



# THE INTERNET STROKE CENTER

PRESENTATIONS AND DISCUSSIONS ON STROKE MANAGEMENT

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## Antithrombotic Therapy & Stroke Prophylaxis



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## Anticoagulants for Stroke Prophylaxis

### Anticoagulants for Stroke Prophylaxis

- Anticoagulants
  - Warfarin (Coumadin)
  - Heparin, low-molecular-weight heparin, and heparinoids,
- 2° Prevention
  - After a prior cardioembolic stroke
  - After other ischemic strokes??
- 1° Prevention
  - Atrial fibrillation (Afib)
  - Prosthetic valves
  - Anterior myocardial infarction (MI)

# Warfarin

**Warfarin**

Wisconsin  
Alumni  
Research  
Foundation  
+  
coumARIN  
= WARFARIN

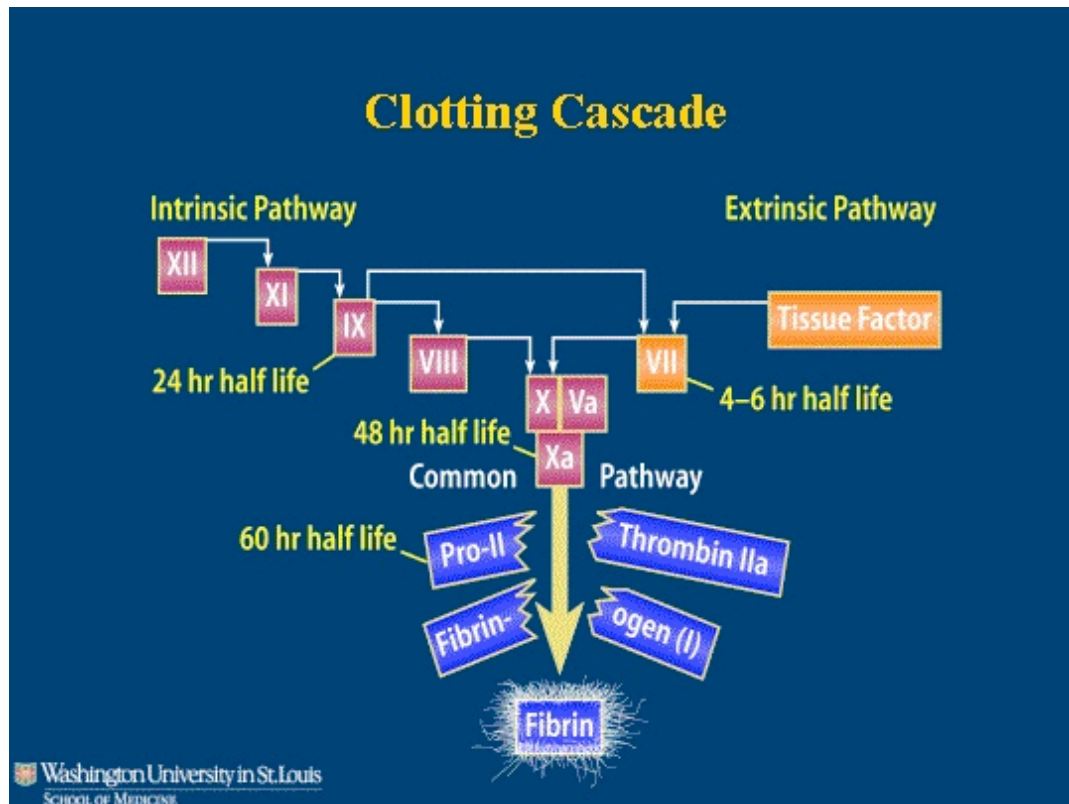
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## Notes:

For more information about warfarin therapy please see:

Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. Am J Med 2000;109:481-488.

# Clotting Cascade



## Notes:

The blood coagulation process can be activated by one of two pathways, the tissue Factor pathway (formerly known as the extrinsic pathway) and the contact activation pathway (known as the intrinsic pathway).

Tissue Factor binds to and activates Factor VII and the Tissue Factor/VIIa complex then activates Factor X and Factor IX to Xa and Ixa respectively. Factor X can also be converted to Xa by Ixa (in the presence of Factor VIII)

The intrinsic pathway is activated when Factor XII comes in contact with a foreign surface. The resulting Factor XIIa then activates Factor XI, which in turn activates Factor IX. Factor Ixa then activates Factor X.

Thus Factor Xa can be generated by activation of the tissue factor or contact activation pathways. Factor Xa then cleaves prothrombin and the resulting thrombin converts fibrinogen to fibrin. Four of these clotting factors (Factors IX, VII, X and prothrombin) are Vitamin K dependent and therefore their

activity is decreased by the Vitamin K antagonist, warfarin. The half-lives of these four Vitamin K dependent clotting factors are shown on this slide.

Factor VII has the shortest half life of the Vitamin K dependent coagulation factors. However, for adequate anticoagulation one needs to reduce the other coagulation factors appropriately, including Factor II (prothrombin) which has a 60 hour half life. It takes several days after initiation of warfarin therapy to reduce Factor II and thus warfarin and heparin need to overlap for approximately 4–5 days when starting therapy.

## Risk Factors for Hemorrhage During Warfarin Therapy

### Risk Factors for Hemorrhage During Warfarin Therapy

- H/o GI bleed
- H/o CNS event (ischemic or hemorrhagic stroke)
- Liver disease
- Renal disease
- Alcohol bingeing
- Recent warfarin initiation
- ? Advanced Age
- ? Use of protime ratio instead of INR

#### Notes:

According to new study by the Mayo Clinic, malignancy was also a risk factor for xs hemorrhage (and for T-E event).

## Relationship of Protime Ratio to International Normalized Ratio (INR)

**Relationship of Protime Ratio to  
International Normalized Ratio (INR)**

$$\text{INR} = \left( \frac{\text{Patient's Protime}}{\text{Control Protime}} \right)^{\text{ISI}}$$

**ISI is the International  
Sensitivity Index**

**E.g. PT Ratio of 1.6 with  
an ISI of 2 equals an INR of  
2.6**

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### Notes:

Although the INR is not perfect, it overcomes the different sensitivities inherent to different thromboplastins.

This heterogeneity arises because thromboplastin is made from biological tissue, esp. rabbit brains.

If I had to guess, I'd say that the type A rabbits, probably accelerate the coagulation cascade, and the type B rabbits probably take their time—maybe taking in a Bugs Bunny movie or something, before clotting.

How people practice at labs that report only the INR? the PTR? both?

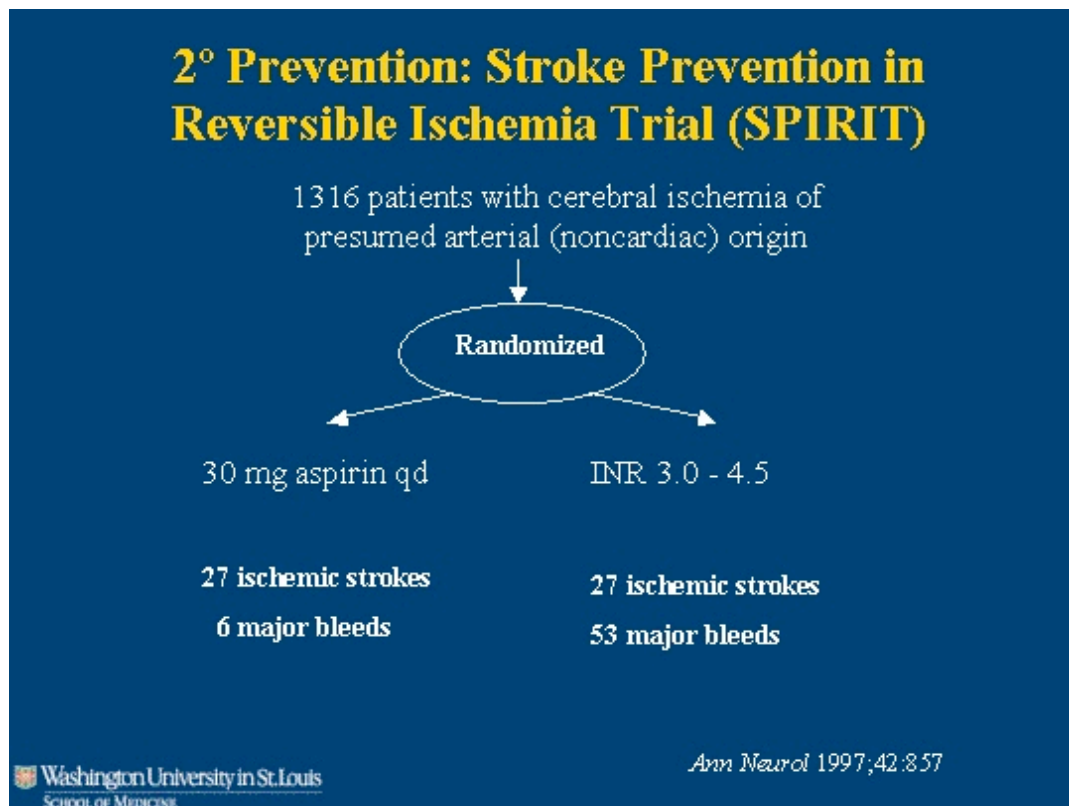
Relying on the PT Ratio is sort of like preparing your handouts with a mimeograph machine—dated and imprecise.

## 2° Prevention: After a Prior Cardio-Embolic Stroke

### 2° Prevention: After a prior cardioembolic stroke

- atrial fibrillation (Afib)
  - mechanical prosthetic valves\*
  - recent myocardial infarction\*
  - left ventricular thrombus\*
  - dilated cardiomyopathy\*
  - mitral stenosis\*
  - marantic endocarditis\*
  - patent foramen ovale\*
- \* No randomized, controlled trials in these populations.

## 2° Prevention: Stroke Prevention in Reversible Ischemia Trial (SPIRIT)



### Notes:

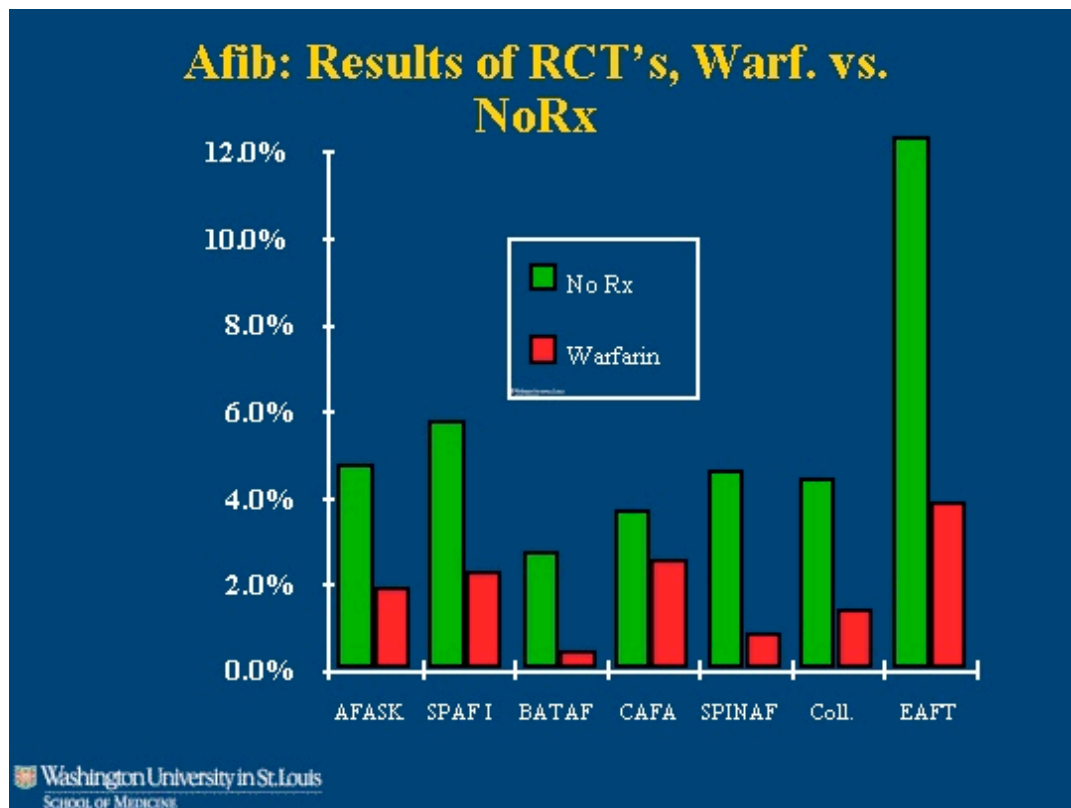
Excluded pts. w/ high-grade carotid artery stenosis.

An ongoing trial, the Warfarin Aspirin Recurrent Stroke Study (WARSS) is comparing a lower target INR (1.4 - 2.8) to 325 mg ASA in a similar population.

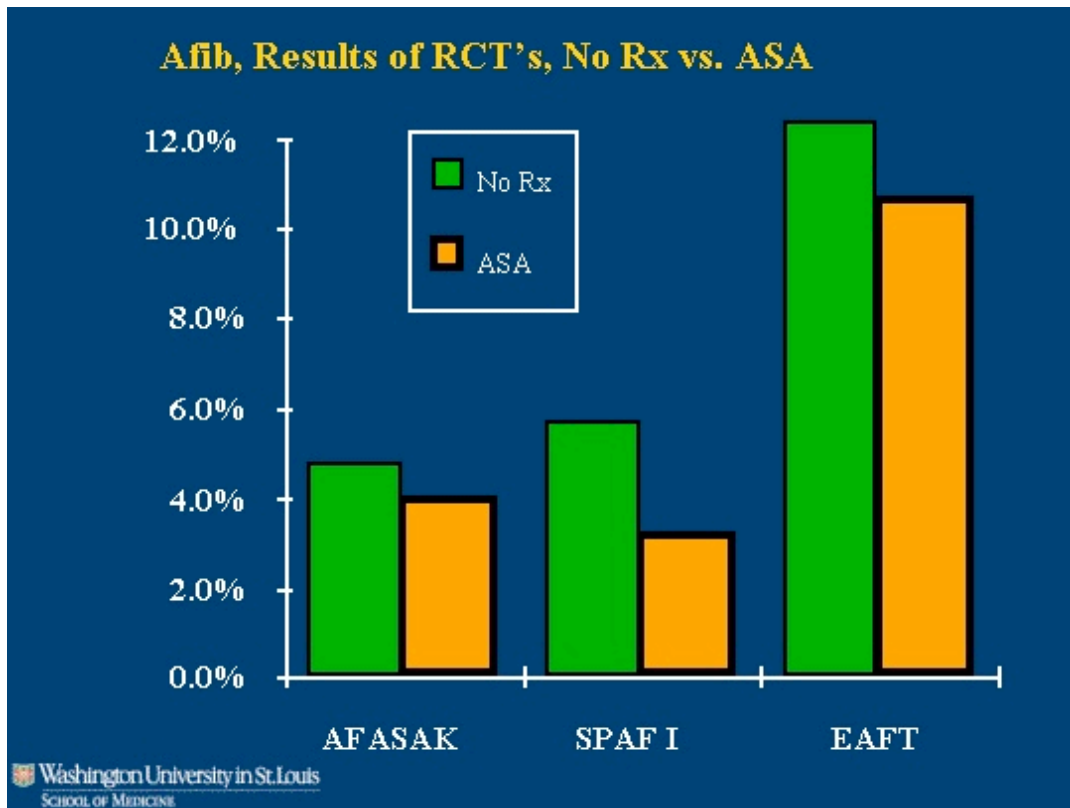
A second ongoing trial, Stroke Prevention with Warfarin and Aspirin Trial (SWAT) by A. Shuaib is comparing 1300 mg ASA vs. 80 mg ASA + INR 2-3.

There may also be a 3rd trial, similar to SPIRIT, in Europe & Australia.

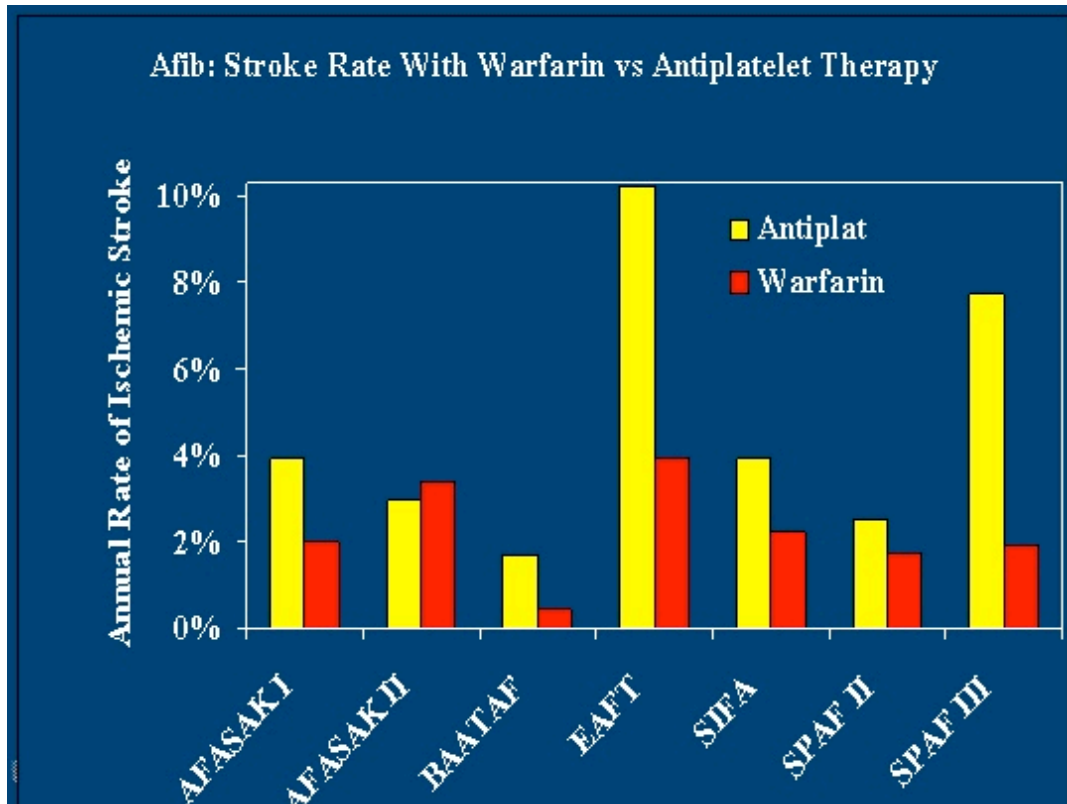
## Atrial Fibrillation: Results of RCT's, Warf. vs. No Rx



## Atrial Fibrillation: Results of RCT's, No Rx vs. ASA



## Atrial Fibrillation: Stroke Rate with Warfarin and Antiplatelet Therapy



### Reference:

Gage BF, Lin T. Antithrombotic Therapy and Atrial Fibrillation, book chapter to appear in Prevention and Treatment of Thrombosis: Issues for the Primary Care Physician, in press. Edited by Merli G, Spandorfer J, Konkle B.

## Atrial Fibrillation: Findings of RCTs

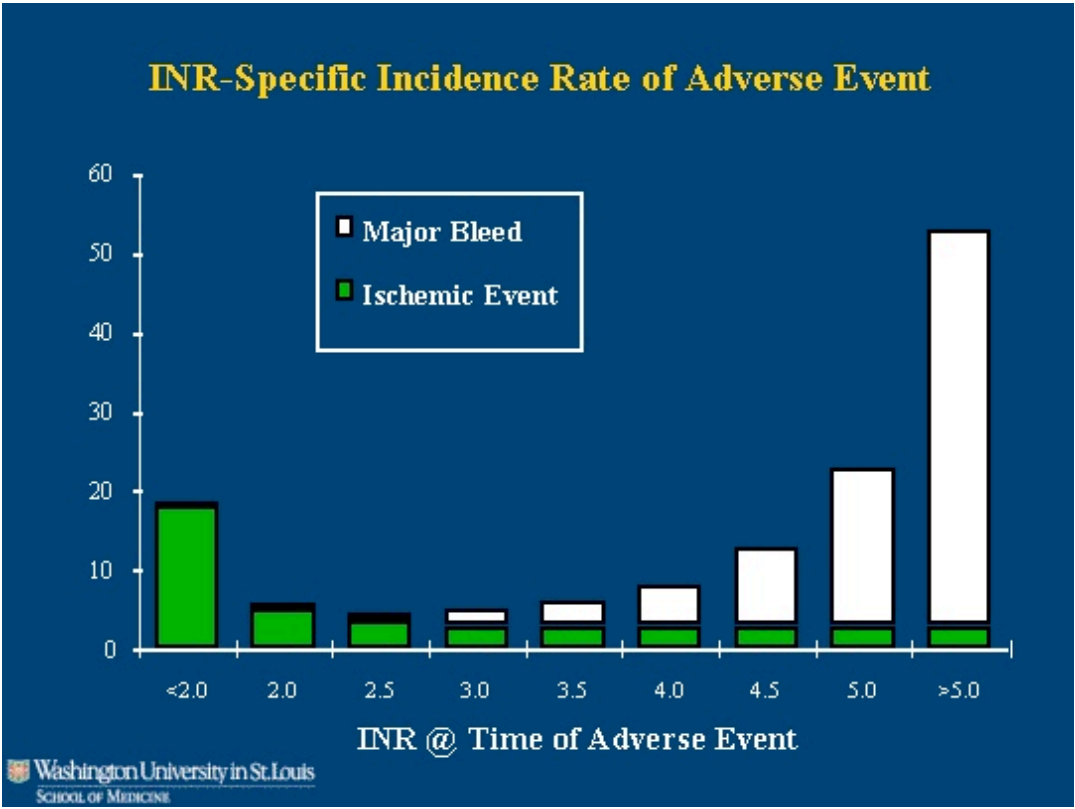
### Atrial Fibrillation: Findings of RCTs

- **Warfarin**
  - Reduces the rate of ischemic stroke by 62%.
  - Major hemorrhage rate of 1.4%.
- **ASA**
  - Reduces the rate of stroke by 22%.
  - Major hemorrhage rate of 0.9%.
- **Stroke rate depends on comorbid conditions:**
  - Low risk: 1 - 2%
  - Medium risk: 3 - 4%
  - High risk: 5 - 6%
  - 2<sup>o</sup> Prevention: 6 -18%

#### Reference:

Hart RG et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. Ann Intern Med 1999;131:492-501

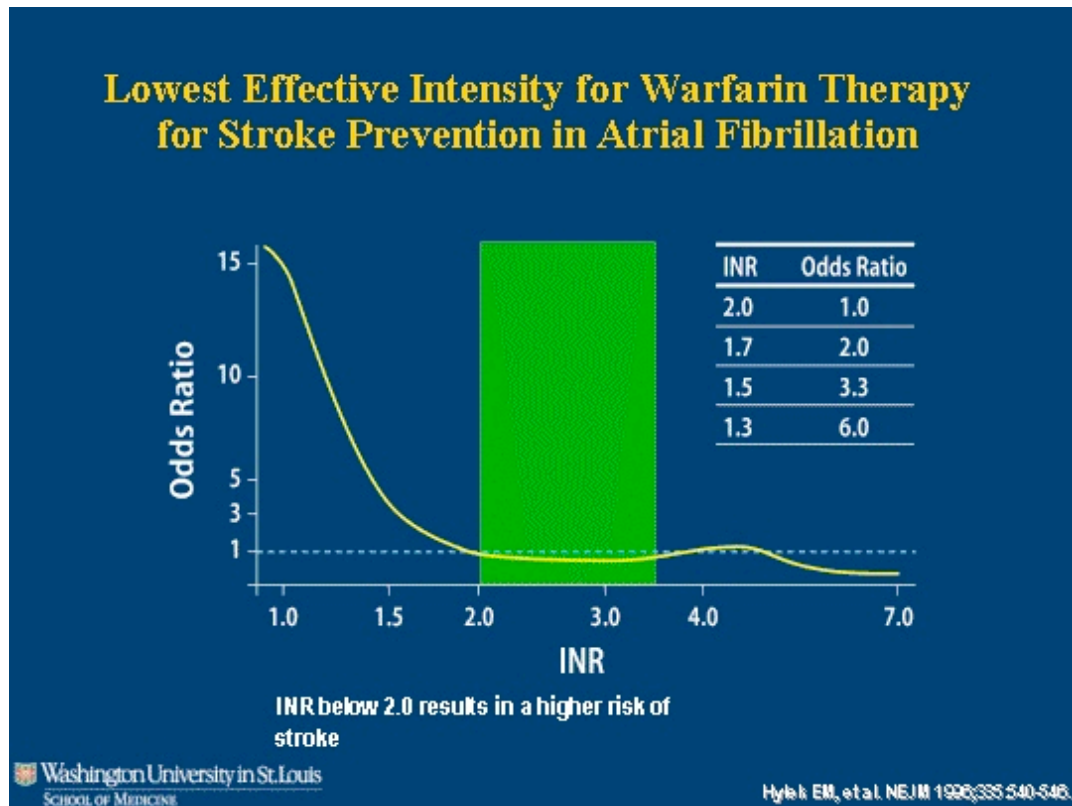
# INR-Specific Incidence Rate of Adverse Event



**Reference:**

The European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. N Engl J Med 1995;333:5-10.

## Lowest Effective Intensity for Warfarin Therapy for Stroke Prevention in Atrial Fibrillation



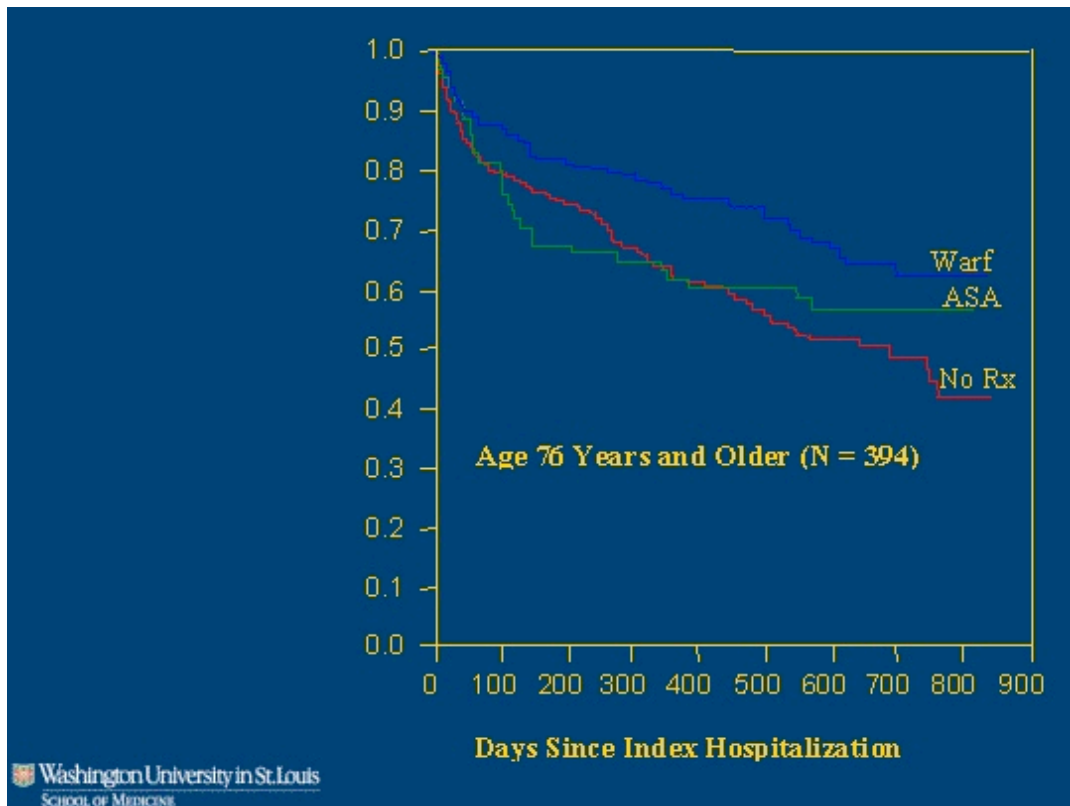
### Reference:

The European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. *N Engl J Med* 1995;333:5-10.

### Notes:

The relationship between the risk of stroke and INR in patients with atrial fibrillation treated with warfarin is shown on this slide. The risk of stroke increases dramatically when the INR falls below 2.0, although there appears to be some protection when the INR is above 1.5.

## Days Since Index Hospitalization



### Reference:

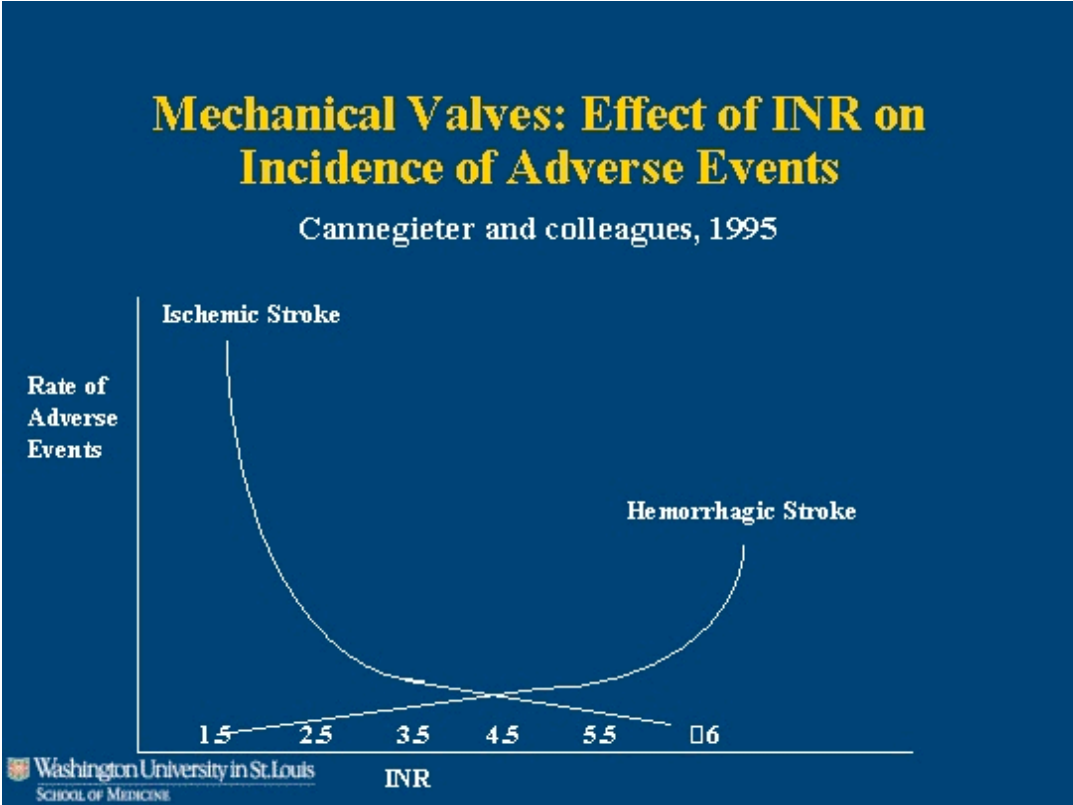
Gage BF et al. Adverse outcomes and predictors of underuse of antithrombotic therapy in Medicare beneficiaries with chronic atrial fibrillation. *Stroke* 2000;31:822-7.

## Recommendations for Atrial Fibrillation

### Recommendations for Afib

- **2° Prevention INR 2.0–3.5**
- **1° Prevention warfarin, INR 2.0–3.0**
  - » Exceptions: high risk of bleeding, low quality of life if taking warfarin, or lone Afib.
- **Patients with Afib who cannot take warfarin should receive aspirin.**

# Mechanical Valves: Effect of INR on Incidence of Adverse Events

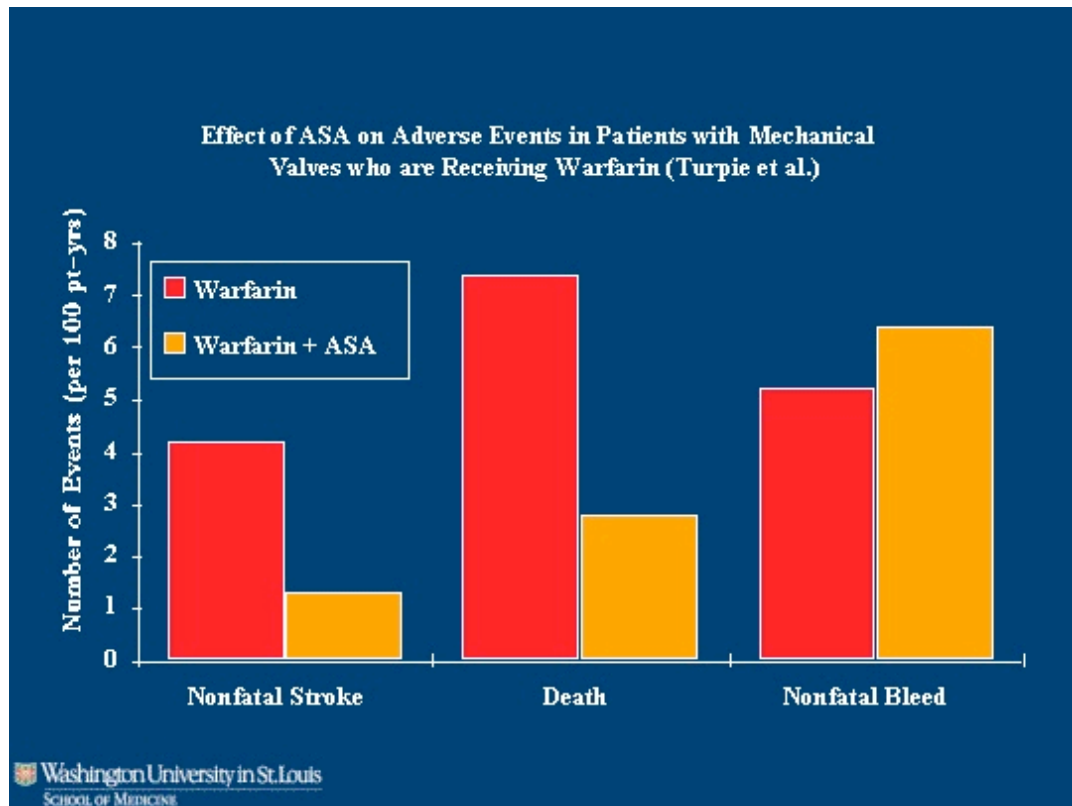


**Notes:**

The optimal tradeoff between risk of hemorrhage and risk of thrombosis appears to be higher than the currently recommended level of anticoagulation of 2.5–3.5. Cannegieter and colleagues recommend a target INR of 3–4.

Would you continue to treat this patient with warfarin alone or also add ASA?

## Effect of ASA on Adverse Events in Patients with Mechanical Valves who are Receiving Warfarin



### Notes:

The rate of major bleeding (excluding ICHs) rose only from 5.2% to 6.4%.

Thus, for every 100 patients like mine whom we add ASA to, we expect to prevent 3 nonfatal strokes, 5 deaths and cause only 1 major nonfatal bleed!

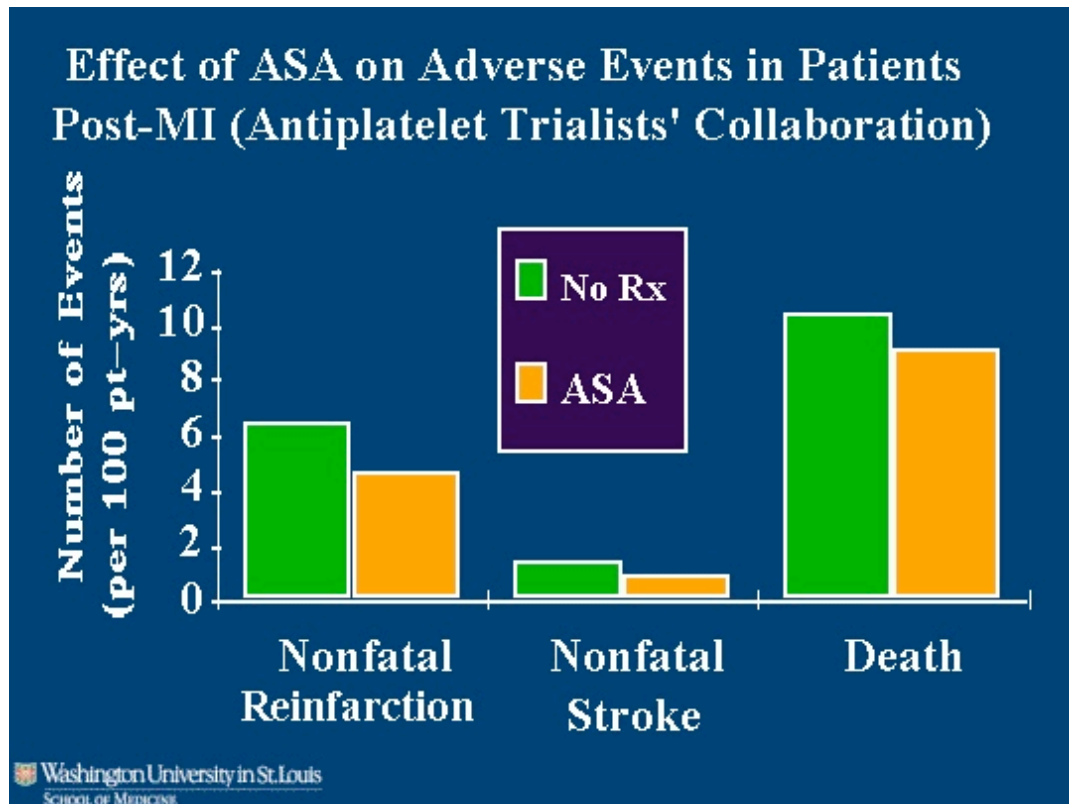
See also: Laffort P. et al. Early and long-term (one-year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St. Jude medical prosthesis: a clinical and transesophageal echocardiographic study. *J Am Coll Cardiol* 2000;35:739-46.

## Recommendations for Mechanical Valves

### Recommendations for Mechanical Valves

- All patients should receive warfarin.
- INR target is usually 3.0 (range 2.5–3.5)
  - Exception: Use 2.5 (range 2.0 – 3.0) for Aortic St. Jude valve.
- Consider increasing the target INR or adding low-dose ASA for anyone of the following:
  - prior ischemic event
  - Afib or prosthetic valve in the mitral position
  - older-model valves (e.g. caged-ball valves)
  - significant CAD
  - other patients at low-risk of hemorrhage.

## Effect of ASA on Adverse Events in Patients Post-MI (Antiplatelet Trialists' Collaboration)

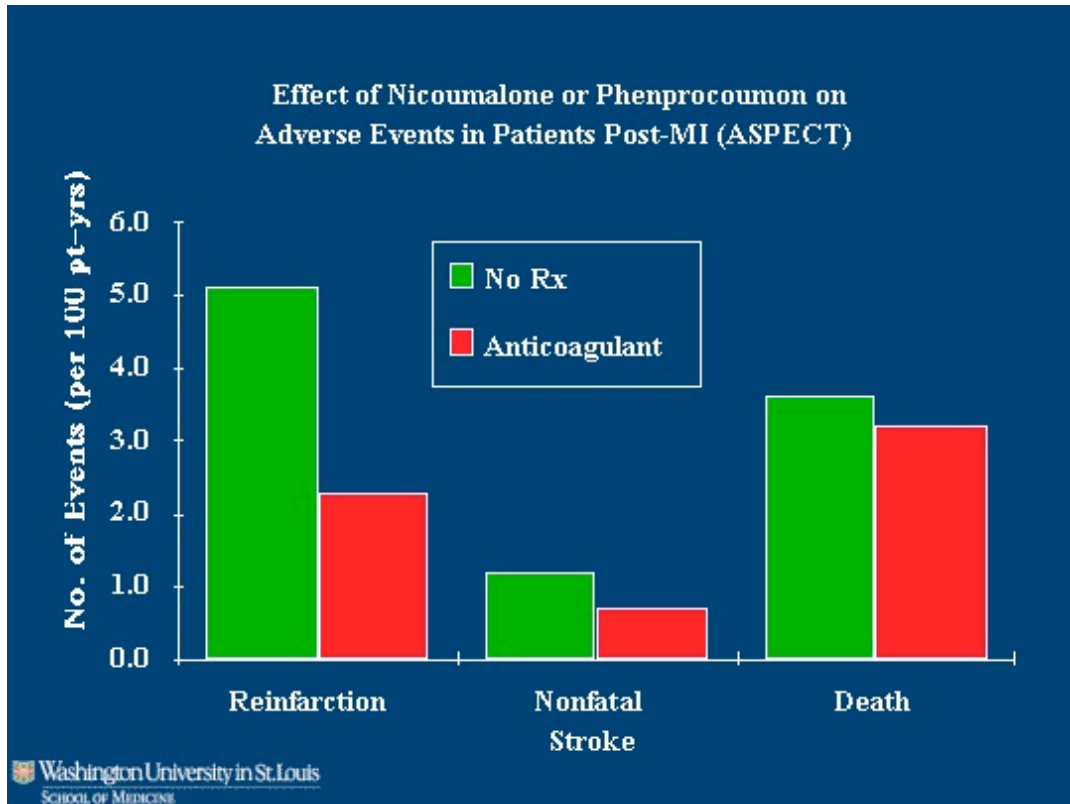


### Notes:

Antiplatelet Trialists' Collaboration:

- Nonfatal reinfarction: reduced by 31% for prior MI, 54% for acute MI
- Nonfatal stroke: reduced by 39%
- Death: reduced by 12% for prior MI, 23% for acute MI
- Major bleeds: not mentioned. Other trials show about a 25% increase
- Although the granulocytopenia caused by ticlopidine is reversible if Dx'd, if not Dx'd, it can be fatal.
- If you do Rx ticlopidine, you'll need to check a white counts q 2 wks x 3 months.
- The reason that Dipyridamole (Persantine)+ ASA is effective at preventing adverse events post-MI is the ASA: Dipyridamole provides no additional benefit.

## Effect of Nicoumalone or Phenprocoumon on Adverse Events in Patients Post-MI (ASPECT)



### Notes:

The Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial (1994) was a randomized, placebo-controlled, double-blind, trial of 3404 p-MI pts.

Pts rec'd either placebo or anticoagulant (nicoumalone or phenprocoumon) adjusted to an INR of 2.8–4.8 and were followed for an avg of 3 yrs.

Reinfarction was decreased:53%

Nonfatal stroke was decreased:40%

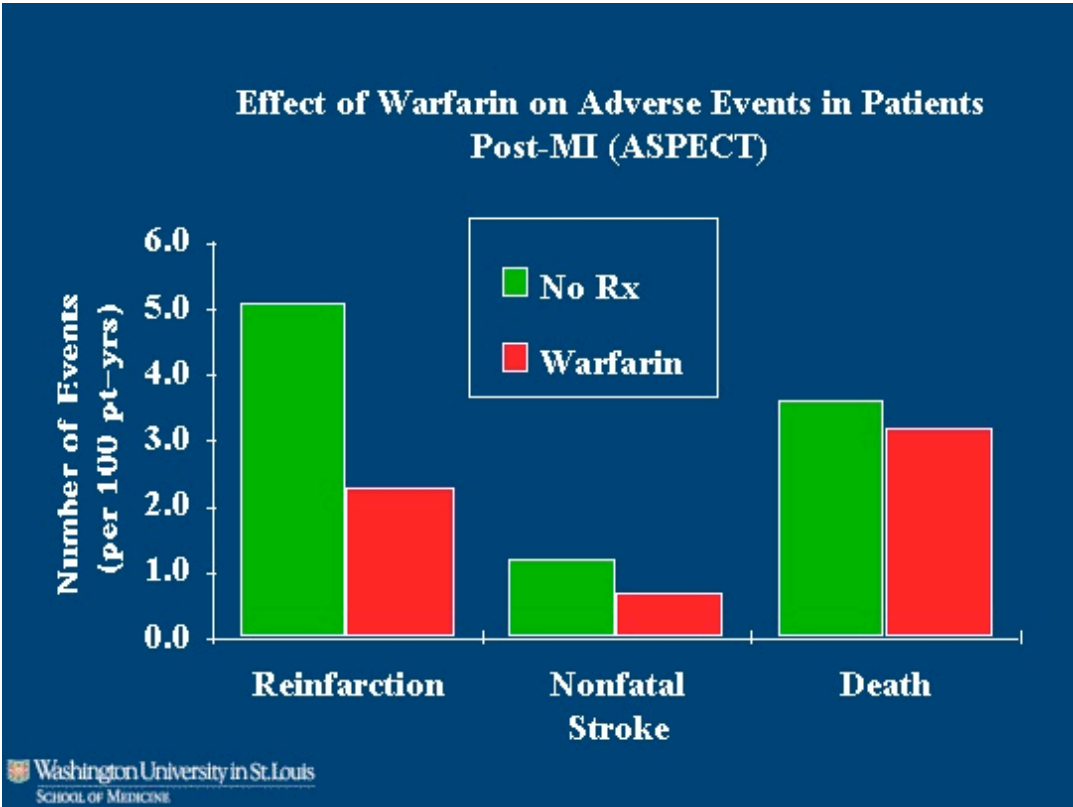
Death was decreased:10%

Major Hemorrhage was increased: 280% (a factor of 3.8).

Per 100 which we intend to Tx w/ anticoagulant instead of placebo we would:

- prevent: 3 MI's, 0.5 CNS events (including ICB), 0.4 deaths
- cause: 1 major (nonfatal) bleed

# Effect of Warfarin on Adverse Events in Patients Post-MI (ASPECT)



## Recommendations for Post-MI Patients

### Recommendations for Post-MI Patients

- ASA, in general
- Warfarin, INR 2–3<sup>†</sup>, may be preferred for 1–3 months with:
  - Anterior MI (Q-wave)
  - Severe LV dysfunction
  - Mural thrombus
  - Prior embolus
  - Afib (chronic warfarin therapy)

#### Notes:

Except for Afib, the optimal duration of anticoagulation for these indication is unknown. A repeat Echo may be helpful for patients who have or are at high-risk of LV thrombus.

## Summary

### Summary

- Post cardioembolic stroke: INR 2.5 (2.0 - 3.0)
- Post non-cardioembolic stroke: antiplatelet therapy
- Afib: INR 2.5 (2-3) usually
  - Use ASA in patients with lone Afib
  - Use INR 2.0 - 3.5 in patients with high-risk Afib
- Mechanical Valve: INR 3.0 (2.5-3.5) usually
  - Aortic St. Jude valve INR 2.5 (2.0 - 3.0)
  - ? Higher INR or low-dose ASA for high-risk valves
- Post-MI: ASA usually
  - INR 2-3† for 1-3 months for some patients:
    - » anterior Q-wave MI, mural thrombus, severe CHF

## References

Gage BF, Fihn SD, White RH. "Management and dosing of warfarin therapy."  
Am J Med 2000;109:481-488.

Hart RG et al. "Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis."  
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The European Atrial Fibrillation Trial Study Group. "Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia."  
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Abstracts from all of Dr. Gage's publications are available at PubMed.