Thrombolyis techniques for iliofemoral DVT

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Disclosure

Speaker name:

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I have the following potential conflicts of interest to report:

- ☐ Consulting
- ☐ Employment in industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ■ Other(s): research grant from BTG

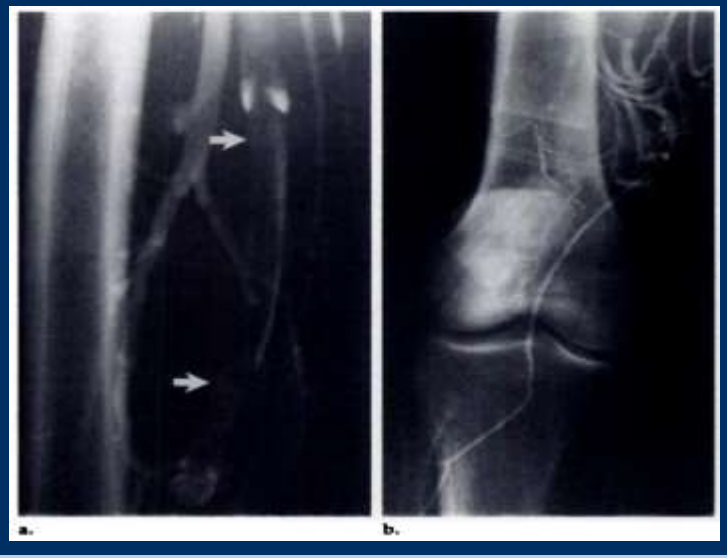
- ☐ I do not have any potential conflict of interest

Thrombolysis for iliofemoral DVT

1. Systemic thrombolysis

- reduces risk of PTS (RR 0.66) but markedly increased bleeding risk (RR 1.73)[1]
- ➢ *Problem…*
  - ➢ *With systemic thrombolysis* clot lysis >50% more frequent in non-occlusive than occlusiv thrombus[2]

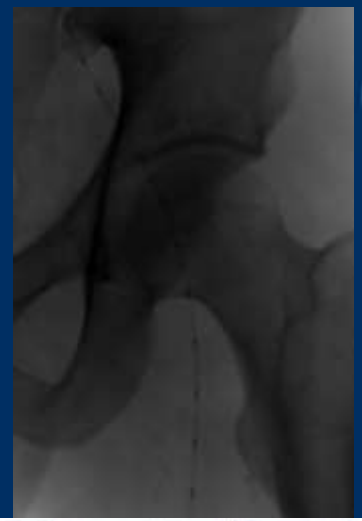
→ **with systemic administration thrombolytic drug does not reach the target…**

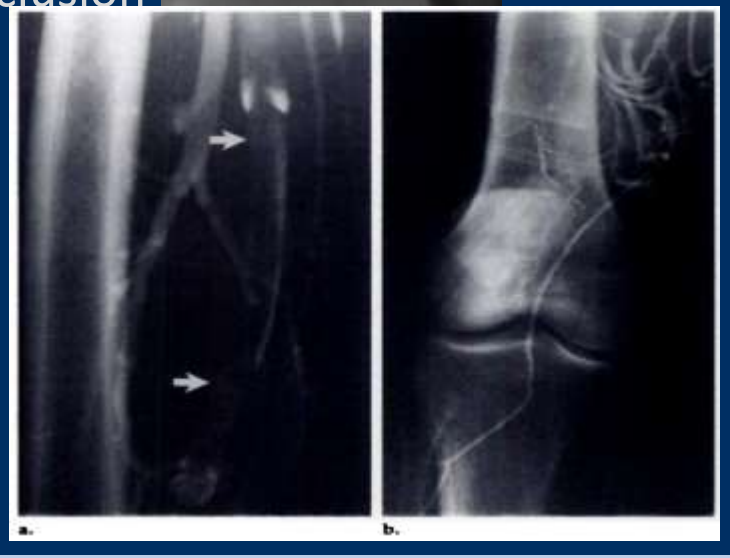


[1]Watson et al, Cochrane Database of Systematic Reviews 2004
[2]Meyerovitz et al, Radiology. 1992

Thrombolysis for iliofemoral DVT

1. **Systemic thrombolysis**
2. **Percutaneous catheter-based techniques**
   1. **CDT = Catheter Directed Thrombolysis**
      - Direct infusion of a thrombolytic drug into the thrombotic occlusion using a multisidehole catheter
   2. PMT = (Pharmaco)-Mechanical Thrombectomy





[1]Watson et al, Cochrane Database of Systematic Reviews 2004
[2]Meyerovitz et al, Radiology. 1992

Catheter-Directed Thrombolysis CDT

- **Advantages:**
  - Minimally invasive
  - In *comparison with systemic thrombolysis*
    - Higher local concentrations: ⬆ **Efficacy**
    - Reduced drug dose: ⬆ **Safety**
  - Allows treatment of **underlying obstructive vein lesions → Stenting!**

- **Drawbacks:**
  - Need for thrombolytic drugs
  - Treatment duration

Popuri/Vedantham, ATVB 2011

CaVenT study

Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial

Tone Enden, Ylva Haig, Nils-Einar Kløw, Carl-Erik Slagsvold, Leiv Sandvik, Waleed Ghanima, Geir Hafsahl, Pål Andre Holme, Lars Olaf Holmen, Anne Mette Njaastad, Gunnar Sandbæk, Per Morten Sandset, on behalf of the CaVenT Study Group

Enden et al, Lancet 2012;379:31-8

CaVenT study → Summary

		CDT group	Control group	P-value	
Ilio-Femoral Patency	6 months	65.9	47.4	0.012	
	2 years	74.7	59.6	0.028	
	5 years	79.1	70.9	0.218	
Femoro-Popliteal Reflux	6 months	65.2	77.1	0.073	
	2 years	66.7	83.2	0.009	
	5 years	62.1	84.3	0.004	
PTS	6 months	30.3	32.2	0.77	
	2 years	41.1	55.6	0.047	→ NNT 7
	5 years	42.5	70.8	0.0001	→ NNT 4

Enden et al, Lancet 2012; Haig et al, JVS Venous Lymph Dis 2014; Haig et al, Lancet Haematol 2016

Which thrombolytic drug?

- The most commonly used **recombinant tissue plasminogen activator (rtPA)**
  - The amount of rtPA and infusion volume varies in the literature from 20 to 120 mL/h, but rtPA should not exceed 1 mg/hour

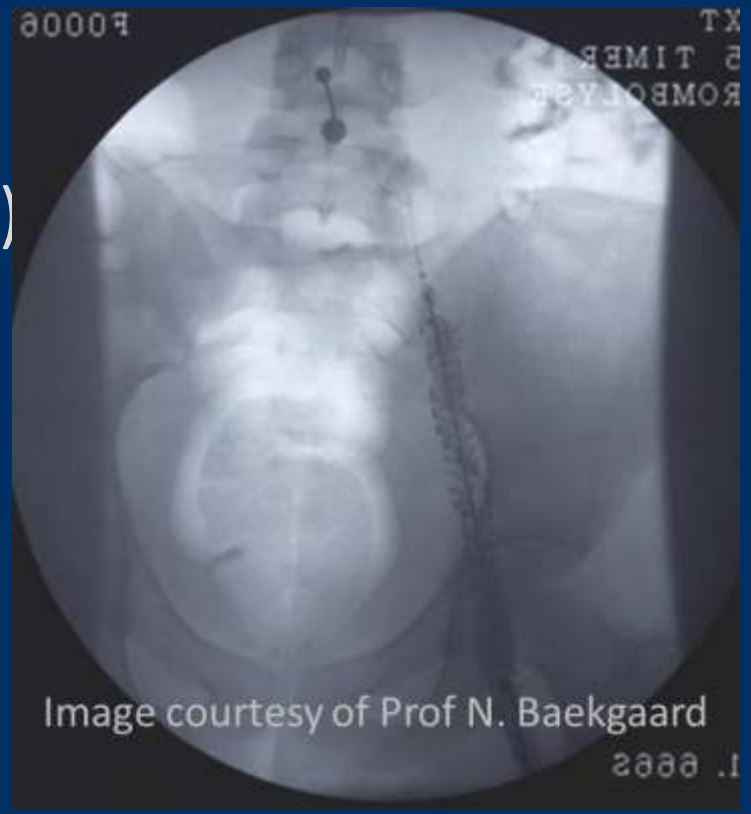
Fibrinolytic	Direct Plasminogen Activator?	Fibrin Specificity (Relative to Fibrinogen)	PAI Resistance*
Streptokinase	No	–	–
Urokinase	No	–	–
Alteplase	Yes	++	++
Reteplase	Yes	+	+
Tenecteplase	Yes	+++	+++

- Infused together with either UFH or LMWH, both weight-adjusted

Kakkos et al. ESVS 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. Eur J Vasc Endovasc Surg 2021;61,9-82; Jaff et al. Circulation 2011;123;1788-1830

How to administer the thrombolytic drug in CDT ?

- **Continuous infusion** (as in CaVenT)
  - e.g. Cragg-McNamara®, UniFuse®, EkoSonic®
- **Pulsatile injections** (“pulse spray technique”)
  - *For CDT* e.g. Pulse Spray® Infusion System®



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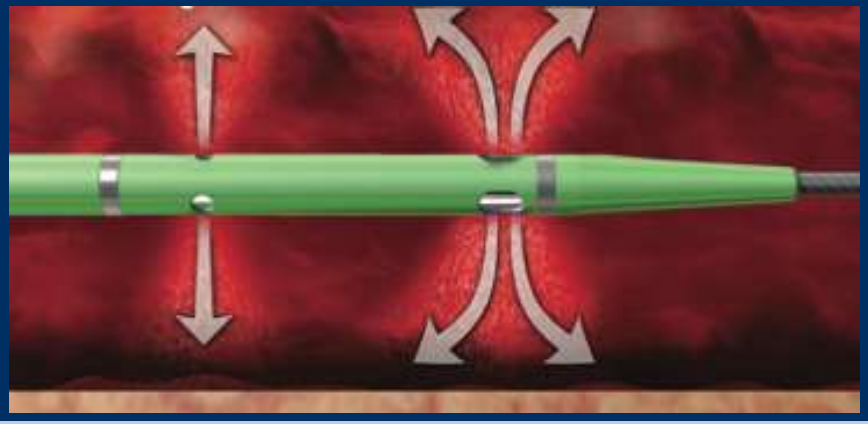

Dopheide, Sebastian, Engelberger et al. Vasa (2018), 47 (1), 56–62
image from https://www.cathlabdigest.com

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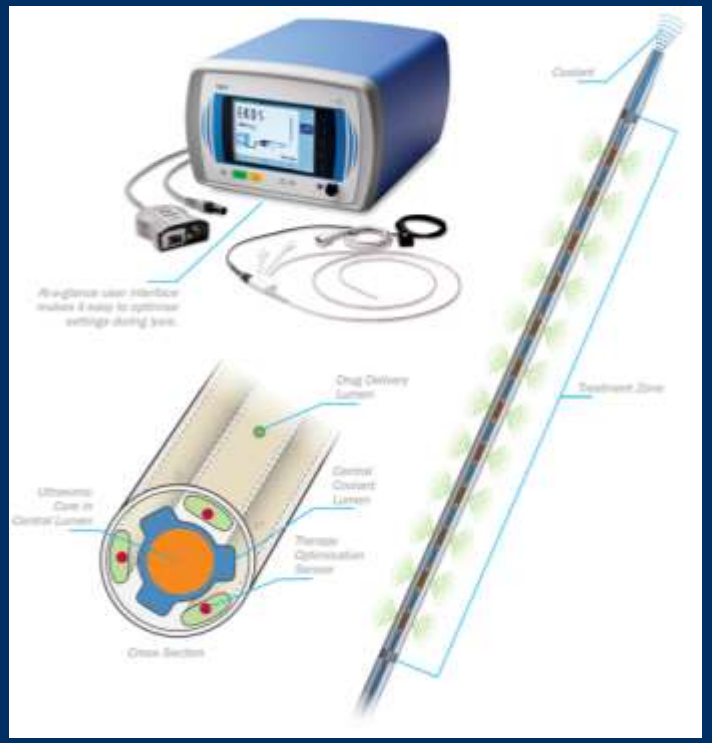
- **Pulsatile injections** (“pulse spray technique”)
  - *For CDT* e.g. Pulse Spray® Infusion System®
  - *For PMT* e.g. Power Pulse® rtPA injection with AngioJet ® catheter
- **Ultrasound-assisted (or accelerated) thrombolysis**
  - e.g. EkoSonic®

Kakkos et al. ESVS 2021 Clinical Practice Guidelines on the Management of Venous Thrombosis. Eur J Vasc Endovasc Surg 2021;61,9-82

Ultrasound-Assisted Thrombolysis (USAT)

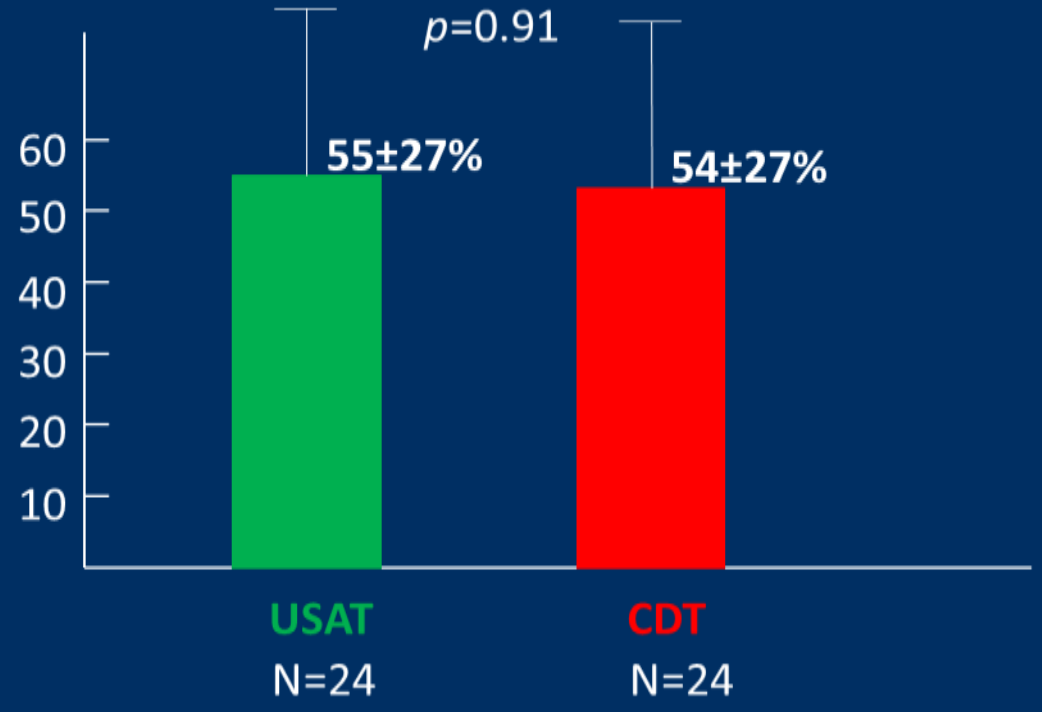


Engelberger & Kucher, Eur Heart J 2014; 35:758-64

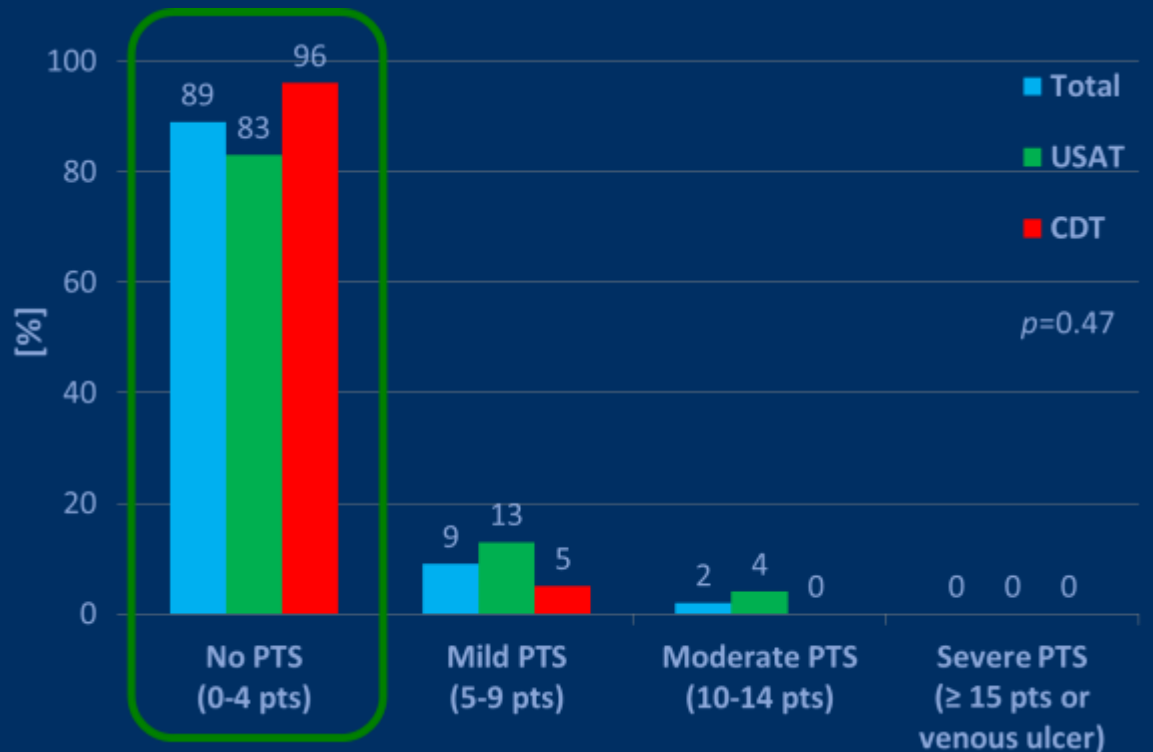
BERNUTIFUL

- **Primary Endpoint:**

% of Thrombus Load Reduction



- **PTS after 1 year - Villalta score**



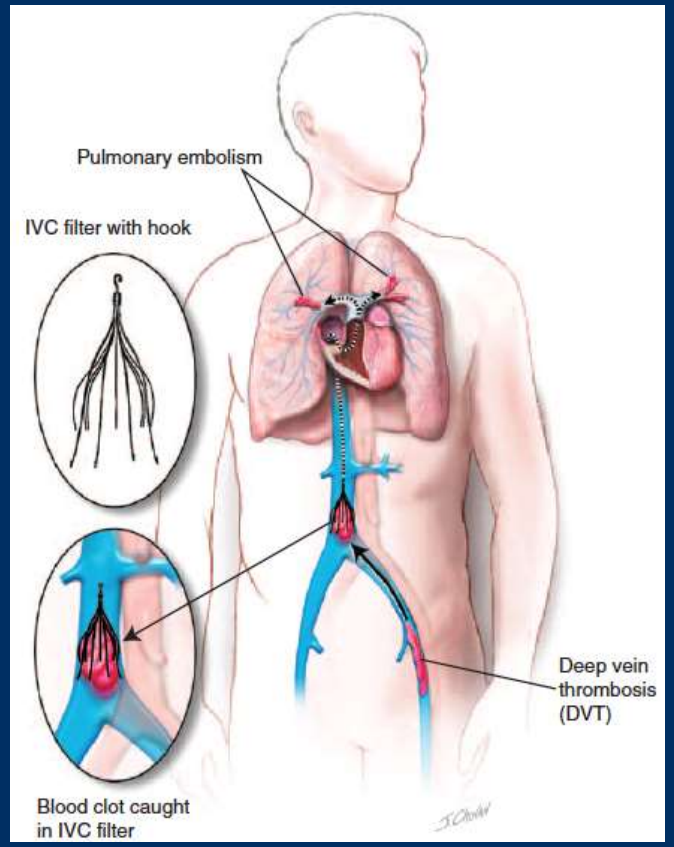
Engelberger et al. Circ Cardiovasc Interv 2015;8:e002027
Engelberger et al, J Thromb Haemost 2017; 15:1351-1360

Duration of CDT?

	Study	Thrombolysis protocol	Treatment duration
Venography controlled	**CaVenT**[1]	0.01 mg $kg^{-1}h^{-1}$ with a maximal dose of 20 mg per 24 h and maximal duration of 96 h	2.4 days (SD 1.1)
	Copenhagen experience[2]	Bolus of 10 mg rtPA followed by rtPA 1.2 mg in 120 ml saline/h	**a. Continuous infusion protocol:** Median 71 h (range 25-146 h) **b. Pulse-spray infusion:** Median 52 h (range 22-142 h)
Fixed duration	**Swiss Venous Stent Registry**[3]	Standard dose of 20mg rtPA over 15h	17.5 h (SD 6.9)

[1]Enden et al, Lancet 2012;379:31-8
[2]Foegh et al, Eur J Vasc Endovasc Surg (2017) 53, 419e424
[3]Sebastian et al, Thrombosis Research 172 (2018) 86–93

IVC filter?



Role of IVC Filters in Endovenous Therapy for Deep Venous Thrombosis: The FILTER-PEVI (Filter Implantation to Lower Thromboembolic Risk in Percutaneous Endovenous Intervention) Trial

Table 1 Interventional approaches used

Approach	Filter group ($n = 70$)	Control group ($n = 71$)
Trellis	34	36
AngioJet	8	9
Thrombolytic therapy via infusion catheter	32	35
Balloon venoplasty	56	54
Stent	18	16
	1/70 = 1.4%	**8/71 = 11.3%**

Carroll S et al. Circulation. 2016;133:e383-e387
Sharifi et al, Cardiovasc Intervent Radiol (2012) 35:1408–1413

Contemporary Trends and Comparative Outcomes With Adjunctive Inferior Vena Cava Filter Placement in Patients Undergoing Catheter-Directed Thrombolysis for Deep Vein Thrombosis in the United States

Insights From the National Inpatient Sample

FIGURE 2 Contemporary Trends in Inferior Vena Cava Filter Placement Among Patients Undergoing Catheter-Directed Thrombolysis in the United States (2005 to 2013)

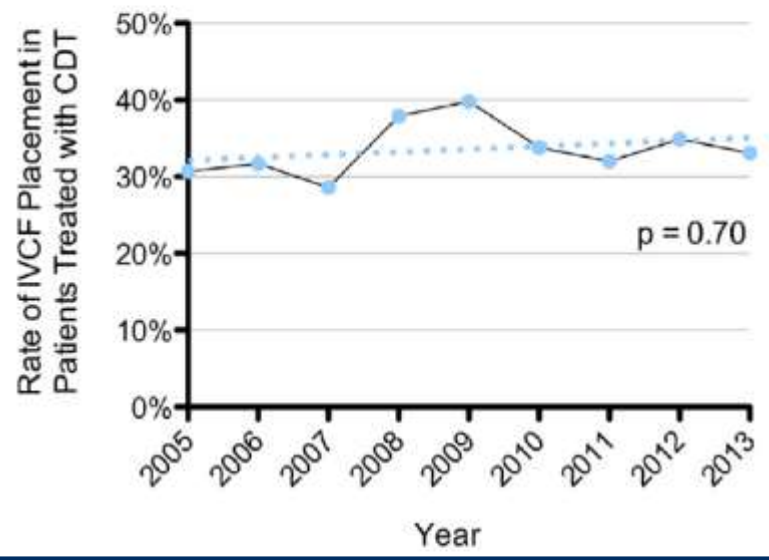


TABLE 2 Matched Race-Adjusted Outcomes of Patients Undergoing Catheter-Directed Thrombolysis With or Without Inferior Vena Cava Filter Placement

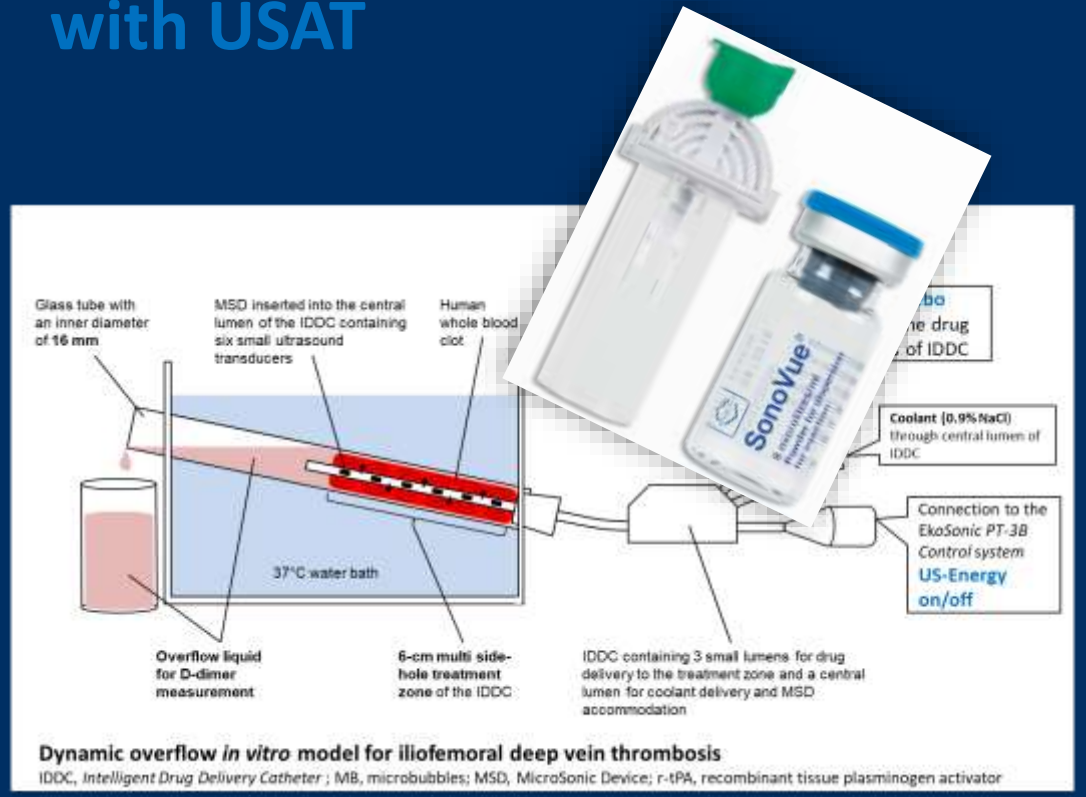
	No IVCF Group	IVCF Group	OR (95% CI)	p Value
Death	23 (1.0)	15 (0.7)	0.67 (0.34-1.26)	0.20
Blood transfusion	237 (10.5)	255 (11.3)	1.09 (0.90-1.31)	0.37
GI bleeding	44 (1.9)	32 (1.4)	0.73 (0.46-1.15)	0.17
Intracranial hemorrhage	13 (0.6)	15 (0.7)	1.16 (0.55-2.45)	0.70
Hematoma	47 (2.1)	76 (3.4)	1.63 (1.13-2.36)	0.009
Procedure-related hemorrhage	23 (1.0)	32 (1.4)	1.40 (0.81-2.39)	0.23
Length of stay (days)	6.0 (3.0-9.0)	6.0 (4.0-9.0)	–	<0.001
Charges ($)	92,881 ± 80,194	104,049 ± 75,572	–	<0.001
Peripheral angioplasty	1329 (58.8)	1394 (61.7)	1.13 (1.001-1.27)	0.048
Peripheral stent	634 (28.1)	673 (29.8)	1.09 (0.96-1.24)	0.20
Procedure-related renal failure	8 (0.4)	4 (0.2)	0.50 (0.15-1.65)	0.25
Acute renal failure	188 (8.3)	195 (8.6)	1.04 (0.84-1.28)	0.71
Transient ischemic attack	2 (0.1)	1 (0.04)	0.50 (0.045-5.49)	0.57
Embolic stroke	2 (0.1)	2 (0.1)	1.01 (0.14-7.20)	0.99
Procedure-related cardiac complications	5 (0.2)	5 (0.2)	1.01 (0.29-3.51)	0.98

Conclusion:
IVCF use was not associated with a decrease in in-hospital mortality but with **higher inpatient charges and longer length of stay**

Akhtar et al, JACC Cardiol Intv 2018;11:1390–7

What brings the future for CDT?

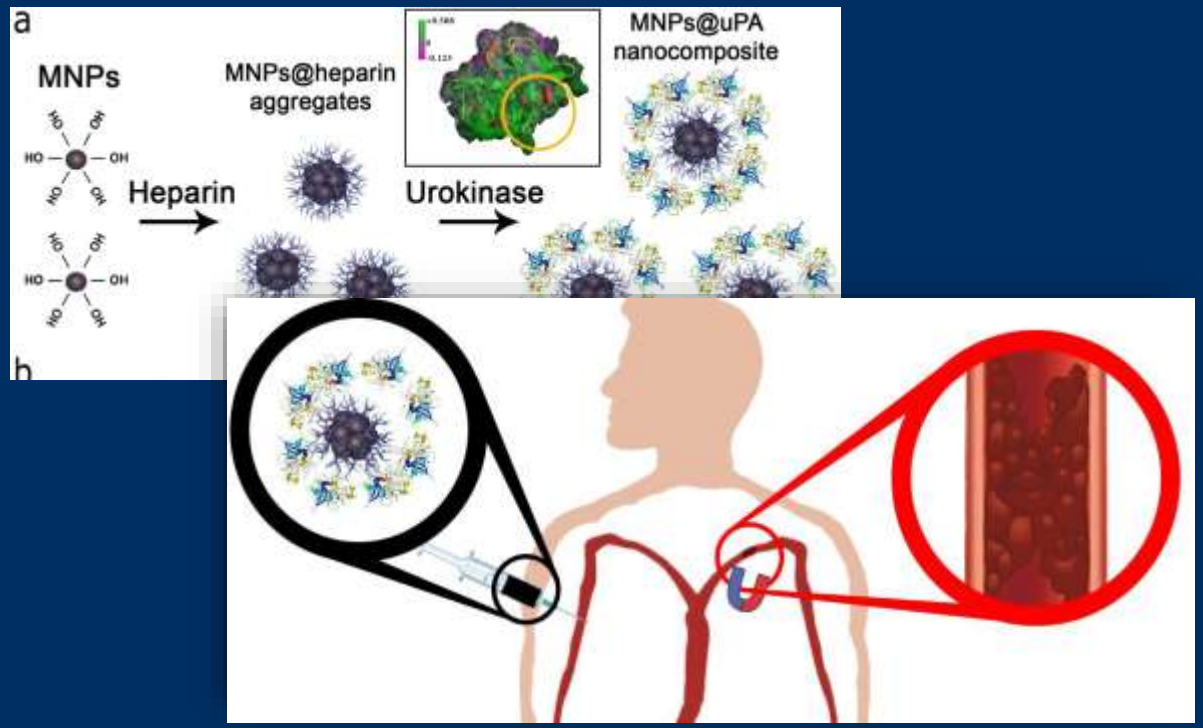
- **Intra-thrombus Microbubbles with USAT**



Dynamic overflow *in vitro* model for iliofemoral deep vein thrombosis

IDDC, *Intelligent Drug Delivery Catheter* ; MB, microbubbles; MSD, MicroSonic Device; r-tPA, recombinant tissue plasminogen activator

- **Magnetic nanoparticles for selected thrombolysis**



Engelberger et al, Thromb Haemost 2019;119:1094-1101

Prilepskii et al, ACS Appl Mater Interfaces 2018;10(43):36764-36775

Conclusion

- Catheter directed thrombolysis a well accepted treatment for iliofemoral DVT
- Pulse spray technique possibly more efficient than continuous infusion
  - but advantage of ultrasound-assisted CDT unclear (…. maybe in combination with MB??)
- However for good clinical outcome, the most important issues are:
  - Good patient selection
  - Concomitant treatment of underlying obstructive vein lesion → Stenting