MANAGEMENT OF OVER-ANTICOAGULATION

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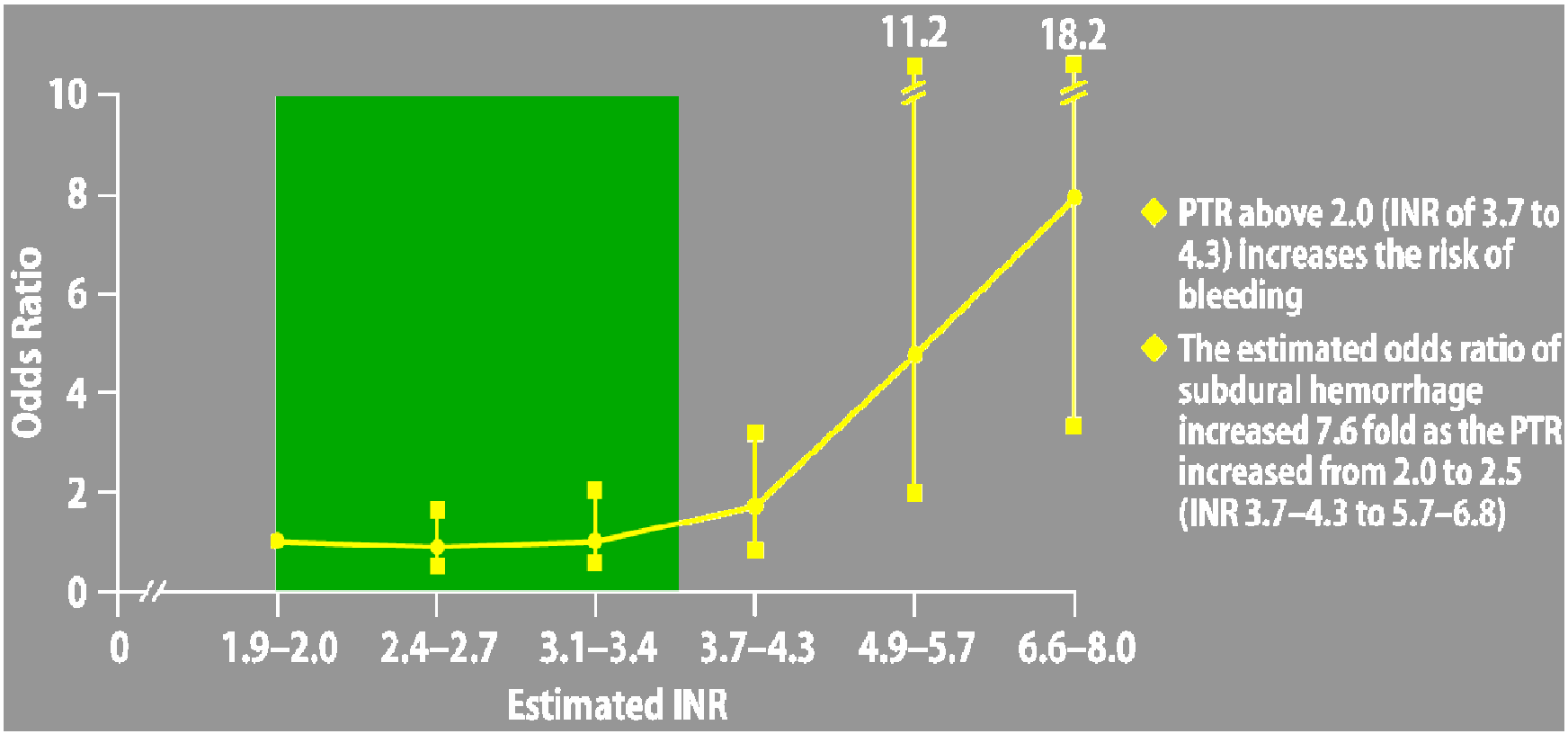
Risk of Intracranial Hemorrhage in Outpatients



(From "Management of Oral Anticoagulant Therapy" by J. Ansell et al, AHA)

Hylek EM, Singer DE, Ann Int Med 1994;120:897-902

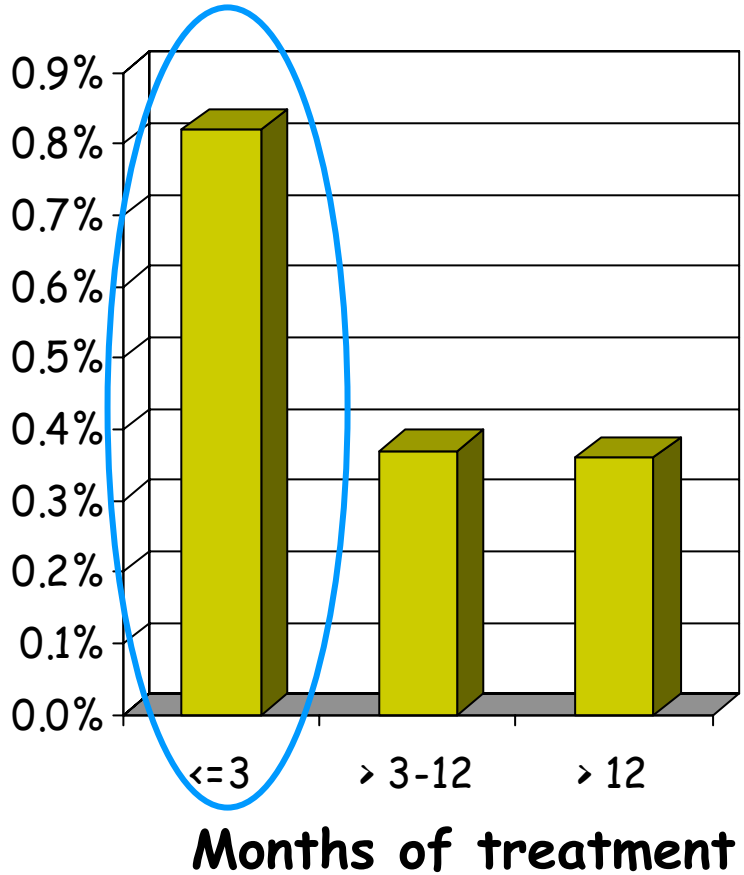
Major Hemorrhage in Outpatients on Warfarin

Site of Major Hemorrhage

- GI (63%)
- Urinary tract (28%)
- Musculoskeletal (15%)
- Nasopharynx (13%)
- Lung (8%)

Risk Factors

- Age (>75 yo)
- h/o prev. bleeding (esp, GIB)
- Comorbid conditions
  - Hypertension
  - CVA
  - Serious heart disease
  - Renal insufficiency
- Alcohol abuse



J Gen Intern Med 1998;13:311

Potential Contributing Factors to Increased Bleeding Risks

Supratherapeutic INR

- Drug-drug interaction
- Concurrent disease states
- Laboratory reporting/technique
- **Genetic polymorphism (CYP2C9 and VKORC1)**
  - ***Science 1999;286(5439):487-91.***
  - ***NEJM 2005;352:2285-93***
  - ***Blood 2005;106:135-140***
- Compliance
- Prescribing error

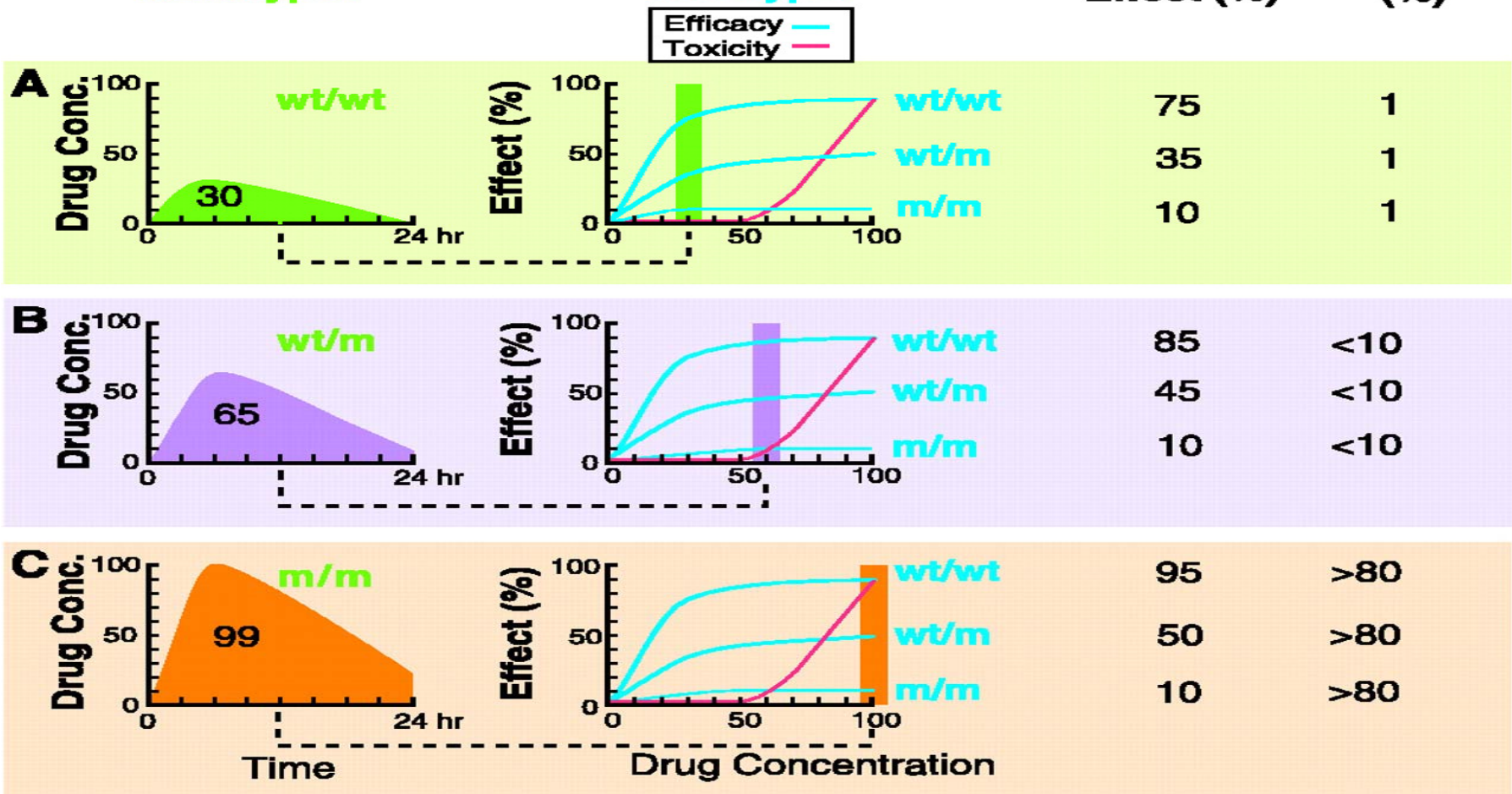
Oral anticoagulation Thresholds

- Significant individual variability in tissue factor coagulation response ***(Circulation 2001;104:2311-2317)***

Pharmacogenomics

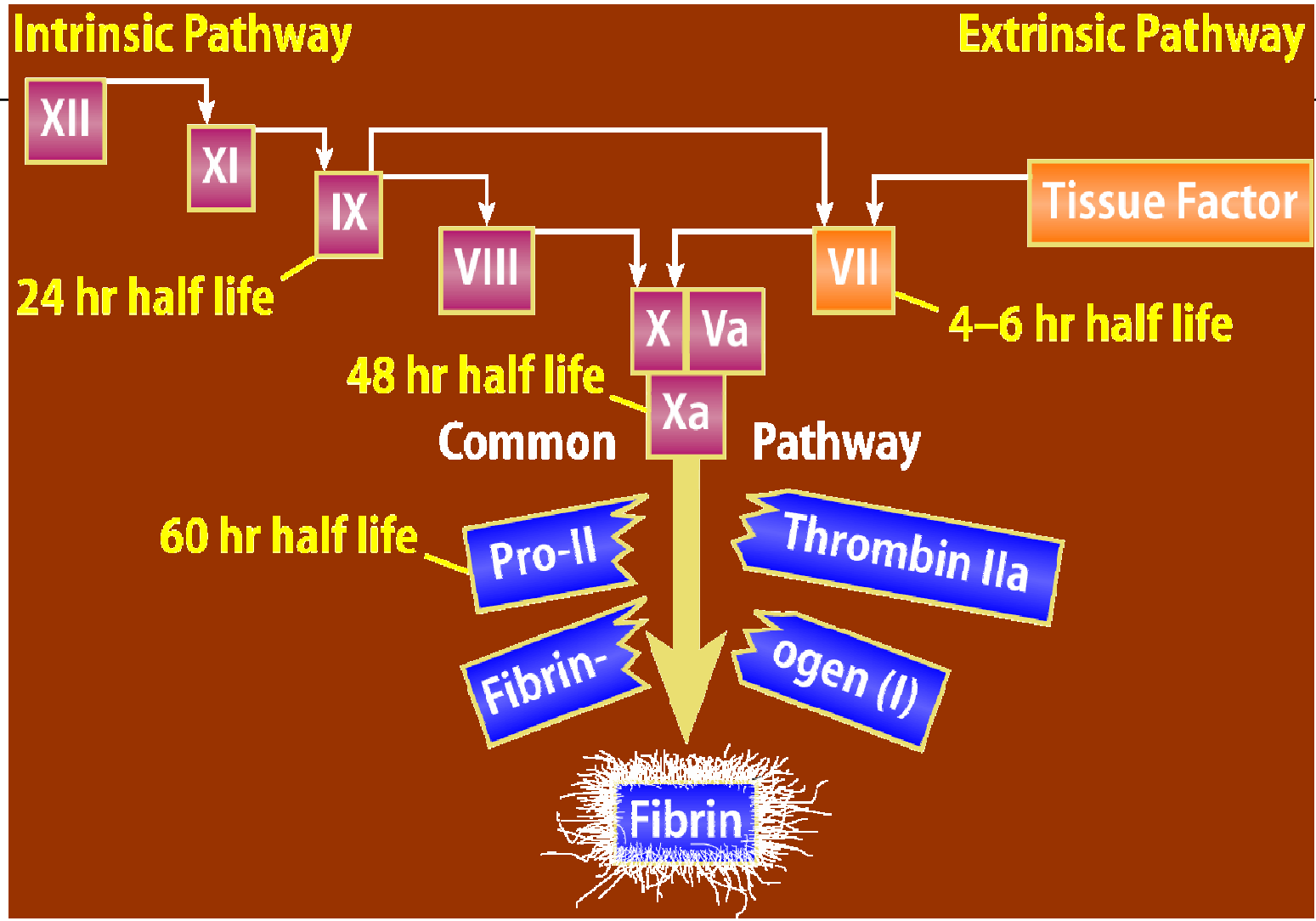
Genetic Polymorphism of Drug Exposure + **Genetic Polymorphism of Drug Sensitivity** = **Genetically Regulated Heterogeneity in Drug Effects**

Drug Metabolism Genotypes | Drug Receptor Genotypes | Therapeutic Effect (%) | Toxicity (%)



Science 1999;286(5439):487-91.

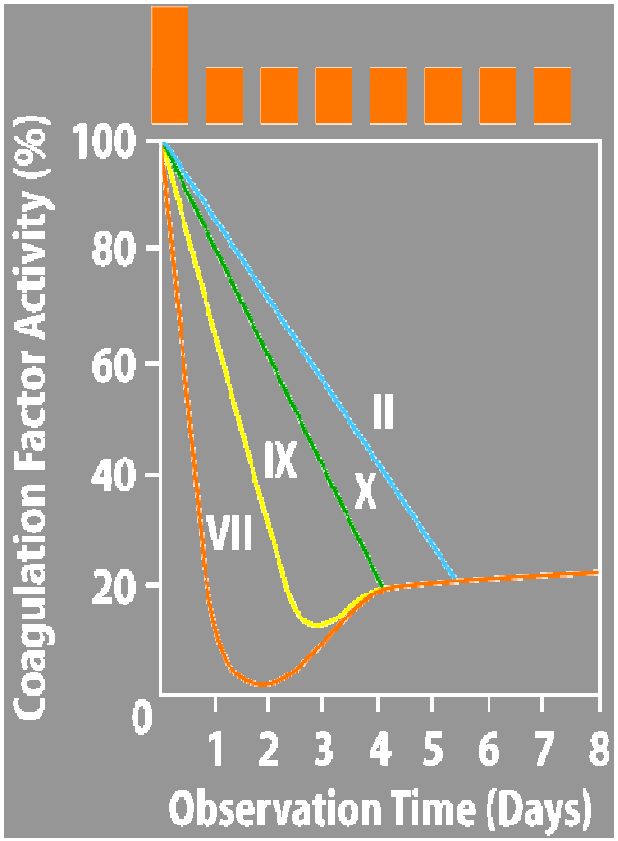
Clotting Cascade



(From "Management of Oral Anticoagulant Therapy" by J. Ansell et al, AHA)

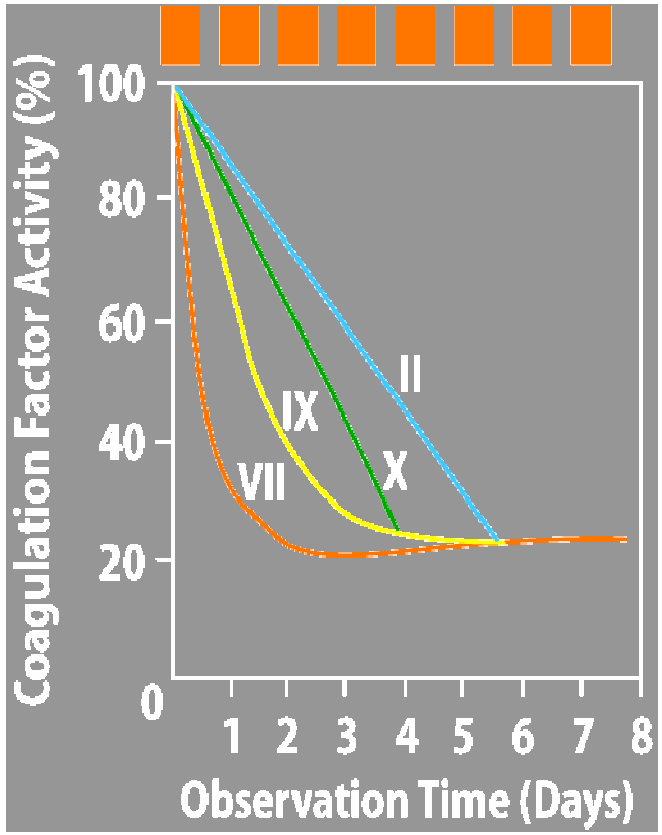
Loading Dose then Maintenance Dose

Daily Dose



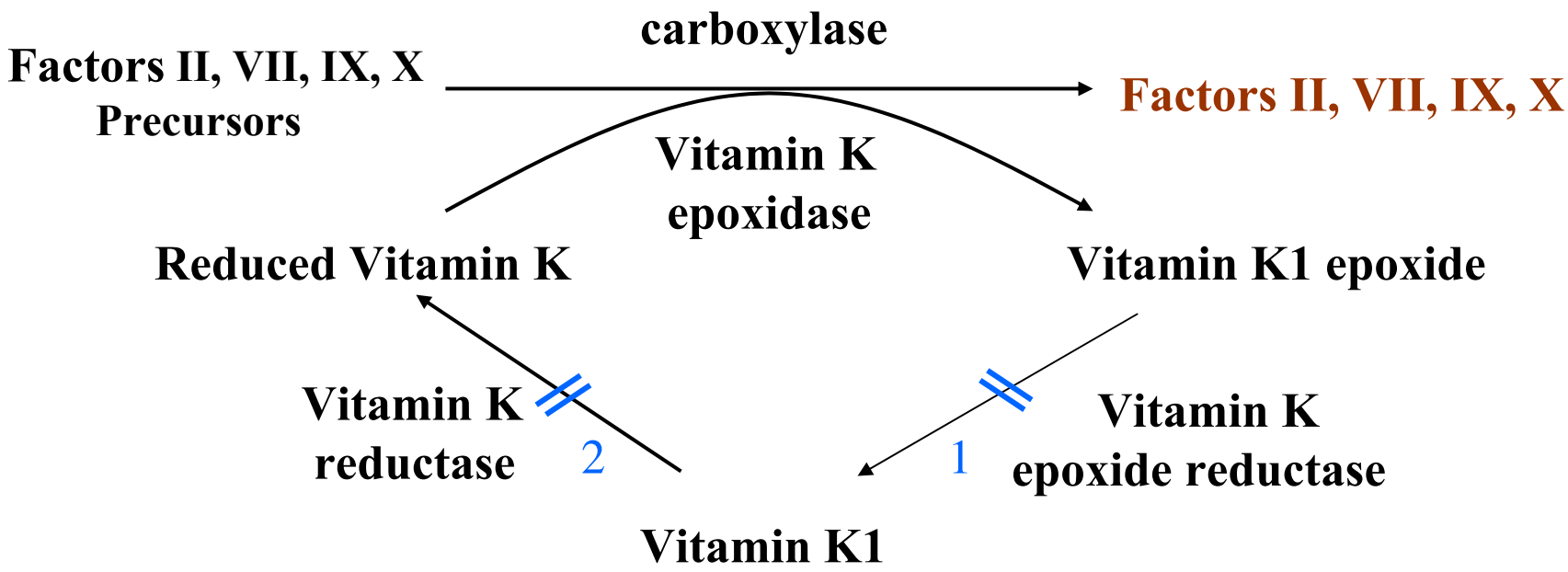
Maintenance Dose Only

Daily Dose



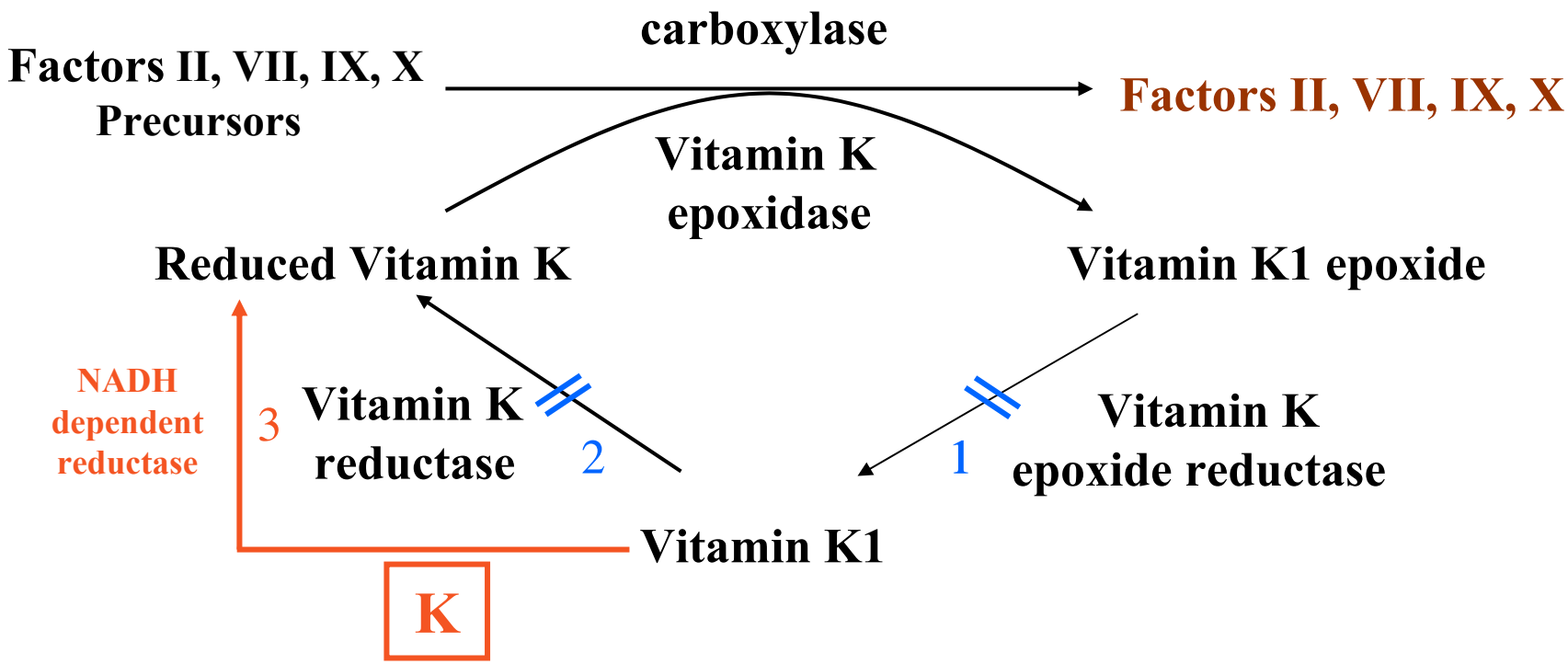
(From "Management of Oral Anticoagulant Therapy" by J. Ansell et al, AHA)

Warfarin Effects on Vitamin K-Dependent Clotting Factors



1. KO-reductase	- warfarin sensitive
2. K-reductase	- warfarin sensitive

Warfarin Effects on Vitamin K-Dependent Clotting Factors



1. KO-reductase	- warfarin sensitive
2. K-reductase	- warfarin sensitive
3. NADH dependent reductase	- warfarin resistant

What We Know Now and Agree

- High dose Vitamin-K
  - **risk of thrombosis & warfarin resistance**
- Rare but serious anaphylactic reaction w/ high & low IV dose
  - **can be avoided by PO route**
- IM or SC administration
  - **erratic and delayed absorption**
- Oral administration
  - **not widely used** **(Arch Intern Med 2002;162:1893-1896)**

Problems with Clinical Studies

- Methodology
  - Retrospective review
  - Small sample size
  - Concurrent diseases states and/or medications
  - Laboratory testing

Low Dose SC Vitamin-K Study

Vitamin K SC:

- 8 ≤ INR <14: 1 mg SC
- 14 ≤ INR < 20: 2 mg SC

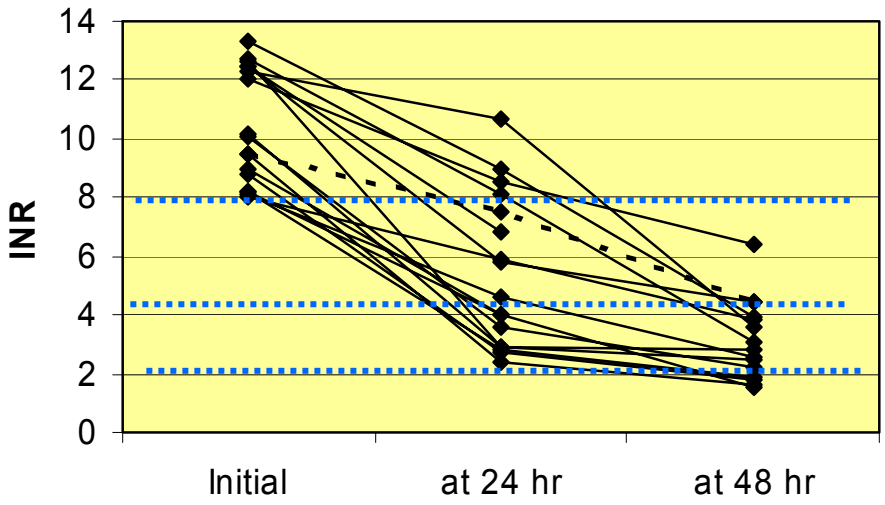
At 24 h:

- 8 ≤ INR <14 : additional 1 mg SC
- 4.5 < INR <8: hold warfarin additional 24 h
- INR ≤ 4.5: resume adjusted dose of warfarin
- follow up at 48 h

Byrd et al, AJHP 1999;56:2312-5

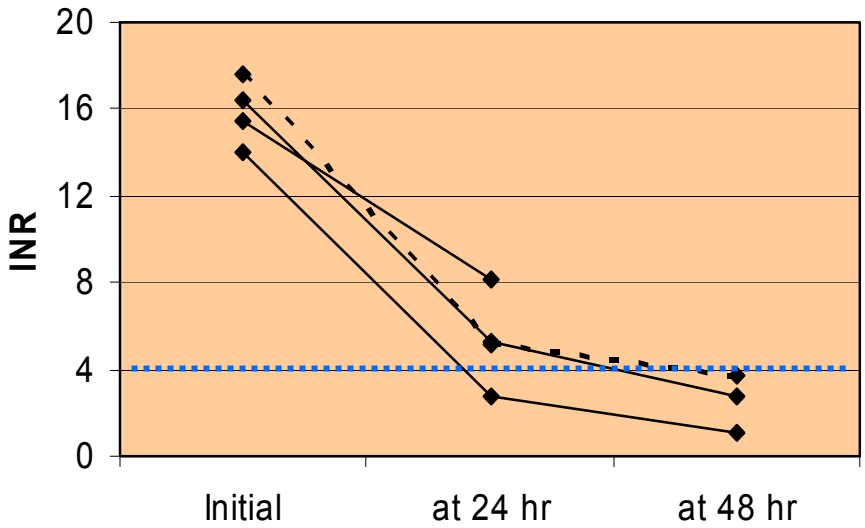
Low Dose SC Vitamin-K

SC 1mg



8 ≤ INR <14

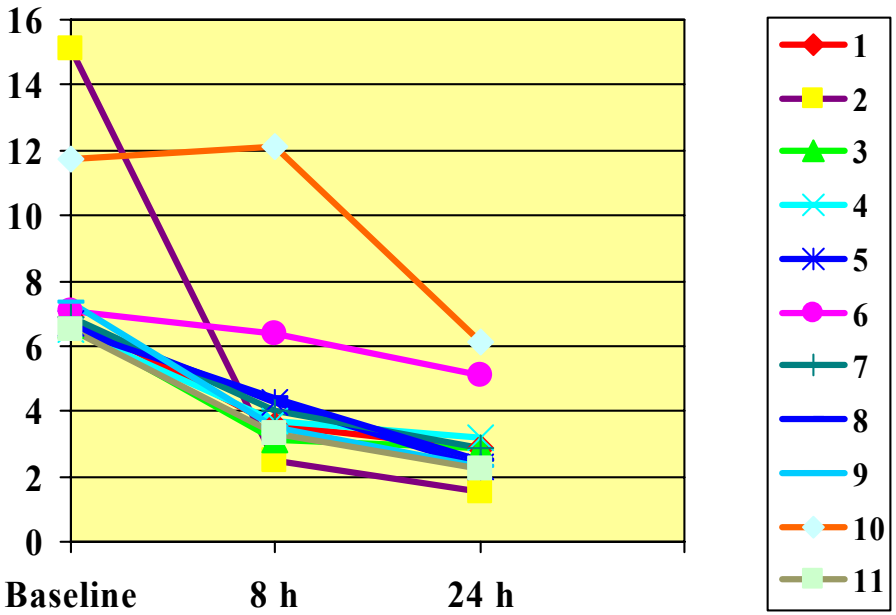
SC 2mg



14 ≤ INR < 20

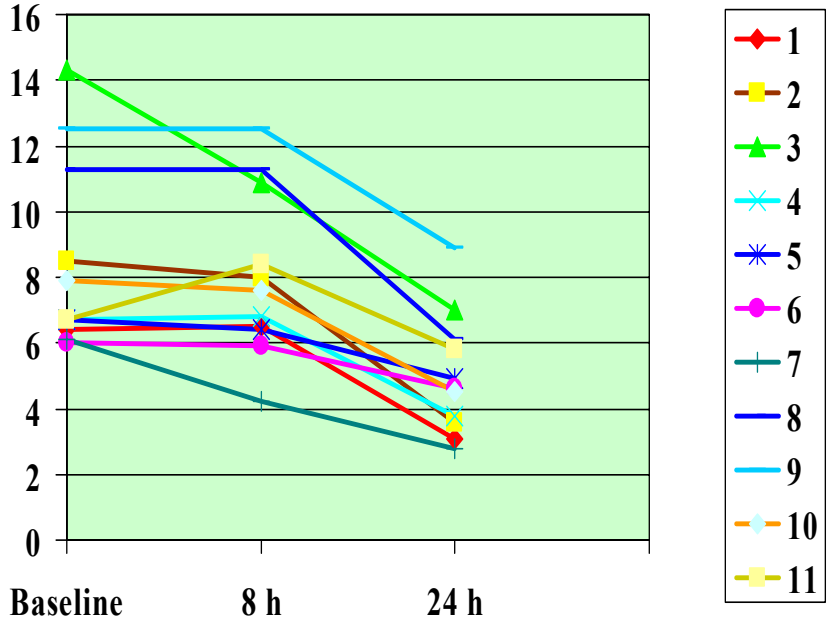
Byrd et al, AJHP 1999;56:2312-5

IV vs SC Vitamin K



INR

Vitamin K 1 mg IV



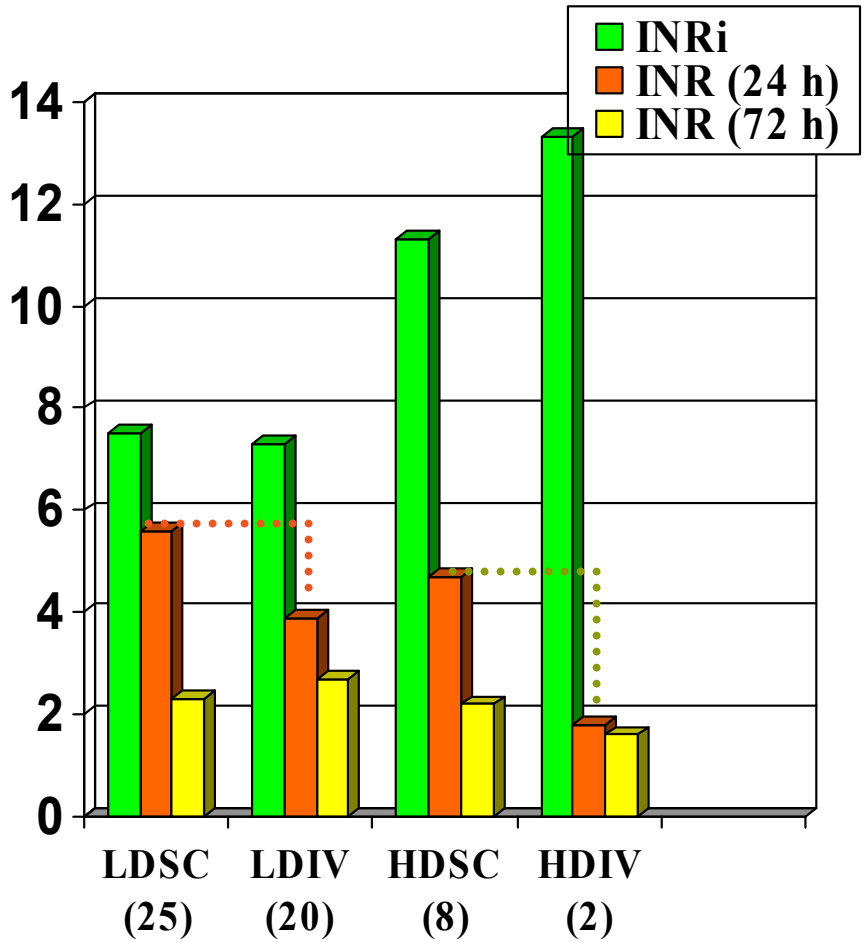
INR

Vitamin K 1 mg SC

Raj G. et al. Arch Intern Med. 1999;159:2721-2724.

IV vs SC Vitamin-K Study

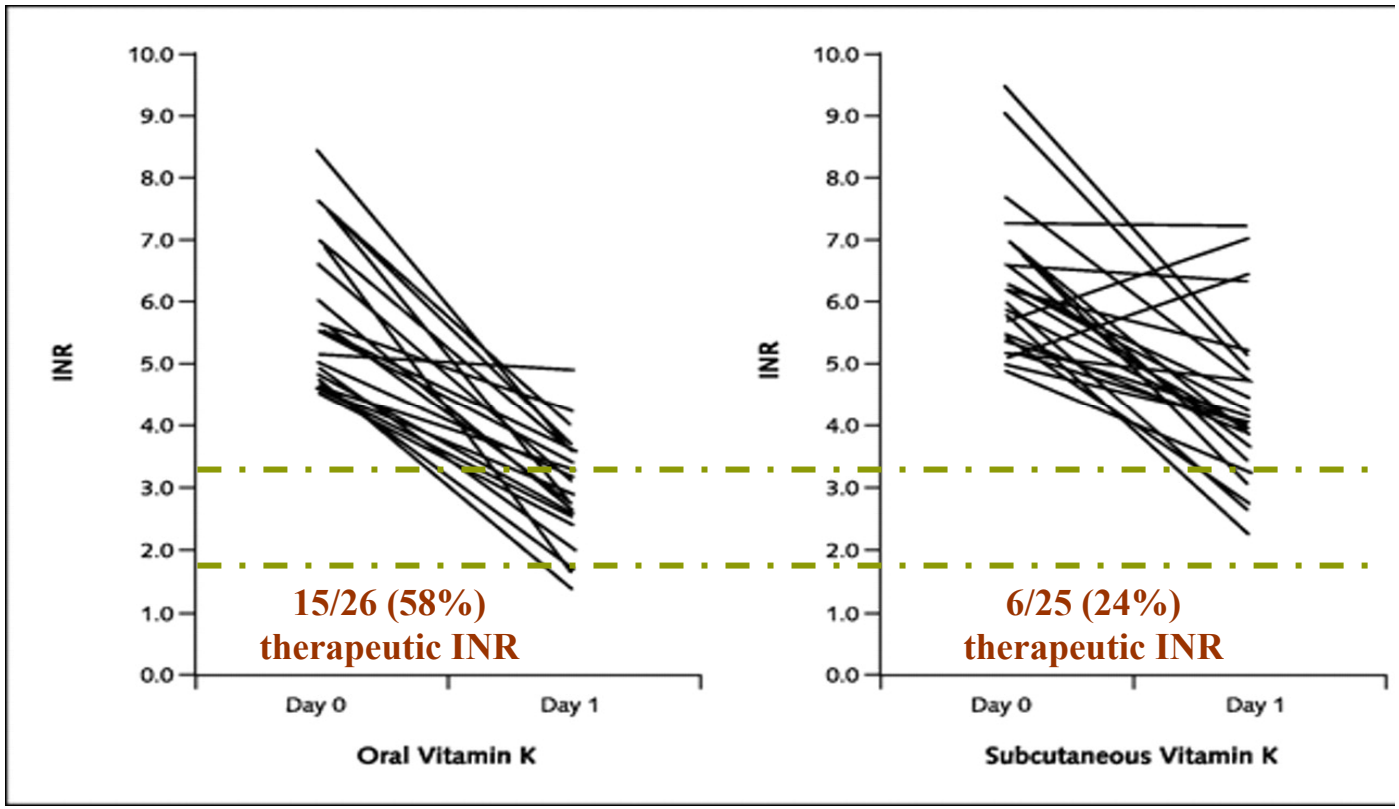
- Double blind, randomized
- INR 6-20 & no bleeding (n>800)
  - INR 6-10: IV or SC 0.5 mg
  - INR >10: IV or SC 3 mg
- Blinding: IV or SC placebo
- INR 24 h, 72 h, 7 d
- Hold dose ≥ 1 dose and dose adjustment



Am J Cardiol 1999;83:286-288

PO vs SC Vitamin K

Multi-center, open label trial in patients with INR 4.5-10 without current or high risk of bleeding



Vitamin K 1 mg PO **Vitamin K 1 mg SC**

Crowther, M. A. et. al. Ann Intern Med 2002;137:251-254

Annals of Internal Medicine

Oral Vitamin-K Administration

- Cohort study: 62 patients of INR 5.79 (4.5-9.5)
- Hold warfarin and 1 mg PO
- Daily INR until INR 2-3 up t 6 days
- Day 1 (16 hrs post) INR 2.86 in 95% patients
  - 2 patients received the further doses 0.5, 2 mg
- 59% resumed warfarin Day 1 and no warfarin resistance observed

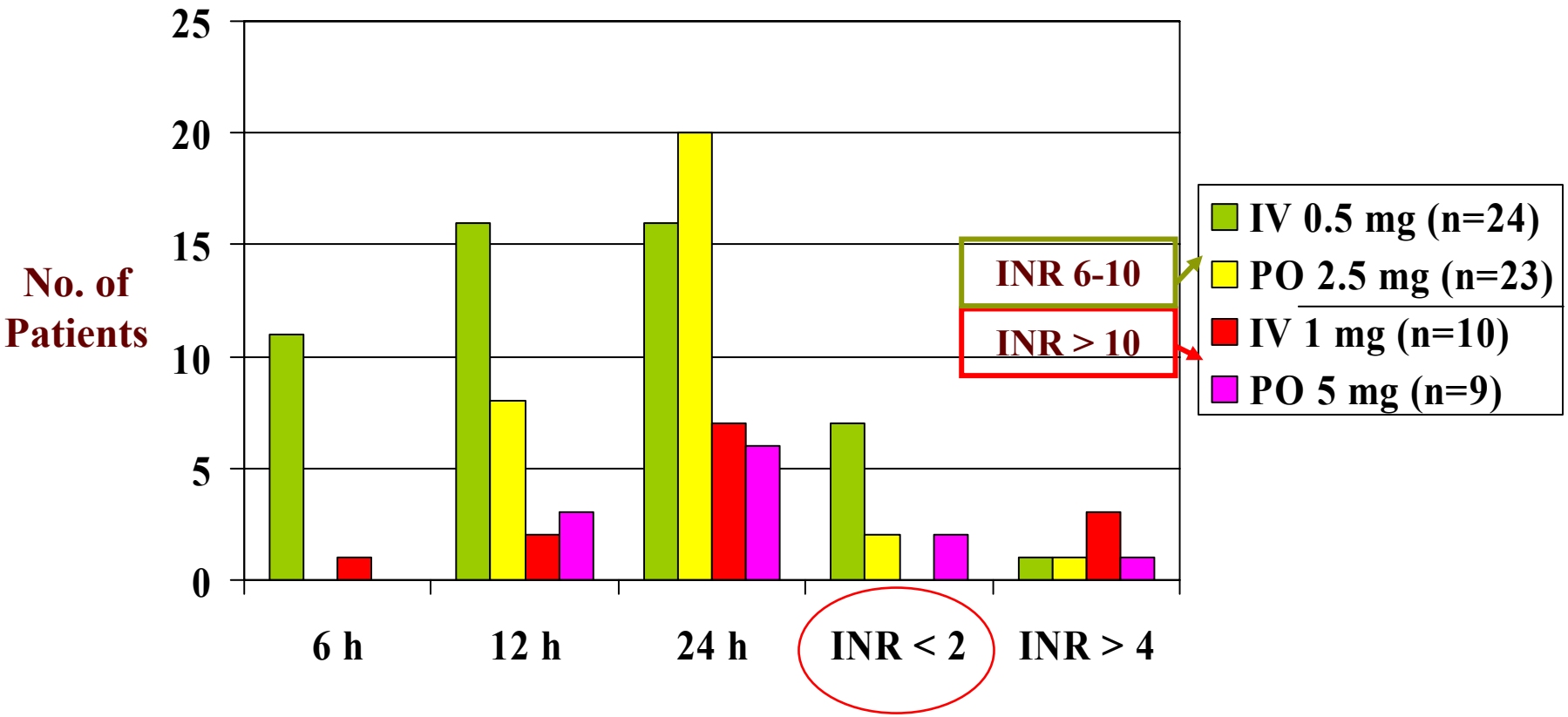
Thromb Hemost 1998:1116

Oral vs IV Vitamin K

- Prospective randomized controlled study of consecutive 61 patients (INR ≥ 6)
  - INR 6-10 (n=44)
    - Vitamin K IV (0.5 mg or oral 2.5 mg)
  - INR > 10 (n=17)
    - Vitamin K IV (1 mg or oral 5 mg)
  - Goal INR 2-4 (“safety zone”)
- Efficacy
  - INR 2-4 @ 6, 12, 24 hrs and major bleeding
- Safety
  - INR < 2, warfarin resistance, thrombosis, or any other side effects
- Duration of follow-up (28 days)

Lubetsky A et al. Arch Intern Med 2003;163:2469-2473

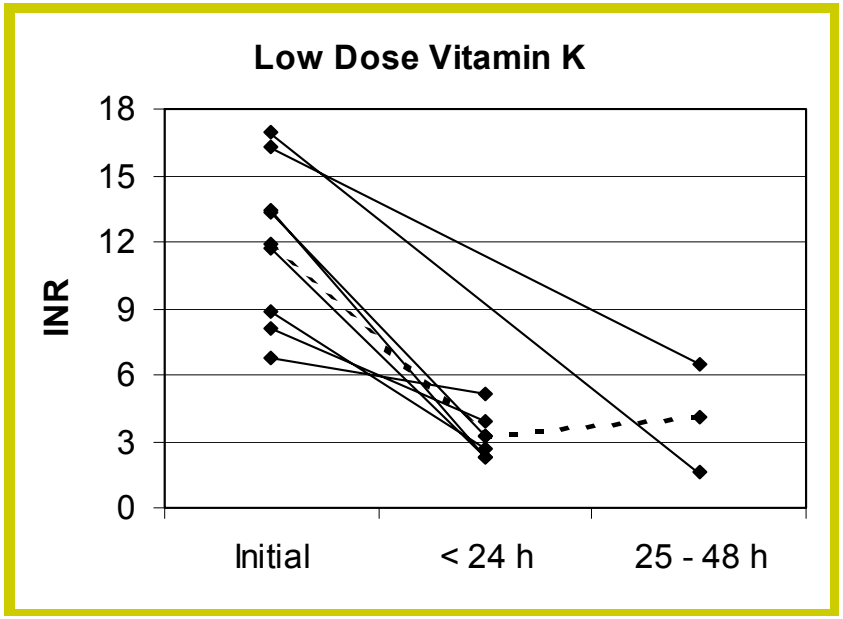
Oral vs IV Vitamin K

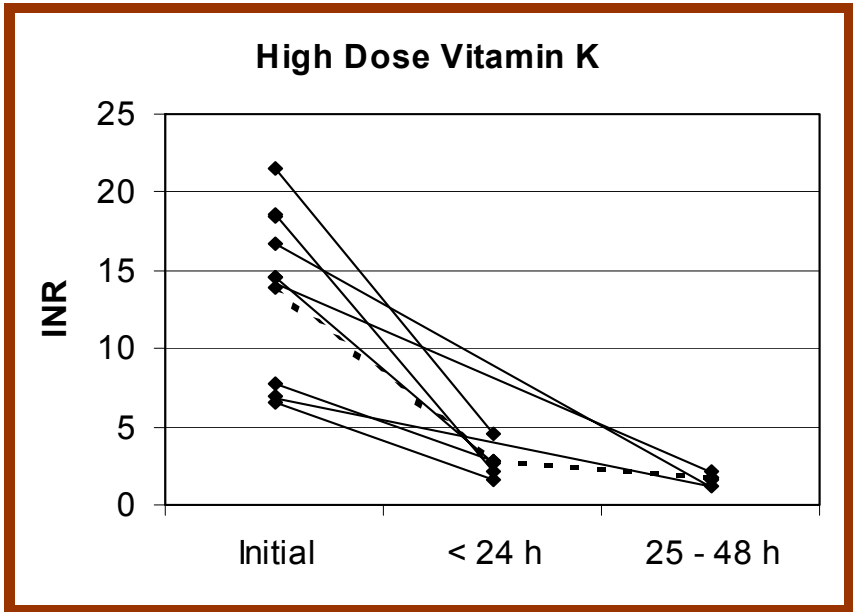


Lubetsky A et al. Arch Intern Med 2003;163:2469-2473

Reversal of Excessive Anticoagulation

Low Dose vs High Dose IV Vitamin-K





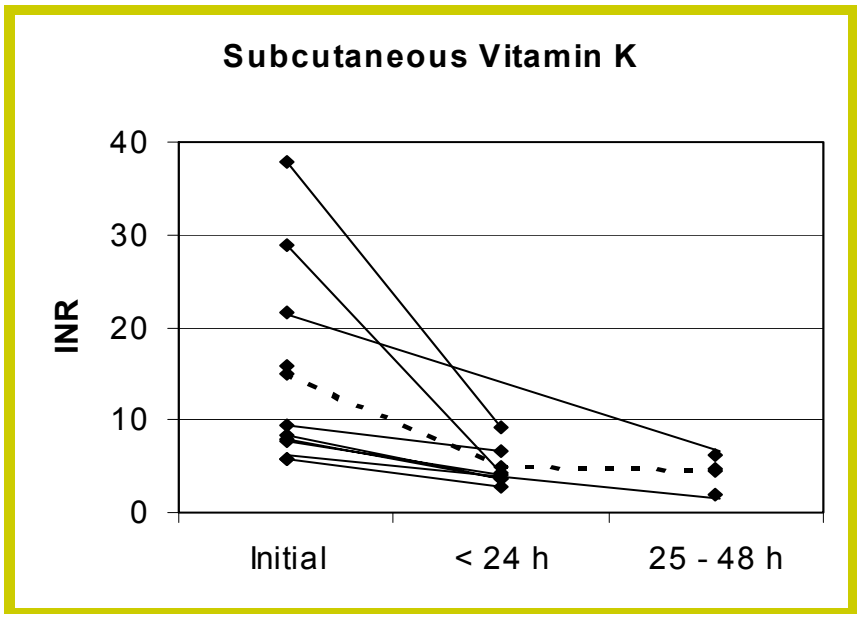
- ✓ LD IV: 0.4 mg (0.1- *0.5* mg)
- ✓ INR mean 11.9 (6.8-17) ⇒ 3.2
- ✓ 1/8 over-correction

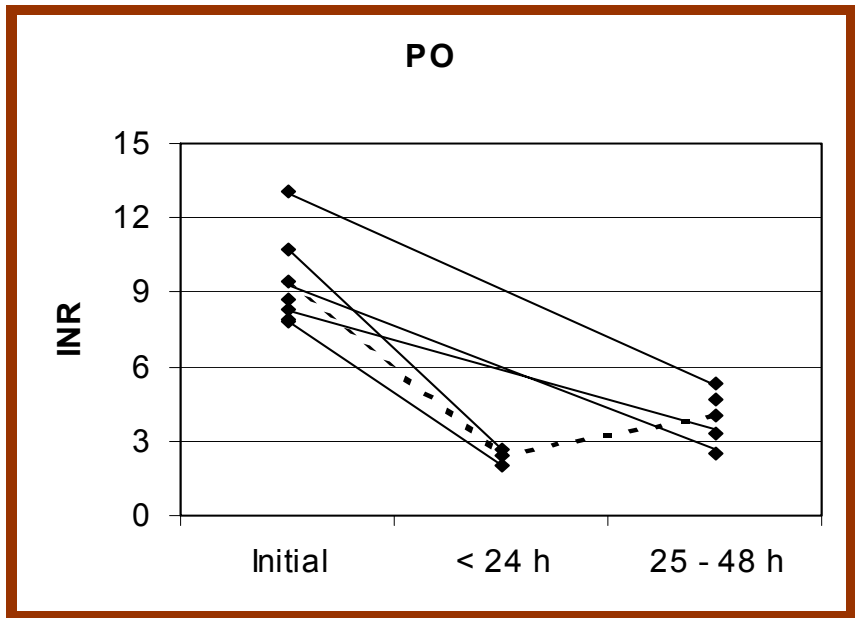
- ✓HD IV: 4.2 mg (1-10 mg)
- ✓INR mean 13.9 (6.6-21.5)⇒ 2.3
- ✓4/9 over-correction

Arch Intern Med 1998:158;2136-40

Reversal of Excessive Anticoagulation

SC vs PO Vitamin-K





SC: 2.5 mg (1-10 mg)
INR 14.9 (5.7-37.8) ⇒ 4.9
No over-correction

PO: 3.8 mg (2.5- 5 mg)
INR 9.4 (7.9-13.1)⇒ 2.4
No over-correction

Arch Intern Med 1998:158;2136-40

Management of Excessive Anticoagulation in a HMO Model

- INR 6-10 (234), INR 10.1-20 (50), INR > 20 (17)
- **Conservative:** hold warfarin until INR within therapeutic
- **Treatment:** Vitamin-K, FFP or both
- **Clinical Outcome:** None, major, minor bleeding, thrombosis, warfarin resistance
- **Cost Analysis:** lab tests, MD visits, ER, Urgent care, visits, hospitalization

Arch Intern Med 1998;158:528

Management of Excessive Anticoagulation in a HMO Model

Clinical Outcomes: Conservative

- 249/301 episodes (83%)
  - Warfarin held for average 3.2 ± 2.0 days
  - 25% dosage reduction at re-initiation of therapy
  - 99% effective
  - No thrombosis
  - No warfarin resistance

Arch Intern Med 1998;158:528

Management of Excessive Anticoagulation in a HMO Model

Clinical Outcomes: Treatment Group

- Vitamin-K, FFP or both in 52 episodes:
  - SC (39%) 12.6 ± 9.7 mg
  - IM (38%) 12.7 ± 14.3 mg
  - PO (16%) 12.2 ± 5.8 mg
  - IV (7%) 5.5 ± 4.5 mg
- 100% effective
- 2 thrombosis: 1 (10mg PO), 1 (20 mg PO, 30 mg SC and 4 units FFP) requiring heparin therapy 2-4 days
- Cost 7 times higher to treat 1 episode with vitamin-K for INR 6-10.

Arch Intern Med 1998;158:528

Vitamin-K SC Administration

- Low dose (1-2 mg) SC is effective
- INR < 4-5 in 24 hrs (25-67%) & in 48 hrs (72-95%)
- Unpredictable and delayed response
- Over-correction/warfarin resistance more common
- For patients who can't tolerate PO
- For patients with history of anaphylactoid reaction with IV administration, no IV access

AHJP 1999: 2312, Am J Cardiol 1999:286, Ann Intern Med 1998:2136

Oral Vitamin-K Administration

- Effective reversal with 1-5 mg po
- Minimal over-correction (INR<2)
- Dosage form
  - small dose from health food store
  - parenteral in insulin syringe (Crowther et al.)
- Not for patients with active bleeding or known history of malabsorption

Vitamin-K IV Administration

- Serious, life-threatening bleeding
- Rapid reversal is needed for procedures
- Low dose (≤1 mg) is effective
- May repeat in 12-24 hrs, if necessary
- Anaphylaxis or hypersensitivity very rare
  - ***To avoid infusion related anaphylaxis, low dose & slow administration over 30 minutes via IVPB (PHD protocol)***
- Over-correction and warfarin resistance is very common with high dose

Chest 2004;126:204S-233S, Mayo Clin Proc 2001;76:260-266, Pharmacotherapy 1999:1415

Clinical Predictors of Prolonged Delay in Therapeutic INR

Table 2. **Independent Risk Factors for INR of 4.0 or Greater after Withholding of Two Doses of Warfarin in Patients with an Index INR Greater than 6.0***

Risk Factor	Adjusted Odds Ratio (95% CI)	*P* Value
Age, per decade of life	1.18 (1.01–1.38)	0.04
Index INR, per unit	1.25 (1.14–1.37)	<0.001
Congestive heart failure	2.79 (1.30–5.98)	0.009
Active cancer	2.48 (1.11–5.57)	0.03
Weekly warfarin dose, per 10-mg increase	0.87 (0.79–0.97)	0.009

* The full multiple logistic regression model included age, index INR, decompensated congestive heart failure, active cancer, weekly warfarin dose, decreased oral intake, and use of potentiating medication. INR = international normalized ratio.

Hylek, E. M. et. al. Ann Intern Med 2001;135:393-400

Annals of Internal Medicine

Clinical Predictors of Prolonged Delay in Therapeutic INR

Hylek, EM et al. **(Ann Intern Med 2001;135:393-400)**

- advanced age
- initial high INR
- decompensated CHF or active cancer
- warfarin dose

Other factors to consider

- lab error
- drug interactions
- warfarin administration, half-life, metabolism
- factor VII deficiency

Management of Excessive Anticoagulation

INR		Therapeutic Intervention
<5.0	No bleeding	Hold and restart @ a lower dose when INR is therapeutic
5.0 ≥ , <9.0	No bleeding	As above
	Risk of bleeding	Hold dose & PO Vit-K (1-2.5 mg).
	If urgent surgery	Vit-K (≤ 5 mg PO) with expectation of INR reduction in 24 hrs.
		May repeat with 1-2 mg if needed.
INR ≥ 9.0	No bleeding	Hold and PO Vit-K (5-10 mg PO) with expectation of INR reduction in 24-48 hrs.
Any INR	Serious bleeding	Vit-K 10 mg IV slow infusion (PHD protocol)
		Supplement with FFP, prothrombin complex concentrate, or Factor VIIa
	Life threatening bleeding	Prothrombin complex concentrate, or Factor VIIa
		Supplement with Vit-K 10 mg IV slow infusion (PHD protocol)

Chest 2004;126:204S-233S

Management of Warfarin for Invasive Procedures

Risk of Thrombosis	Risk of Bleeding: Low	Risk of Bleeding: High
Low	Dental; cutaneous biopsies; open procedures; cataracts	Major thoracic, abdominal, or pelvic surgery; CNS surgery; polypectomy via colonoscopy
	AF; valvular heart disease ± aortic prosthesis; old DVT/PE	AF; valvular heart disease ± aortic prosthesis; old DVT/PE
	Do procedure at: subtherapeutic INR range or lower	**Do procedure at normal INR**; use no alternative or use LDH, AdjDH or FDH
	Dental; cutaneous biopsies; open procedures; cataracts	Major thoracic, abdominal, or pelvic surgery; CNS surgery; polypectomy via colonoscopy
High	Prosthetic valves, esp. in mitral position; AF + history of CVA; very recent DVT/PE	Prosthetic valves, esp. in mitral position; AF + history of CVA; very recent DVT/PE
	Do procedure at: therapeutic or subtherapeutic INR	**Do procedure at:** normal INR range; use FDH

(From "Management of Oral Anticoagulant Therapy" by J. Ansell et al, www.americanheart.org)

Management of Warfarin for Invasive Procedures

Low risk of TE	• Hold warfarin x 4 days to near-normal INR • If risk of thrombosis, prophylactic LDUFH or LMWH with warfarin
Intermediate risk of TE	• Hold warfarin x 4 days to near-normal INR • LDUFH or prophylactic LMWH pre-op x 2 days • Post-op, restart warfarin with LDUFH or LMWH
High risk of TE	• Hold warfarin x 4 days to normal INR • FDUFH or LMWH pre-op x 2 days • Stop FDUFH 5 hr or LMWH 12-24 hr pre-op • Post-op, restart warfarin with LDUFH or LMWH
Low risk of bleeding	• Continue warfarin at a lower dose and operate at INR 1.3-1.5 • Post-op, restart warfarin with LDUFH or prophylactic LMWH, if necessary
Dental procedure to control local bleeding	• Tranexamic acid mouthwash or epsilon aminocaproic acid mouthwash without interrupting warfarin

Chest 2004;126:204S-233S

Anticoagulants

Agents	$T_{½}$ (hrs)	Duration of Effect
Heparin	1-1.5	2 hrs
Dalteparin (Fragmin)	2-5	10-24 hrs
Enoxaparin (Lovenox)	3-7 (SQ)	24 hrs (longer in RI)
Argatroban	0.5-1	2-4 hrs
Bivalirudin (Angiomax)	0.5	1 hr
Lepirudin (Refludan)	1-2hrs	2 days in renal failure

Fragmin ® 2003; Lovenox® 2003; Argatroban 2003; Angiomax®2004; Refludan® 2002

Therapeutic Options

- **Unfractionated Heparin**
  - Antidote: Protamine
  - Within minutes: 1 mg protamine/100 units UFH
  - 30-60 min: 0.5-0.7 mg/100 units UFH
  - > 2 hours: 0.25-0.375 mg/100 units UFH
  - No more than 50 mg protamine within 10 min

AHFS 2003; DI Handbook 2003

Therapeutic Options

- **Enoxaparin**
  - Protamine 1 mg/1 mg enoxaparin
  - May repeat 0.5 mg protamine per 1 mg enoxaparin in 2-4 hours
  - No more than 50 mg protamine within 10 min
  - Anti-Xa activity will NOT completely be reversed with protamine (~60%)

Lovenox® PI Dec 2003

Therapeutic Options

- Direct Thrombin Inhibitors
  - Lepirudin, argatroban, bivalirudin
  - **No specific antidotes** available
  - Blood transfusion and supportive therapy for major bleeding

Antiplatelets

Agents	$T_{1/2}$(hrs)	Duration of Effect
Aspirin	2.5 – 7	5-7 days (irreversible)
Clopidogrel (Plavix)	7-8	5-7 days (irreversible)
Cilostazol (Platal)	11-13	12-48 hrs (reversible)
Abciximab (Reopro)	0.5-6	48 hrs (up to 15 days)
Eptifibatide (Integrilin)	2.5	4 hrs (reversible)
Tirofiban (Aggrastat)	1.5-3	3-8 hrs (reversible)

Integrilin® 2003; Lovenox® 2003; Plavix® (clopidogrel) 2003; Pletal® 2004; Refludan® 2002; Reopro® 2003

Thrombolytics

Agents	$T_{½}$ (hrs)		Duration of Effect
Alteplase	26-46 (min)	NA	Patency: ~75% @90 min, then increases to 90% by 24 hours ("late" reperfusion) The levels of fibrinogen, plasminogen, α_2-antiplasmin return to 80% of baseline within 24 hours
Reteplase	13-16 (min)	NA	
Tenecteplase	20 (min)	1.5-2	
Urokinase	10-20 (min)	NA	

Summary: Pharmacologic Reversal for Life-Threatening Hemorrhage

- Anticoagulants
  - UFH/LMWH: protamine, FFP
  - Oral anticoagulant: FFP or PCC in combination with vitamin-K IV (1-10 mg slow IV infusion over 30 min)
  - Recombinant factor VII
    - Reversal of OAC: 15mcg/kg (reversal of OAC)
    - ICH: **40-**120 mcg/kg
- Antiplatelets
  - platelet transfusion, if serious bleeding