ANTICOAGULANT THERAPY REVISITED 2004

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

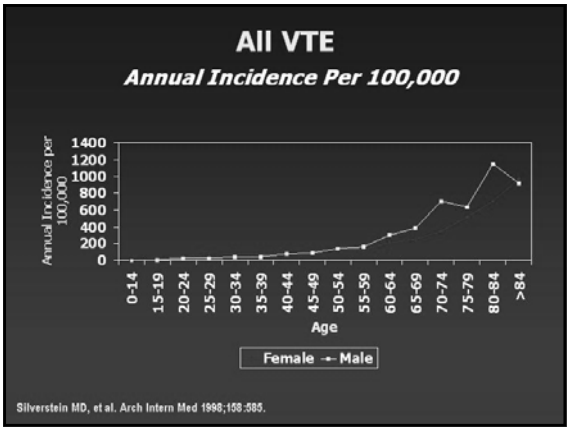
- Focus on venous thromboembolism (VTE)
- Focus on parenteral therapy
- Not topics for discussion today:
  - Thrombolytic therapy
- Oral anticoagulants (warfarin) & new agents @ end

ANTICOAGULANT THERAPY 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***



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/past history of VTED
Advanced age
Obesity
Varicose veins
Venous insufficiency
Thombophilia

Extrinsic factors
Pregnancy/puerperium
Estrogen therapy
Paralysis
Immobilization
Previous 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
protein C
protein S
antiphospholipid antibody/ lupus anticoagulant
Prothrombin gene mutation
Methylene tetrahydrofolate reductase mutation

Risk Factors are Cumulative[1]

1. Salzman EW, Hirsh J. In: Colman RW, et al,. Eds. Hemostasis and thrombosis: Basic principles and clinical practice. 3rd ed. Philadelphia: Lippincott Company, 1994:1276-1296.

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

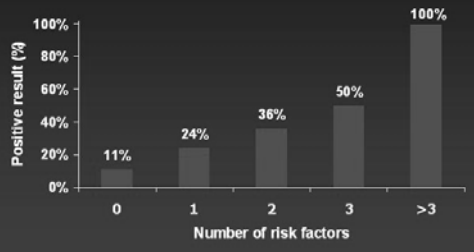
- Major surgery
- Acute MI
- Major trauma
- Paralytic stroke
- Cancer
- Spinal cord injury
- Pelvic fracture

Secondary Risk Factors for VTE

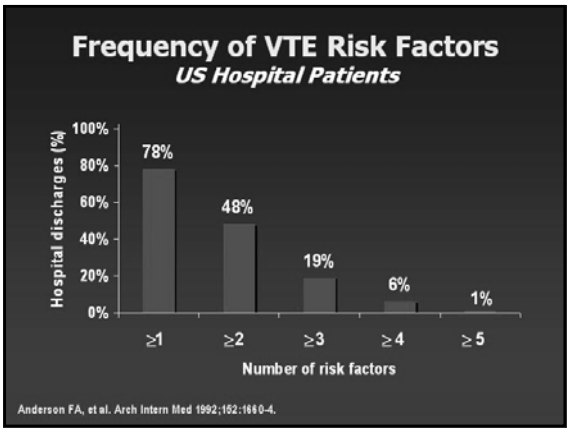
- Congestive heart failure
- Previous VTE
- Immobilization
- Obesity
- Chronic respiratory failure
- Increasing age
- Hematological disorders
- Central venous catheter
- Varicose veins
- Pregnancy
- Estrogen treatment
- Hospitalization

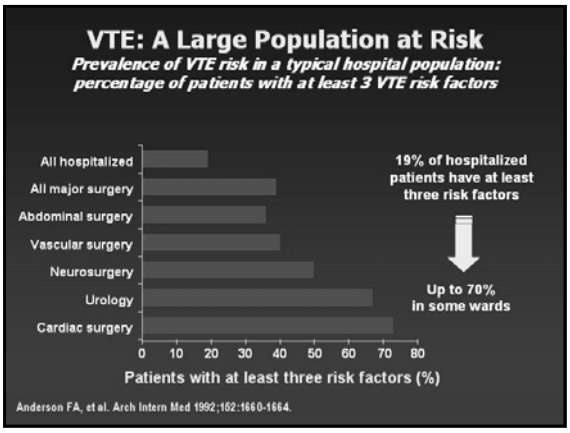
Incidence of DVT

Correlation with the number of risk factors



Wheeler, et al. Arch Surg 1981.





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
Problems - 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

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

- Higher bioavailability; makes dosing without monitoring a reality (except in renal disease, morbid obesity, cachexia)
- Longer half-life; therefore can be given subcutaneously1-2x/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 - 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

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
- 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 (Refludan®)
  - 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/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
  - $INR=(PTI)^{ISI}$; 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 out-patient, 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, ? 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