Bolus Fibrinolysis
Risk, Benefit, and Opportunities

Paul W. Armstrong, MD; Christopher Granger, MD; Frans Van de Werf, MD

Fibrinolytic therapy for acute ST-segment elevation myocardial infarction has made a major contribution to the care of thousands of patients worldwide. Over the past decade, there have been tremendous advances in the care of such patients, including an enhanced assessment of both the risks of the infarction and the potential for complicating intracranial hemorrhage (ICH), more effective reperfusion strategies, and commensurate improvements in the approach to primary angioplasty and stenting. Recently, a meta-analysis of phase III megatrials involving several different fibrinolytic agents used for acute myocardial infarction suggested that agents administered as a bolus are associated with an excess risk of ICH.

The advantages of long-acting, third-generation fibrinolytic agents administered as a simple, single- or double-bolus injection are substantial when compared with prior agents that require sustained infusions and are often introduced by a bolus, with or without a step-down infusion. Within contemporary emergency departments, physicians and nurses are required to deal with a growing and increasingly complicated array of available therapies, not only for acute coronary syndromes, but for many other conditions as well. These demands are often accentuated by resource constraints; hence, simple bolus fibrinolytic regimens are a welcome innovation for those healthcare workers on the front lines, and such regimens are less likely to engender medication errors. However, the relationship between fibrinolytic dosing errors and morbidity and mortality is complex. Thus, whereas a higher frequency of modest dosing errors was identified after therapy with recombinant tissue-type plasminogen activator (rt-PA) than with tenecteplase (TNK-tPA) in the Assessment of the Safety of a New Thrombolytic (ASSENT) 2 study and 30-day mortality was also higher with incorrect dosing of rt-PA in this study, the excess mortality was evident whether patients received rt-PA or rt-PA placebo. This analysis emphasizes the important role of confounding factors in the ascertainment of causal relationships.

Notwithstanding these findings, the implications for more general use outside a clinical trial may be different. In this regard, medication errors were noted to occur in 15% of the National Registry of Myocardial Infarction population with administration of the weight-adjusted 90-minute step-down infusion of rt-PA after its initial bolus. Excessive rt-PA dosing was associated with a 49% increase in the incidence of ICH after adjustment for relevant baseline covariants. When ICH complicates fibrinolytic therapy, the implications are often devastating, with approximately two-thirds of patients dying and two-thirds of the survivors experiencing important residual disability. Unfortunately, the symptoms that permit recognition of complicating ICH develop some hours after the completion of current fibrinolytic therapy, and modification of their administration regimen is not a feasible remedy to circumvent this problem.

It is well recognized that the difference in properties between the fibrinolytic agents currently in general use has a substantial impact on their efficacy and safety. Hence, whereas rt-PA administered over 90 minutes in a bolus and step-down infusion produces superior early coronary patency, improved preservation of left ventricular function, and enhanced survival when compared with streptokinase, it is also associated with a higher ICH rate, especially in elderly patients. From its beginnings in the early Thrombolysis in Myocardial Infarction (TIMI) experience, dosing of rt-PA was found to be critical as it relates to the risk of ICH; hence, an unacceptably high rate of 1.89% was found with the 150-mg dose, leading to a reduction in the dose to 100 mg and a decline in ICH to 0.54%. A similar experience occurred in the TIMI 10B Phase II evaluation of the triple substitution mutant of rt-PA (ie, TNK-tPA). These 3 modifications of TNK-tPA confer a diminished plasma clearance rate, a higher resistance to plasminogen activator inhibitor-1 inhibition, and more pronounced fibrin specificity.

In the TIMI 10B study, 886 patients with acute ST-segment elevation myocardial infarction presenting within 12 hours were randomized in a non–weight-adjusted fashion to receive either a single bolus of 30 or 50 mg of TNK-tPA versus accelerated rt-PA. Because of a concerning early rate of ICH (3 of the first 78 patients; ie, 3.8% at 50 mg), the 50-mg dose
was replaced by a 40-mg dose. Weight adjustment ultimately proved to be important in the phase II dose-finding studies; therefore, it was used in the ASSENT 2 phase III study.\(^1\) A second bolus fibrinolytic, lanoteplase, a novel plasminogen activator (nPA), is a deletion mutant of rt-PA lacking the fibrinectin finger-like and epidermal growth factors, which lead to both a slower clearance and lesser fibrin specificity than rt-PA.\(^1\) Although the Intravenous nPA for Treatment of Infarction Myocardium Early (InTIME) 2 study evaluating lanoteplase (nPA) versus rt-PA is as-yet unpublished, the excess ICH rate with nPA may again be a result of overdosing with a novel agent, the same affliction experienced by rt-PA in its early development.\(^1\) There may well be a tradeoff between superior fibrinolytic potency leading to enhanced coronary reperfusion but higher ICH risk; thus, streptokinase, with the lowest 90-minute coronary patency rate, also has the lowest risk of ICH. The central problem of selecting an optimal dose from phase II studies is confounded by the lack of a universal standard methodology to quantify fibrinolytic potency on the one hand and the low frequency of occurrence of ICH on the other.\(^1\) An important conclusion of the ASSENT 2 study was not only equivalence in mortality rates and the incidence of ICH (0.93% for bolus TNK-tPA and 0.94% for bolus/infusion of rt-PA; relative risk 0.991), but also a significant reduction in noncerebral bleeding and the need for transfusion with bolus TNK-tPA.\(^1\) These data, which are at variance with the experience with nPA, highlight the heterogeneity in fibrin specificity between these 2 rt-PA mutants with extended half-lives that permit bolus injection.

Maintaining high-quality coronary patency after successful reperfusion, especially with relatively fibrin-specific agents, is critically dependent on coexistent antithrombin therapy, and it is imperative to consider both the benefits and risks of the overall pharmacological strategy used. That the extent of concomitant anticoagulation with heparin bore a direct relationship to the risk of ICH was shown in the Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries (GUSTO I) study, where an activated partial thromboplastin time (aPTT) >70 seconds was associated with this phenomenon.\(^1\) The combined results of TIMI 9a and GUSTO IIa, which were designed to evaluate the relative efficacy of the antithrombin hirudin versus conventional unfractionated heparin in conjunction with fibrinolytic therapy, also demonstrated the potential of antithrombin therapy for excess ICH. In these studies, an unacceptable rate of ICH was found both with rt-PA and streptokinase when excess heparin (up to 1300 U bolus with the target aPTT of 60 to 90 seconds) was employed.\(^1\) Subsequently, in the revised second phase of these studies, a commensurate reduction in ICH and systemic hemorrhage ensued when the maximum bolus was reduced to 5000 U followed by a continuous infusion of 1000 U per hour with a more conservative aPTT target of 55 to 85 seconds.\(^1\)

An important additional observation of the InTIME 2 investigators on this subject was reported in February 2000. They noted a 25% reduction in the rate of ICH when the initial adjunctive heparin bolus was omitted in conjunction with nPA therapy.\(^2\) Interestingly, the difference in the incidence of ICH in the 2 rt-PA anchor arms of InTIME 2 and

### Comparison of rPA and TNK-tPA with rt-PA

<table>
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<tr>
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<th>OR (95% CI)</th>
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<tr>
<td>GUSTO III</td>
<td>1.039 (0.722-1.495)</td>
</tr>
<tr>
<td>ASSENT II</td>
<td>0.991 (0.725-1.354)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.911 (0.796-1.285)</td>
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Odds ratios (OR) and 95% confidence intervals (CI) comparing ICH rates for reteplase (r-PA; GUSTO III) and TNK-tPA (ASSENT 2) with accelerated rt-PA.

ASSENT 2 (0.62% and 0.94%, respectively) with identical rt-PA dosing regimens may well have related to the more conservative heparin strategy used in InTIME 2 in conjunction with down-titration of the heparin dose, if earlier measurements of aPTT exceeded 70 seconds. The advantage of lower dose heparin was incorporated into the new ACC/AHA recommendations concerning lesser adjunctive heparin therapy as well as closer and earlier surveillance of heparin monitoring in conjunction with rt-PA administration. Hence, the recommended regimen is now 60 U/kg heparin as a bolus followed by initial maintenance of 12 U kg\(^{-1}\) h\(^{-1}\) (maximum, 4000 U bolus and 1000 U/h infusion for patients weighing >70 kg), with the goal of maintaining an aPTT of 50 to 70 seconds.\(^2\)

It is noteworthy that of 6 bolus regimens examined in a prior meta-analysis on this subject, only reteplase, a single-chain nonglycosylated deletion variant of rt-PA with a half-life of 15 minutes and reduced fibrin specificity compared with r-PA and TNK-tPA, is likely to have major future clinical relevance.\(^5\) Neither reteplase nor TNK-tPA seems to have an increased risk of ICH when compared with accelerated rt-PA, as demonstrated in the separate and combined analyses from that meta-analysis depicted in the Figure. Because the pharmacodynamic and pharmacokinetic profile of TNK-tPA (recently approved for use in the United States by the Food and Drug Administration) when administered as a single bolus is similar to those of accelerated rt-PA, similar rates of ICH would be expected and indeed were observed in ASSENT 2.\(^1\)\(^2\)\(^3\)\(^4\) Further enhancement in pharmacological reperfusion for patients with acute myocardial infarction is likely to occur along at least 2 major new pathways. There is unequivocal evidence that earlier delivery of therapy is associated with greater myocardial salvage and improved prognosis.\(^5\)\(^2\)\(^6\) Although some success has been achieved in abbreviating the door-to-needle time as it relates to the administration of fibrinolytic therapy, the same cannot be said for the delay that persists between symptom onset and hospital arrival. Indeed, despite an understanding of the demographic, cultural, and other barriers that exist and a concerted effort through intense public education programs to abbreviate the time from symptom onset to presentation for appropriate therapy among patients with chest pain syndromes, no improvement in time
to arrival to hospital has been achieved.\textsuperscript{27} Hence, among regions and countries where these delays are an important factor, and especially where emergency medical services transport times exceed 1 hour, there is now substantial motivation to move toward prehospital bolus fibrinolysis in the ambulance or home. Bolus fibrinolytic therapy may be even more advantageous in this setting, where simplicity and lack of need for multiple intravenous lines is at a premium.

A second stimulus for the further development of bolus therapy has emerged from the impressive phase II observations concerning combination fibrinolytic therapy in conjunction with intravenous glycoprotein IIb/IIIa platelet inhibitor therapy.\textsuperscript{28} This therapy has demonstrated promising evidence of faster and enhanced reperfusion. Whether the hopes for reduced reocclusion and a lesser frequency of ICH will be realized is currently the subject of large phase III studies. Clearly, if both novel antithrombin and glycoprotein IIb/IIIa inhibitor therapy become part of an accepted pharmacological strategy for acute myocardial infarction, the need for simple, safe, and effective bolus fibrinolysis will be accentuated. These issues are under active investigation, and we eagerly anticipate the results of the ongoing phase III studies.

\textbf{References}


\textbf{Key Words}: brain \| circulation \| fibrinolysis
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