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CARDIOLOGY Rounds™

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New directions in thrombolytic therapy

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The most frequent cause of acute myocardial infarction is occlusive thrombus of the coronary arteries. Optimal therapeutic strategies must aim to achieve early and complete reperfusion of the infarct-related artery. The validity of this open-artery concept has been demonstrated by the angiographic substudy of the GUSTO trial.[1] The superiority of tissue plasminogen activator (tPA) over streptokinase (SK) was linked to a higher percentage of early (90-minute) and more complete (TIMI-3 flow) reperfusion, suggesting that these variables are crucial determinants of therapeutic success.

Nevertheless, only 54% of patients treated with tPA (versus 30% for streptokinase) achieved complete early reperfusion (TIMI-3 flow at 90 minutes). Furthermore, current administration protocols for tPA and SK require continuous infusions and more simple regimens (for example, a single or double bolus) may lead to more rapid time to thrombolytic treatment. Thus, new pharmacologic reperfusion strategies are being developed for the treatment of myocardial infarction. They incorporate new thrombolytic protocols, new thrombolytic agents, and therapy adjuvant to thrombolysis. Figure 1 outlines some pertinent recent and current studies of thrombolytic strategies.

Currently-used thrombolytic agents

Two thrombolytic agents in current use in Canada are streptokinase (SK) and tissue plasminogen activator (tPA).

Streptokinase

SK is the most commonly used agent in Europe. It is not an enzyme; rather, it activates the fibrinolytic system by forming a 1:1 stoichiometric complex with plasminogen, which in turn converts uncomplexed plasminogen to plasmin. As a nonspecific fibrinolytic, it causes systemic conversion of plasminogen to plasmin, as well as extensive depletion of circulating fibrinogen, plasminogen, and factors V and VIII. This systemic lytic state may promote sustained thrombotic dissolution and SK has not been linked to an increase in bleeding complications relative to more fibrin-specific agents. Most patients receiving SK have pre-formed antistreptococcal antibodies, although few patients experience allergic reactions. Hypotension is a frequent side effect of SK administration.

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Figure 1: Some recently completed and ongoing large scale trials of thrombolytic therapy

Trial	Design	Patients	Intervention	End-point	Results
COBALT[2]	RCT open-label equivalence	n = 8,000 ST elevation <6h cp onset	double-bolus tPA vs front-loaded tPA	30-day mortality	7.98% vs 7.54% abs diff mortality 0.44% 95% CI (-0.61% to 1.49%) equivalence not demonstrated
INJECT[5]	RCT double-blind equivalence	n = 6,000 ST elevation <12h cp onset	rPA vs SK	35-day mortality	8.90% vs 9.43% abs diff mortality 0.53% 90% CI (-1.24% to 0.71%) equivalence demonstrated
GUSTO-III[6]	RCT double-blind	n = 15,000 ST elevation <6h cp onset	rPA vs tPA	30-day mortality	7.47% vs 7.24% p = 0.54 abs diff mortality 0.23% 95% CI (-0.66% to 1.1%) not designed as equivalence trial
ASSENT-II	RCT double-blinded equivalence	n = 16,500 ST elevation <6h cp onset	TNK-tPA vs tPA	30-day mortality	currently under way
In-TIME 2	RCT double-blind	n = 18,000	nPA vs tPA	30-day mortality	currently under way

RCT = randomized controlled trial tPA = tissue plasminogen activator rPA = reteplase plasminogen activator
nPA = lanoteplase cp = chest pain SK = streptokinase CI = confidence interval

Tissue plasminogen activator

This naturally occurring enzyme is produced by a number of tissues, including the vascular endothelium, and it is the most commonly used agent in North America. It is relatively fibrin-selective, attaching itself preferentially to pre-formed thrombi and lysing them while avoiding extensive activation of plasminogen in the general circulation. This relative fibrin specificity has led to lysis of clots more rapidly than SK. However, this advantage is accompanied by an increased rate of re-occlusion (due to lack of systemic fibrinogen depletion), requiring concomitant IV heparin therapy. In addition, there is a small increase in the risk of intracranial bleeding as compared to SK.

New protocol: Double-bolus tPA

Observations that the generation of thrombin associated with thrombolytic use is less pronounced with short infusions, and that the lytic effects of tPA are sustained after its clearance from the circulation, have led to administration of tPA as a double bolus.

The COBALT study[2] was a multicentre, randomized, controlled, open-label trial designed to demonstrate equivalence between double-bolus tPA (50 mg, then 50 mg 30 minutes later) and traditional front-loaded tPA. Inclusion criteria were the same as those utilized in the GUSTO trial, and over 8,000 patients were expected to be randomized. The primary endpoint was 30-day mortality. The COBALT investigators decided that for double-bolus tPA to be considered equivalent to front-loaded (accelerated) tPA, the upper limit of the one-sided 95% CI of the difference could not exceed 0.4%. This difference corresponds to the lower 95% confidence limit of the absolute difference in 30-day mortality between front-loaded tPA and SK in the GUSTO-I trial.

After 7,200 patients had been randomized to treatment, the trial was stopped early due to slightly poorer clinical outcomes in the double-bolus arm. That group's 30-day mortality was 7.98% versus 7.53% for the front-loaded tPA arm (0.55% absolute difference; 95% CI -0.61%, 1.49%). Thus, according to the predetermined definition in this study, equivalence could not be demonstrated.

New agents

Several new thrombolytic agents are currently being investigated. These include mutants and variants of tPA (reteplase) as well as plasminogen activators from animals and bacteria.

Mutants and variants of plasminogen activators

Reteplase (rPA)

Reteplase (rPA) is a deletion mutant of the wild-type tPA. The fibronectin finger, epidermal growth factor, and kringle-1 regions have been deleted. The resulting agent has a prolonged half-life compared with tPA (18 vs 5 min.), which allows it to be administered as a double bolus as opposed to a continuous infusion.

Reteplase is highly fibrin-specific but does not have high fibrin affinity like tPA. This high fibrin affinity can cause high concentrations of tPA to accumulate at surface receptors on a fibrin clot. Thus, lower fibrin affinity might allow for more efficient clot penetration and lysis. In two angiographic trials,[3,4] rPA compared favorably with tPA and front-loaded tPA with regard to enhanced patency of the infarct-related artery and the incidence of bleeding complications.

Two larger clinical trials, INJECT[5] and GUSTO-III,[6] have compared the efficacy and safety of rPA with SK and tPA respectively. The INJECT trial was a randomized double-blind trial designed to determine whether the effect of rPA on survival was at least equivalent to that of SK. The authors used a less stringent definition of equivalence than used in the COBALT study, requiring that the lower 90% CI for the point estimate for difference in mortality between rPA and SK not include 1.0% (i.e., mortality with rPA is not >1% worse than that seen with SK). Over 6,000 patients participated. At 35 days, mortality was 8.90% for rPA and 9.43% for SK (90% CI for mortality difference, -1.24% to 0.71%). Thus, using the predetermined definition of equivalence in this study, rPA was demonstrated to be at least as effective as SK. In-hospital stroke rates and bleeding complications were similar between the two groups.

GUSTO-III was a large, randomized, double-blinded trial comparing the efficacy of rPA and front-loaded tPA. At 30 days, mortality rates were similar (7.47% rPA, 7.24% tPA). The 95% CI for mortality difference was -0.66% to 1.1%. Therefore, rPA did not provide any additional survival benefit and the primary hypothesis of superiority of rPA was therefore not realized. Further, the GUSTO-III data are consistent with an absolute difference in mortality between the rPA and tPA groups ranging from 0.6% in favour of rPA to 1.1% in favour of tPA. If one "applies" the equivalency criterion used in the COBALT study – that the excess mortality in the rPA group should be less than 0.4% – one cannot conclude that rPA and tPA are equivalent. Although the absolute mortality rates are of similar magnitude, GUSTO-III has not demonstrated equivalence if one accepts that the 0.4% absolute difference is indeed clinically important.

TNK-tPA

Another approach to modification of the tPA molecule involves multiple-point mutations. In TNK-tPA, multiple-point mutations effectively enlarge the molecule, resulting in a longer half-life (18 minutes). The agent can thus be given as a single bolus. There also appears to be reduced inhibition by PAI-1. A dose-ranging trial (TIMI-10A[7]) recently showed favorable 90-minute reperfusion rates when compared with tPA. In addition, a 2000 patient safety trial (ASSENT-I) demonstrated that a 40 mg bolus did not result in any greater risk for intracranial hemorrhage than that seen with other thrombolytic agents. A large-scale, randomized double-blinded trial comparing TNK-tPA and front-loaded tPA, ASSENT-II, is currently under way. ASSENT II is an equivalence study with a planned sample size of 16,500 patients and a primary endpoint of 30-day mortality.

Lanoteplase (nPA)

Lanoteplase is a deletion (finger, epidermal growth factor regions) and point mutant of wild-type tPA. It has a longer half-life than tPA (30–45 min.), which also allows it to be administered as a single bolus. nPA appears to have reduced fibrin affinity with improved lytic activity. A large-scale randomized trial of nPA versus front-loaded tPA is also currently under way (In-TIME-2).

Plasminogen activators from animals

Bat-PA

The saliva of the vampire bat *Desmodus rotundus* contains the plasminogen activator Bat-PA. It appears to be extremely fibrin selective, has increased PAI-1 resistance, and has a prolonged half-life. In animal studies, Bat-PA induced prompt and frequent recanalization of occluded vessels without causing overt plasminemia. It is moderately antigenic.

Plasminogen activators from bacteria

Staphylokinase

Staphylokinase is an indirect plasminogen activator like SK; and therefore it needs to form a complex with plasminogen. Staphylokinase, however, is very fibrin-specific. A recent small, randomized, angiographic trial, the Bolus Staphylokinase Trial,[8] compared staphylokinase (15-mg bolus x 2) with front-loaded tPA. There was a trend toward higher 90-minute and 24-hour TIMI-3 flow rates. There was also induction of circulating neutralizing antibodies in most patients; however, the clinical significance of this is uncertain.

Adjuvant therapy

Increased platelet activation/aggregation and thrombin activity are associated with the administration of thrombolytic therapy, and may contribute to vessel reocclusion after successful thrombolysis. Antagonists of the platelet membrane glycoprotein IIb/IIIa have recently become available. This glycoprotein (GP) receptor binds fibrinogen, allowing platelet crosslinking and the formation of thrombus. GP IIb/IIIa antagonists have been demonstrated to be effective in patients undergoing PTCA,[9–12] and they appear promising in unstable angina.

More recently, several phase-II studies (TAMI-8,[13] IMPACT-AMI,[14] PARADIGM[15]) have been completed using adjunctive intravenous GP-IIb/IIIa inhibitors with thrombolytic therapy in the setting of acute myocardial infarction. The hope is that by inhibiting platelets more fully than with ASA (acetylsalicylic acid) alone, the establishment and adequacy of coronary reperfusion will be substantially heightened. Each of these trials has shown (angiographically or by continuous electrocardiography) an improvement in restoring coronary perfusion. Large-scale phase-III studies will be needed to determine the clinical importance of improving coronary reperfusion with adjunctive GP-IIb/IIIa inhibitors.

Conclusion

Reperfusion rates with current thrombolytic regimens remain less than optimal. Thus, new pharmacologic reperfusion strategies are being developed with the goal of achieving earlier, more complete, and sustained coronary artery patency. New protocols of administering tPA as a double bolus have not proven to be effective. Further results for the most-widely investigated third-generation thrombolytic agent, rPA, have failed to demonstrate superiority over tPA. Whether rPA is equivalent to existing thrombolytic agents is controversial and depends to a large extent on the definition of therapeutic equivalence.

The efficacy of other third-generation thrombolytic agents, as well as adjunctive therapy with intravenous GP-IIb/IIIa inhibitors, is currently under investigation in large phase-III clinical trials. Even after the results of these trials become available, the controversy about the "best" thrombolytic will likely continue. However, modest differences in efficacy between thrombolytic agents is less important than the benefits realized with administering therapy to all eligible patients with as little delay as possible.

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Upcoming Scientific Meetings

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20-24 Oct 98
Canadian Cardiovascular Society 1998 Annual Meeting
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(Venue West Conference Services Ltd.)
CONTACT: 604-681-5226

Abstracts of Interest

Abciximab (ReoPro) potentiates thrombolysis in ST elevation myocardial infarction: Results of TIMI 14 Trial.

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To determine whether the platelet GPIIb/IIIa receptor antagonist abciximab enhances thrombolysis, the TIMI 14 trial is randomizing patients with ST ↑ MI ≤12 h of symptoms to receive: accelerated full dose tPA versus ReoPro (bolus 0.25 mg/kg, infusion 0.125 µg/kg/min x 12 h) alone or with reduced doses of streptokinase (SK) or tPA. All patients receive aspirin (150-325 mg) and heparin (aPTT 50-70 s). Results to date in the dose finding phase (groups of 35 pts) are:

Regimen:	tPA	ReoPro	SK+ReoPro	tPA+ReoPro		
ReoPro	–	+	+	+	+	+
SK (U x 10^3)	–	–	500	750	–	–
tPA (mg)	100	–	–	–	20	35
TIMI 3 flow (90 min)	60%	31%	42%	37%	55%	71%
Major Hemorrhage (%)	5	6	6	8	6	0

Other doses of lytics to be tested with abciximab include 1.25 MU SK and 50 mg tPA. The optimum regimen(s) will then be evaluated in a dose confirmation phase.

Conclusion: In ST ↑ MI, platelet inhibition alone with abciximab does not achieve desirable levels of TIMI 3 flow. However, it has a synergistic effect with markedly reduced doses of thrombolytics, producing flow rates as high as those obtained with conventional doses of SK or tPA. In the regimens tested to date, this appears to be accomplished without an increase in bleeding risk, suggesting that abciximab and low dose thrombolytics may be an attractive new approach to reperfusion.

Resolution of ST-segment elevation 90 minutes after thrombolysis for acute myocardial infarction predicts outcome: a GUSTO-III substudy

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Resolution of ST-segment elevation 180 min. after thrombolysis for acute MI predicts acute outcomes, but if a 90-min. ECG is also predictive earlier intervention is possible. This substudy enrolled 1783 pts from an international trial of alteplase vs. reteplase treatment within 6 h of MI. ECGs were obtained at baseline, 90 and 180 min. after lytics. The sum of the ST-segment resolution at 90 and 180 min. was categorized as <30%, 30%-70%, or >70% resolved versus baseline. We compared groups to determine if ST resolution at 90 min. was as predictive as at 180 min.

30-day outcomes

		ST resolution			
		<30%	30-70%	>70%	p
90 min.	ReMI	7.5%	3.0%	2.6%	0.01
	Death	10.8%	6.0%	3.1%	0.01
180 min.	ReMI	8.4%	2.9%	3.4%	0.04
	Death	14.3%	6.5%	3.4%	<0.0001

Conclusion: Persistent ST-segment elevation as early as 90 min. after thrombolysis is prognostically important, as is elevation persisting at 3 hours. These data should help identify pts who may benefit from early intervention. Treatment strategies should be developed for pts with continued ST-segment elevation after thrombolysis.

Does enrollment into acute myocardial infarction investigational protocols delay time to thrombolytic therapy?

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Time to treatment with thrombolytic therapy (TT) influences outcome for patients (pts) with acute myocardial infarction (AMI). Although investigational protocols (IP) for AMI may ultimately identify superior thrombolytic treatments, it is possible that IP contribute to TT delays. We determined the influence of IP enrollment on AMI diagnosis and treatment by reviewing 957 AMI patients who were treated with TT. Pts were enrolled into five sequential IP's between 1989 and 1997. Time to EKG (Dx time) and TT (TT time) were measured (minutes ± sd) for each enrolled pt and compared to pts not entered into an IP (controls) during the same time period.

	n	Dx time	P	TT time	P
IP 1	45	17 ± 14	0.942	64 ± 33	0.660
Control 1	156	18 ± 12		68 ± 58	
IP 2	55	13 ± 7	0.331	62 ± 32	0.160
Control 2	210	14 ± 9		53 ± 40	
IP 3	165	16 ± 16	0.419	39 ± 24	0.001
Control 3	187	16 ± 15		52 ± 40	
IP 4	12	20 ± 35	0.464	65 ± 5	0.428
Control	59	15 ± 14		53 ± 40	
IP 5	21	12 ± 10	0.171	40 ± 15	0.411
Control	47	21 ± 29		53 ± 70	

We conclude that enrolling AMI pts in IP for TT does not significantly delay, and for some IP may shorten, time to TT. This suggests that delays to TT may be reduced by the application of rigorous protocols for AMI pts.

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