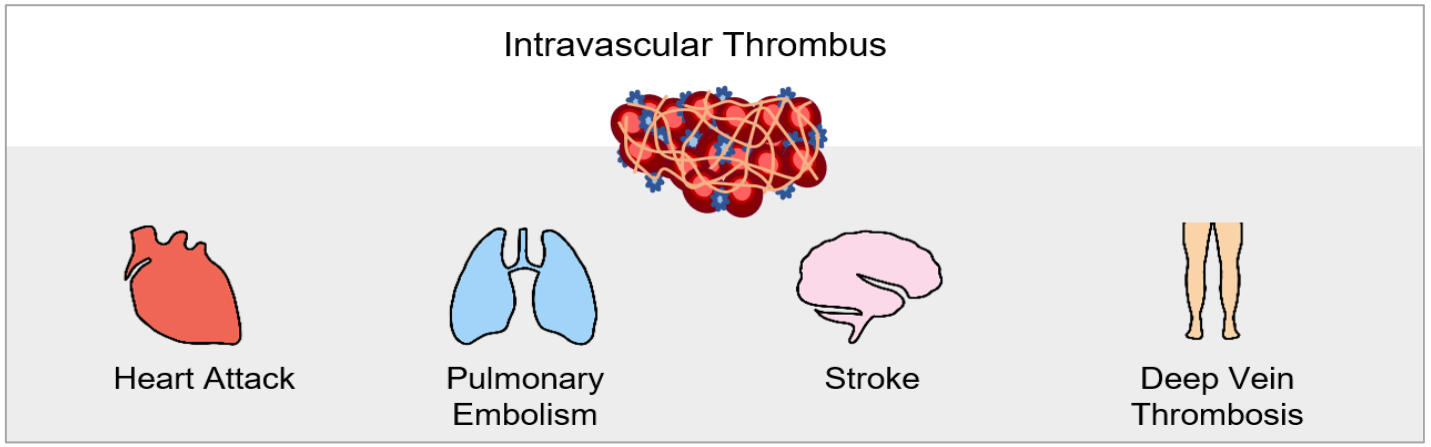
The First SAFE clot-buster

SNJ Pharma Inc

Hyeon J Kim, President

Thrombus and thrombosis

- Thrombosis underlies many cardiovascular diseases.

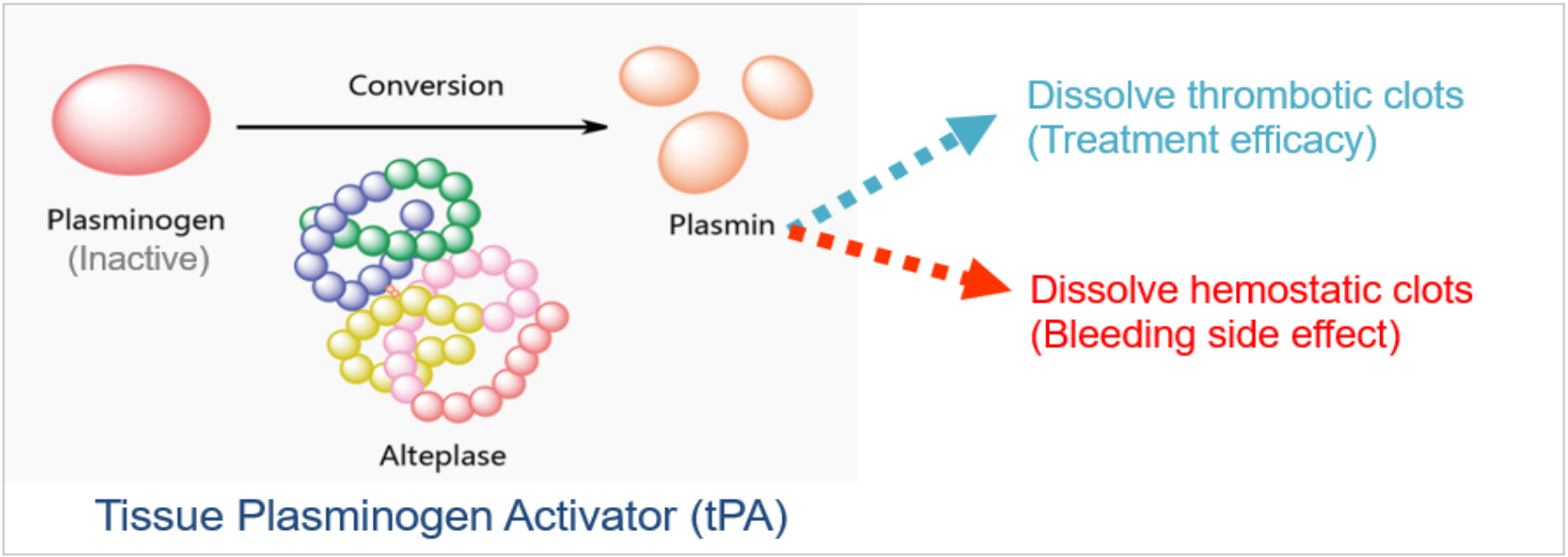


  - Globally 240 million cases of stroke and ischemic heart disease
  - Leading cause of mortality, accounting for 1 in 4 deaths
  - Leading cause of serious long-term disability

- Huge impacts socially and economically.
  - The combined medical cost for ischemic heart disease and stroke is about $300B per year in the US.
  - Total cost of cardiovascular diseases was $363B ($216B in direct costs and $147B in indirect costs) between 2016 to 2017 in the US.

Current treatment is UNSAFE

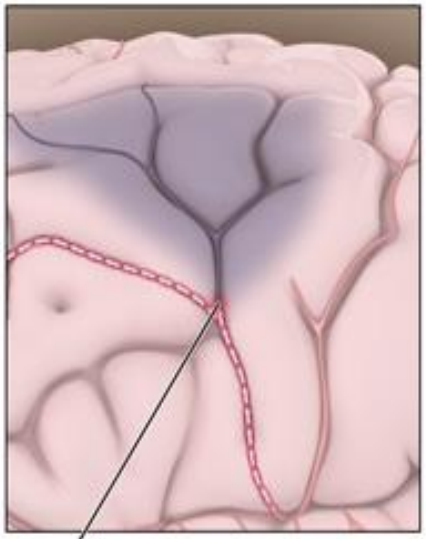
- Current treatment is unsafe, causing fatal bleeding.
  - Thrombosis needs to be treated to restore blood flow.
  - Current treatment with plasminogen activators (PA) is limited.
  - PA generates plasmin, a general protease that lyses thrombotic clots as well as hemostatic clots, contributing to fatal excessive bleeding.
  - PA also degrades fibrinogen, interfering with blood coagulation.



Current treatment is UNSAFE

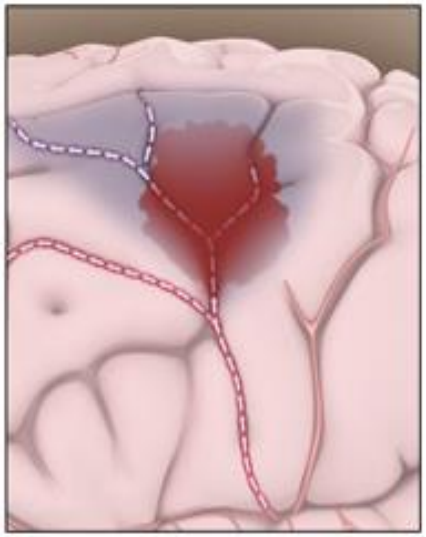
- NINDS trial reported that treated patients had a 10-fold increase in the incidence of hemorrhage over placebo.

- **Without treatment** → Ischemic stroke



A clot blocking blood flow to an area of the brain

- **With PA treatment** → Hemorrhagic stroke



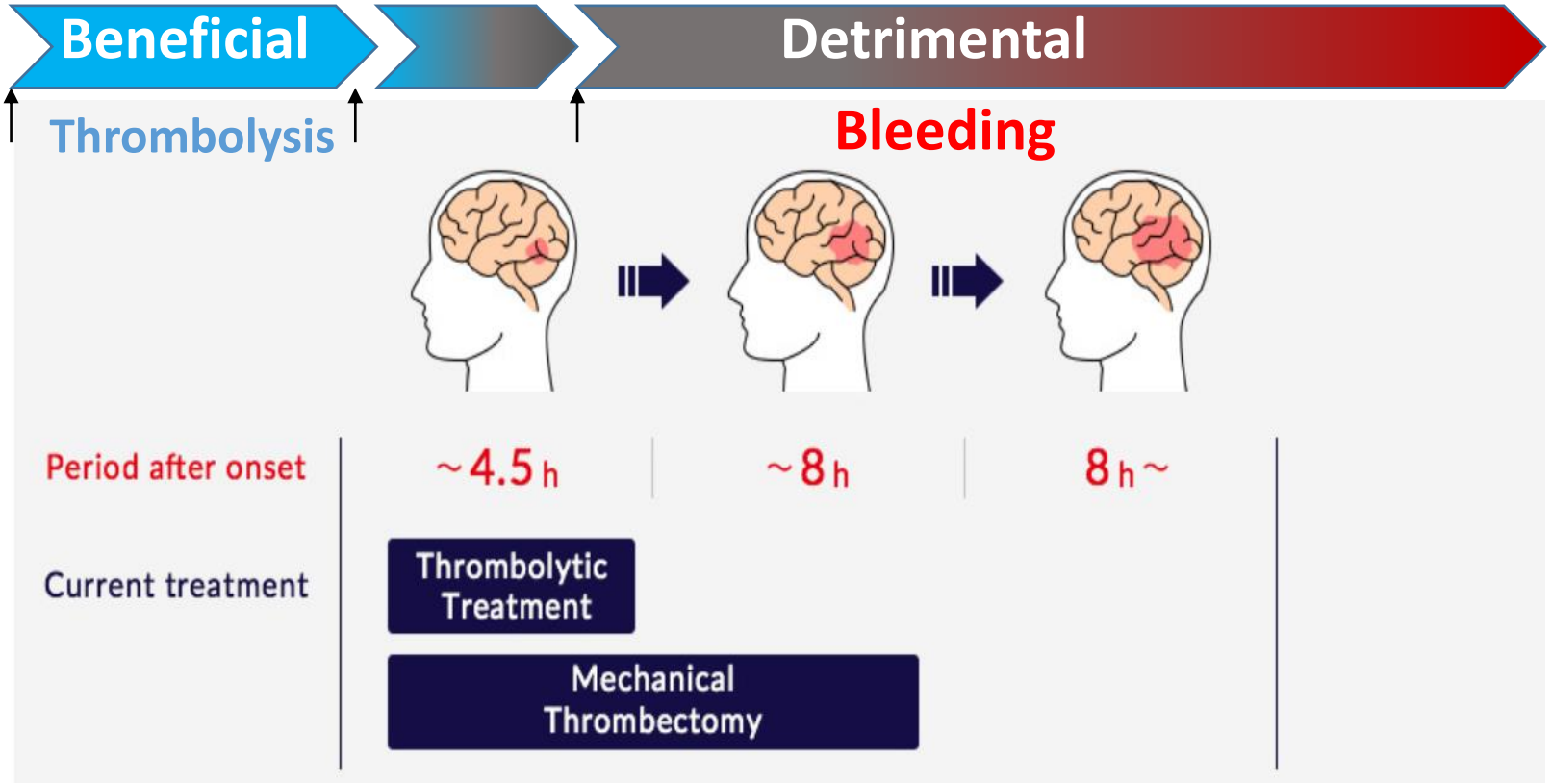
Bleeding inside or around brain tissue

Table 2. Major bleeding and intracranial bleeding in prospective trials.

Treatment	*n*	Major bleeding rate (%)	ICH rate (%)	Reference
Urokinase 50,000 units/lb	82	32.9	NR	[UPET 1970]
t-PA 0.6 mg/kg	33	0	0	[Levine *et al.* 1990]
t-PA 40–80 mg	9	11.1	0	[PIOPED Investigators, 1990]
r-PA 20 units	23	4.3	0	[Tebbe *et al.* 1999]
t-PA 100 mg	13	7.7	0	[Tebbe *et al.* 1999]
t-PA 100mg	20	15	NR	[Dalla-Volta *et al.* 1992]
Urokinase 3 million units	45	10.9	2.2	[Goldhaber *et al.* 1992]
t-PA 100 mg	44	15.9	4.5	[Goldhaber *et al.* 1992]
Urokinase 57,200 units/kg	29	27.6	3.4	[Meyer *et al.* 1992]
t-PA 100 mg	34	20.6	0	[Meyer *et al.* 1992]
t-PA 100 mg	46	NR	2.2	[Goldhaber *et al.* 1993]
t-PA 0.6 mg/kg	60	3.3	0	[Goldhaber *et al.* 1994]
t-PA 100 mg	27	7.4	7.4	[Goldhaber *et al.* 1994]
t-PA 0.6 mg/kg	36	8	0	[Sors *et al.* 1994]
t-PA 100 mg	17	6	0	[Sors *et al.*1994]
STK 1.45 million units	25	12	NR	[Meneveau *et al.* 1997]
t-PA 100 mg	25	16	NR	[Meneveau *et al.* 1997]
STK 1.5 million units	43	8	NR	[Meneveau *et al.* 1998]
t-PA 100 mg	23	20	NR	[Meneveau *et al.* 1998]
t-PA 100 mg	118	0.8	0	[Konstantides *et al.* 2002]
t-PA 100 mg	7	0	0	[Muhl *et al.* 2007]
STK 9 million units	8	0	0	[Muhl *et al.* 2007]
TNK 30–50 mg	525	NR	2.7	[Bottiger *et al.* 2008]
TNK 30–50 mg	28	7.1	3.6	[Becattini *et al.* 2010]
t-PA 50 mg	55	3.6	1.8	[Wang *et al.* 2010]
t-PA 100 mg	48	10.4	0	[Wang *et al.* 2010]
t-PA 100 mg	37	5.4	0	[Fasullo *et al.* 2011]
t-PA 50 mg	61	0	0	[Sharifi *et al.* 2013]
STK 2.65–5.05 million units	75	1.3	1.3	[Patra *et al.* 2013]
TNK 30–50 mg	25	0	0	[Patra *et al.* 2013]
TNK 30–50 mg	506	11.5	2.0	[Meyer *et al.* 2014]
STK 2.65–5.05 million units	105	1.9	NR	[Patra *et al.* 2014]
TNK 30–50 mg	25	0	NR	[Patra *et al.* 2014]
TNK 30–50 mg	40	2.5	2.5	[Kline *et al.* 2014]
t-PA 10–20 mg	30	0	0	[Kucher *et al.* 2014]

Current treatment is LIMITED!

- Current treatment requires a 'Time window', resulting in treatments in less than 5% of patients.



Thrombase: SAFE therapeutic agent

Thrombase, An endogenous enzyme to remove intravascular thrombotic clots

I. 1st plasmin-independent thrombolytic agent that does not produce plasmin
II. Specifically lyses thrombotic clots while preserves hemostatic clots
III. Safe without bleeding complications since it permits normal wound healing

Circulation Research, 2021

Identification and Characterization of Plasmin-Independent Thrombolytic Enzymes

Md. Mehedi Hassan, Shirina Sharmin, Hyeon-Jin Kim, Seong-Tshool Hong

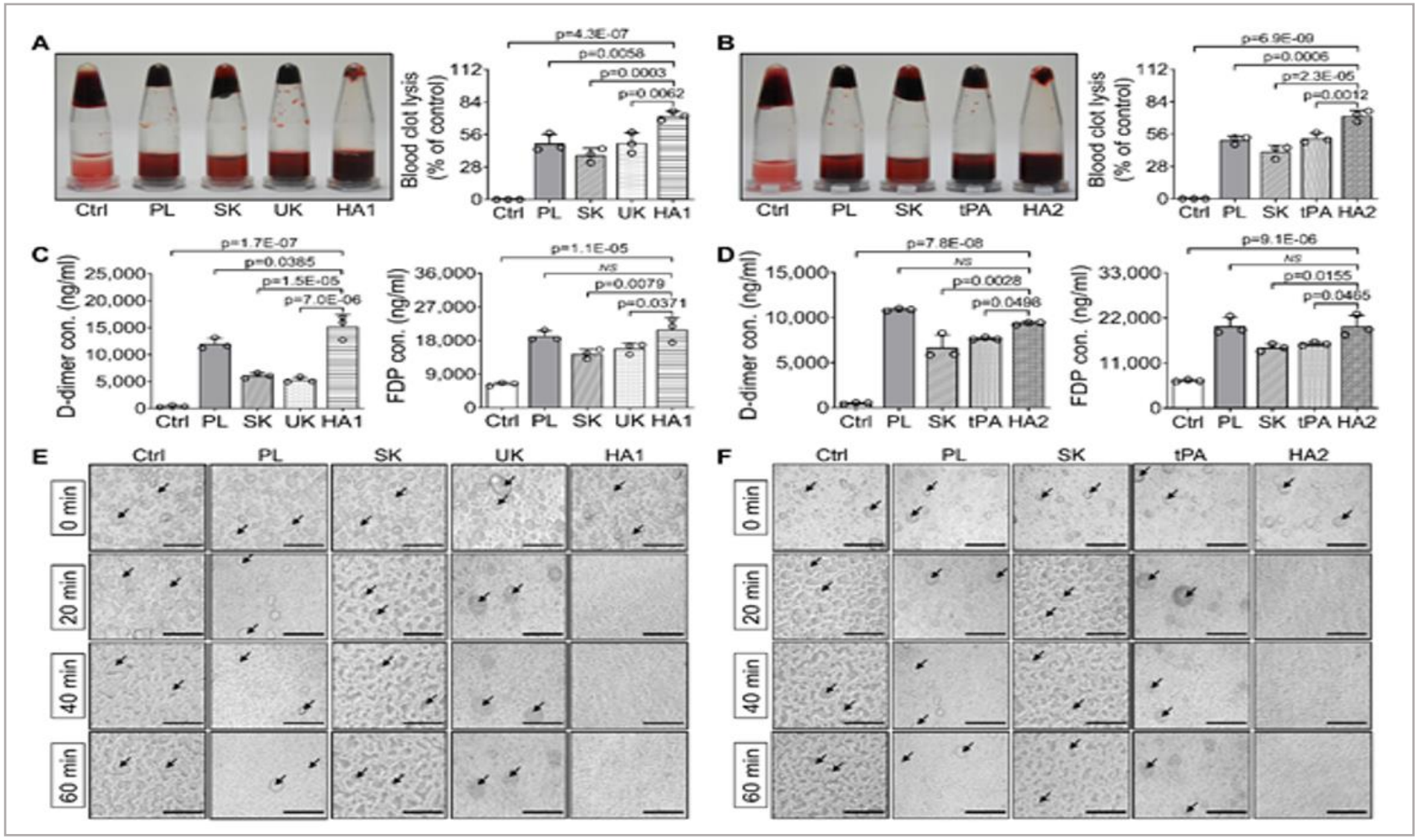
RATIONALE: Current thrombolytic agents activate plasminogen to plasmin which triggers fibrinolysis to dissolve thrombi. Since plasmin is a nonspecific proteolytic enzyme, all of the current plasmin-dependent thrombolytics lead to serious hemorrhagic complications, demanding a new class of fibrinolytic enzymes independent from plasmin activation and undesirable side effects. We speculated that the mammalian version of bacterial heat-shock proteins could selectively degrade intravascular thrombi, a typical example of a highly aggregated protein mixture.

OBJECTIVE: The objective of this study is to identify enzymes that can dissolve intravascular thrombi specifically without affecting fibrinogen and fibronectin so that the wound healing processes remain uninterrupted and tissues are not damaged. In this study, HtrA (high-temperature requirement A) proteins were tested for its specific proteolytic activity on intravascular thrombi independently from plasmin activation.

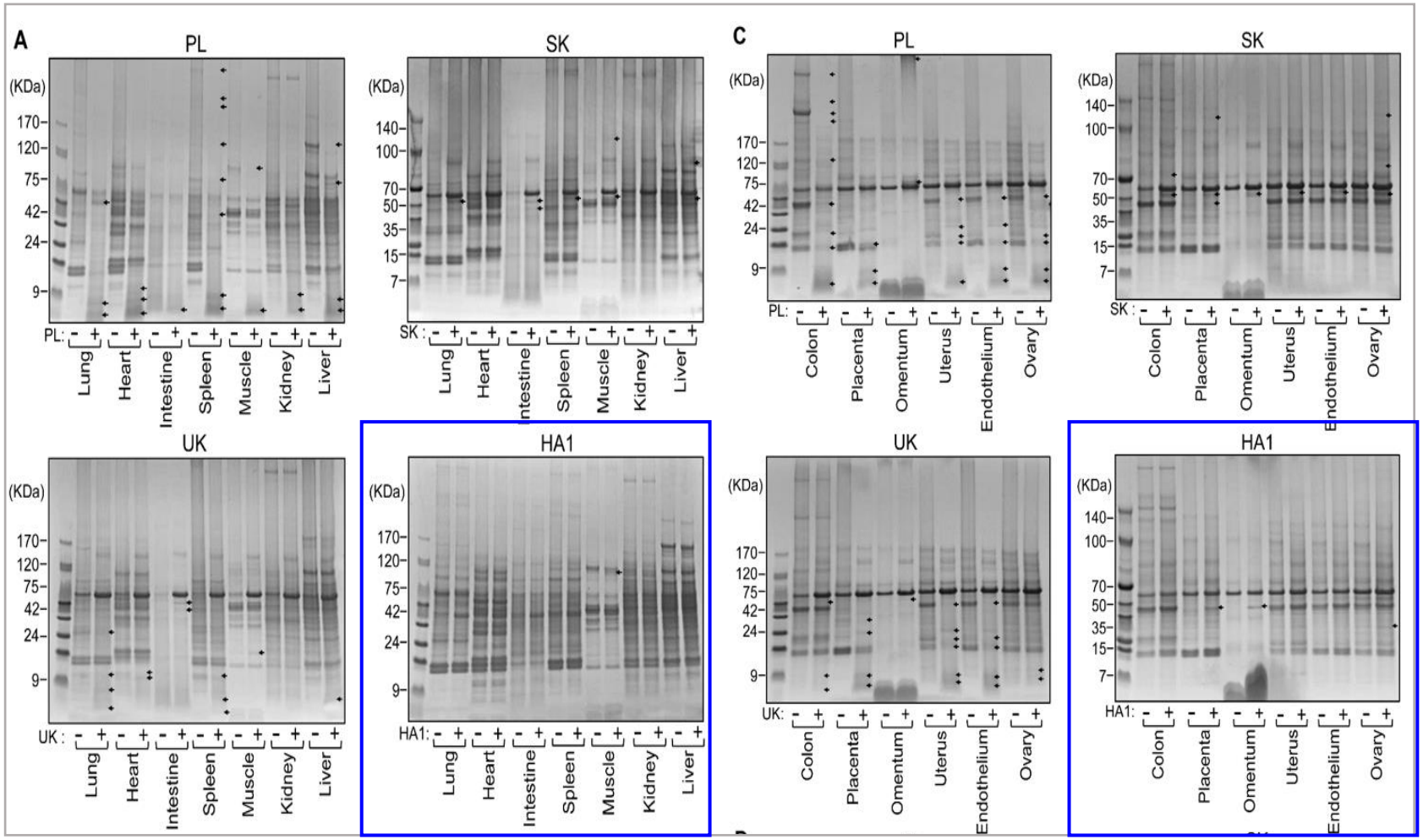
METHODS AND RESULTS: HtrA1 and HtrA2/Omi proteins, collectively called as HtrAs, lysed ex vivo blood thrombi by degrading fibrin polymers. The thrombolysis by HtrAs was plasmin-independent and specific to vascular thrombi without causing the systemic activation of plasminogen and preventing nonspecific proteolysis of other proteins including fibrinogen and fibronectin. As expected, HtrAs did not disturb clotting and wound healing of excised wounds from mouse skin. It was further confirmed in a tail bleeding and a rebleeding assay that HtrAs allowed normal clotting and maintenance of clot stability in wounds, unlike other thrombolytics. Most importantly, HtrAs completely dissolved blood thrombi in tail thrombosis mice, and the intravenous injection of HtrAs to mice with pulmonary embolism completely dissolved intravascular thrombi and thus rescued thromboembolism.

CONCLUSIONS: Here, we identified HtrA1 and HtrA2/Omi as plasmin-independent and highly specific thrombolytics that can dissolve intravascular thrombi specifically without bleeding risk. This work is the first report of a plasmin-independent thrombolytic pathway, providing HtrA1 and HtrA2/Omi as ideal therapeutic candidates for various thrombotic diseases without hemorrhagic complications.

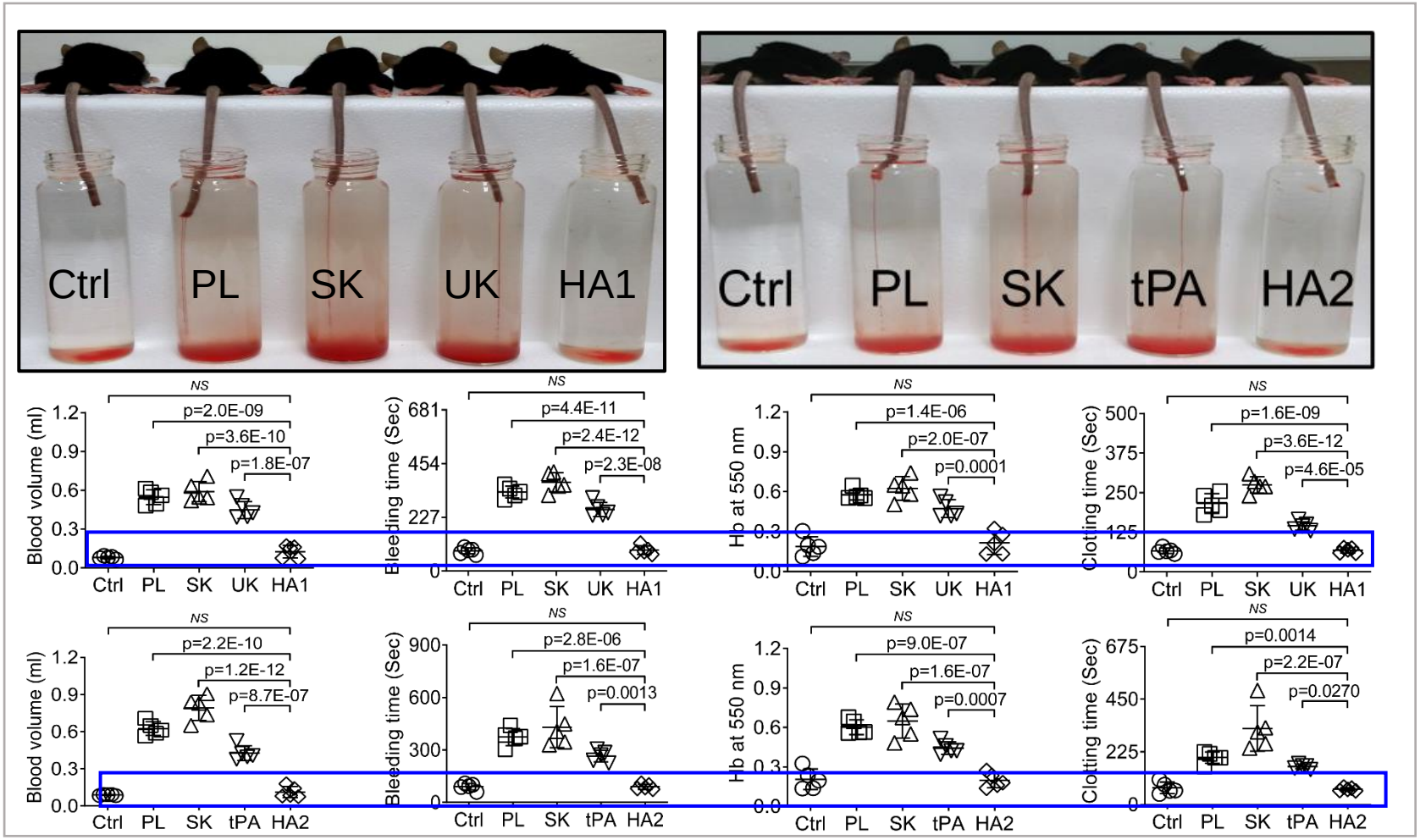
Thrombase: Dissolves thrombotic clots



Thrombase: Preserves normal proteins

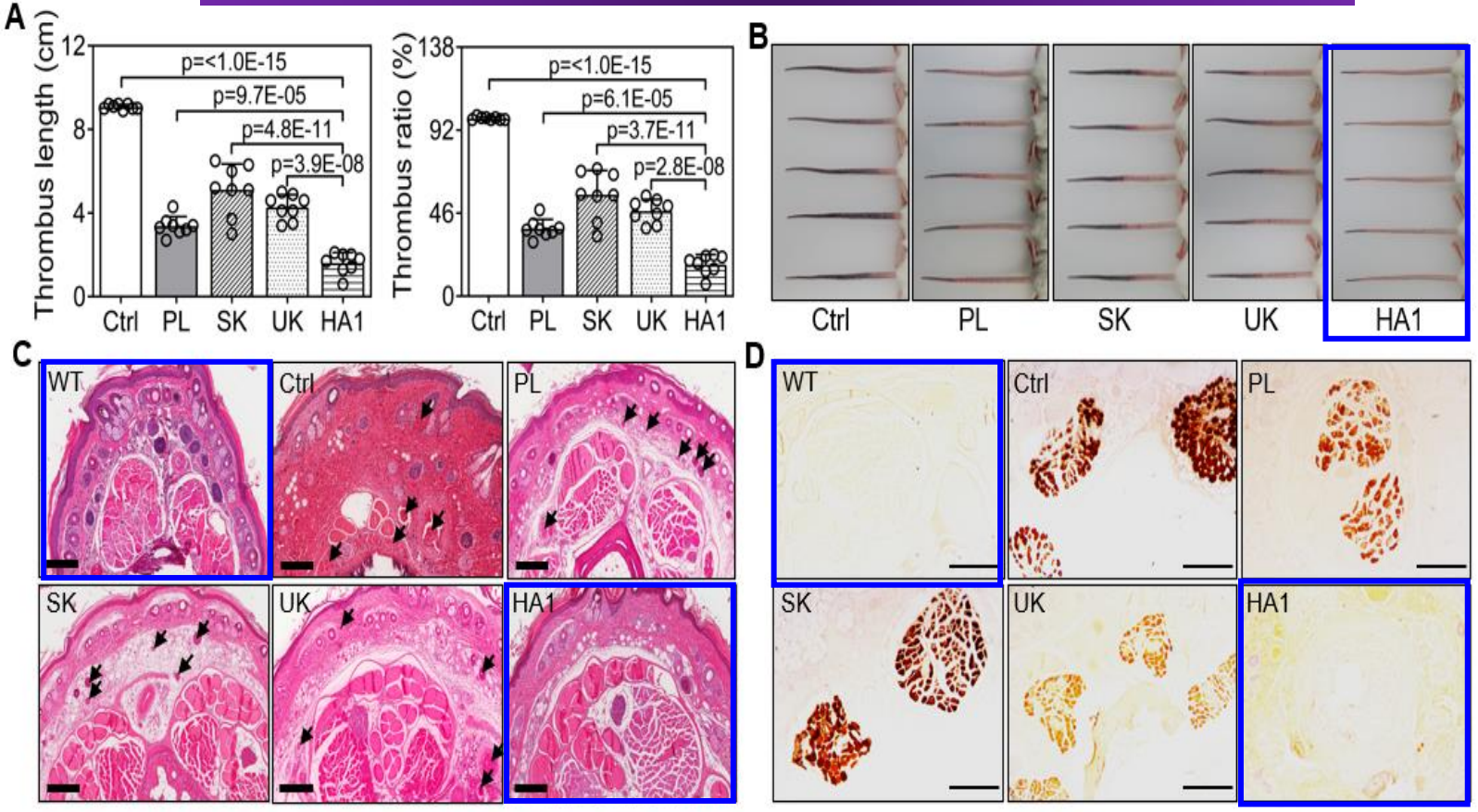


Thrombase: Does not cause bleeding



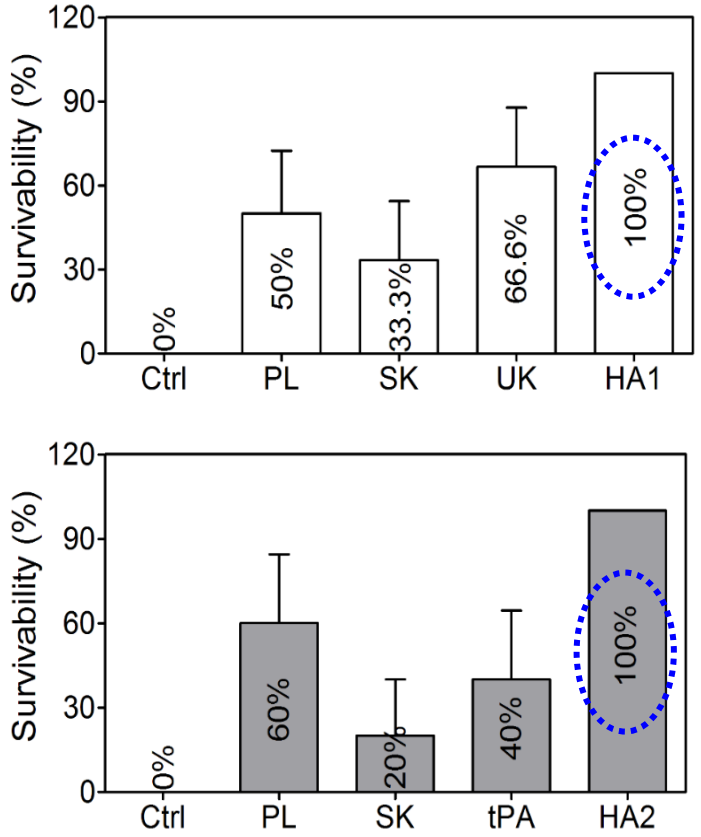
Thrombase: Cures thrombosis safely

Complete cure of tail thrombosis

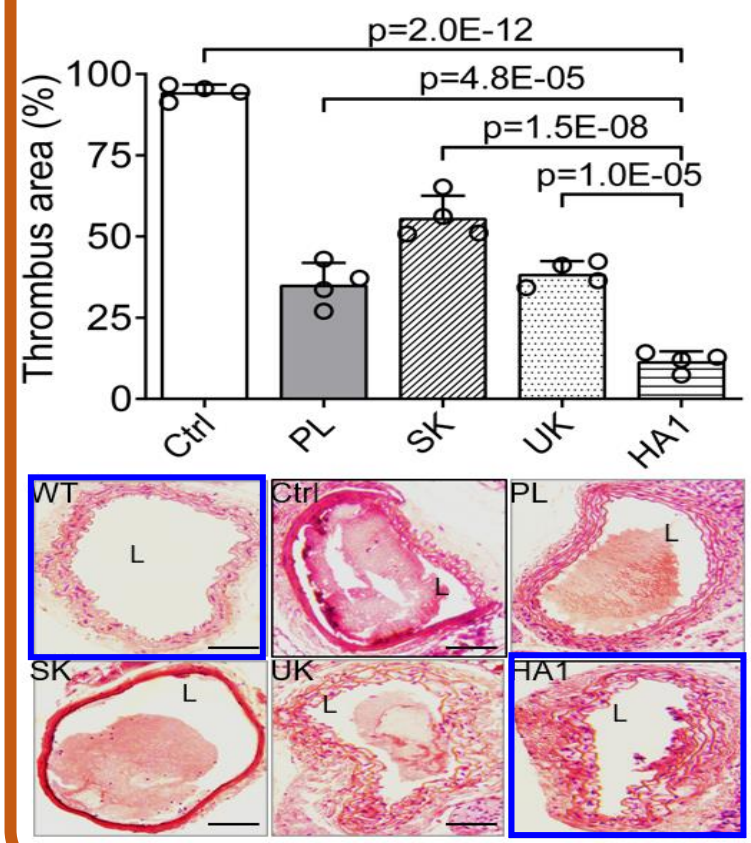


Thrombase: Cures PE & CAS safely

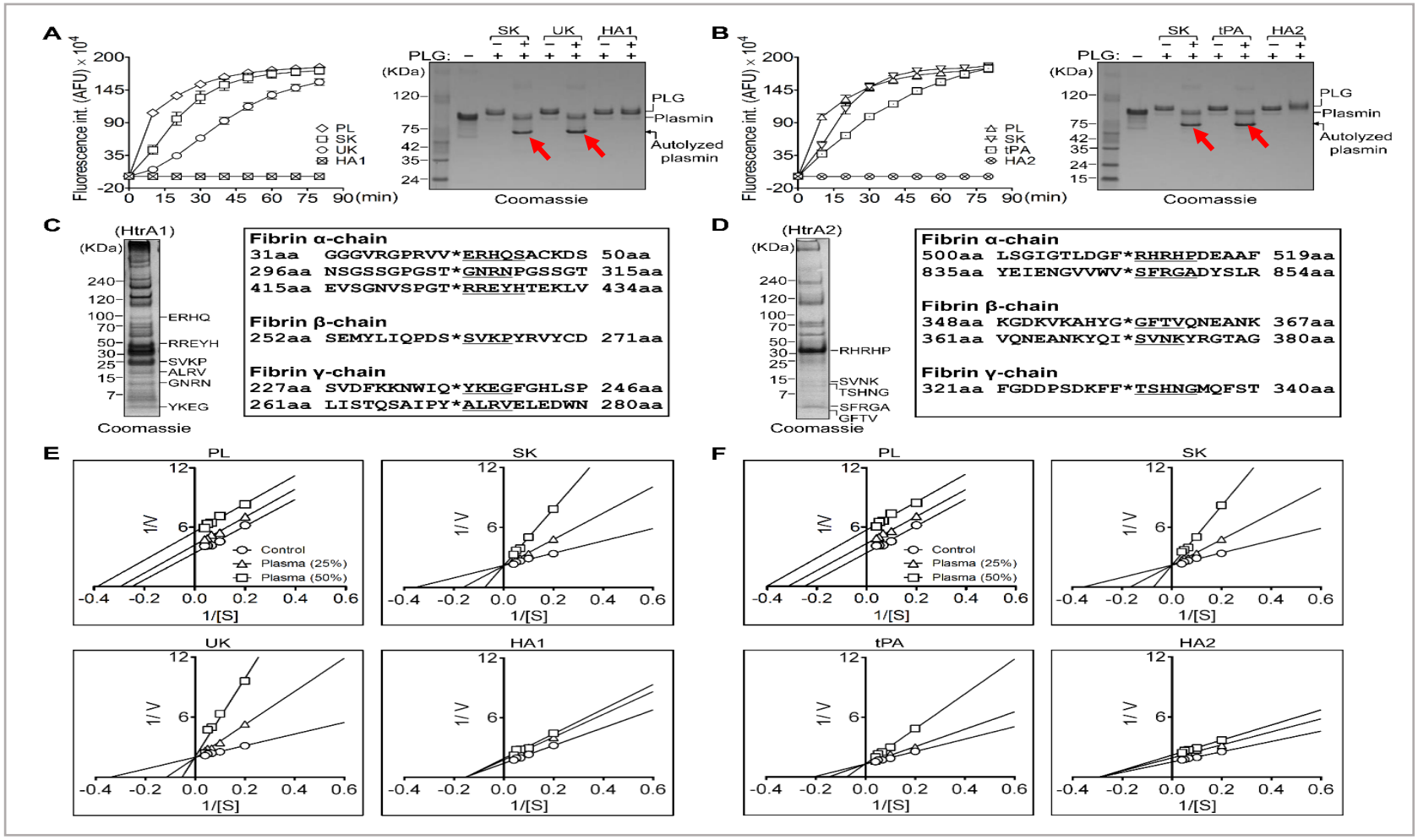
Pulmonary Embolism



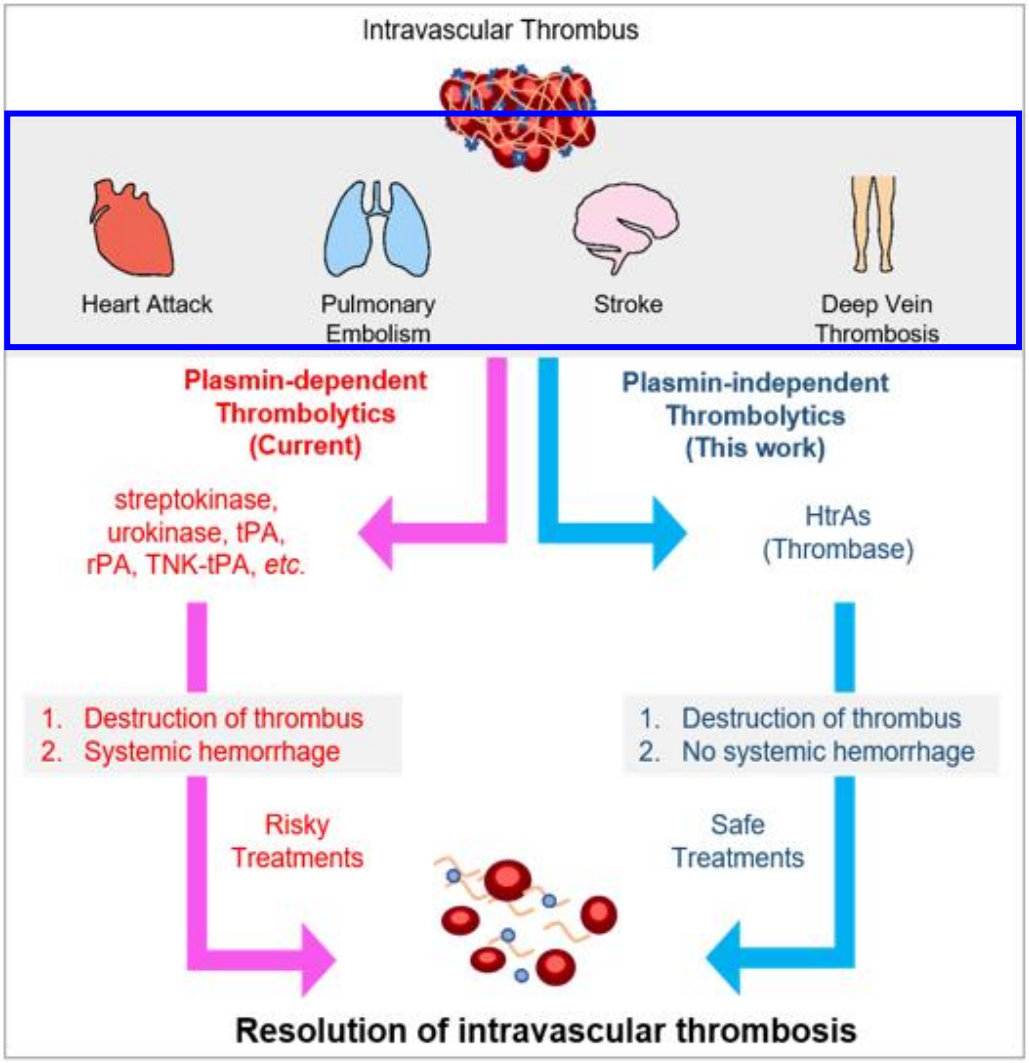
Carotid Artery stenosis



Thrombase: New Mode of Action

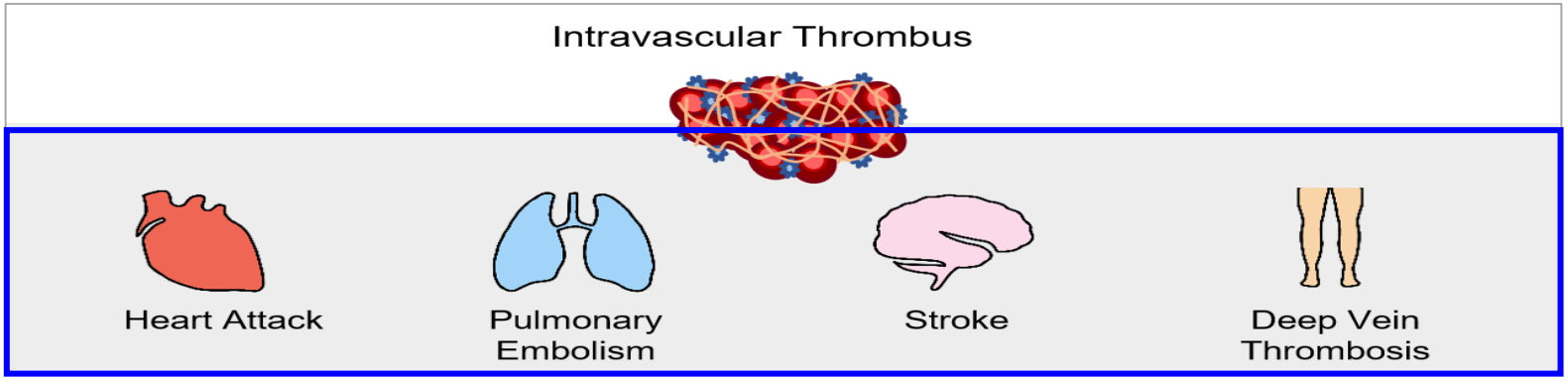


Thrombase is EFFECTIVE & SAFE



American Heart Association®

Market Potential

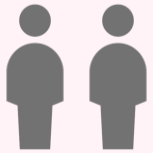


	Patients (240 millions)	Drug Market Size (Combined $32B)
I. Acute Ischemic Stroke	104 million	$9B
II. Ischemic heart disease (Heart attack, chest pain, ..)	126 million	$22B
III. Venous Thromboembolism (PE, DVT, vein thrombosis, ..)	10 million	$1B

Market Potential

❑ Cancer

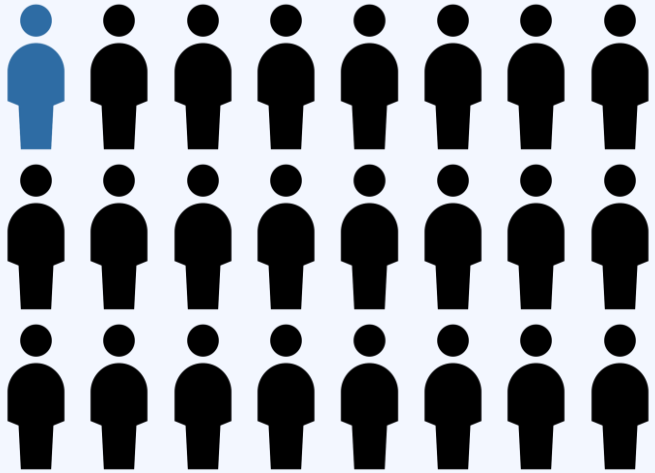
- 19 million cases/year
- 643 oncology drugs (NCI)
- >700 drugs in late stages



Source: NCI & seer.cancer.gov

❑ Thrombosis

- 240 million cases/year
- PA drug with bleeding risk
- Only 3% treated



Treated vs Untreated

Competitor & Advantages

	Alteplase Activase®/Roche	**Thrombase** SNJ Pharma
Indication	MI, AIS, PE	TBD
Drug class	Plasminogen Activator	Thrombolytic
Plasmin production	Yes	No
Lysis of hemostatic clots	Yes	No
Systemic fibrinolysis	Yes	No
Interruption of wound healing	Yes	No
Hemorrhagic complications	Yes	No
Treatment time window	Yes	No
Safety	Low	Very High
$/100 mg vial	$8,300 (high cost)	Affordable (TBD) (<< 1/10 cost)

* Disadvantages (Red) & Advantages (Blue)

Strategy: Expedited EUA process

Financing: Grant & Partnership

IMPACT score: 18 | Kim, Hyeon Jin

SCIENTIFIC REVIEW OFFICER'S NOTES

NIH National Institutes of Health

RESUME AND SUMMARY OF DISCUSSION: The current standard of treatment for stroke is medications that promote the conversion of plasminogen to plasmin to lyse the pathological clot. Unfortunately, these agents do not discriminate between pathological clots and normal wound healing. This Phase I application proposes a novel treatment for ischemic stroke by using HtrA1 protein that performs thrombolysis, but without involving plasmin. It is supported by strong data in animals and preliminary data. These results have been published in Circulation Research in February 2021. The proposed approaches are rigorous. Both aims are sound. SABV is addressed. The investigative team is outstanding. The environment is excellent. The product does not cause bleeding complications, which is highly significant. One reviewer requests further characterization of the protein. Reviewers agree that this is an almost perfect application. They are very enthusiastic for its possible impact on the field.

SNJ Team

Dr. Hyeon Jin Kim, President/Founder

- PhD in Mol. Pharm. & Biol. Chem. Northwestern University, IL
- 20 years of biotech experience as CEO of JINIS
- Author of 40 publications including Circulation Research
- Inventor of 70 patents including the novel thrombolytic agent

Dr. Seong T. Hong, Advisory board

- PhD in Biochemistry & Biophysics, Oregon State Univ., OR
- Professor at Jeonbuk National Univ. Med. Sch.
- Author of 110 publications with 2,980 citations
- Co-Inventor of patents including the novel thrombolytic agent

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Thank You

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