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

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**ANTICOAGULANT THERAPY REVISITED 2004**

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

**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

**Goals of Therapy**

- PREVENTION OF FURTHER 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*

![Graph showing annual incidence per 100,000](image)

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)

Risk Assessment

### Intrinsic factors
- Family history, prior history of VTE
- Advanced age
- Obesity
- Varicose veins
- Venous insufficiency

### Extrinsic factors
- Pregnancy, preeclampsia
- Exogenous estrogens
- Paralysis
- Immobilization
- Presence or current malignancy
- Chronic heart failure
- Chronic respiratory failure
- Inflammatory bowel disease

Molecular risk factors
- Factor V Leiden mutation
- Activated protein C resistance
- Deficiencies:
  - Antithrombin III
  - Protein C
  - Protein S
- Hyperhomocysteinemia
- Lupus anticoagulant

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

Primary Risk Factors for VTE

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

Secondary Risk Factors for VTE

- Congestive heart failure
- Previous VTE
- Obesity
- Chronic respiratory failure
- Increasing age
- Hematological disorders
- Central venous catheter
- Varicose veins
- Pregnancy
- Estrogen treatment
- Hospitalization

Incidence of DVT

**Correlation with the number of risk factors**

- 0 risk factors: 11%
- 1 risk factor: 24%
- 2 risk factors: 38%
- 3 or more risk factors: 58%
- >3 risk factors: 100%
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 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 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**

- 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 – 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 Problems - Prophylaxis**

- 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 THERAPY (VTE)

- Standard of care: Weight based heparin
- Various protocols, but all start at 1.5-18 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

- Work best as prophylactic agents when given preoperatively
- Cannot be given in setting of regional anesthesia (incidence of epidural hematomas noted in this setting)
- When given post-op, offer little advantage over prophylactic dose heparin or adjusted dose warfarin for DVT prevention
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
- Studies for Rx of VTE ongoing

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
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

- 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

- 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

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

- 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
  - Enoxaparin, Dalteparin, Tinzaparin equivalent
  - ? Role for fondaparinux (at 7.5 mg QD)
  - Converting to oral agent problematic (mostly because of health care systems)
  - Financial disincentive for physicians to do this
**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 – 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 – HIT/HITT**

- 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
  - \( \text{INR} = (\text{PTI})^{\text{ISI}} \); 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)
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!!!

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 outpatient, but should get into therapeutic range before leaving hospital

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, 1 at lower INR range
- Second or greater DVT
  - Indefinite warfarin unless major contraindication

Future Agents (Not yet approved)
- Melagatran/Ximelagatran – Direct thrombin inhibitors; 2nd drug is orally active & could potentially replace warfarin
- ? Other direct thrombin inhibitors for uses other than HIT
- ? Orally active heparin/LMWH derivatives