Current Perspectives

Toward a New Frontier in Myocardial Reperfusion Therapy
Emerging Platelet Preeminence

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For more than a decade, intravenous thrombolytic therapy has been validated for the reduction of mortality in evolving MI.1-3 Reperfusion therapy is the standard of care for patients with acute MI who present early (within 12 hours of symptom onset) and have significant ECG ST-segment elevation.4 However, the limitations of the therapy are especially impressive.

First, even the most potent established thrombolytic therapy does not achieve restoration of early and complete coronary blood flow in ≈50% of patients.5 This ≈50% failure rate is particularly important because the relationship of successful reperfusion and survival is quite strong,5,6 such that the death rate among patients who fail to achieve early reperfusion is at least twofold to threefold higher.5,7

Second, thrombolytic therapy induces a relatively high rate of intracerebral hemorrhage. Although the incidence is ≈1 in 150 to 200 treated patients,8 the event is usually catastrophic, resulting in fatality or a disabling stroke. Of note, the ability to predict intracerebral bleeding is quite limited; save for the commonly present demographic factors of the aged and hypertension, little is known about who is predisposed or why this dreaded complication occurs. In the recently completed third Global Utilization of Strategies to Open Occluded Arteries (GUSTO-III) trial, which assessed reteplase and alteplase, the incidence of hemorrhagic stroke was increased compared with previous trials. The overall rate of 0.9%, or ≈1 in 100 patients, reflects, in part, the enrollment of more elderly and hypertensive patients9 and emphasizes the significance of the problem in contemporary trials and likely clinical practice.

Third, thrombolytic therapy has been shown to be inferior to catheter-based reperfusion for achieving infarct vessel patency and reducing the incidence of death or nonfatal MI.10-14 Furthermore, the incidence of hemorrhagic stroke is reduced with primary balloon angioplasty.15 The superiority of mechanical over pharmacological reperfusion points out the limited efficacy of the latter but at the same time sets a higher standard that can be achieved with respect to improved clinical outcomes. Because mechanical reperfusion is available only in specialized centers and is logistically cumbersome, a primary objective is to achieve parity between a pharmacological strategy, which is eminently more practical and universally available, and catheter-based reperfusion, if at all possible.

At present, for patient triage, a critical decision has to be made to choose between these two alternatives. The reason this has evolved is that the clinical trials that tested immediate balloon angioplasty after thrombolytic therapy all showed a higher rate of major complications compared with thrombolytic therapy alone or balloon angioplasty performed without antecedent thrombolysis.16-20 These trials were performed in the mid to late 1980s and have had a remarkable impact in dichotomizing the two alternative reperfusion strategies. The explanation for the phenomenon of the untoward effects of angioplasty after thrombolysis is probably the prothrombotic tendencies of fibrinolytic agents, as will be fully discussed. Virtually all of these limitations of pharmacological reperfusion therapy may be abrogated, at least in part, with newly available potent antiplatelet inhibitors. In this article, their potential to affect a radical change in our approach to myocardial reperfusion will be reviewed.

Why Thrombolysis Fails

There are many possible explanations for the observed failure in the 45% to 50% of patients who do not achieve early and complete restoration of coronary blood flow. The leading hypothesis is tied to the prothrombotic effects of thrombolytic agents coincident with a lack of a sound antiplatelet approach.

The term “thrombolytics” is a key misnomer, because this implies that these agents are capable of actually dissolving thrombus. Plasminogen activators are better known as fibrinolytics, as depicted in Fig 1, because their principal action is to lyse fibrin. When this occurs, there is exposure of thrombin and marked evidence of enhanced thrombin activity, as reflected by heightened levels of fibrinopeptide A.21,22 The result of exposed thrombin is not only the autocatalytic formation of more thrombin but also the marked proaggregatory effect on platelets. Thrombin is one of the most, if not the most, potent biological activators of platelets known. The more fibrinolytic therapy is given, with lysis of fibrin clot leaving its major constituent, thrombin, as substrate, the more the prothrombotic tendency is engendered.

Platelets are at the core of a coronary thrombus, owing to their activation and adhesion to the exposed subendothelial matrix elements with plaque fissuring or rupture.23 Although this “white clot” nidus is typically a small component relative to the “red” fibrin and erythrocyte-rich thrombus, both types are present and have been directly visualized by angioscopy.24 The platelet thrombus is fully resistant to fibrinolytic therapy, not only on a mass basis but also because platelets are especially

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Selected Abbreviations and Acronyms

CAPTURE = Chimeric 7E3 Anti-platelet in Unstable angina Refractory to standard treatment trial
EPIC = Evaluation of IIb/IIIa platelet receptor antagonist 7E3 in Preventing Ischemic Complications trial
EPILOG = Evaluation of PTCA to Improve Long-term Outcome by c7E3 GP IIb/IIIa receptor blockade trial
FANTASTIC = Full Anticoagulation versus Ticlopidine plus Aspirin after STent Implantation: a randomized multicenter European study
GP = glycoprotein
IMPACT = Integrin to Manage Platelet Aggregation to Combat Thrombosis trial
ISAR = Intracoronary Stenting and Antithrombotic Regimen trial
MI = myocardial infarction
PAI-1 = plasminogen activator inhibitor-1
PARADIGM = Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction
PARAGON = Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network Randomized multicenter European study
PRISM = Platelet Receptor inhibition for Ischemic Syndrome Management study
PRISM PLUS = Platelet Receptor inhibition for Ischemic Syndrome Management study Plus
PTCA = percutaneous transluminal coronary angioplasty
Pursuit = Platelet IIb/IIIa Underpinning the Receptor for Suppression of Unstable Angina Trial
RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis trial
STARS = STent Anticoagulation Regimen Study
t-PA = tissue plasminogen activator
TAMI-8 = Thrombolysis and Angioplasty in Acute Myocardial Infarction

Figure 1. Prothrombotic effects of fibrinolytic therapy. Coronary thrombus is composed of a platelet core with fibrin-thrombin admixture (“white” and “red” clot). After fibrinolytic therapy, there is exposure of free thrombin, which autocatalytically begets more thrombin and strongly promotes platelet aggregation (note more platelet mass). Platelets themselves are resistant to fibrinolytic therapy and furthermore secrete large amounts of PAI-1, which is a potent antagonist to fibrinolysis.

Classic Studies

The pioneering efforts and insights provided by Willerson’s group have clearly laid the groundwork for a platelet-directed therapeutic strategy in acute MI. These investigations have documented the preeminent role of platelets and their dynamic responsiveness as well as release of thrombocoxane, serotonin, and other vasoactive amines in the setting of acute coronary syndromes. Indeed, antagonists to the thromboxane A2 or serotonin S2 receptors led to facilitated thrombolysis or avoidance of reocclusion of the infarct vessel in experimental models. Although these studies can, in retrospect, be viewed as classic, the pivotal role of platelets in this clinical setting and the potent pharmacological interventions were not fully appreciated or available until more than a decade later.

Missing the Target

The recent experience with coronary artery stenting has been instructive for routine administration of an incorrect, misguided therapy. Since coronary stenting began in 1986, there has been an empirical use of prolonged heparin and switchover to extended oral warfarin. This approach led to an alarming rate of peri–access site and other serious bleeding complications, along with a prolonged hospital stay to discharge of patients with an international normalized ratio of ≥2.0. Despite heparin and warfarin, a significant problem of subacute thrombosis was occurring in at least 3% to 4% of patients, often resulting in MI or death. Of note, aspirin was typically included in this heparin/warfarin strategy and still today is the official (package insert) Food and Drug Administration label for adjunctive pharmacological therapy after stent implantation. More recently, however, clinical trials addressed the
potential strategy of a pure antiplatelet approach compared with heparin, warfarin, and aspirin.\textsuperscript{40-42} The three trials that assessed this critical question, as summarized in Fig 2, have convincingly demonstrated the marked superiority of an enhanced antiplatelet approach over the traditional red clot-directed strategy. The combined use of aspirin and ticlopidine has subsequently radically changed the field, with a subacute thrombosis rate of $<1\%$ and no excess of bleeding complications compared with balloon angioplasty.\textsuperscript{43} Rather than a 4-day hospital stay, patients can be discharged within 24 hours of the procedure. This valuable lesson provides the foundation and insight for a similar “missing of the target” in the therapy for patients with acute MI. What mechanistically separates these two clinical syndromes is the difference between “man-made,” angioplasty-induced coronary arterial trauma versus spontaneous plaque fissuring or erosion. Otherwise, the parallels are extensive, and the possibility of a partially misguided therapy is raised.

### Emerging Role of Antiplatelet Therapy

The 1990s marked the introduction of the platelet GP IIb/IIIa inhibitors in clinical investigation and trials.\textsuperscript{44-53} This class of agents represents one of the most significant advances in the therapy of ischemic heart disease today. The receptor, or integrin adhesion molecule, on the surface of platelets is activated and exteriorized when platelets are stimulated. More than 50 000 to 80 000 receptors are present on each and every platelet, making this the most densely expressed component of the platelet surface. The molecular and cellular biological breakthrough was the determination that this receptor acts as the final common pathway for platelet aggregation, such that agents that block the receptor directly or compete with its primary ligand, fibrinogen, have a marked effect on inhibiting platelet–platelet interaction, ie, fully blocking aggregation.

A family of agents is now available for clinical investigation, and one agent, abciximab, a Fab antibody fragment directed against the receptor, was approved for use in percutaneous coronary intervention in early 1995. The other agents, unlike the monoclonal antibody preparation, are all competitive inhibitors and are either peptides (Integrilin) or small molecules (Tirofiban, Lamifiban, Sibrafiban, Lefradafiban, Xemilofiban, Orbofiban, and others).

### Figure 2. Results of three trials evaluating antiplatelet versus anticoagulant or aspirin-alone therapy for stent prophylaxis. Aspirin and ticlopidine led to significant reduction of death, MI, or need for urgent revascularization. Data from References 40, 41, and 42.

Collectively, nine large clinical trials of more than 1000 patients have been performed.\textsuperscript{44-52} Five of these were in patients undergoing percutaneous coronary interventions, and four were conducted in patients with unstable angina or non–Q-wave MI. Viewed in aggregate, as demonstrated in Fig 3, these trials have all demonstrated benefit in the reduction of death or nonfatal MI for the combination of a GP IIb/IIIa blocker plus aspirin compared with placebo plus aspirin. The consistency between the trials is quite striking with respect to the directionality of the benefit. The magnitude has differed somewhat, with the most pronounced reduction of death and nonfatal MI achieved with the abciximab preparation. Overall, there is a highly significant 20% reduction in death or MI, which, interestingly, is similar to the extent of improvement ($\approx 25\%$) in the original aspirin-versus-placebo trials performed more than a decade ago.\textsuperscript{54}

Beyond the early benefit at 30 days that is presented in Fig 3, there is evidence of durability and incremental late benefit in some of the trials. For example, in the EPIC trial, the 6–month benefit for the overall cohort of 2099 patients was a sustained reduction of the composite of death, MI, and revascularization procedures. In particular, a significantly lessened need for repeat revascularization procedures was noted.\textsuperscript{55} At 3-year follow-up of this trial, the patients who presented with acute coronary syndromes had a 60% reduction in mortality in the group assigned to abciximab bolus and infusion compared with placebo (Fig 4).\textsuperscript{56} Despite only a 12-hour infusion, the delayed, sustained, and in some respects incremental benefit over time after abciximab was not fully anticipated. The findings raise the hypothesis that arterial passivation was achieved, such that the intervention was capable of transforming the vessel wall surface from one that supports platelet-thrombus deposition to one that cannot do so. The findings of late benefit, manifesting well after the infusion was completed, are further corroborated by the study of Lamifiban in unstable angina and non–Q-wave MI in the PARAGON trial.\textsuperscript{57} Whereas the 30-day relative benefit for reduced death or MI was quite modest at 9% to 10% for Lamifiban, at 6 months there was an $\approx 40\%$ reduction for low-dose Lamifiban compared with placebo that was highly statistically significant.\textsuperscript{58} Therefore, two distinct trials of GP
IIb/IIIa inhibitors of different agents and clinical indications have yielded impressive long-term results. These findings lend support to the passivation hypothesis, because it is otherwise difficult to explain further improvement in clinical outcomes at a time that is temporally dissociated from drug administration.

The strong evidence of efficacy of the GP IIb/IIIa blockers has fortunately not been overshadowed by an excess of bleeding complications. Although this was raised as a concern early in the clinical trial experience, the recent trials have not shown an excess of even minor bleeding complications for the GP IIb/IIIa inhibitor intervention. Most notably, in the EPILOG trial, with reduced heparin dosing on a weight-adjusted basis along with limited peri–access sheath indwelling time, the bleeding events were quite infrequent and no more likely than with placebo. In Table 1, the rates of intracerebral hemorrhage for the five coronary intervention trials are provided. Of note, compared with fibrinolytic therapy, which carries an important liability for intracerebral bleeds, there has been no excess in more than 12 000 patients in clinical trials thus far. The improved safety profile of the GP IIb/IIIa inhibitors is most likely a result of preserved platelet adhesion, left intact despite fibrinogen receptor blockade, and differences in untoward hemorrhagic events as a function of the coagulation proteins vis-à-vis platelet aggregation. Still uncertain, however, is the combined use of GP IIb/IIIa inhibitors in patients receiving fibrinolytic therapy in adequate numbers (thousands) of patients to be able to provide more definitive assurance of the lack of risk of intracerebral bleeding.

### Experimental Studies

Over the past decade, a substantial number of preclinical investigations of fibrinolytic therapy combined with GP IIb/IIIa inhibitors have been carried out (summarized in Table 2). Cumulatively, these studies have shown that the dose of fibrinolytic therapy can be substantially reduced to 50% or even 25% of the dose required in control experiments and that fibrinolysis occurs much more rapidly and more completely and is much more stable, as reflected by the absence of cyclic flow variations or reocclusion once flow is restored. Nicolini and associates showed that a low dose of a GP IIb/IIIa inhibitor combined with a low dose of a direct thrombin inhibitor (hirudin) also markedly facilitated coronary fibrinolysis in the canine electrolytic model. The demonstrated benefit has been confirmed with abciximab and other GP IIb/IIIa inhibitors such as Integrilin, Kistrin, Echistatin, and Bistatin; the latter three agents are snake venom derivatives. Owing to the concerns about bleeding complications in the face of fibrinolytic therapy, aspirin, and heparin, there was an unfortunate and substantial lag before the findings from these encouraging experimental studies led to the launch of clinical trials.

### Table 1. Rates of Major Bleeding and Intracerebral Hemorrhage

<table>
<thead>
<tr>
<th>Trial</th>
<th>Major Bleeding,* %</th>
<th>Intracerebral Hemorrhage, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Drug Placebo Drug</td>
<td></td>
</tr>
<tr>
<td>EPIC</td>
<td>7.0 14.0</td>
<td>0.3 0.3</td>
</tr>
<tr>
<td>IMPACT</td>
<td>4.8 5.1</td>
<td>0.1 0.1</td>
</tr>
<tr>
<td>RESTORE</td>
<td>4.5 6.0</td>
<td>0.2 0.1</td>
</tr>
<tr>
<td>CAPTURE</td>
<td>1.9 3.8</td>
<td>0.0 0.0</td>
</tr>
<tr>
<td>EPILOG</td>
<td>3.1 2.0</td>
<td>0.0 0.1</td>
</tr>
<tr>
<td>Pooled</td>
<td>4.4 6.0</td>
<td>0.1 0.1</td>
</tr>
</tbody>
</table>

*Major bleeding defined by transfusion of ≥2 units.

### Table 2. Experimental Models of MI Testing Platelet GP IIb/IIIa and Fibrinolytic Therapy

<table>
<thead>
<tr>
<th>First Author Year Reference</th>
<th>Agents</th>
<th>Primary Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold 1988 58</td>
<td>7E3, 1-PA</td>
<td>Increased speed of reperfusion; lower doses of 1-PA needed</td>
</tr>
<tr>
<td>Yasuda 1990 59</td>
<td>7E3, 1-PA</td>
<td>Reperfusion can be achieved with 7E3</td>
</tr>
<tr>
<td>Mickelson 1990 62</td>
<td>7E3, 1-PA</td>
<td>Reduction of size with 7E3, given after 1-PA</td>
</tr>
<tr>
<td>Yasuda 1991 61</td>
<td>Kistrin, 1-PA</td>
<td>Increased speed and durability of reperfusion; less 1-PA needed</td>
</tr>
<tr>
<td>Shebushi 1990 60</td>
<td>Bitistatin, 1-PA</td>
<td>Acceleration of reperfusion timing, prevention of reoclussion</td>
</tr>
<tr>
<td>Holahan 1991 63</td>
<td>Echistatin, 1-PA</td>
<td>Prevention of reoclussion</td>
</tr>
<tr>
<td>Modi 1996 64</td>
<td>TP-9201, 1-PA</td>
<td>Prevention of reoclussion</td>
</tr>
<tr>
<td>Nicolini 1994 65</td>
<td>Integrilin, 1-PA</td>
<td>Increased speed of reperfusion, prevention of reoclussion, additivity with hirudin</td>
</tr>
<tr>
<td>Roux 1993 66</td>
<td>Ro43-5054, 1-PA</td>
<td>Prevention of reoclussion</td>
</tr>
<tr>
<td>Rapold 1993 67</td>
<td>G4120, 1-PA</td>
<td>Prevention of reoclussion</td>
</tr>
<tr>
<td>Yasuda 1993 68</td>
<td>G4120, 1-PA</td>
<td>Increased speed of reperfusion, prevention of reoclussion, decreased dosage of 1-PA</td>
</tr>
</tbody>
</table>
Pilot Clinical Studies

Three studies that have combined fibrinolytic therapy and GP IIb/IIIa inhibitors are summarized in Table 3.72-74 The first of these, TAMI-8, tested only the murine 7E3 monoclonal antibody Fab 3 to 24 hours after t-PA was administered at full doses.72 No simultaneous administration of the two classes of agents was assessed. Even so, the limited sample of 68 patients showed enhanced infarct vessel patency, as detected by subacute angiography, and less ST-segment oscillatory activity by continuous 12-lead ECG monitoring, suggesting reduced cyclic flow. The second trial performed, known as IMPACT-MI,73 evaluated the combined use of full-dose, accelerated t-PA with variable dosing of Integrilin and heparin. As summarized in Table 3, this pilot study suggested that with higher doses of Integrilin, there was improved infarct vessel patency compared with placebo. Via systematic coronary angiography, rates of TIMI 3 patency >80% were achieved at certain dose combinations, substantially better than would be expected with t-PA alone. As in the preceding trial, the digital 12-lead ECG monitoring showed faster and more stable resolution of the ST-segment elevation. A major problem in interpretation of these data is that the dose of Integrilin was subsequently shown to be inadequate owing to an in vitro artifact of previous platelet aggregation measurements.73 Accordingly, even with doses of Integrilin that were 50% of what would be necessary to reliably achieve 80% inhibition of platelet aggregation, there were trends toward angio graphic and clinical outcome improvements. Noteworthy was the lack of excess of any significant bleeding complications among the combined t-PA–and Integrilin-treated group of patients. The sample was too small, however, to make any definitive assessment of the dose combination or even an advantage over fibrinolytic therapy alone (with heparin and aspirin instead of GP IIb/IIIa blockade).

More recently, the PARADIGM trial enrolled 345 patients treated with either t-PA or streptokinase at full doses and concomitant intravenous Lamifiban (at three different doses) or placebo.65 At higher doses of Lamifiban (such as 400 μg bolus and 2.0 μg/min infusion), there was an excess transfusion requirement and no clear-cut clinical outcome benefit. Although the number of patients per Lamifiban dose group was relatively small and the patients received either t-PA or streptokinase treatment, there was no trend of reducing adverse clinical outcomes such as death (at a 2.0-μg dose, 4.3% versus 1.8% for treatment versus control; at a 1.5-μg dose, 0.9% and 3.3%, respectively). There was little difference in clinical reinfarction or recurrent ischemia between the treated and control patient groups. Conversely, the digital 12-lead ECG analysis extended previous experimental studies showing much more rapid ST resolution and significantly less oscillatory ST-segment fluctuation among treated patients.

The potential of sole GP IIb/IIIa inhibitor therapy as a reperfusion strategy was evaluated by Gold and colleagues76 in both the canine model and a limited number of patients. In the preclinical studies, in which abciximab was given with heparin and aspirin, 80% achieved reperfusion. In a series of 13 patients who had angiographically confirmed occlusion of the infarct-related artery, flow improved in 85% within 10 minutes of abciximab administration. These data indicate that abciximab, on its own, is capable of achieving coronary clot lysis in some patients, most likely as a function of active disaggregation of platelets. Although it is improbable that GP IIb/IIIa blockade alone will be sufficient in most patients, the finding that such therapy with heparin and aspirin can achieve coronary recanalization is important.

Low-Dose Fibrinolytics

The three small trials that evaluated combined therapy of GP IIb/IIIa blockade and fibrinolytics unfortunately used full doses of the latter. As discussed, it is essential to avoid higher doses of a plasminogen activator to minimize the prothrombotic effects. Furthermore, the potential for intracerebral hemorrhage and the cost of the therapy strongly support the low-dose plasminogen activator approach. Many critical questions remain, however. How low a dose can be maximally efficacious? Should this be 25% or 50% of the usual dose or some proportion in between? Which fibrinolytic is the optimal agent to combine with GP IIb/IIIa blockade? Should it be a short-acting one like t-PA, as is being assessed in the TIMI 14 trial, or a longer-acting agent given as a bolus, such as r-PA, as assessed in the GUSTO 4 pilot trial? What is the appropriate dose and duration of the GP IIb/IIIa inhibitor? Does heparin need to be administered, and if so, how much? How will such a strategy combine with catheter-based reperfusion?

Catheter-Based Reperfusion

Initial results combining primary balloon angioplasty and platelet GP IIb/IIIa blockade in the EPIC trial subgroup have been especially encouraging for a durable reduction in adverse events.77 On the basis of these findings, a randomized trial of catheter-based reperfusion with abciximab or placebo was conducted in 500 patients with demonstration of >40% reduction in the composite of death, reinfarction, or urgent revascularization at 30 days.78
The use of low-dose fibrinolytic and GP IIb/IIIa blockade as an initial pharmacological strategy has the potential not only to achieve reperfusion in a high proportion of patients but also to support acute-phase intervention. Instead of confronting the prothrombotic state of fibrinolytic therapy alone, as was tested in angioplasty trials performed in the 1980s,6–10 such a platelet-directed strategy may promote the safety of full infarct vessel revascularization. Without the hazard of promoting coronary thrombosis or inducing serious bleeding complications, combined low-dose fibrinolytic and GP IIb/IIIa blockade has considerable potential to bridge the long-term gap between mechanical and pharmacological reperfusion therapies.

Future Directions

A transmutation from our current approach to reperfusion to one that is “platelet-centric” is likely to occur over the next few years. Large-scale clinical trials that compare conventional fibrinolytic therapy with platelet GP IIb/IIIa inhibitors and low-dose plasminogen activator will be undertaken to validate this new approach. Ultimately, a keener appreciation of the importance and prior benign neglect of the white clot of acute coronary thrombus may be acknowledged. A highly effective pharmacological strategy that does not complicate percutaneous intervention has the potential to resolve the longstanding debate about whether to use fibrinolytic therapy or catheter-based reperfusion. Although undoubtedly the search for even more effective therapies for our most important public health problem will continue, the new plateau of reperfusion therapy would represent a significant step forward.

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56. Tcheng JE. Glycoprotein IIb/IIIa receptor inhibitors: putting the EPIC, PARAGON, and IMPACT II, RESTORE, and EPILOG trials into perspective. Cardiol Cardiol. 1996;175:135.


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