

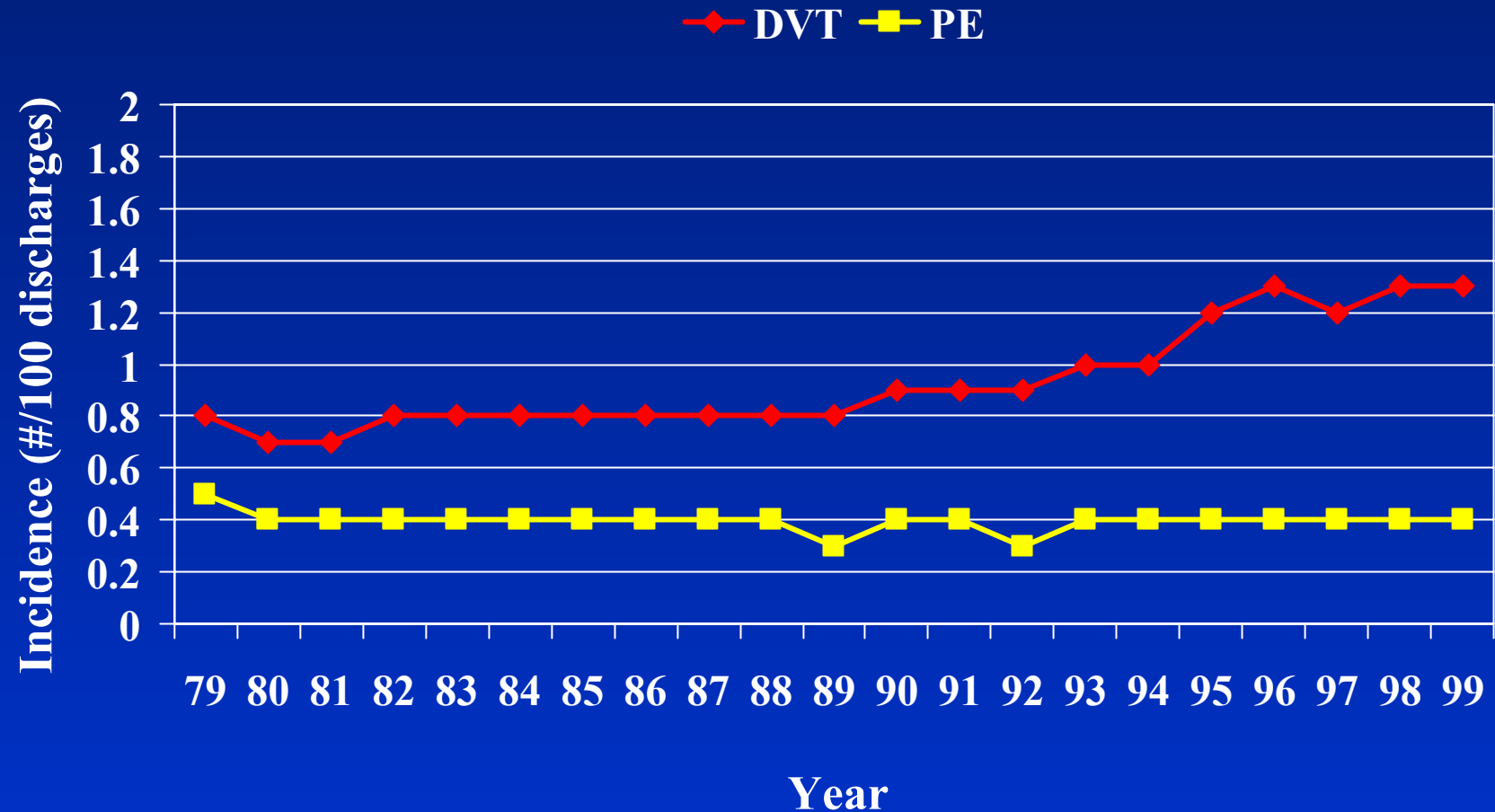
Topics in the management of venous thromboembolism and anticoagulation

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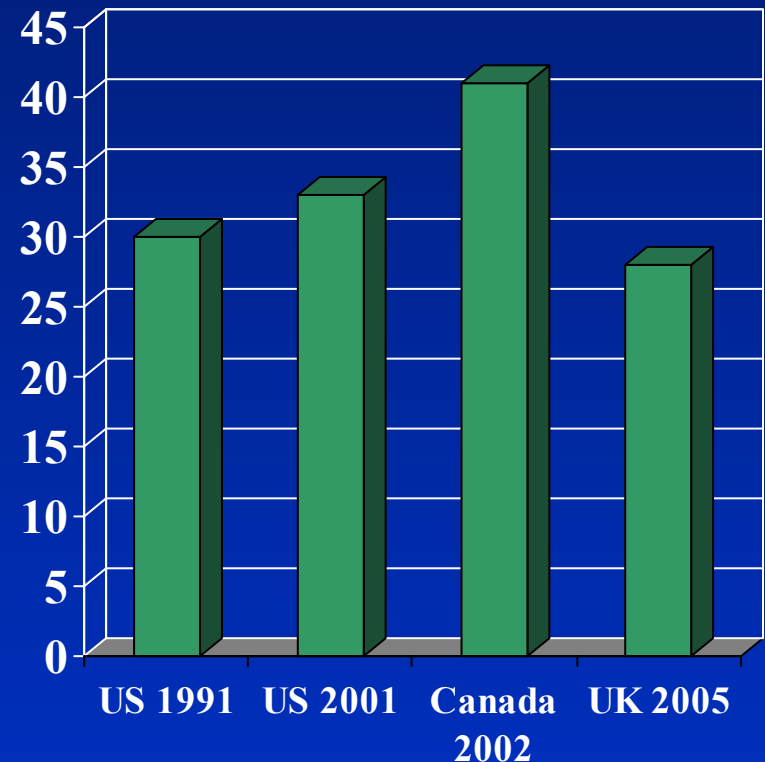
Division of Hematology

National trends in VTE 1979-99



DVT prophylaxis is underutilized

- DVT-FREE- prospective registry of 5,451 pts. At 183 US centers
- Sixty-two percent- medical patients
- Only 32% of medical patients with DVT received DVT prophylaxis
(Goldhaber S and Tapson V Am J Cardiol 2004)



DVT Prophylaxis: Medical inpatients

- Low risk
 - Freely ambulatory medical inpatient
 - Ambulation order
- Moderate risk
 - Bedridden medical inpatient w/o major risk factors
 - UFH 5000 IU sc q12h **OR**
 - TEDS or SCDs
- High risk
 - Bedridden medical inpatient w/ major risk factors (Age > 60, cancer, cardiopulmonary failure, recent CVA with paresis, previous VTE, thrombophilia)
 - UFH 5000 IU sc q8h **OR**
 - Enoxaparin 40 mg sc q24 **OR**
 - TEDS/SCDs

Contraindications to pharmacological prophylaxis

- Active bleeding
- High risk of bleeding
- Systemic anticoagulation
- Cerebral or dissecting aortic aneurysm
- Bacterial endocarditis
- Pericarditis
- Active peptic ulcer or GI ulcer disease
- Malignant hypertension
- Severe head trauma

Contraindications to anticoagulant prophylaxis

- Known bleeding disorder
- PT INR or aPTT ratio > 1.5 (excluding lupus anticoagulant)
- Threatening abortion
- Platelet count $< 50,000/\mu\text{L}$
- Recent TURP
- Eye or CNS surgery within 24 hours

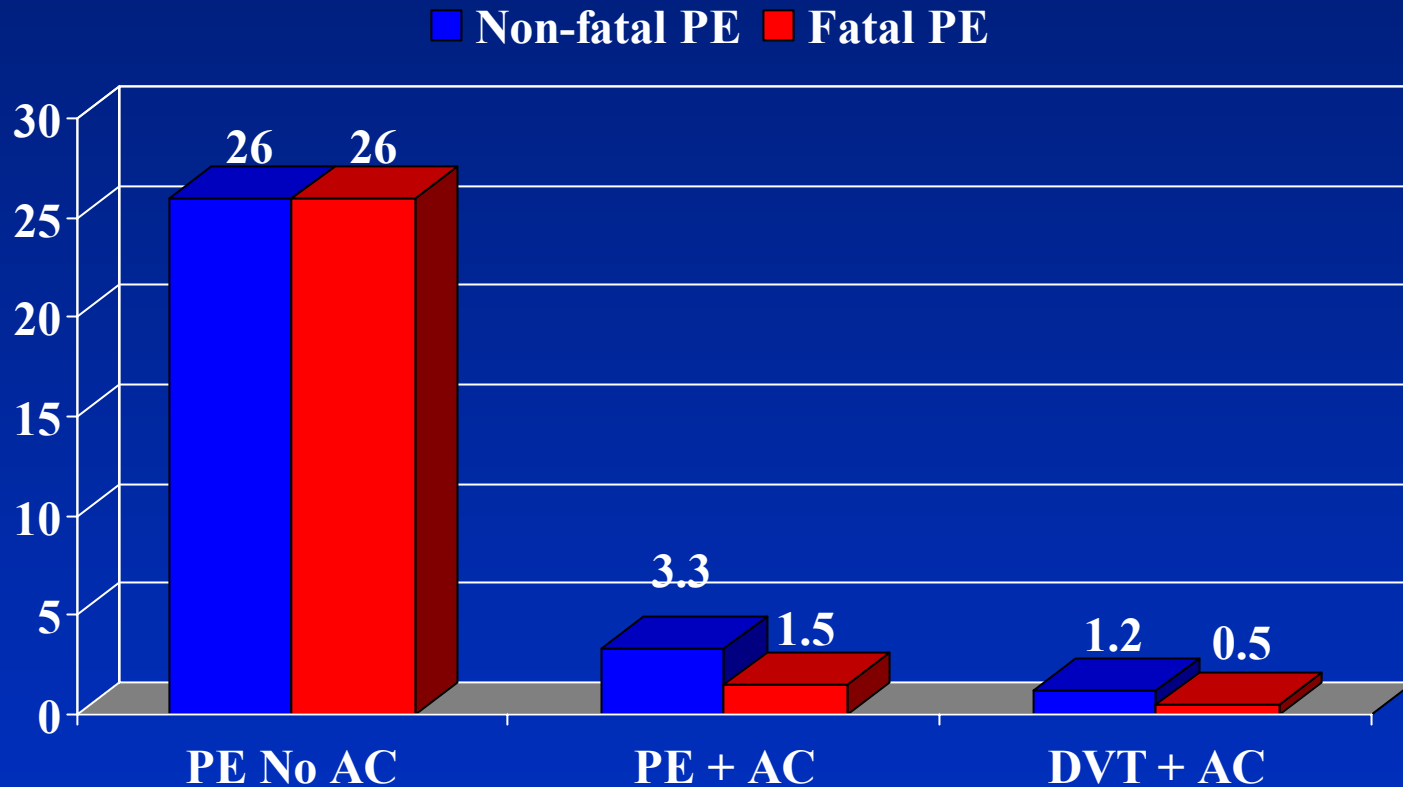
Contraindications to prophylaxis

- Heparin or Enoxaparin- History of HIT
- Enoxaparin- epidural catheter or its recent removal (< 2 hrs.), weight < 45 kg, CrCl < 30 ml/min
- Fondaparinux- epidural catheter, CrCl < 30ml/min, weight < 50kg
- SCDs- open wounds, extremity with known DVT
- TEDs- arterial insufficiency

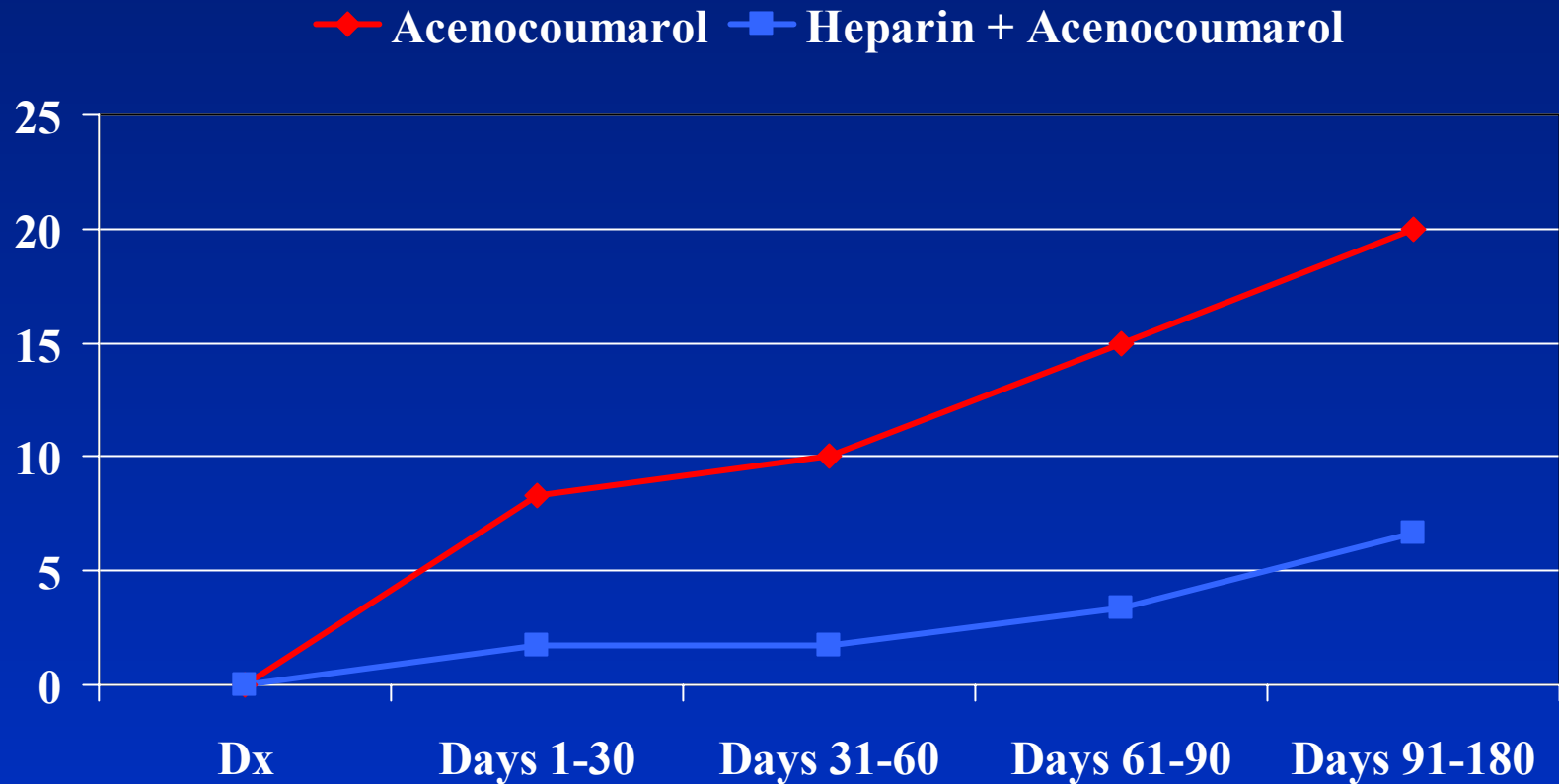
VTE Treatment

- Acute anticoagulation
 - Unfractionated heparin
 - Low molecular weight heparin
 - Fondaparinux
- Chronic anticoagulation
 - Vitamin K antagonist
 - Low molecular weight heparin
 - Unfractionated heparin

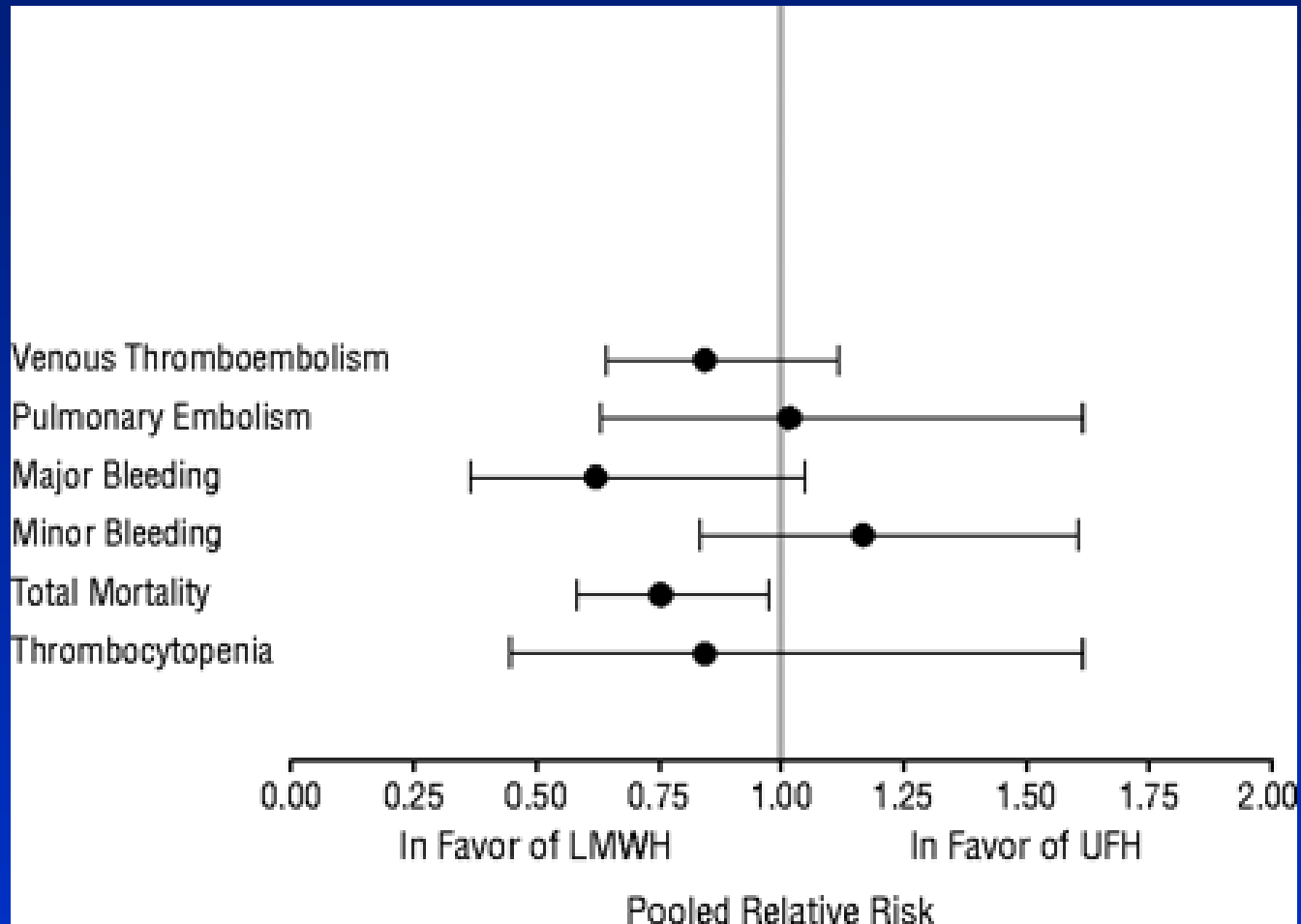
Anticoagulation effectively reduces the risk of PE



Warfarin alone is not enough



UFH and LMWH are equally efficacious



Unfractionated heparin

- Pre-therapy data
 - Objectively confirmed VTE or high clinical suspicion
 - Baseline Heme 8, PT, aPTT
- Bolus
 - 60-80 IU/kg (cap at 7500 IU)
- Infusion
 - 16-18 IU/kg/hr (cap at 1600 IU/hr)
- Monitoring
 - First aPTT in 4-6 hours

Unfractionated heparin dosing

<u>aPTT ratio</u>	<u>Bolus</u>	<u>Infusion</u>	<u>Repeat aPTT</u>
< 1.2	1 X original	+ 4 IU/kg/hr	4-6 hrs.
1.2-1.4	0.5 X original	+ 2 IU/kg/hr	4-6 hrs.
1.5-2.5	0	No change	6 hrs.
2.6-3.2	0	-2IU/kg/hr	6 hrs.
3.3-4.0	0	Hold 60 min then -4IU/kg/hr	6 hrs.
4.1-5.0	0	Hold 120 min then - 6IU/kg/hr	6 hrs.
>5.0	0	Hold until aPTT ratio <4.0 then - 7IU/kg/hr	6 hrs.

Enoxaparin Dosing

- General population
 - 1 mg/kg sc q12h or 1.5 mg/kg sc q24h
- Renal insufficiency (< 30ml/hr)
 - 1mg/kg sc q24h
 - Caution with Cr Cl < 20 or hemodialysis
- Cancer
 - 1 mg/kg sc q12h
- Obesity
 - 1 mg/kg sc q12h

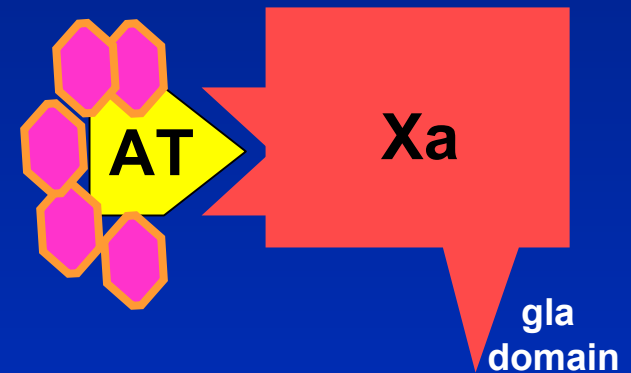
Enoxaparin- special precautions

- Avoid in patients with changing renal function
- Avoid in patients likely to have invasive procedures
- Avoid in patients at high risk of bleeding

Fondaparinux (Arixtra[®])

- Synthetic pentasaccharide
- Half-life- 17-21 hours
- Clearance- renal
- Daily Dose
 - < 50 kg = 5.0 mg
 - 50-100 kg = 7.5 mg
 - >100 kg = 10.0
- Avoid with Cr Cl < 30 ml/min, bleeding risk or surgery
- No HIT or osteoporosis

FONDAPARINUX

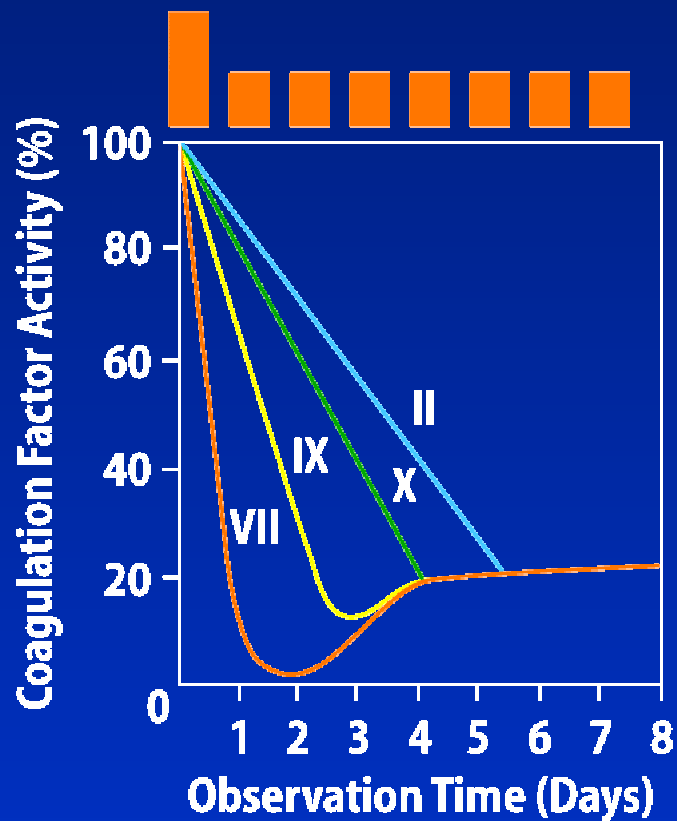


Warfarin Dosing

- No loading dose
- Initiate once therapeutic on acute AC
- Goal is to start with expected maintenance dose
 - Start 5-10 mg or previous home dose
 - Start 2.5mg
 - Liver dysfunction
 - CHF
 - Interacting drugs
 - Malnutrition
 - Elderly
- Daily PT/INR in hospital
- Every 2-3 days as outpatients
 - Expect INR to \uparrow 0.2-0.3 per day if good dose
 - INR \uparrow $>$ 0.3- 0.4 in one day requires dose reduction
- Overlap at least 5 days with acute AC and continue until INR $>$ 2

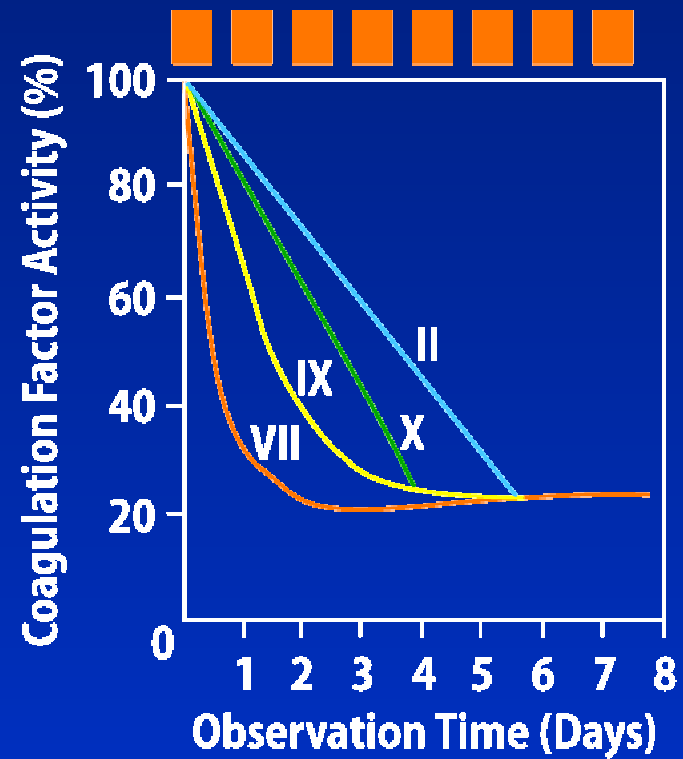
Loading Dose then Maintenance Dose

Daily Dose



Maintenance Dose Only

Daily Dose



Warfarin-Drug interactions

Increase INR

Trimetho/sulfametha

Metronidazole

Amiodarone

Azole anti-fungals

Broad-spectrum antibiotics

Saquinavir

Thyroid hormones

Decrease INR

Rifampin, rifabutin

Barbiturates

Carbamazepine

Phenytoin

Sucralfate

Ritonavir

Vitamin K

Oncology Warfarin-Drug interactions

- Increase INR

- Capecitabine
- Erlotinib
- Fluorouracil
- Flutamide
- Gefitinib
- Gemcitabine
- Ifosfamide
- Imatinib
- Trastuzumib

- Decrease INR

- Azathioprine
- Mitotane

Management of warfarin by INR

- INR > 0.3 below range- increase weekly dose by 10-20% or no change
- INR 0.1-0.3 below range- increase 5-10% or no change
- INR in range- no change
- INR 0.1-0.5 above range- decrease 5-10% or no change
- INR > 0.6 above range (up to 4.5)- Hold dose and decrease 10-20% or no change

Management of supratherapeutic INR

- INR < 5 – Hold 1-2 doses and decrease dose 10-20%
- INR 5-9, no bleeding – Hold 1-2 doses, Vit. K 1-2.5 mg, decrease dose 20%, recheck INR in 24-48 hrs.
- INR > 9 , no bleeding – Hold dose, Vit. K 2.5-5 mg, decrease dose, follow INR
- Warfarin associated bleeding- refer to ED

Warfarin associated bleeding

- Vitamin K₁ – 5-10 mg po/sc
- FFP 15ml/kg IV
- Prothrombin complex concentrates or rhFVIIa
 - FEIBA 50u/kg X 1
 - NovoSeven 30µg/kg X 1
- Follow PT closely

Inclusion criteria for outpatient LMWH

- Documented DVT/PE
- Able to administer medication
- Follow up for outpatient lab testing
- Compliant
- Accessible by telephone

Exclusion criteria for outpatient LMWH

- Absolute Contraindications
 - Active bleeding
 - Cardiopulmonary instability
 - History of HIT/heparin allergy
 - Symptomatic pulmonary embolism
 - Symptomatic venous obstruction
 - Recent major surgery (within 7 days)

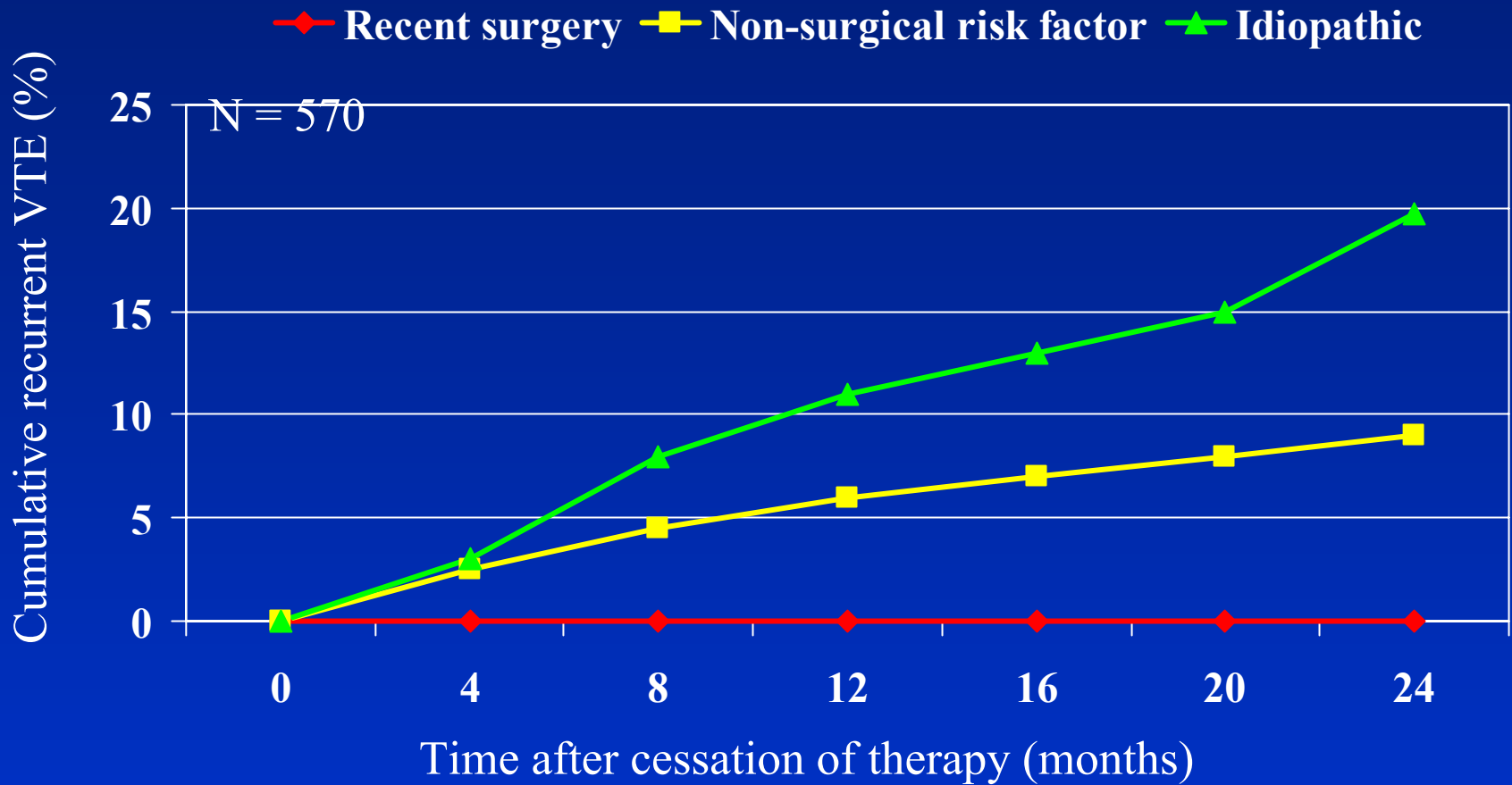
Exclusion criteria for outpatient LMWH

- Relative contraindications
 - Thrombocytopenia (platelets < 100,000/ μ L)
 - Significant hepatic dysfunction
 - Stable pulmonary embolism
 - GI, GU bleeding within the last 6 months
 - Weight < 45 kg or >155 kg

Warfarin-Therapeutic Range

- Indications (INR goal 2.0-3.0)
 - Prophylaxis of venous thrombosis (high-risk surgery)
 - Treatment of DVT, PE
 - Prevention of systemic embolism
(Tissue heart valves, AMI, valvular disease, afib)
 - Bileaflet mechanical valve in aortic position (sinus rhythm, normal LA)
 - Antiphospholipid Antibody syndrome
- Indications (INR goal 2.5-3.5)
 - Mitral bi-leaflet prosthetic valves (high risk)
 - Mechanical valve + Afib, ↑ LA, low EF or systemic embolism – add ASA 81 qd

VTE treatment: Duration of therapy



VTE treatment: Duration of therapy

- DVT- transient risk factor- 3 months
- DVT- idiopathic- at least 6 months
- PE- transient risk factor- at least 3 months
- PE- idiopathic- at least 6-12 months
- Recurrent VTE- indefinite
- Cancer- until malignancy resolved
- Antiphospholipid syndrome – indefinite therapy
- Significant inherited thrombophilia – 6 months - indefinite

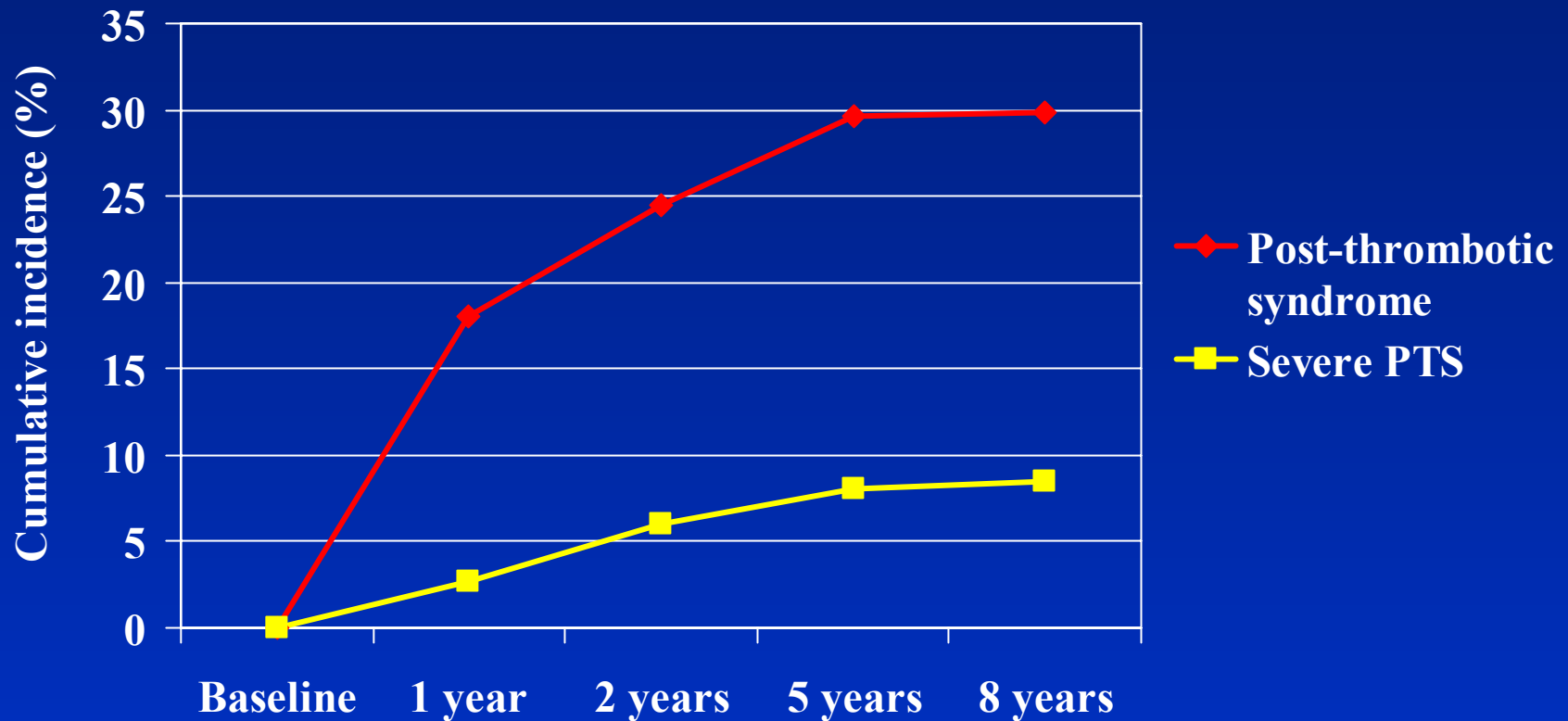
Post-phlebotic syndrome

- Symptoms
 - Heaviness
 - Pain
 - Cramps
 - Pruritis
 - Paresthesias
- Signs
 - Pretibial edema
 - Induration
 - Hyperpigmentation
 - New venous ectasia
 - Redness
 - Pain during calf compression
 - Ulceration



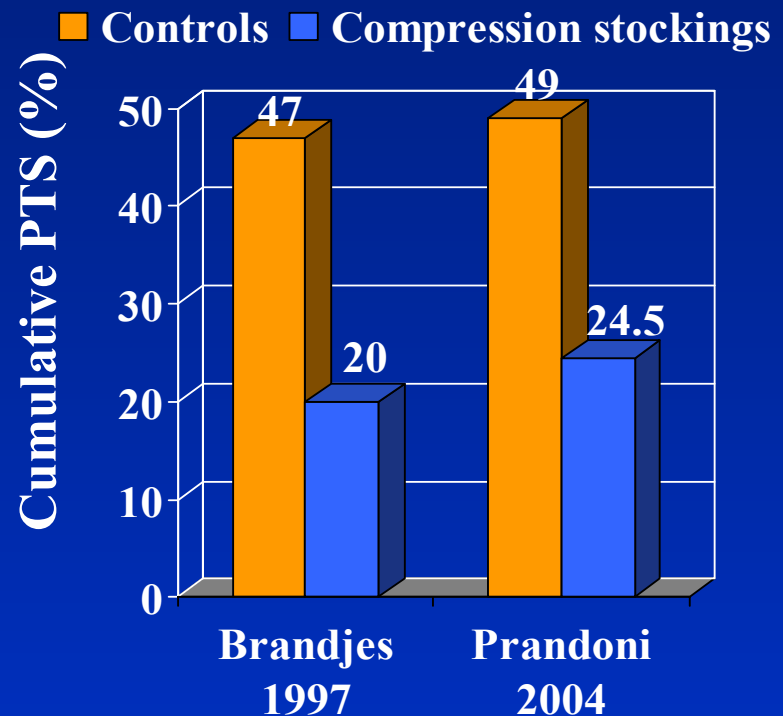
Bernardi and Prandoni. *Curr Opin Pulm Med* 2000;6:335-342.

Incidence of post-thrombotic syndrome



VTE treatment: Compression stockings reduce the incidence of PTS

- PTS occurs in 29% of DVT patients by 8 years
- Compression stockings (30-40 mm Hg) reduce the incidence of PTS
- Compression stockings should be prescribed for 2 years in all patients with DVT

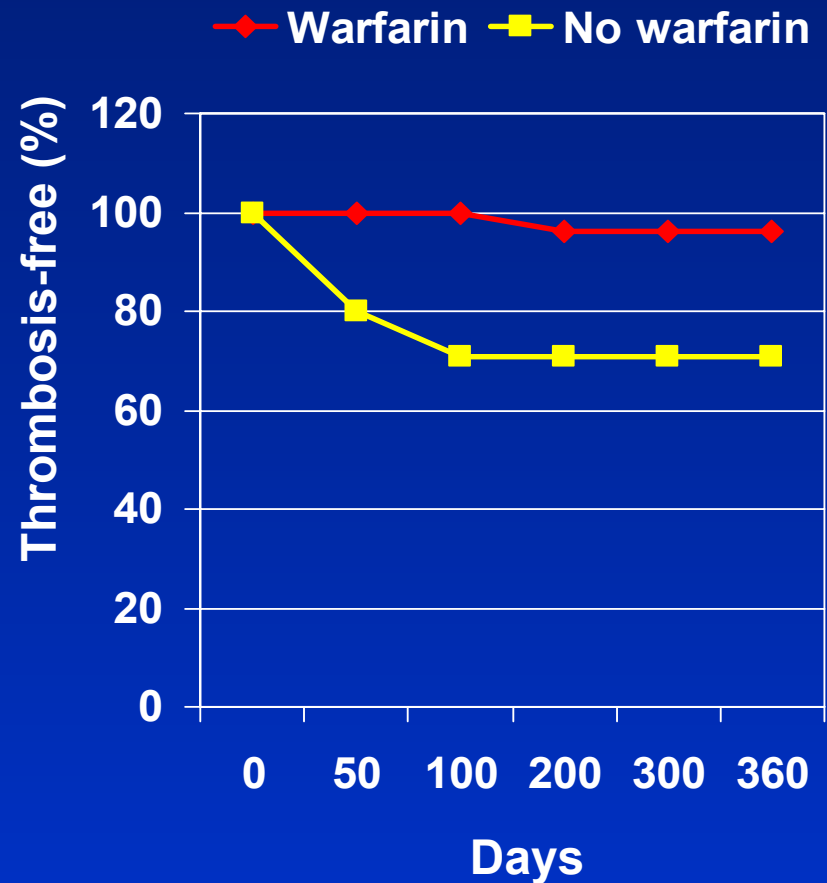


Recurrent VTE on anticoagulation

- Subtherapeutic anticoagulation
- Heparin-induced thrombocytopenia
- Antiphospholipid antibody syndrome
- Trousseau syndrome
- Anatomic abnormalities
 - May-Thurner syndrome
 - Paget-von Schroetter syndrome

Treatment of Calf DVT

- Short course AC associated with recurrent VTE (Lagerstedt et al. Lancet 1985)
- Treat as a DVT
- Target INR range (2-3)
- Duration of therapy- 6-12 weeks (Pinede et al. Circulation 2000)



Treatment of superficial venous thrombophlebitis

- Location
 - Greater saphenous vein- 60-80%
 - Lesser saphenous vein- 10-20%
 - Other- 10-20%
- Cause
 - Varicose veins
 - Behcet disease
 - Buerger disease
 - Thrombophilia
 - Malignancy
- Document superior aspect of clot with proximal vein involvement
- Treatment
 - NSAIDs
 - Elastic stockings
 - Surgical thrombectomy?
 - Anticoagulation?

Results of studies of anticoagulation “bridging” with LMWH

- **Turpie and Johnson (2001)**
 - 294 pts.
 - Dalteparin 100IU/kg sc q12h
 - Results-no TE events; 2 major bleeds, No deaths
- **Heit et al. (2002)**
 - 532 pts.;
 - Enoxaparin 20%; Dalteparin 80%
 - 1 fatal TE (0.2%)
- **Douketis et al. (2004)**
 - 650 pts.
 - Dalteparin 100 IU sc q12h
 - Results- 2 TE (0.4%); 4 Major bleeds (0.7%) ; 2 deaths (0.4%)
- **Kovacs et al. (2004)**
 - 224 pts.
 - Dalteparin 200 IU/kg/day
 - Results- 8 TE (3.6%); 15 major bleeds (6.7%)

LMWH AC Bridging

- Check INR 1-2 weeks before the procedure
- Discontinue warfarin 5-7 days prior to OR
- Start Enoxaparin 1mg/kg sc q12h 36 hours after DC warfarin (8AM/PM schedule)
- Last Enoxaparin dose 24 hours before procedure
- Check INR 24-36 hours before OR
 - If INR 1.5 or more, give vitamin K 1-2.5 mg po
 - Recheck INR before OR

Assessing Peri-procedural Thrombosis Risk

- Low Thrombosis Risk
 - First VTE > 3 months
 - Non-valvular A Fib w/o thrombosis risk factors
- High Thrombosis Risk
 - First VTE < 3 months
 - Recurrent VTE
 - VTE and Cancer or Antiphospholipid syndrome
 - A Fib with risk factors
 - Mechanical heart valve
 - Dual > Mitral > Aortic

A Fib risk factors: HTN, CHF, LV dysfunction (EF < 40%), mitral stenosis, age > 65 years, diabetes, mechanical heart valve, recent CVA or TIA, large left atrium, recent MI (6 months).

Assessing Peri-procedural Bleeding Risk

- Low risk procedures
 - Endoscopy w/o biopsy
 - Urologic procedure w/o biopsy
 - Skin biopsy
 - Simple dental procedures (single extraction, cleaning, etc.)
- High risk procedures
 - Major surgery
 - Endoscopy with biopsy
 - Complex urologic procedure (TURP, prostate bx, lithotripsy)
 - Complex dental procedures
 - Interventional radiology procedures
 - Kidney biopsy
 - Bone marrow biopsy

Perioperative management- low thrombotic risk

- Low bleeding risk
 - No change in dose, or hold warfarin 2-3 days prior to allow INR to go < 2.0
 - Restart warfarin post-op
- High bleeding risk
 - Stop warfarin 5 days pre-operatively
 - Check INR 1 day prior to surgery
 - If INR > 1.5 , give 1-2.5 mg of vitamin K1 and recheck INR immediately pre-op
 - Restart warfarin post-op

Perioperative management- high thrombotic risk

- Low bleeding risk
 - Continue warfarin keep INR in 2-2.5 range
- High bleeding risk
 - Hold warfarin 5-7 days pre-op
 - Begin LMWH in AM 3-4 days pre-op (Lovenox 1mg/kg sc q12h)
 - Last dose of LMWH 24 hours before procedure
 - If INR >1.5 24 hrs.pre-op give vitamin K1
 - Start UFH w/o a bolus or LMWH when deemed safe
 - Start warfarin at usual dose if no bleeding with heparin

Restarting AC post-op

- **High risk procedures**
 - Neurosurgery, prostatectomy/bladder surgery, cardiac surgery, vascular surgery, renal biopsy, polypectomy, major cancer surgery
 - Low dose AC- 24-48 hrs.; Full-dose AC- 72 hrs.
- **Moderate risk procedures**
 - Major general surgery, orthopedic surgery, pacemaker insertion
 - Low dose AC- 12-24 hrs.; Full dose AC- 24-48 hrs.
- **Low risk procedures**
 - Cataract extraction, cutaneous surgery, lap cholecystectomy, hernia repair, cardiac cath
 - Low dose AC- evening of procedure; Full dose AC- 24 hrs.

Questions ?

