Antithrombotic Prophylaxis in the Acutely Ill Medical Patient

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Medical

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What is wrong with the guidelines?
Contraceptive Advice?

Celibates
Medical Advice ?
Overview

- In-hospital thromboprophylaxis
- Extended thromboprophylaxis (inpatient and outpatient)
- Guidelines
- New Studies
- Conclusions
Overview

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# Medical thromboprophylaxis

<table>
<thead>
<tr>
<th>Study</th>
<th>RRR</th>
<th>Thromboprophylaxis</th>
<th>Patients with VTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDENOX$^1$</td>
<td>63%</td>
<td>Placebo</td>
<td>14.9$^*$</td>
</tr>
<tr>
<td>p &lt; 0.001</td>
<td></td>
<td>Enoxaparin</td>
<td>5.5</td>
</tr>
<tr>
<td>PREVENT$^2$</td>
<td>49%</td>
<td>Placebo</td>
<td>5.0$^*$</td>
</tr>
<tr>
<td>p = 0.0015</td>
<td></td>
<td>Dalteparin</td>
<td>2.8</td>
</tr>
<tr>
<td>ARTEMIS$^3$</td>
<td>47%</td>
<td>Placebo</td>
<td>10.5$^{†}$</td>
</tr>
<tr>
<td>p = 0.029</td>
<td></td>
<td>Fondaparinux</td>
<td>5.6</td>
</tr>
</tbody>
</table>

$^*$VTE at day 14; $^{†}$VTE at day 15.

RRR = relative risk reduction

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Contemporary studies of extended thromboprophylaxis in hospitalised patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Primary efficacy endpoint* (%)</th>
<th>Major bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCLAIM (2010)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Placebo</td>
<td>4.0</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Extended enoxaparin Day 10–38</td>
<td>2.5</td>
<td>0.8</td>
</tr>
<tr>
<td>MAGELLAN&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Enoxaparin/placebo</td>
<td>5.7</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Extended rivaroxaban Day 1–35</td>
<td>4.4</td>
<td>1.1</td>
</tr>
<tr>
<td>ADOPT&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Enoxaparin/placebo</td>
<td>3.1</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Extended apixaban Day 1–30</td>
<td>2.7</td>
<td>0.5</td>
</tr>
</tbody>
</table>


<sup>2</sup>Cohen AT et al. ACC 2011 Oral Pres.
<sup>3</sup>Goldhaber SZ et al. NEJM. 2011; epub 13 Nov.
Novel oral anticoagulants

Hit the target
Summary

- In-hospital thromboprophylaxis
- Extended thromboprophylaxis (inpatient and outpatient)

Guidelines

- New studies
- Conclusions
Looks can be deceptive
Looks can be deceptive
Looks can be deceptive

- They look evidence based but they are not!

- They may have evidence of risk but NOT evidence of response to preventive therapy
Guidelines

- IUA – International Consensus Statement
  - Published in International Angiology
  - No evidence of a rigorous process of evaluation

- ACP
  - Published in Annals of Internal Medicine

- ACCP
  - Published in Chest

- NICE (National Institute of Healthcare and Clinical Excellence)
  - Published in UK
guff (ɡʌf)  n

[C19: Norwegian *gufts* puff of wind]

Word Origin & History: guff
"empty talk, nonsense," 1888, from earlier sense of "puff of air" (1825), of imitative origin.
American College of Physicians

ACP
Conclusion of the Abstract:

“Heparin prophylaxis had no significant effect on mortality, may have reduced PE in medical patients and all patients combined, and led to more bleeding and major bleeding events, thus resulting in little or no net benefit.”

ACP recommends pharmacologic prophylaxis with heparin or a related drug for venous thromboembolism in medical (including stroke) patients unless the assessed risk for bleeding outweighs the likely benefits (Grade: strong recommendation, moderate-quality evidence).

Qaseem A et al. Annals of Internal Medicine, 2011;155:625-632
Large Hadron Collider

Higgs boson or “God” particle
## Total Mortality in Nonsurgical Patients – Am Coll Phys

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of studies</th>
<th>~patients</th>
<th>Intervention n/N (%)</th>
<th>Control n/N (%)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical patients</td>
<td>10</td>
<td>21,000</td>
<td>679/10,466 (6.5)</td>
<td>679/10,251 (6.6)</td>
<td>0.94 (0.84 to 1.04)</td>
</tr>
<tr>
<td>Patients with stroke</td>
<td>8</td>
<td>15,000</td>
<td>496/5276 (9.4)</td>
<td>990/10,129 (9.8)</td>
<td>0.91 (0.70 to 1.18)</td>
</tr>
<tr>
<td>All patients combined</td>
<td>18</td>
<td>36,000</td>
<td>1175/15,742 (7.5)</td>
<td>1669/20,380 (8.2)</td>
<td>0.93 (0.86 to 1.00)</td>
</tr>
</tbody>
</table>

Sample size – best case

- 8% (5-10%) mortality at 3 months
- 10% (6-14%) die from PE
- 0.8% of all deaths
- Thromboprophylaxis results in a 70% reduction in PE deaths (0.56%)
- (RR 0.93)

- Death rates 8% and 7.44%
- Alpha 5%, beta 0.2 (80% power)
- 72,000
ACCP
Prince
The Artist Formerly Known As Prince
Prevention of VTE

This is 1A

General Medical Patients
- LDH (Grade 1A)
- LMWH (Grade 1A)

Prevention of VTE

This is 1B
Formerly known as 1A

General Medical Patients
- LDH (Grade 1B)
- LMWH (Grade 1B)

Khan S et al. Chest 2012
For acutely ill medical patients admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, we recommend thromboprophylaxis with LMWH (Grade 1A), LDUH (Grade 1A), or fondaparinux (Grade 1A).

Geerts W et al, ACCP 2008 Chest 2008
Risk Assessment Model: Padua observational study of 1180 patients – all patients admitted to a medical department

<table>
<thead>
<tr>
<th>Baseline features</th>
<th>Score</th>
</tr>
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<tr>
<td>Active cancer*</td>
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</tr>
<tr>
<td>Previous VTE (with the exclusion of superficial vein thrombosis)</td>
<td>3</td>
</tr>
<tr>
<td>Reduced mobility†</td>
<td>3</td>
</tr>
<tr>
<td>Already known thrombophilic condition‡</td>
<td>3</td>
</tr>
<tr>
<td>Recent (≤1 month) trauma and/or surgery</td>
<td>2</td>
</tr>
<tr>
<td>Elderly age (≥70 years)</td>
<td>1</td>
</tr>
<tr>
<td>Heart and/or respiratory failure</td>
<td>1</td>
</tr>
<tr>
<td>Acute myocardial infarction or ischemic stroke</td>
<td>1</td>
</tr>
<tr>
<td>Acute infection and/or rheumatologic disorder</td>
<td>1</td>
</tr>
<tr>
<td>Obesity (BMI ≥30)</td>
<td>1</td>
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<tr>
<td>Ongoing hormonal treatment</td>
<td>1</td>
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**Risk Assessment Model: Padua – Admission diagnoses**

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<th>Table 1 Risk assessment model (high risk of VTE: ≥4)</th>
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*Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy .. performed in the previous 6 mo. † Anticipated bed rest with bathroom privileges (either because of patient’s limitations or on physician’s order) for at least 3 d.
What stops us from doing better?
“Evidence-based .. guidelines”

For acutely ill hospitalized medical patients at low risk of thrombosis, we recommend against the use of pharmacologic prophylaxis or mechanical prophylaxis (Grade 1B).

Kahn SR et al. Prevention of VTE in Nonsurgical Patients. Chest 2012; 141(2) (Suppl);e195S-e226S
**Guff**

- **guff** (ɡʌf)  
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ACCP Guidelines 2012
Nonsurgical Patients

“Evidence-based .. guidelines”

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines panelists used a “feeling thermometer” with anchors at 0 (representing death) and 100 (representing full health) to rate patient scenarios.

Kahn SR et al. Prevention of VTE in Nonsurgical Patients. Chest 2012; 141(2) (Suppl);e195S-e226S
A feeling thermometer
Medical patients

- If mobility significantly reduced for ≥ 3 days
- or
- If expected to have ongoing reduced mobility relative to normal state plus any VTE risk factor.
VTE risk factors

- Active cancer or cancer treatment
- Age > 60 years
- Critical care admission
- Dehydration
- Known thrombophilias
- Obesity (BMI > 30 kg/m2)
- One or more significant medical comorbidities (for example: heart disease; metabolic, endocrine or respiratory pathologies; acute infectious diseases; inflammatory conditions)
- Personal history or first-degree relative with a history of VTE
- Use of HRT
- Use of oestrogen-containing contraceptive therapy
- Varicose veins with phlebitis
All medical patients should be routinely assessed and considered for thromboprophylaxis

Is the patient >40 years old with acute medical illness and reduced mobility?

Yes

Does the patient have one of the following acute medical illnesses/conditions?

- Acute MI
- Acute heart failure – NYHA III/IV
- Severe infection/sepsis
- Respiratory diseases (respiratory failure with/without mechanical ventilation; exacerbation of chronic respiratory disease)
- Rheumatic disease (including acute arthritis of lower extremities, and vertebral compression)
- Ischaemic stroke*
- Paraplegia

No

Does the patient have one of the following predisposing risk factors?

Evidence-based in acutely ill medical patients:

- History of VTE
- History of malignancy
- Complicating acute infectious disease
- Age >75 years

Consensus-based from strong evidence in other settings:

- Prolonged immobility
- Age >60 years
- Varicose veins
- Obesity
- Hormone therapy
- Pregnancy/post-partum
- Nephrotic syndrome
- Dehydration
- Thrombophilia or thrombocytosis

No

No evidence for the benefits of thromboprophylaxis. However, patients should be considered for thromboprophylaxis on a case-by-case basis

Yes

Is pharmacological thromboprophylaxis contraindicated?

No

LMWH (enoxaparin 40 mg o.d.) or UFH (5,000 IU t.i.d.) (LMWH preferred due to better safety profile)

Yes

Mechanical thromboprophylaxis with graduated compression stockings or intermittent pneumatic compression is recommended

No evidence for the benefits of thromboprophylaxis. However, patients should be considered for thromboprophylaxis on a case-by-case basis

*Note: the patient’s risk of haemorrhagic transformation should be assessed before giving thromboprophylaxis

Cohen AT et al Thromb Haem 2005
Contraceptive Advice?

Celibates
Medical Advice?

Statisticians

Fisher
Common books to set standards
Summary

- In-hospital thromboprophylaxis
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APEX Study Design

Primary efficacy Endpoint: Composite of any of the following through 35 days
- Asymptomatic proximal DVT (Ultrasound)
- Symptomatic DVT (proximal or distal)
- Non-fatal PE,
- or VTE-related death

Randomize

Hospitalization

Screen

Enoxaparin (either 40 or 20 mg SQ QD) for 10 ± 4 days with betrixaban placebo

Betrixaban (either 80 or 40 mg PO QD) with enoxaparin placebo SQ QD

Safety follow-up visits

Day 10 ± 4

35 ± 7 days

65+5 days

Ultrasound

Dose based on patients who are receiving a concomitant strong P-gp inhibitor or who have severe renal insufficiency.
Recurring themes
Elevated baseline D-dimer predicts higher risk of post-hospital VTE

Source: 2011 Cohen et. al; Subpopulation Kyoto presentation MAGELLAN study; Sherman et al PREVAIL study Lancet 2007; 3369-1347-55
MARINER

Medical Illness Patients

- Rivaroxaban once-daily compared with placebo
- Reduction of the risk of symptomatic VTE
- 45 days after hospital discharge.
- 8,000 patients in more than 15 countries.
Summary

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- New Studies

Conclusions
My conclusions

- We need to go back to basics with guidelines
- Thromboprophylaxis in medical patients reduces morbidity from DVT, PE, PE death, and has the potential to reduce total mortality.
- New studies with different designs and more careful patient selection are underway
Never miss a good chance to shut up

Texas Wisdom