Venous Thrombo-embolism in ICU Patients

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VTE (DVT and/or PE) is a serious complication of critical illness.

It is associated with morbidity and can be fatal that all of us would like to prevent it rather than treat it.

In this presentation, I will focus on evidence-based thromboprophylaxis in ICU patients and present results of a study that was conducted at our ICU.
Incidence of DVT in the ICU

DVT is not uncommon in critically ill patients. When routine screening was performed in ICU patients who are not receiving thromboprophylaxis, DVT occurred in 13-31% in 4 studies.

<table>
<thead>
<tr>
<th>Source</th>
<th>ICU Setting</th>
<th>Design</th>
<th>DVT Screening Test</th>
<th>Patients, No.</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moser et al (1981)</td>
<td>Respiratory ICU</td>
<td>Prospective cohort</td>
<td>Fg LS for 3–6 d</td>
<td>23</td>
<td>13%</td>
</tr>
<tr>
<td>Cade (1982)</td>
<td>General ICU</td>
<td>Blinded RCT</td>
<td>Fg LS for 4–10 d</td>
<td>60</td>
<td>29%</td>
</tr>
<tr>
<td>Fraisse et al (2000)</td>
<td>Ventilated COPD</td>
<td>Blinded multicenter RCT</td>
<td>Venography</td>
<td>85</td>
<td>28%</td>
</tr>
</tbody>
</table>

Fg LS: 125I-fibrinogen leg scanning, high rates of false-positive and false-negative results.
DVT in the ICU

- Of note is that the majority of these DVTs were asymptomatic and clinically unsuspected.
Incidence of PE in the ICU

- PE in ICU patients is not as well studied as DVT.

- Five postmortem studies found that PE occurred in 13% of ICU deaths (range=7-27%).
  - Most of these PEs were clinically unsuspected.

- Moser KM et al. JAMA 1981; 246:1422–1424 (patients with respiratory failure)
- Cullen DJ, Nemeskal AR. Intensive Care Med 1986; 12:399–403 (autopsy study in surgical ICU)
Can VTE be prevented in ICU patients?
RCTs on Thromboprophylaxis in ICU Patients

3 RCTs in which routine screening for DVT was performed:

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cade (1982)</td>
<td>placebo</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>Heparin, 5,000 U SC bid</td>
<td>13%</td>
</tr>
<tr>
<td>Kapoor et al (1999)</td>
<td>placebo</td>
<td>31%</td>
</tr>
<tr>
<td></td>
<td>Heparin, 5,000 U SC bid</td>
<td>11%</td>
</tr>
<tr>
<td>Fraisse et al (2000)</td>
<td>placebo</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>Nadroparin, ~70 AXa U/kg SC qd</td>
<td>15%</td>
</tr>
</tbody>
</table>

But is it that simple?
The answer is NO.
Our decision to use DVT prophylaxis is affected by other factors.
One factor is that the decision on DVT prophylaxis requires assessment of **benefit vs. bleeding risk**

**Anticoagulation**
- benefit

**Bleeding risk**
- active gastroduodenal ulcer
- bleeding in 3 m before admission
- platelet count < 50 x 10⁹/L
- age > 85 years
- hepatic failure
- severe renal failure

- recent surgery
- trauma, SCI
- sepsis
- respiratory failure
- heart failure
- renal failure
- obesity
- immobilization
- sedation
- paralysis
- previous VTE
- malignancy
- heart failure
- renal failure
- obesity
- immobilization
- sedation
- paralysis
- previous VTE
- malignancy
Other factors: new studies and clinical guidelines

- New studies are performed to resolve uncertainties and are then reported.

- Guidelines are periodically published and may change based on reevaluation of evidence.
8.0 Critical Care

8.1. For patients admitted to a critical care unit, we recommend routine assessment for VTE risk and routine thromboprophylaxis in most (Grade 1A).

8.2. For critical care patients who are at moderate risk for VTE (eg, medically ill or postoperative general surgery patients), we recommend using LMWH or LDUH thromboprophylaxis (Grade 1A).

8.3. For critical care patients who are at higher risk (eg, following major trauma or orthopedic surgery), we recommend LMWH thromboprophylaxis (Grade 1A).

8.4. For critical care patients who are at high risk for bleeding, we recommend the optimal use of mechanical thromboprophylaxis with GCS and/or IPC at least until the bleeding risk decreases (Grade 1A). When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C).
For example, the third recommendation was based on:

A meta-analysis (4 RCTs, 219 patients) demonstrated that LDUH was not more effective than no thromboprophylaxis (OR, 0.97; 95% CI, 0.35 to 2.64).

For example, the third recommendation was based on:

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Design</th>
<th>Interventions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geerts et al</td>
<td>344 major trauma patients</td>
<td>LE fracture 54% No ICH</td>
<td>RCT</td>
<td>LDUH bid vs. Enoxaparin 30 mg bid</td>
</tr>
<tr>
<td>Ginzburg et al</td>
<td>486 major trauma patients</td>
<td>No contraindication to anticoagulant LE fracture 35%</td>
<td>RCT</td>
<td>IPC vs. Enoxaparin 30 mg bid</td>
</tr>
</tbody>
</table>

No difference in major bleeding between control and treatment groups in both studies. Major bleeding occurred in < 2% of patients.

Since then, we have newer evidence
The PROTECT Study

- An RCT evaluated dalteparin (5000 U SC QD) vs. unfractionated heparin (5000 U SC BID) in 3764 patients expected to remain in ICU for ≥3 days in 67 ICUs in Canada, Australia, Brazil, Saudi Arabia, USA and UK.

- Exclusion criteria included:
  - major trauma
  - orthopedic surgery
  - need for therapeutic anticoagulation
  - contraindication to heparin or blood products

The PROTECT Study

Results:

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin N = 1873</th>
<th>U Heparin N = 1873</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal DVT, N (%)</td>
<td>96 (5.1)</td>
<td>109 (5.8)</td>
<td>0.92 (0.68–1.23)</td>
<td>0.57</td>
</tr>
<tr>
<td>Any PE, N (%)</td>
<td>24 (1.3)</td>
<td>43 (2.3)</td>
<td>0.51 (0.30–0.88)</td>
<td>0.01</td>
</tr>
<tr>
<td>Any VTE, N (%)</td>
<td>154 (8.2)</td>
<td>186 (9.9)</td>
<td>0.87 (0.69–1.10)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

The PROTECT Study

Results:

<table>
<thead>
<tr>
<th></th>
<th>Dalteparin 1873</th>
<th>U Heparin 1873</th>
<th>Hazard ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>5.5%</td>
<td>5.6%</td>
<td>1.00 (0.75–1.34)</td>
<td>0.98</td>
</tr>
<tr>
<td>HIT</td>
<td>0.3%</td>
<td>0.6%</td>
<td>0.47 (0.16–1.35)</td>
<td>0.16</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>15.2%</td>
<td>16.2%</td>
<td>0.97 (0.82–1.15)</td>
<td>0.71</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>22.1%</td>
<td>24.5%</td>
<td>0.92 (0.80–1.05)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

ACCP recommendations (2012)

Significant changes in the strength of recommendations compared to ACCP guidelines 2008.

Impact of Innovations on the Recommendations

Readers of AT9 will find many weak recommendations replacing the strong recommendations of AT8. One major reason for this change is the more critical look at the evidence and the resulting inferences that some evidence is lower quality than previously believed. A second is the recognition of variability in values and preferences. Third, in the small number of controversial recommendations that came to a formal vote using anonymous electronic voting, we required the endorsement of >80% of panelists to make a strong recommendation. Finally, the exclusion of conflicted experts, who often hold strong opinions about optimal management approaches, from final decisions regarding quality of evidence and strength of recommendations also may have contributed.
ACCP recommendations (2012)

For critically ill patients, we suggest using LMWH or LDUH thromboprophylaxis over no prophylaxis (Grade 2C).

Compared to

8.1. For patients admitted to a critical care unit, we recommend routine assessment for VTE risk and routine thromboprophylaxis in most (Grade 1A).
ACCP recommendations (2012)

For major trauma patients, we suggest use of LDUH (Grade 2C), LMWH (Grade 2C), or mechanical prophylaxis, preferably with IPC (Grade 2C), over no prophylaxis.

Compared to

8.3. For critical care patients who are at higher risk (e.g., following major trauma or orthopedic surgery), we recommend LMWH thromboprophylaxis (Grade 1A).
Prospective Observational Cohort Study at the ICU of KAMC

Sponsored by Sanofi-Aventis
Methods

- Prospective observational study

- All patients admitted to the 21-bed medical and surgical ICU of KAMC-Riyadh (900 bed hospital) from January 1, 2006 to June 30, 2008 were followed for the development of symptomatic VTE (DVT or PE).

- The hospital has its VTE prophylaxis guidelines.
Results

Patients’ Characteristics, N=796

- Age: 50.0 ± 21.2 years
- 67% of patients were males
- Admission APACHE II score: 24.2 ± 9.2

Reasons for ICU Admission

- ~28% Sepsis
- ~24% Trauma
- ~18% Resp failure
- Others:
  - CVA, seizures
  - Cardiac failure, arrest
  - Postoperative
Results

57 (7.2%) patients had symptomatic VTE:

The distribution of VTE events during the study period:

- 3.6% DVT alone
- 3.0% PE alone
- 0.5% DVT + PE
# Results

<table>
<thead>
<tr>
<th>VTE prophylaxis</th>
<th>VTE</th>
<th>No VTE</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>75%</td>
<td>62%</td>
<td>0.95</td>
</tr>
<tr>
<td>LMWH</td>
<td>32%</td>
<td>28%</td>
<td>0.79</td>
</tr>
<tr>
<td>GCS</td>
<td>35%</td>
<td>24%</td>
<td>0.48</td>
</tr>
<tr>
<td>SCD</td>
<td>23%</td>
<td>32%</td>
<td>0.48</td>
</tr>
</tbody>
</table>
Results: Pharmacologic prophylaxis

Adjusted analysis for VTE risk:

- LMWH vs. no pharmacological prophylaxis:
  aHR = 0.28 (95% CI: 0.09 - 0.89, p = 0.03).

- UFH vs. no pharmacological prophylaxis:
  aHR = 0.71 (95% CI: 0.32 - 1.58, p = 0.41).

Arabi et al. Am J Respir Crit Care Med 183;2011:A4123
Results: Mechanical prophylaxis

Adjusted analysis for VTE risk:

- GCS vs. no-mechanical device: aHR = 0.97 (95% CI 0.52-1.82, p = 0.94)
- IPC vs. no-mechanical device: aHR = 0.39 (95% CI 0.17-0.89, p = 0.03)
- GCS vs. IPC: aHR = 2.59 (95% CI 1.11-6.02, p = 0.03)

Arabi et al. Am J Respir Crit Care Med 183;2011:A3171
## Results

### Outcomes of patients:

<table>
<thead>
<tr>
<th></th>
<th>VTE</th>
<th>No VTE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU mortality</td>
<td>25%</td>
<td>21%</td>
<td>0.53</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>44%</td>
<td>36%</td>
<td>0.25</td>
</tr>
<tr>
<td>ICU LOS, mean ± SD, days</td>
<td>25 ± 29</td>
<td>15.7 ± 29.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Hospital LOS, mean ± SD, days</td>
<td>79.3 ± 81.3</td>
<td>68.1 ± 111.6</td>
<td>0.33</td>
</tr>
<tr>
<td>MV duration, mean ± SD, days</td>
<td>12.4 ± 9.7</td>
<td>9.5 ± 12.4</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Conclusions

- Vast majority of ICU patients are at increased risk for VTE, making VTE prevention an important goal.

- Even though VTE prevention guidelines have been softened, they still favor anticoagulant thromboprophylaxis.

- Most evidence on thromboprophylaxis in ICU patients is of low to moderate quality, indicating the need for additional and better conducted studies.
Conclusions

- Our data suggest that LMWH is superior to unfractionated heparin in preventing VTE with most benefit in major trauma patients.

- Our data also suggest that IPC devices have a role in VTE prophylaxis of ICU patients.
Thank You