A marriage of enhancement: fibrinolysis and conjunctive therapy

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Summary
Pharmacologic reperfusion of patients with acute ST segment elevation myocardial infarction is designed to achieve prompt high-quality reperfusion, prevent recurrent ischemia and reinfarction, maintain long-term patency, and to enhance patient survival and quality of life. Because monotherapy with fibrinolysis is by itself unable to achieve all of these objectives, antithrombotic, anti-platelet, and other novel agents are required. We discuss herein the role of unfractionated and enoxaparin, the potential added value of direct thrombin inhibitors, and the importance of aspirin. Despite the promise of glycoprotein IIb/IIIa inhibitors, risks associated with intracranial hemorrhage in the elderly have led to restraint in their application to broad populations. Facilitation of urgent percutaneous coronary intervention with combination reduced-dose fibrinolytic and glycoprotein IIb/IIIa inhibitors remains a promising potential future pathway. The future is likely to emphasize greater application of the already effective therapies at our disposal and the development of novel anti-platelet and anti-thrombin agents as well as those directed toward inflammation.

Keywords
Clinical trials, fibrinolytic therapy, clinical trials, heparins / LMWH

The modern era of pharmacologic reperfusion was ushered in by the Gruppo Italiano per lo Studio Della Streptochinasi nell’infarto Miocardio (GISSI) investigators almost twenty years ago when they demonstrated the effectiveness of intravenous streptokinase in improving survival after acute ST elevation myocardial infarction (STEMI) (1). The evolution of this therapy’s lexicon from thrombolytic to fibrinolytic treatment has a historical precedent given Sherry’s appreciation of the fibrinolytic potential of B-hemolytic streptococci and its initial capacity to dissolve clotted blood from a patient’s hemotherax (2). Subsequently, enhanced appreciation of the contents of a coronary thrombus, and in particular the notion that it is not only fibrin, but also platelets that comprise the obstruction, supported this altered terminology (3). A dense thrombin and platelet mesh linked by fibrin forms the backbone of coronary thrombi and the introduction of systemic fibrinolytic therapy paradoxically leads to the release of pro-coagulant forces that counterbalance the original objectives (4). Hence, key considerations that follow involve the exposure of surface-bound thrombin, a potent procoagulant agent, and the activation of platelets which in turn may extrude plasminogen activator inhibitor-1, alpha II antiplasmin, platelet factor IV, and be an abundant source of factor Xa (Fig. 1) (4).

The objectives of reperfusion therapy are: 1) to achieve prompt, high-quality coronary reperfusion, 2) to prevent recurrent ischemia and reinfarction, 3) to maintain long-term coronary artery patency, 4) to prevent thromboembolic complications, and therefore enhance patient survival and quality of life. Given the limitations of monotherapy with fibrinolysis, ancillary agents designed to complement this approach have been termed conjunctive pharmacologic therapy, and will be the subject of this review. Our discussion will focus on antithrombotic
therapy, antiplatelet therapy, and novel future agents, which show interesting potential partnering opportunities with fibrinolysis.

**Antithrombin therapy**

Thrombin is an essential comment of the coagulation cascade catalyzing the conversion of fibrinogen to fibrin with platelet cross-linking leading to early clot formation. Thrombin is also a potent activator of platelets leading to exposure of the IIb/IIIa receptor and release of adenosine di-phosphate (ADP) and thromboxane A2 (TxA2) with propagation of platelet activation. Endogenous antithrombin III acts to inhibit these reactions by binding to thrombin and forming an inactive thrombin-antithrombin III complex. Multiple antithrombotic agents have been developed that modulate these reactions.

**Unfractionated heparin**

Unfractionated heparin has unquestionably been the most common antithrombotic fibrinolytic partner. Despite extensive study, there is a relative lack of rigorous, randomized trials supporting its efficacy and residual uncertainty about the optimal dose, timing and duration of therapy (5). The non-specific binding of heparin to plasma proteins, its inability to inactivate thrombin bound to fibrin, and the substantial variation in dose response contribute to the difficulty in balancing efficacy and safety. Due to the demonstrated improvement in safety with reduced dose heparin in conjunction with nPA in the Intravenous nPA for the treatment of infarcting myocardium early study (INTIME II), coupled with other observations, the ACC/AHA guidelines were revised for the use of unfractionated heparin (class IIa) (6, 7). For patients undergoing reperfusion therapy with rt-PA the current recommendation provides for a bolus of unfractionated heparin 60 U/kg (maximum 4000 U), followed by an infusion of 12 U/kg·h (maximum, 1000 U/h) targeting a PTT of 50 to 70 seconds during the initial 48 hours.
with provision for down-titration at 3 hours if the PTT is >70 seconds (7). Confirmation of the safety and efficacy of this recommendation has recently been acquired in the Assessment of the Safety and Efficacy of a New Thrombolytic III study (ASSENT-III) where it was found that reduced dose heparin maintained efficacy with less systemic bleeding then a non-randomized comparison with the unfractionated comparator arm of Assessment of the Safety and Efficacy of a New Thrombolytic II study (ASSENT-II) (8, 9). The data supporting the use of unfractionated intravenous heparin with streptokinase is less clear, with no obvious advantage of intravenous over subcutaneous heparin (10).

Low molecular weight heparin
The emergence of low molecular-weight heparin has attracted considerable interest given the ease of administration, stability of anticoagulant effect, circumvention of a need for laboratory monitoring, and greater degree of factor Xa inhibition (11). Phase II and the larger scale ASSENT III study highlight the utility of enoxaparin as opposed to unfractionated heparin as it relates to the prevention of recurrent ischemia, reinfarction, and reocclusion with some excess in systemic bleeding (3.33 vs 2.35%) (95% C.I. 0.508-0.959) (8, 11). A review of the combined ASSENT III and III plus experience, where enoxaparin was used for a median of five days versus the 48 hour protocol for unfractionated heparin, raises the question as to whether the best balance between safety and efficacy for enoxaparin would be a duration of therapy of approximately 72 hours (12). It is important to note that patients with significant renal dysfunction i.e. serum creatinine of 2.5 mM in men and 2.0 mM in women were excluded from these trials. In the recent pre-hospital ASSENT III plus experience, an excess of intracranial hemorrhage was observed in patients over the age of 75 receiving enoxaparin: this seemed to occur predominantly in low body weight females, and its use in the elderly cannot therefore be recommended at this juncture (13).

Direct thrombin inhibitors
Direct thrombin inhibitors are capable of not only inactivating free thrombin as do the heparins, but also that bound to fibrin, thereby theoretically attenuating the potential for the thrombin-generated procoagulant state (14). The most extensively studied of these agents is bivalirudin, which has recently been approved for patients with unstable angina who are undergoing percutaneous coronary intervention. Promising phase II studies suggesting bivalirudin could enhance outcomes of patients treated with streptokinase without excess bleeding, led to the performance of a large phase III study, the Hirulog and Early Reperfusion or Occlusion II study (HERO II), which compared bivalirudin and unfractionated heparin in patients receiving streptokinase for STEMI within 6 hours of symptom onset (15, 16). Although bivalirudin led to a lower rate of reinfarction (1.6% versus 2.3% p = 0.005) no mortality benefit was evident, and there was a tendency towards excess systemic and intracranial bleeding. Hence, its use in this setting cannot be advocated unless considered as an option for those patients with established heparin-induced thrombocytopenia.

The other direct thrombin inhibitor on which extensive investigation has been performed is hirudin. Unlike bivalirudin, hirudin is cleared by the kidneys, has a longer plasma half-life, and its demonstrable benefits over heparin in acute coronary syndromes are less clear. Given concerns about safety, the somewhat disappointing experience on efficacy, and issues around cost of production, further development of hirudin for acute coronary syndromes appears unlikely (14).

Antiplatelet therapy
Activated platelets cross-linked with fibrin form the core of coronary thrombosis. Once a platelet is activated through contact with collagen or thrombin or exposure to epinephrine, ADP, and TxA₂ platelets release further ADP and TxA₂ with a subsequent propagation of platelet activation. Multiple antiplatelets agents have been developed that inhibit the spread of activation or directly inhibit platelet function.

One of the most convincing demonstrations of antiplatelet therapy’s benefit in conjunction with fibrinolytic therapy was the efficacy of aspirin in the second International Study of Infarct Survival (ISIS-II) (17). Its efficacy as monotherapy and an apparent synergism when combined with streptokinase, has firmly enounced its role as effective initial therapy (17). Since aspirin’s effect is mediated through TxA₂ inhibition, and sub optimal efficacy of therapy persists despite incorporating aspirin, a search for incremental benefit through alternative antiplatelet agents has been a focus of major investigative study. Greater understanding of the role of the microcirculation, and the emergence of platelet microemboli as a key therapeutic target has engendered great interest in such therapy (3).

The elucidation of the glycoprotein IIb/IIIa platelet receptor, and the development of a monoclonal antibody (abciximab) to this receptor that blocks the binding of fibrin to platelets have had a profound impact on the management of patients with unstable coronary syndromes, and those undergoing percutaneous coronary interventions (18). Given the encouraging results from the use of glycoprotein IIb/IIIa inhibitors in non-STA elevation acute coronary syndromes, a number of phase II studies in STEMI that coupled reduced-dose fibrinolytic therapy with abciximab and other agents followed: these suggested the ability to enhance pharmacologic reperfusion and even the potential for reducing the frequency of recurrent myocardial infarction (19-21). Enthusiasm for this approach even lead to the hypothesis that the lower dose of fibrinolytic therapy might be rewarded with a lower frequency of intracranial hemorrhage. As discussed in detail elsewhere, however, phase II studies did not
provide clear evidence of prevention of reocclusion yet did identify the potential for excess systemic and intracranial bleeding in populations of patients substantially younger than those studied in large phase III trials (22). The first test of this hypothesis in a large-scale study was GUSTO V, which randomized 16,588 patients within 6 hours of symptom onset to either standard double-bolus reteplase, or 1/2 dose double-bolus reteplase with full dose abciximab (23). No difference in mortality was achieved in this study, although less reinfarction with combination therapy was evident (2.3 versus 3.5% p < 0.0001). There was also a promising reduction in clinically relevant non-fatal complications including recurrent ischemia, and severe ventricular arrhythmia, but these benefits were associated with an excess of severe bleeding (1.1 versus 0.5% p <0.0001) and a trend toward excess intracranial hemorrhage in patients above the age of 75 (2.1 versus 1.1% p = 0.069). When partnered with 1/2 dose tenecteplase in ASSENT III, the 2017 patients receiving combination therapy using abciximab also showed a reduction in reinfarction as compared with unfractionated heparin (2.2 versus 4.2% p = 0.0009) and a commensurate reduction in refractory ischemia (8). However, there was an excess of major systemic bleeding, and the rates of intracranial hemorrhage were increased in patients over the age of 75 years. Whereas both trials revealed a statistically significant reduction in reinfarction, this did not translate into improved mortality when patients were followed for one year after entry (24, 25).

Hence, at this juncture, the role of glycoprotein IIb/IIIa conjunctive therapy with fibrinolysis remains uncertain. Reasonable arguments can be marshaled for its use in patients under the age of 75, especially with large myocardial territories at risk such as those exhibiting anterior myocardial infarction. Others have argued that the combination of a IIb/IIIa receptor inhibitor and reduced dose fibrinolytic may facilitate mechanical co-intervention, thereby garnering the synergistic benefit of early reperfusion and sustained patency with intracoronary stenting of the culprit lesion (22). This approach has recently been evaluated in a modest size study of 253 STEMI patients randomized within 12 hours of symptom onset to either 1/2 dose reteplase with abciximab versus abciximab alone prior to transfer for urgent PCI: the BRAVE trial (Bavarian Reperfusion

### Table 1: Ongoing trials of fibrinolysis and conjunctive therapy.

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Patients (n)</th>
<th>Trial Design (Endpoint)</th>
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<tbody>
<tr>
<td><strong>Trials of Facilitated PCI/Conjunctive Therapy</strong></td>
<td></td>
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<tr>
<td>ASSENT 4 PCI</td>
<td>4000</td>
<td>PCI vs. TNK + UFH + PCI</td>
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<tr>
<td></td>
<td></td>
<td>(Death/shock/CHF – 90 days)</td>
</tr>
<tr>
<td>FINESSE</td>
<td>3000</td>
<td>PCI vs. abciximab + PCI vs. 1/2 dose rtPA + abciximab + PCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Death/re-MI/CHF/shock/V.Fib – 90 days)</td>
</tr>
<tr>
<td>TIGER</td>
<td>5000</td>
<td>TNK + Enox + PCI vs. TNK + Enox + Eptifibatide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Death/re-MI/CHF/Stroke – 30 days)</td>
</tr>
<tr>
<td><strong>Trials of Conjunctive Therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLARITY TIMI-28</td>
<td>2200</td>
<td>Lytic + UFH with Clopidogrel vs. placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Angio rate of TIMI 0-1 or death/re-MI – day 8)</td>
</tr>
<tr>
<td>ExTRACT MI TIMI - 25</td>
<td>17000</td>
<td>Lytic + UFH vs. Lytic + Enoxaparin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Death/re-MI – 30 days)</td>
</tr>
<tr>
<td>MICHELANGELO OASIS - 6</td>
<td>10000</td>
<td>Reperfusion (lytic or PCI) with Fondaparinux vs. UFH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Death/ re-MI – 9 days)</td>
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Alternatives Evaluation) failed to show any difference in infarct size, but was insufficiently powered to evaluate clinical outcomes (26). The feasibility of pharmacologic reperfusion linked to urgent PCI is currently being tested in larger clinical trials involving various therapies versus primary PCI alone (Table 1).

Another antiplatelet strategy popularized for the treatment of patients with non-ST elevation acute coronary syndromes is thienopyridine therapy (ADP receptor blockers). Since this therapy is now standard for patients undergoing percutaneous coronary intervention the possibility exists that it may also be of added value if administered with fibrinolytic therapy (27, 28). Such an approach, however, remains speculative at this time, and there are no data to support its implementation.

**Progress of pharmacological reperfusion**

Attempts to enhance pharmacological reperfusion by combining fibrinolysis with novel conjunctive anti-thrombotic and anti-platelet therapy have been associated with variable degrees of success due to the complex interaction of clinical efficacy and safety. In figure 2 the progress of pharmacologic reperfusion therapy with fibrinolysis and conjunctive therapy that forms the body of this review are summarized. Beginning with the ISIS-II study in 1988 (17) relative efficacy and the benefits in morbidity and mortality achieved by this chronological transition are depicted above the horizontal line. Safety issues are shown below and represent a composite of systemic and intracranial bleeding, the relative proportions of which vary between the differing treatment strategies. Exact dosing of conjunctive therapy that has either been recommended from guidelines or used in large-scale clinical trials is shown in table 2.

**Novel future approaches**

Although advances in pharmacological reperfusion with fibrinolysis and conjunctive therapy have been achieved, substantial morbidity and mortality remains in STEMI patients. Current opportunities are provided through improved 'systems' approach to acute cardiac care with expanded implementation of evidence-based medicine. These include greater utilization of paramedical professionals to enhance recognition and timely...
initiation of reperfusion therapy in light of the importance of time to treatment and registry evidence indicating that 1/3 of eligible patients receive no form of reperfusion. Enhanced understanding of platelet structure and function has led to the emergence of a variety of future potential receptor-mediated antiplatelet agents. These involve potential modulation of one or more of the ADP receptor pathways affecting the shedding of pro-inflammatory CD40 ligands from the platelet membrane, antagonism of P selectin, and interference with V onWillebrand factor-dependent platelet adhesion (29). Novel antithrombin approaches more proximal in the pathway of coagulation include inhibition of tissue factor, an interference with the propagation of thrombin generation through inhibitors of Xa, IXa, and protein C activation (30). Finally, better understanding the link between inflammation and thrombosis may lead to the evolution of novel agents that further enhance the efficacy of fibrinolysis, agents that inhibit complement, interfere with neutrophil adhesion, inhibit matrix metallo proteinases amongst others are promising pathways for future investigation (31, 32).

### Table 2: Clinical advances in reperfusion therapy.

<table>
<thead>
<tr>
<th>Fibrinolytic (reference)</th>
<th>Anti-thrombotic</th>
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<tbody>
<tr>
<td>Streptokinase (10)</td>
<td>1) Heparin SQ 7500 - 12,500 bid or</td>
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<tr>
<td>1,500,000 units IV in 30-60 min.</td>
<td>2) Heparin 5000 IU bolus and 1000 IU/hr (PTT 60-90) or</td>
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<tr>
<td></td>
<td>3) Bivalirudin 0.1 mg/kg bolus and 0.25 mg/kg/h #</td>
</tr>
<tr>
<td>Tissue Plasminogen activator (tPA) (7, 10)</td>
<td>1) Heparin 5000 IU bolus and 1000 IU/hr (PTT 60-90) *</td>
</tr>
<tr>
<td>15 mg bolus + 0.75mg/kg in 30 min. (max 50mg) + 0.5 mg/kg in 60 min. (max. 35mg)</td>
<td></td>
</tr>
<tr>
<td>Reteplase (rPA) (29, 30)</td>
<td>1) Heparin 5000 IU bolus and 1000 IU/hr (PTT 60-90) *</td>
</tr>
<tr>
<td>10 mg + 10 mg double bolus (q 30 minutes)</td>
<td></td>
</tr>
<tr>
<td>Tenecteplase (TNK-tPA) (8, 9, 12, 13)</td>
<td>1) Heparin 5000U bolus and 1000IU/hr (PTT 60-90) or</td>
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<tr>
<td>Weight adjusted (30-50mg) single bolus</td>
<td>2) Heparin 60 U/kg bolus (max 4000U) and 12 U/kg/h (max 1000 U/h) targeting a PTT of 50 to 70 * or</td>
</tr>
<tr>
<td></td>
<td>3) Enoxaparin 30mg bolus and 1mg/kg SQ bid (not recommended &gt;75yrs)</td>
</tr>
</tbody>
</table>

NB – all combinations include ASA 160 – 325 mg chew and swallow ASAP
# - recommended only when heparin is contraindicated
* - AHA/ACC guidelines recommend reduced dose heparin i.e. 60 U/kg (max 4000 U) and 12 U/kg/h (max 1000 U/h) targeting a PTT of 50 - 70

### References


