Venous Thromboembolism Prophylaxis
Who, when and what?

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Johannesburg Hospital
University of the Witwatersrand
Introduction and Background

Virchow’s triad describes predisposing factors to venous thrombosis

- Stasis
- Hypercoagulability
- Endothelial damage

Risk factors present in > 90% cases

VTE Facts

- 3rd most common type cardiovascular disease
- > 500,000 deaths in Europe and 300,000 deaths in USA / yr
- Cause of in-hospital mortality in 1 in 8 patients
- Number of in-hospital deaths due to VTE is 5 x the total number of deaths from all hospital-acquired infections

Goldhaber SZ. Thromb Haemost 2007; 5:1607-1609
Heit JA, et al. ASH Annual meeting Abstracts 2005; 106: 910
VTE Facts

• Deaths attributable to VTE estimated to exceed total combined number of deaths from breast cancer, prostate cancer, AIDS and traffic accidents combined

• **Commonest preventable cause of hospital death**

• Doubles length of stay and costs

• ~70% hospital-acquired

Pulmonary Embolism

• Most cases recognised by the true expert in this field ............
Pulmonary Embolism

- Most cases recognised by the true expert in this field .......... *the pathologist*
Prevention Strategies

- Pharmacological interventions
- Physical methods
Prevention Strategies

- **Prophylactic drugs**
  - unfractionated heparin (UF)
  - low molecular weight heparin (LMWH)
  - oral anticoagulants: coumarins
  - thrombin inhibitors: hirudin
  - indirect factor Xa inhibitors: fondaparinux
  - new oral agents: Dabiatran, Rivaroxaban
Prevention Strategies

- Prophylactic physical methods
  - graduated compression stockings
  - intermittent pneumatic compression devices
  - early mobilisation

*Improve endogenous fibrinolysis and increase venous blood flow*
Prevention of Venous Thromboembolism

W. Geerts
D. Bergqvist
G. Pineo
J. Heit
C.M. Samama
M. Lassen
C. Colwell

8th ACCP Guidelines on Antithrombotic Therapy

Chest – June 2008
## Risk of DVT in hospitalised patients

If no prophylaxis given + routine screening for DVT

<table>
<thead>
<tr>
<th>Patient group</th>
<th>DVT prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical patients</td>
<td>10-20</td>
</tr>
<tr>
<td>General surgery</td>
<td>15-40</td>
</tr>
<tr>
<td>Major gynecological surgery</td>
<td>15-40</td>
</tr>
<tr>
<td>Major urologic surgery</td>
<td>15-40</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>15-40</td>
</tr>
<tr>
<td>Stroke</td>
<td>20-40</td>
</tr>
<tr>
<td>Hip, knee arthroplasty, hip fracture</td>
<td>40-60</td>
</tr>
<tr>
<td>Major trauma</td>
<td>40-80</td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>60-80</td>
</tr>
</tbody>
</table>

**Critical Care patients 10=80%**

Thromboprophylaxis

What is the evidence?

- Hundreds of randomised trials
- Thromboprophylaxis reduces:
  - DVT
  - PE
  - all-cause mortality
  - costs
Thromboprophylaxis...

What is the evidence?

- Thromboprophylaxis is the number 1 ranked patient safety practice in hospitalised patients.

- More than 25 published evidence-based guidelines since 1986 showing clear evidence of benefit and safety.
Anticoagulation is Effective

Comparison of thrombophylaxis vs. no thromboprophylaxis

Numbers needed to treat to prevent one additional episode

- DVT : 7
- Symptomatic PE : 143
- Fatal PE : 182
- All-cause mortality : 97

Geerts W et al. Chest 2008; 133: 381-453
### Thromboprophylaxis in moderate risk patients

| Patients | • Medical  
|          | • Surgical - general, gynaecological, urologic, neurosurgery |
| Options  | • Low molecular weight heparin  
|          | • Low dose heparin  
|          | • Fondaparinux  
|          | • Mechanical if high bleeding risk  
| Duration | • Until discharge |

## Thromboprophylaxis in high risk patients

### Patients
- Major orthopaedic hip and knee arthropalasty, hip fracture repair
- Major trauma

### Options
- Low molecular weight heparin
- Fondaparinux
- Warfarin (INR 2-3)
- Mechanical if high bleeding risk

### Duration
- At least 10 days (2-5 weeks)

1.2 VTE Prophylaxis Policy

1.2.1 We recommend that every general hospital develop a formal, active strategy that addresses the prevention of VTE [Grade 1A]

Compliance with Prophylaxis Guidelines for VTE

- Retrospective evaluation compliance in hospitalised patients at risk for VTE wrt ACCP thromboprophylaxis guidelines
- 123,304 hospital admissions, 2001-2005
- Only 15.3% at-risk patients received prophylaxis in accordance with guidelines
- Omission, inadequate prophylaxis duration, wrong type

**Conclusion**
Poor compliance with guidelines for thromboprophylaxis

Current Rates of Prophylaxis

ENDORSE Study

- Large international trial; 32 countries
- 68,183 patients; 358 hospitals
- Risk for VTE common: 52% patients
  - 64% surgical cases & 42% medical cases
- Only 59% surgical patients and 40% medical at risk patients received prophylaxis

National standards for prevention and care of VTE: VTE Performance Measures

VTE Risk Assessment/Prophylaxis

All patients should receive VTE prophylaxis within 24 hours of hospital admission or surgery end time (or have documentation why no prophylaxis was given)

www.qualityforum.org.projects/ongoing/vet/comments/index.asp
Venous thromboembolism – prophylactic and therapeutic practice guideline
Venous Thromboembolism – prophylactic and therapeutic practice guideline

- Reflect current best practice
- Assess each patient on merit and individualise
- Drug recommendations based on current MCC registration

Risk Assessment

• **Patient-related risk factors**
  - age, previous history VTE, immobility, underlying malignancy, pregnancy, oestrogen replacement therapy, obesity, underlying hereditary thrombophilic state, underlying inflammatory bowel disease, HIV

• **Procedure-related risk factors**
  - duration of procedure, degree of tissue damage, degree immobility post surgery, nature surgical procedure
<table>
<thead>
<tr>
<th>Predisposing risk factor</th>
<th>Relative risk weighting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombophilia</td>
<td>High</td>
</tr>
<tr>
<td>History of VTE</td>
<td>High</td>
</tr>
<tr>
<td>Malignancy</td>
<td>High</td>
</tr>
<tr>
<td>Drugs, e.g.</td>
<td>High</td>
</tr>
<tr>
<td>• Tuberculosis treatment</td>
<td></td>
</tr>
<tr>
<td>• Steroids</td>
<td></td>
</tr>
<tr>
<td>• Thalidomide</td>
<td></td>
</tr>
<tr>
<td>HIV infection</td>
<td>High</td>
</tr>
<tr>
<td>Advanced age (&gt;60yrs = VTE risk)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Chronic cardiac insufficiency</td>
<td>Moderate</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30 kg/m²)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Oestrogen therapy</td>
<td>Moderate</td>
</tr>
<tr>
<td>Pregnancy &amp; the postpartum period</td>
<td>Minor</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>Minor</td>
</tr>
<tr>
<td>Varicose veins</td>
<td>Minor</td>
</tr>
</tbody>
</table>
Subcategories of VTE risk in surgical and non-surgical patients

**Low VTE Risk**

**Surgical patients**
- Surgery lasting < 30 minutes
- Injuries without or with only minor soft tissue trauma
- No or only minor, additional predisposing risk factors

**Medical patients**
- Infection or acute inflammatory disease without bed rest
- Central venous catheters
- No or only minor, additional predisposing risk factors
Subcategories of VTE risk in surgical and non-surgical patients

Moderate VTE Risk

Surgical patients
- Surgery procedures of longer duration
- Immobilisation of lower limb with plaster cast
- Lower limb arthroscopic procedures
- No or only minor, additional predisposing risk factors

Medical patients
- Acute cardiac insufficiency (NYHA III/IV)
- Acute decompensated COPD without ventilation
- Infection or acute inflammatory diseases with bed rest
- No or only minor, additional predisposing factors
Subcategories of VTE risk in surgical and non-surgical patients

High VTE Risk

Surgical patients
- Major surgical procedures for malignancy
- Multiple trauma or severe trauma of the spine, vertebrae or lower limbs
- Major orthopaedic surgery, e.g. hip or knee replacement
- Major surgical procedure of cardiothoracic and pelvic region

Medical patients
- Stroke with paralysis
- Acute decompensated COPD with ventilation
- Sepsis
- ICU patients
Medical Patients

- Risk of DVT *comparable* to moderate-risk surgical patients
- 75% of hospital related PE deaths
- Efficacy of heparins in preventing VTE well established
- LMWH or UFH (LMWH superior)

Thromboprophylaxis of Medical Patients
Clear benefits over placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>RRR</th>
<th>NNT</th>
<th>Prophylaxis</th>
<th>Pts with VTE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDENOX</td>
<td>63%</td>
<td>10</td>
<td>Placebo Enoxaparin 40mg</td>
<td>14.9</td>
</tr>
<tr>
<td>n=1102</td>
<td></td>
<td></td>
<td></td>
<td>5.5</td>
</tr>
<tr>
<td>PREVENT</td>
<td>45%</td>
<td>45</td>
<td>Placebo Dalteparin</td>
<td>5.0</td>
</tr>
<tr>
<td>n=3706</td>
<td></td>
<td></td>
<td></td>
<td>2.8</td>
</tr>
<tr>
<td>ARTEMIS</td>
<td>47%</td>
<td>20</td>
<td>Placebo Fondaparinux</td>
<td>10.5</td>
</tr>
<tr>
<td>n=849</td>
<td></td>
<td></td>
<td></td>
<td>5.6</td>
</tr>
</tbody>
</table>

Aspects of VTE Guideline

• **Timing of prophylaxis**
  - controversial
  - spectrum: preoperatively to 6-12 hours postop

• **Duration**
  - major cancer surgery: 5 weeks
  - hip replacement surgery: 5 weeks
  - knee replacement surgery: 2 weeks
  - prophylaxis should be continued *until patient fully mobile*

Aspects of VTE Guideline

Centroneuro-axial blockade

- Catheters should not be placed or removed within 12 hours of dose LMWH
- LMWH can be given after 2 hours following insertion or removal
- Fondaparinux: limited data
  - long half-life
  - catheter removal not < 36 hours after last dose

Neuraxial blocks

Several guidelines recommend “At least 2 half lives”
Arixtra with Epidural Catheters

**Fondaparinux (“Arixtra”)**

- **Half life**: 17 – 21 hours
- **C Max**: 2 hours

<table>
<thead>
<tr>
<th>Last dose</th>
<th>2 half-lives</th>
<th>Removal of Catheter</th>
<th>8 – C Max</th>
<th>Next dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>21 x 2 = 42 hours</td>
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<td>8 – 2 = 6 hours</td>
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</tr>
<tr>
<td>Day 1</td>
<td>8:00</td>
<td>Day 3 2:00</td>
<td>Day 3 14:00</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>08:00</td>
<td>Day 3 14:00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.5 days without treatment
### Enoxaparin (“Clexane”)

- **Half life**: 4 - 5 hours
- **C Max**: 1 - 4 hours

<table>
<thead>
<tr>
<th>Last dose</th>
<th>2 half-lives</th>
<th>Removal of Catheter</th>
<th>8 – C Max</th>
<th>Next dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>5 x 2 = 10 hours</td>
<td></td>
<td>8 – 4 = 4 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8:00</td>
</tr>
<tr>
<td>18:00</td>
<td></td>
<td></td>
<td></td>
<td>8:00</td>
</tr>
<tr>
<td>22:00</td>
<td></td>
<td></td>
<td></td>
<td>8:00</td>
</tr>
</tbody>
</table>

**Next day 8:00**

### 0 days without treatment
Monitoring of Patients on LMWH

- Platelet count – check on *initiation*, *after 5 days and regularly thereafter* while on therapy
- Anticoagulant activity measured using *anti-Xa activity* assay
- Anti-Xa measurement – pregnancy, renal failure, excessively obese
- 5 ml citrated blood taken 3 hrs post LMWH dose
Monitoring of Patients on LMWH

Target levels

- **Prophylaxis**: 0.3 – 0.5 anti-Xa units / ml of blood
- **Therapeutic**: 0.6 – 1.0 anti-Xa units / ml of blood
- **Pregnant patients with artificial cardiac valve**: 1 – 1.2 anti-Xa units / ml of blood

Adequate Thromboprophylaxis in Critically Ill Patients

• Critically ill patients may need much higher doses of LMWH than other patients

• Reasons
  - full immobilisation
  - limited bioavailability (oedema, vasopressors)
  - impaired protein binding

Robinson S, et al. Critical Care 2010; 14: R41
Levi M. Critical Care 2010; 14: 142
Intermittent Pneumatic Compression

- Meta-analysis 19 trials
- 2255 patients
- Reduced incidence of DVT by 66% compared to controls

Intermittent Pneumatic Compression

- Meta-analysis to evaluate effectiveness of IPC to prevent DVT in postoperative patients
- Inclusion criteria
  - randomized controlled trial IPC vs. no prophylaxis
  - at least 20 patients per group
  - at least 1 diagnostic imaging test in all patients
  - clinical follow-up for at least duration hospitalisation
- 15 eligible studies, 2270 patients, 1970-2004
- IPC devices ↓ risk of DVT by 60% vs. no prophylaxis

Deep Vein Thrombosis Research Today 2006
Intermittent Pneumatic Compression

- Review 25 studies all medical settings
- **Conclusion**
  - in almost all medical settings IPC contributes to a significant reduction in incidence of DVT
  - minimal negative side effects
  - cost effective

Combined Intermittent Pneumatic Compression & Pharmacological Prophylaxis

- **Cochrane Review**
  - 11 studies (6 RCT)
  - 7431 patients
  - *combined prophylaxis modalities significantly decrease the incidence of VTE*


- **Further review**
  - 17 studies (6 RCTs), 9998 patients
  - *significant ↓ DVT & PE compared to single modalities*

Prophylactic Physical Methods

• Venous Foot Pumps
  - designed to simulate effect of walking
  - limited and inconsistent data on efficacy
  - further studies needed

• Ambulation
  - VTE rates lower in *ambulatory patients*
  - ambulation & prophylaxis in at-risk patients decreases risk further
Elastic Compression Stockings

Cochrane Review

- 18 RCTs
- GCS applied on day of before surgery or on day of surgery and worn up until day of discharge or until patient fully mobile
- Conclusion
  - effective in diminishing risk of DVT
  - more effective in conjunction with another mode of prophylaxis

New anticoagulation drugs and their coagulation cascade targets

Intrinsic pathway

- XII → XIIa
- XI → Xla
- IX → IXa

Extrinsic pathway

- TFPI → NAPc2 → FVIIa

Direct
- Lepirudin
- Bivalirudin
- Argatroban
- Dabigatran etexilate
- TGN-167

Indirect
- Fondaparinux
- Idraparinux
- Biotinylated SP-123781

Direct
- Rivaroxaban
- Apixaban
- DX-9065a
- DU-176b
- LY-517717
- YM=150

Direct
- Lepirudin
- Bivalirudin
- Argatroban
- Daiatran TGN-167
# New anticoagulants
## Summary of pharmacology

<table>
<thead>
<tr>
<th>Target enzyme</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran etexilate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability %</td>
<td>60</td>
<td>90</td>
<td>6</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (Median, h)</td>
<td>3</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>8–15</td>
<td>7–11</td>
<td>14–17</td>
</tr>
<tr>
<td>Renal elimination (%)</td>
<td>25</td>
<td>33 (in active form)</td>
<td>80</td>
</tr>
</tbody>
</table>

Adapted from Mavrakanas T, Bounamaeaux H. Pharmacol Ther 2011;130:46–58.
New Oral Anticoagulants

Advantages

- No laboratory coagulation monitoring
- No dose adjustment
- Rare drug-drug interactions
- No “bridging” required iv to oral or s/c
New Oral Anticoagulants

Disadvantages

- No specific antidote for OD
- Laboratory testing to monitor effect intensity
Influence of factor Xa and IIa inhibitors on blood coagulation

Extrinsic / intrinsic activation

Factor X

Fondaparinux plus antithrombin

Factor Xa

Phospholipids
Factor Va – Factor Xa
Ca\(^ {2+}\)

INR sensitive!

Rivaroxaban
Apixaban

INR sensitive!

Dabigatran

aPTT sensitive!

Prothrombinase-complex

Prothrombin → Thrombin

Fibrinogen → Fibrin
Correlation of prothrombin time with rivaroxaban plasma concentration

Healthy human subjects

Prothrombin time (s)

Plasma concentration of rivaroxaban (µg/L)

Caveat: INR values must not be compared with those obtained with warfarin !!!

# Influence of factor Xa and IIa inhibitors on conventional clotting tests

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>aPTT</th>
<th>Thromboplastin-time/INR/Quick %</th>
<th>Anti-Xa-activity</th>
<th>Anti-IIa-activity</th>
<th>Thrombin time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td></td>
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</tr>
</tbody>
</table>

Haas S, Schellong S. VASA. In press.
Dosing of new oral anticoagulants for VTE prevention

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Dosing for VTE prevention</th>
<th>First dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran etexilate</td>
<td>220 mg or 150 mg qd once daily</td>
<td>1-4 h postop. with half daily dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>10 mg qd</td>
<td>6-10 h postop.</td>
</tr>
<tr>
<td>Apixaban</td>
<td>2.5 mg bid</td>
<td>12-14 h postop.</td>
</tr>
</tbody>
</table>
# Dabigatran ("Pradaxa")

<table>
<thead>
<tr>
<th>Last dose</th>
<th>2 half-lives</th>
<th>Removal of Catheter</th>
<th>8 – C Max</th>
<th>Next dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td>17 x 2 =</td>
<td></td>
<td>8 – 2 =</td>
<td>24:00</td>
</tr>
<tr>
<td></td>
<td>34 hours</td>
<td></td>
<td>6 hours</td>
<td></td>
</tr>
</tbody>
</table>

Day 1
- 8:00

Day 2
- 18:00

Day 3
- 8:00

## 2 days without treatment

- Half life: 14 – 17 hours
- C Max: 0.5 – 2 hours

- **Pradaxa with Epidural Catheters**
Rivaroxaban ("Xarelto")

- **Half life**: 7 – 11 hours
- **C Max**: 2 – 4 hours

<table>
<thead>
<tr>
<th>Last dose</th>
<th>2 half-lives</th>
<th>Removal of Catheter</th>
<th>8 – C Max</th>
<th>Next dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11 x 2 =</td>
<td></td>
<td>8 – 4 =</td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 hours</td>
<td></td>
<td>4 hours</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00</td>
<td></td>
<td></td>
<td>10:00</td>
</tr>
<tr>
<td>Next day</td>
<td>6:00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.25 days without treatment
Other Aspects

- **Upper limb thrombosis**  

- **Aspirin**

- **Vena caval filters**

- **Heparin induced thrombocytopenia**
VTE and Statins

• Statin treatment associated with 2/3rds lower rate VTE in cancer patients
• Pleiotropic effects – anti-inflammatory and antithrombotic

Khemasasuwan D. Chest 2008; 134: 8003S
Practical VTE Prophylaxis

- **Dose**
  - High-risk patients benefit from combined mechanical and pharmacological prophylaxis
  - Continue until patient fully mobile
    - subgroup extended prophylaxis
- **Bleeding risk** : mechanical devices
- **Timing**
- **Neuraxial anaesthesia**
Conclusion

- We know who’s at risk for VTE
- We know the consequences of unprevented VTE
- We know how to prevent VTE with effective, safe, simple and inexpensive interventions
- BUT we don’t do it nearly as often as we should
Conclusion

- Primary prevention is key to managing VTE
- 1 life lost to VTE is 1 too many

So... Just do it!
“Thoroughness is the most difficult habit to acquire, but it is the pearl of great price, worth all of the worry and of the search”

Sir William Osler
“To all students of medicine
Who listen, look, touch and reflect
May they hear, see, feel and comprehend”