LINC: Deep vein thrombosis & pulmonary embolism

Compression & anticoagulation therapy for acute proximal DVT: How good is it?

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I have the following potential conflicts of interest to report:

- Consulting: Abbott Endovascular, Medtronic, EV3, Cordis, Sanofi Aventis, Daiichi Sankyo, Bayer, Boeringer Ingelheim, and AstraZeneca
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s) Owner of two pairs of sports compression stockings offered by Sigvaris and Salzman
Outcome and management of proximal DVT

Potential outcomes of venous thrombosis

**Antithrombotic Therapy for VTE Disease**

**Background:** This article addresses the treatment of VTE disease.

**Methods:** We generated strong (Grade 1) and weak (Grade 2) recommendations based on high-quality (Grade A), moderate-quality (Grade B), and low-quality (Grade C) evidence.

**Results:** For acute DVT or pulmonary embolism (PE), we recommend initial parenteral anticoagulant therapy (Grade 1B) or anticoagulation with rivaroxaban. We suggest low-molecular-weight heparin (LMWH) or fondaparinux over IV unfractionated heparin (Grade 2C) or subcutaneous unfractionated heparin (Grade 2B). We suggest thrombolytic therapy for PE with hypotension (Grade 2C). For proximal DVT or PE, we recommend treatment of 3 months over shorter periods (Grade 1B). For a first proximal DVT or PE that is provoked by surgery or by a nonsurgical transient risk factor, we recommend 3 months of therapy (Grade 1B, Grade 2B if provoked by a nonsurgical risk factor and low or moderate bleeding risk); that is unprovoked, we suggest extended therapy if bleeding risk is low or moderate (Grade 2B) and recommend 3 months of therapy if bleeding risk is high (Grade 1B); and that is associated with active cancer, we recommend extended therapy (Grade 1B, Grade 2B if high bleeding risk) and suggest LMWH over vitamin K antagonists (Grade 2B). We suggest vitamin K antagonists or LMWH over dabigatran or rivaroxaban (Grade 2B). We suggest compression stockings to prevent the postthrombotic syndrome (Grade 2B). For extensive superficial vein thrombosis, we suggest prophylactic-dose fondaparinux or LMWH over no anticoagulation (Grade 2B), and suggest fondaparinux over LMWH (Grade 2C).

**Conclusion:** Strong recommendations apply to most patients, whereas weak recommendations are sensitive to differences among patients, including their preferences.

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Mid-to-moderate post-thrombotic syndrome

- single centre
- non-placebo
- small sample sizes (n=90/group)
- ~ 50% reduction in PTS
Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial

Dr Susan R Kahn, MD, Stan Shapiro, PhD, Philip S Wells, MD, Marc A Rodger, MD, Michael J Kovacs, MD, David R Anderson, MD, Vicky Tagalakis, MD, Adrielle H Houweling, MSc, Thierry Ducruet, MSc, Christina Holcroft, ScD, Mira Johri, PhD, Susan Solymoss, MD, Maria-José Miron, MD, Erik Yeo, MD, Reginald Smith, PharmD, Sam Schulman, MD; Jeannine Kassler, MD, Clive Kearon, MB, Isabella G, Hanmiak, MD, Scott Katsanis, MD, PhD, Sue Blais, MA

4012 patients assessed for eligibility

1265 declined to participate
1941 were excluded (some for >1 reason)
127 had more than 14 days since diagnosis of DVT
133 not planned for anticoagulant therapy
43 had symptomatic arterial claudication
575 had an expected lifespan of less than 6 months
379 were unable to apply the stockings
15 planned for thrombolysis of acute DVT
261 were geographically inaccessible for follow-up
488 were unable to provide informed consent
66 met exclusion criteria related to celecoxib intervention (discontinued)

806 randomly assigned to receive intervention

410 assigned to receive active ECS
408 received allocated intervention
1 did not receive allocated intervention
1 was ineligible (excluded from analysis)

30-40mmHg

396 assigned to receive placebo ECS
392 received allocated intervention
2 did not receive allocated intervention
2 were ineligible (excluded from analysis)

5mmHg

23 were lost to follow-up
33 withdrew from the study
36 died

409 assessed

21 were lost to follow-up
37 withdrew from the study
36 died

394 assessed
Ginsberg's criteria of ipsilateral pain and swelling of at least 1 month's duration that are typical in character.
**Outcomes by treatment group**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Active stockings (n=409)</th>
<th>Placebo stockings (n=394)</th>
<th>Hazard ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
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<tr>
<td>Number of post-thrombotic syndrome events as assessed by Ginsberg’s criteria† (cumulative incidence‡)</td>
<td>44 (14.2%)</td>
<td>37 (12.7%)</td>
<td>1.13 (0.73-1.76)</td>
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<tr>
<td>Secondary outcomes</td>
<td></td>
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<tr>
<td>Number of post-thrombotic syndrome events as assessed by Villalta’s criteria§ (cumulative incidence¶)</td>
<td>176 (52.6%)</td>
<td>168 (52.3%)</td>
<td>1.00 (0.81-1.24)</td>
</tr>
<tr>
<td>Villalta severity category¶¶</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>None (score ≤5)</td>
<td>185 (51.3%)</td>
<td>179 (51.4%)</td>
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<tr>
<td>Mild (6-9)</td>
<td>119 (33.0%)</td>
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<td></td>
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<tr>
<td>Moderate (10-14)</td>
<td>30 (8.3%)</td>
<td></td>
<td></td>
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<tr>
<td>Severe (&gt;14 or ulcer)</td>
<td>27 (7.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral leg ulcer¶¶</td>
<td>17 patients (4.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent venous thromboembolism</td>
<td>36 patients (8.1%);</td>
<td></td>
<td></td>
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<tr>
<td>(36 DVT, 9 pulmonary)</td>
<td></td>
<td></td>
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<tr>
<td>Recurrent ipsilateral DVT</td>
<td>16 patients (3.9%)</td>
<td></td>
<td></td>
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<tr>
<td>Ipsilateral venous valvular reflux at 12 months**</td>
<td>120/291 (41.2%)</td>
<td></td>
<td></td>
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<tr>
<td>Death††</td>
<td>36 (8.8%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Analysis of prespecified subgroups**

- **Sex**
  - Male (n=478)
  - Female (n=217)
  - Hazard ratio (95% CI) p=0.047

- **BMI**
  - <25 (n=210)
  - 25-30 (n=303)
  - >30 (n=282)
  - Hazard ratio (95% CI) p=0.60

- **Age category (years)**
  - <40 (n=132)
  - 40-65 (n=435)
  - >65 (n=228)
  - Hazard ratio (95% CI) p=0.38

- **Most proximal extent of DVT**
  - Iliac or common femoral vein (n=307)
  - Femoral or popliteal vein (n=488)
  - Hazard ratio (95% CI) p=0.55

**Comparison of treatment groups**

- Compression: 30-40 mmHg
- Control: 5 mmHg

**Comparison metrics**

- Favorable outcomes: active stockings vs. placebo stockings
- Unfavorable outcomes: placebo stockings vs. active stockings
Graduated compression stockings to treat acute leg pain associated with proximal DVT
A randomised controlled trial

Susan R. Kahn; Stan Shapiro; Thierry Ducruet; Philip S. Wells; Marc A. Rodger; Michael J. Kovacs; and David Ansell

Pain scores

<table>
<thead>
<tr>
<th>Visit</th>
<th>Mean (SD)*</th>
<th>Active ECS N=272</th>
<th>Placebo ECS N=291</th>
<th>Difference in means (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>5.08 (3.33)</td>
<td>5.27 (3.33)</td>
<td>0.19 (-0.36, 0.74)</td>
<td>0.50</td>
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<tr>
<td>14-day</td>
<td>2.20 (2.54)</td>
<td>2.40 (2.63)</td>
<td>0.21 (-0.22, 0.64)</td>
<td>0.35</td>
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<tr>
<td>1-month</td>
<td>1.73 (2.50)</td>
<td>1.71 (2.36)</td>
<td>-0.02 (-0.42, 0.38)</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>60-day</td>
<td>1.35 (2.24)</td>
<td>1.10 (1.88)</td>
<td>-0.25 (-0.59, 0.10)</td>
<td>0.16</td>
<td></td>
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</tbody>
</table>

*numbers who attended the one-month follow-up visit were 388, active ECS, and 378, placebo ECS.

* mean (standard deviation) numerical pain rating score, based on a scale of 10 (0, no pain; 10, worst possible pain).
Anticoagulation and VTE recurrence

Rate of DVT per 100 patient-years

Months since DVT

OAK

STOP OAK
Anticoagulation and VTE recurrency

Rate of DVT per 100 patient-years

Months since DVT

STOP OAK
Anticoagulation and VTE recurrence
Anticoagulation and VTE recurrence

Phases of anticoagulation:
- Initial: (0 to ~7 days)
- Long-term: (~7 days to ~3 months)
- Extended: (~3 months to indefinite)

Initial phase:
- Parenteral*: Heparin, LMWH, fondaparinux

Long-term phase:
- Vitamin K antagonist or other agent†: Includes LMWH, dabigatran, rivaroxaban

Extended phase:

Rate of DVT per 100 patient-years

Months since DVT

OAK: On-anticoagulation
STOP OAK: Stop anticoagulation
Anticoagulation and VTE recurrency

A. Acute DVT Study

Cumulative Event Rate for Primary Efficacy Outcome (%)

Rate of DVT per 100 patient-years

No. at Risk
- Rivaroxaban: 1731, 1668, 1648, 1621, 1424, 1412, 1220, 400, 369, 363, 345, 309, 297, 266

P<0.001 for noninferiority

Einstein, NEJM; 2012
Prolonged Anticoagulation and VTE recurrency

Einstein, NEJM; 2012
How good is anticoagulation for VTE/Bleeds?

Einstein, NEJM; 2012, Drugs 2014, J of Thrombosis&Hemostasis 2014
How good is anticoagulation for VTE/Bleeds?

Major bleeding rate: 0.45 %/year
Fatal bleeding rate was 0.14%/ year
Recurrency rates: 7.4-10%/year (unprovoked DVT)

Net event rate: ~8-10%

Einstein, NEJM; 2012, Drugs 2014, J of Thrombosis&Hemostasis 2014
How good is anticoagulation for VTE/Bleeds?

No anticoagulation

- Major bleeding rate: 0.45 %/year
- Fatal bleeding rate: 0.14%/ year
- Recurrency rates: 7.4-10%/year
  (unprovoked DVT)

Anticoagulation

- Bleeding rate: 1.4-2 %/year
- Fatal bleeding rate was 0.1%/ year
- Recurrency rates: 1.3-3%/year

Net event rate:
- No anticoagulation: ~8-10%
- Anticoagulation: ~2.8-5%

Einstein, NEJM; 2012, Drugs 2014, J of Thrombosis&Hemostasis 2014
How good is anticoagulation for PTS?

Subtherapeutic anticoagulation after a first unprovoked DVT was significantly associated with the development of PTS.
Conclusion

- **Compression:** *Not as good as we thought it would be*
  - No real benefit in clinical outcome & pain relief
  - Compression therapy for those pts. with physical benefit
  - Await “The IDEAL Deep Venous Thrombosis (DVT) Study”

- **Anticoagulation:** *Good and getting better*
  - Decreases risk of recurrence initial phase and long term
  - Fairly balanced risk of bleeds
  - Therapeutic anticoagulation may prevent PTS
“To understand thrombosis, we need to look beyond thrombosis”