Thrombolysis for DVT
Nobody likes it
Confession

I use it all the time
DVT BLOOD CLOTS AFFECT UP TO 900,000 AMERICANS EACH YEAR¹
Prevalence of clinical venous thromboembolism in the USA

Deitelzweig SB, Johnson BH, Lin J, Schulman KL.
Ochsner Clinic Foundation

• Retrospective analysis of commercial and Medicare databases, 2002 through 2006
• 12.7 million study eligible; 200,007 with VTE. Overall prevalence increased by 33% during the study period.
• Total number of VTE cases projected to rise from 950,000 to 1,820,000 by 2050.
• Number of deaths related to Pulmonary embolism estimated at between 50 - 200,000 per year.

Kumar et al. Basic Pathology 2010
DVT
Tissue plasminogen Activator - tPA

• Endogenous protease released into the blood by endothelial cells, and also produced by tissues in many parts of the body (brain, lungs, liver, ...)

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![Tissue plasminogen Activator - tPA](image-url)
Tissue plasminogen Activator

- MOA – Direct plasminogen activator with a high affinity for fibrin bound thrombus
- Impairs platelet activation by inhibiting vWF and GP1b. **Not an anticoagulant.**
- ½ life 4-7 minutes
- Recommended dosage of 0.05 mg/kg/hr
- RCT showed no difference if efficacy when compared to other agents.
Recombinant t-PA (alteplase) binds to fibrin in thrombus, converts entrapped plasminogen to plasmin that initiates local fibrinolysis.
Tissue plasminogen Activator

- **Alteplase** — t-PA, a fibrin specific thrombolytic molecule, synthesized as a single chain polypeptide from a melanoma cell line.

- **Activase** — t-PA produced by recombinant DNA technology.
tPA - effects

- Can also affect permeability of the BBB via induction off MMP synthesis, leading to edema and hemorrhage
- Shown to have both neurotoxic, and neuroprotective apoptotic effects. Immature cells (developing brain) and oligodendrocytes appear most vulnerable.
- ...exogenous tPA was independently associated with seizure occurrence (a mechanism that involves tPA)\textsuperscript{101} and a worse outcome at 3 months in this seizure subgroup of patients.\textsuperscript{102}
Tissue plasminogen Activator - tPA

• tPA has multiple systemic effects, many of which are still poorly understood.
Direct Thrombolytic Agents

First generation

Not fibrin specific – can lead to a systemic fibrinolysis and increased bleeding. A decrease in systemic plasminogen and paradoxic impairment of clot lysis: **Plasminogen steal**

Second generation

Fibrin specific: Activate enzymatic conversion of fibrin complexed plasminogen, decreasing the risk of systemic fibrinolysis.
Direct Thrombolytic Agents

First generation
Streptokinase, Urokinase

Second generation
Alteplase, Recombinant t-PA

Third generation
Tenecteplase, Reteplase
Risk Factors and Contraindications to the use of thrombolytic agents

- Major Contraindications
  - Structural intracranial disease, h/o intracranial hemorrhage or ischemic stroke within 3 months
  - Active bleeding
  - Recent brain or spinal surgery
  - Recent head trauma with fracture or brain injury
  - Bleeding diathesis
- Relative contraindications
  - Systolic BP >180, Diastolic BP >110
  - Recent bleeding (non-intracranial), surgery or invasive procedure
  - Ischemic stroke more than 3 mo previously
  - Anti-coagulated (eg, VKA therapy)
  - Traumatic cardiopulmonary resuscitation, pericarditis or pericardial effusion
  - Diabetic retinopathy
  - Pregnancy
  - Age >75 y, low body weight (< 60 kg)
CONTRAINDICATIONS TO ALTEPLASE THERAPY

Pneumonic: SAMPLE STAGES

- **Stroke** or head trauma within the last 3 months.
- Anticoagulation with INR>1.7 or prolonged PTT.
- **MI** (recent).
- **Prior** Intracranial Haemorrhage.
- **Low** Platelet Count (<100,000/mm³)
- **Elevated** BP: Systolic>185 or Diastolic >110mmHg

- Surgery in the past 14 days.
- **TIA** (mild symptoms or rapid improvement of symptoms).
- **Age<18**
- GI or urinary bleeding in the past 21 days
- **Elevated** (>400mg/dl) or Decreased (<50mg/dl) Blood glucose.
- **Seizures** present at the onset of stroke.
Complications of lytic therapy

- Life-threatening hemorrhage
  - 7 - 45% incidence
  - Risk factors
    - Increased number of Invasive procedures during therapy
    - Increased duration of therapy
- Bleeding typically occurs in interval between cessation of lytic therapy and initiation of heparin
- Treatment
  - FFP, cryoprecipitate
Complications of systemic therapy
Complications of systemic therapy

• Intracranial hemorrhage
  – 1% incidence
  – Time to onset 3 – 36 hours
  – 66% mortality
  – Risk factors:
    • Advanced age
    • Low body weight
    • Anticoagulation tx prior to admission
    • Increased dose of lytic agent
Complications of catheter directed therapy
ACCP guidelines 2016

• In patients with acute proximal DVT of the leg, we suggest anticoagulant therapy alone over CDT (Grade 2C).

• Remarks: Patients who are most likely to benefit from CDT (see text), who attach a high value to prevention of postthrombotic syndrome (PTS), and a lower value to the initial complexity, cost, and risk of bleeding with CDT, are likely to choose CDT over anticoagulation alone.
• …37 patients (43%; 95% CI 33–53) allocated to catheter-directed thrombolysis developed post-thrombotic syndrome, compared with 63 (71%; 95% CI 61–79) allocated to the control group (p<0·0001), corresponding to an absolute risk reduction of 28% (95% CI 14–42) and a number needed to treat of 4 (95% CI 2–7). Four (5%) patients assigned to catheter-directed thrombolysis and one (1%) to standard treatment had severe post-thrombotic syndrome (Villalta score ≥15 or presence of an ulcer). Quality-of-life scores with either assessment scale did not differ between the treatment groups.
ATTRACT Trial

• NIH sponsored, prospective, multicenter randomized trial to determine if pharmacomechanical catheter directed therapy prevents the development of post-thrombotic syndrome over two years.
• No significant difference in primary (PTS) outcome (46.7 v 48.2).
• Higher incidence of major (1.7 v .3%) and minor (4.5 v 1.7%) bleeding complications when compared to control arm.
• “Pharmacomechanical catheter-directed thrombolysis does not prevent post-thrombotic syndrome, and does increase bleeding. The ATTRACT data suggest that most deep vein thrombosis patients can avoid an [adjunctive] unhelpful procedure...”
Restoration of Patency in Iliofemoral Deep Vein Thrombosis with Catheter-Directed Thrombolysis Does Not Always Prevent Post-Thrombotic Damage

Yang Jin Park, Joon Young Choi, Seung-Kee Min, Taeseung Lee, In Mok Jung, Jung Kee Chung, Jin Wook Chung, Jae Hyung Park, Sang Joon Kim, Jongwon Ha

- Retrospective review of 34 pts who underwent CDT
- 97% technical success rate; 68% complete, 29% partial thrombolysis
- 4 year f/u. 32% rethrombosis rate, 47% demonstrated post-phlebitic change.
- Stent patency at 3% 56.7%
- “Conclusion: Long-term results of CDT are not satisfactory because of the high recurrence rate of DVT and it cannot prevent chronic post-thrombotic damage to the affected vessels despite long-term anticoagulation therapy.”
Alternative forms of Thrombectomy

- Open Surgical thrombectomy
- Percutaneous/rheolytic thrombectomy

- Restoration of iliofemoral patency, and maximal clearance of thrombus are the most important goals in management of DVT.
Iliofemoral thrombectomy
Saline jets enclosed in catheter create strong vacuum at inflow windows.
Percutaneous mechanical thrombectomy

Femoral vein
RESULTS:
Initial technical success rate was 89.2% (66 patients). Stenting was performed in 55 patients. The failures were due to underlying chronic thrombi/DVT (n = 7) and stent failure due to huge pelvic mass (n = 1). There was no procedure-related complication. In the 26 midterm follow-up patients for a duration of 6-48 months, there was no recurrence (n = 20), stent occlusion (n = 3), or femoral vein occlusion (n = 3). One-year primary patency rate in stent/iliac vein, femoral vein, and popliteal/infrapopliteal vein were 88.5, 88.5, and 96.2%, respectively.

CONCLUSION:
Single-session aspiration thrombectomy for acute and subacute lower extremity DVT using large introducer catheters without pharmacologic thrombolysis is feasible with acceptable immediate and midterm results, excluding complications related to pharmacologic thrombolysis.
tPA -cost

- Price increased 111% between 2005 and 2014.
- 100 mg vial $6,400. (Estimated $8,300 currently)
- The base payment for tPA-treated stroke admissions was $11,173 in 2006, and $12,064 in 2013, an 8 percent increase, while the cost of tPA increased from 27 percent of the payment in 2006 to 53 percent in 2013.
- One half of the reimbursement dollars go for payment of the drug.
- ?
WALL STREET

“GREED IS GOOD.”
— Gordon Gekko
Conclusions

• tPA/pharmacologic thrombolysis is a very useful and often successful treatment modality in appropriately selected patients.

• Systemic effects not clearly understood.

• Complications, when they occur, can be devastating.

• As in life, everything in moderation = Less is more.
Thank you