Thrombolysis in Venous Thromboembolism*
An International Perspective
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Two promising novel recombinant tissue-type plasminogen activator (rt-PA) regimens for pulmonary embolism (PE) are being actively investigated: 100 mg/2 h as a continuous peripheral intravenous infusion, and bolus rt-PA, adjusted to weight, as a 2-min infusion. For deep venous thrombosis (DVT), less progress has been made in finding an optimal dosing regimen of rt-PA. Our mandate for the 1990s is to use the best possible thrombolytic dosing regimens in large clinical trials of PE and DVT. The primary objective of these planned clinical studies is to determine which patients with PE and DVT will benefit the most from thrombolysis followed by anticoagulation rather than anticoagulation alone.

The management of acute myocardial infarction (MI) has improved dramatically in the past two decades and serves as a yardstick for measuring the progress of venous thromboembolism treatment. Monitoring of cardiac rhythm and utilization of electrical defibrillation in coronary care units have decreased mortality from ventricular fibrillation. Strategies to reduce myocardial oxygen demand (eg, beta-blockers) and to increase coronary artery blood flow (eg, nitrates and mechanical revascularization with angioplasty or bypass surgery) have limited infarct size and reduced the frequency of cardiogenic shock. Although the role of thrombolytic therapy remained uncertain in the 1970s despite many promising studies,1,2 two large-scale trials, the Gruppo Italiano per lo Studio della Streptochinas nell'Infarto Miocardico (GISSI-1) and the Second International Study of Infarct Survival (ISIS-2),4 have proved that thrombolytic therapy can reduce mortality in many patients with MI. The fear of hemorrhagic stroke after thrombolysis is balanced by a realization that overall stroke rate may not increase, but that some thrombotic strokes may be converted to hemorrhagic stroke after lytic therapy.5 Subsequent placebo-controlled trials of thrombolysis have confirmed these findings and have convinced the medical community that thrombolysis should be considered in the management of most patients with MI. Issues that remain to be studied focus on the extent to which indications for thrombolysis should be liberalized (eg, any age patient? any duration of symptoms?) and the optimal choice, dose, and infusion time of the lytic agent. In addition, the one-fifth reduction in mortality achieved with aspirin therapy in the ISIS-2 study virtually ensures that low-dose aspirin will become standard therapy for all patients with MI except those with active bleeding or documented allergy to aspirin. Thus, within two decades, MI care has evolved from prescription of bed rest, morphine, and oxygen to aggressive management that includes arrhythmia monitoring, aspirin, heparin, thrombolytic therapy, nitrates, and, if ischemia persists or cardiogenic shock develops, urgent catheterization and mechanical revascularization. The rapid strides necessary to prove the benefit of this contemporary treatment approach have been facilitated by dedicated internists and cardiologists who have participated enthusiastically in randomized controlled trials of MI treatment, and by an extremely constant, high level of public awareness of the important issues being tested.

In contrast, innovative approaches to venous thromboembolism (VTE) treatment have languished, apart from the realization that the dose of Coumadin could be less intense and therefore safer but equally effective.6 Unlike the therapeutic strategy for MI, the proper role of thrombolytic therapy in pulmonary embolism (PE) and deep venous thrombosis (DVT) remains to be elucidated. Should lytic therapy be reserved only for life-threatening PE and limb-threatening DVT? Does lytic therapy reduce the frequency of adverse clinical events among patients with VTE? Would a strategy of routine thrombolysis for PE reduce the mortality and the frequency of chronic pulmonary hypertension? Would routine lysis for DVT reduce the frequency of PE (by dissolving thrombus in situ) or of chronic venous insufficiency (by minimizing damage to venous valves)? Could patients treated with thrombolysis safely receive a shorter course of heparin, thus yielding a shorter hospital stay (eg, four instead of seven days) and reducing hospital costs? To date, these important questions have not been answered satisfactorily.

Why have advances in PE and DVT treatment lagged so far behind those of MI? First, VTE is more

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diagnosed than acute MI. The prodrome of symptoms is often nonspecific (e.g., dyspnea or syncope) and there is no rapid screening test (such as an electrocardiogram) to aid in establishing the diagnosis or in making it much less likely. Second, public awareness of VTE is minimal, even though most individuals have relatives or acquaintances who have been stricken with these diseases. Third, treatment of VTE is not undertaken by a particular medical subspecialty. PE and DVT are treated by family practitioners, internists, pulmonologists, cardiologists, hematologists, and vascular surgeons. It is much more difficult to coordinate trials when physicians from so many different specialties are involved in patient care, compared with organizing internists and cardiologists who look after patients with MI. Therefore, mobilizing support for PE and DVT trials among the Fellows of the American College of Chest Physicians, an international and interdisciplinary organization of cardiopulmonary physicians, assumes special importance. In the future, perhaps the ACCP will help organize a public awareness group of patients with VTE and their relatives and friends to help advocate advances in the management of this disease.

From an international perspective, management of VTE varies considerably from country to country. For example, in the United States, lytic therapy for PE is often reserved for patients with thrombus that is anatomically massive and on the verge of causing hemodynamic instability manifested by hypotension and tachycardia. Among DVT patients, thrombolysis is used primarily in otherwise young, healthy patients with extensive proximal leg or arm thrombus that threatens to cause permanent residual disability. However, in continental Europe, the threshold for utilizing thrombolytic agents among DVT patients appears to be lower. The lack of a consistent international approach emphasizes the need for continued and intensified clinical research in VTE.

Phase I of the Urokinase Pulmonary Embolism Trial demonstrated that urokinase (UK) accelerates clot lysis and pulmonary tissue reperfusion compared with heparin alone.7 However, the rate of major bleeding was doubled among UK-treated patients and, after seven days of UK, there was no difference between the UK and heparin groups in the degree of pulmonary tissue reperfusion as judged from serial lung scans. Although UK and SK received approval from the Food and Drug Administration (FDA) for treatment of PE in 1977, and SK also was approved for treatment of DVT, these therapies were not employed widely in the United States during the subsequent decade.

In 1985, phase I of the Thrombosis in Myocardial Infarction Trial (TIMI-I) demonstrated the superior efficacy of recombinant human tissue-type plasminogen activator (rt-PA) compared with SK in angiographically proven lysis of intracoronary thrombus during MI.8 The advent of rt-PA renewed interest and excitement in undertaking thrombolysis for VTE. Therefore, we organized a multicenter research group to study PE and DVT in a methodical manner. The core of our group consists of dedicated nurses and clinicians (pulmonologists, cardiologists, hematologists, vascular medicine specialists, general internists) who work closely with interventional angiographers, nuclear medicine physicians, echocardiographers, and coagulation experts in order to recruit and randomize VTE patients in a series of clinical trials.

Pulmonary Embolism Trials

Personal Series

For PE, our goal is to identify effective and relatively safe thrombolytic regimens that can be used subsequently to compare thrombolysis with heparin. To help achieve this objective, our group has undertaken four clinical PE trials, two completed and two in progress, and is actively planning future trials (Table 1).

PE Trial 1, an open label study of 47 patients with angiographically documented PE, showed that 50 to 90 mg of rt-PA in 2 to 6 h caused clot lysis in 94 percent of cases.9,10 During the third and subsequent hours of therapy, however, an increased frequency of bleeding, particularly at the femoral vein puncture site used for pulmonary angiography, caused us to shorten the duration and intensify the rt-PA dose (to...

Table 1—PE Trials Undertaken by Our Research Group

| PE Trial 1. | An open label study of rt-PA among patients with angiographically proven PE that assessed efficacy with 2 h and, if necessary, 6 h angiograms after the initiation of therapy. The dose was 50 mg/2 h and, if significant clot lysis had not occurred, an additional 40 mg/4 h. In all our trials, the lytic agents are administered through a peripheral vein rather than through a pulmonary artery catheter. |
| PE Trial 2. | A randomized controlled trial of rt-PA (100 mg/2 h) vs urokinase (2,000 U/F as a bolus, followed by 2,000 U/F/h for either 2 h [if lysis occurred] or 24 h) among PE patients with baseline lung scans and pulmonary angiograms. The principal end points were improvement on the 2 h angiogram and 24 h lung scan. |
| PE Trial 3. | A randomized controlled trial of rt-PA (100 mg/2 h) vs urokinase (1,000,000 U as a bolus over 10 min, followed by 2,000,000 U as a continuous infusion over 110 min) among PE patients with baseline lung scans and pulmonary angiograms. The principal end points of this ongoing study are improvement on the 2 h angiogram and 24 h lung scan. |
| PE Trial 4. | A randomized controlled trial of rt-PA (100 mg/2 h) vs heparin among PE patients with either baseline high probability ventilation-perfusion lung scans or positive pulmonary angiograms. The objective of the trial is to determine whether rt-PA accelerates improvement in right ventricular function compared with heparin, as assessed by serial echocardiography. |
ANGIOGRAPHIC LYSIS WITHIN 2 HOURS (N=45)

rt-PA

Moderate 59%
Slight 23%
Worse 9%
None 9%

UK

None 39%
Worse 35%
Marked/Moderate 13%
None 13%

FIGURE 1. Lysis after 2 h of therapy: rt-PA vs UK. (From Goldhaber SZ. Chest 1989; 95:282S-89S. Reproduced by permission.)

PE Trial 2 compared this novel rt-PA dose with the 24-h FDA-approved UK infusion (2,000 U/lb as a bolus followed by 2000 U/lb/h for 24 h). Forty-five patients with angiographically proven PE were randomized to rt-PA or UK; by 2 h, clot lysis was more frequent in rt-PA-treated patients (Fig 1). At 2 h, rt-PA-treated patients had received more lytic therapy (100 mg of rt-PA) than the UK-treated patients (1,100,000 U, on average). During the remainder of the UK infusion, bleeding problems intensified (Fig 2). By 24 h, there was no difference in scintigraphic improvement between rt-PA and UK patients. Thus, in the doses employed, rt-PA dissolved thrombus more rapidly and more safely than UK.

Our PE Trial 3 (Fig 3) has modified the dose of UK to make it more comparable to the high concentration/short infusion period that was used for rt-PA. The novel UK dose being tested is 3,000,000 U/2 h, with the first 1,000,000 U given as a bolus over 10 min. A dose of high molecular weight UK (not available in the United States) similar to the UK dose used in PE Trial 3 was found to be effective and safe in the German Activator Urokinase Study of patients with acute MI. To date, 55 patients have been enrolled in our ongoing trial.

PE Trial 4, unlike the first three studies, does not investigate which thrombolytic regimen is optimal. Instead, PE Trial 4 is based on observations by Come et al and is designed to determine whether rt-PA accelerates improvement in right ventricular function compared with heparin (Fig 4). To date, 32 patients

PREMATURE TERMINATION OF UK (N=10)

Allergy (1.75)

Grog Bleed (9.3)

Hematemesis (8)

Hematuria (6.5)

FIGURE 2. Time in two clocks, each representing 12 h of UK infusion. The clock on the left represents 0 to 12 h of UK; the clock on the right represents 12 to 24 h of UK. Reasons for discontinuing UK were distributed evenly throughout the 24-h infusion period. If the protocol had required a 2-h rather than 24-h infusion of UK, only one patient would have had the drug discontinued before completion of the intended infusion. (From Goldhaber SZ. Chest 1989; 95:282S-89S. Reproduced by permission.)
FIGURE 4. Subcostal two-dimensional images at end-diastole in a patient with PE who presented with syncope and “heart failure.” Left, before rt-PA, the right ventricle (RV) is markedly enlarged and the left ventricular (LV) diameter is reduced. Right, after rt-PA, a remarkable decrease in RV size and a corresponding increase in LV size are apparent. RA = right atrium; SEP = septum; PW = posterior wall. (From Come PC, et al. J Am Coll Cardiol 1987; 10:971-78. Reproduced by permission.)

have been enrolled in this ongoing trial.

Other Series

Internationally, there is further research into the optimal rt-PA dosing regimen. Agnelli and co-workers have carried out intriguing experiments in rabbits that suggest that a bolus of rt-PA is efficacious and potentially safer than a prolonged rt-PA infusion. Prewitt’s group has obtained similar results in a dog model. Clinically, Levine and Hirsh have completed a PE study in which patients were randomized to bolus rt-PA (dosed by weight) or to heparin. Follow-up was undertaken with serial perfusion lung scintigraphy. Bolus rt-PA, administered over 2 min, was found to be both efficacious and safe. In Europe, Charbonnier has compared 100 mg of rt-PA administered over 7 h with 50 mg of rt-PA administered over 2 h and has found the 50 mg/2 h dose to be equally effective. Verstraete et al. compared peripheral IV vs intrapulmonary rt-PA in 34 patients with PE and found that intrapulmonary rt-PA conferred no advantage over peripheral administration of the drug. Currently Verstraete’s group is comparing rt-PA (100 mg/2 h) with a 12 h infusion of UK.

Future PE trials are being actively planned. The current fixed dosing regimen of rt-PA that we are using may in future trials be tested against a weight-adjusted bolus of rt-PA administered over a very short period of time (eg, 15 min instead of 2 h). Importantly, the

CLOT LYSIS : 6 RANDOMIZED TRIALS

RISK RATIO

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\[ \text{RRw (95\% CL)} = 3.7 (2.5, 5.7) \]

* \( p < 0.001 \)

FIGURE 5. Overview of six randomized trials of SK vs heparin for acute DVT indicates an overall 3.7 times superior lysis rate (heavy vertical line) for SK vs heparin. A risk ratio greater than 1 indicates a beneficial effect of SK for clot lysis. The pooled risk ratio is statistically significant (\( p < 0.001 \)), with 95 percent confidence limits (CL) (hatched vertical lines) of 2.5 to 5.7. In each of the six individual trials, SK achieved superior lysis (open circles), but the lower 95 percent confidence limit (closed circle, left side of each solid horizontal line) was greater than 1, indicating statistical significance, in only two of the six individual trials. (From Brown WD, et al. Chest 1989; 95:769S-785. Reproduced by permission.)
The objective is to determine whether routine use of thrombolytic therapy should be utilized in PE treatment requires critical evaluation in a randomized trial. We have conceived of a study of approximately 400 patients randomized to thrombolytic therapy followed by heparin vs heparin alone. The objective is to determine whether routine use of thrombolysis in a broad spectrum of patients with PE can reduce the frequency of adverse clinical events such as death, recurrent PE (by functioning as a pharmacologic embolectomy that lyse in situ the common sources of PE in the pelvic and deep leg veins), and persistent DVT (as determined by a predischarge ultrasound examination). This trial should be of sufficient size to yield a definitive answer regarding whether thrombolytic therapy should be used more often in PE treatment.

**Deep Venous Thromboembolism Trials**

With respect to DVT, the optimal role of thrombolytic therapy is even more uncertain than for PE. Previous randomized trials of lytic therapy\(^1\) have indicated that SK is more effective than heparin for lysis of DVT (Fig 5). However, the benefit of clot dissolution is accompanied by an increased risk of hemorrhage (Fig 6). Initial trials of rt-PA for DVT treatment have yielded similar results both for the McMaster University Group\(^8\) and for us.\(^9\) In Europe, a regimen of 100 mg and 50 mg of rt-PA administered IV over 8 h on two subsequent days in heparinized patients yielded a one-third reduction in thrombus as measured on venograms.\(^9\) However, this was achieved with a parallel 30 percent rate of major hemorrhage. It is apparent that in DVT management, we have not yet achieved an rt-PA regimen with satisfactory efficacy and safety.

Future studies will focus on administration of agents such as rt-PA given in boluses or given in bursts, separated by heparin therapy. In addition, the use of venography is rapidly becoming outmoded as an end point in DVT trials because venous ultrasound has proved to be accurate and suitable for repeated follow-up studies.\(^9\) With respect to long-term clinical improvement, the rate of chronic venous insufficiency should be assessed in future DVT trials to determine whether it occurs less frequently among lysed patients (who presumably suffer less permanent damage to venous valves).

**Future Perspective**

In the 1990s, expensive and potentially risky therapy for diseases that are considered, rightly or wrongly, to be relatively benign will not gain widespread application unless sufficient time and resources are invested in properly designed and conducted clinical trials. Previous surveys have indicated that about half of patients with PE use and approximately one-fifth of patients with DVT have no major contraindications to thrombolytic therapy. The challenge for this decade is to plan and undertake carefully conceived trials to determine what proportion of those VTE patients who are eligible for thrombolysis will benefit from this treatment. For MI patients, two decades of research were necessary before routine thrombolysis became accepted as standard care. For VTE patients, we should try to determine definitively the role of thrombolysis during the current decade so that this issue, addressed in the 1960s when the Urokinase Pulmonary Embolism Trial\(^7\) was designed, does not hover over us for another generation.

**References**


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**MAJOR BLEEDING COMPLICATIONS: 3 RANDOMIZED TRIALS**

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**Figure 6.** An overview of three trials of SK vs heparin (three of the trials in Figure 5 provided inadequate information on bleeding complications) for acute DVT indicates an overall 2.9 increase in the major bleeding rate (heavy vertical line) for SK compared with heparin. A risk ratio greater than 1 indicates more major bleeding complications associated with SK than with heparin. The pooled risk ratio is statistically significant (p = 0.04), but the 95 percent confidence limits are wide, reflecting the small sample size among the individual trials. (From Brown WD, et al. Chest 1989; 95:765-785. Reproduced by permission).


5 Tiefenbrunn AJ, Ludbrook PA. Coronary thrombolysis: it’s worth the risk. JAMA 1989; 261:2107-08


