Anticoagulation in Long Term Care

- Prophylaxis of VTE
- Treatment of VTE
- Long-term oral A/C
- Bridging therapy
Anticoagulation in Long Term Care

• Simple
  - No monitoring
  - No IV
  - Oral (monitoring)
  - SC (once or twice daily)
Anticoagulation in Long Term Care

Special Considerations
- Elderly
- Renal insufficiency
- Comorbid conditions
- Multiple drugs
Prophylaxis of VTE

- Acute medical illness
- CVA
- Post orthopaedic surgery
- Post cancer surgery
- Spinal cord injury
Treatment of VTE

- Acute DVT
- Acute PE
- Secondary prophylaxis
Long – term oral anticoagulants

- Atrial fibrillation
- Heart valve replacement
- Post-MI
- VTE
Venous Thromboembolism

- Third most common vascular disease
- PE leading preventable cause of death
- 200,000 cases of PE annually in USA
Venous Thromboembolism

Deep vein thrombosis  

Pulmonary embolism
Complications of Deep Vein Thrombosis

- Permanent vascular damage
- Post-phlebitic syndrome
- Pulmonary embolism (PE)
- Pulmonary hypertension
Venous Thromboembolism

- Secondary
  - surgery
  - medical
- Idiopathic
Fatal Pulmonary Embolism

Prophylaxis
Classification of DVT risk

- **Low risk**
  - Minor surgery
  - Age <40
  - No other risk factors

- **Moderate risk**
  - Major surgery
  - Age >40
  - No other risk factors

- **High risk**
  - Major surgery
  - Age >40
  - MI
  - Additional risk factors
  - History of VTE
  - Hip fracture
  - THR or TKR
  - CVA
  - Spinal cord injury
  - Trauma
  - Malignancy
  - Congenital hypercoagulability

VTE, venous thromboembolism; THR, total hip replacement; TKR, total knee replacement; MI, myocardial infarction; CVA, cerebrovascular accident

*Chest* 1998;114:531S-60S
## Frequency of VTE/PE according to risk level

<table>
<thead>
<tr>
<th>Events</th>
<th>Low risk (%)</th>
<th>Moderate risk (%)</th>
<th>High risk (%)</th>
<th>Very high risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calf vein thrombosis</td>
<td>2.0</td>
<td>10-20</td>
<td>20-40</td>
<td>40-80</td>
</tr>
<tr>
<td>Proximal vein thrombosis</td>
<td>0.4</td>
<td>2.4</td>
<td>4.8</td>
<td>10-20</td>
</tr>
<tr>
<td>Clinical PE</td>
<td>0.2</td>
<td>1-2</td>
<td>2-4</td>
<td>4-10</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>0.002</td>
<td>0.1-0.4</td>
<td>0.4-1.0</td>
<td>1-5</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism

*Chest* 1998;114:531S-60S
Methods of DVT prophylaxis

- Unfractionated heparin (UFH)
- Oral anticoagulants (warfarin)
- Dextran
- Antiplatelet therapy
- Mechanical compression and early ambulation
- Low-molecular-weight heparins (LMWHs)
Heparin

- Venous thromboembolism
  - prophylaxis
  - treatment
- Ischaemic heart disease
  - unstable angina
  - acute MI
  - post-thrombolysis
- Embolic stroke
- Extracorporeal circulation
- Haemodialysis
- Peripheral arterial disease
New Anticoagulants

- Low Molecular Weight Heparins
- Low Molecular Weight Heparinoids
- Parenteral Direct Thrombin Inhibitors
- Oral Direct Thrombin Inhibitors
- Pentasaccharides
Schematic Molecular-Weight Distribution
## Low-molecular-weight heparin (LMWH)

<table>
<thead>
<tr>
<th></th>
<th>Median molecular weight</th>
<th>Anti-Xa IU/mg</th>
<th>Anti-IIa IU/mg</th>
<th>Xa/IIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>4800</td>
<td>104</td>
<td>32</td>
<td>3.3</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>5000</td>
<td>122</td>
<td>60</td>
<td>2.0</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>4500</td>
<td>94</td>
<td>31</td>
<td>3.0</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>4500</td>
<td>90</td>
<td>50</td>
<td>1.8</td>
</tr>
<tr>
<td>Clivarine</td>
<td>3900</td>
<td>130</td>
<td>40</td>
<td>3.3</td>
</tr>
</tbody>
</table>
Low-Molecular-Weight Heparins

Potential Advantages:

• Lack of binding to plasma proteins and endothelium

• Good bioavailability

• Stable dose response

• Long half-life

• Resistance does not develop
### Frequency of DVT without prophylaxis

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>DVT incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall incidence in general surgery</td>
<td>19-29% [1]</td>
</tr>
<tr>
<td>Major abdominal surgery (over age 40)</td>
<td></td>
</tr>
<tr>
<td>malignancy</td>
<td>30-35% [2]</td>
</tr>
<tr>
<td>benign disease</td>
<td>25-29% [2]</td>
</tr>
<tr>
<td>Gynaecological surgery</td>
<td></td>
</tr>
<tr>
<td>malignancy</td>
<td>22% [3]</td>
</tr>
<tr>
<td>benign disease</td>
<td>14% [3]</td>
</tr>
<tr>
<td>Urological surgery</td>
<td></td>
</tr>
<tr>
<td>retropubic prostatectomy</td>
<td>30-35% [2]</td>
</tr>
<tr>
<td>transurethral prostatectomy</td>
<td>10-12% [2]</td>
</tr>
</tbody>
</table>

Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin

Collins et al. New England Journal of Medicine, 318 (18) 1162-1173 1988

- 68% reduction in DVT following surgery
- 67% reduction in PE following surgery
- 21% reduction in total mortality (p <0.02)
### Prevention of DVT

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery</td>
<td>9683</td>
<td>6878</td>
<td>0.12</td>
</tr>
<tr>
<td>Orthopaedic surgery</td>
<td>2692</td>
<td>1294</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Prevention of PE

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery</td>
<td>9146</td>
<td>5731</td>
<td>0.12</td>
</tr>
<tr>
<td>Orthopaedic surgery</td>
<td>2475</td>
<td>1172</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Major bleeding

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery</td>
<td>9683</td>
<td>3943</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>Orthopaedic surgery</td>
<td>2692</td>
<td>1294</td>
<td>&gt;0.6</td>
</tr>
</tbody>
</table>

**ENOXACAN II**

*Study Design*

332 Patients undergoing abdominal or pelvic surgery for cancer

- **Pre-op Treatment Period**
  - Enoxaparin sc qd 40mg
  - 10-14h Pre-op

- **Open Treatment Period**
  - Enoxaparin sc qd 40mg
  - 6-10 days

- **Double-blind Treatment Period**
  - Enoxaparin, sc qd 40mg
  - 19-21 days*

- **Follow-up**
  - Placebo
  - 3 months

* Venography between days 25-31

ENOXACAN II

Results

ENOXACAN II

Conclusions

• Prolonged post-operative prophylaxis with enoxaparin significantly reduced VTE incidence by 60%
• Number needed to treat to avoid one VTE is 14
• Benefit maintained at 3 months

<table>
<thead>
<tr>
<th>RISK CATEGORY</th>
<th>RECOMMENDATION</th>
<th>LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Early ambulation</td>
<td>C1</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>LDUH, LMWH, IPC, ES</td>
<td>A1</td>
</tr>
<tr>
<td>High risk</td>
<td>LDUH or Higher dose LMWH (40mg/day) or IPC if high risk of bleeding</td>
<td>A1</td>
</tr>
<tr>
<td>Very high risk</td>
<td>LDUH or higher dose LMWH combined with IPC or warfarin (INR 2.0-3.0)</td>
<td>B1</td>
</tr>
</tbody>
</table>
Deep Vein Thrombosis
Major Orthopaedic Surgery

*Increasing numbers - currently 2.2 million procedures per year*

- Marked growth in the number of major orthopedic surgery procedures:
  - Technical advances
  - Patient aging
- Age is NOT a contraindication to surgery
- Cultural differences exist in patient management
- Despite major advances in patient care, the risk of VTE remains high.
# Frequency of VTE in orthopaedic patients no prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>DVT (%)</th>
<th>Prox VT (%)</th>
<th>PE (%)</th>
<th>Fatal PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TKR</td>
<td>40–85</td>
<td>9–20</td>
<td>2–7</td>
<td>0.5</td>
</tr>
<tr>
<td>Hip #</td>
<td>35–60</td>
<td>15–35</td>
<td>4–24</td>
<td>4–13</td>
</tr>
<tr>
<td>Leg #</td>
<td>60–80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>20–65</td>
<td></td>
<td>2–22</td>
<td></td>
</tr>
<tr>
<td>Arthroscopy</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Prevention of Venous Thromboembolism

*Geerts et al, Chest 2001; 119:132*

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Trials</th>
<th>Patients</th>
<th>DVT Prevalence% (95% CI)</th>
<th>RRR%</th>
<th>Prox DVT Prevalence% (95% CI)</th>
<th>RRR%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>12</td>
<td>626</td>
<td>54.2 (50-58)</td>
<td>---</td>
<td>26.6 (23-31)</td>
<td>---</td>
</tr>
<tr>
<td>Comp Stock.</td>
<td>4</td>
<td>290</td>
<td>41.7 (36-48)</td>
<td>23</td>
<td>25.5 (21-31)</td>
<td>4</td>
</tr>
<tr>
<td>Aspirin</td>
<td>6</td>
<td>473</td>
<td>40.2 (35-45)</td>
<td>26</td>
<td>11.4 (8-16)</td>
<td>57</td>
</tr>
<tr>
<td>LDH</td>
<td>11</td>
<td>1016</td>
<td>30.1 (27-33)</td>
<td>45</td>
<td>19.3 (17-22)</td>
<td>27</td>
</tr>
<tr>
<td>Warfarin</td>
<td>13</td>
<td>1828</td>
<td>21.1 (20-24)</td>
<td>59</td>
<td>5.2 (4-6)</td>
<td>80</td>
</tr>
<tr>
<td>IPC</td>
<td>7</td>
<td>423</td>
<td>20.3 (17-24)</td>
<td>63</td>
<td>13.7 (11-17)</td>
<td>48</td>
</tr>
<tr>
<td>Hirudin</td>
<td>3</td>
<td>1172</td>
<td>16.3 (14-19)</td>
<td>70</td>
<td>4.1 (3-5)</td>
<td>85</td>
</tr>
<tr>
<td>LMWH</td>
<td>30</td>
<td>6216</td>
<td>16.1 (15-17)</td>
<td>70</td>
<td>5.9 (5-7)</td>
<td>78</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>3</td>
<td>441</td>
<td>15.6 (12-19)</td>
<td>71</td>
<td>4.1 (2-6)</td>
<td>85</td>
</tr>
<tr>
<td>Adjusted Hep</td>
<td>4</td>
<td>293</td>
<td>14.0 (10-19)</td>
<td>74</td>
<td>10.2 (7-14)</td>
<td>62</td>
</tr>
</tbody>
</table>
Hip fracture: An increasing problem

Hip Fracture surgery:  
A common and increasingly frequent condition

- By 2050, numbers will increase 3 fold from 1.7 million to 6.3 million
- Unprecedented increases will occur in developing countries over next 50 years
- Life time risk of fracture will rise to an incredible 35% for women, 17% of men

A Global Health Problem

### Hip Fracture Surgery:

The highest risk of VTE

<table>
<thead>
<tr>
<th>Procedure</th>
<th>% DVT rate</th>
<th>% PE rate (range)</th>
<th>Any PE</th>
<th>Fatal PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip replacement</td>
<td>45–57</td>
<td>0.7–30</td>
<td>0.1–0.4</td>
<td></td>
</tr>
<tr>
<td>Total knee replacement</td>
<td>40–84</td>
<td>1.8–7.0</td>
<td>0.2–0.7</td>
<td></td>
</tr>
<tr>
<td>Hip fracture</td>
<td>36–60</td>
<td>4.3–24</td>
<td>3.6–12.9</td>
<td></td>
</tr>
</tbody>
</table>

Primary causes of death in patients undergoing hip fracture surgery

- Pneumonia: 50%
- Pulmonary Embolism: 10%
- Cardiac failure: 10%
- Myocardial infarction: 5%

Pulmonary Embolism
A leading cause of mortality following hip fracture surgery

Mortality following hip fracture

887 patients undergoing major orthopaedic surgery

Mortality rate at 6 months %

- Total hip replacement: 1.0%
- Total knee replacement: 1.3%
- Hip fracture surgery: 14.8%

Hip fracture Surgery:
50% of patients don’t receive adequate prophylaxis

Percentage of patients receiving Grade 1 recommended prophylaxis

- Total Hip replacement: ~95%
- Total Knee replacement: ~70%
- Hip fracture surgery: ~40%

Guidelines for Antithrombotic Therapy
Major Orthopaedic Surgery

• Elective THR
LMWH (started either 12 hours before or 12-24 hours after surgery) or adjusted dose warfarin INR target 2.5, range 2.0-3.0; started preoperatively or immediately after surgery). *Grade 1A*. Adjusted-dose heparin started preoperatively is an acceptable alternative.  *Grade 2A*

• Elective TKR
LMWH or adjusted-dose warfarin. *Grade 1A*. IPC is an alternative option.  *Grade 1B*

• Hip fracture
LMWH or adjusted-dose warfarin. *Grade 1B*
Guidelines for Antithrombotic Therapy
Major Orthopaedic Surgery

• Anticoagulant prophylaxis should be continued for at least 7-10 days. *Grade 1A*

• Extended out-of-hospital LMWH prophylaxis is recommended for high-risk patients. *Grade 2A*
VTE events post orthopedic surgery: 2/3 occur beyond hospital discharge

## Relative Risk for All Deep Venous Thrombosis During the Out-of-hospital Time Interval

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>LMWH Group n/n (%)</th>
<th>Control Group n/n (%)</th>
<th>Relative Risk (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergqvist et al.</td>
<td>1996</td>
<td>21/117 (17.9)</td>
<td>45/116 (38.8)</td>
<td></td>
</tr>
<tr>
<td>Planes et al. (30)</td>
<td>1996</td>
<td>6/85 (7.1)</td>
<td>17/88 (19.3)</td>
<td></td>
</tr>
<tr>
<td>Dahl et al. (31)</td>
<td>1997</td>
<td>11/93 (11.8)</td>
<td>23/89 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Lassen et al. (32)</td>
<td>1998</td>
<td>5/113 (4.4)</td>
<td>12/102 (11.8)</td>
<td></td>
</tr>
<tr>
<td>Hull et al. (45)</td>
<td>2000</td>
<td>14/291 (4.8)</td>
<td>14/133 (10.5)</td>
<td></td>
</tr>
<tr>
<td>Comp et al. (46)</td>
<td>2001</td>
<td>15/152 (9.9)</td>
<td>39/138 (28.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>72/911 (7.9)</td>
<td>150/666 (22.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Results**: LMWH results favour patients over controls.

**Results**: Placebo results do not favour any group.
### Relative Risk for Symptomatic Venous Thromboembolism During the Out-of-Hospital Time Interval

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>LMWH Group</th>
<th>Control Group</th>
<th>Patients with Events</th>
<th>Relative Risk (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergqvist et al.</td>
<td>1996</td>
<td>2/131 (1.5)</td>
<td>10/131 (7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planes et al. (30)</td>
<td>1996</td>
<td>3/90 (3.3)</td>
<td>7/89 (7.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dahl et al. (31)</td>
<td>1997</td>
<td>4/117 (3.4)</td>
<td>6/110 (5.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lassen et al. (32)</td>
<td>1998</td>
<td>2/140 (1.4)</td>
<td>3/141 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hull et al. (45)</td>
<td>2000</td>
<td>4/389 (1.0)</td>
<td>3/180 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comp et al.(46)</td>
<td>2001</td>
<td>0/224 (0.0)</td>
<td>7/211 (3.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>15/1091 (1.4)</strong></td>
<td><strong>36/862 (4.2)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results: Favor LMWH
Venous Thromboembolism

Deep vein thrombosis

Pulmonary embolism

Treatment
### Guidelines for Antithrombotic Therapy

#### Treatment of Venous Thromboembolism

*ACCP Chest 2001*

<table>
<thead>
<tr>
<th>Suspected VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC LMWH or IV heparin bolus (5000u)</td>
</tr>
<tr>
<td>Confirm diagnosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Confirmed VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue LMWH or UFH for 5 days</td>
</tr>
<tr>
<td>Monitor UFH with APTT and adjust dose</td>
</tr>
<tr>
<td>Start warfarin 5mg, target INR 2.5 (2.0-3.0)</td>
</tr>
<tr>
<td>Overlap minimum 4-5 days and until INR &gt;2.0 for 2 days</td>
</tr>
<tr>
<td>Daily platelet count with UFH; x 1 for LMWH</td>
</tr>
</tbody>
</table>
LMWH at Least as Effective and Safe as UFH

Odds Ratio (OR, Peto), LWMH vs UFH with 95% confidence interval (13 comparative studies)

- Sympt recurrent VTE: OR = 0.66 [0.51–0.86]
- Major bleeding: OR = 0.56 [0.38–0.83]
- Overall mortality: OR = 0.68 [0.53–0.88]

Van der Heijden, Cochrane 2001

LMWH better  UFH better
Treatment of VTE:
Advantages of LMWH

- Efficacy: better than UFH
- Safety: safer than UFH
- Mortality: perhaps a mortality benefit
- Patient satisfaction: outpatient treatment
- Clinical utility: once-a-day injections
- Cost savings: substantial
Guidelines for Antithrombotic Therapy Long-Term Anticoagulation

• All patients: Continue oral anticoagulation for at least 3 months at target INR of 2.5 (range 2.0-3.0). (This does not apply to patients with isolated calf-vein thrombosis). *Grade 1A*

• Oral anticoagulation contraindicated or inconvenient: LMWH or adjusted-dose s.c. heparin in therapeutic doses. *Grade 1A*

ACCP Chest 2001
Guidelines for Antithrombotic Therapy
Long-Term Anticoagulation in VTE

- Patients with reversible or time-limited risk factors: treat for at least 3 months. Grade 1A
- Patients with a first episode of idiopathic VTE: treat for at least 6 months. Grade 1A
- Patients with recurrent idiopathic VTE or a continuing risk factor such as cancer, antithrombin deficiency, or anticardiolipin syndrome: treat for at least 12 months. Grade 1C
- Patients with protein C or S deficiency, multiple thrombophilic conditions, homocysteinemia, or factor V Leiden: treat for at least 6 months. Grade 1C

ACCP Chest 2001
Guidelines for Antithrombotic Therapy Long-Term Anticoagulation

• Symptomatic isolated calf-vein thrombosis: treat for at least 6-12 weeks. *Grade 1A*

• Alternatively, serial non-invasive studies over the next 10-14 days to assess for proximal extension of thrombus. *Grade 1C*
Deep Vein Thrombosis

Priority

Use adequate primary prophylaxis
Atrial Fibrillation: Antithrombotic Therapy
Laupacis et al, Chest 1998; 114 (5):579-589

- Oral Anticoagulants vs Aspirin
- Efficacy vs safety
- Risk stratification
  - Major
  - Intermediate
  - Low
Atrial Fibrillation: Risk Factors for Stroke

Laupacis et al, Chest 1998; 114 (5):579-589

High Risk

- Age >75 years
- Prior TIA, stroke or systemic embolism
- Hypertension or history of hypertension
- Poor LV function (clinical or 2-D echo)
- Rheumatic mitral valve disease
- Heart valve replacement
Atrial Fibrillation: Risk Factors for Stroke
Laupacis et al, Chest 1998; 114 (5):579-589

Intermediate Risk

- Age 65-75 years
- Diabetes
- CAD
- Thyrotoxicosis
Atrial Fibrillation: Risk Factors for Stroke

Laupacis et al, Chest; 114 (5):579-589

Low Risk

- Age <65 years
- No cardiac abnormality
Stroke Relative Risk Reduction in Atrial Fibrillation Patients

- 68 vs 21

Relative Risk Reduction %

Warfarin*  ASA**

*Based on AFASAK, BAATAF, CAFA, SPAFI, SPINAF (vs control)

** Based on AFASAK, SPAFI, EAFT (vs placebo)

Adapted from AFI. Arch Intern Med 1994;154:1449-1457 & 1997;157:1237-1240
Risk/Benefit Analysis of Anticoagulation in Atrial Fibrillation

1,000 patients treated with warfarin for 1 year

**Benefit**
35 fewer thromboembolic events

**Risk**
1 more intracranial or major bleed

# Summary of ACCP Recommendations in Atrial Fibrillation

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk Factors</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 years</td>
<td>Absent</td>
<td>ASA</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Warfarin (Target INR 2.5; range 2.0-3.0)</td>
</tr>
<tr>
<td>65-75 years</td>
<td>Absent</td>
<td>ASA or warfarin</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>Warfarin (Target INR 2.5; range 2.0-3.0)</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>All Patients</td>
<td>Warfarin (Target INR 2.5; range 2.0-3.0)</td>
</tr>
</tbody>
</table>

Odds Ratios of Intracranial Hemorrhage

PTR above 2.0 (INR of 3.7 to 4.3) dramatically increased the risk of bleeding.

Odds Ratios for Stroke

INR below 2.0 results in a higher risk of stroke.

Antithrombotic Therapy in Heart Valve Replacement

ACCP, 2000

Aortic

• St. Jude bileaflet INR 2.5 (2.0-3.0)
• Carbomedics bileaflet INR 2.5 (2.0-3.0)
• Medtronic Hall tilting disk INR 2.5 (2.0-3.0)
• Atrial fibrillation (any) INR 3.0 (2.5-3.5)
Antithrombotic Therapy in Heart Valve Replacement

ACCP, 2000

Mitral

- Bileaflet INR 3.0 (2.5-3.5)
- Tilting disk INR 3.0 (2.5-3.5)
- Any (atrial fib) INR 3.0 (2.5-3.5)
- Caged ball/disk INR 3.0 (2.5-3.5)

Aspirin 80 mg/day
Antithrombotic Therapy in Heart Valve Replacement

ACCP 2000

Mechanical Valves

- Previous embolism INR 3.0 (2.5-3.5) + Aspirin 80mg/day
Bridging Therapy
Bridging Therapy - Options

- D/C oral A/C
- Reduce INR
- D/C oral A/C: IV heparin
- D/C oral A/C: LMWH
Background

• Most clinicians opt for anticoagulant cover with intravenous heparin. However, there are a number of limitations to this approach including a requirement for hospitalization.
  • Costs of hospitalization
  • Limited availability of hospital beds

• Low molecular weight heparins have pharmacological and pharmacokinetic advantages over heparin that allow outpatient treatment by self-administered subcutaneous injection.
Methods

- Prospective cohort
- Patients on long-term oral anticoagulants
- Temporary discontinuation
- Low molecular weight heparin
- Out-patient management
Patients

Number of patients = 1082

Male/Female = 618/464

Average age (yrs) = 65.6
Anticoagulant Management

- Discontinue oral A/C day 5 pre-procedure
- INR day 4/5 pre-procedure
- If INR <2.0 start LMWH (enoxaparin or dalteparin)
- If INR >2.0 repeat above next day
- Continue LMWH until evening prior to procedure
Dalteparin Regimen

- 100 antifactor Xa units/kg subcutaneously twice daily
- Last injection administered 12 hours prior to procedure
- First injection after the procedure 8-12 hours post and after haemostasis secure
- Oral anticoagulants resumed evening of procedure or next day
- Dalteparin continued until INR therapeutic
Enoxaparin Regimen

• 1mg/kg subcutaneously twice daily
• Last injection administered 12 hours prior to procedure
• First injection after the procedure 8-12 hours post and after haemostasis secure
• Oral anticoagulants resumed evening of procedure or next day
• Enoxaparin continued until INR therapeutically
## Indications for Long-term Anticoagulants

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical MVR (sinus)</td>
<td>65</td>
</tr>
<tr>
<td>Mechanical MVR (AF)</td>
<td>61</td>
</tr>
<tr>
<td>Mechanical AVR (Sinus)</td>
<td>170</td>
</tr>
<tr>
<td>Mechanical AVR (AF)</td>
<td>29</td>
</tr>
<tr>
<td>Bioprosthetic MVR (Sinus)</td>
<td>2</td>
</tr>
<tr>
<td>Bioprosthetic MVR (AF)</td>
<td>12</td>
</tr>
<tr>
<td>Bioprosthetic AVR (Sinus)</td>
<td>6</td>
</tr>
<tr>
<td>Bioprosthetic AVR (AF)</td>
<td>9</td>
</tr>
<tr>
<td>Other valve</td>
<td>47</td>
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</table>
## Indications for Long-term Anticoagulants

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>Lone AF</td>
<td>392</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>87</td>
</tr>
<tr>
<td>Embolic CVA/TIA/VTE</td>
<td>116</td>
</tr>
<tr>
<td>Lupus with VTE</td>
<td>7</td>
</tr>
<tr>
<td>CAD +/- LV thrombus</td>
<td>62</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>15</td>
</tr>
<tr>
<td>PVD</td>
<td>2</td>
</tr>
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</table>
# Reasons for Interruption of Anticoagulants

<table>
<thead>
<tr>
<th>Medical Category</th>
<th>Total</th>
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<tbody>
<tr>
<td>General surgery</td>
<td>227</td>
</tr>
<tr>
<td>Major</td>
<td>95</td>
</tr>
<tr>
<td>Minor</td>
<td>132</td>
</tr>
<tr>
<td>Urological surgery</td>
<td>36</td>
</tr>
<tr>
<td>Major</td>
<td>22</td>
</tr>
<tr>
<td>Minor</td>
<td>14</td>
</tr>
<tr>
<td>Invasive diagnostic procedures</td>
<td>346</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>230</td>
</tr>
<tr>
<td>Major</td>
<td>77</td>
</tr>
<tr>
<td>Minor</td>
<td>153</td>
</tr>
<tr>
<td>Orthopaedic surgery</td>
<td>51</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>35</td>
</tr>
<tr>
<td>Dental surgery</td>
<td>116</td>
</tr>
<tr>
<td>Eye surgery</td>
<td>40</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>1</td>
</tr>
</tbody>
</table>
Peri-operative Regimens

Days off oral anticoagulants  6.00

LMWH doses pre-procedure  5.60

LMWH doses post-procedure  5.38
## Peri-operative Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pre-procedure LMWH</td>
<td>25</td>
</tr>
<tr>
<td>Pre-procedure Vit K</td>
<td>13</td>
</tr>
<tr>
<td>No post-procedure LMWH</td>
<td>196</td>
</tr>
<tr>
<td>- cardiac surgery</td>
<td></td>
</tr>
<tr>
<td>- epidural catheter</td>
<td></td>
</tr>
<tr>
<td>- major urological surgery</td>
<td></td>
</tr>
<tr>
<td>- IV heparin</td>
<td></td>
</tr>
</tbody>
</table>
## Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor bleeding</td>
<td>28</td>
<td>7.6%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3</td>
<td>0.27%</td>
</tr>
<tr>
<td>Bruising at injection site</td>
<td>38</td>
<td>3.5%</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Deaths</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>
Average Nursing Time

Teach self-injection
Arrange drug supply
Give specific written instructions

30-45 minutes

Patients given a contact telephone number in case of problems with injections
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Self</td>
<td>956 (88.3%)</td>
</tr>
<tr>
<td>Family</td>
<td>77 (7.1%)</td>
</tr>
<tr>
<td>Nurse</td>
<td>49 (4.6%)</td>
</tr>
</tbody>
</table>
Conclusion

• Low molecular weight heparin administered sc on an outpatient basis is a practical alternative to iv heparin to cover temporary interruption of oral anticoagulants for operative, dental or invasive diagnostic procedures in patients who are at a high risk for recurrent thrombosis or systemic embolic events.

• Low molecular weight heparin can be self-administered subcutaneously by most patients for this indication.
New Anticoagulants

Coagulation cascade

Initiation

TF/VIIa

TFPI

NAPc2

Propagation

Xa

IX

IXa

VIIa

Fondaparinux

DX9065a

Thrombin activity

IIa

II

Va

Ximelagatran

Adapted with permission from Weitz J, Hirsh J. Chest. 2001;119:95S.