysis in myocardial infarction**

| Trial | Drug combination | TIMI 3 patency* |
|---|---|---|
| INTEGRITI | Eptifibatide + tenecteplase | 62% (60 min) |
| IMPACT-AMI[9] | Eptifibatide + alteplase | 69% (90 min) |
| INTRO-AMI | Eptifibatide + alteplase | 56% (60 min) |
| TIMI-14[10] | Abciximab + alteplase | 72% (60 min) |
| SPEED[11] | Abciximab + reteplase | 61% (60 min) |

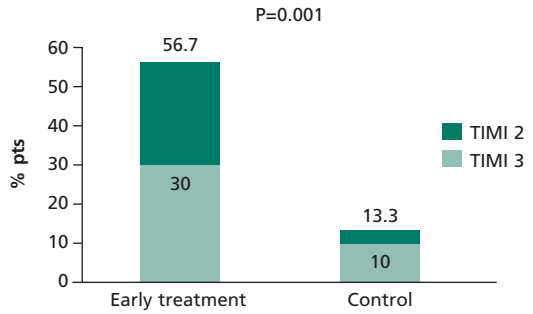
*Data are from patients given the highest dose of the GP IIb/IIIa inhibitor.

2 µg/kg/min infusion and a repeat bolus of 90 µg/kg, 180/2/90). In Part 2, patients were randomized to 2 doses of eptifibatide (180/2/90 and 180/2/180) combined with a fixed dose of TNK-tPA (0.25 mg/kg or 50% of the dose used in monotherapy). In the dose-confirmation protocol, patients were randomized to full-dose TNK-tPA, no eptifibatide and UFH according to ACC/AHA guideline or 50% TNK-tPA, eptifibatide (180/2/180) and low dose UFH. A total of 418 patients were recruited. Median time between symptom onset and therapy was 2.9 hours.

Preliminary results of INTEGRITI were recently presented at the American Heart Association Scientific Sessions. In Part 1 of the dose-findings phase, the percent of patients who achieved TIMI 2 (77% and 64%) and TIMI 3 flow (79% and 68%) did not differ between 50% and 75% TNK-tPA dose. In Part 2, 95% of patients achieved TIMI 2 flow in the high dose (180/2/180) eptifibatide-treated group. Angiographic results of the dose confirmation studies are shown in Figure 4. Compared to TNK-tPA alone, patients treated with 50% TNK-tPA and full dose eptifibatide (180/2/180) tended to have a higher frequency of achieving TIMI 2 and TIMI 3 flow. When the data were combined with the 55 patients from the dose-finding study, TIMI 2 and 3 flow were achieved in 88% and 62% of patients, respectively. ST-segment resolution at 60 minutes occurred in 61% of patients with TNK-tPA alone and in 71% of patient on 50% TNK-tPA and full dose eptifibatide (61% versus 71%, p=0.08). Including patients from the dose-finding study, ST-segment resolution was achieved in 75% of the 89 patients who took 50% TNK-tPA and eptifibatide (180/2/180). The infarct artery patency rates in the INTEGRITI study exceed those achieved from earlier studies that examined lower doses of eptifibatide in conjunction with alteplase,[9] and compare favourably with those observed in studies that examined the combination of abciximab and reteplase (rPA)[10,11] (Table 1). These data therefore suggest that the combination therapy with reduced dose TNK-tPA and full dose eptifibatide may produce angiographic results and ST-segment resolution comparable or better than full dose fibrinolytic therapy alone.

Another potentially attractive treatment strategy for patients with STEMI is to initiate GP IIb/IIIa inhibitor therapy at the time of diagnosis in the emergency department. This approach may serve to increase culprit vessel patency and stabilize the patient prior to facilitated PCI. The Rapid Administration of Platelet GP IIb/IIIa Inhibitor Integrilin in the Emergency Room (RAPIER) study was designed to assess the hypothesis that initiation of GP IIb/IIIa inhibitor therapy in the emergency department in patients with STEMI would acquire more superior angiographic results at subsequent PCI. Thirty consecutive patients with STEMI and symptoms <6 hours were treated with eptifibatide (180/2/180) initiated in the emergency department before facilitated PCI. Thirty age-matched patients served as controls, these patients received GP IIb/IIIa therapy after baseline angiography. The primary endpoint was the proportion of patients with TIMI 2 or 3 flow. The secondary endpoints included proportion of patients with TIMI 3 flow, corrected TIMI frame count, total PCI procedure time and total stent length. Data for the primary outcome are shown in Figure 5. Patients treated with eptifibatide in the emergency room had a significantly higher rate of early reperfusion than the control group. The proportion of patients with TIMI 3 flow was not statistically different (30% versus 10% (p = 0.053), and neither were the procedure duration and the corrected TIMI frame counts. Stent-length was significantly shorter in the treated group (19.5±7.5 versus 26.2±13.3 mm, p=0.03). None of the patients pretreated with eptifibatide experienced any adverse outcome (death, MI, repeat revascularization, or transfusion, 0% versus 3.3%, difference not significant). These findings suggest a clinical potential of early initiation of GP IIb/IIIa therapy in patients with STEMI for whom PCI is planned. Further studies involving large number of patients are warranted to optimally evaluate this approach.

**Figure 5: RAPIER: Primary endpoint**




## GP IIb/IIIa inhibitors in non-ST-segment elevation acute coronary syndrome: new data

Results of recent trials with GP IIb/IIIa inhibitors in patients undergoing PCI and in those with NSTE ACS suggest that >80% platelet aggregation inhibition (PAI) is required to achieve significant clinical benefits.[12] Pharmacodynamic studies with the currently approved GP IIb/IIIa inhibitors all sought to identify optimal dosing regimens that would maintain >80% inhibition of *ex vivo* platelet aggregation. Direct comparison of these prior studies have been confounded by different anticoagulants (sodium citrate versus PPACK) and platelet agonists (ADP versus TRAP), as well as different concentrations of ADP. In an attempt to address this issue, two studies have compared the time course and magnitude of PAI using various GP IIb/IIIa inhibitors in the setting of PCI and ACS. Light transmission aggregometry assays were performed under conditions that closely resembled the *in vivo* environment (PPACK anticoagulant and 20 µmol ADP agonist).

The first study (TAM-1) evaluated comparative pharmacodynamics of eptifibatide (180/2/180, infusion for 18-24 hours) and tirofiban (10 µg/kg bolus + 0.15 µg/kg/min for 18-24 hours) in 40 patients undergoing PCI. Seven blood samples were obtained over 18-24 hours. Preliminary results indicate that eptifibatide produced more rapid and sustained >80% inhibition of platelet aggregation. Furthermore, there appeared to be more variability in PAI in the tirofiban-treated patients with 30% to 40% of patients falling below 80% inhibition at 10 to 30 minutes.

The second study (TAM-2) assessed comparative pharmacodynamics of eptifibatide (180/2 for at least 24 hours) and abciximab (0.25 mg/kg bolus + 0.125 µg/kg/min infusion for at least 24 hours) in 40 patients with NSTE ACS. Preliminary results are so far available on 26 patients, which again demonstrate that eptifibatide produces a more consistent inhibition of platelet aggregation, with 11 of 13 patients who received eptifibatide having sustained inhibition >80%, whereas patients treated with abciximab have substantial variability in PAI.

Findings of TAM-1 are consistent with those reported earlier by Kereiakes et al. They compared the pharmacodynamic effects of the approved dosing regimens for abciximab (0.25 mg/kg bolus + 0.125 µg/kg/min), eptifibatide (180 µg/kg bolus + 2 µg/kg/min) and tirofiban (0.4 µg/kg/min for 30 minutes + 0.1 µg/kg/min) in 30 patients with ACS undergoing PCI.[13] The median PAI achieved by tirofiban was <80% at all time points, whereas that of abciximab and eptifibatide exceeded 80% throughout the treatment period. Indeed, the preliminary data of TAM-1 and TAM-2 raise an intriguing question about whether pharmacodynamics may explain in part the lack of overwhelmingly positive effects of the GP IIb/IIIa inhibitor agent used in TARGET (tirofiban was inferior to abciximab) and GUSTO V (half-dose rPA plus abciximab was not superior to full-dose rPA alone).[14,15]

Three large clinical trials, namely the Platelet Glycoprotein IIb/IIIa in Unstable Angina Using Integrilin Therapy (PURSUIT) study using eptifibatide,[16] the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) and PRISM studies with tirofiban,[17] and the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) study with abciximab,[18] have demonstrated that early initiation of GP IIb/IIIa inhibitor therapy produces a significant reduction of adverse events in patients with NSTE ACS; these beneficial effects were generally maintained during follow-up.

On the basis of this evidence, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for management of NSTE ACS recommend early use of eptifibatide or tirofiban in patients with intermediate to high risk findings and symptoms, regardless of planned management.[19] The use of abciximab is confined to patients for whom PCI is planned within the next 24 hours. Early initiation of GP IIb/IIIa inhibitor therapy may prevent an accumulation of events while patients are waiting for revascularization procedures. This may explain in part the greater reduction in 6-month mortality and MI in patients who underwent coronary artery bypass graft surgery and received eptifibatide within 72 hours of surgery in the PURSUIT trial,[20] and the reduction of combined mortality, MI and rehospitalization from early invasive strategy preceded by GP IIb/IIIa inhibitor therapy in the recent TACTICS-TIMI 18 study.[21]

Despite the ACC/AHA guidelines' recommendations, early use of GP IIb/IIIa inhibitors in clinical practice has been low. A recent study that evaluated the outcome of elderly patients who had suffered an MI suggested that admission to a hospital ranked high on the list of "America's Best Hospitals" and was associated with lower 30-day mortality.[22] A substantial portion of the survival advantage was associated with the these hospitals' more frequent use of aspirin and ß-blockade therapy. Accordingly, the ongoing Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of

the ACC/AHA Guidelines (CRUSADE) registry is assessing the current standards of care for patients with NSTE ACS in up to 600 hospitals in the United States. Preliminary data (as of Q3 of 2001) from the National Myocardial Infarction Registry (NRMI-4) have indicated that in U.S. hospitals, the use of aspirin, ß-blockers, heparin, and GP IIb/IIIa inhibitors in patients with ACS is 84%, 65%, 72%, and 24%, respectively. Furthermore, the 30-day mortality rate in these patients declined in parallel to the extent of adherence of the hospitals to ACC/AHA guidelines. The results from CRUSADE will allow each hospital to compare its own quality of care against that practiced in other hospitals, at the national level and in best practices.

## GP IIb/IIIa inhibitors in clinical practice: what have we learned and where are we going?

Randomized controlled trials have demonstrated convincingly that the parenteral GP IIb/IIIa inhibitors reduce ischemic complications in patients undergoing PCI and those with NSTE ACS. Whereas the majority of patients scheduled for PCI now receive GP IIb/IIIa inhibitor therapy, the use of these agents in the setting of NSTE ACS remains low. Accordingly, one of the key challenges will be to increase the early use of these agents in high-risk patients with NSTE ACS, as per the ACC/AHA guidelines' recommendation, to become a standard of care in these patients.

Another important goal is to define optimal antithrombotic combinations in various clinical situations. In the setting of PCI, the use of a GP IIb/IIIa inhibitor and a thienopyridine is widely adopted, but it is unclear whether a LMWH may be safer or more effective than UFH. In patients with NSTE ACS, better improvement in clinical outcomes may be achieved with a combination of a GP IIb/IIIa inhibitor and clopidogrel than either agent alone, but this remains to be proven. With respect to anticoagulation, although LMWH appears to be superior to UFH in medically managed patients with NSTE ACI, its role in patients who undergo invasive procedures remains to be defined.

The next frontier is undoubtedly STEMI. In these patients, GP IIb/IIIa inhibitors may improve clinical outcomes, either as part of a pharmacologic reperfusion regimen, including facilitated PCI, or as an adjunct to primary PCI. The promising and provocative new data discussed in this review have raised several important questions that will likely be addressed in future studies.

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