Imagine where we can go.

EKOS
Venous Thromboembolism

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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)\(^3,5,6\)

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PE: A silent and fatal epidemic

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

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th># of deaths/yr</th>
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<tbody>
<tr>
<td>PE\textsuperscript{4,5}</td>
<td>Up to 200,000</td>
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<td>Highway fatalities\textsuperscript{6}</td>
<td>42,116</td>
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<tr>
<td>Breast Cancer\textsuperscript{7}</td>
<td>40,200</td>
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<td>AIDS\textsuperscript{8}</td>
<td>14,499</td>
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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
“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

The DVT PTS Correlation

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

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

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

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%)

<table>
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<th></th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
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<tbody>
<tr>
<td>No PTS</td>
<td>88%</td>
<td>92%</td>
<td>94%</td>
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<tr>
<td>No visible signs of venous disease</td>
<td>51%</td>
<td>53%</td>
<td>61%</td>
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</table>

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

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<tr>
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<th>Alteplase (t-PA)</th>
<th>Reteplase (r-PA)</th>
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<tr>
<td>EKOS®¹ (n=14)</td>
<td>2.02 MU</td>
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<td>CDT² (n=38)</td>
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<td>EKOS®¹ (n=22)</td>
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<tr>
<td>CDT² (n=12)</td>
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<tr>
<td>Alteplase</td>
<td>14.0 mg</td>
</tr>
<tr>
<td>Reteplase</td>
<td>6.9 U</td>
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<table>
<thead>
<tr>
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<th>Median Infusion Time</th>
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<tr>
<td>Urokinase</td>
<td>19.3 hr</td>
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<tr>
<td>Alteplase</td>
<td>18.0 hr</td>
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<tr>
<td>Reteplase</td>
<td>24.0 hr</td>
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Acoustic Pulse Thrombolysis™ achieves lower bleeding rates than CDT

**Bleeding Rates**

- **EKOS® Acoustic Pulse Thrombolysis™**: 3.8%
- **Warfarin**: 3.7%
- **NVR (National Venous Registry)**: 11.4%

2. Levine et al. Chest 2004; 126:287-310

NVR – registry of DVT patients treated with CDT
Acoustic Pulse Thrombolysis™ results in greater clot clearance than CDT


NVR – registry of DVT patients treated with CDT
Imagine where we can go.

EKOS Technology:
- EkoSonic® Endovascular System
- Mechanism of Action
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
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

Active Drug Delivery
Drug is actively driven into clot by “Acoustic Streaming”

Fibrin without Ultrasound
Fibrin With Ultrasound

Acoustic streaming drives lytic into clot

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.

**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.