EKOS
Venous Thromboembolism

Imagine where we can go.

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Peripheral Vascular Clot is Significantly Under Treated

VTE: Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE)

- 600,000 cases per year[1]
  - Combined with recurrent cases, estimates suggest 900,000+
  - For up to 200,000 of those with PE, the blood clot in the lung proves fatal—killing more people than AIDS and breast cancer combined[9]
- It is estimated that more than 250,000 patients are hospitalized annually with VTE[7]
- Estimated 30% of DVT/PE patients die within 3mths
- Up to 50% treated with blood thinners alone develop post-thrombotic syndrome (PTS)[3,5,6]

1. Society of Interventional Radiology. Fact Sheet. March 2005
2. White RH. The epidemiology of venous thromboembolism. Circulation 2003; 107[23 suppl 1]:14-18
3. Kahn SR, et al Relationship between deep venous thrombosis and the post thrombotic syndrome. Arch Intern Med 2004; 164:17-26
4. Biolex Therapeutics Researchers Present Preclinical Data for direct-acting thrombolytic BLX-155 at scientific conference March 2007
5. O'Donnell TF, Browse WL, Burnand KE, Thomas ML: The socio-economic effects of an iliofemoral deep venous thrombosis. J Surg Res 1977; 22: 483-88.
6. Linder DJ, Edwards JM, Phinney ES, et al: Long term sequelae of lower extremity deep venous thrombosis. J Vasc. Surg 1986; 4: 436-42.
7. Lacroix, P., et al. High prevalence of undiagnosed patients with peripheral arterial disease in patients hospitalised for non-vascular disorders. Int J Clin Pract., Jan 08, 62, 1 59-64

PE: A silent and fatal epidemic

- PE causes or contributes to 15% of all hospital deaths[1,2]
- More people die each year from PE than highway fatalities, breast cancer and AIDS combined[3]

Cause of Death	# of deaths/yr
PE[4,5]	Up to 200,000
Highway fatalities[6]	42,116
Breast Cancer[7]	40,200
AIDS[8]	14,499

1. Kasper et al. *J Am Coll Cardiol*. 1997;30:1165-1171
2. According to http://www.sirweb.org/patients/deep-vein-thrombosis/
3. Goldhaber. Deep-vein thrombosis: Advancing awareness to protect patient lives. American Public Health Association White Paper. 2003.
4. Anderson et al. *Arch Intern Med.* 1991;151:933-938.
5. Silverstein et al. *Arch Internal Med.* 1998;158:585-593.
6. National Highway and Traffic Safety Association. Fatality Analysis Reporting System (FARS) Web-Based Encyclopedia. Accessed January 31, 2002.
7. American Cancer Society. Breast cancer facts and figures, 2001-2002. Accessed January 31, 2002.
8. Centers for Disease Control Report. *HIV/AIDS Surveillance Report* 2001. Volume 13, Number 2.

Deep Vein Thrombosis (DVT)
Risk Factors

- Age 40 years or older
- Being overweight
- A personal or family history of blood clots
- Birth control pills
- Hormone replacement therapy (HRT)
- Cancer
- Certain heart problems
- Stroke
- Respiratory failure
- Varicose veins
- Pregnancy
- Surgery including hip, knee, or stomach surgery
- Restricted mobility due to a long illness, injury, or surgery

The more risk factors a person has, the greater the chances may be of developing DVT

Post Thrombotic Syndrome (PTS)

- Chronic condition in 30% to 75% of DVT patients within 2 years[1]
- Irreversible damage to veins and valves
- Enlarged veins may lead to insufficient valve closure
- Significant and lasting impact on quality of life
- Nearly 90% of patients are unable to work due to leg symptoms 10 years after iliofemoral DVT[2]

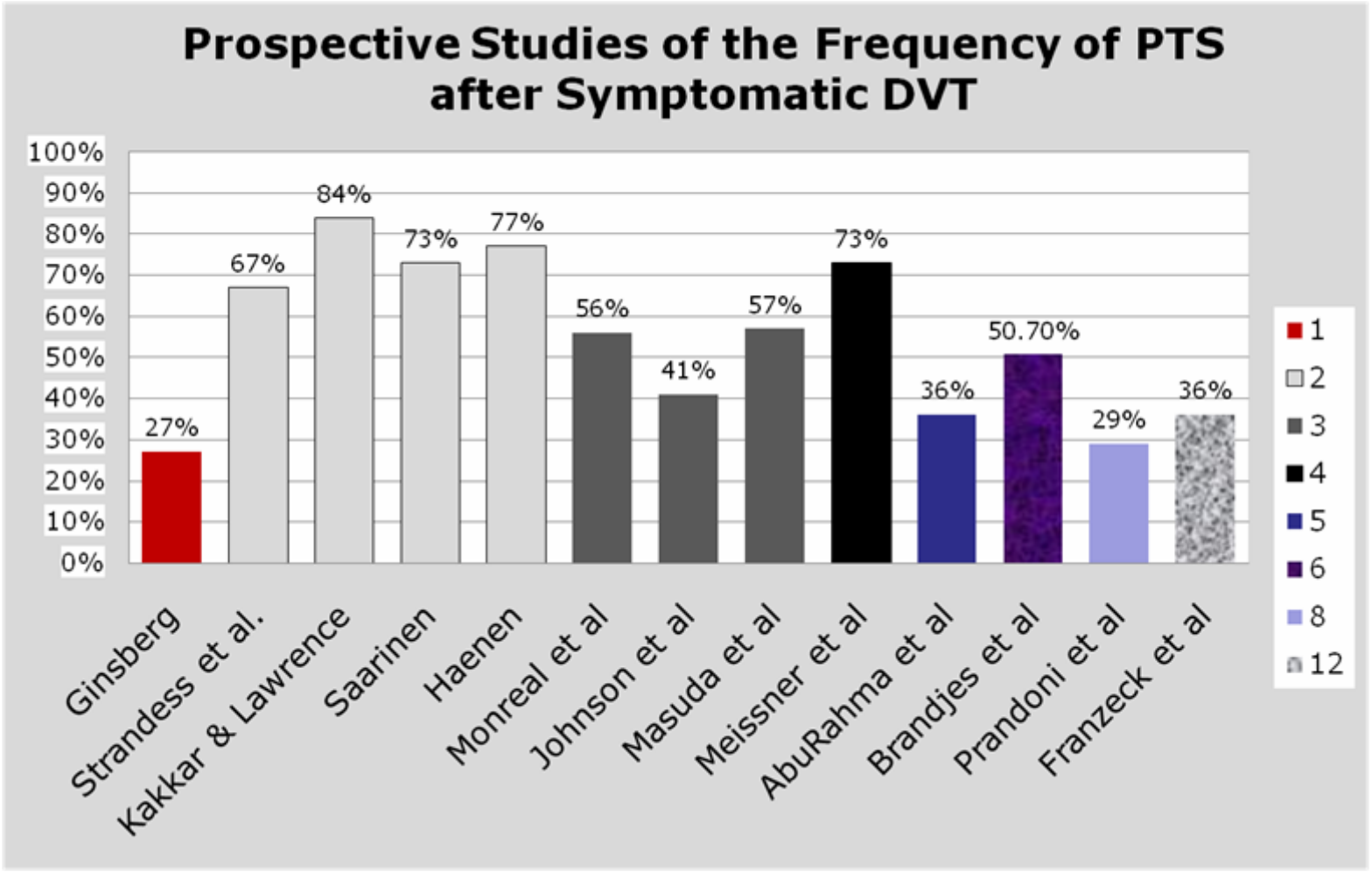
1. Parikh et al JVIR 2008 19; 521-528
2. Kahn SR, Ginsberg JS. "Relationship Between Deep Venous Thrombosis and the Post thrombotic Syndrome". Arch Intern Med 2004; 164:17–26.

" The long term sequelae of DVT in the lower limb comprising the post-thrombotic syndrome generate severe disability and marked compromise in quality of life."

- Chronic venous insufficiency
- Edema
- Ulceration
- Pain
- Claudication
- Discoloration
- Varicose Veins
- Amputation

Delis KT, et al. "Venous Claudication in Iliofemoral Thrombosis: Long Term Effects on Venous Hemodynamics, Clinical Status and Quality of Life". Ann Surg 2004; 239:118-126.

The DVT PTS Correlation

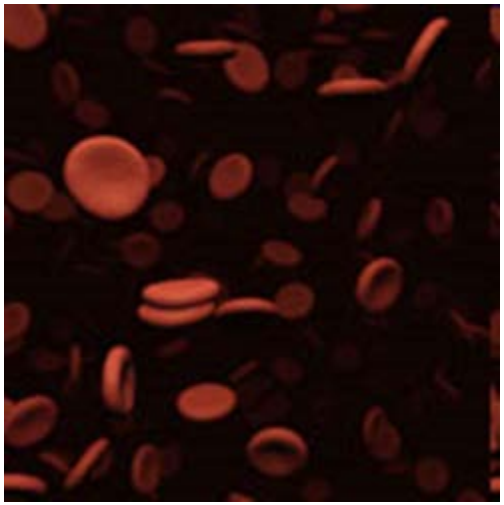


Kahn, S, et al.. *The Relationship between Deep Venous Thrombosis and The Post-Thrombotic Syndrome*. Arch Internal Medicine. Volume 164, January 12, 2004.

Standard treatment is inadequate

Anticoagulation Therapy

- Does not reduce or eliminate the existing thrombus
- 50% of patients on oral therapy are at sub-therapeutic levels
- Does not prevent long-term damage to the vein and valves, leading to high levels of PTS
- While it reduces the risk of Pulmonary Embolism, the risk remains significant



Current alternative treatments are inadequate

Systemic Thrombolysis

- Requires high drug doses
- Not locally targeted
- Increased drug dosage resulting in higher bleed rates (13-20%)

Traditional Endovascular (Catheter-Directed) Thrombolysis

- Long treatment times
- Associated with high levels (> 10%) of bleeding complications[1]

[1]Mewissen et al. Radiology. 1999 Apr;211(1):39-49.

CDT improves patency and reduces PTS compared to anticoagulation

CaVenT Trial:

Randomized, controlled clinical trial determining benefit of CDT

- 209 patients in 20 Norwegian hospitals; first time, acute IFDVT
- Treatment: anticoagulation vs. anticoagulation + CDT with tPA
- CDT group achieved more improved patient outcomes than anticoagulation:
  - Lower rate of PTS at 24 months f/u
  - Higher patency at 6 months f/u

Enden et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study). Lancet. 2012 Jan 7;379(9810):31-8.

Greater thrombus removal results in lower PTS rate

Study to evaluate correlation between residual thrombus and post-thrombotic syndrome (PTS)

- 71 consecutive IFDVT patients treated with CDT
- Blinded comparison of pre- and post-treatment phlebograms and evaluation of CEAP/Villalta scores
- **Direct** and **significant** correlation between PTS scores and thrombus clearance

CONCLUSION
When thrombus clearance is complete, PTS can be avoided

Comerota et al. Postthrombotic morbidity correlates with residual thrombus following catheter-directed thrombolysis for iliofemoral deep vein thrombosis. J Vasc Surg. 2012 Mar;55(3):768-73.

Acoustic Pulse Thrombolysis™shows high long-term patency, low bleeding rate and high PTS- free rates on DVT

- Prospective study of 87 consecutive iliofemoral DVT patients treated with EKOS® and stenting of underlying venous stenosis
- Fixed dose regimen of EKOS as primary therapy with 20 mg tPA over 15 hours
- Follow up at 3, 6, and 12 months measuring primary treatment success (Villalta PTS scale and CEAP classification).
- 1 major bleeding (1%), 6 minor bleedings (7%)

	3 months	6 months	12 months
No PTS	88%	92%	94%
No visible signs of venous disease	51%	53%	61%

Engelberger et al. Fixed Low-dose ultrasound-assisted catheter-directed thrombolysis followed by routine stenting or residual stenosis for acute ilio-femoral deep-vein thrombosis; Thrombosis and Haemostasis 111.6/2014.

Acoustic Pulse Thrombolysis™ for chronic DVT minimizes the risk of PTS

Single center registry at the Memorial Atasehir Hospital, Istanbul

- Inclusion: patients with DVT > **28** days symptomatic
- Treatment with a 5 mg bolus, followed by 0.02 mg/kg/hr tPA, followed by PTA and stenting if <50% thrombus clearance
- Follow-up examination at monthly intervals (Doppler and Villalta score)

EKOS® treatment of chronic DVT resulted in:

- a high rate of complete lysis with minimal adjunctive therapy
- >80% of the patients to be PTS-free & patency at long-term f/u.

Dumantepe et al. Treatment of Chronic Deep Vein Thrombosis Using Ultrasound Accelerated Catheter-directed Thrombolysis. Eur J Vasc Endovasc Surg. 2013 Sep;46(3):366-71

Acoustic Pulse Thrombolysis™ results in greater clot clearance than CDT

Multicenter registry of DVT cases treated using EKOS®:

- 8 sites
- 53 cases (acute, subacute, chronic, acute-on-chronic)
- EKOS® used with urokinase, reteplase, alteplase or tenecteplase

CONCLUSIONS:

- Ultrasound-accelerated thrombolysis was shown to be a safe and efficacious treatment for DVT.
- The addition of Ultrasound reduces total infusion time and provides a greater incidence of complete lysis with a reduction in bleeding rates.

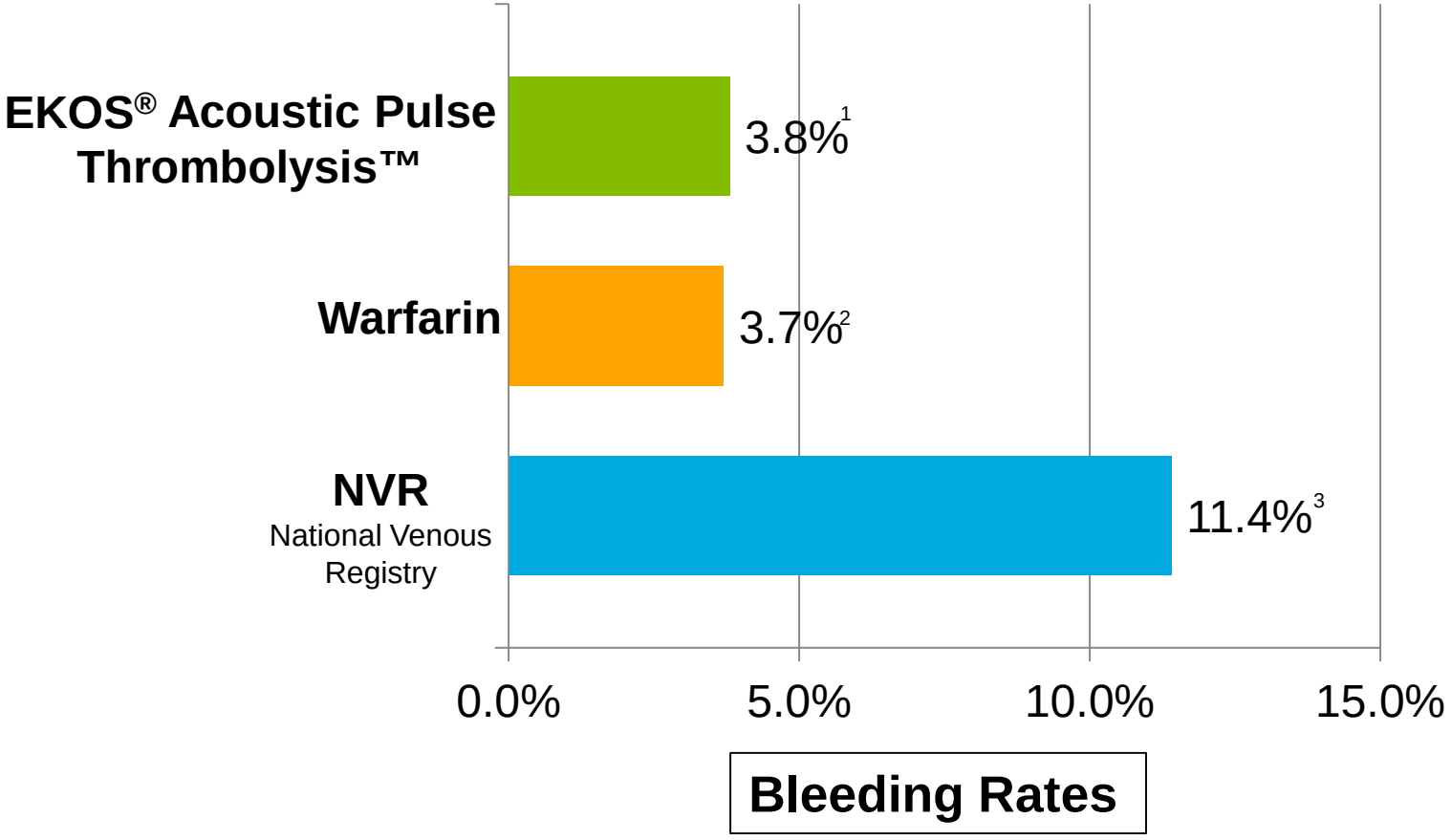
Parikh et al. Ultrasound-accelerated Thrombolysis for the Treatment of Deep Vein Thrombosis: Initial Clinical Experice. J Vasc Interv Radiol. 2008 Apr;19(4):521-8.

Acoustic Pulse Thrombolysis™ achieves clearance with lower lytic dose and infusion time than CDT

	Urokinase		Alteplase (t-PA)		Reteplase (r-PA)	
	EKOS®[1] (n=14)	CDT[2] (n=38)	EKOS®[1] (n=9)	CDT[2] (n=32)	EKOS®[1] (n=22)	CDT[2] (n=12)
Median Drug Dose	2.02 MU	4.36 MU	14.0 mg	21.6 mg	6.9 U	21.4 U
Median Infusion Time	19.3 hr	40.6 hr	18.0 hr	30.8 hr	24.0 hr	24.3 hr

1.Parikh et al. Ultrasound-accelerated Thrombolysis for the Treatment of Deep Vein Thrombosis: Initial Clinical Experice. J Vasc Interv Radiol. 2008 Apr;19(4):521-8.
2. Hofmann and Grunwald. J Vasc Interv Radiol. 2004 Apr;15(4):347-52.

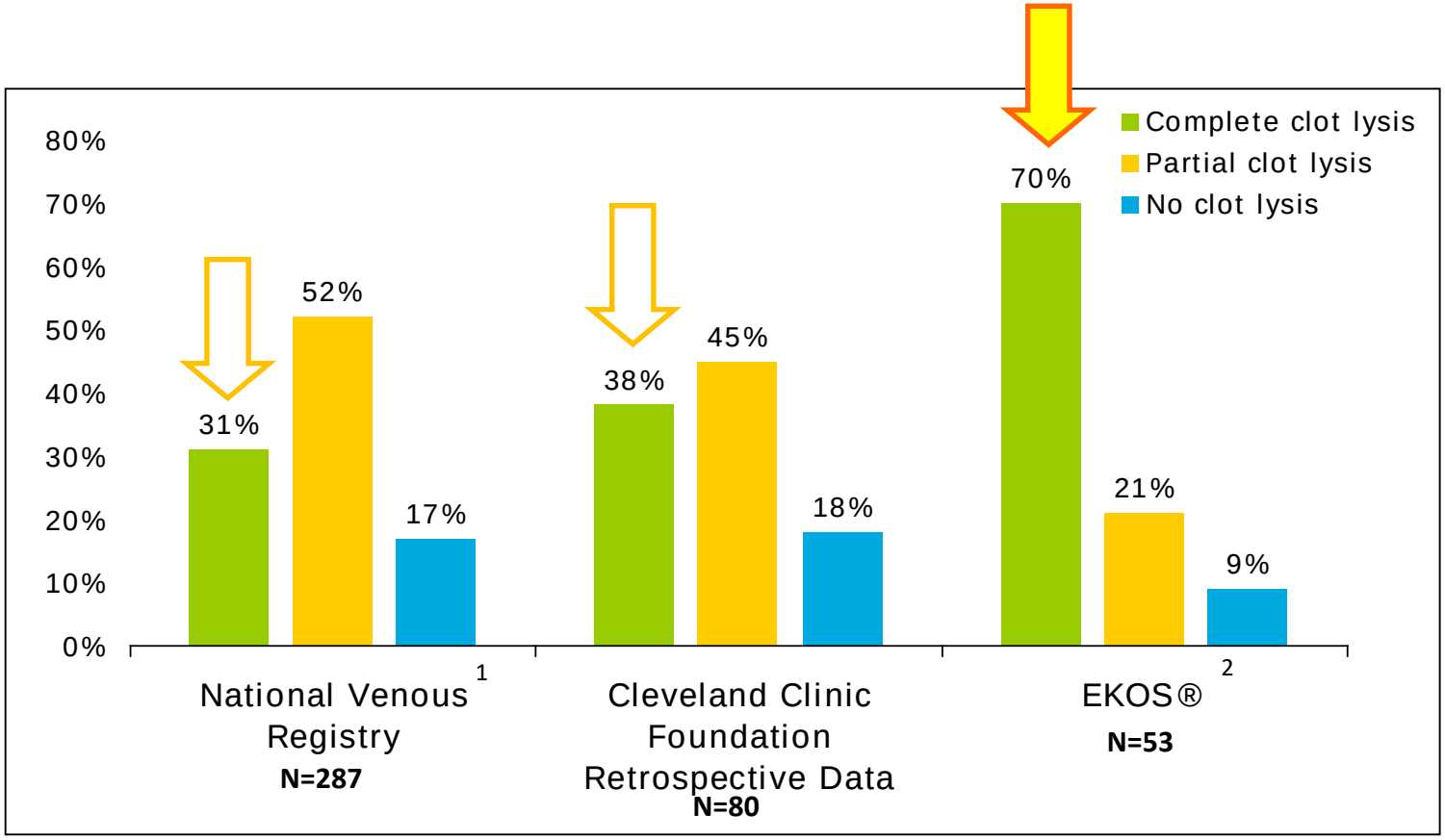
Acoustic Pulse Thrombolysis™ achieves lower bleeding rates than CDT



1. Parikh et al. J Vasc Interv Radiol. 2008 Apr;19(4):521-8.
2. Levine et al. Chest 2004; 126:287-310
3. Mewissen, et al. Radiology. 1999 Apr;211(1):39-49

NVR – registry of DVT patients treated with CDT

Acoustic Pulse Thrombolysis™ results in greater clot clearance than CDT



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EKOS Technology:

- EkoSonic® Endovascular System
- Mechanism of Action

EkoSonic® Endovascular Device

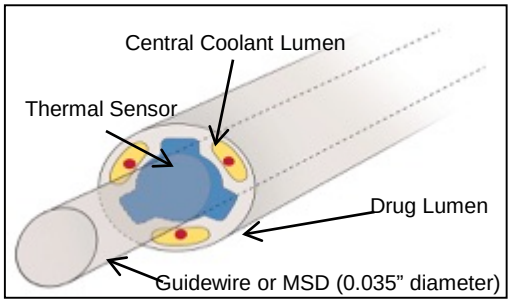
FDA clearance

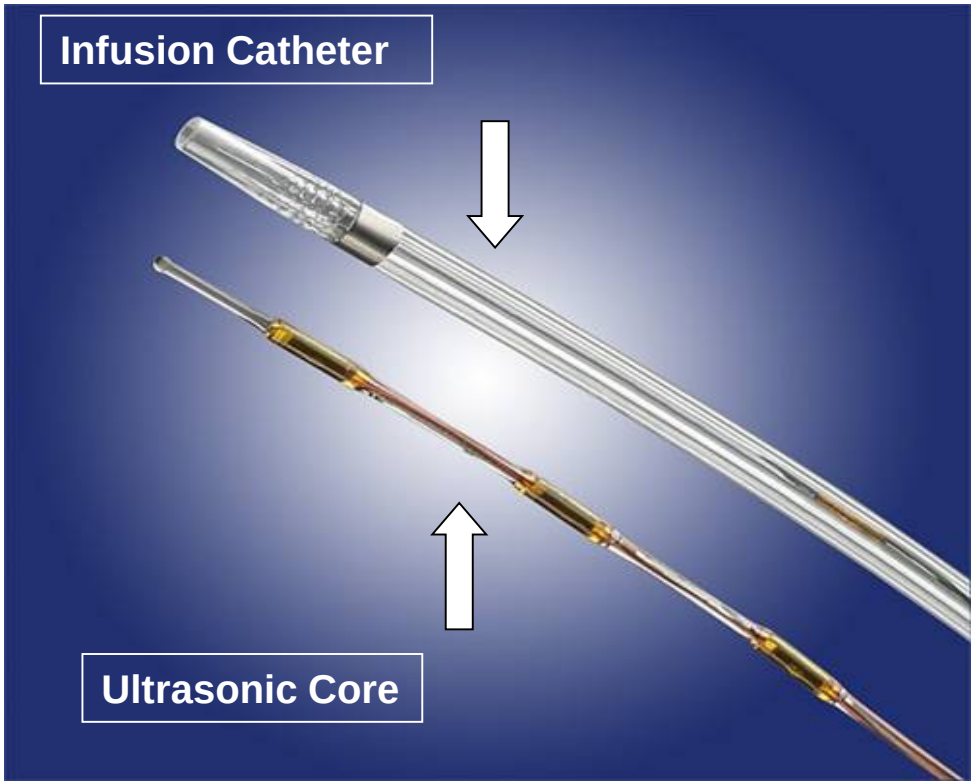
The EkoSonic® Endovascular System is intended for:

- controlled and selective infusion of physician-specified fluids, including thrombolytics, into the peripheral vasculature
- Infusion of solutions into the pulmonary arteries
- the ultrasound facilitated, controlled and selective infusion of physician-specified fluids, including thrombolytics, into the vasculature for the treatment of pulmonary embolism

http://www.ekoscorp.com/6084-001_H_IFU,%20Control%20Unit,%20EkoSonic%20with%20MACH4e%20Software%20(English).pdf
http://www.ekoscorp.com/fall2013/MACH4,%205.4F%20Peripheral%20(English).pdf
http://www.ekoscorp.com/fall2013/6225001_E_IFU%20EkoSonic%20MACH4,%205.4F%20PA%20(English).pdf
http://www.ekoscorp.com

EkoSonic® Endovascular System



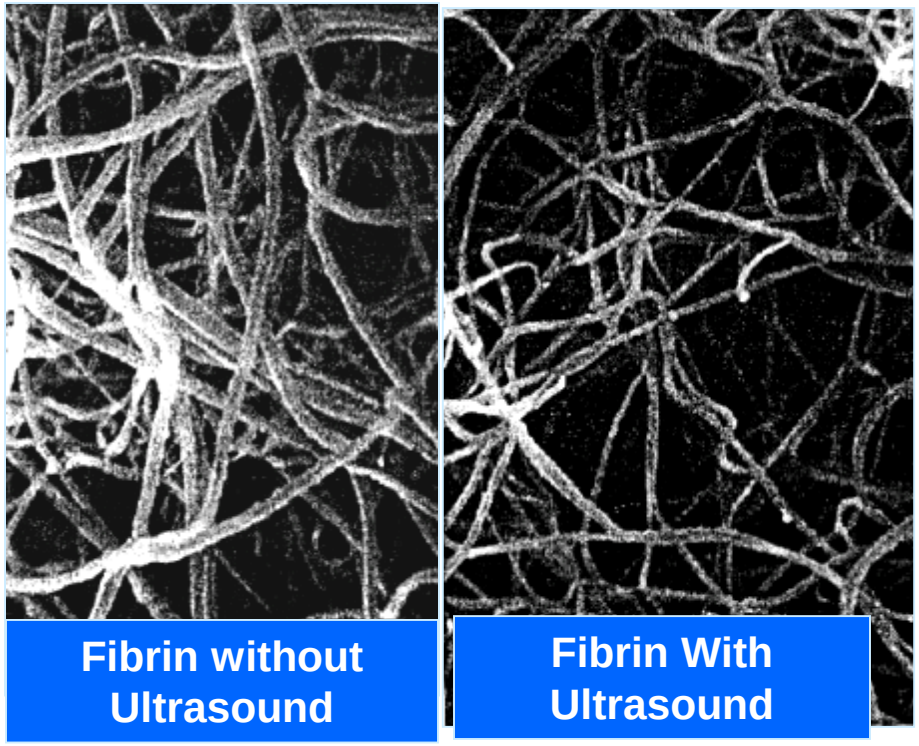


Features

- **5.4 Fr catheter**
- **106 and 135 cm working length**
- **6, 12, 18, 24, 30, 40 and 50 cm treatment zones**

Acoustic Pulse Thrombolysis™
Mechanism of action

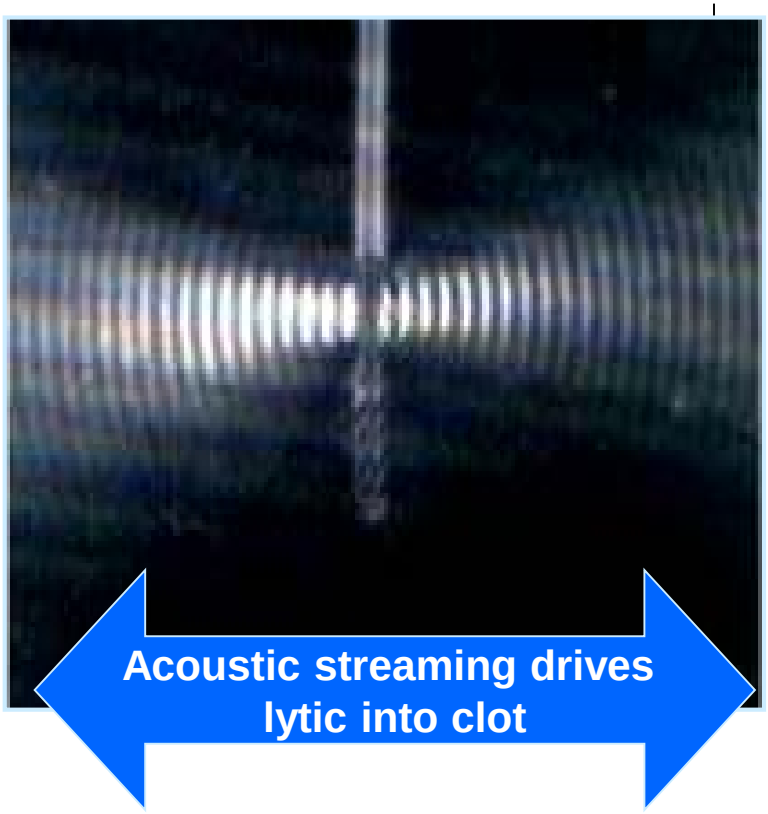
Fibrin Separation
Non-cavitational ultrasound separates fibrin without fragmentation of emboli



Fibrin without Ultrasound

Fibrin With Ultrasound

Active Drug Delivery
Drug is actively driven into clot by "Acoustic Streaming"



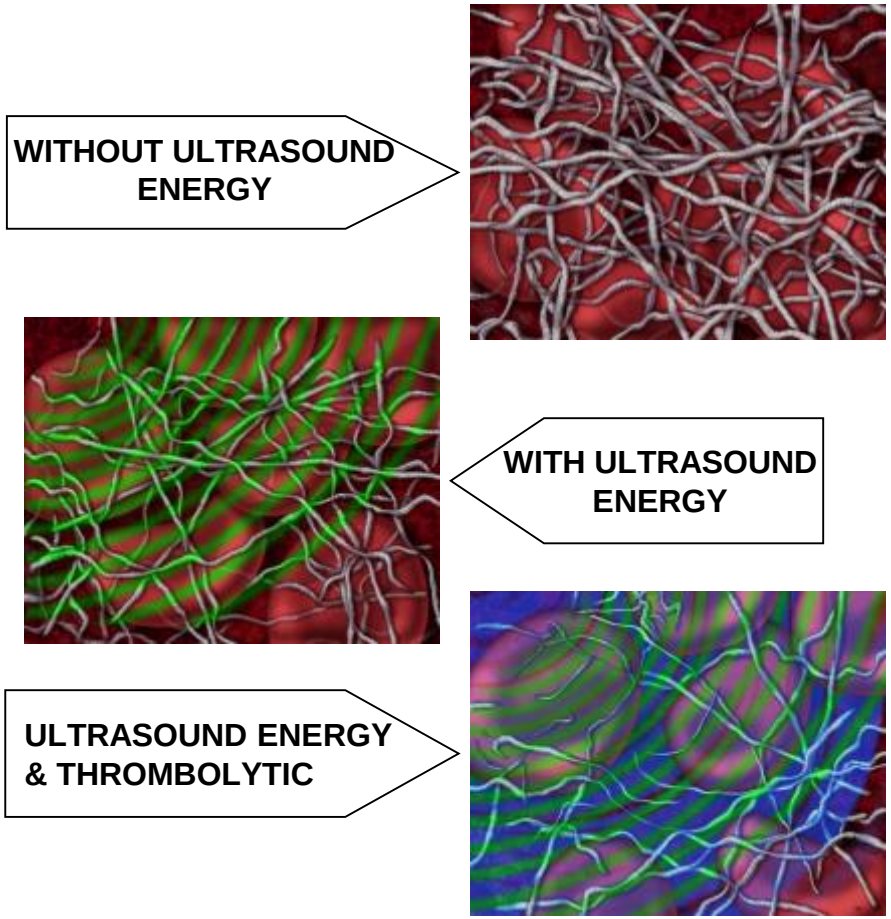
Braatan et al. Thrmob Haemost 1997;78:1063-8.
Francis et al. Ultrasound in Medicine and Biology, 1995;21(5):419-24.
Soltani et al. Physics in Medicine and Biology, 2008; 53:6837-47.

EkoSonic® Endovascular System

Mechanism of action

How ultrasonic energy unlocks the clot?

- Ultrasonic energy causes fibrin strands to thin, exposing plasminogen receptor sites and fibrin strands to loosen
- Thrombus permeability and lytic penetration are dramatically increased
- Ultrasound pressure waves force lytic agent deep into the clot and keep it there



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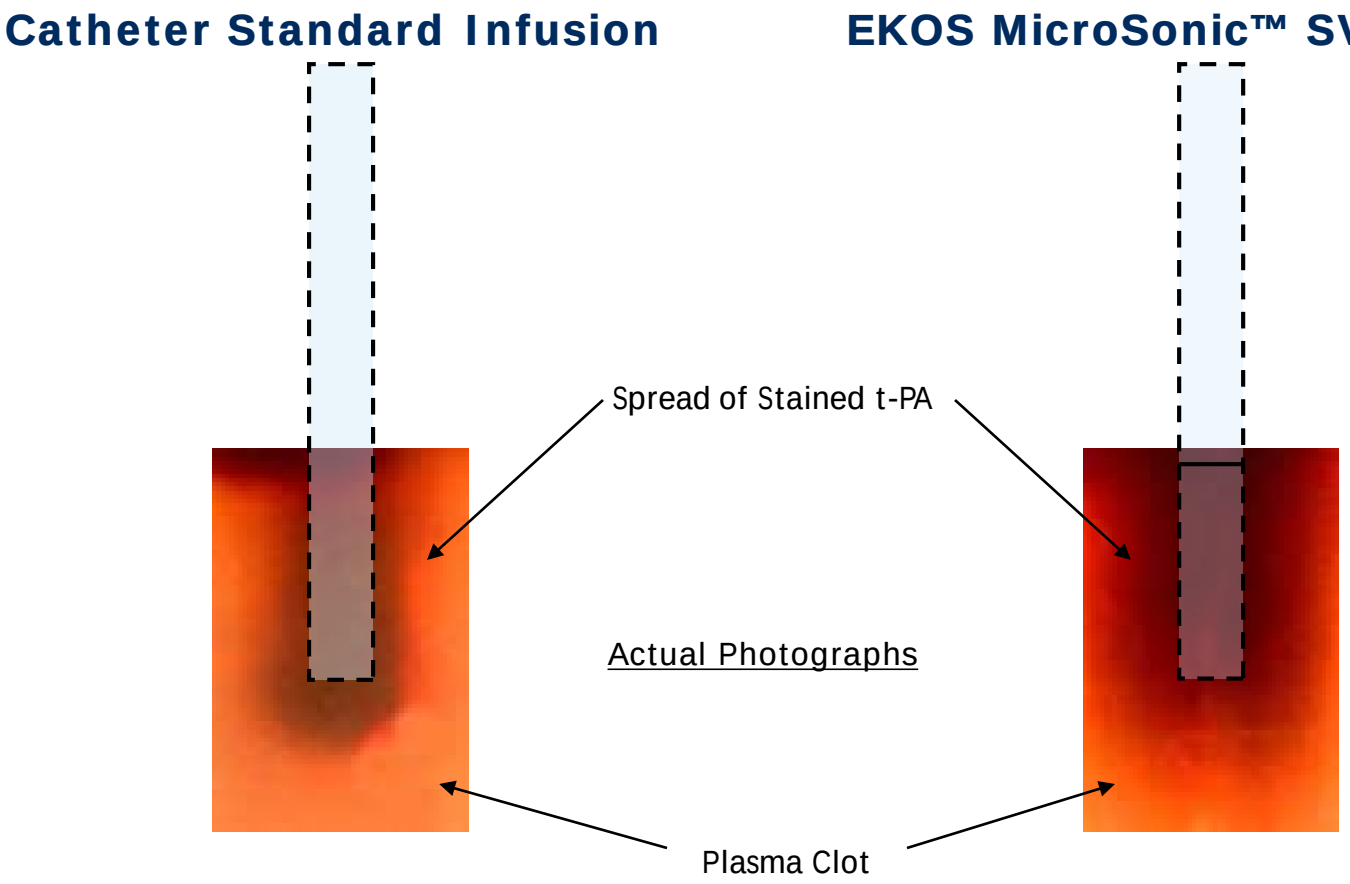
Soltani et al. Physics in Medicine and Biology, 2008; 53:6837-47.

Superior Lytic Penetration



In vitro demonstration: Human plasma clots were formed in culture tubes and identical volumes of tPA were delivered over 5 minutes through a standard end-hole catheter and a EKOS® microcatheter, followed by 10 minutes of dispersion time. The EKOS® catheter's ultrasound was activated for the entire 15 minutes. Following catheter removal, the dispersed tPA molecules were immuno-stained a dark red color showing the enhanced lytic penetration produced by the ultrasound