

Appropriate Therapy for Stroke Reduction in AFib

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Overview

- The Problem
- Risk assessment
- Rationale for warfarin
- Review coagulation cascade
- Dosing/Monitoring
- New developments

The Stroke Issue

- Atrial Fibrillation
 - Most common arrhythmia
- ~ 100,000 ischemic strokes/yr in the US
 - Many are avoidable
- Strokes from AF may be larger

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QuickTime™ and a decompressor are needed to see this picture.

| CHADS score | n | strokes | Yearly stroke risk |
|-------------|-----|---------|--------------------|
| 0 | 120 | 2 | 1.9 |
| 1 | 463 | 17 | 2.8 |
| 2 | 523 | 23 | 4.0 |
| 3 | 337 | 25 | 5.9 |
| 4 | 220 | 19 | 8.5 |
| 5 | 65 | 6 | 12.5 |
| 6 | 5 | 2 | 18.2 |

CHADS₂ for Nonvalvular AFib

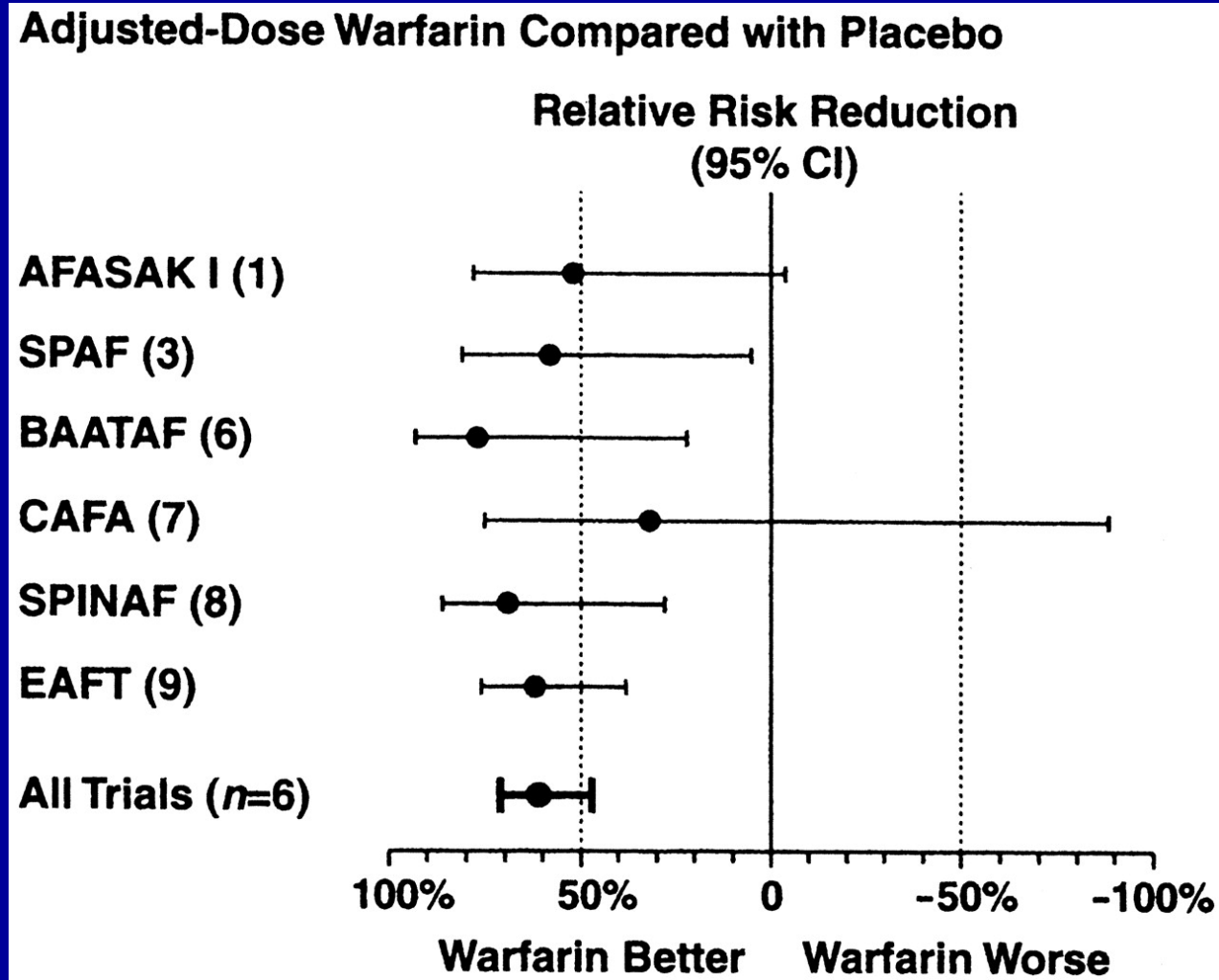
- CHF
- HTN
- Age >75
- DM
- Stroke=2

0-Aspirin 1-warfarin vs aspirin, 2- warfarin

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Antithrombotic therapy for prevention of stroke (ischemic and hemorrhagic) in patients with nonvalvular AF: adjusted-dose warfarin compared with placebo

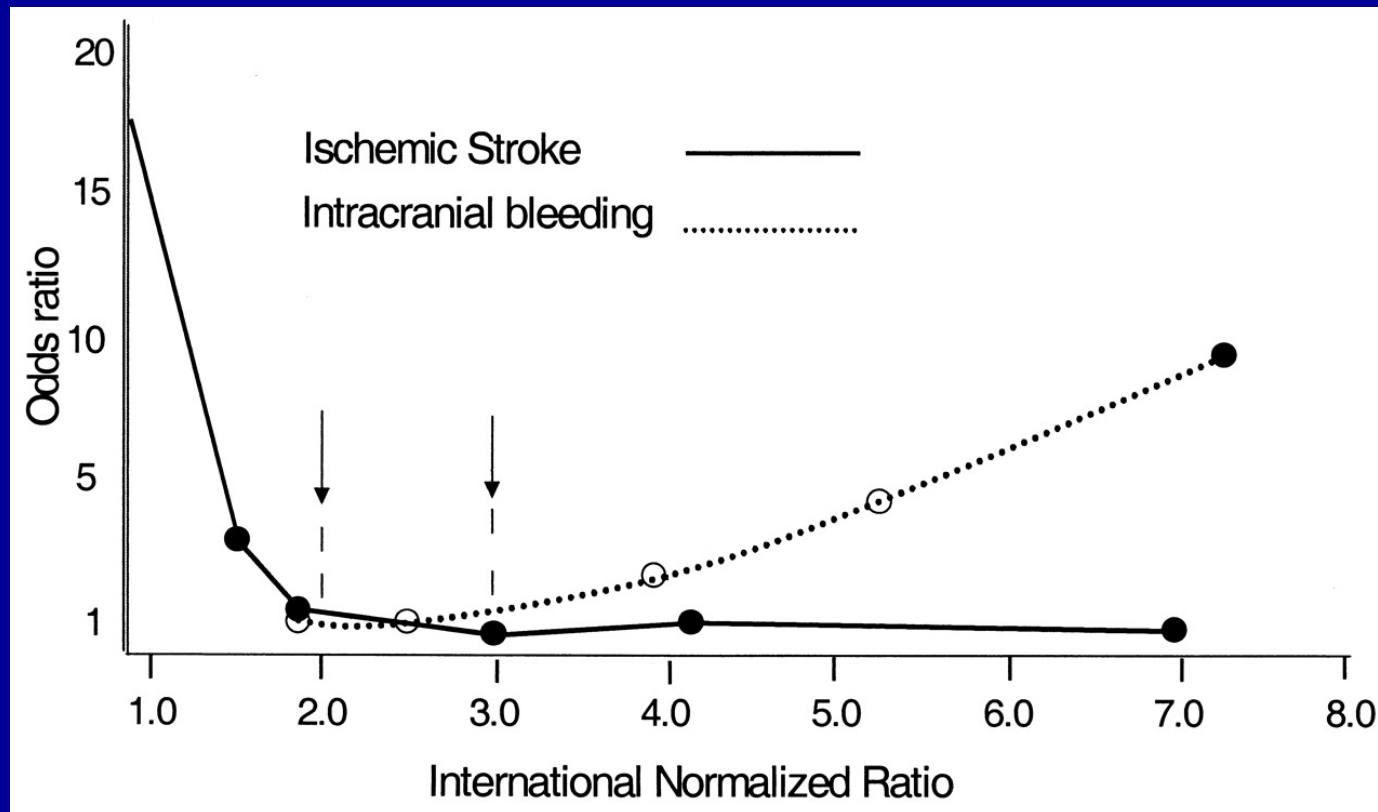


Fuster, V. et al. J Am Coll Cardiol 2001;38:1231-1265

Warfarin vs Aspirin

- Warfarin 38% stroke reduction
- Increased bleeding
- No benefit in low risk patients
 - Bleeding risk >> than stroke risk
- Difficult to use

Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation in randomized trials of antithrombotic therapy for patients with AF



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Concerns about Warfarin

- Perceived risk of bleed vs stroke
- Difficult to use
- Interactions
- Patient perception
 - Procedures
 - Travel
 - “Rat poison”

Limitations of Warfarin

- Limitations
 - Slow onset
 - Narrow therapeutic window
 - Food and drug interactions
 - Variation in metabolism
- Consequence
 - Overlap with parenteral anticoag
 - No uniform dosing
 - Frequent monitoring
 - Frequent monitoring

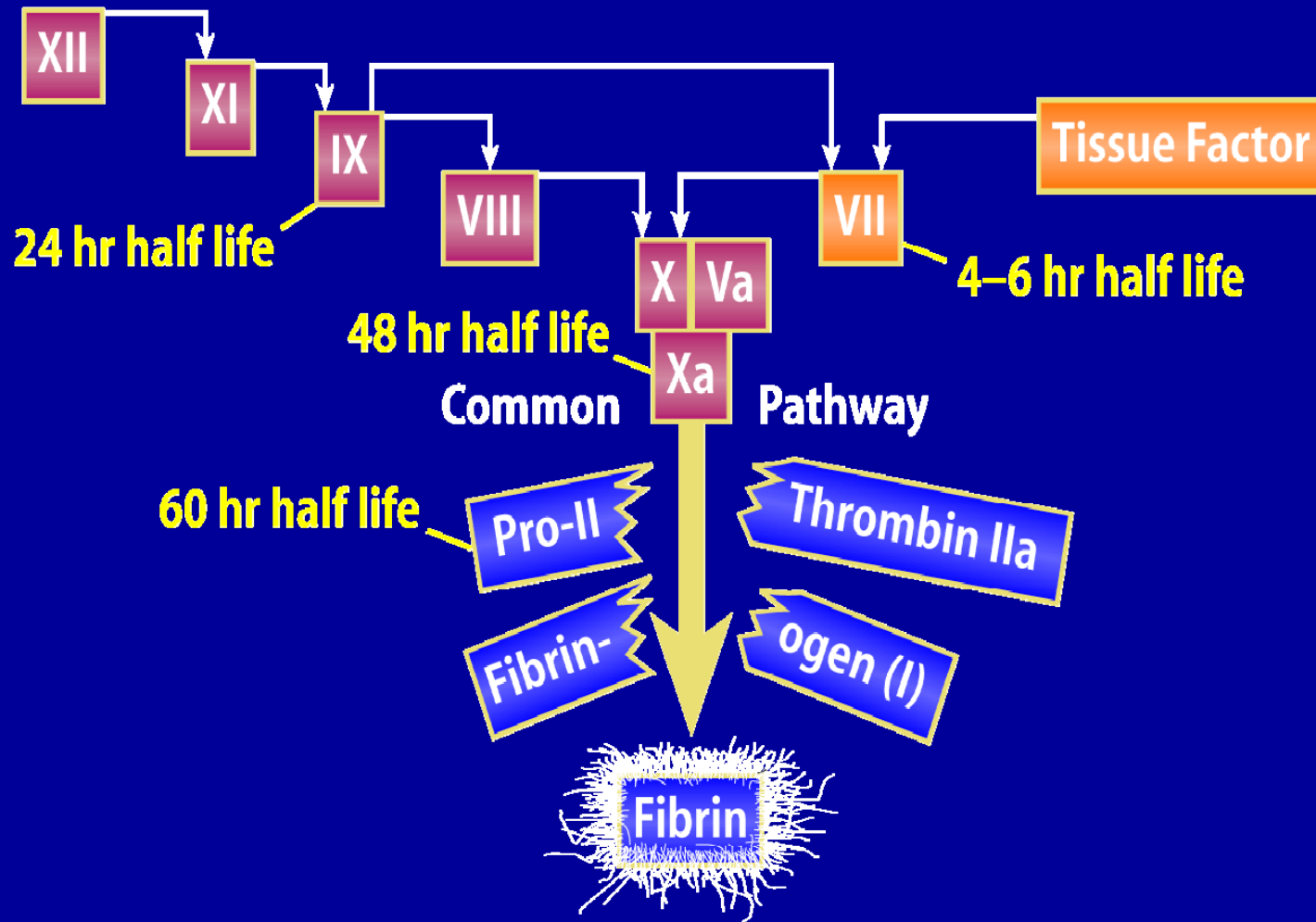
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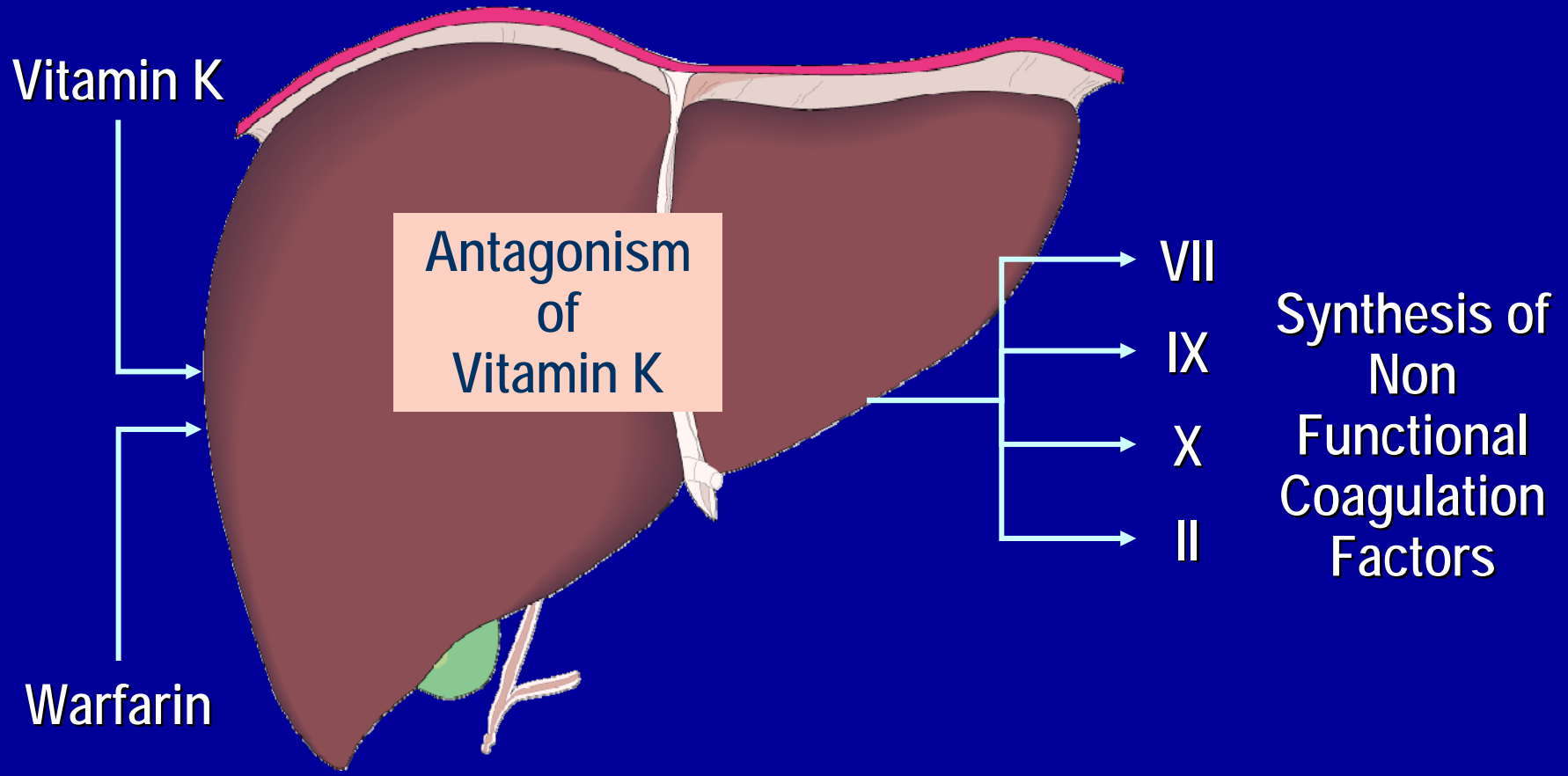
Clotting Cascade

Intrinsic Pathway

Extrinsic Pathway



Warfarin Mechanism of Action



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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

Suggestions to Ease Use of Warfarin

- Use one tablet
- Make alternate doses easy to remember
- Remember drug interactions
- Changes in diet or bowel
- Educate patients on Vit K containing foods
- Use Vitamin K to reverse quickly

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

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

Managing High INR Values

Clinical Situation

Guidelines

INR >therapeutic range but <5.0, no clinically significant bleeding, rapid reversal not indicated for reasons of surgical intervention

Lower the dose or omit the next dose; resume at a lower dose when the INR approaches desired range

If the INR is only minimally above therapeutic range, dose reduction may not be necessary

INR >5.0 but <9.0, no clinically significant bleeding

No additional risk factors for bleeding; omit the next two doses of warfarin, monitor INR more frequently, and resume at a lower dose when INR is therapeutic

Increased risk of bleeding: omit next dose of warfarin and give vitamin K₁ (1.0 to 2.5 mg orally)

Rapid reversal before urgent surgery or dental extraction: vitamin K₁ (2–4 mg orally); if the INR remains high at 24 h, an additional dose of 1–2 mg

Managing Patients with High INR Values/ Serious Bleeding

Clinical Situation

Guidelines

INR >9.0, no clinically significant bleeding

Vitamin K₁ (3–5 mg orally); closely monitor the INR; if the INR is not substantially reduced by 24–24 h, the vitamin K₁ dose can be repeated

Serious bleeding, or major warfarin overdose (e.g., INR >20.0) requiring very rapid reversal of anticoagulant effect: Vitamin K₁ (10 mg by slow IV infusion), with fresh plasma transfusion or prothrombin complex concentrate, depending upon urgency; vitamin K₁ injections may be needed q12h

Life-threatening bleeding or serious warfarin overdose

Prothrombin complex concentrate, with vitamin K₁ (10 mg by slow IV infusion); repeat if necessary, depending upon the INR

Continuing warfarin therapy indicated after high doses of vitamin K₁

Heparin, until the effects of vitamin K₁ have been reversed, and patient is responsive to warfarin

Peri-op adjustment

- Procedural bleeding risk
- Stroke risk
- When to bridge
- When to resume anticoagulation

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Active-A

- Aspirin vs Clopidogrel/ASA
 - ? Unsuitable for warfarin
- Strokes reduced with addition of Clopidogrel
 - 2.4%/yr vs 3.3%/yr
- Increased bleeding with Clopidogrel
 - 2%/yr vs 1.3%/yr

Dabigatran

- Direct Thrombin Inhibitor
- Onset < 1hr
- Half-life ~ 13 hrs
- Renally excreted
- No food interactions
- Simplified monitoring
- Dyspepsia

Discontinuation of the Study Drug, Adverse Events, and Liver Function According to Treatment Group

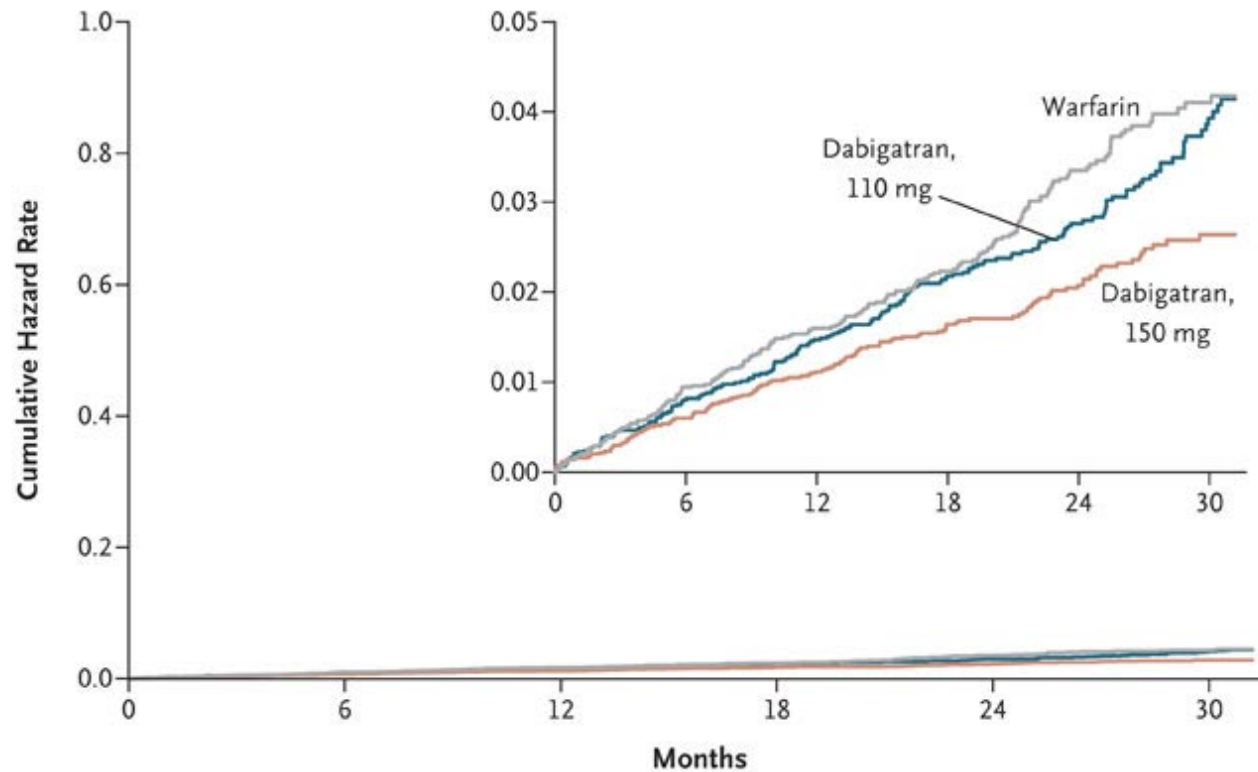
- Slightly higher rate of D/C
 - 21% vs 17%
 - Pt choice #1 reason
- Dyspepsia only significant AA
- No difference in LFTs vs warfarin

Connolly S et al. N Engl J Med 2009;10.1056/NEJMoa0905561



The NEW ENGLAND
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Primary Outcome of Stroke or Systemic Embolism



No. at Risk

| | | | | | | |
|--------------------|------|------|------|------|------|------|
| Warfarin | 6022 | 5862 | 5718 | 4593 | 2890 | 1322 |
| Dabigatran, 110 mg | 6015 | 5862 | 5710 | 4593 | 2945 | 1385 |
| Dabigatran, 150 mg | 6076 | 5939 | 5779 | 4682 | 3044 | 1429 |

Trial Summary

- Equivalent to Warfarin
- Easier to Administer
- Less Monitoring
- Fewer Interactions
- Issues
 - ? Cost
 - Renally excreted
 - Dyspepsia