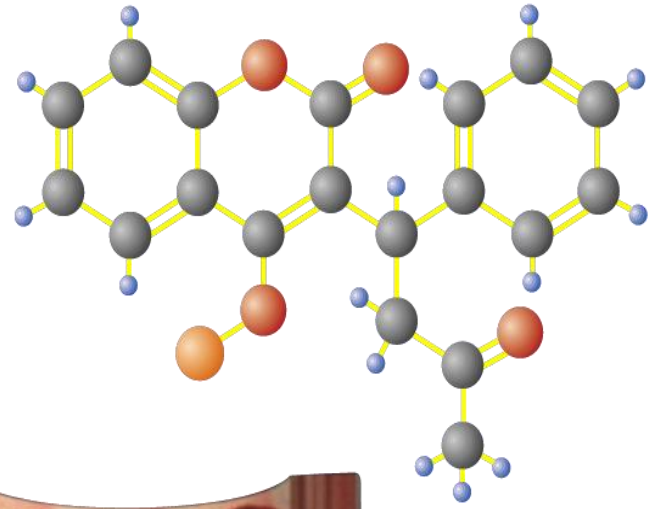
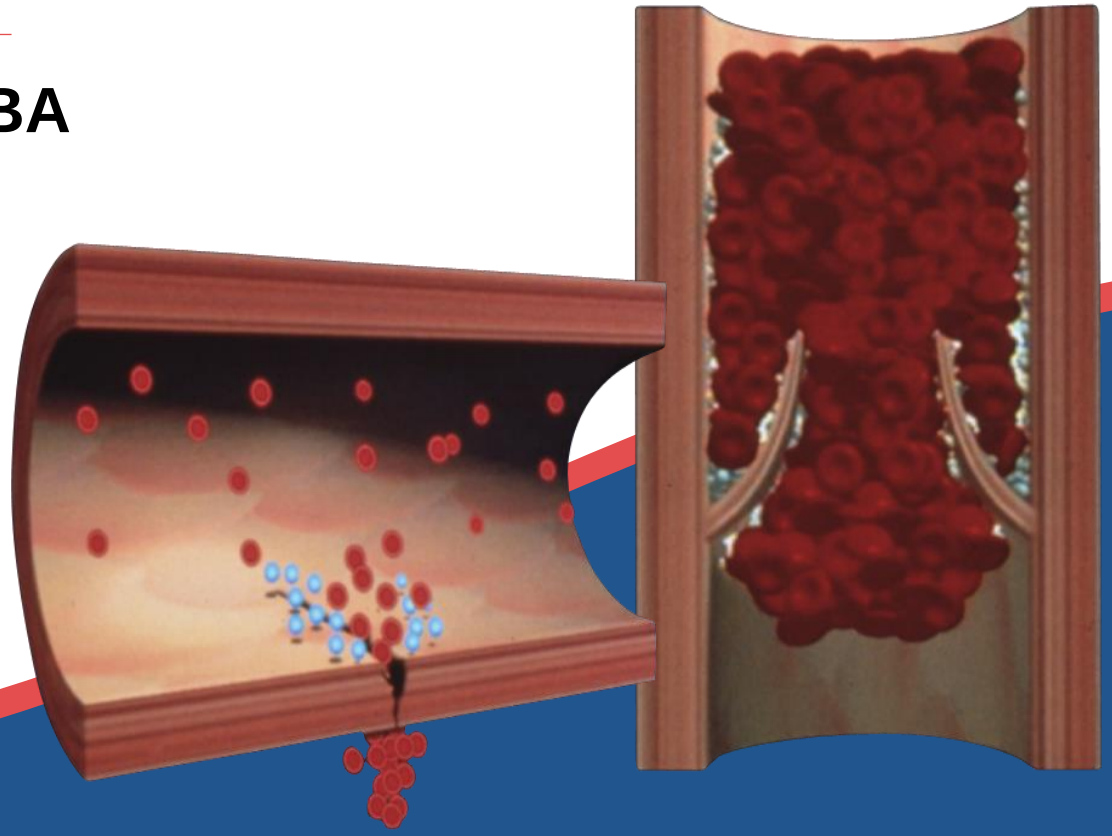
# Role of Warfarin in Patient Management: 2023 and Beyond

**Charles A Carter, PharmD, MBA**





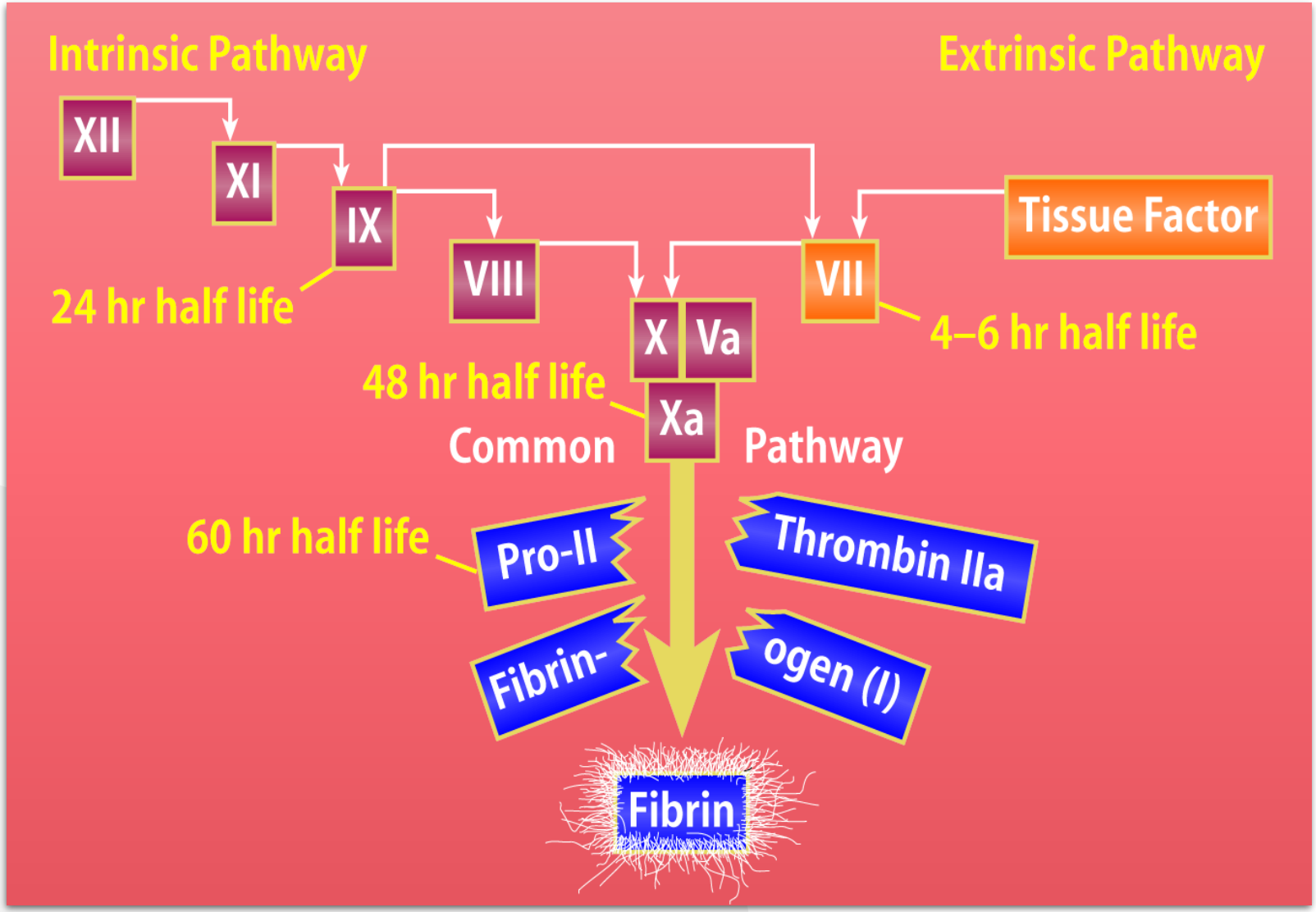
# History of Warfarin

- **Story of warfarin began on a winter day in the mid-1930s when a farmer showed presented at a lab at the University of Wisconsin in Madison**
  - “He apparently showed up in a blizzard, and he had this can of cow's blood with him," says Kevin Walters, a graduate student in history at the University of Wisconsin who has studied the warfarin story
  - The blood came from a cow that had eaten sweet clover hay that had some mold growing in it. The farmer said quite a few of his cows had eaten the moldy hay and had fallen ill with what became known as sweet clover disease
  - "The cows eat the hay, and a few days later, they die from bleeding internally, because their blood does not clot," said Walters

# History of Warfarin

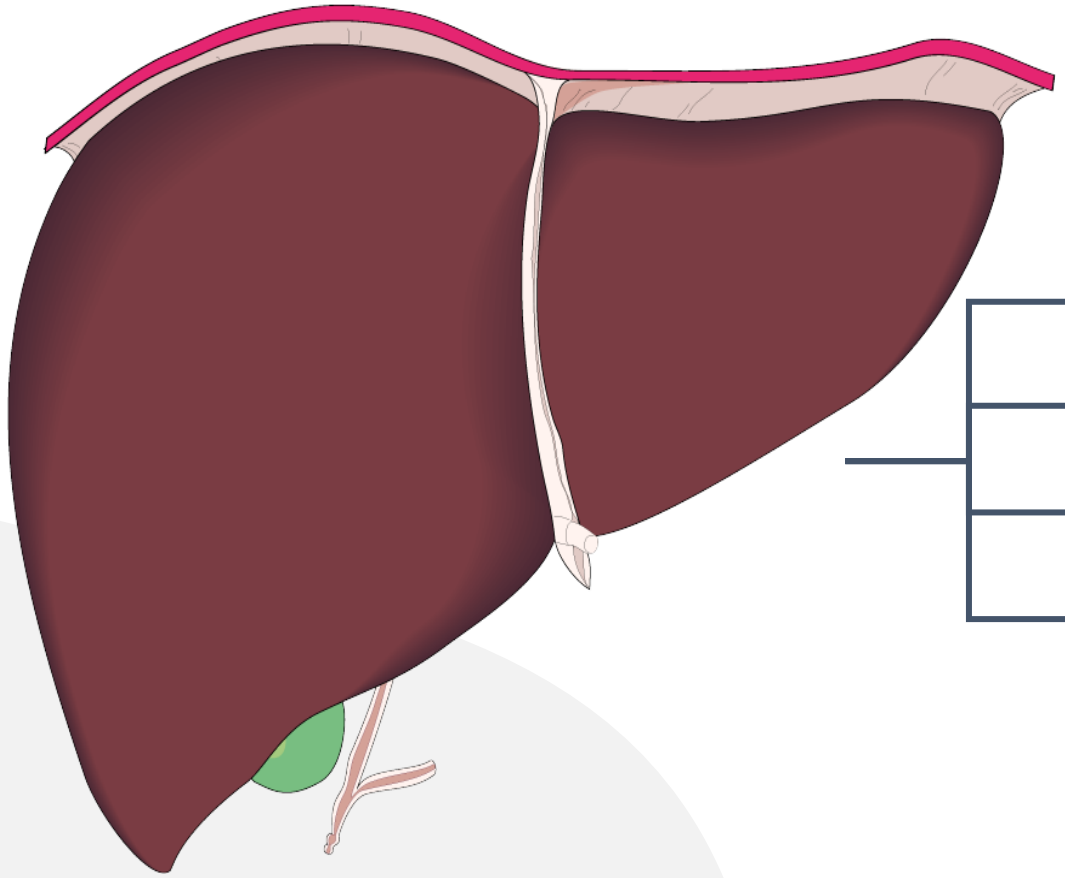
- **The laboratory belonged to a chemist named Karl Paul Link**
  - Link was intrigued by the farmer's problem and decided to try to figure what was happening
- **The name warfarin was coined by Link**
  - Mashup of **W**isconsin **A**lumni **R**esearch **F**oundation (**WARF**) and coum**arin**, the chemical found in sweet clove hay

# Clotting Cascade



# Vitamin K-Dependent Clotting Factors

Vitamin K



VII

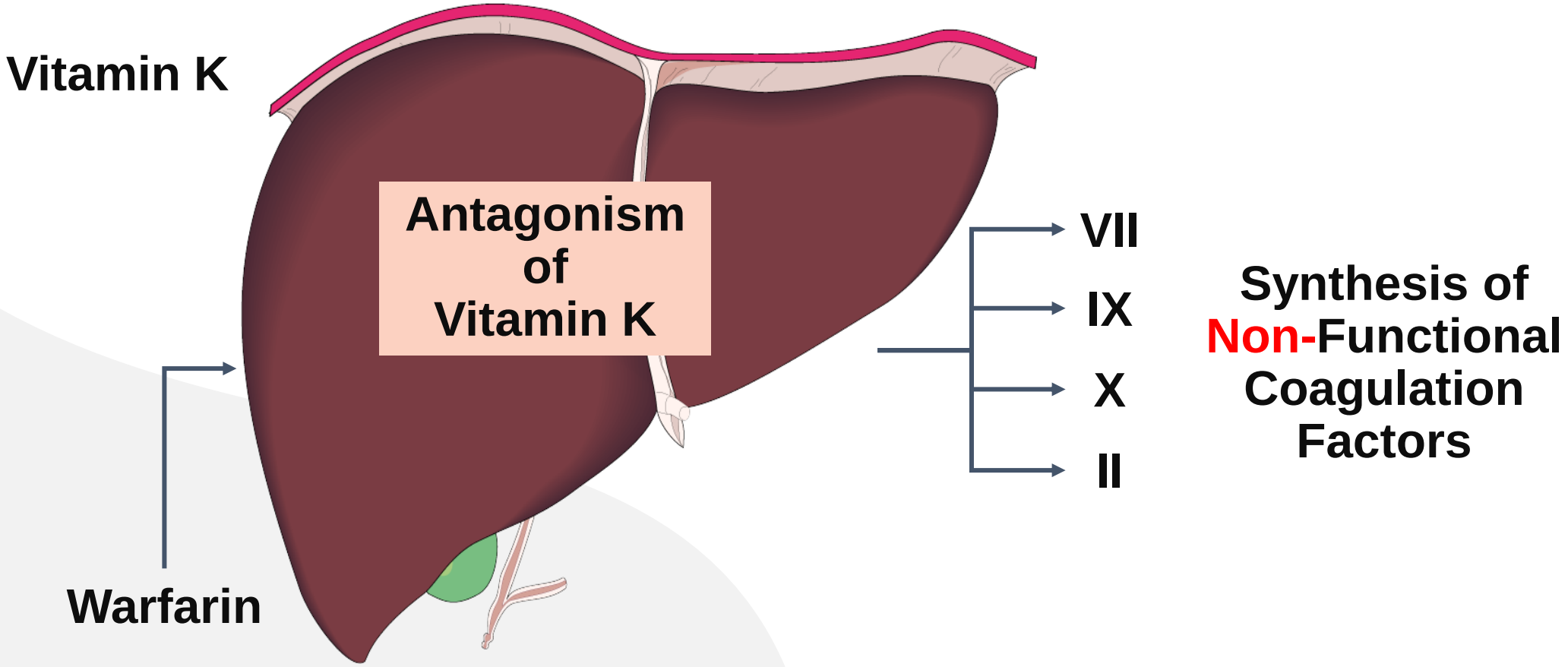
IX

X

II

Synthesis of Functional Coagulation Factors

# Vitamin K-Dependent Clotting Factors



# Antithrombotic Agents

- **Anticoagulants**
  - Prevent clot formation and extension
- **Antiplatelet drugs**
  - Interfere with platelet activity
- **Thrombolytic agents**
  - Dissolve existing thrombi

# Warfarin Indications

- **Prophylaxis and/or treatment**
  - Venous thrombosis and its extension
  - Pulmonary embolism
  - Thromboembolic complications associated with AF and cardiac valve replacement
- **Post MI to reduce the risk of death, recurrent MI, and thromboembolic events such as stroke or systemic embolization**
- **Prevention and treatment of cardiac embolism**

# Warfarin
# Major Adverse Effect – Hemorrhage

- **Significant consideration**
  - Benefit:Risk assessment
- **Factors that may influence bleeding risk**
  - Intensity of anticoagulation
  - Concomitant clinical disorders
  - Concomitant use of other medications
  - Quality of management

# Special Considerations in the Elderly

- ↑ age associated with ↑ sensitivity at usual doses
- Comorbidities
- ↑ drug interactions
- ↑ bleeding risk independent of the above

# Warfarin Dosing in Elderly Patients

| | Mean Warfarin Daily Dose (mg) | | | | |
|---|---|---|---|---|---|
| Patient Age | <50 | 50–59 | 60–69 | 70–79 | >80 |
| Gurwitz, et al [n=530] | 6.4 | 5.1 | 4.2 | 3.6 | ND |
| James, et al [n=2,305] | 6.1 | 5.3 | 4.3 | 3.9 | 3.5 |

**Increasing age has been associated with an increased response to the effects of warfarin**

Gurwitz JH, et al. Ann Int Med 1992; 116(11): 901-904.
James AH, et al. J Clin Path 1992; 45: 704-706.

# Prothrombin Time (PT)

- **Historically, a most reliable and “relied upon” clinical test**
- **However:**
  - Proliferation of thromboplastin reagents with widely varying sensitivities to reduced levels of vitamin K-dependent clotting factors has occurred
  - Concept of correct “intensity” of anticoagulant therapy has changed significantly (low intensity)
  - Problem addressed by use of INR (International Normalized Ratio)

# INR: International Normalized Ratio

- A mathematical “correction” (of the PT ratio) for differences in the sensitivity of thromboplastin reagents
- Relies upon “reference” thromboplastins with known sensitivity to antithrombotic effects of oral anticoagulants
- INR is the PT ratio one would have obtained if the “reference” thromboplastin had been used
- Allows for comparison of results between labs and standardizes reporting of the prothrombin time

J Clin Path 1985; 38:133-134; WHO Tech Rep Ser. #687 983.

# INR Equation

$$INR = \left( \frac{\text{Patient's PT in Seconds}}{\text{Mean Normal PT in Seconds}} \right)^{ISI}$$

INR = International Normalized Ratio
ISI = International Sensitivity Index

# Potential Problems with the INR

## Limitations

- Unreliable during induction
- Loss of accuracy with high ISI thromboplastins
- Incorrect ISI assignment by manufacturer
- Incorrect calculation of INR due to failure to use proper mean normal plasma value to derive PT ratio

## Solutions

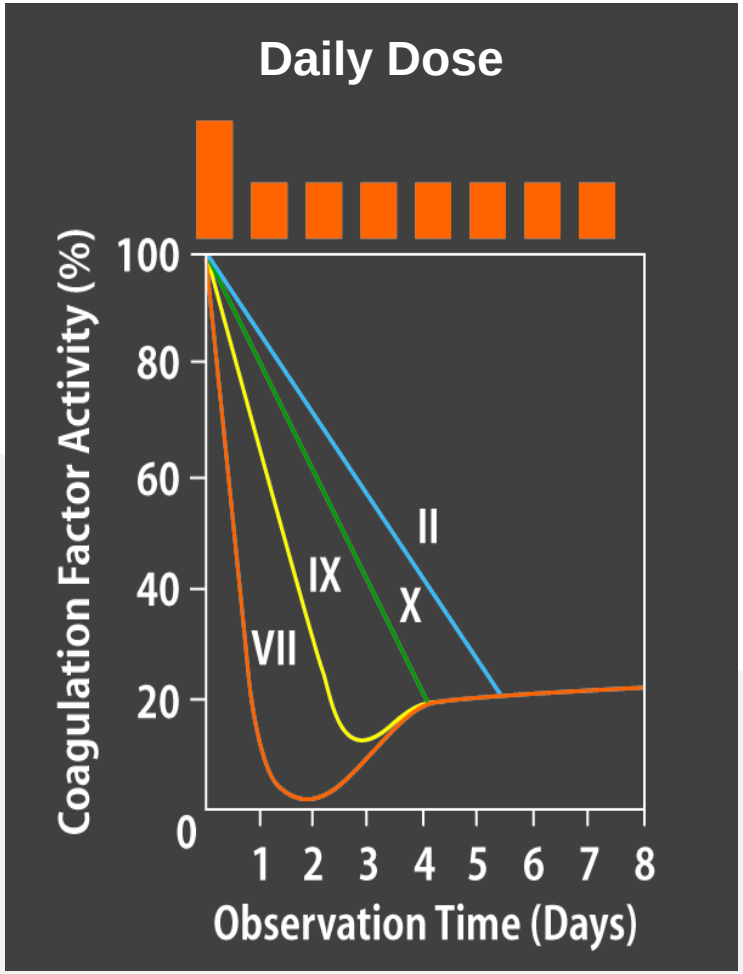
- Use thromboplastin reagents with low ISI values (<1.5)
- Use thromboplastin reagents with low ISI values and use plasma calibrants with certified INR values
- Use “mean normal” PT derived from normal plasma samples for every new batch of thromboplastin reagent

# Warfarin: Dosing Information

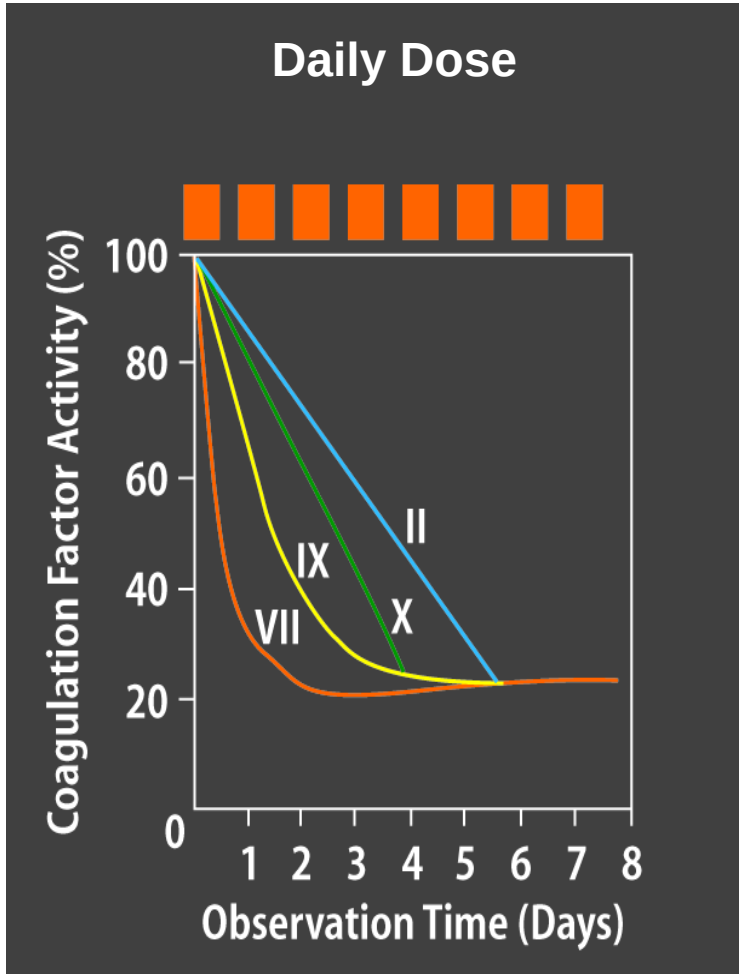
- **Individualize dose according to patient response (as indicated by INR)**
- **Use of large loading dose not recommended***
  - May increase hemorrhagic complications
  - Does not offer more rapid protection
- **Low initiation doses are recommended for elderly, frail, liver-diseased, or malnourished patients**

*Harrison L, et al. Ann Intern Med 1997;126:133-136.

## Loading Dose then Maintenance Dose




## Maintenance Dose Only



# Conversion from Heparin/LMWH to Warfarin

- **Should begin concomitantly with heparin/LMWH therapy for management of VTE**
- **Heparin/LMWH should be continued for a minimum of FIVE days and until the INR has been therapeutic for at least 24 hours**

# Warfarin: Dosing & Monitoring

- **Start low**
  - Initiate 5 mg daily*
  - Educate patient
- **Stabilize**
  - Titrate to appropriate INR
  - Monitor INR frequently (daily then weekly)
- **Adjust as necessary**
- **Monitor INR regularly (every 1–4 weeks) and adjust**

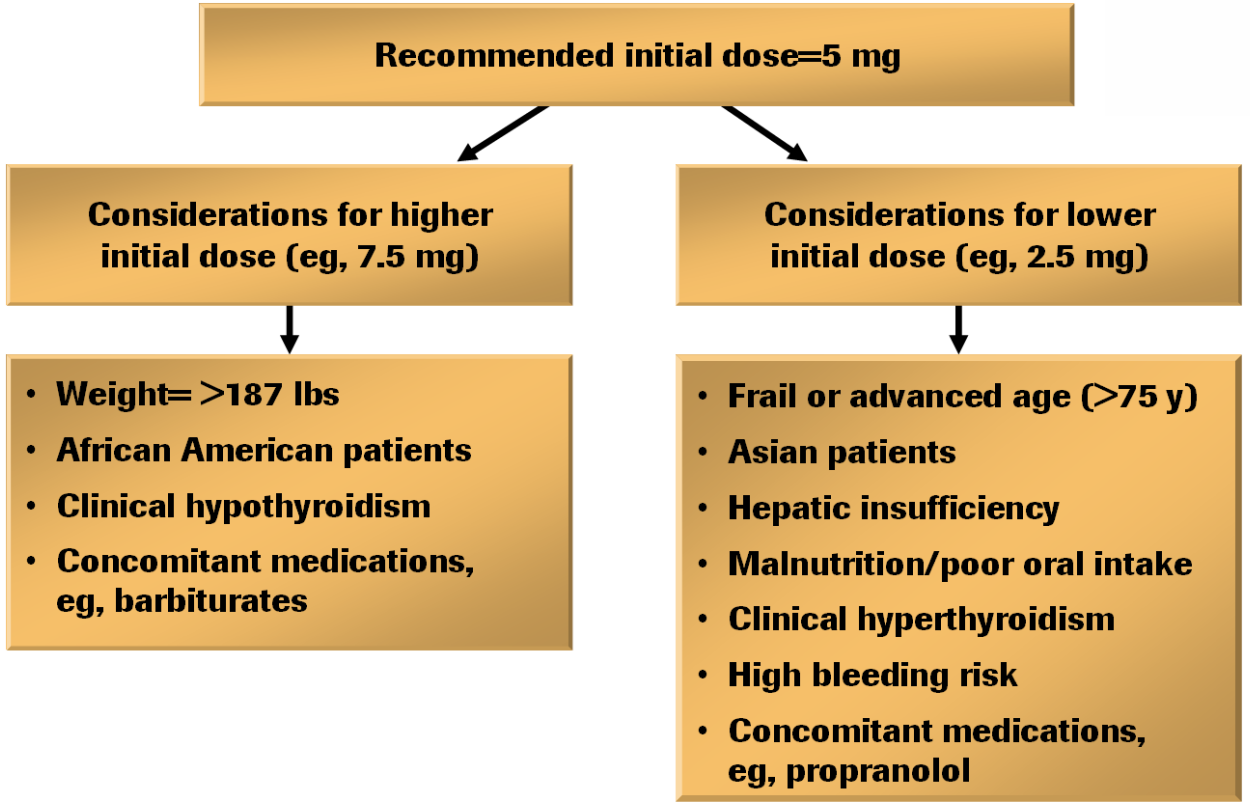
*** Elderly, frail, liver disease, malnourished: 2 mg/day**

# Recommendations for Warfarin Initiation

## Criteria for Initiating Warfarin Therapy[1-3]

Roche Diagnostics

***Recommendations Differ Based on Individual Patients***

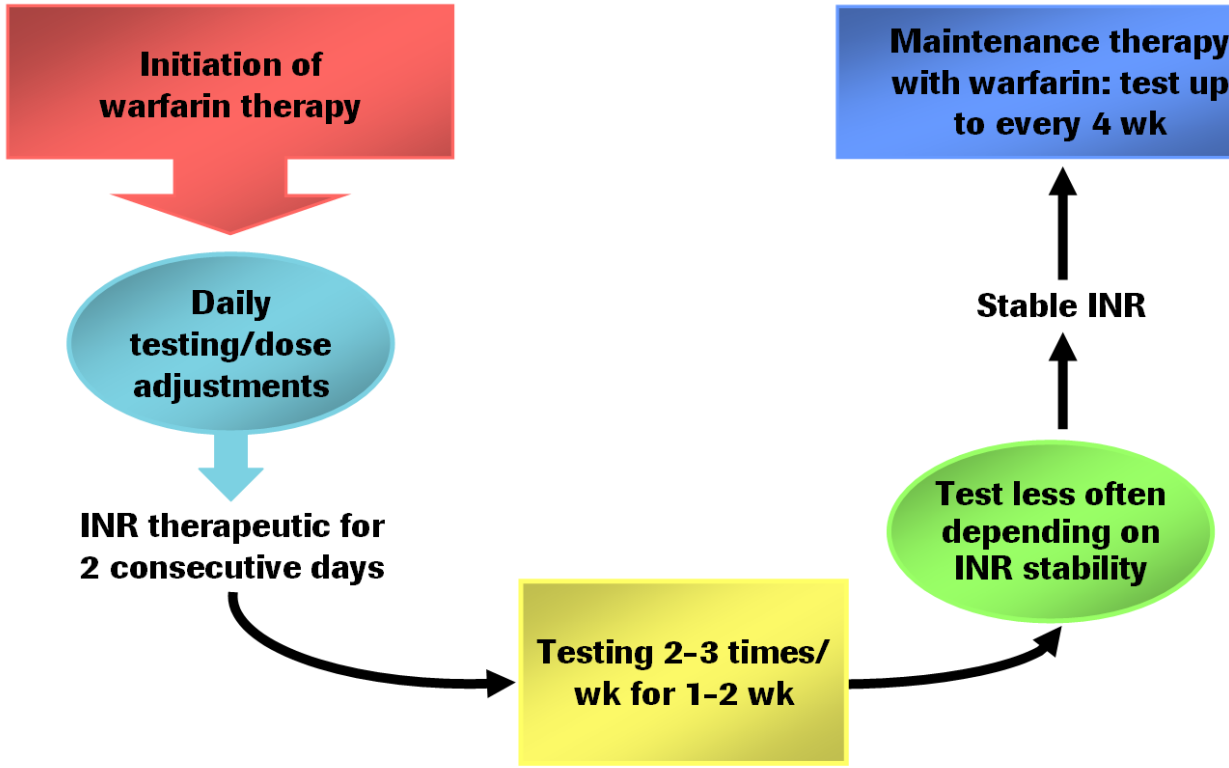



1. Horton JD, Bushwick BM. *Am Fam Physician.* 1999;59:1-24. 2. Kayser SR. *Prog Cardiovasc Nurs.* 2005;20:80-85.
3. Ansell J et al. *Chest.* 2004;126:204S-233S.

# Recommendations for Warfarin Initiation

## International Normalized Ratio (INR) Testing Frequency[1]

***Create Stability of INR with Proper Warfarin Management***




1. Horton JD, Bushwick BM. *Am Fam Physician*. 1999;59:1-24.

# Warfarin Dosing Schedule

| Mon | Tue | Wed | Thu | Fri | Sat | Sun | Total Weekly Dose |
|---|---|---|---|---|---|---|---|
| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 35 mg |
| 2.5 | 5 | 5 | 2.5 | 5 | 5 | 5 | 30 mg |
| 2.5 | 5 | 2.5 | 5 | 2.5 | 5 | 5 | 27.5 mg |

# Dosage Adjustment Algorithm

| | | Current Daily Dose (mg) | | | | |
|---|---|---|---|---|---|---|
| | | 2.0 | 5.0 | 7.5 | 10.0 | 12.5 |
| **INR** | **Warfarin Dose Adjustment*** | **Adjusted Daily Dose (mg)** | | | | |
| 1.0-2.0 | Increase x 2 days | 5.0 | 7.5 | 10.0 | 12.5 | 15.0 |
| 2.0-3.0 | No change | — | — | — | — | — |
| 3.0-6.0 | Decrease x 2 days | 1.25 | 2.5 | 5.0 | 7.5 | 10.0 |
| 6.0-10.0† | Decrease x 2 days | 0 | 1.25 | 2.5 | 5.0 | 7.5 |
| 10.0-18.0§ | Decrease x 2 days | 0 | 0 | 0 | 0 | 2.5 |
| >18.0§ | Discontinue warfarin and consider hospitalization/reversal | | | | | |

† Consider oral vitamin K, 2.5–5 mg
§ Oral vitamin K, 2.5–5 mg
* Allow 2 days after dosage change for clotting factor equilibration. Repeat prothrombin time 2 days after increasing or decreasing warfarin dosage and use new guide to management (INR = International Normalized Ratio). After increase or decrease of dose for two days, go to new higher (or lower) dosage level (e.g., if 5.0 qd, alternate 5.0/7.5; if alternate 2.5/5.0, increase to 5.0 qd).

# Warfarin: Current Indications/Intensity

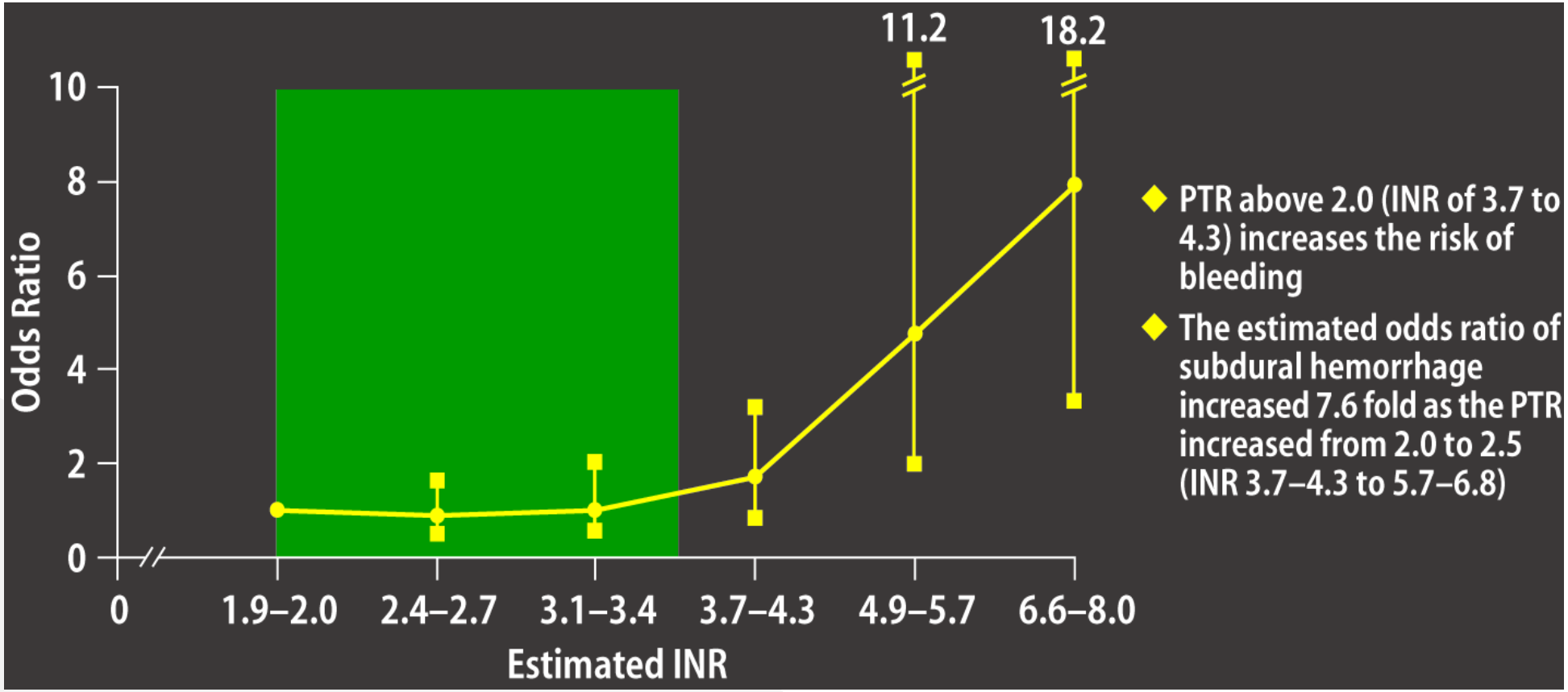
| Indication | INR Range | Target |
|---|---|---|
| Prophylaxis of venous thrombosis (high-risk surgery)<br>Treatment of venous thrombosis<br>Treatment of PE<br>Prevention of systemic embolism<br>Tissue heart valves<br>AMI (to prevent systemic embolism)<br>Valvular heart disease<br>Atrial fibrillation | 2.0–3.0 | 2.5 |
| Mechanical prosthetic valves (high risk)<br>Patients w/thrombosis & antiphospholipid syndrome<br>AMI (prevent recurrent AMI) | 2.5–3.5 | 3.0 |
| Bileaflet mechanical valve in aortic position, NSR | 2.0–3.0 | 2.5 |

# Relationship Between INR and Efficacy/Safety

- **Low-intensity treatment:**
  - Efficacy rapidly diminishes below INR 2.0*
  - No efficacy below INR 1.5
- **High-intensity treatment:**
  - Safety compromised above INR 4

* Effective below 2.5

# Risk of Intracranial Hemorrhage in Outpatients




**An intensity of anticoagulation expressed as a prothrombin time ratio (PTR) above 2.0 (roughly corresponding to an INR of 3.7 to 4.3) resulted in an increase in the risk of bleeding**



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

# Relative Contraindications to Warfarin Therapy

- **Pregnancy**
- **Situations where the risk of hemorrhage is greater than the potential clinical benefits of therapy**
  - Uncontrolled alcohol/drug abuse
  - Unsupervised dementia/psychosis

# Signs of Warfarin Overdosage

- **Blood in stools or urine**
- **Excessive menstrual bleeding**
- **Bruising**
- **Excessive nose bleeds/bleeding gums**
- **Persistent oozing from superficial injuries**
- **Bleeding from tumor, ulcer, or another lesion**

# Dosage Adjustments based on INRs

## Management of Elevated International Normalized Ratios (INRs) for Patients Without Significant Bleeding[1]

### *Dosing Adjustments for Increased INR*

| INR | Intervention |
|---|---|
| **Supratherapeutic but <5.0** | • Reduce or omit dose of warfarin<br>• Check INR in 3-7 d<br>• Resume at same or lower dose when INR within range |
| **5.0–9.0** | • Omit next 1 or 2 doses<br>• Check INR every 24-48 h<br>• Resume at lower dose when INR within range<br>• Consider 1-4 mg of oral vitamin K |
| **>9.0** | • Omit warfarin<br>• Give ~5 mg of oral vitamin K<br>• Check INR in 12-24 h<br>• If still >9.0, repeat vitamin K<br>• Check INR in 24 h<br>• Resume at lower dose when INR within range<br>• If high risk of bleeding, may consider fresh frozen plasma |

1. Ansell J et al. *Chest.* 2004;126:204S-233S.

Roche Diagnostics

# Drug Interactions with Warfarin: Potentiation

| Level of Evidence | Potentiation |
|---|---|
| I | Alcohol (if concomitant liver disease) amiodarone (anabolic steroids, cimetidine,† clofibrate, cotrimoxazole, erythromycin, fluconazole, isoniazid [600 mg daily] metronidazole), miconazole, omeprazole, phenylbutazone, piroxicam, propafenone, propranolol,† sulfinpyrazone (biphasic with later inhibition) |
| II | Acetaminophen , chloral hydrate , ciprofloxacin, dextropropoxyphene, disulfiram, itraconazole, quinidine, phenytoin (biphasic with later inhibition), tamoxifen, tetracycline, flu vaccine |
| III | Acetylsalicylic acid, disopyramide, fluorouracil, ifosflhamide, ketoprofen, iovastatin, metozalone, moricizine, nalidixic acid, norfloxacin, ofloxacin, propoxyphene, sulindac, tolmetin, topical salicylates |
| IV | Cefamandole, cefazolin, gemfibrozil, heparin, indomethacin, sulfisoxazole |

†In a small number of volunteer subjects, an inhibitory drug interaction occurred.

# Drug Interactions with Warfarin: Inhibition

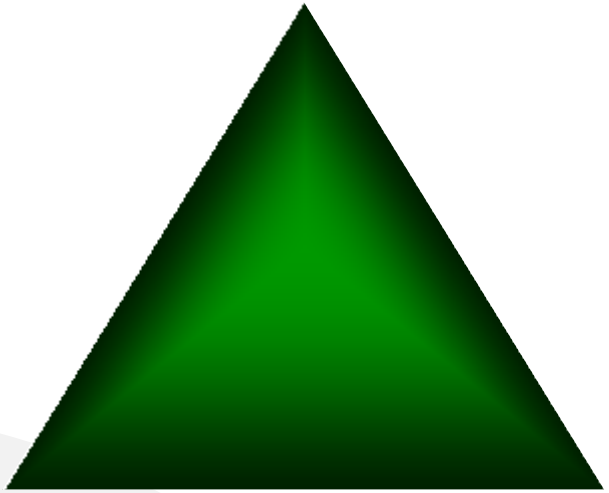
| Level of Evidence | Inhibition |
|---|---|
| I | Barbiturates, carbamazepine, chlordiazepoxide, cholestyramine, griseofulvin, nafcillin, rifampin, sucralfate |
| III | Dicloxacillin |
| IV | Azathioprine, cyclosporine, etretinate, trazodone |

# Effective Patient Education and Re-education Required

- Teach basic concepts of safe, effective anticoagulation
- Discuss importance of regular INR monitoring
- Counsel on use of other medications, alcohol
- Develop creative strategies for improving compliance
- Appreciate the need for re-education

# Factors Influencing Variability

**Patient / Disease State**



**Process of Care**

**Narrow Therapeutic Index**

# Future of Warfarin

- **Significantly less use since the introduction of DOAC's**
- **Less than optimal than DOACs in most patients secondary to limitations**
  - Bleeding risks
  - Monitoring requirements
  - Variances in dosing requirements
  - Interactions with drugs and food
  - Total care costs
- **Time tested and provider experience**
- **Patient equity in care**
- **"…we will always have warfarin" until we can teach the DOACs to do a better job in mechanical prosthetic heart valves and in the antiphospholipid syndrome**

# Thank you
# Questions

I would like to thank GTF for the opportunity to participate in this symposium

Special appreciation to Dr. James B Groce for assistance in preparing this presentation

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