

# Stroke Prevention in Atrial Fibrillation: Are We Stuck with Warfarin?

Peter Tilkemeier, MD, FACC  
Associate Professor,  
Warren Alpert Medical School of  
Brown University

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# Current State of the Art

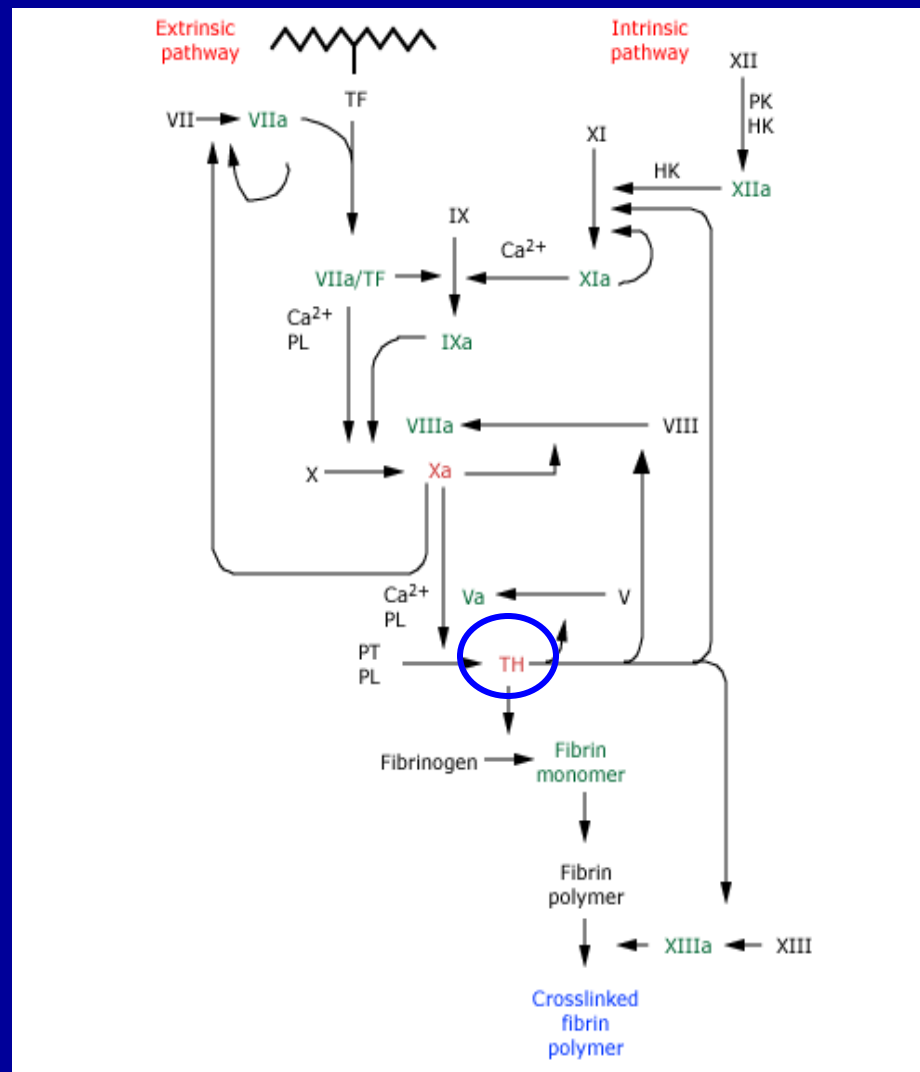
## Warfarin

- Not so current – last decade without change
- Not so state of the art
  - Narrow therapeutic index
  - Requires monitoring
  - Multiple drug interactions
- Current alternatives
  - Aspirin
  - Clopidogrel

# Current Alternatives

- Aspirin alone
  - Consistently and substantially less effective than warfarin
  - 2.3 more ischemic strokes per 100 patients/year
- Low dose warfarin and aspirin
  - Much higher morbidity/mortality compared to adjusted dose warfarin
- Aspirin plus clopidogrel
  - Less effective than warfarin with similar if not higher bleeding risk

# Coagulation Cascade



# Direct Thrombin Inhibitors

- Intravenous
  - Hirudin, Lepirudin, Argatroban, Bivalirudin
- Oral agents
  - Ximelagatran – withdrawn due to hepatic toxicity
  - Dabigatran – available in Europe, FDA review

# Dabigatran

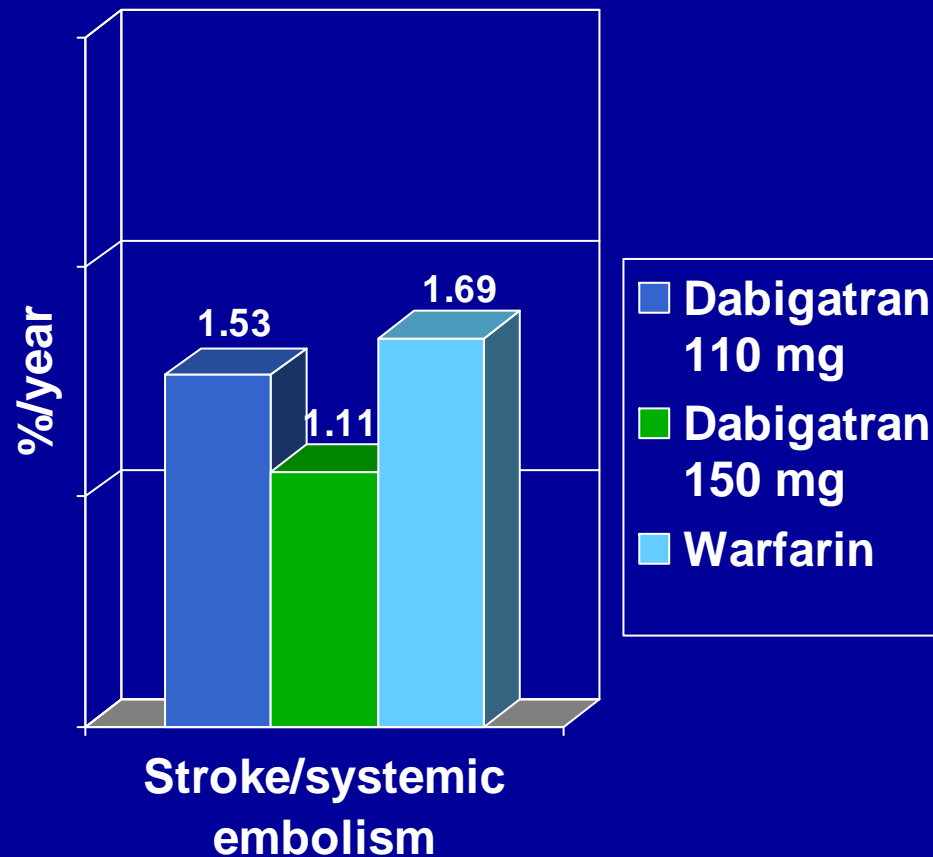
- Current use:
  - VTE prophylaxis following knee and hip surgery
  - Treatment of acute VTE
- Future use:
  - Risk reduction for arterial thromboembolism in non-valvular atrial fibrillation (RE-LY Trial)

# RE-LY Trial

- 18,113 patients with non-valvular atrial fibrillation randomized to:
  - Usual warfarin therapy (6,022)
  - Dabigatran 110 mg (6,015)
  - Dabigatran 150 mg (6,076)
- Discontinuation at 2 years
  - Dabigatran 21%
  - Warfarin 16.6%

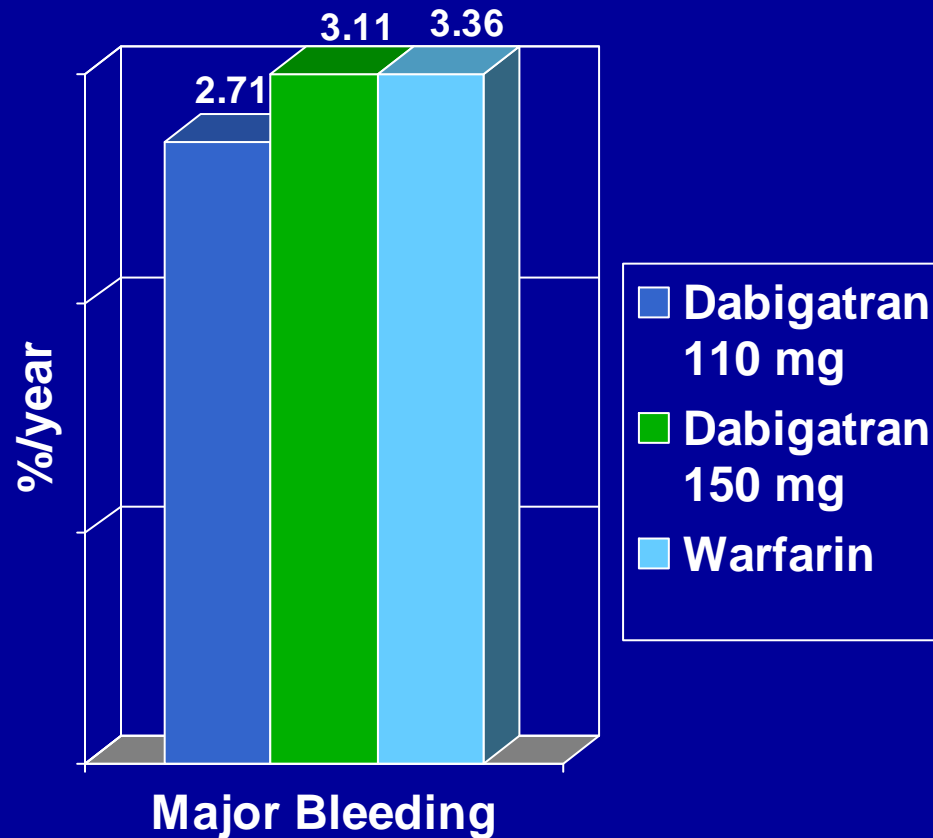


# RE-LY Results



- Dabigatran 150 mg superior to warfarin ( $p < 0.001$ )
- Dabigatran 110 mg non-inferior to warfarin
- Stroke decreased in Dabigatran 150 mg ( $p < 0.001$ )
- Differences driven by reduction in ischemic stroke

# RE-LY Results



- Dabigatran 110 mg less bleeding than warfarin ( $p=0.03$ )
- Dabigatran 150 mg similar to warfarin ( $p=0.31$ )
- Hemorrhagic stroke (0.12, 0.10 and 0.38 %/year, respectively)

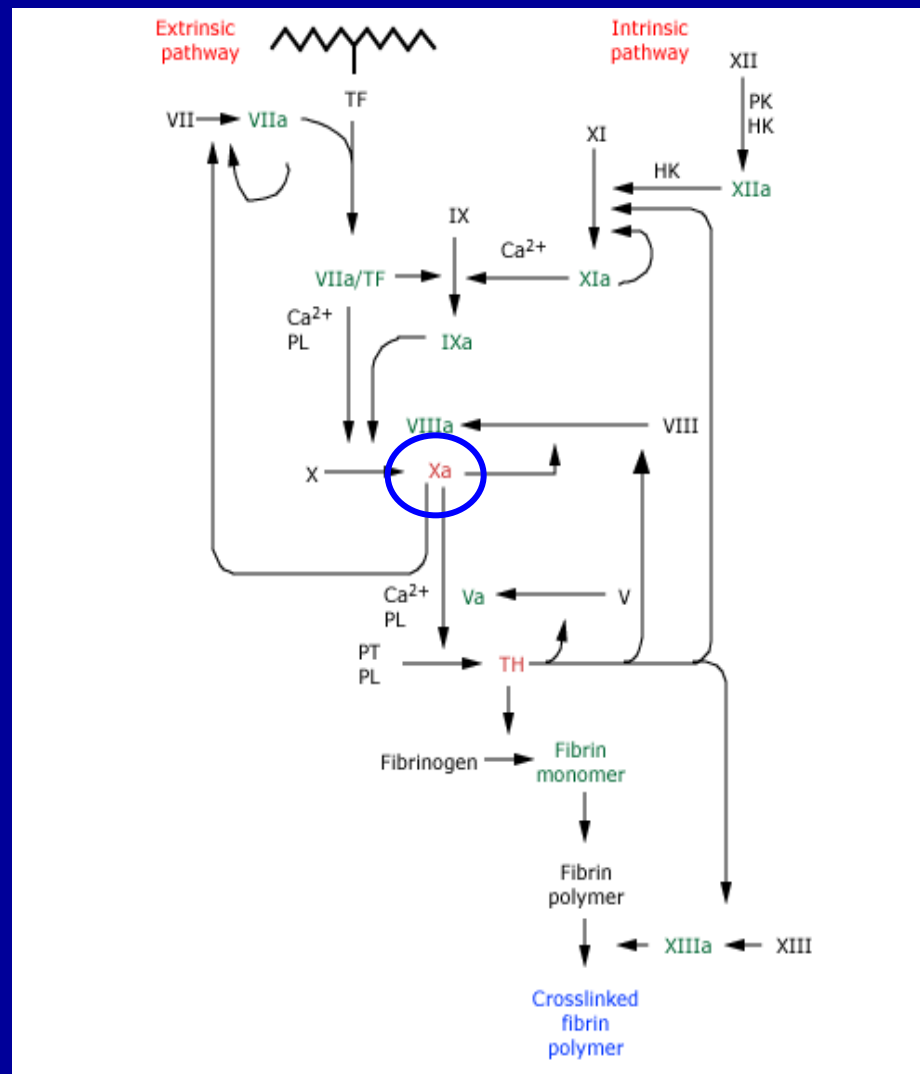
# Dabigatran

- Advantages
  - Does not require INR monitoring
  - Less susceptible to drug/dietary interactions
- Disadvantages
  - Twice daily dosing
  - Lack of long term safety data
  - High cost
  - Lack of an antidote
  - Potential need for dose adjustment in patients with chronic kidney injury

# Dabigatran (Pradaxa®)

- Approved by FDA cardiovascular and renal drugs advisory committee (9/21/2010)
- No recommendation on dosing regimen
- Balance between bleeding and therapeutic effects

# Coagulation Cascade



# Factor-Xa Inhibitors

- Rivaroxaban
- Apixaban
- Razaxaban

# Rivaroxaban

- VTE treatment
  - Effective in phase II trials
  - Phase III trial data available later this year
    - EINSTEIN DVT and EINSTEIN PE
- Stroke Prevention in AF
  - Phase III trial (ROCKET) comparing to dose adjusted warfarin is ongoing
- ACS
  - Phase III trial (ATLAS ACS TIMI 51) ongoing

# Apixaban

- VTE treatment
  - Effective in phase II trials
  - Phase III trial data is ongoing (ortho/oncology)
- Stroke Prevention in AF
  - Phase III trial (ARISTOTLE) comparing to dose adjusted warfarin is ongoing
- ACS
  - Dose dependent increase in bleeding and reduction in ischemic events



# Conclusions

- Warfarin remains preferred for those who can tolerate it (Level of Evidence - Grade 1A if dabigatran not available or 2B if available)
- If dabigatran is available, use in patients whose INR levels are erratic or are non-compliant with INR monitoring rather than ASA plus clopidogrel (Grade 2B)

# Conclusions

- If warfarin is not tolerated and dabigatran is not available use ASA plus clopidogrel rather than ASA alone (Grade 2A) unless intolerance is bleeding risk then risk is equal