

# Canadian Society of Internal Medicine

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## How to Prevent and Manage the Post-Thrombotic Syndrome?

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Medicine  
UNIVERSITY OF TORONTO



**Sunnybrook**  
HEALTH SCIENCES CENTRE

## CSIM Annual Meeting 2017

The following presentation represents the views of the speaker at the time of the presentation. This information is meant for educational purposes, and should not replace other sources of information or your medical judgment.

### **Learning Objectives:**

- The open-vein hypothesis, rationale for CDT
- Brief presentation of ATTRACT trial results
- Overview of PTS – other - preventative measures

# CSIM Annual Meeting 2017

## Conflict Disclosures

**Definition:** A Conflict of Interest may occur in situations where the personal and professional interests of individuals may have actual, potential or apparent influence over their judgment and actions.

I have the following conflicts to declare

	Company/Organization	Details
Advisory Board or equivalent	Bayer	
Speakers bureau member		
Payment from a commercial organization. (including gifts or other consideration or 'in kind' compensation)	Daiichi Sankyo Leo Pharma	
Grant(s) or an honorarium		Bayer Pfizer
Patent for a product referred to or marketed by a commercial organization.		
Investments in a pharmaceutical organization, medical devices company or communications firm.		
Participating or participated in a clinical trial	Bayer Daichi Sankyo	

# Background

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- **Post thrombotic syndrome (PTS) refers to clinical manifestations of chronic venous insufficiency following a DVT**
- **Non fatal disease but...**
  - **Frequent**
    - Up to 40% of patients after proximal DVT
    - 5-10% will develop severe PTS
  - **High Morbidity**
    - Impact on QOL similar to chronic diseases such as with diabetes or arthritis
  - **Expensive**
    - 40% increase of medical cost

# Background

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- Exact pathophysiology is poorly understood
  - Consequence of venous stasis due to obstruction or reflux
- There is no curative treatment of established PTS

**Cornerstones of PTS management lie on its prevention, including CDT at the acute phase of DVT**

# Early Thrombus Removal Techniques

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- **IV thrombolysis = OLD**
  - No convincing data on effectiveness
  - Certain higher bleeding risk
- **CT directed thrombolysis:**
  - Refers to direct intrathrombus administration of a fibrinolytic drug via a catheter or device embedded within the thrombus , usually introduced via popliteal vein, using imaging guidance
    - t-PA instillation into thrombus
    - Prolonged t-PA infusion
    - Mechanical / US thrombectomy
    - Venous balloon angioplasty
    - Venous stent

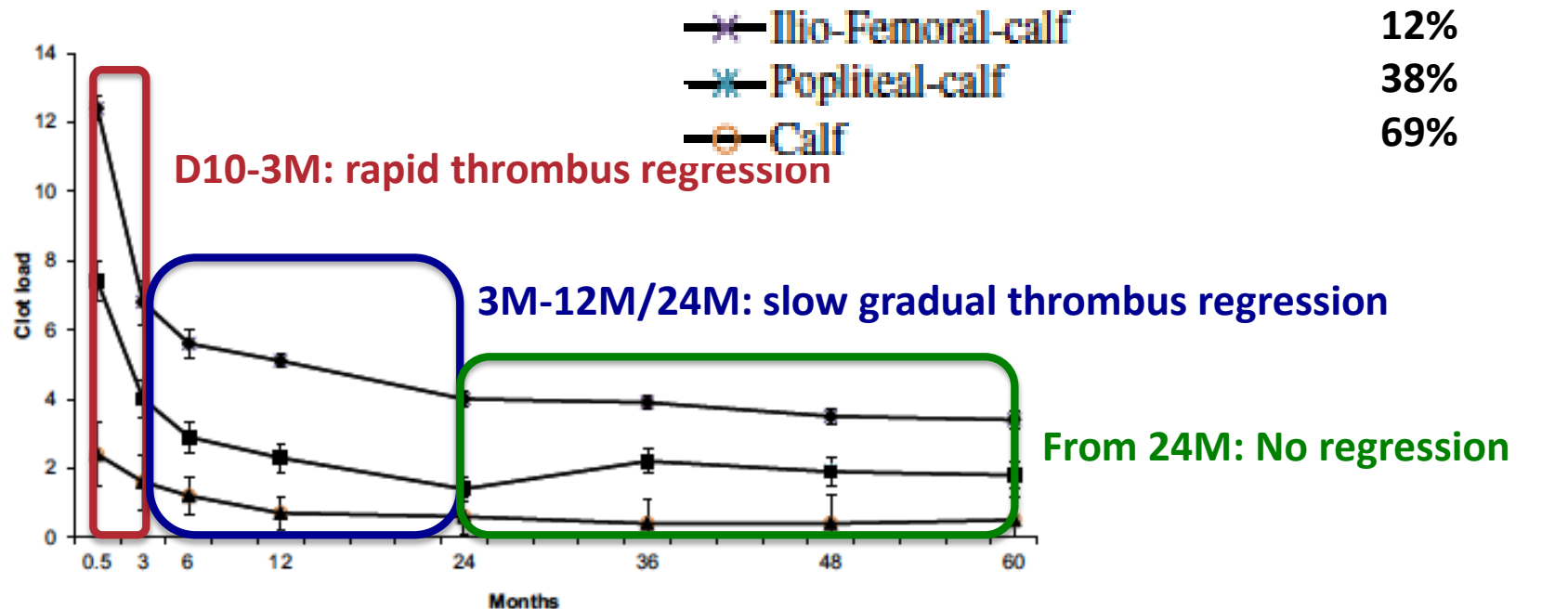
**Effectiveness of CDT to prevent PTS based on “open-vein hypothesis”**

# Prospective Study of Natural History of Deep Vein Thrombosis: Early Predictors of Poor Late Outcomes

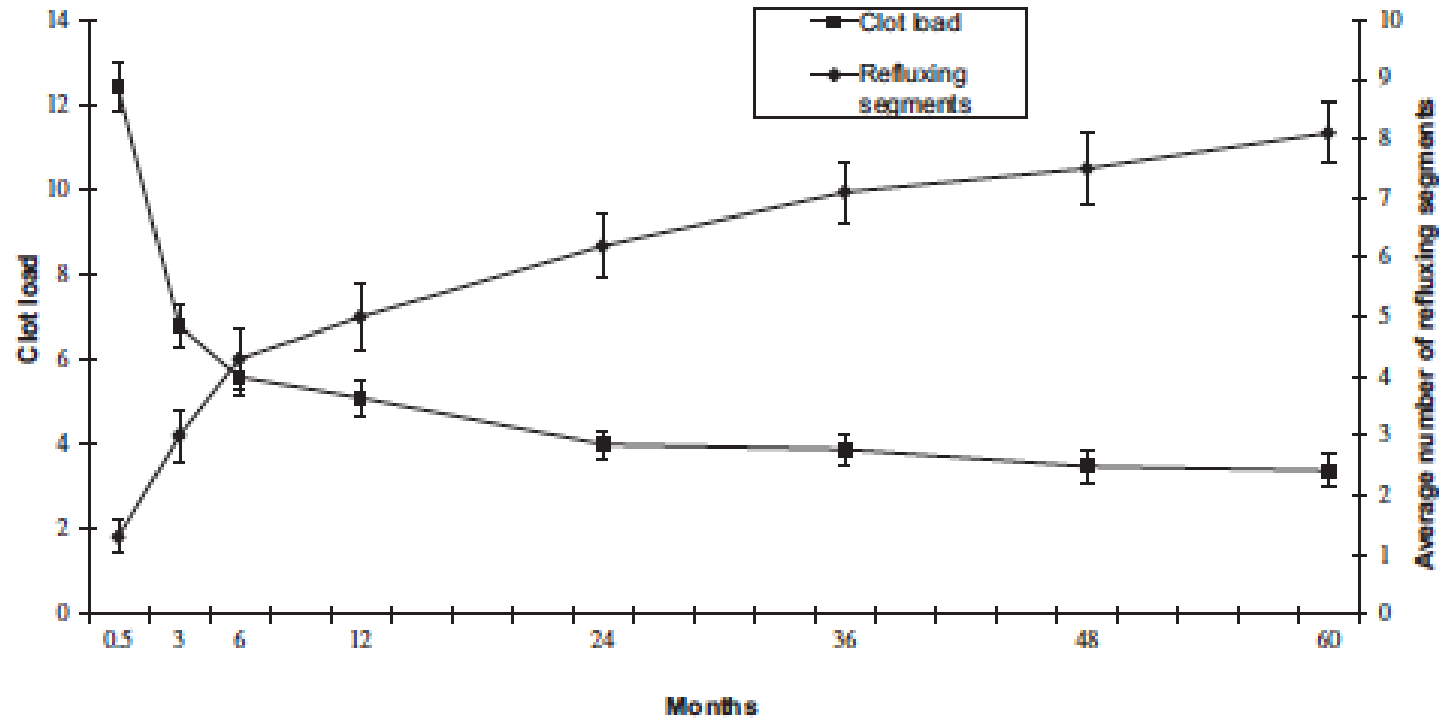
André M. van Rij, Gerry Hill, Jo Krysa, Samantha Dutton, Riordon Dickson, Ross Christie, Judi Smillie, Ping Jiang, and Clive Solomon, Dunedin, New Zealand

*Ann Vasc Surg* 2013; 27: 924–931

- 114 patients with DVT
- 5 years of FU with CUS
- **Thrombus regression, 3 phases**



- Venous reflux



Decrease in clot load mirrored by a simultaneous increase in reflux score

Nber refluxing segments significantly greater in case of extensive DVT

The soonest recanalisation is achieved, the less the risk of reflux is



## **PTS pathophysiology**

- **Venous return is impaired either by obstruction or reflux**
- **Reflux follows obstruction**
- **Early clot resolution is associated with better valve function preservation and less reflux**

**Early thrombus removal strategies have the potential to treat all major components of PTS pathophysiology**

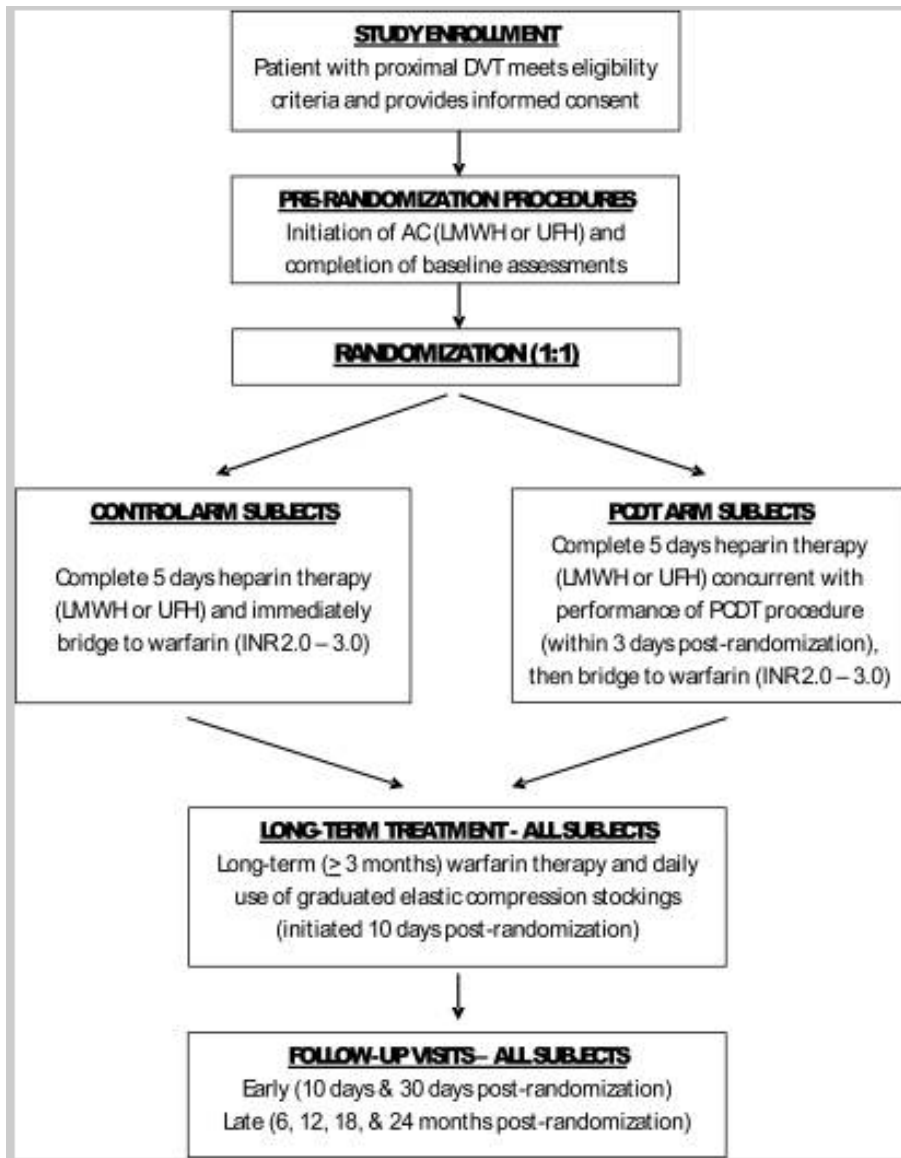
**“Open Vein Hypothesis”**

**Considering that Ilio-femoral DVT is**

- **Location of DVT at highest risk of PTS**
- **Only provider of venous claudication (up to > 40%!)**
- **Complete venous recanalisation with conventional AC ttnt is uncommon in case of IF-DVT**

**Ili-femoral DVT: best candidate for venous recanalization**

# ATTRACT Study (NEJM 2017)



- Iliac, CF or SF DVT
- Exclusion:
  - Symptoms > 14 days
  - <16 and >75 yrs
  - high bleeding risk
  - Cancer
- Rando DVT extent & centre
- Hypothesis: 30% RR PTS (from 30% to 20%)

# Results

- 691 patients randomized
- Age 53 years
- 57% of Iliac or CF DVT
- 88% adjunctive treatment to CDT:
  - balloon maceration, ATL, Thrombectomy, Stent, Aspiration

Outcome	PCDT n=336	No-PCDT n=355	P Value
<b>Any PTS</b>	47%	48%	0.56
<b>Moderate/Severe PTS</b>	18%	24%	0.035
MS-PTS: IF-DVT	18%	28%	
MS-PTS: FP-DVT	17%	18%	
Leg Pain (10 d)	- 1.6	- 1.3	0.019
Leg Swelling (10 d)	- 0.3	+ 0.3	0.024
<b>Major Bleeding (10 d)*</b>	1.7%	0.3%	0.049
Any Bleeding (10 d)	4.5%	1.7%	0.034
<b>Recurrent VTE</b>	13%	8%	0.09

# Conclusion ATTRACT

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## CDT

- Does not prevent PTS
- May reduce the severity of PTS in patients with Iliac or CF DVT
- Reduces acute symptoms
- But increases bleeding

# Prevention of PTS and large RCTs...

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- CDT: Failed to prevent PTS (ATTRACT)
- Compression stockings:
  - Failed to prevent PTS (SOX)
  - Removed from Guidelines as a strategy to prevent PTS

**How can we prevent PTS in 2017?**

# Anticoagulation and PTS: « Back to the... Past »

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- **Anticoagulation**
  - Prevents clot extension and embolization
  - ... but does not dissolve existing thrombi
  
- **However...**

# THROMBOSIS

## EARLY DIAGNOSIS AND ABORTIVE TREATMENT WITH HEPARIN

GUNNAR BAUER  
M.D.

*From the Mariestad Hospital, Mariestad, Sweden*

TABLE VII—THROMBOSIS LOCALISED TO LOWER LEG. COMPARISON OF RESULTS UP TO 3 YEARS. (After Bauer 1942)

Symptoms and signs		Non-heparinised (19 cases)	Heparinised (38 cases)
Swelling	None ..	..	30
	Severe ..	100%	0%
Induration	None ..	5	38
	Mild ..	9	..
	Severe ..	5	..
Ulceration	Absent ..	10	28
	Present ..	16%	0%
Heaviness in leg, pains	Absent ..	1	22
	Present ..	95%	5%

Introduction of AC has dramatically decreased the risk of PTS

# Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome

C. J. J. VAN DONGEN,\*† P. PRANDONI,‡ M. FRULLA,‡ A. MARCHIORI,‡ M. H. PRINSS and B. A. HUTTEN\*†

**Table 2** Estimated risk for development of the postthrombotic syndrome *J Thromb Haemost* 2005; (univariate and multivariate analysis)

	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Age > 65 year	2.33	1.34–4.05	2.56	1.39–4.71
Female vs. male	1.74	1.00–3.01	1.65	0.90–3.02
Cancer vs. no cancer	1.05	0.53–2.09	1.17	0.58–2.69
BMI > 25	1.12	1.04–2.00	1.14	1.06–1.23
Ipsilateral recurrence	6.91	2.15–22.2	9.57	2.64–34.7
Percentage of time in lowest INR range*	2.42	1.36–4.32	2.71	1.44–5.10

\*More than 50% time vs. < 50% spent beneath the target range. INR, International Normalized Ratio; OR, odds ratio.

- Similar results were reported in the REVERSE study

**Poor INR initial control : 3 times increased risk of PTS** 06



## Home Therapy of Venous Thrombosis with Long-term LMWH versus Usual Care: Patient Satisfaction and Post-thrombotic Syndrome 2009

Russell D. Hull, MBBS, MSc,<sup>a</sup> Graham F. Pineo, MD,<sup>a</sup> Rollin Brant, PhD,<sup>b</sup> Jane Liang, MSc,<sup>a</sup> Roy Cook, MD,<sup>a</sup> Susan Solymoss, MD,<sup>c</sup> Man-Chiu Poon, MD, MSc,<sup>a</sup> Gary Raskob, PhD,<sup>d</sup> for the LITE Trial Investigators

<sup>a</sup>University of Calgary, Calgary, AB, Canada; <sup>b</sup>University of British Columbia, Vancouver, BC, Canada; <sup>c</sup>McGill University, Montreal, QC, Canada; <sup>d</sup>College of Public Health, University of Oklahoma Health Sciences Center, Oklahoma City.

- RCT Home-LITE
- 480 Proximal DVT treated for 3 months
- Tinzaparine alone vs Tinzaparine + VKA
- PTS assessment with auto-questionnaire **at 3 months:**
  - SPT: OR= 0.77 [0.67 – 0.90]
- Confirmed upon a meta-analysis evidencing better recanalization under LMWH

**LMWH could be > to VKA in PTS prevention**

- **Anti-inflammatory effect?**
- **Prevention of infra-clinic recurrence?**

# Post-thrombotic syndrome in patients treated with rivaroxaban or enoxaparin/vitamin K antagonists for acute deep-vein thrombosis

## A post-hoc analysis

Y. Whitney Cheung<sup>1</sup>; Saskia Middeldorp<sup>1</sup>; Martin H. Prins<sup>2</sup>; Akos F. Pap<sup>3</sup>; Anthonie W. A. Lensing<sup>3</sup>; Arina J. ten Cate-Hoek<sup>4,5</sup>; Sabina Villalta<sup>6</sup>; Marta Milan<sup>7</sup>; Jan Beyers-Westendorf<sup>8</sup>; Peter Verhamme<sup>9</sup>; Rupert M. Bauersachs<sup>10,11</sup>; Paolo Prandoni<sup>7</sup>; on behalf of the Einstein PTS Investigators Group\*

Thromb Haemost 2016;

	Rivaroxaban N=162	Enox + VKA N=174	
Age	57	58	
BMI	28	28	
Ilio-femoral DVT	57%	67%	
ECS use	69%	80%	
Time INR <2		21%	
FU Months	58	57	
PTS	29%	40%	<b>HR= 0.76 (0.5–1.1)</b>
Leg ulcer	2%	6%	

### DOAC

- At least as effective as VKA
- could be > to VKA in PTS prevention

# The Stockings Dilemma

## Venous Compression for Prevention of Postthrombotic Syndrome: A Meta-analysis

Muzamil H. Musani, MD,<sup>a</sup> Fadi Matta, MD,<sup>b</sup> Abdo Y. Yaekoub, MD,<sup>c</sup> Jane Liang, MSc,<sup>d</sup> Russell D. Hull, MBBS, MSc,<sup>d</sup> Paul D. Stein, MD<sup>a</sup>

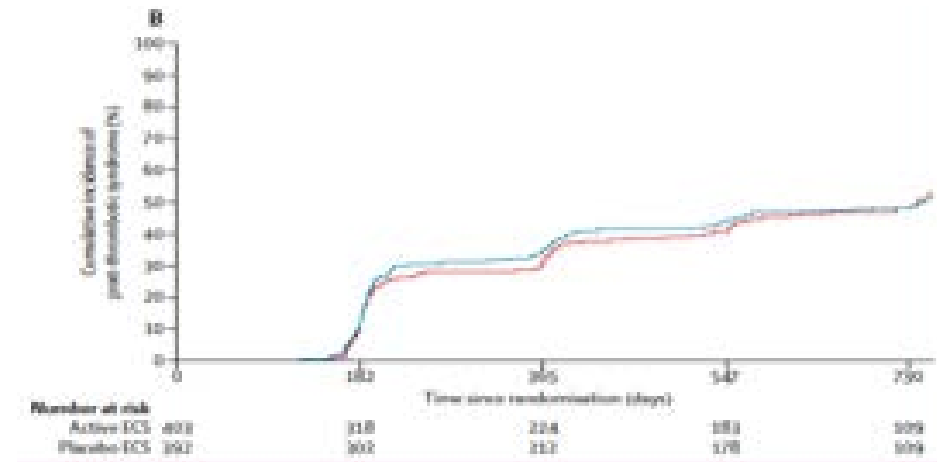
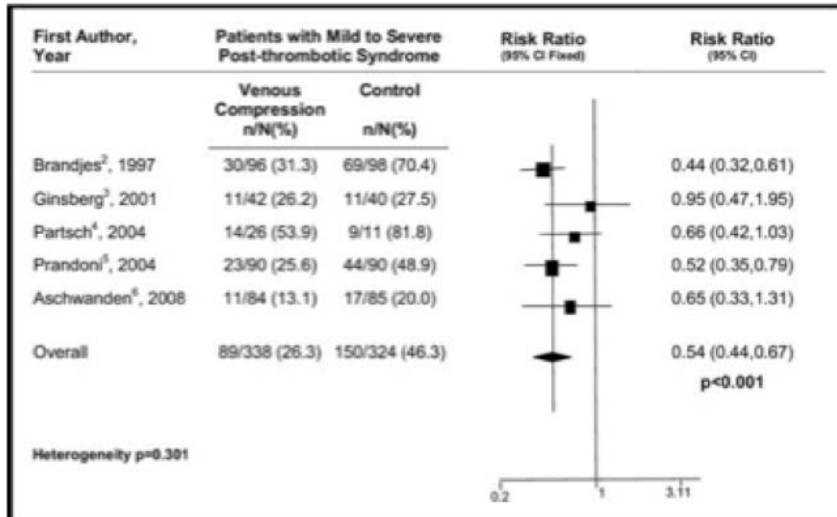
THE AMERICAN  
JOURNAL of  
MEDICINE®

2010

## Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial

Susan R Kahn, Stan Shapiro, Philip S Wells, Marc A Rodger, Michael J Kovacs, David R Anderson, Vicky Tagalakis, Adriëtte H Houweling, Thierry Ducruet, Christina Holcroft, Mira Johni, Susan Solymoss, Marie-José Miron, Erik Yeo, Reginald Smith, Sam Schufman, Jeannine Kassis, Clive Kearon, Isabelle Chagnon, Turnly Wong, Christine Demers, Rajendar Hanmiah, Scott Kaatz, Rita Selby, Rita Rathbun, Sylvie Desmarais, Lucie Opatrný, Thomas L Ortel, Jeffrey S Ginsberg, for the SOX trial investigators

Lancet 2014



Small open-label RCTs  
662 patients  
... High potential for placebo effect

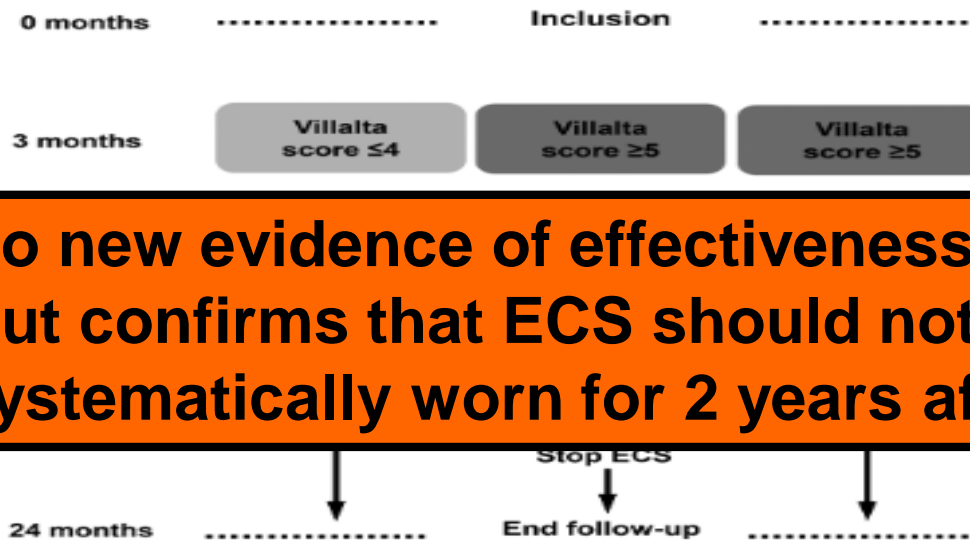
Large double blind-RCT  
> 800 patients  
... Poor compliance

# LB 01.3 | The IDEAL DVT Study, Individualised Duration of Elastic Compression Therapy against Long-term Duration of Therapy for the Prevention of Post-thrombotic Syndrome: A Randomised Controlled Trial

A.J. ten Cate-Hoek, the IDEAL DVT investigators

*Maastricht University Medical Center +, Thrombosis Expertise Center, Cardiovascular Center, Maastricht, The Netherlands*

- ECS 2 Years vs. Tailored duration based on clinical examination
- 865 Proximal DVT



• No new evidence of effectiveness of ECS  
• But confirms that ECS should not be systematically worn for 2 years after a DVT

**28.9% (TD) vs. 27.8% (C2a), HR 1.13 (0.88 - 1.46)**

# Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial

Ylva Haig, Tone Ender, Ole Grøtta, Nils-Einar Kløv, Carl-Erik Slagsvold, Waleed Ghanima, Leiv Sandvik, Geir Hafslahl, Pål Andre Holme, Lars Olaf Holmen, Anne Mette Njøaastad, Gunnar Sandbæk, Per Morten Sandset, on behalf of the CaVenT Study Group\*

Lancet Haematol 2016;

LT FU (5 years) of CaVenT RCT on CDT in 189 patients with of 1<sup>st</sup> iliac or CFV DVT  
At 2 years: 41.1% vs. 55.6%, p=0.047

	Adjunctive catheter-directed thrombolysis (n=87)		Standard treatment (n=89)		p value*	Risk difference (absolute risk reduction)
Post-thrombotic syndrome	37	42.5% (32.7-53.0)	63	70.8% (60.6-79.3)	<0.0001	28% (14-42)
Villalta severity category						
Mild (score 5-9)	31/37	83.8% (68.5-92.7)	49/63	77.8% (66.0-86.4)	-	-
Moderate (score 10-14)	2/37	5.4% (0.57-18.6)	12/63	20.6% (12.2-32.3)	-	-
Severe (score >14)	4/37	10.8% (3.7-25.3)	1/63	1.6% (0.0-9.3)	-	-
Iliofemoral patency†	68/86	79.1% (69.2-86.4)	61/86	70.9% (60.6-79.5)	0.218	-8% (-21 to 5)
Femoropopliteal reflux	54/87	62.1% (51.6-71.6)	75/89	84.3% (75.2-90.5)	<0.0004	22% (10-35)

Data are n, n/N, or % (95% CI), unless otherwise stated. \* $\chi^2$  test. †Four patients had inconclusive iliofemoral patency assessments at 5 years.

Table 2: Post-thrombotic syndrome 5 years after acute deep vein thrombosis

	Adjunctive catheter-directed thrombolysis (n=87)	Standard treatment (n=89)	p value*
Quality of life			
EQ-5D	0.78 (0.72-0.84)	0.79 (0.74-0.84)	0.874
Disease-specific quality of life			
VEINES-QOL	50.5 (49.0-52.0)	49.6 (48.2-50.9)	0.365
VEINES-Sym	51.0 (49.4-52.5)	49.1 (47.5-50.6)	0.086

Data are mean (95% CI). \* $\chi^2$  test.

Table 3: Quality-of-life scores 5 years after acute proximal deep vein thrombosis

- In CDT arm
  - Persistent & increased benefit of CDT
  - Very few additional PTS
- But...
  - No impact on rate of severe PTS
  - No impact on QOL

# Conclusion... Take Home Message

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- Optimal management of PTS lies on its prevention after a DVT
- Optimal anticoagulation = best preventative measures ++
  - Good INR monitoring during first 3 months is crucial
  - DOAC could be > to VKA
  - ? LMWH few days in case of very symptomatic prox DVT
- Benefit of ECS to prevent PTS is debated **BUT**
  - ECS are useful at acute phase of symptomatic DVT to treat symptoms
  - Duration ECS should be extended in persistent symptomatic patients (no need to treat 2 years asymptomatic pts)
- Benefit of CDT is likely but in very limited number of pts
  - Should be reserved to extensive obstructive iliac/CFV DVT