ANTICOAGULANT THERAPY REVISITED 2005

or, Which one(s) of these (#$%$#!@#^) drugs should be the one(s) I use, and for what?

ANTICOAGULANT THERAPY

One of most common treatments in hospital & out
2nd most common cause of iatrogenic complications (behind only infections)
2nd most expensive source of increased hospital stays

ANTICOAGULANT THERAPY

Focus on venous thromboembolism (VTE)
Focus on parenteral therapy
Not topics for discussion today:
- Thrombolytic therapy. Anti-platelet therapy
- Oral anticoagulants (warfarin) & new agents @ end

ANTICOAGULANT THERAPY

Goals of Therapy

PREVENTION OF THROMBOEMBOLISM!!!
- Stop propagation of clot
- Prevent formation of further clot
- Allow dissolution of clot
- Can be used for prophylaxis against clot formation

Anticoagulant Therapy

Hemorrhage is a complication of overaggressive anticoagulant therapy

Thrombosis is a complication of underaggressive anticoagulant therapy

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All VTE
Annual Incidence Per 100,000

Annual Incidence

Age

Female + Male

Prophylaxis vs TE Disease

- Requires smaller dose than does treatment
- Less risk of bleeding with prophylaxis doses
- Stratified by risk of developing thromboembolic disease
- In surgery patients, pre-op therapy generally more effective than post-op therapy (with one exception)

Primary Risk Factors for VTE

- Major surgery
- Acute MI
- Major trauma
- Paralytic stroke
- Cancer
- Spinal cord injury
- Pelvic/hip fracture

Risk Assessment

<table>
<thead>
<tr>
<th>Intrinsic Factors</th>
<th>Molecular Risk Factors</th>
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</thead>
<tbody>
<tr>
<td>Family history/Past History VTED</td>
<td>Factor V Leiden Mutation</td>
</tr>
<tr>
<td>Advanced Age</td>
<td>Activated Protein C Resistance</td>
</tr>
<tr>
<td>Obesity</td>
<td>Antithrombin III</td>
</tr>
<tr>
<td>Varicose Veins</td>
<td>Protein C</td>
</tr>
<tr>
<td>Venous insufficiency</td>
<td>Protein S</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>Plasminogen</td>
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</table>

<table>
<thead>
<tr>
<th>Extrinsic Factors</th>
<th>Antithrombin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy/Puerperium</td>
<td>Factor VII</td>
</tr>
<tr>
<td>Estrogen therapy</td>
<td>Antithrombin III</td>
</tr>
<tr>
<td>Paralysis</td>
<td>Protein C</td>
</tr>
<tr>
<td>Previous or current malignancy</td>
<td>Protein S</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>Antithrombin III</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Protein C</td>
</tr>
</tbody>
</table>

Risk Factors Are Cumulative

Venous Thromboembolism – Indications for Prophylaxis

- Primary VTE Risk Factors
  - Sufficient indication for VTE Prophylaxis
- Secondary VTE Risk Factors
  - Insufficient indication by themselves

Incidence of DVT

Correlation with the number of risk factors

-11% 24% 36% 50% 100%

Number of risk factors

Positive result (%)
Prophylaxis vs TE Disease

- **Low Risk** – Minor procedure, otherwise healthy
  - No medications; rapid mobilization
- **Moderate Risk** – Abdominal surgery, thoracic surgery, Medical patient
  - Multiple medical regimens effective
- **High Risk** – Paraplegic, hemiplegic, pelvic surgery, leg surgery
  - Moderate risk therapy ineffective; more clearly needed

Available Anticoagulants

- Before 1987, only heparin and warfarin were available
- Now,
  - 4 low molecular weight heparins (3 available in US)
  - 1 heparinoid (not available in US)
  - 1 Factor Xa inhibitor
  - 3 direct thrombin inhibitors
  - 1 coumarin derivative
- More to come

Heparin

- Potentiates inactivation of activated enzymes of clotting cascade, via binding to antithrombin III
- Functions as chemical catalyst
- Natural heparin-like molecules on endothelial surfaces make these surfaces antithrombotic in nature
- Commercially available x 50+ years
- Lots of knowledge RE: use of drug
Heparin

- Multiple sources – most commonly used are porcine intestine and bovine lung
- Short-acting (1/2 life c. 1 hour)
- Bioavailability is variable from source to source & from batch to batch
- Monitoring usually considered to be necessary to assess the effect of treatment

Heparin

- **Monitoring important to ensure that the desired anticoagulant effect is being achieved; NOT to avoid giving too much heparin!!!!**

Heparin

- Multiple studies show that in treatment of thromboembolic disease, failure to achieve anticoagulant effect within 48 hours of beginning treatment with ANY medication increases complication rate by 4-10X
- NO study shows that keeping any monitoring test below a certain level results in decreased bleeding complications

**HEPARIN Treatment Regimens**

- Prophylaxis vs. DVT
  - 5000 units SQ BID
  - Doesn’t require monitoring
  - Clearly effective in preventing venous thromboembolism in low & moderate risk patients
  - Doesn’t increase risk of hemorrhage

**HEPARIN Treatment Regimens – pre-1990’s**

- Treatment of thromboembolic disease
  - Heparin 5000 unit bolus
  - Continuous infusion at 800-1000 units/hr
  - Measure aPTT @ 6 hours post-bolus
  - Adjust up or down to maintain heparin at 1.5-2.5 x normal aPTT value

**HEPARIN THERAPY Problems - Prophylaxis**

- Prophylaxis only effective in low or moderate risk groups; ineffective in patients at high risk of VTE (risk of VTE 35-50%)
  - Lower extremity orthopedic surgery
  - Radical pelvic surgery
  - Paraplegia/quadriplegia
  - Hemiplegia
  - ? Prothrombotic conditions
- Higher dose heparin more effective, but requires monitoring, & risk of bleeding increased
### Heparin Therapy (VTE)
- **Standard of care**: Weight based heparin
- **Various protocols**, but all start at 13-18 units heparin/kg/hr, up to a weight of 100-125 kg
- On these, can achieve therapeutic levels 90-95% of the time within 48 hours
- Still need to get aPTT values in a timely fashion

### Low Molecular Weight Heparins - Problems
- More expensive than heparin
- Longer acting, and only partially reversible with protamine
- Renally excreted, making dosing problematic in renal disease
- Cross-reactive with HIT causing antibodies
- Much more effective for prophylaxis if given pre-op
- All carry black box warning vs. use with regional anesthesia

### Low Molecular Weight Heparins
- Higher bioavailability; makes dosing without monitoring a reality (except in renal disease, morbid obesity, cachexia)
- Longer half-life; therefore can be given subcutaneously 1-2x/day
- Much lower (but not 0) risk of de novo thrombocytopenia
- At least as effective for treatment; more effective for high risk prophylaxis than heparin
- Mechanism of action similar to heparin

### Low Molecular Weight Heparins - Therapy
- Most patients with formed thrombus are relatively heparin resistant
- Generally requires 15-20 units heparin/kg/hour to achieve therapeutic aPTT in VTE patients
- In normal sized adult, often takes several days to get patient therapeutic on heparin

### Heparin Problems - Therapy
- If > 48 hours to therapeutic range, risk of complications of Rx rise 4-10x & stay up x 6 months
- Longer to therapeutic causes increased risk of HIT/HITTS
- Longer to therapeutic increases risk of length-of-stay police
Low Molecular Weight Heparins (US)

- Enoxaparin (Lovenox®) – Approved for VTE prophylaxis, VTE treatment, acute coronary syndrome
- Dalteparin (Fragmin®) – Same as enoxaparin RE: approvals, except for VTE treatment
- Tinzaparin (Innohep®) – Approved for treatment of VTE
- Ardeparin (Normiflo®) – Not being marketed in US
- All behave similarly, but dosing of each is different

FACTOR Xa INHIBITOR

- Fondaparinux (Arixtra®) – Semisynthetic sulfated pentasaccharide; active moiety of heparin
- Only inhibits factor Xa
- Bioavailability virtually 100%; can be given QD
- No thrombocytopenia seen in trials (does not bind to platelet factor IV)
- Data clearly shows it to be superior to LMWH when given postoperatively, & probably superior to LMWH given preoperatively

FONDAPARINUX

- Offers possibility of post-op prophylaxis against DVT with same or better efficacy as preop administration of LMWH
- Small but real incidence of wound hematomas (nil if given > 6 hrs post-op); bleeding risk otherwise similar to LMWH
- Avoids problems with administration of drug during regional anesthesia, since can be given after the epidural catheter is pulled
- Approved for treatment of VTE
- Longer prophylactic treatment better than shorter

Direct Thrombin Inhibitors

- Block active site of thrombin
- Inhibit both clot-bound and free thrombin
- More potent inhibitors than heparin
- All are short-acting, IV infusions

Direct Thrombin Inhibitors

- Lepirudin (Refudan®)
  - Hirudin derivative
  - Half life 30-40 minutes
  - Problematic in renal disease
  - Not reversible
  - Approved for Heparin-Induced Thrombocytopenia and Thrombosis

Direct Thrombin Inhibitors

- Argatroban®
  - Small molecule active site blocker of thrombin
  - Half life 30-40 minutes
  - Problematic in liver disease
  - Not reversible
  - Approved for Heparin-Induced Thrombocytopenia and Thrombosis & for Acute Coronary Syndromes
Direct Thrombin Inhibitors

- Bivalirudin (Angiomax®)
  - Hirudin derivative
  - Short-acting
  - Not reversible
  - Approved for unstable angina/angioplasty

Current Recommendations

- Acute coronary syndromes
  - Enoxaparin superior to dalteparin, which is marginally superior to unfractionated heparin
- Differences small
- In institutions with aggressive intervention programs, unfractionated heparin remains drug of choice for most cardiologists

Heparin-Induced Thrombocytopenia

Type II - Treatment

- Warfarin alone can lead to increased thrombosis
- Low molecular weight heparin has significant cross-reactivity with anti-heparin antibodies, and can lead to recurrent thrombocytopenia and thrombosis
- Ancrod, prostacyclin analogues ineffective

Current Recommendations

- On Ward, Rx of VTE:
  - Unfractionated heparin, weight based
  - Low molecular weight heparin, weight based (treatment dosing)
    - Enoxaparin, dalteparin, tinzaparin probably equivalent, at appropriate doses

Current Recommendations

- In OR: Unfractionated heparin
- In ICU – Treatment of VTE: Unfractionated heparin, weight-based
  - Reversibility in these settings critical, as is short duration of action

Current Recommendations

- Either can be used; I prefer the latter, except in renal insufficiency
  - Decreased incidence of HIT
  - Decreased incidence of subtherapeutic values
  - Decreased problems with laboratory monitoring of therapy
Current Recommendations

- Outpatient Treatment of VTE
  - Low molecular weight heparin/fondaparinux
  - Enoxaparin, Dalteparin, Tinzaparin
    Fondaparinux equivalent
  - Converting to oral agent problematic (mostly because of health care systems)
  - Financial disincentive for physicians to do this

Current Recommendations – VTE Prophylaxis

- High Risk Patients
  - Fondaparinux 2.5 mg SQ QD (especially in the perioperative setting)
  - Enoxaparin 30 mg SQ Q 12h
  - Adjusted dose warfarin (begin 1 day pre-op and maintain INR at 1.5-2)
  - Adjusted dose heparin – to maintain midpoint aPTT at 1.5 x control

Current Recommendations – VTE Prophylaxis

- Low Risk – No medications; early ambulation
- Moderate Risk (Medical or Surgical) – Enoxaparin 40 mg SQ QD or Dalteparin 5000 units SQ QD; ± pneumatic compression

Current Recommendations – VTE Prophylaxis (Controversial)

- Avoid SQ heparin except in severe renal dysfunction
- SQ heparin equally effective as LMWH in these situations; however,
  - In prophylaxis, no need to take risk of HIT
- ?? – extra cost of LMWH outweighed by cost of only a few cases of HIT

Current Recommendations – HIT/HITTS

- Lepirudin if patients don’t have renal disease
- Argatroban if patients don’t have liver disease
- AVOID warfarin alone!!

WARFARIN

- Goal - Prevention of further thromboembolism, while minimizing risk of bleeding as much as possible
WARFARIN Monitoring

- International Normalized Ratio (INR) should be used for all monitoring of warfarin therapy
  - INR=(PTI)\textsuperscript{ISI}; ISI is a fudge factor that corrects for differences in reagents between different laboratories
- INR Values: 2-3 for most patients; 2.5-3.5 for prosthetic valves; ? Higher for hypercoagulation disorders (controversial)
- Except ---

WARFARIN Acute Treatment

- No Loading Dose
- Effect of dose of warfarin seen 36 hours later
- Multiple meds affect sensitivity to warfarin
- Final adjustment needs to be done as an out-patient, but should get into therapeutic range before leaving hospital

WARFARIN Warfarin – 2

- LMWH preferred for Rx of oncology patients with VTE
- ?? APLA syndrome patients - ? Rx with LMWH

WARFARIN Duration of Therapy

- Post-operative DVT’s, no risk factors
  - 6 weeks warfarin therapy
- First DVT, no risk factors for thrombosis, NOT post-op
  - 6 months warfarin therapy; ? Indefinite Rx, ? at lower INR range
- Second or greater DVT
  - Indefinite warfarin unless major contraindication

WARFARIN Acute Treatment

- Can start warfarin once therapeutic on heparin or LMWH
- Delayed onset of action; need to be covered with parenteral anticoagulant for a minimum of 5 days, or until INR is therapeutic for a minimum of 48 hours, WHICHEVER IS LONGER!!!

Future Agents (Not yet approved)

- Melagatran/Ximelagatran – Direct thrombin inhibitors; 2nd drug is orally active, & could potentially replace warfarin
  - Not approved on initial go-round @ FDA (approved in Europe)
- ?? Other direct thrombin inhibitors for uses other than HIT
- ?? Orally active heparin/LMWH derivatives