The Epidemiology of Venous Thromboembolism

2003

Torben Bjerregaard Larsen, MD, Ph.D
Odense University Hospital
Denmark
Deep venous thrombosis
Deep venous thrombosis
VTE (venous thromboembolism)

Incidence: 1.5 per 1000 per year

Increased risk in older age

Increasing severity
Natural history of VTE - calf vein versus proximal veins

- Most DVT start in the calf but rarely causes leg symptoms
- About 25% of untreated symptomatic calf DVT becomes proximal
- 80% of symptomatic DVT involve the proximal veins
- Isolated calf DVT is associated with about half the risk of recurrence
Agenda

- Relative incidence
- Gender and ethnicity
- Primary versus secondary VTE
- VTE and Cancer
- Risk of pregnancy-associated VTE
- Clinically important problems
  - Recurrence
  - Surgery and VTE
  - Pulmonary embolism
  - Morbidity and mortality
- Patophysiological considerations
Relative incidence

Age
- 25-35 years old  30 cases/100,000 persons
- 70-79 years old  3-500 cases/100,000 persons

Relative incidence of PE vs DVT
- Absent autopsy  33% PE; 66% DVT
- With autopsy    55% PE; 45% DVT

Circulation 2003;107:I-4-I-8
Relative incidence of DVT, PE or both

“Cumulative probability of developing VTE between ages 50 – 80 > 10 %”

Relative incidence in Denmark for people aged 15-49

L Mellemkjaer - BMJ. 1999;319:820
**Gender**

- Probably no overall difference between males and females
  - despite oral contraceptives and hormone replacement therapy

- **Danish Twin Study (Epidemiology – TB Larsen et al. 2003)**
  - major *male* susceptibility for VTE inheritance:

  - **Heritability 55 percent**

![Graph showing OR for Dizygote and Monozygote twins]

**Percent of Co-twins Affected**
<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hispanics</td>
<td>0.7</td>
<td>(0.3 - 1.5)</td>
</tr>
<tr>
<td>Asians</td>
<td>0.2</td>
<td>(0.1 - 0.5)</td>
</tr>
<tr>
<td>Afro americans</td>
<td>&gt;1</td>
<td>NA</td>
</tr>
</tbody>
</table>

Circulation 2003;107:1-4-I-8
**Primary versus secondary VTE**

- **Primary (no known risk factors)**
  - About 25 - 50 percent

- **Secondary**
  - Cancer
  - Pregnancy or puerperium
  - Trauma
  - Surgery
  - Immobilization
Risk of pregnancy-associated VTE

- Incidence about 1 per 1000 deliveries
- In approximately two-thirds:
  - Age > 35 years
  - High parity (four or more)
  - Intercurrent illness
  - Immobility
  - Caesarean section

McColl et al, 1997
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n=136)</th>
<th>Controls (n=272)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood groups (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>27.1</td>
<td>40.3</td>
</tr>
<tr>
<td>A</td>
<td>56.4</td>
<td>40.3</td>
</tr>
<tr>
<td>B</td>
<td>10.5</td>
<td>13.8</td>
</tr>
<tr>
<td>AB</td>
<td>6.0</td>
<td>5.6</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>27.6 (16 - 43)</td>
<td>27.8 (18 - 40)</td>
</tr>
<tr>
<td>Birth weight in grams (range)</td>
<td>3091.8 (566 - 4800)</td>
<td>3445.3 (808 - 4692)</td>
</tr>
<tr>
<td>Active smokers (%)</td>
<td>50</td>
<td>28.6</td>
</tr>
<tr>
<td>Gestational age &gt; 37 (%)</td>
<td>79.8</td>
<td>91.4</td>
</tr>
<tr>
<td>Primipara (%)</td>
<td>45.7</td>
<td>33.6</td>
</tr>
<tr>
<td>Caesarian section (%)</td>
<td>22.8</td>
<td>10.7</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>1.5</td>
<td>2.2</td>
</tr>
<tr>
<td>IVF pregnancy (%)</td>
<td>5.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Blood group</td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)*</td>
</tr>
<tr>
<td>-------------</td>
<td>------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>O</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>2.0 (1.2-3.2)</td>
<td>2.2 (1.1-4.1)</td>
</tr>
<tr>
<td>B</td>
<td>1.0 (0.5-2.2)</td>
<td>1.0 (0.4-2.5)</td>
</tr>
<tr>
<td>AB</td>
<td>1.5 (0.6-3.9)</td>
<td>2.3 (0.8-7.2)</td>
</tr>
</tbody>
</table>

*Adjusted for age, smoking, parity, clomiphene citrate stimulation, caesarian section, birth weight, gestational age, diabetes mellitus and BMI.
VTE - Clinically Important Problems

- Recurrence
- Surgery and VTE
- Pulmonary embolism
- Morbidity and mortality
Recurrent VTE

- 1. year overall incidence between 7 and 14 % (highest in cancer)
- 5. year overall incidence about 22 %
- 10. year overall incidence about 30 %

Circulation 2003;107:I-4-I-8
Arch Intern Med. 1991;151:933
Risk of progression is greater with continuing risk factors present
Orthopedic surgery has about twice the risk compared to general surgery
75% of DVT after orthopedic surgery occur in the operated leg
Risk of symptomatic VTE is highest within 2 weeks of surgery, but remains elevated for 2-3 months
The highest risk period for fatal postoperative PE occurs 3 to 7 days following surgery
## Incidence of Postoperative DVT - Fibrinogen Data

<table>
<thead>
<tr>
<th>Surgery</th>
<th># Publications</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>22</td>
<td>59%</td>
</tr>
<tr>
<td>General</td>
<td>28</td>
<td>29%</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>6</td>
<td>29%</td>
</tr>
<tr>
<td>Gynecologic</td>
<td>8</td>
<td>19%</td>
</tr>
<tr>
<td>Prostatic</td>
<td>13</td>
<td>11%</td>
</tr>
</tbody>
</table>

Bergqvist 1983
Fatal venous thrombosis - pulmonary embolism

Migration

Embolization

Thrombus
The majority of patients with symptomatic proximal DVT and without chest symptoms have evidence of PE on lung scans.

About 70% of patients with symptomatic PE have DVT – but

Less than 25% with symptomatic PE have *clinical* evidence of DVT.

Without treatment 50% of patients with symptomatic proximal DVT or PE have recurrent thrombosis within 3 months.
10% of symptomatic PE are fatal within one hour of first symptoms
Clinical diagnosis of PE is established in a minority of patients dying from PE
50% with diagnoses PE have right ventricular dysfunction on echocardiography associated with high short-term mortality
### Postoperative fatal PE - Incidence without prophylaxis

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Surgery</td>
<td>0.5 - 1%</td>
</tr>
<tr>
<td>Trauma Surgery</td>
<td>1 - 2%</td>
</tr>
<tr>
<td>Elective Hip Surgery</td>
<td>2 - 5%</td>
</tr>
<tr>
<td>Hip Fracture Surgery</td>
<td>5 - 10%</td>
</tr>
</tbody>
</table>

*Bergqvist 1983*
Annual Incidence of Fatal Pulmonary Embolism in Denmark

2000

1,000
Incurable Illnesses

1,000
Potentially Curable

Lives Saved
With Prophylaxis
800

Death From PE
Despite Prophylaxis
200
Conditions associated with Fatal PE

- Systolic arterial hypotension
- Congestive heart failure
- Cancer
- Tachypnea
- Right ventricular hypokinesis
- Chronic obstructive pulmonary disease
- Age > 70

SZ Goldhaber – Lancet 1999;253:1386
### Mortality after initial VTE event

<table>
<thead>
<tr>
<th>Author</th>
<th>DVT %</th>
<th>PE %</th>
<th>Case fatality time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushman 2001</td>
<td>9.4</td>
<td>15.1</td>
<td>28 days</td>
</tr>
<tr>
<td>Silverstein 1998</td>
<td>5.5</td>
<td>8.0</td>
<td>30 days</td>
</tr>
<tr>
<td>Siddique 1996</td>
<td>-</td>
<td>12.9</td>
<td>30 days</td>
</tr>
<tr>
<td>White 1998</td>
<td>10.5</td>
<td>14.7</td>
<td>6 months</td>
</tr>
<tr>
<td>Prandoni 1996</td>
<td>16.7</td>
<td>-</td>
<td>12 months</td>
</tr>
<tr>
<td>Anderson 1991</td>
<td>5.0</td>
<td>23.0</td>
<td>2 – 3.5 yr</td>
</tr>
</tbody>
</table>
Patophysiology

Flow

Endothelia

- Inflammation
- Surgery
- Cancer
- Hormones
- Puerperium
- Plasminogen activators

Blood

- Procoagulant activity
- Platelets
- Haematological diseases
- Pregnancy
- Exogene hormones
- Genes

Virchow’s triad
Primary (hereditary) thrombophilia

- Antithrombin deficiency
- Protein C & S deficiency
- Activated protein C resistance (FV Leiden)
- Prothrombin allele G20210A
- Hyperhomocysteinaemia
- Fibrinolytic disorders
Prevalence of VTE Risk Factors in Hospital Patients

Fred Anderson 2001 CHEST
Deficiency of:
Antithrombin
Protein C+S
FV Leiden mutation
FII 20210 mutation
High FVIII conc.
High Homocystein conc.
Low Fibrinolytic activity
Antiphospholipid AB.
Unknown

Interaction

Thrombophilia

VTE

Surgery

Immobilisation

Obesity

Cancer

Other

Superficial thrombophlebitis
Recurrent miscarriage
Stroke
Preeclampsia?
“Fair is what we see, even more so what we have perceived most wondrous is what is still in veil”

Niels Stensen