

# ALTEPLASE vs. RETEPLASE: Comparative Results with Dose Ranging Protocols in 200 Patients

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# ALTEPLASE vs. RETEPLASE

## Introduction

- **Most of the controlled data compares UK vs Surgery**
  - Catheter directed thrombolysis accepted method of treatment over surgery for acute ischemia
- **UK became mainstay of lytic therapy**
- **Results of thrombolysis**
  - Predictable outcomes
  - Excellent safety profile---Low ICH rate  $\approx 0-2.1\%$
  - 24-72 hour infusions
  - Amputation-free survival  $\approx 83-90\%$  @ 30d
  - Major hemorrhage rates  $\approx 11-23\%$
  - Facilitated adjunctive percutaneous interventions
  - Lesser surgical interventions

(Topas I & II, Rochester, STILE, & PURPOSE)

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# ALTEPLASE vs. RETEPLASE

## Introduction

- **Late '98 FDA suspends sales of UK**
- **Lytic agents available in the US**
  - **Streptokinase - Streptase®**, SK
  - **Alteplase - Activase®**, rt-PA
  - **Reteplase - Retavase®**, r-PA
  - **Anistreplase - Eminase®**, APSAC
  - **Tenecteplase - TNKase™**, TNK-tPA
- **STILE trial reports equivalent efficacy and safety of rt-PA and UK**

# ALTEPLASE vs. RETEPLASE

## Methods & Materials

- 200 Pts divided into 5 groups

- rt – PA      70 Pts      1.5mg/hr      (PTT 40 – 60)
- rt – PA      29 Pts      0.5mg/hr      (400 – 500 U/hr heparin)
- r – PA      30 Pts      0.5 U/hr      (400 – 500 U/hr heparin)
- r – PA      37 Pts      0.25U/hr      (400 – 500 U/hr heparin)
- r – PA      34 Pts      0.125U/hr      (400– 500 U/hr heparin)

# ALTEPLASE vs. RETEPLASE

## Methods & Materials

### Similarities

- All lower extremity only
- All Hx of acute & subacute symptoms
- All single or coaxial catheter
- If clot not penetrated, end-hole cath used
- Attempts at angiographically documenting lysis progression in early AM and late PM

# ALTEPLASE vs. RETEPLASE

## Methods & Materials

### Differences

- Both rt-PA groups were retrospective chart reviews
- All r-PA groups were IRB sponsored and prospective, non-randomized evaluating 3 decreasing dosing regimens in chronological order
- Only first rt- PA (high dose) received therapeutic anticoagulation no clear conclusions.

*Semba et al. SCVIR advisor panel, JVIR*

# ALTEPLASE vs. RETEPLASE

## Methods & Materials

### Definitions

- Success rate:  
≥ 95% thrombolysis with return of antegrade flow
- Major bleeding complication:  
Any hemorrhage leading to surgical, extended hospitalization or transfusion (modified TIMI, PURPOSE)

# ALTEPLASE vs. RETEPLASE

## Methods & Materials

### *rt-PA High Dose*

- **70 pts with 74 limbs**
- **Technique**
  - **Similar to UK protocol**
  - **Initial 10 pt treated at 3-6 mg/hr**
  - **Subsequent patients tx @ 1.5 mg/hr ( $\approx 86\%$ )**

# ALTEPLASE vs. RETEPLASE

## Methods & Materials

### rt-PA High Dose

- **Technique**
  - **Infusion preparation**
    - **50 mg rt-PA in 1 L NS**
    - **Concentration =.05 mg/ml**
    - **Infuse at 30 ml/hr (1.5 mg/hr)**
  - **Systemic heparinization used - ≈PTT 40-60**

# ALTEPLASE vs. RETEPLASE

## Methods & Materials

### *rt-PA Low Dose*

- **29 pts with 29 limbs**
- **Similar technique except;**
  - **Decreased dose rate 0.5 mg/hr ( > 93% )**
    - \***Only 2 patients > .5 <1.5mg/hr**
  - **Decreased heparin dose (400 - 500 U/hr)**

# ALTEPLASE vs. RETEPLASE

## Methods & Materials

### *r-PA*

- IRB to prospectively collect data
- Prospective non-randomized study evaluating decreasing dosing regimens

# ALTEPLASE vs. RETEPLASE

## Methods & Materials

### r-PA

- Retavase prepared as:
  - 10 units in 250cc NS or (.04 u/ml),
  - more recently 4 units in 200cc NS (.02 u/ml)
- Allowed infusion protocols
  - 0.125 u/hr (3.125 cc/hr)
  - 0.25 u/hr (6.25 cc/hr)
  - .50 u/hr (12.5 cc/hr)
  - 1.00 u/hr (25.00 cc/hr)
  - 1.50 u/hr (37.5 cc/hr)

# ALTEPLASE vs. RETEPLASE

## Methods & Materials

*r-PA*

**30 pts**

**37 pts**

**34 pts**

**0.5u/hr**

**0.25u/hr**

**0.125u/hr**

# ALTEPLASE vs. RETEPLASE

## Results

### Patient Characteristics

	70	29	30	37	34
Patients (n)	70	29	30	37	34
Dose	>1.5	<1.5	.5	.25	.125
Mean Age (yr)	66.4 (40-100)	67.51±10.21	69.47±12.16	66.41±13.53	67.15±10.21
Male	35 (50%)	14 (48%)	14 (47%)	19 (51%)	20 (59%)
Female	35 (50%)	15 (52%)	16 (53%)	18 (49%)	14 (41%)
Comorbidities					
Smoking	48 (69%)	19 (65%)	20 (67%)	23 (62%)	20 (58.8%)
Coronary Artery Disease	23 (33%)	9 (31%)	14 (47%)	15 (40.5%)	5 (14.7%)
CHF	5 (7%)	2 (6.8)	4 (13%)	3 (8.1%)	1 (2.9%)
Arrhythmias	10 (14%)	3 (10.%)	5 (17%)	2 (5.4%)	2 (5.9%)
Hypertension	42 (60%)	16 (55%)	20 (67%)	19 (51.4)	16 (47.1%)
Hypercholesterolemia	27 (37%)	10 (34.5%)	11 (37%)	8 (21.6)	11 (32.4%)
Diabetes	18 (26%)	7 (24%)	8 (37%)	7 (18.9)	11 (32.4%)
TIA	3 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
COPD	12 (17%)	4 (14%)	4 (13%)	5 (13.5%)	4 (11.8%)

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# ALTEPLASE vs. RETEPLASE

## Results

## Occlusion Characteristics

Patients (n)	70	29	30	37	34
Dose	>1.5	<1.5	.5	.25	.125
Native Artery	32 (43%)	12 (41%)	10 (33%)	17 (46%)	13 (38%)
Bypass Graft	42 (57%)	17 (59%)	20 (67%)	20 (54%)	21 (62%)
Synthetic Vein	32 (43%)	12 (42%)	17 (85%)	17 (85%)	15 (71%)
Composite	2 (3%)	2 (7%)	1 (5%)	0 (0%)	6 (29%)
Thrombus	8 (11%)	3 (10%)	2 (10%)	3 (15%)	0 (0%)
Embolus	62 (84%)	25 (86%)	29 (97%)	37 (97%)	33 (97%)
Duration of Symptoms (Days)	12 (16%)	4 (14%)	1 (5%)	0 (0%)	1 (3%)
SVS/ISCVS Class	11.94±9.6	10.8±7.01	8.44±8.03	14.06±21	16.9±23.6
I	41 (58.6%)	18 (62%)	63%	81%	79%
II a	16 (22.9%)	7 (24%)	20%	14%	20%
II b	13 (18.6%)	4 (14%)	17%	5%	0%

# ALTEPLASE vs. RETEPLASE

## Results

rt - PA

	1.5 mg/hr	0.5mg/hr
<b>Total infusion time(hrs)</b>	<b>27.9</b>	<b>35.9</b>
<b>Total dose (mg)</b>	<b>38.7</b>	<b>21.0</b>

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# ALTEPLASE vs. RETEPLASE

## Results

*rt - PA*

**Success Rate**

**1.5mg/hr**

**86%**

**0.5mg/hr**

**87%**

# ALTEPLASE vs. RETEPLASE

## Results

*rt-PA*

### Major Bleeding Complication

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Dose	1.5mg/hr	0.5mg/hr	p value
Major	27%	10%	< 0.05
Transfusion	21%	10%	< 0.05

# ALTEPLASE vs. RETEPLASE

## Results

r-PA

<u>Dose</u>	<u>0.5u/hr</u>	<u>0.25u/hr</u>	<u>0.125u/hr</u>
Total infusion time (hrs)	28.4 (±14.5)	30.7 (±11.5)	42.1* (±21.7)
Total r-PA Used (u)	14.2 ** (±7.5)	9.2 (±6.2)	6.0 (±3.0)

\* $p < .001$ , \*\* $p < .001$

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# ALTEPLASE vs. RETEPLASE

## Results

*r-PA*

**Success Rate**

**0.5u/hr**

**0.25u/hr**

**0.125u/hr**

**86.7% (26/30)**

**83.8% (31/37)**

**85.3% (29/34)**

# ALTEPLASE vs. RETEPLASE

## Results

*r-PA*

### Major Bleeding Complications

Dose	0.50u/hr	0.25u/hr	0.125u/hr
Major	n=4 (13%)	n=2 (5%)	n=1 (3%)
ICH	n=1 (3%)	n=0 (0%)	n=0 (0%)

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## Results

### Fibrinogen levels

<b>Dose</b>	<b>0.5u/hr</b>	<b>0.25u/hr</b>	<b>0.125u/hr</b>
<b>Fibrinogen Pre</b>	<b>362.93</b>	<b>367.51</b>	<b>393.81</b>
	(± 168.83)	(± 172.13)	(±162.33)
<b>Fibrinogen Post</b>	<b>337.66</b>	<b>346.15</b>	<b>358.54</b>
	(± 159.0)	(± 144.68)	(± 159.68)
<b>Fibrinogen nadir</b>	<b>268.97</b>	<b>281.41</b>	<b>310.81</b>
	(± 149.49)	(± 141.66)	(± 179.56)

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# ALTEPLASE vs. RETEPLASE

## Results Summary

Agent	rt-PA (1.5 mg/ hr)	rt-PA (0.5 mg/ hr)	r-PA (.5U/hr)	r-PA (.25U/hr)	r-PA (.125U/hr)
Patients (n=200)	70	29	30	37	34
Duration of infusion (hr)	27.9	35.9+	28.4	30.7	42.1+
Total dose	38.7mg*	21.0mg	14.8u*	9.4u	6.0u
Duration of symptoms (d)	11.9	11.9	8.4	14.1	16.9

+P<0.05, \*P<0.001

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## Results Summary

Agent	rt-PA (1.5 mg/ hr)	rt-PA (0.5 mg/ hr)	r-PA (.5U/hr)	r-PA (.25U/hr)	r-PA (.125U/hr)
<b>Patients (n=200)</b>	<b>70</b>	<b>29</b>	<b>30</b>	<b>37</b>	<b>34</b>
<b>Lytic success</b>	<b>86%</b>	<b>87%</b>	<b>87%</b>	<b>84%</b>	<b>85%</b>
<b>Major bleeding</b>	<b>27%*</b>	<b>10%</b>	<b>13%</b>	<b>5%</b>	<b>3%</b>
<b>Transfusion</b>	<b>22%*</b>	<b>10%</b>	<b>13%</b>	<b>5%</b>	<b>3%</b>
<b>30-d AFS</b>	<b>93%</b>	<b>93%</b>	<b>87%</b>	<b>95%</b>	<b>94%</b>

\*  $P < 0.05$

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## Conclusions

- All dose groups are very similar (demographics and co morbidities)
- Success rate is similar for all groups
- Both alteplase and the 0.5 U/h reteplase groups are associated with higher major bleeding complications (27,10, & 13.3% vs 5.4 & 2.9%)
- The 0.5mg/h alteplase and the 0.125 U/h reteplase infusion times are  $\approx 1/3$  longer than other dose groups

# ALTEPLASE vs. RETEPLASE

## Conclusions

- The higher infusion time of the 0.125 group is:
  - NOT related to low infusion volume of lowest dose (3.2cc/hr first 16 pts. vs next 18 pts. ↑ to 6.4cc/hr)
  - NOT related to ↑ vein grafts ( 29% vs ≤ 5% others)

# ALTEPLASE vs. RETEPLASE

## Conclusions Summary

- We feel that Reteplase at 0.25 u/hr maximizes thrombolytic efficacy with an acceptable major bleeding rate (5.4%) ( $\leq$  half that of alteplase and higher reteplase doses).

# ALTEPLASE vs. RETEPLASE

## Conclusions Summary

- Existing data on these agents in the periphery poorly controlled to non-existent
- Need for well controlled comparative studies