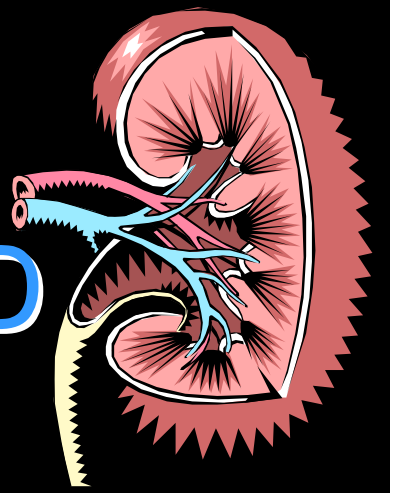
The Challenges of Anticoagulation in the HD Patient



Joanne Jung, BScPharm, ACPR

Renal Pharmacists Network

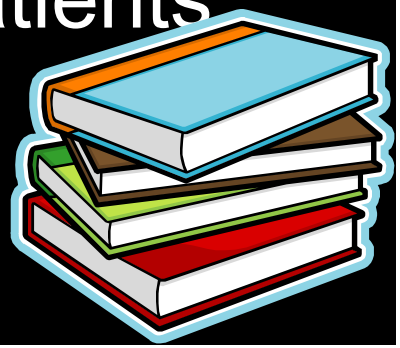
Education Dinner Seminar Oct 2009

Disclosure Information

I have no conflict of interest to declare

Learning Objectives

- Overview of warfarin
- Common indications for warfarin in HD patients
- Unique characteristics of ESRD pts
- Review the literature of warfarin in ESRD patients
- Final recommendations for renal patients

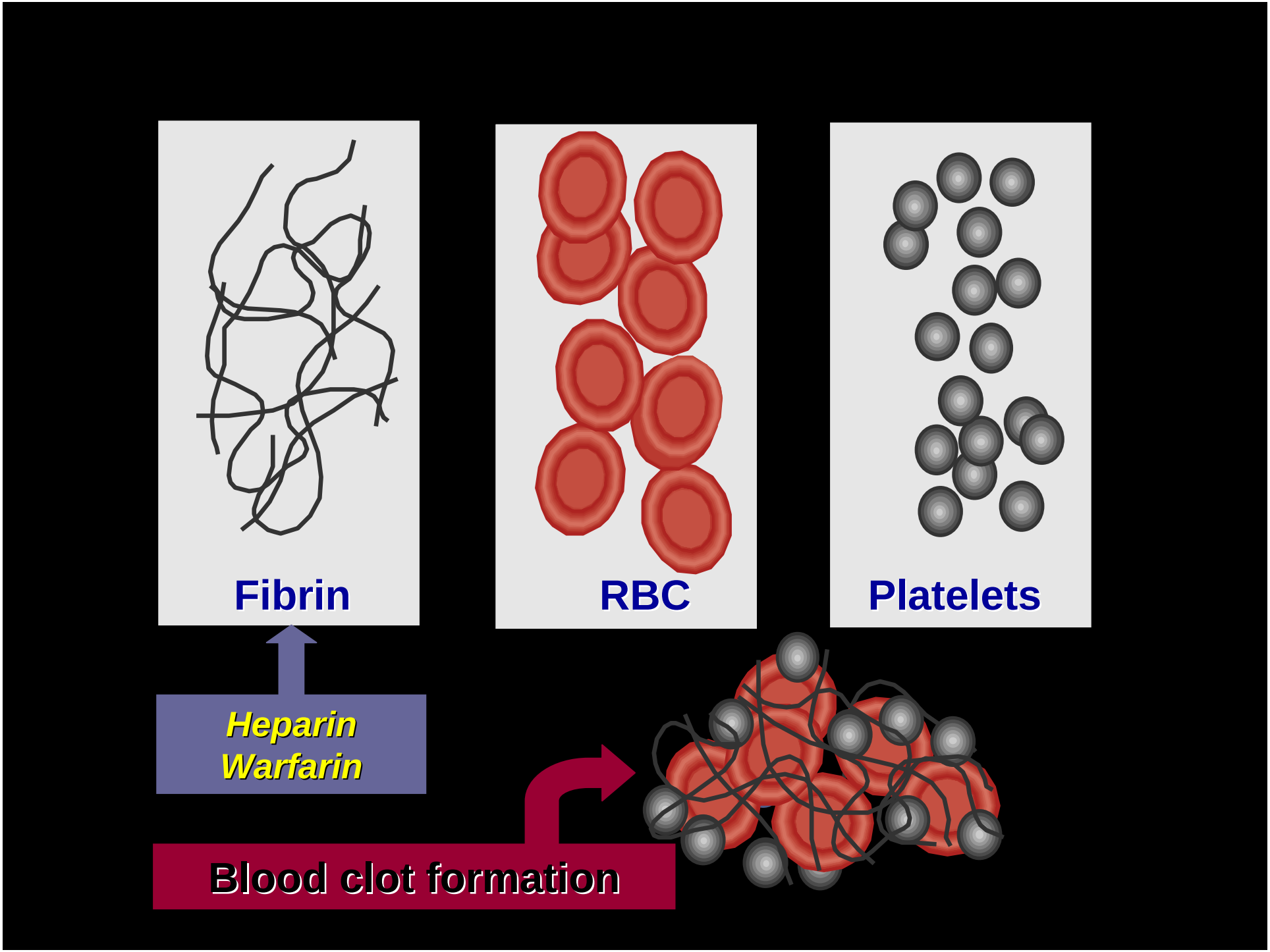


Warfarin

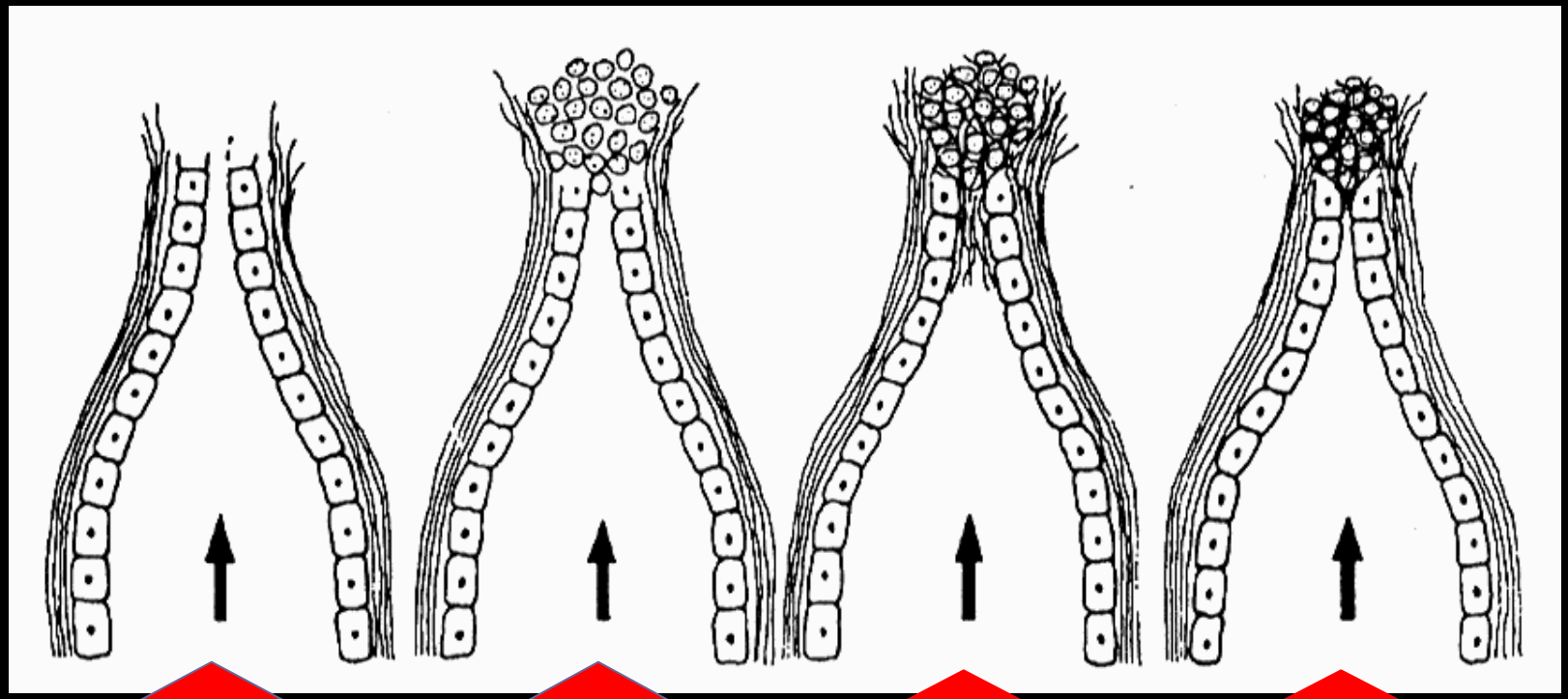
- Rapidly absorbed from the GI tract
- 99% protein bound
- Half life is approximately 40 hr

- Interactions
  - Albumin binding/displacement
  - Liver clearance effects

- Monitoring
  - INR (International Normal Ratio)
  - Target usually 2-3 (depending on indication)


Fibrin
RBC
Platelets
Heparin
Warfarin
Blood clot formation

Hemostasis



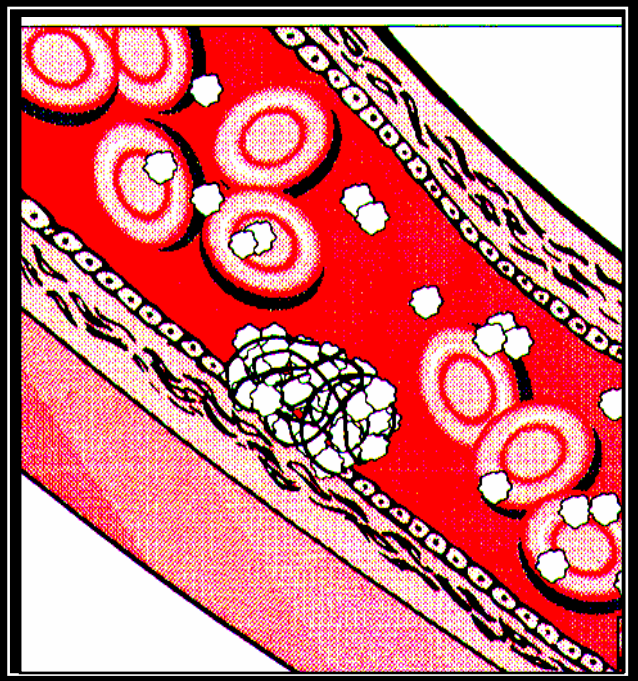
Vessel contraction

Platelet adhesion/ aggregattion

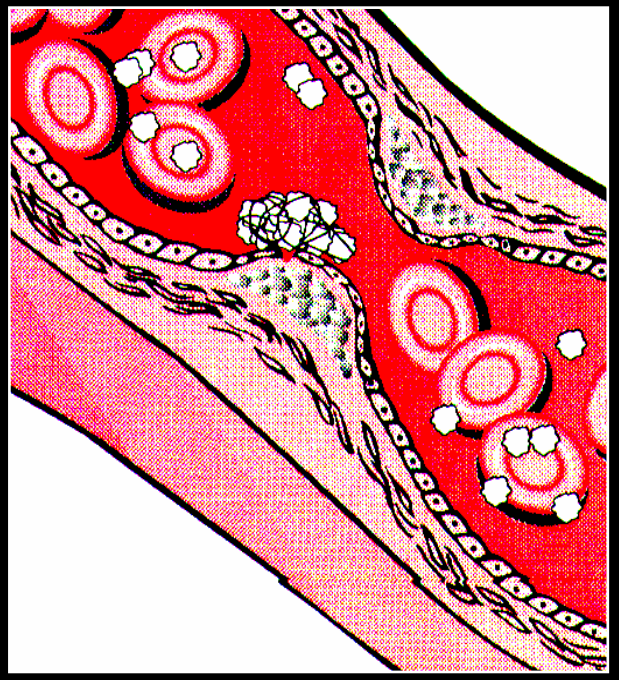
Fibrinogenesis

Retraction

Coagulation vs Thrombosis



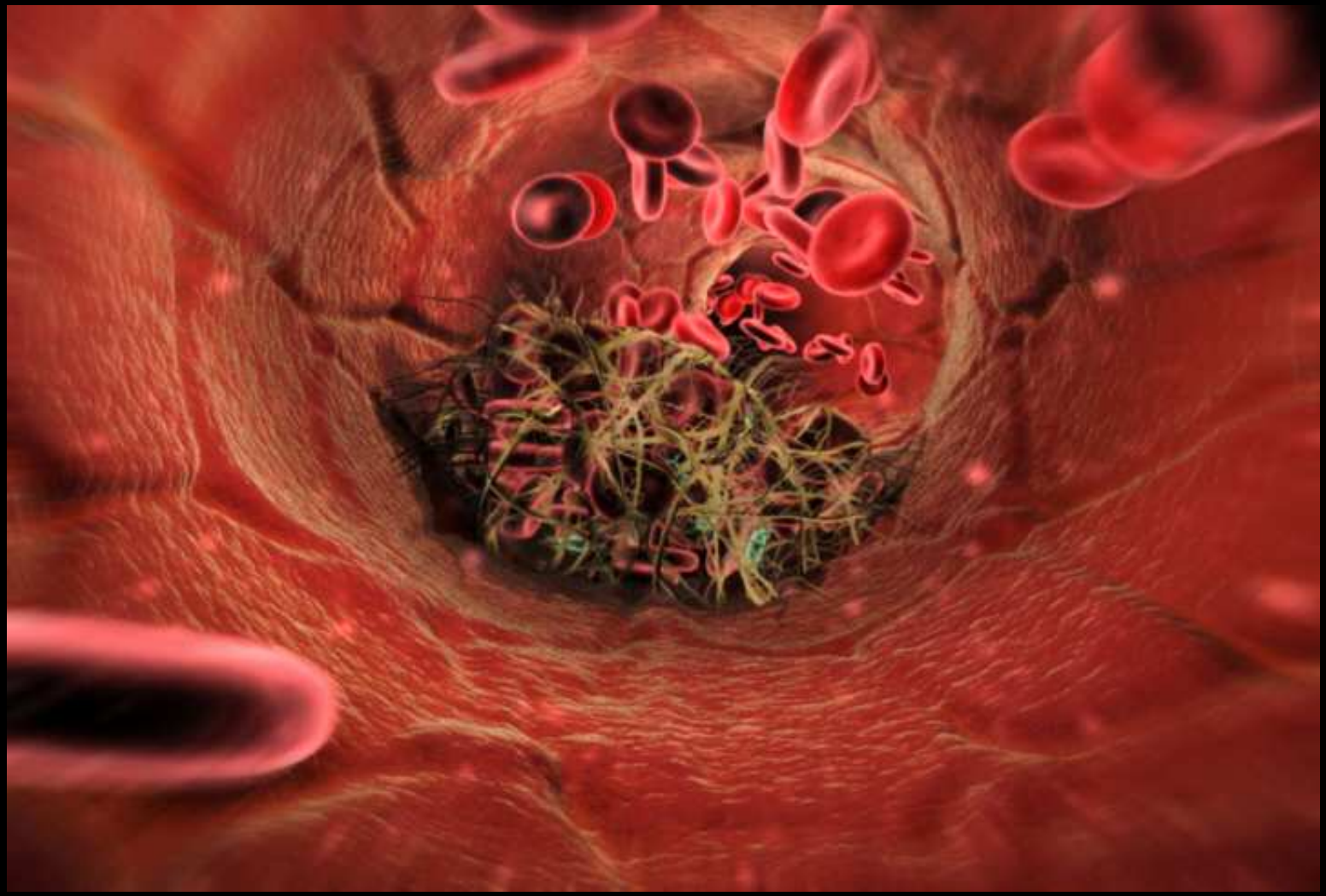
Coagulation (hemostasis)



Thrombosis

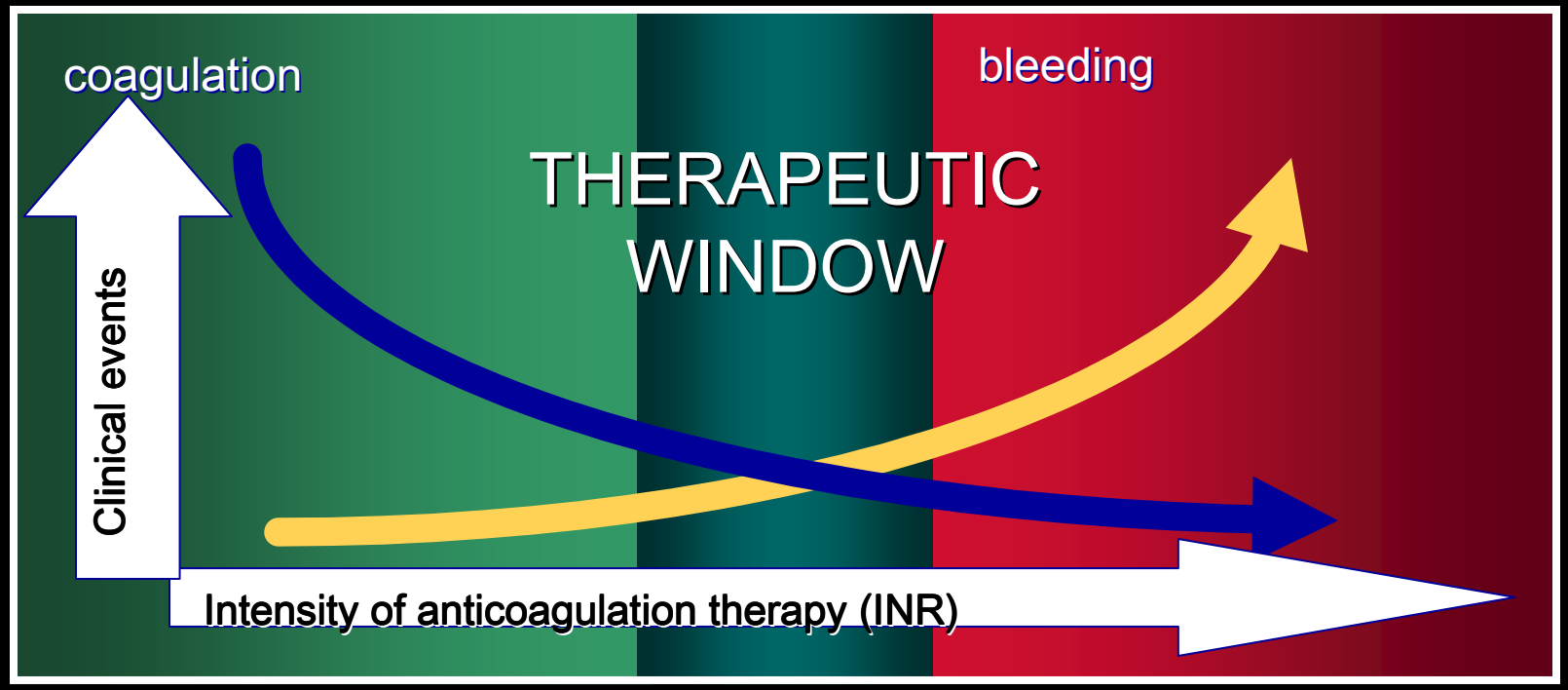
Physiological protection mechanism	Danger to life, pathophysiological process

Formation of a THROMBUS



Management of OAC Therapy

Goal: To maintain INR in therapeutic window.

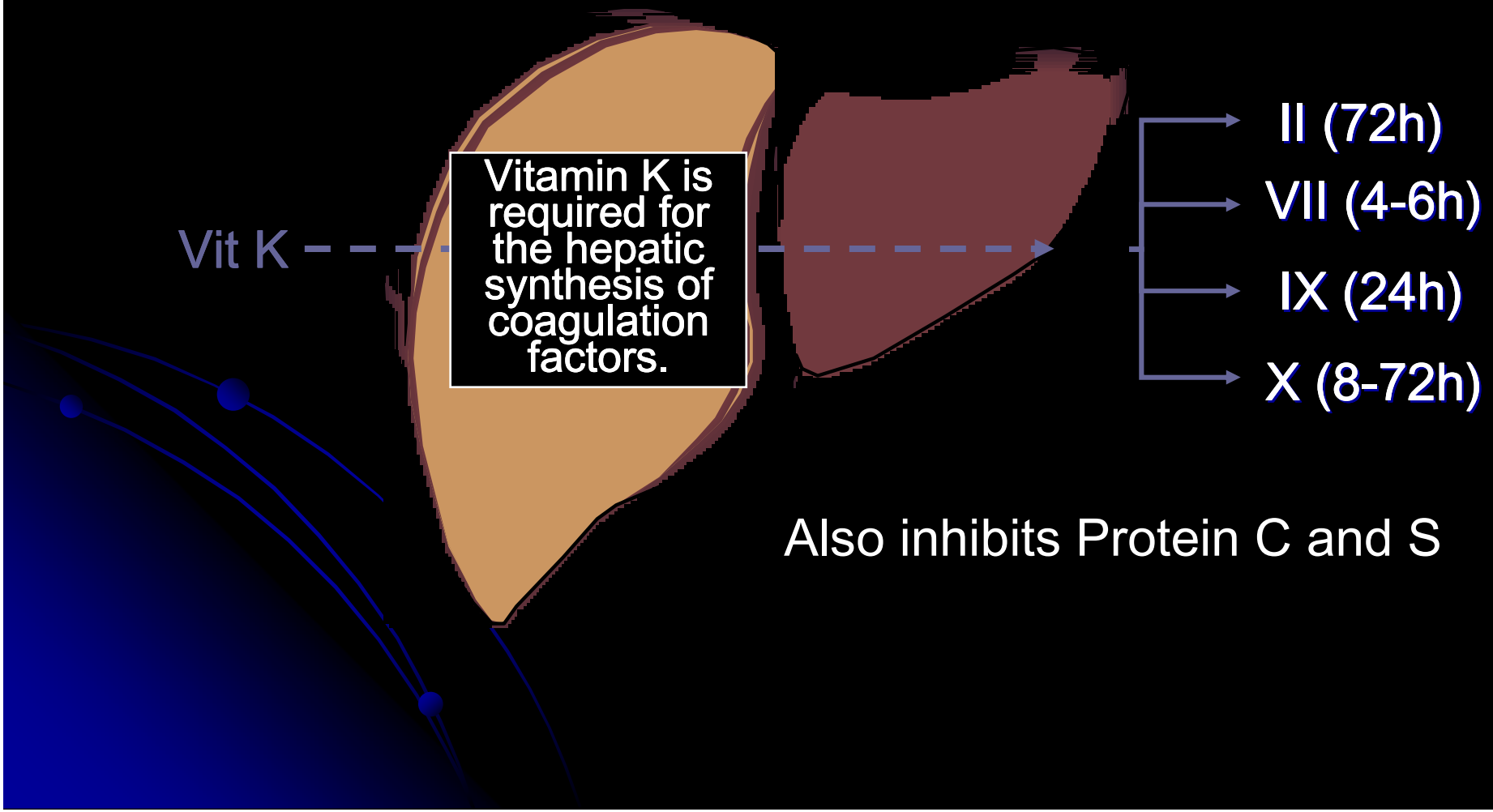


↑ DRUG

2.0 to 3.0
2.5 to 3.5

↓ DRUG

Warfarin: Mechanism Of Action



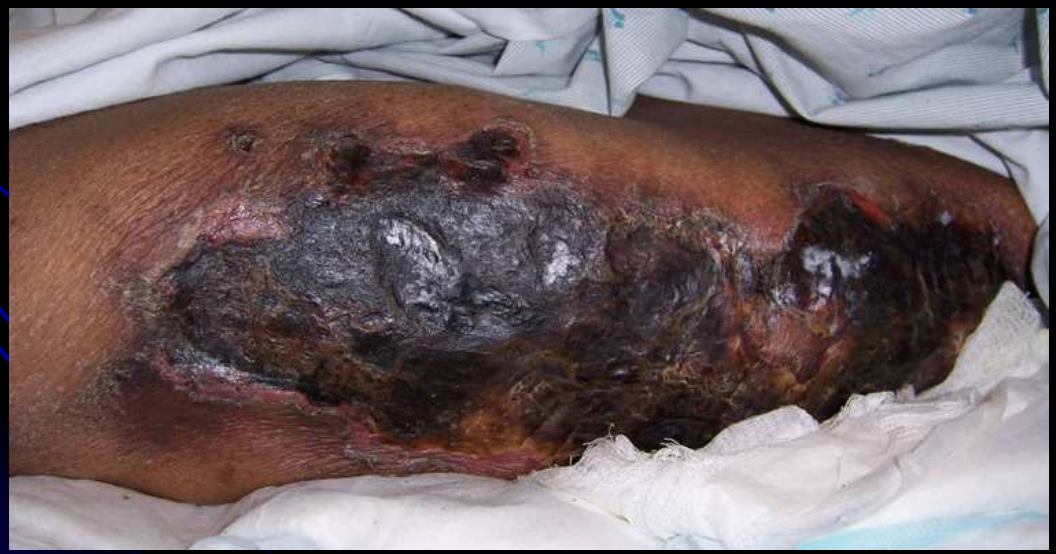
Also inhibits Protein C and S

Mechanism of Action

- Interferes with 2 other Vitamin K dependent proteins (within the vasculature)
  - Matrix G1a Protein (MGP)
    - Prevents vascular calcification
  - Growth Arrest Specific gene 6 (Gas 6)
    - Growth factor in vascular smooth muscle and mesangial cells
  - Is warfarin a risk factor for calciphylaxis?

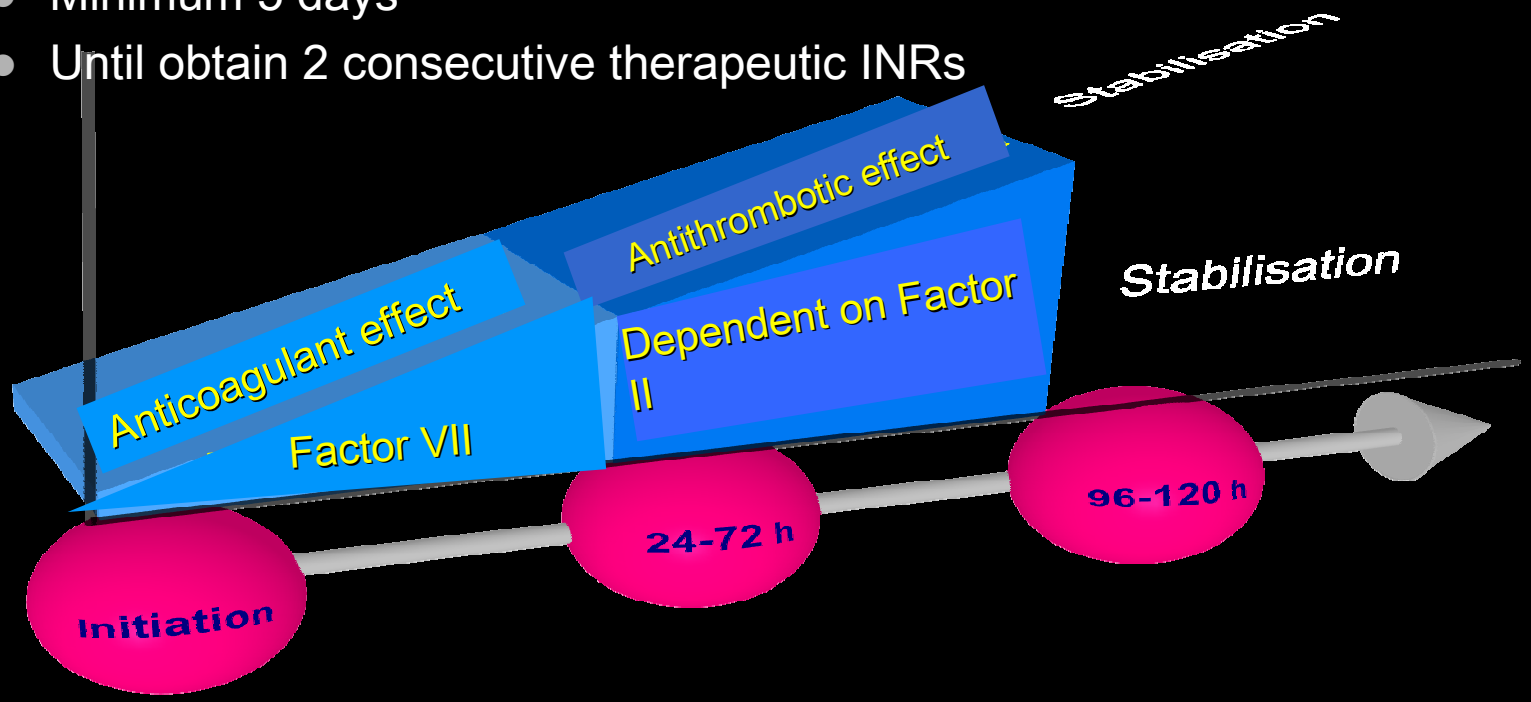
Calciphylaxis

- An extreme form of vascular calcification
- Results in chronic non-healing wounds
- Known as “calcific uremic arteriopathy”
- 45% mortality by 12 months

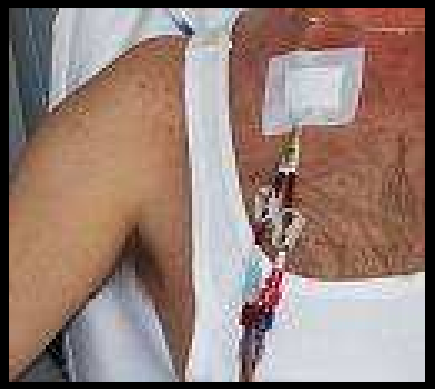


Pharmacodynamics of Warfarin

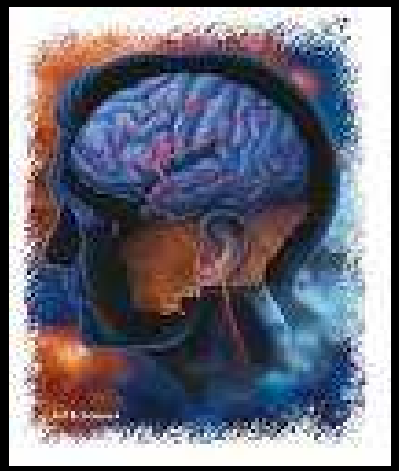
- Need to overlap with heparin or low-molecular weight heparin (LMWH):
  - Initial rapid inhibition of Protein C which favours thrombus formation
  - Minimum 5 days
  - Until obtain 2 consecutive therapeutic INRs



Indications for Warfarin



- Maintain Vascular Access
  - Hemodialysis catheters
  - AV fistula/grafts
- Prevent Thromboembolic Event
  - Atrial fibrillation
  - Valve replacement
  - MI
  - Deep vein thrombosis
  - Pulmonary embolus



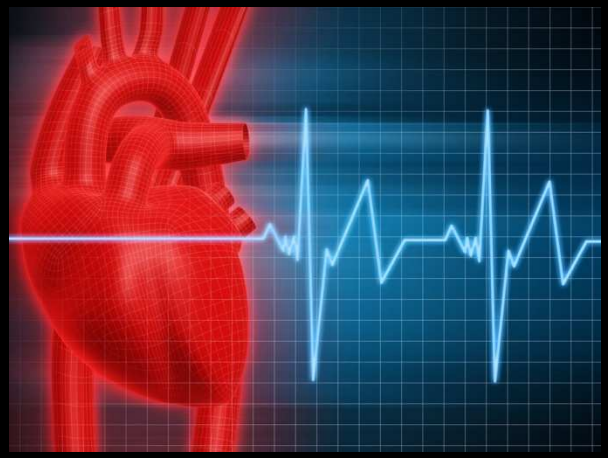
Preventing Catheter Thrombosis

Fixed mini-dose	Mokrzycki et al	P,DB,PC RCT	1mg warf vs placebo	NSS
1.5-2.0	Zellweger et al	NR, Obsv'l	High risk vs low risk	NSS
1.8-2.5	Coli et al	RCT	Early vs late warfarin	p<0.01
2.0-3.0	Obialo et al	Pros, Obsv'l	Warfarin vs ASA 325mg	NSS

Vercaigne et al, Seminars in Dialysis 2008;21(1):71-77

ATRIAL FIBRILLATION

- Definition: rapid irregular rhythm
  - Atrial rate up to 350 BPM
  - Ventricular rate often > 100 BPM



- Symptoms:
  - Palpitations
  - Dyspnea
  - Fatigue
  - Many patients ASYMPTOMATIC
- Risks:
  - Stasis of blood in atria can lead to blood clot formation
  - Right atrium: PE
  - Left atrium: CVA

Alterations in Renal Patients

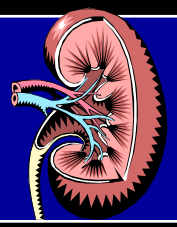
Bleeding Risk

- Uremic platelet dysfunction
- Altered platelet-vessel wall interaction
- Uremic toxins →PTH
- EPO deficiency

Clotting Risk

- Atherosclerosis/endo-thelial damage
- Dysfunctional protein C metabolism
- Elevated plasminogen activator inhibitor-1 to tissue-type plasminogen activator ratios/plasmin inhibition
- Defects in the expression of glycoprotein GP1b

JASN 2009;20:705-711

	Normal Population	ESRD 
Prevalence of Atrial Fibrillation	0.4 – 1% (≥80yr ~8%)	7 - 27 %
Incidence of ischemic stroke	2.6%*	15.1%
2yr mortality following CVA	28%	74%
Relative risk reduction (with warfarin tx)	66%	???
Absolute risk reduction (warfarin)	5.7%	???

* 2.6% in matched pts

US Renal Data System 2006 Ann Report

Risk vs Benefit

Bleeding Risk in HD Patients

Holden et al, Clin J Am Soc Nephrol. 2008 ; 3(1): 105–110

- Retrospective chart review of 255 HD patients (1028 person yrs) (mean f/u = 3.6yrs)
- *Overall*:
  - 26 pts (2.5%) had a bleeding event (95% CI 1.7 to 3.7%)
- *Meta-analysis of observational studies in the general high risk population:*
  - 3% (95% CI 2.5 to 3.4%)

TX	Pts	Major Bleeds	IR(95 % CI)	*p*
None	178	4	0.8% (0.2-2)	n/a
Warf Only	89	5	3.1% (1-7.3)	0.076
ASA Only	107	12	4.4% (2.3-7.7)	0.002
ASA/ Warf	50	5	6.3% (2.1-15)	0.006

Outpatient Bleeding Risk Index

Table 2—*Modified ORBI*

Score	Risk Group	Annual Risk of Bleeding in Patients Without ESRD	Annual Risk of Bleeding in Patients With ESRD
0	Low	3	10
1–2	Moderate	8	Approximately 32*
3	High	30	54

Scoring system is as follows: 2 points for both current and previous stroke and 1 point for each of age > 65 years, current or previous stroke, history of GI bleed, creatinine concentration > 133 μmol, recent myocardial infarct, severe anemia, diabetes mellitus, and atrial fibrillation.

*Moderate bleeding risk was determined as the midpoint of risk between the high-risk and low-risk groups: (high − low)/2 + low.

Sood et al, Chest 2009;136:1128-1133

Table 4—*Comparison of Major Bleeding Rates Between Patients With ESRD on OAC and the General Population*

Study	Major Hemorrhage Rate Without OAC	Major Hemorrhage Rate With OAC
General population		
Estes et al[6]	0.7	1.3
ORBI low risk		3
ORBI medium risk		8
ORBI high risk		30
ESRD population		
Holden et al[23]	0.8	3.1
Elliott et al[24]	2.5–11	26–54

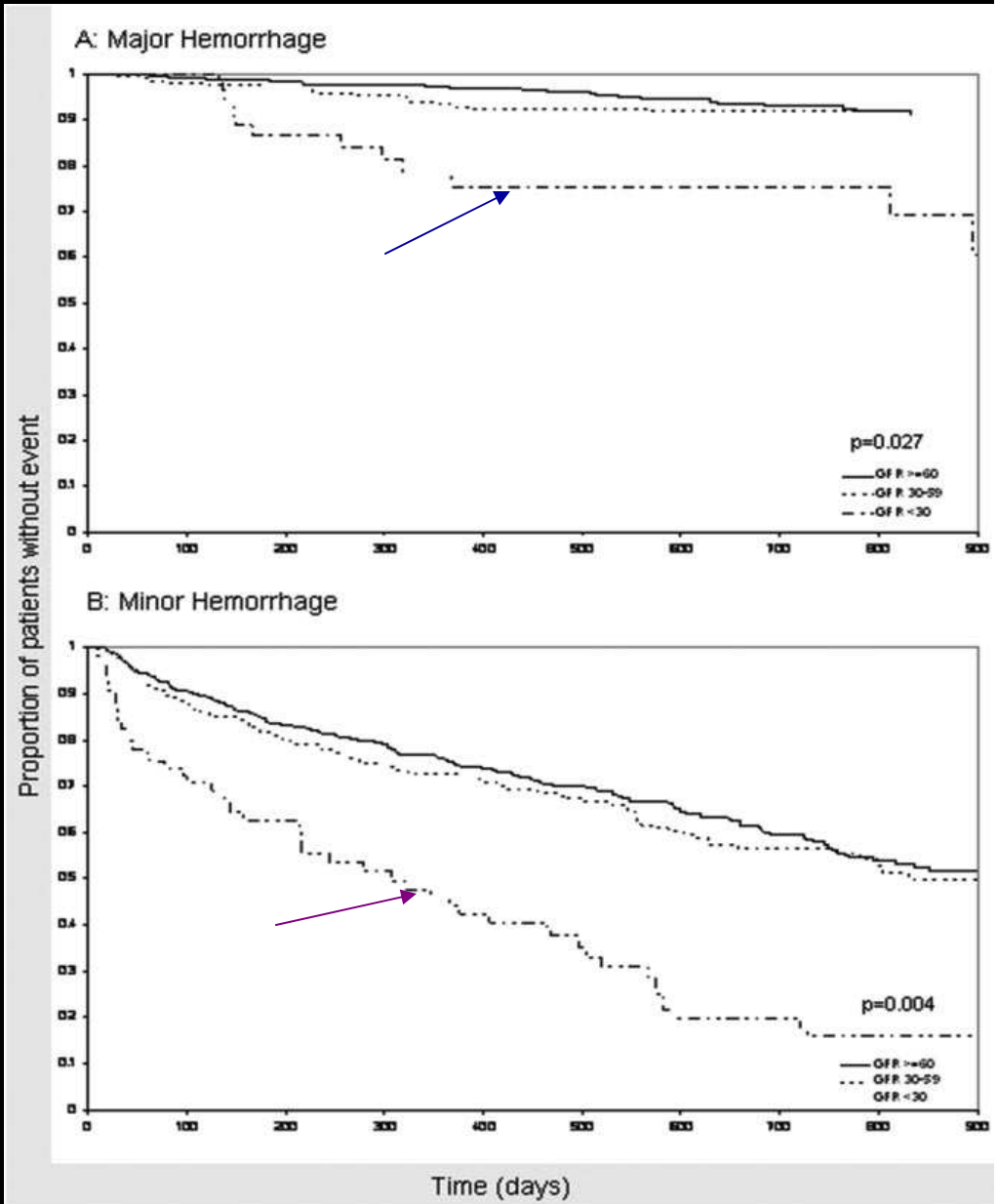
All data are presented as % per year.

Sood et al, Chest 2009;136:1128-1133

TIME TO MAJOR AND MINOR HEMORRHAGE

Limdi et al, J Am Soc Nephrol 2009;20:912-921

- Secondary analysis of a prospective cohort of 578 pts with CKD
- Warfarin dosage
- Anticoagulation control
- Hemorrhagic complications
- **eGFR<30mL/min**
  - ↓ warfarin dose (p=0.0002)
  - Less time in target INR (p=0.049)
  - Higher risk for INR>4 (p=0.052)



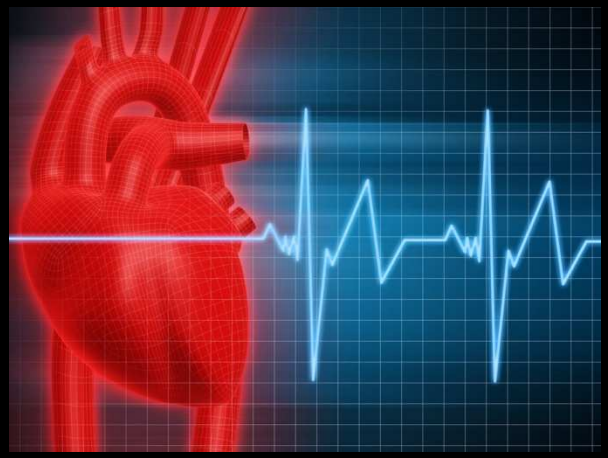
STROKE IN CKD

- The rate of stroke is markedly higher in all stages
- Nakayama et al, Neph Dial Tran 2007;22:1910-1915
  - Observational study – Hazard rate ratios
    - 1.9 eGFR 40-70 ml/min
    - 3.1 eGFR <40 mL/min
- VALIANT trial - NEJM 2004;351:1285
  - Excluded ESRD patients
  - ↑ 2-6% after 3yrs with eGFR ≥75ml/min→<45mL/min

Dilemmas in the Management of Atrial Fibrillation in CKD

Atrial fibrillation

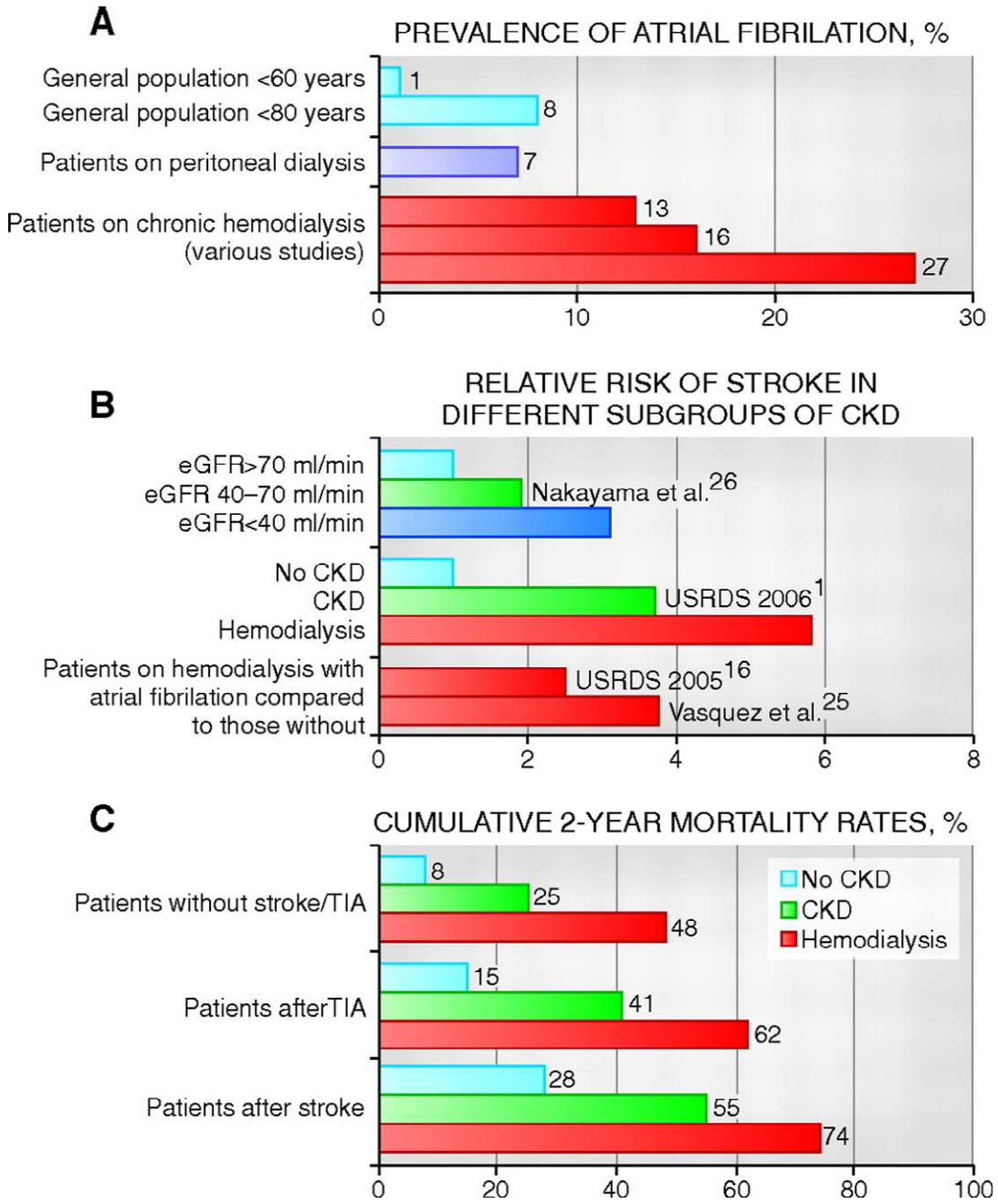
- Incidence in the general population
  - 0.4-1% (8% in patients >80yrs)



Predisposing factors in CKD patients

- CAD
  - Accelerated calcifications
  - Left ventricular hypertrophy
- Fluctuating levels of electrolytes
- Sympathetic nervous system activation
- Modulation of the renin-angiotensin system

- Reinecke H et al,J Am Soc Nephrol 2009;20:705-711



Reinecke, H. et al. J Am Soc Nephrol 2009;20:705-711

Individual Risk Stratification

Table 2. **Risk for Stroke Stratified by $CHADS_2$ Score***

$CHADS_2$ Score	Adjusted Stroke Rate (95% CI)	$CHADS_2$ Risk Level
0	1.9 (1.2–3.0)	Low
1	2.8 (2.0–3.8)	Low
2	4.0 (3.1–5.1)	Moderate
3	5.9 (4.6–7.3)	Moderate
4	8.5 (6.3–11.1)	High
5	12.5 (8.2–17.5)	High
6	18.2 (10.5–27.4)	High

* The $CHADS_2$ score is calculated by adding 1 point each for recent congestive heart failure (i.e., active within the past 100 days or documented by echocardiography), hypertension (systolic and/or diastolic), age at least 75 years, and diabetes mellitus, and adding 2 points for a history of stroke or transient ischemic attack. A score of 0 to 1 was designated as low risk; a score of 2 to 3 was designated as moderate risk; and a score of 4, 5, or 6 was designated as high risk. The adjusted stroke ratio is the expected stroke rate per 100 patient-years from the exponential survival model from the National Registry of Atrial Fibrillation.

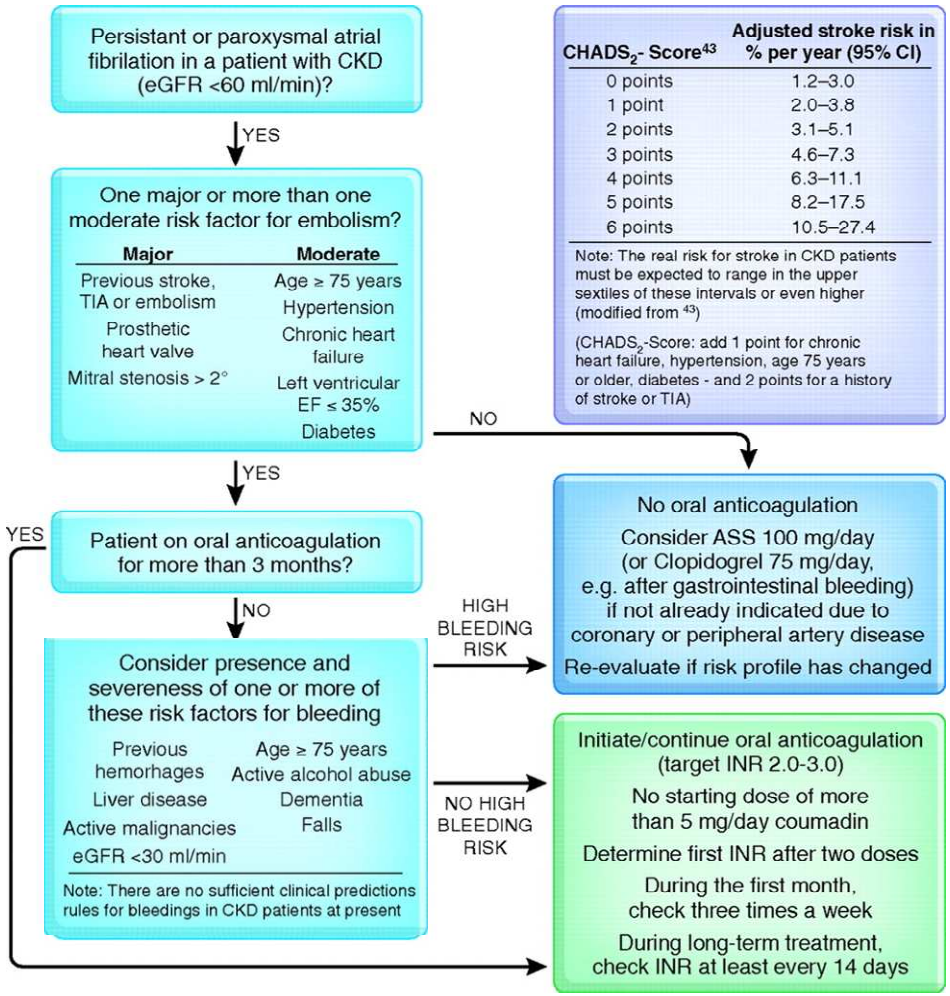
Snow, V. et. al. Ann Intern Med 2003;139:1009-1017

CHADS2 SCORE

One point for each :

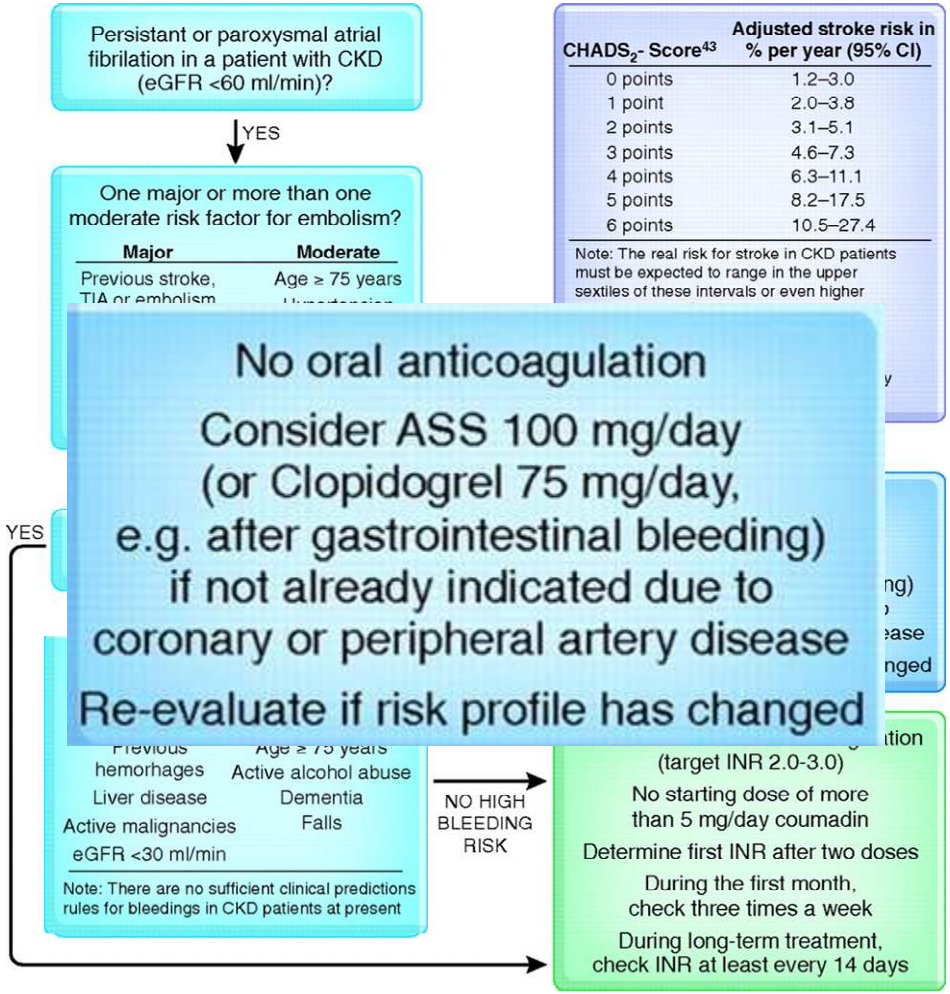
- Congestive Heart Failure/LV dysfunction
- Hypertension
- Age (greater or equal to 75)
- Diabetes
- Stroke (2 pts for history of CVA or TIA)

Figure 2. Algorithm for oral anticoagulation in atrial fibrillation and CKD



Reinecke, H. et al. J Am Soc Nephrol 2009;20:705-711

Figure 2. Algorithm for oral anticoagulation in atrial fibrillation and CKD



Reinecke, H. et al. J Am Soc Nephrol 2009;20:705-711

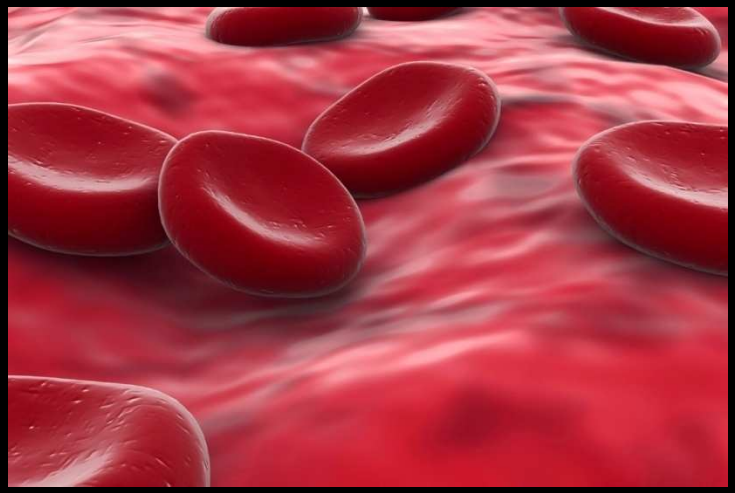
JASN

Presenter's Opinion

- ESRD pts with atrial ibrillation with a LOW or MODERATE risk for stroke (CHADS2 Score 0-3) but HIGH risk for bleeding should NOT receive warfarin
- More frequent INR testing
  - Every dialysis run x 2 weeks, followed by weekly INR's.
  - Mininum frequency: every 2 weeks for carefully selected, stable patients
- Very thorough counselling and observation by the pharmacist to screen for drug interactions, diet and compliance.

High Risk Factors for Bleeding

- Previous hemorrhages
- Dementia
- Liver disease
- Active malignancies
- Age >75yrs
- Active alcohol abuse
- Falls



Factors Affecting Warfarin Therapy

- Stress
- Diet
- Medications
- Lifestyle (e.g. smoking, alcohol)
- Compliance
- Comprehension

Foods Rich In Vitamin K

- The following foods each contain more than 15 mcg of vitamin K per 100 g portion:

Dried kelp
Raw broccoli
Brussels sprouts
Watercress
Rutabaga leaves
Cheese
Canola oil
Soya oil
Lentils
Green tea
Raw asparagus
Green cabbage
Cauliflower
Spinach
Beef liver
Green beans
Olive oil
Lettuce
Peas

Herbal Products and Warfarin

Product	Potential Interaction
Feverfew	↑ bleeding
Garlic	↑ bleeding
Ginger	↑ bleeding
Ginkgo Biloba	↑ bleeding
CoEnzymeQ10	↓ INR
Cranberry Juice	↑ INR
Danshen	↑ INR
Devil's Claw	Purpura
Dong Quai	↑ INR
Ginseng	↓ INR
Green Tea	↓ INR
Papain	↑ INR

Heck et al, Amer Jour Health Sys Phar 2000

Five Major Mechanisms of Drug Interactions with Warfarin

- Altered platelet function (eg ASA, clopidogrel)
- Direct gastrointestinal injury (eg NSAIDS)
- Altered gut vitamin K synthesis (eg antibiotics)
- Altered warfarin metabolism (eg co-trimoxazole, metronidazole, fluconazole amiodarone)
- Interference with vit K cycle (eg acetaminphen) CMAJ 2007;177(4):371

Pharmacist's Role

- Warfarin dosing adjustment
- Recommend more frequent INR's
- Anticipate drug interactions
- Thorough medication history
- Dispense 1mg tablets - INITIALLY

Conclusions

- To date, there is no strong evidence supporting the benefit of WARFARIN in ESRD patients
- There is strong evidence to suggest that ESRD patients are at higher risk of bleeding
- Theoretically, warfarin may ENHANCE calcification so discontinue if pt diagnosed with calciphylaxis
- ESRD pts should be more tightly monitored with more frequent INR testing
- Pharmacists play a key role in optimizing the efficacy and safety of warfarin