อ.นพ.สงคราม โชติกอนุชิต

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Stroke Case Manager

โรงพยาบาลศิริราช

Recombinant tissue plasminogen activator (rt-PA)

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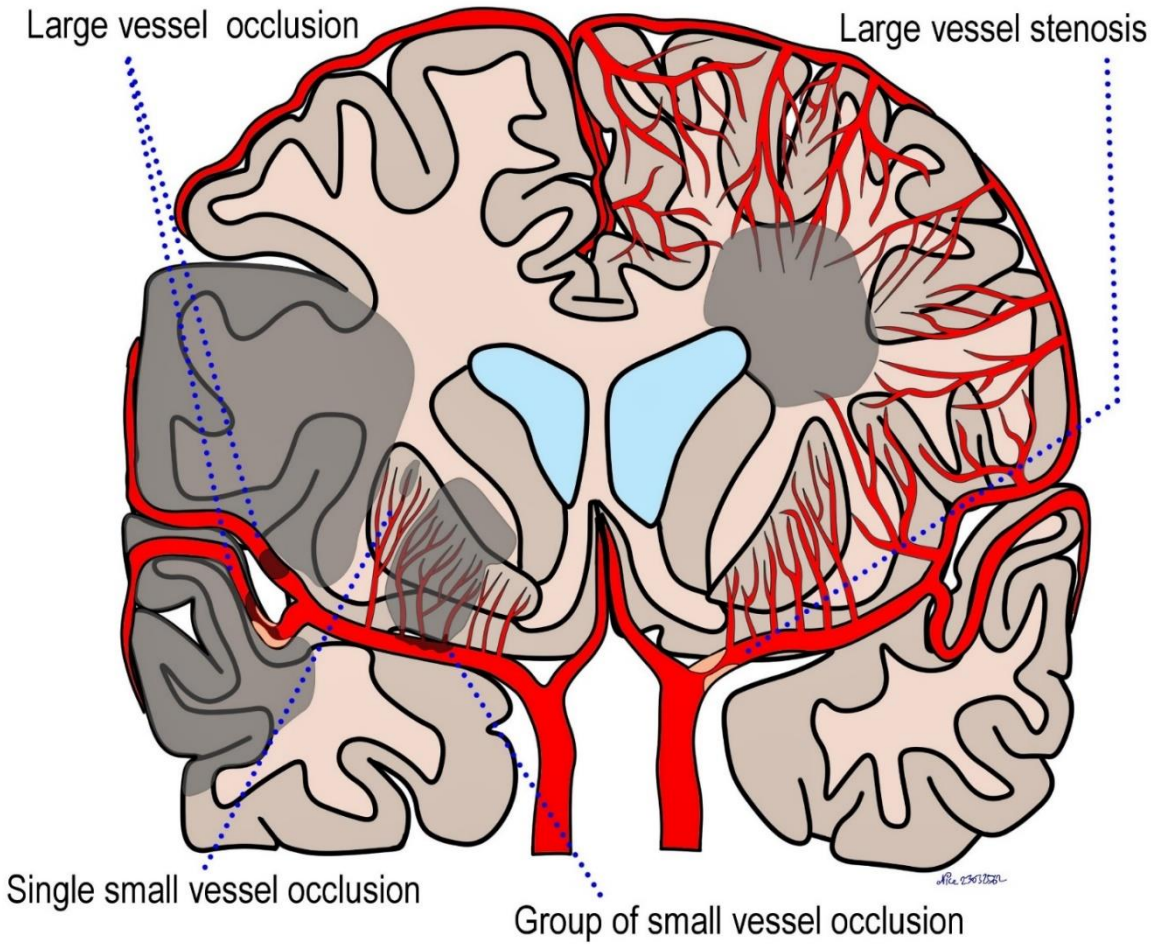
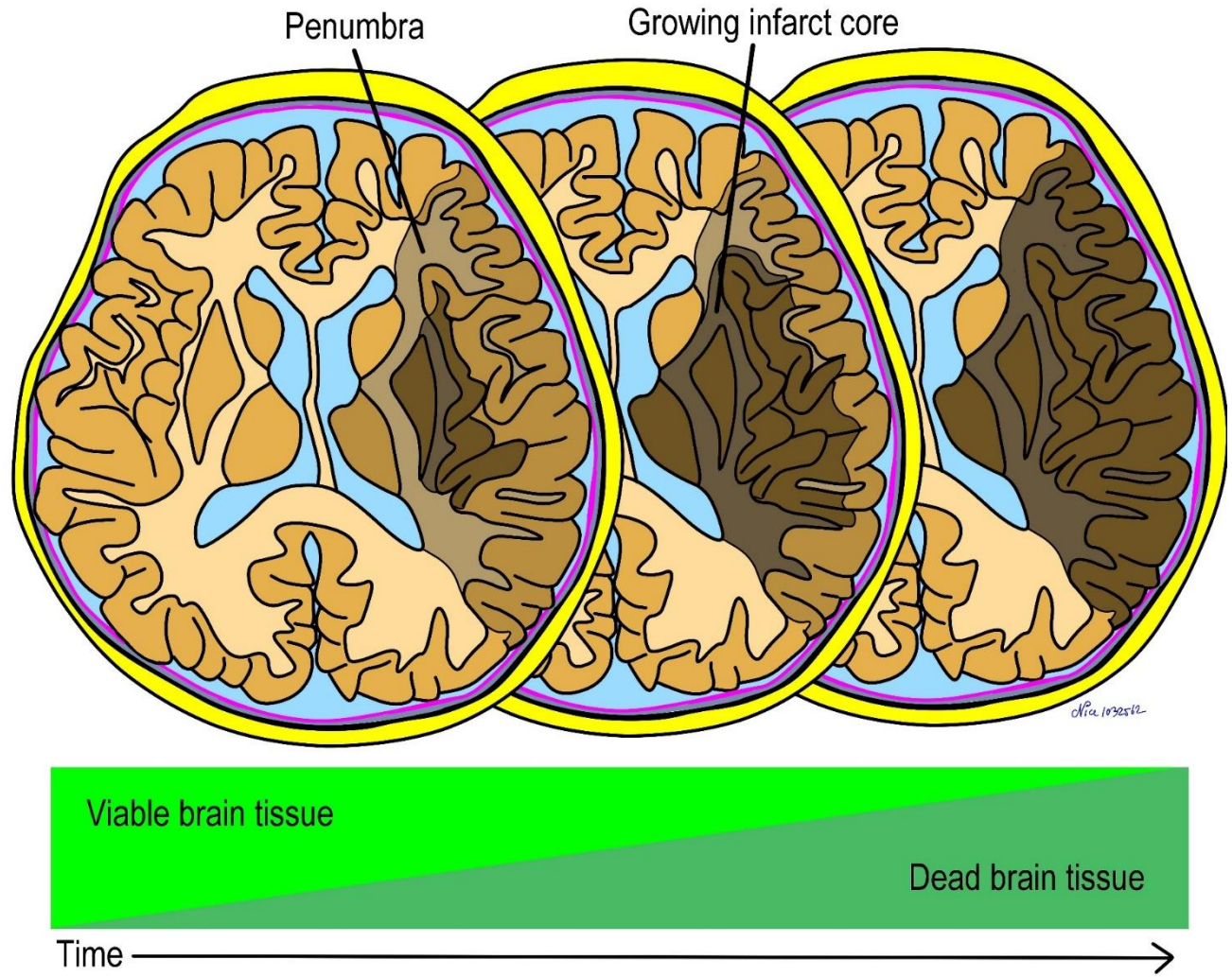
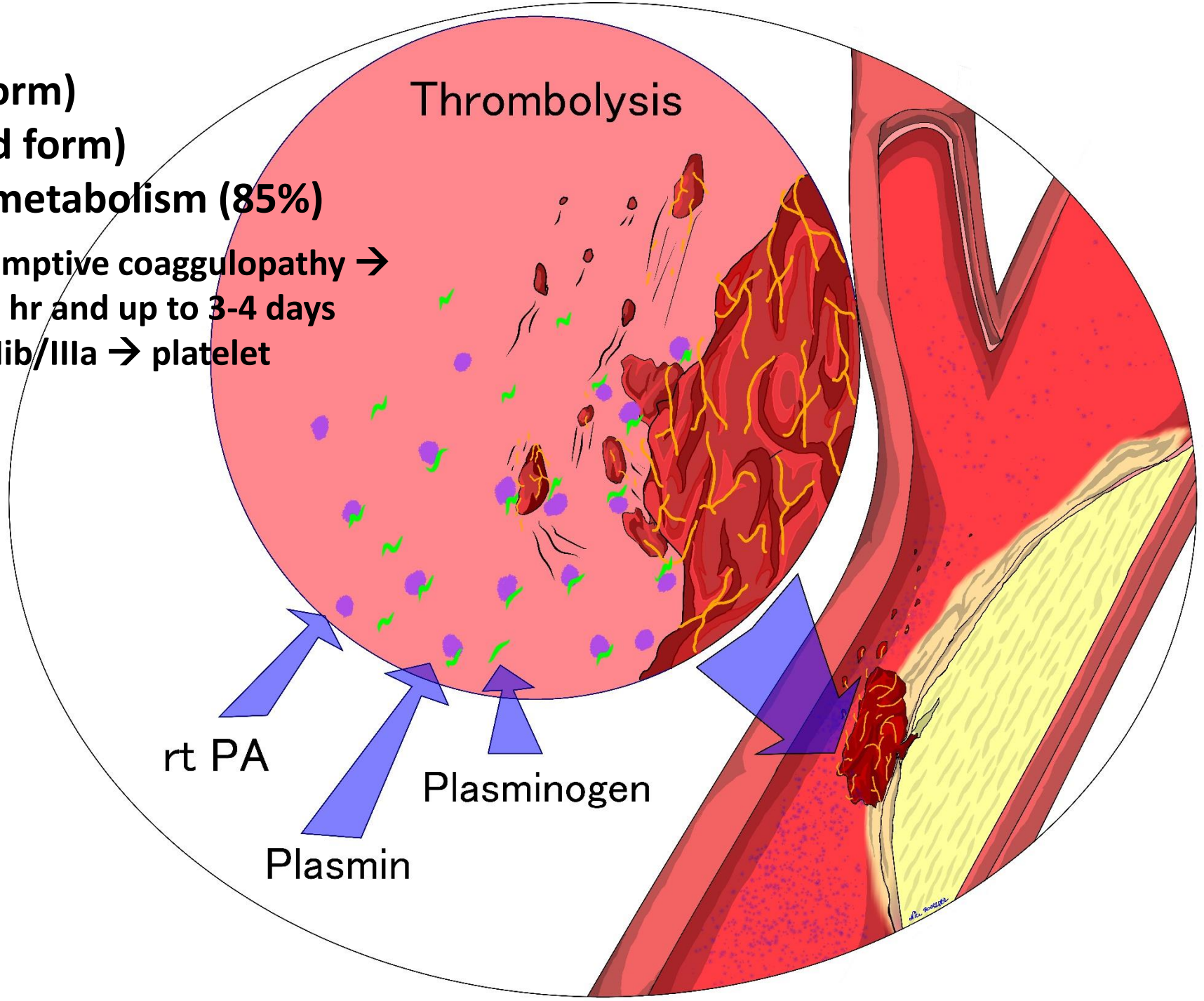
Patterns of ischemic stroke





- **Half life 5 minutes (free form)**
- **Half life 72 minute (bound form)**
- **Renal excretion, Hepatic metabolism (85%)**
- **Fribrinolytic activity and consumptive coaggulopathy → decrease fibrinogen level at 24 hr and up to 3-4 days**
- **?Increased in D-dimer and GP Iib/IIIa → platelet dysfunction?**
- **sICH 4-7%**
  - Dosage dependence
  - Older age
  - more NIHSS
    - 1.6% in NIHSS 5-10
    - 6.8% in HIHSS >21
  - more BS
  - more BP
  - Renal impairment
  - Visible brain infarct
  - Use of antiplatelets



Absolute and Relative Contraindications to IV rt-PA for Acute Ischemic

Jennifer E. Fugate, DO and Alejandro A. Rabinstein, MD. Stroke The Neurohospitalist 2015, Vol. 5(3) 110-121

Absolute contraindication

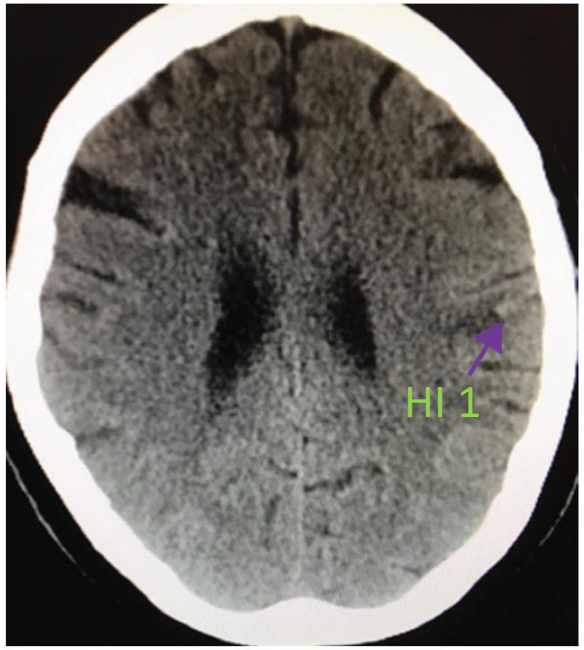
- Acute ICH including HI
- History of ICH (microbleed is not contraindicated)
- BPs >185 mmHg, BPd >110 mmHg (HTN my be correlated with sICH).
- Serious head trauma or stroke <3 months
- Thrombocytopenia (<100,000/mm3) and coagulopathy (PT >15, INR >1.7)
- LMWH within 24 hr (38% risk of sICH, 29% risk of death, 33% favorable outcomes, od 8.4 for sICH, od 5.3 for death)
- DTIs (TT is sensitive to the presence of DITs)
- Factor Xa inhibitor (may notice to their T1/2)
- Severe hypoglycemia (<50 mg/dl) and hyperglycemia (>400 mg/dl) may be permitted for IVT.
- Early radiographic ischemic changes (>1/3 MCA)

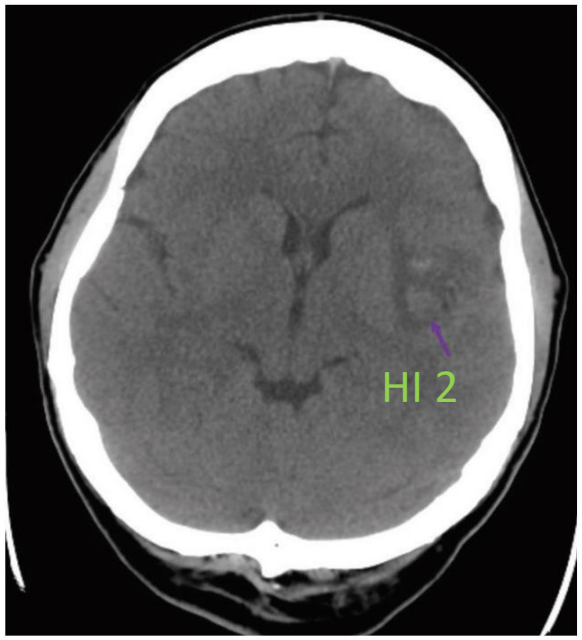
Relative contraindication

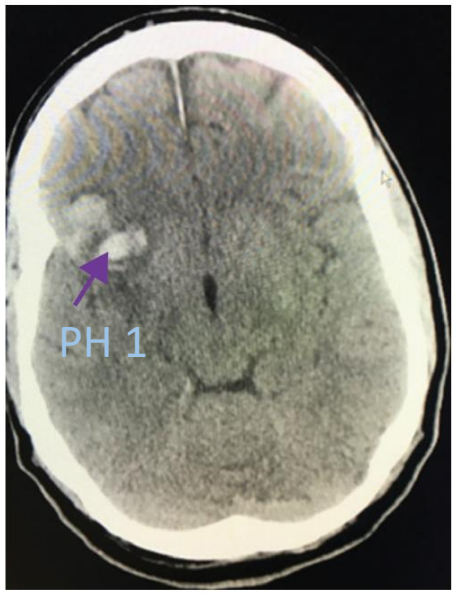
- Advanced age (>80 y) (ns for sICH compared with the younger)
- Mild or improving stroke (NIHSS<5)
- Severe stroke (IVT should be cautiously administer in NIHSS >25 at 3-4.5 hrs)
- Major surgery within 2 weeks (some 3 months)
- Arterial puncture of none compressible site
- Recent GIB or GUB within 3 weeks
- Seizure at onset
- Recent MI within 3 months
- Intracranial structure abnormality (axial tumor, AVM, aneurysm)
- Dementia

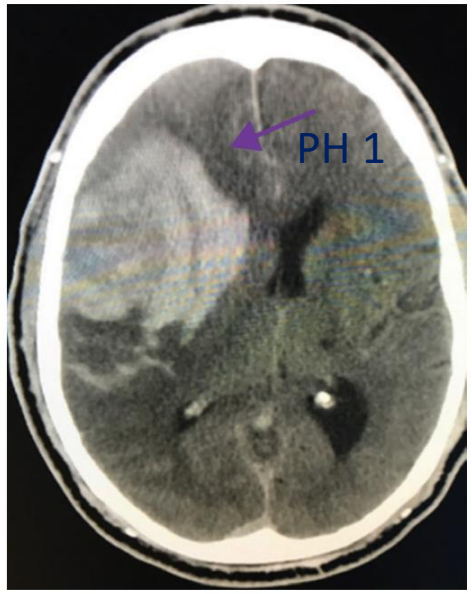
Treatment and Outcome of Hemorrhagic Transformation After Intravenous Alteplase in Acute Ischemic Stroke.

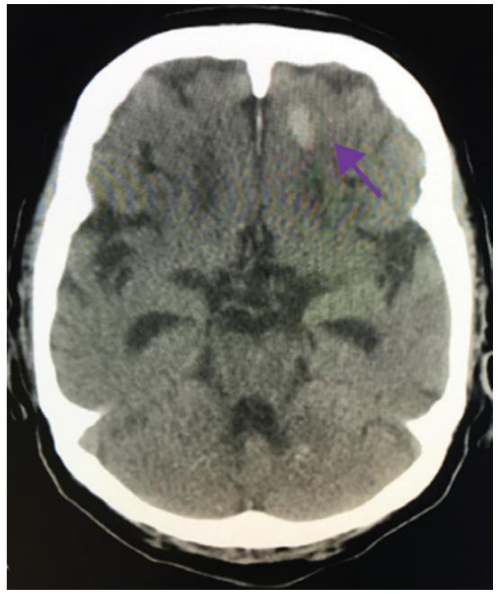
Stroke. 2017;48:e343–e61.











Risk of sICH

- Fibrinogen level <200 mg/dL at 2 hrs after infusion
- Reduction of fibrinogen level of 200 mg/dL or more within 6 hrs of rTPA
- Poor collateral circulation
- Blood brain barrier disruption (average 13 hrs after onset)
- Hyperglycemia
- Usage of antiplatelet prior to thrombolysis may increase the risk of conversion of asICH to sICH

Timing of sICH

- 85-90% sICH occurred within 24 hrs
- At >36 hrs sICH it may be unlikely to be thrombolysis related sICH
- Timing of sICH was 5-10 hr after thrombolysis, (median time 8 hrs)
- NHSS and VS monitoring q15 x 2 hrs, q30 x 6 hrs, q60 x 16 hrs

Reversal of Vitamin K Antagonist Therapy Before Thrombolysis for Acute Ischemic Stroke.

Nicolas Chausson, MD, PhD; Djibril Soumah, MD; Manvel Aghasaryan, MD; Tony Altarcha, MD; Cosmin Alecu, MD, PhD; Didier Smadja, MD. Stroke. 2018;49:2526-2528

Inclusion:

- AIS patient with INR >1.7
- Eligible for iv thrombolysis

Method:

- 4F-PCC (Kanokad) and >1hr iv dripping of Vit K were initiated.
- iv thrombolysis was immediately administered.
- INR level was measured at 5 min, 4-6 hrs and 24 hrs after 4F-PCC infusion.
- PT INR >1.7 reversal procedure was repeated.

Outcomes:

sICH, mortality, arterial occlusion and DVT at 72 hrs

Result:

- No sICH or systemic thrombotic complications were detected.
- No new cerebral artery infarction was seen in imaging.

	Value (n=26)
Age	77.8+/-12.8
AF	84.6%
NIHSS	11.6+/-5.6
MCA (M1,M2)	16/26
Initial INR	2.3+/-0.6
Onset-treatment	238+/-70 min (n24)
Death	11.5%
mRS 0-2 (90 days)	65.1%
Recurrent stroke (30 days)	7.7% (compare with 5-8% d14)
HI 1/ HI 2	7.7% / 26.9%
Major systemic bleeding	3.8%

Use of Intravenous Recombinant Tissue Plasminogen Activator in Patients With Acute Ischemic Stroke Who Take Non–Vitamin K Antagonist Oral Anticoagulants Before

Stroke Circulation. 2017;135:1024–35.

- From the American Heart Association Get With The Guidelines-Stroke Registry
- Ischemic stroke patients who received NOACs or warfarin (INR <1.7) or not on anticoagulation (1289 registry hospitals sine October 2012 to March 2015).

	NOACs (251)	VKA (1,500)	None (41,136)	P
Median age	74	79	71	<0.001
AF/Af	78%	77.3%	18.1%	<0.001
Prior stroke/TIA	30.7%	36.0%	25.6%	<0.001
Dabigartran	34.7%	-	-	
Apixaban	13.9%	-	-	
Rivaroxaban	51.4%	-	-	
VKA	-	100%	-	
Antiplatelets	30.3%	27.1%	47.8%	<0.001
INR	1.0-1.2	1.1-1.4	1.0-1.1	<0.001
O-D(min)	60(37-90)	56(37-85)	60(40-94)	<0.001
D-N(min)	65(50-88)	69(54-91)	61(47-83)	<0.001
NIHSS	*12(6-18)*	*13(7-19)*	9(5-15)	<0.001

	None	NOAC (OD)	VKA (OD)
sICH <36hrs	3.9%	*4.8% (ns)*	*4.9% (ns)*
Any fetal bleeding	0.8%	*0.4% (ns)*	0.9% (ns)
mRS 0-1 (at D/C)	29.3%	*24.0% (ns)*	*17.7% (s)*
mRS 0-2 (at D/C)	39.1%	*31.2% (ns)*	*25.8% (ns)*
Independent (at D/C)	49.3%	46.1% (ns)	*33.3% (ns)*
Inhospital death	6.3%	*4.8% (ns)*	*4.9% (ns)*

- rt-PA is contraindicated in patients taking NOACs, unless time since last intake is >48 hours or sensitive laboratory tests are normal (AHA/ASA guidelines)
- T1/2 : dabigatran (12–14 hours), rivaroxaban (5–9 hours), apixaban (12 hours), normal coagulation may be expected 24 hours after last intake.

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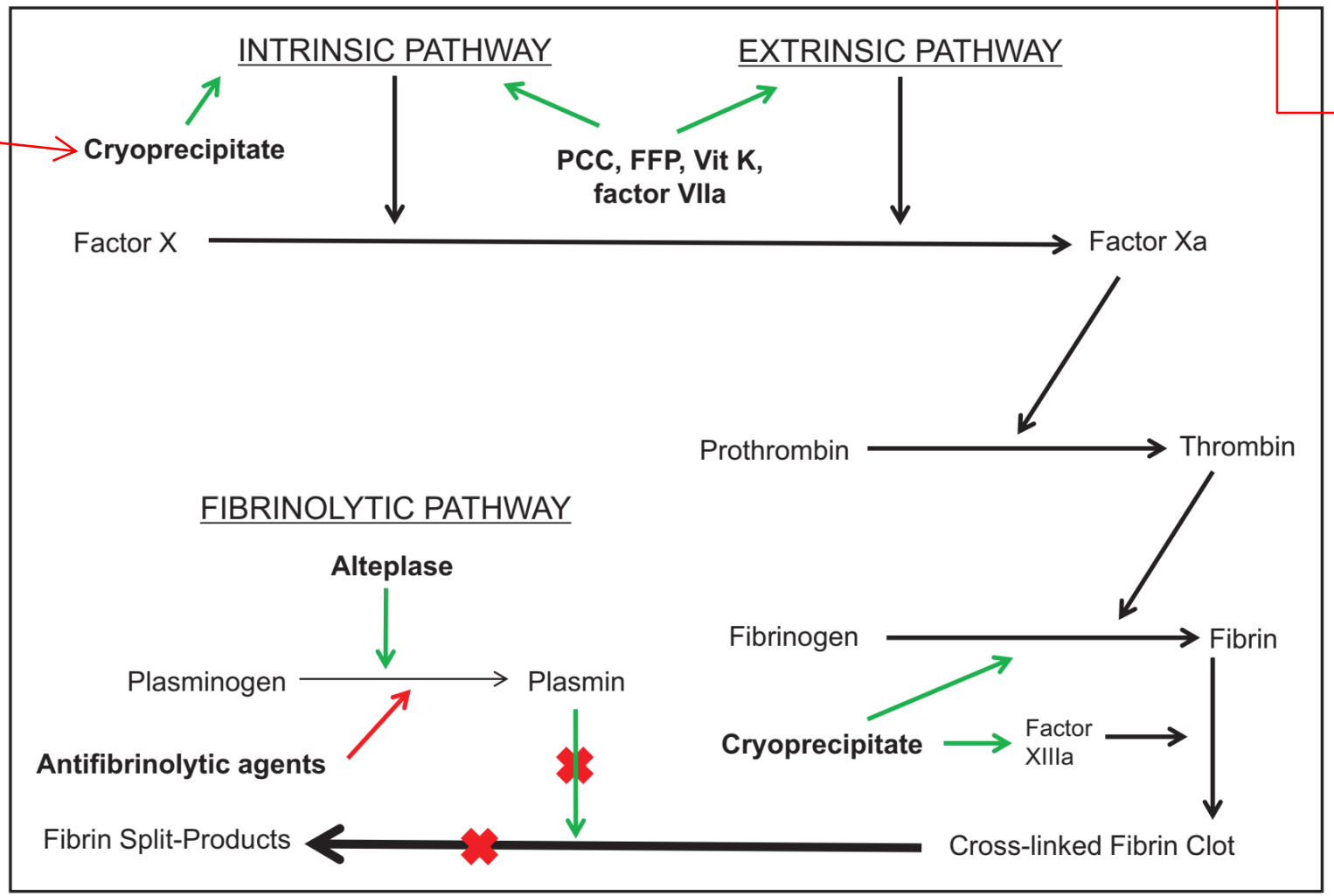
Cryoprecipitate
- F VIII, F XIII, Fibrinogen, von Willebrand factor
- Should be the first choice
- 10 units may be reasonable
- may keep fibrinogen level of >150 mg/dL

FVIIa
- Dose dependent bleeding reduction (20-160 ug/kg given within 4 hrs of onset)
- 4% risk of stroke or MI
- Currently experimental usage



FFP
- 12 mL/kg
- It may be considered in VKA treated patient prior to thrombolysis

PCCs
- Concentrated Vit K dependent factors including protein C and protein S
- Predominately useful in VKA anticoagulated patient
- coagulation risk : 1%
- May be adjuvant treatment in VKA treated patient
- 25-50 U/kg

Platelet transfusion
- Some retrospective study shown the more increasing rate of hematoma expansion
- Should be used in patient with platelet of <100,000/uL.

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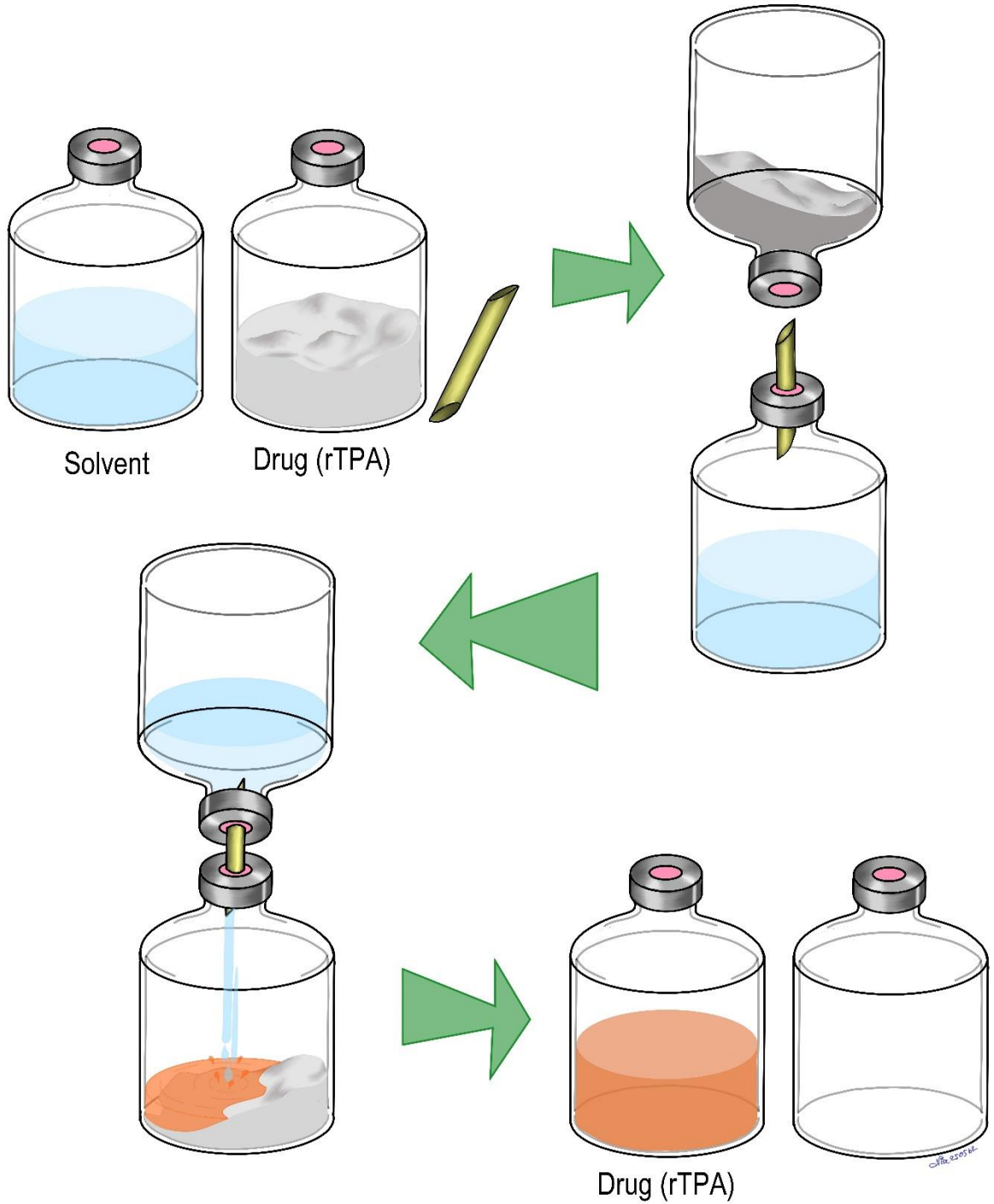
Solvent
Drug (rTPA)
Drug (rTPA)

Thank you for your attention