

**Differentiating between lytic agents:
reintroducing urokinase**

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Current Thrombolytic Practices

- Late '98 Abbott withdraws UK from the market
- So life goes on and vessels keep clotting
- Lytic agents available in the US
 - Streptokinase - Streptase®, SK
 - Anistreplase - Eminase®, APSAC
 - Alteplase - Activase®, rt-PA
 - Reteplase - Retavase®, r-PA
 - Tenecteplase - TNKase™, TNK-tPA

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**Current Thrombolytic Practices:
rt-PA**

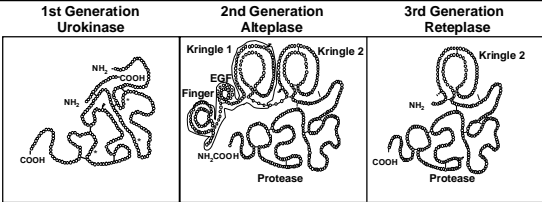
- STILE trial reports equivalent efficacy and safety of rt-PA and UK
- Most started with t-PA
- Use of r-PA emerged

– FDA approved for treatment of:

- AMI (IV); t-PA, r-PA
- PE (IV); t-PA
- Stroke (IV); t-PA

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Molecular Structures of Urokinase, Alteplase, and Reteplase



MW ~30,000 Native protein (glycosylated) 527 amino acids, MW 65,000 Mammalian cells (glycosylated) 355 amino acids, MW 39,000 *E. coli* (not glycosylated)

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Current Thrombolytic Practices: OSF Experience

Summary of OSF experience

Agent	rt-PA (>1.5 mg/hr)	rt-PA (<1.5 mg/hr)	r-PA (.5U/hr)	r-PA (.25U/hr)	r-PA (.125U/hr)
Patients (n=184)	70	29	30	37	34
Lytic success	86%	87%	87%	84%	85%
Major bleeding	27%*	10%	13%	5%	3%
Transfusion	22%*	10%	13%	5%	3%
30-d AFS	93%	93%	87%	95%	94%

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Current Thrombolytic Practices: OSF Experience

Summary of OSF experience

Agent	rt-PA (>1.5 mg/hr)	rt-PA (<1.5 mg/hr)	r-PA (.5U/hr)	r-PA (.25U/hr)	r-PA (.125U/hr)
Patients (n=179)	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

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Current Thrombolytic Practices: UK Returns

- **October 2002 UK reintroduced into market**
- **2000 Abbott renovates manufacturing facility**
- **2001 donor source within US**
 - Cells from neonates at least 27 weeks gestational age
 - Death between 0-28 days
 - Death from natural causes
 - Identified via national tissue banks
 - Enhanced screening of mother and donor
 - Screening specifications exceed FDA and AATB (American Assn. Tissue Banks)

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Current Thrombolytic Practices: Specific vs nonspecific agents

- **Is there a need for UK in our practice?**
- **Efficacy?**
- **Cost?**
- **Safety?- fibrin specific agents vs non-specific agents**
 - Anecdotal information
 - Past experience with UK
 - Narrow window of safety with specific agents, i.e. ↑ dosing, heparin use
 - Scientific information

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Current Thrombolytic Practices: Specific vs nonspecific agents

- Few studies directly comparing the safety and efficacy of UK and rt-PA
- Additionally, the highest incidences of complications have been seen with rt-PA over UK
 - Major hemorrhage
 - Highest with UK in any study was 24% (Korn)
 - rt-PA major hemorrhage was as high as 46% (Cina, McNamara)
 - ICH Bleeding
 - Highest with UK was 4% (Neudeck)
 - Highest with rt-PA was 9% (Ward)

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Current Thrombolytic Practices: Specific vs nonspecific agents

- Cina CS, et al. J Vasc Surg 1999;13:571-575
- 58 limbs; 34 UK and 24 rt-PA
- UK 150,000 U bolus then 50,000 U/hr
- rt-PA 5 mg bolus then 1 mg/hr
 - 1mg remains in the range of current dosing regimens
- Lysis 79% UK vs 75% rt-PA
- Major hemorrhage 9% UK vs 46% rt-PA (p = 0.0018)
- ICH 0.0% UK vs 4.2% rt-PA

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Current Thrombolytic Practices: Specific vs nonspecific agents

- Ouriel K, et al. JVIR 2000
- 527 limbs for PAO; 404 UK, rt-PA 132
- Average dosing
 - UK: 4,000 IU/min
 - rt-PA: .05 to .1 mg/kg/hr
- ICH: 0.6% UK vs 2.8% TPA (p=0.03)
- Hematoma: 21.9% UK vs 43.8% (p<0.0001)
- Transfusions: 12.4% UK vs 22.2% (p=0.004)
- Major Complications: 1.5% UK vs 4.92% rt-PA (p=0.15)
- Mortality: 2.7% UK vs 6.2% rt-PA (p=0.2)

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Current Thrombolytic Practices: Specific vs nonspecific agents

- Mahler, et al. J Endovasc Ther 2001; 8:633

	rt-PA (124; 2.5mg/hr)	UK (110; 100,000 IU/hr)
Hematoma	9.6%	7.3%
Bleeding	2.4%	1.8%
ICH	0.8%	0.0%
Total:	12.8%	9.1%

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Current Thrombolytic Practices: Specific vs nonspecific agents

Study	Agent/Total Infusion	Technical Success	Major Bleeding	ICH
Graor et al (1993)	UK 2 MM IU (n=22)	86%	9%	0%
	rt-PA 30mg (n=23)	91%	18%	0%
Schweizer et al (1996)	UK 4 MM IU (n=60)	86%	0%	0%
	rt-PA 25 mg (n=60)	85%	15%	0%
STILE (1994)	UK 5.5 MM IU (n=112)	49%	6%	0.9%
	rt-PA 45mg (n=137)	59%	6%	1.2%

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Current Thrombolytic Practices: Specific vs nonspecific agents

- **Bleeding remains most common major complication despite;**
 - increased specificity/ affinity (rt-PA, r-PA)
 - shorter half-life (rt-PA)
- **Why?**
- **Are fibrin specific agents simply causing plasminogen activation at distant thrombus (fibrinolysis)?**

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Current Thrombolytic Practices: Specific vs nonspecific agents

- **Not likely**
- **Likely that fibrinogenolysis plays a role**
 - Fibrinogenolysis primarily responsible for bleeding (TIMI, phase I & II)
 - STILE trial, hemorrhage rates- UK = rt-PA
 - Bleeding related to fibrinogen depletion
 - Fibrinogen levels in patients with hemorrhage was 188 mg/dl versus 310 mg/dl in those without hemorrhage

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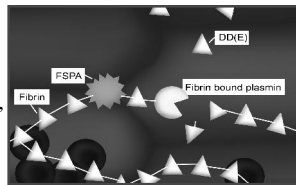
Current Thrombolytic Practices: Specific vs nonspecific agents

- How do fibrin specific drugs cause fibrinogenolysis?
 - rt-PA 400-1000 times more likely to convert plasminogen to plasmin when fibrin bound (fibrinolysis) vs when freely circulating (fibrinogenolysis)

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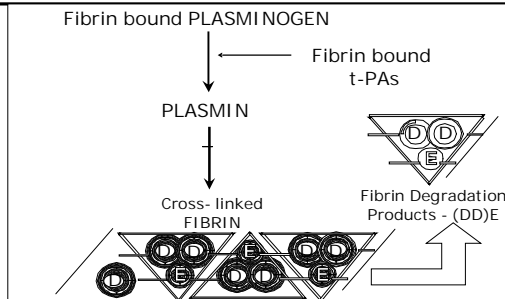
Current Thrombolytic Practices: Fibrinolysis

- **Fibrinolysis**
- Fibrin-bound plasmin degrades cross-linked fibrin into multiple soluble fibrin degradation products (FDPs), primarily (DD)E
- (DD)Es enter systemic circulation



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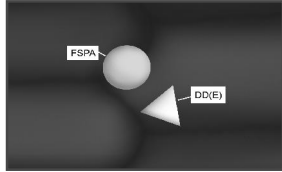
Current Thrombolytic Practices: Fibrinolysis



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Current Thrombolytic Practices: Path To Fibrinogenolysis

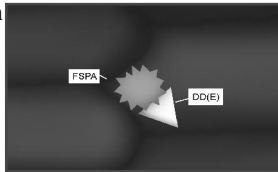
- Fibrin specific plasminogen activator (FSPA) actively binds to circulating (DD)E with an affinity comparable to its affinity for fibrin



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Current Thrombolytic Practices: Path To Fibrinogenolysis

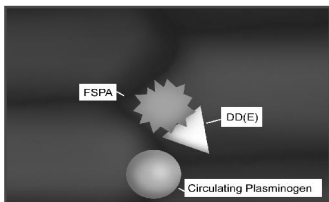
- FSPA binds to (DD)E, undergoes conformational change and is 350X more active in the conversion of plasminogen to plasmin
- Specificity of FSPA to (DD)E equal to that of fibrin



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Current Thrombolytic Practices: Path To Fibrinogenolysis

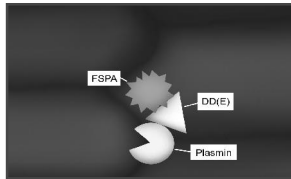
- Circulating plasminogen binds to (DD)E with equal affinity as for fibrin



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Current Thrombolytic Practices: Path To Fibrinogenolysis

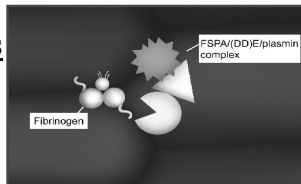
- (DD)E bound plasminogen is converted to plasmin by (DD)E bound FSPA
- Forms circulating FSPA/ (DD)E /Plasmin complex



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Current Thrombolytic Practices: Fibrinogenolysis

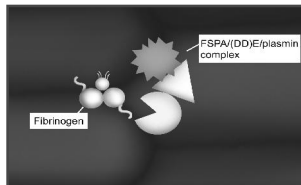
- Circulating FSPA/ (DD)E /Plasmin complex degrades circulating fibrinogen
- So begins **Fibrinogenolysis**



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Current Thrombolytic Practices: Fibrinogenolysis

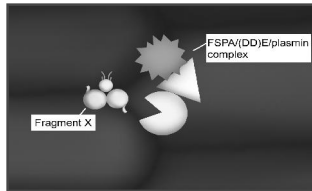
- **How does fibrinogenolysis lead to distant bleeding?**



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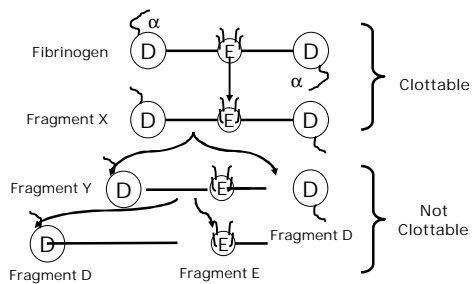
Current Thrombolytic Practices: Fibrinogenolysis

- First step in fibrinogenolysis is Fragment X formation

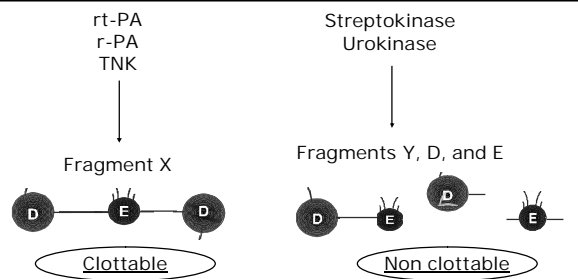


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Plasmin-Mediated Fibrinogenolysis

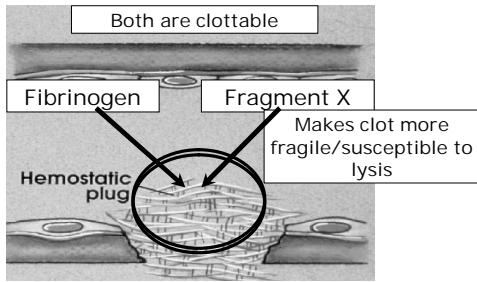


Current Thrombolytic Practices: Specific vs nonspecific agents



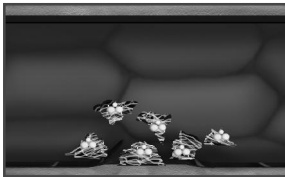
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Current Thrombolytic Practices: Specific vs nonspecific agents



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Significance of Fragment X



- Fragment X promotes lysis¹
- *In Vivo* data suggests Fragment X linked to remote bleeding²
- Fragment X in plasma at 24 hours¹
- Accumulation of Fragment X may lead to unpredictable bleeding episodes, including late bleeding

1. Owen J, et al. *J Clin Invest.* 1987;79:1642-1647

2. Weitz JL, *J Vasc Interv Radiol.* 1995;6(6 Pt 2 Su):19S-23S

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Current Thrombolytic Practices: Specific vs nonspecific agents

Agent	Fibrin	(DD)E	Fibrinogen
rt-PA	Finger + Kringle 2	Kringle 2	Kringle 2
r-PA	Kringle 2	Kringle 2	Kringle 2
Tenecteplase	Finger + Kringle 2	Kringle 2	Kringle 2
Streptokinase/ Urokinase	—	—	—

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Current Thrombolytic Practices: Specific vs nonspecific agents

- Although more specific than UK and SK, not specific enough to prevent fibrinogenolysis
- Yet specific enough to promote Fragment X accumulation
- Intermediate fibrin specificity responsible for apparent paradoxical bleeding complications

1. Weitz et al. J Clin Invest 1991; 87:1082-1090
2. Weitz et al. J Clin Invest 1993; 91:1243-1350
3. Weitz et al. JVir 1996; 6:188-238

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Current Thrombolytic Practices: Specific vs nonspecific agents

- Although shorter 1/2 life than UK;
 - In thrombus, fibrin protects plasmin from alpha 2-antiplasmin
 - ↑ affinity promotes lytic environment
 - Animal and clinical data confirm delayed and durable systemic lytic effect with rt-PA compared to UK

Agnelli et al. Blood 1985;66:399-401
Verstraete et al. J Pharmacol Exp Ther 1985;2:506-512
Agnelli et al. Chest 1990; 97:1615-1675

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Current Thrombolytic Practices: OSF IR meets Pharmacy

- Strategy to re-establish UK on formulary
 - Partner consensus
 - Use in selected patients
 - High risk of bleeding
 - Elderly > 80 yrs. of age
 - Recent GI bleed (within 2 weeks)
 - Recent surgery/intervention
 - Recent CVA (within previous 3 months)

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Current Thrombolytic Practices: OSF IR meets Pharmacy

- Strategy to re-establish UK on formulary
 - Desire to use full anticoagulation
 - Severe limb ischemia (\geq SVS IIb)
 - Distal/small vessels
 - Upper extremity lysis
 - Hypercoagulable state

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Thrombolysis in Interventional Radiology

- Conclusions
 - Thrombolysis remains mainstay for the Tx of acute peripheral arterial occlusion
 - Newer agents are different than UK
 - Bleeding remains the most significant complication even with more fibrin specific agents
 - Fibrin-specific drugs not specific enough to prevent fibrinogenolysis

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Thrombolysis in Interventional Radiology

- Conclusions
 - But specific enough to produce fragment X accumulation
 - Existing data on agents other than UK in the periphery poorly controlled to very limited
 - Need for well controlled comparative studies
 - Until then forced to “connect the dots” to create a picture of safety

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