

ANTICOAGULANT THERAPY REVISITED 2006

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:
 - Antiplatelet therapy
 - Thrombolytic therapy
- Oral anticoagulants (warfarin) & new agents @ end

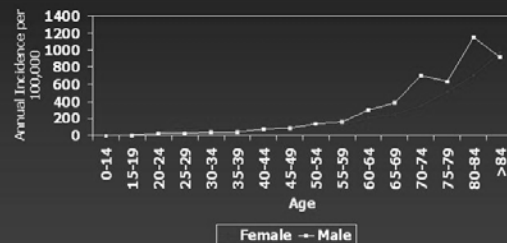
ANTICOAGULANT THERAPY Goals of Therapy

- 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**

All VTE Annual Incidence Per 100,000



Silverstein MD, et al. Arch Intern Med 1998;158:585.

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 VTED
Advanced Age
Obesity
Varicose Veins
Venous insufficiency
Thrombophilia

Extrinsic Factors

Pregnancy/Puerperium
Estrogen therapy
Paralysis
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 III
Protein C
Protein S
Plasminogen
Prothrombin gene mutation
Antiphospholipid antibody syndrome/lupus anticoagulant
Excess Factor VIII

Risk Factors Are
Cumulative

Modified from: Salzman, EW & Hirsh, J. in Colman, RW, et al - Eds. Hemostasis and Thrombosis - Basic Principles and Clinical Practice, 3rd ed. Philadelphia: Lippincott Company, 1994: 1275-1296.

Venous Thromboembolism – Indications for Prophylaxis

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

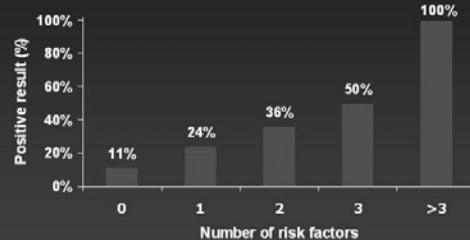
Primary Risk Factors for VTE

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

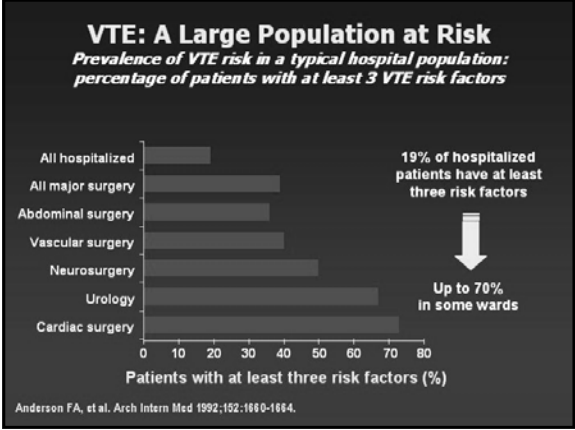
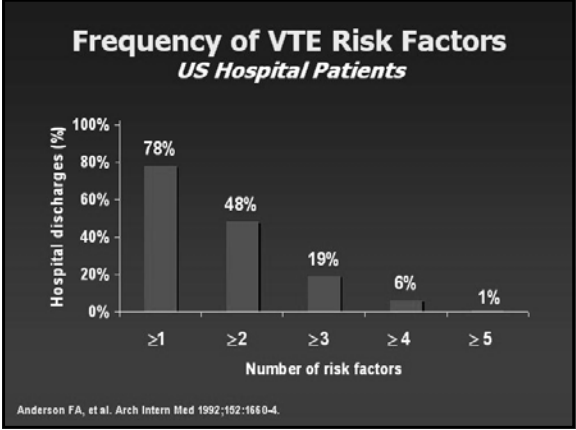
Secondary Risk Factors for VTE

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

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/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

- 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
 - Not approved on initial go-round @ FDA; approval rescinded in Europe
- Razaxaban – Direct factor Xa inhibitor; in final FDA stages now
- ? Other direct thrombin inhibitors for uses other than HIT
- ? Orally active heparin/LMWH derivatives