

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

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Current State of the Art

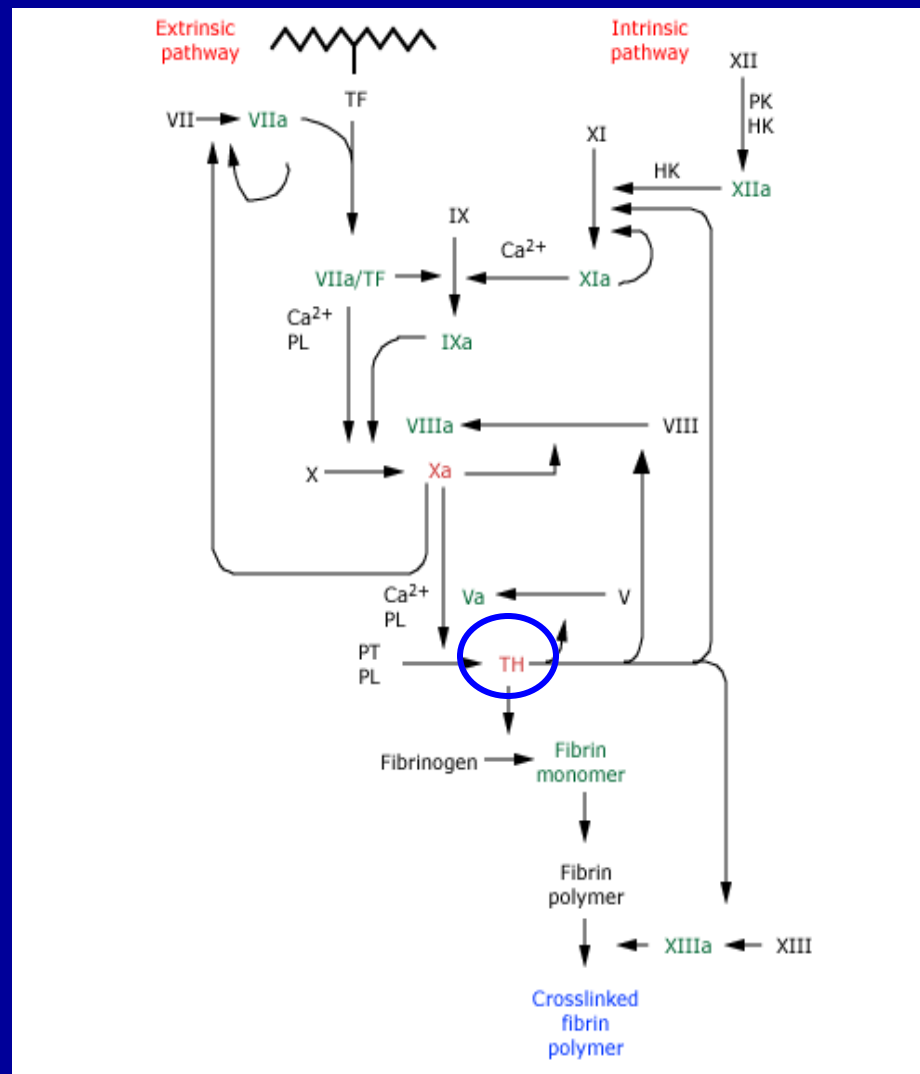
Warfarin

- 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 - Ximelagatran – withdrawn due to hepatic toxicity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

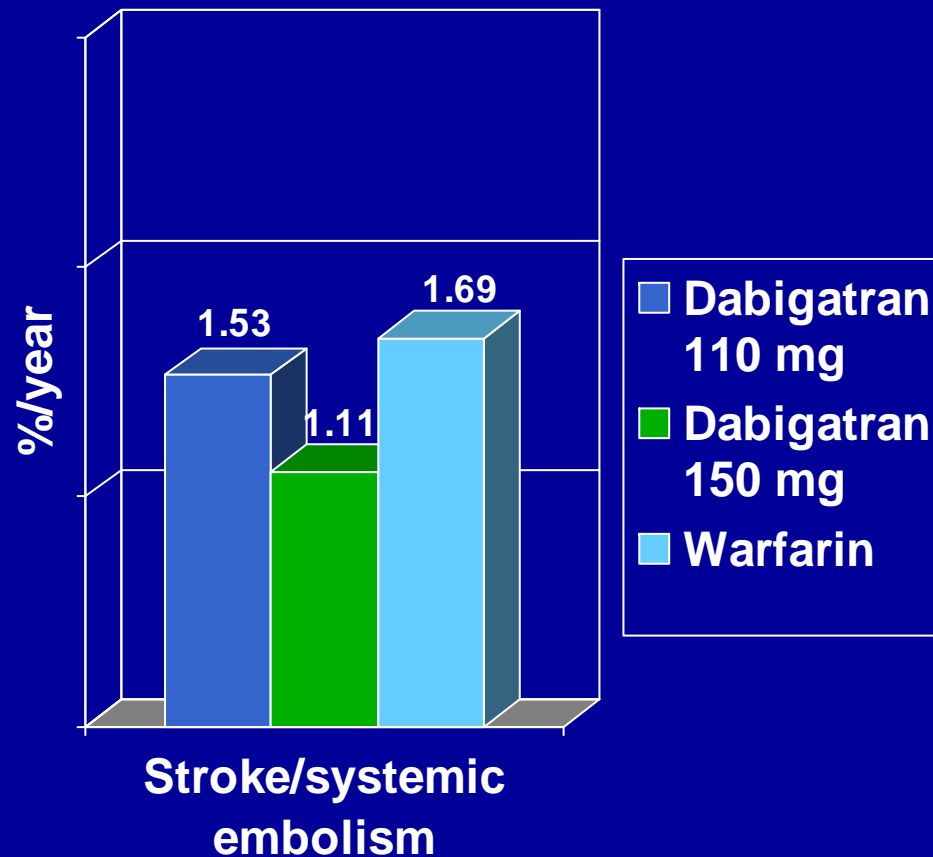
Dabigatran

- 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

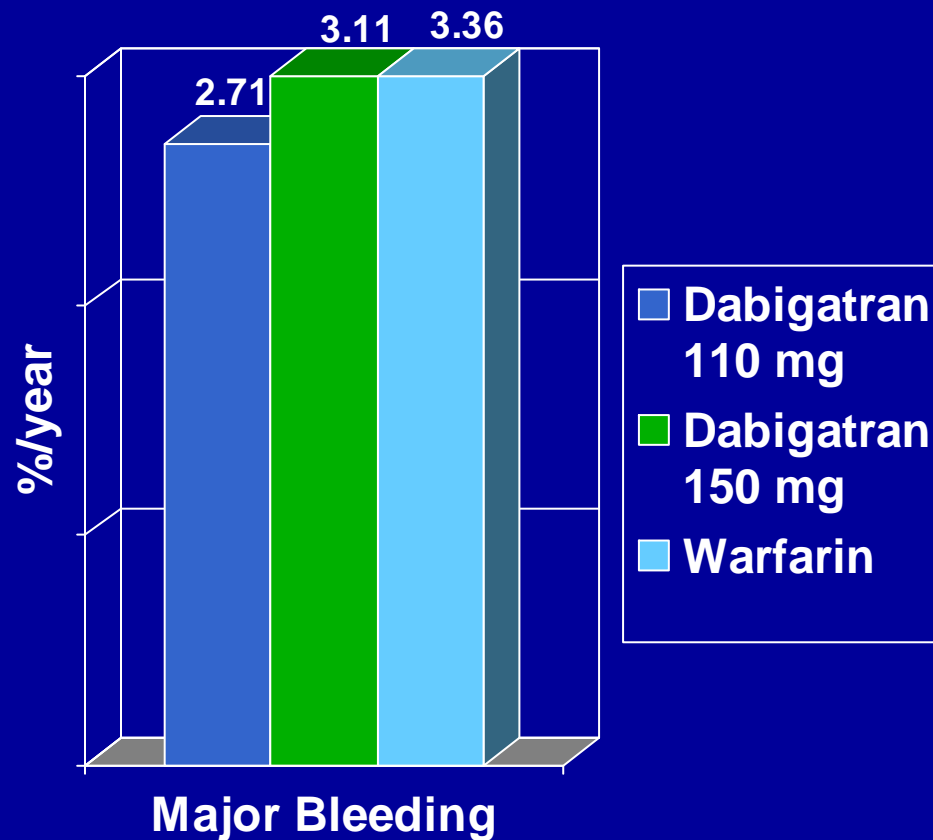
- 18,113 patients with non-valvular atrial fibrillation randomized to:
 - Usual warfarin therapy (6,022)
 - Dabigatran 110 mg (6,015)
 - Dabigatran 150 mg (6,076)
- Discontinuation at 2 years
 - Dabigatran 21%
 - Warfarin 16.6%

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)

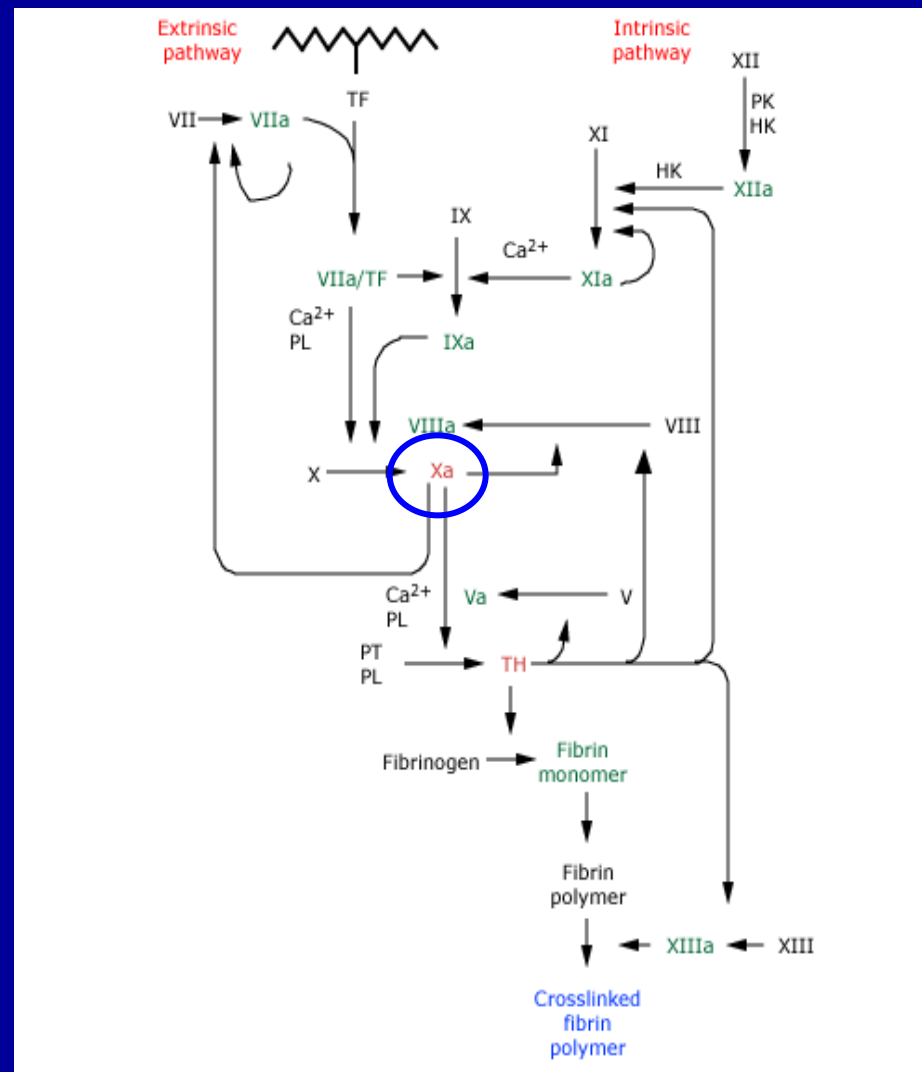
Dabigatran

- 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