새 항응고제를 1차 선택 약으로 먼저 사용하면 안 된다

아주 의대
황 교 승

Treatment of Atrial Fibrillation (AF)

- Rate control
- Rhythm control
- Stroke prevention

Stroke prevention with safe and effective antithrombotic therapy is a critical goal in the AF population

Risk of Stroke in AF Stratified by CHADS2 Score*

$CHADS_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	NRAF Crude Stroke Rate per 100 Patient-Years	NRAF Adjusted Stroke Rate, (95% CI)†
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

*$CHADS_2$ score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack. CI indicates confidence interval.

†The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken.

Gage, B. F. et al. JAMA 2001;285:2864-2870

HAS-BLED bleeding risk score

Letter	Clinical characteristic	Score
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age >65years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Eur Heart J. 2010;31:2369-2429

Stroke Prevention With Warfarin

- reduces the stroke risk by 64%
- increases the risk of all major bleeding by 69%
- warfarin is hampered by
  - slow onset of action
  - narrow therapeutic range
  - requirement for regular monitoring
  - drug and food interactions
  - pharmacogenetic variability
  - risk of hemorrhage

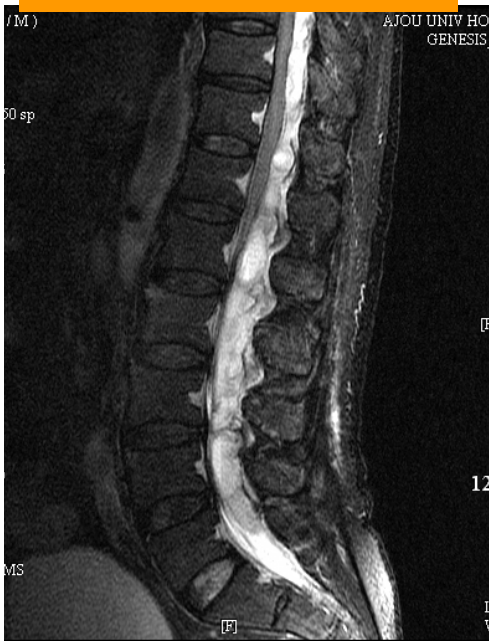
Eur Heart J. ***2005;26:2422–2434.***

Stroke Prevention With Warfarin

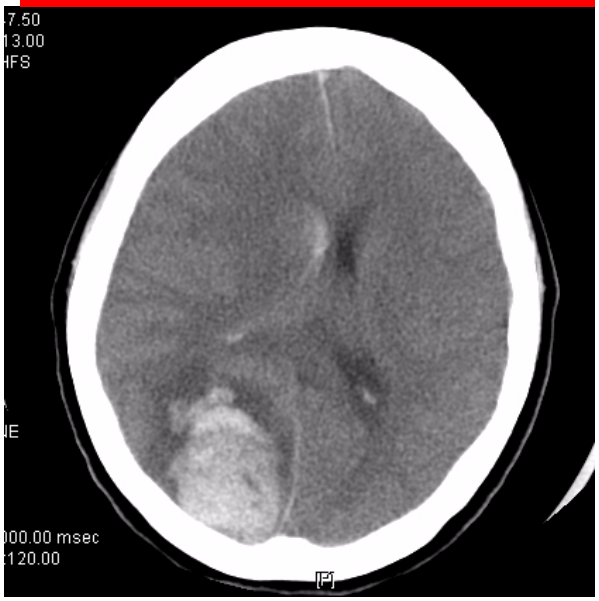
The good, The bad, and The ugly

Risk reduction:
44-81%

M/69, **AF,**
mitral stenosis
INR: 2.9

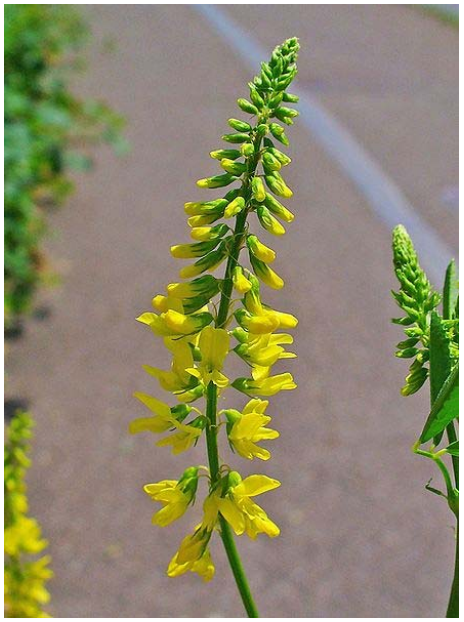


F/36, **AF,**
Rheumatic mitral valve
INR: 1.9-3.0



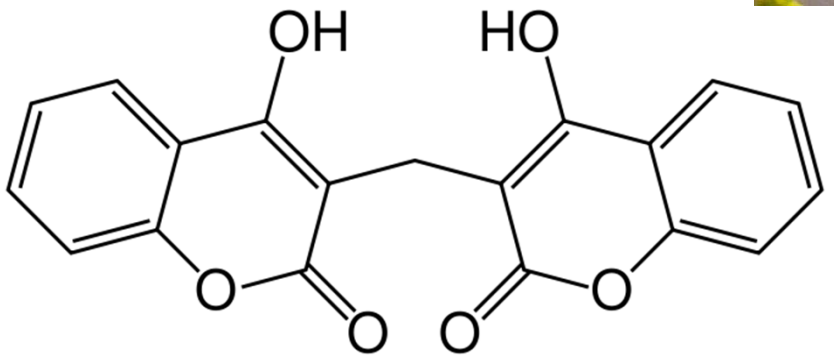
Vitamin-K Antagonists (VKA)

Dicumarol

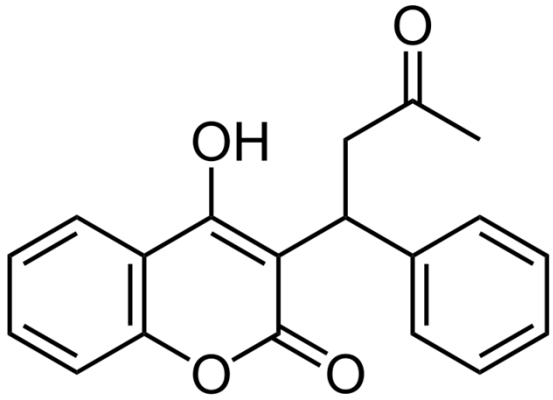


Sweet clover

Warfarin

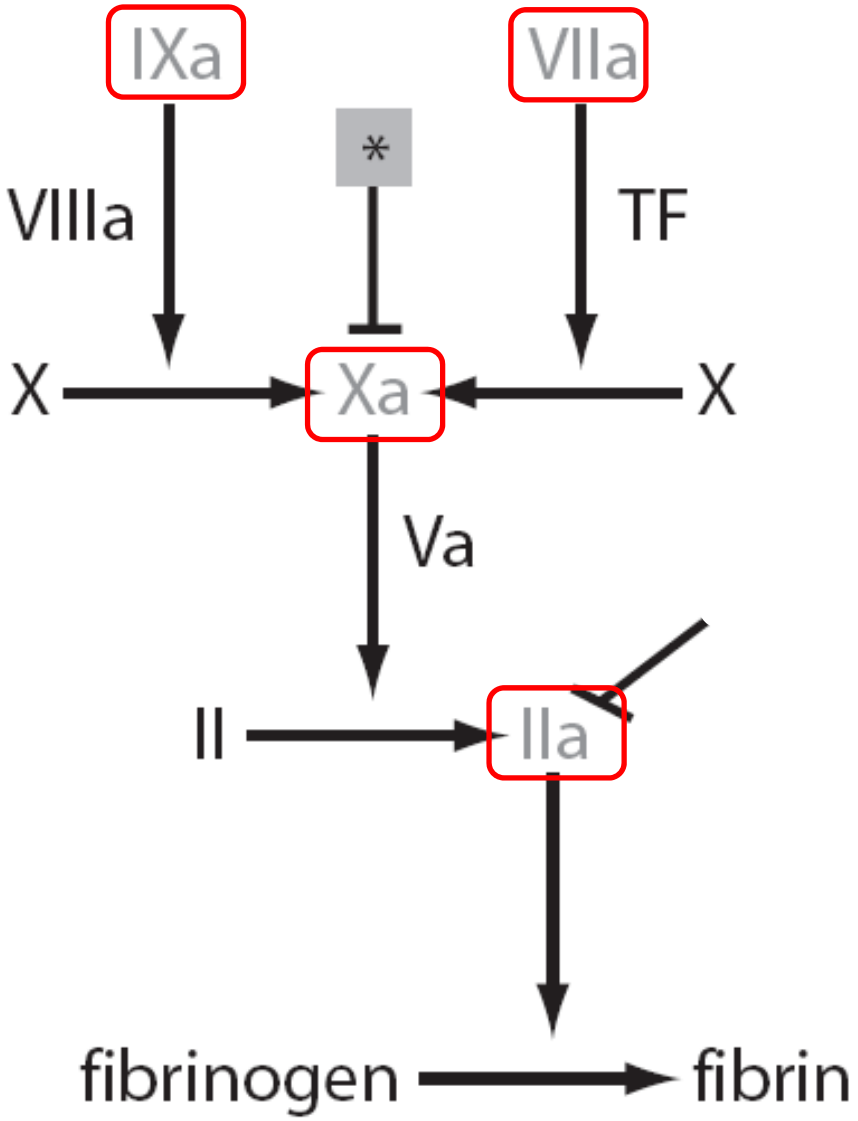


In 1940



In 1954

The Coagulation Cascade

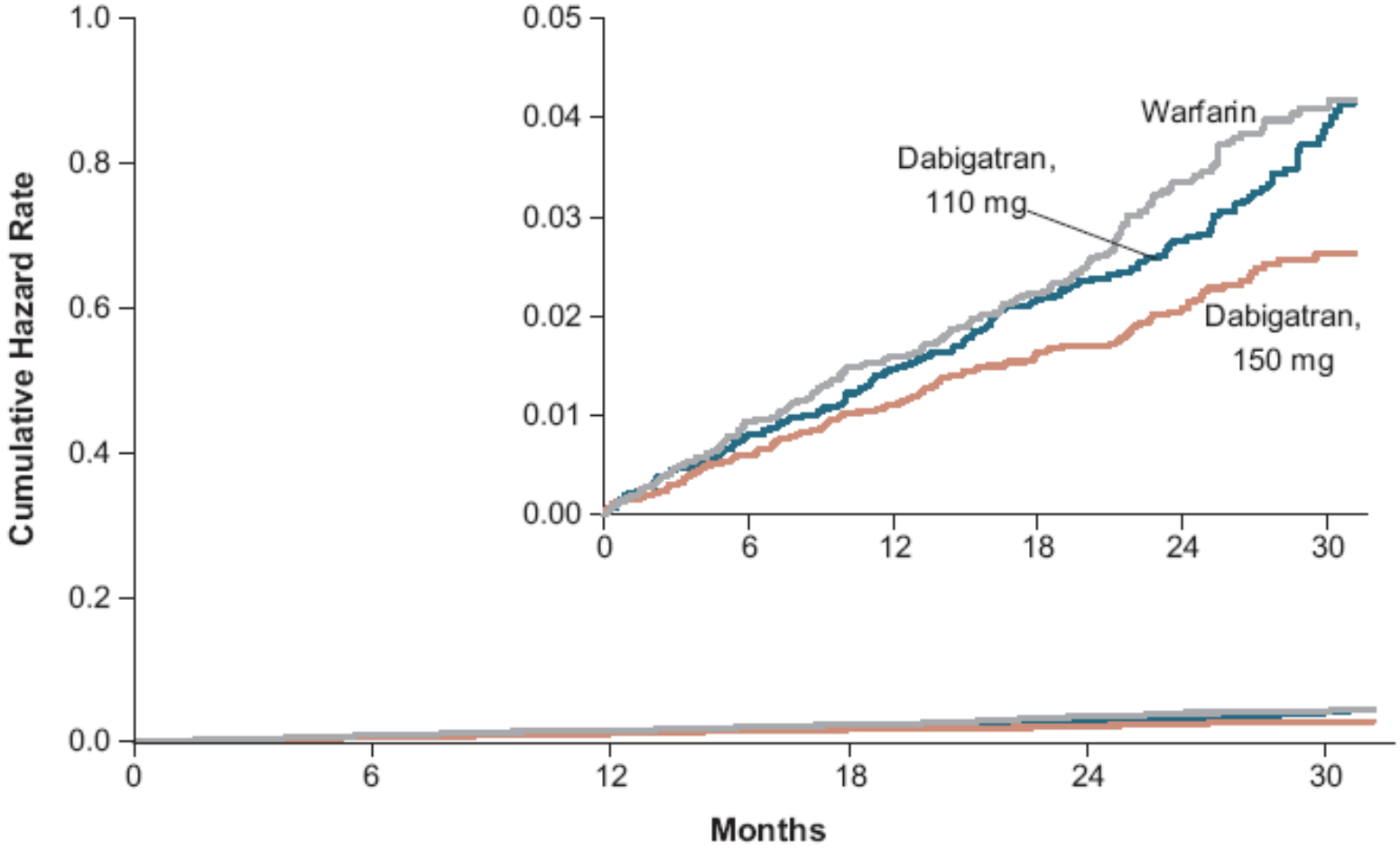


warfarin

Disadvantage of VKA

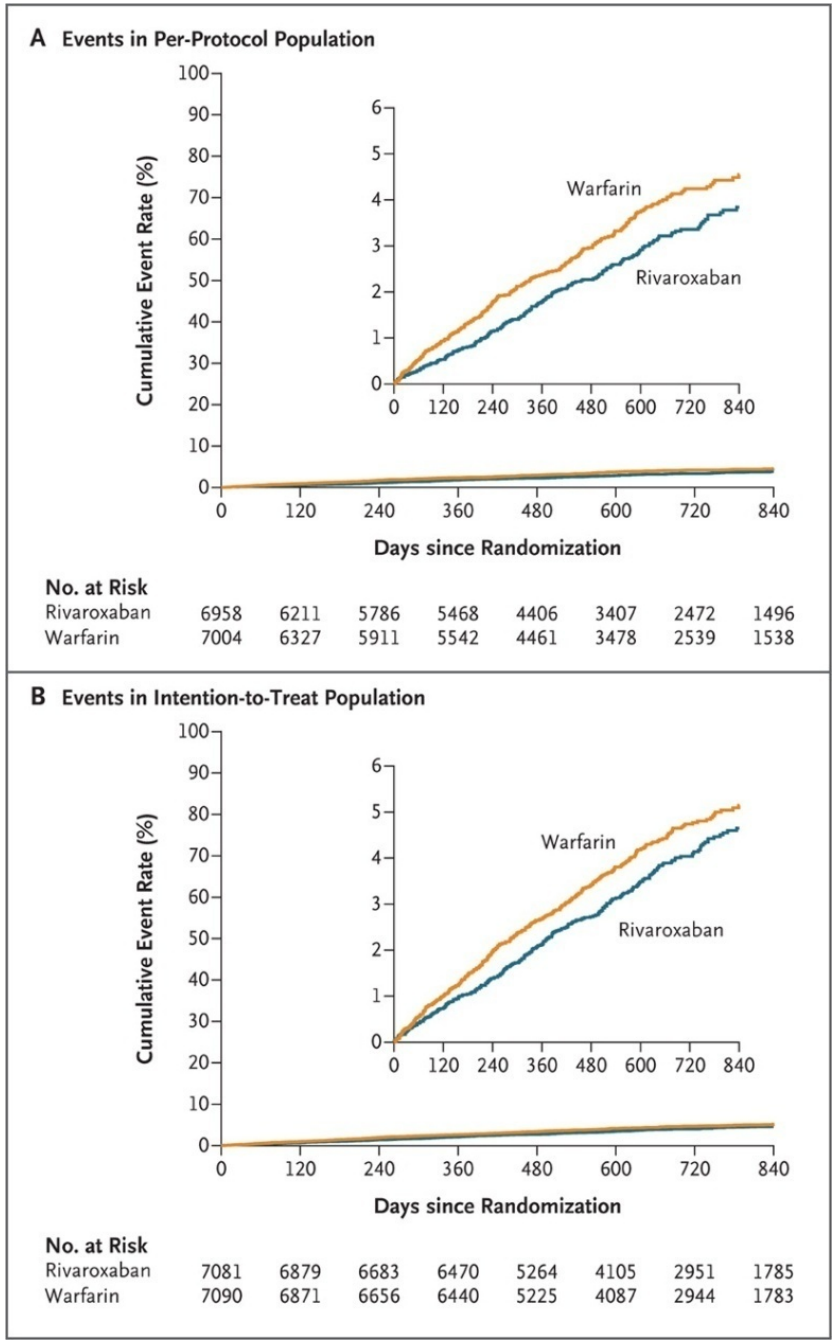
- Dietary restrictions regarding the amount of vitamin-K–containing foods
- Significant interactions with numerous medications
- Nnarrow therapeutic window, with a poorly predictable dosing range
- The delayed onset and delayed reversal of VKA-induced anticoagulation

Dabigatran vs Warfarin in Patients with AF: the RE-LY trial



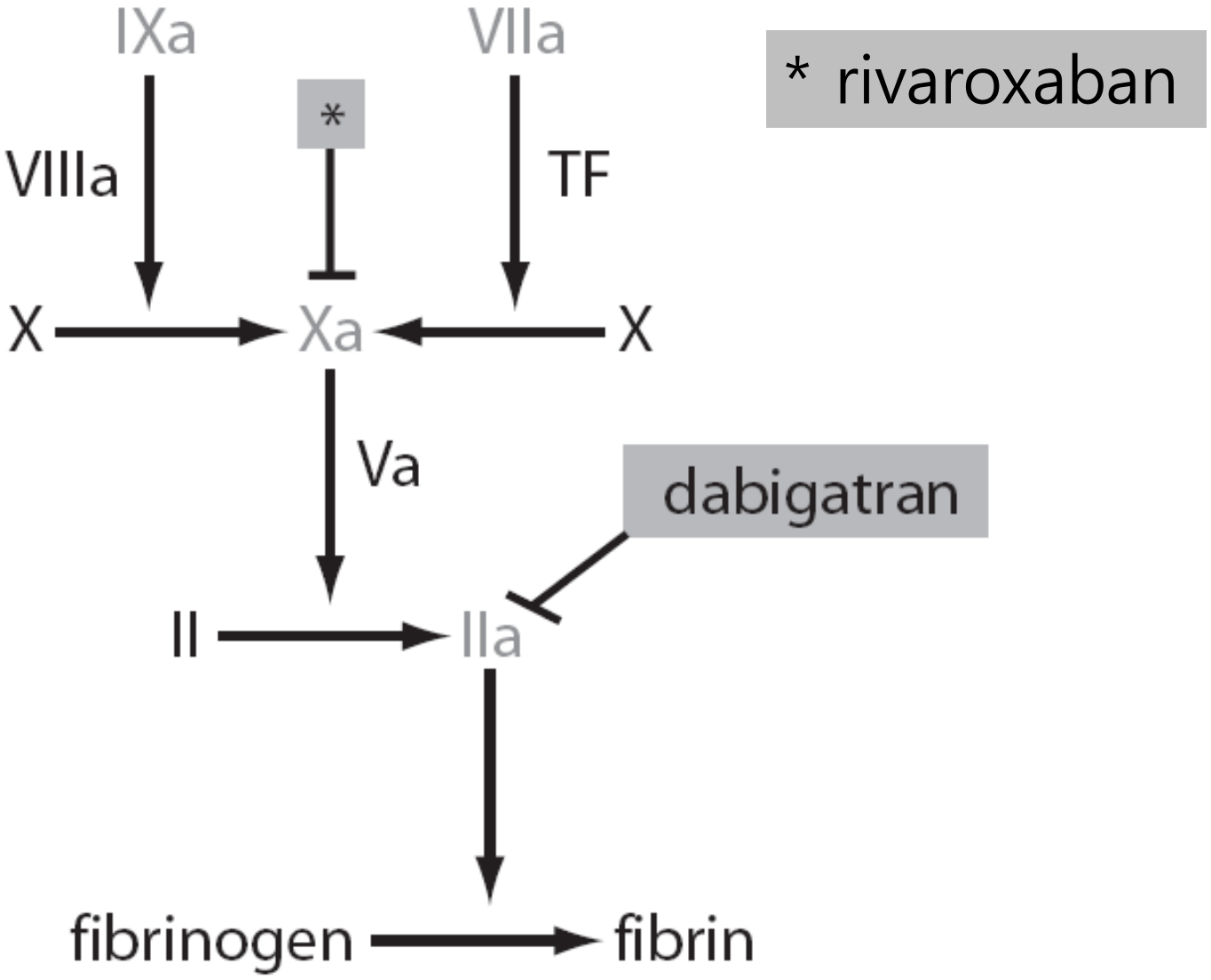
N Engl J Med. 2009;361(12):1139-1151

Rivaroxaban vs Warfarin in Nonvalvular AF (ROCKET AF)



N Engl J Med 2011; 365:883-891

The Coagulation Cascade



New Oral Anticoagulants (OACs) Currently Available or in Development for Prevention of Stroke in AF

Agent	Mechanism of Action	Relevant Clinical Trial/Trials
Apixaban	Direct factor Xa inhibitor	ARISTOTLE, AVERROES[26,28]
Rivaroxaban	Direct factor Xa inhibitor	ROCKET-AF[24]
Edoxaban	Direct factor Xa inhibitor	ENGAGE-AF[27]
Betrixaban	Direct factor Xa inhibitor	EXPLORE-Xa[25]
Dabigatran	Direct thrombin inhibitor	RE-LY[22,23]

New OACs vs VKA

Both doses of dabigatran (In RE-LY)

- Associated with significantly higher rates of dyspepsia and a trend toward increased rates of myocardial infarction
- Higher 2-year discontinuation rates of both doses of dabigatran (21%) compared with warfarin (17%)

N Engl J Med. 2009;361(12):1139-1151

New OACs vs VKA

- Dabigatran has a 12- to 17-hour half-life, lapses of dabigatran therapy could be more problematic than lapses of warfarin
- Lack of an effective antidote
- The lack of a reliable serum test (either to assess for treatment failure or on compliance or to titrate the intensity of therapy)
- Bottled medication must be used within 60 days of opening

Thromb Haemost. 2010;103(6):1116-1127

Safety Considerations

For patients with chronic kidney disease

- The lower dabigatran dose of 75 mg was FDA approved for CrCl between 15 and 30 mL/min despite never being tested in a randomized fashion

- Testing renal function prior to starting therapy and annually thereafter in patients 75 years of age or older or patients with CrCl <50 mL/min.

N Engl J Med. 2011;364(19):1788-1790

Safety Considerations

There is no reported data for new OACs

- patients with mechanical prosthetic heart valves
- coronary stent implantation requiring dual antiplatelet therapy
- during pregnancy

Drug Interactions

- Dabigatran is a substrate of the efflux transporter P-glycoprotein [P-gp] inhibitors

- Rifampin (P-gp inducers) and dabigatran should not be used in combination

Thromb Haemost. 2010;103(6):1116-1127

- In RE-LY, amiodarone and verapamil (inhibitors of P-gp)
  : no specific increase in bleeding in patients taking these P-gp inhibitors and concurrent dabigatran compared with concurrent warfarin

EuroIntervention. 2010;6(2):220-226

Drug Interactions

- Dronedarone
  : increase the serum concentration of dabigatran (about 1.7- to 2.0-fold)
  suggesting a dose of 75 mg bid when dronedarone and dabigatran are prescribed together in patients with moderately reduced renal function

- Concomitant use of P-gp inhibitors in patients with severe renal dysfunction (CrCl 15-30 mL/min) is contraindicated.

2011;http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm243762.htm. Accessed July 23, 2011.

Cost-Effectiveness for AF Population

In USA

warfarine: $1 for 1 day's generic dose

dabigatran: $9 per day at the 150 mg bid dosing

Circulation. 2011;123(22):2562-2570

In Korea

warfarin 2 mg: 39원
warfarin 5 mg: 82원

dabigatran: 6000원/day
rivaroxaban: ?

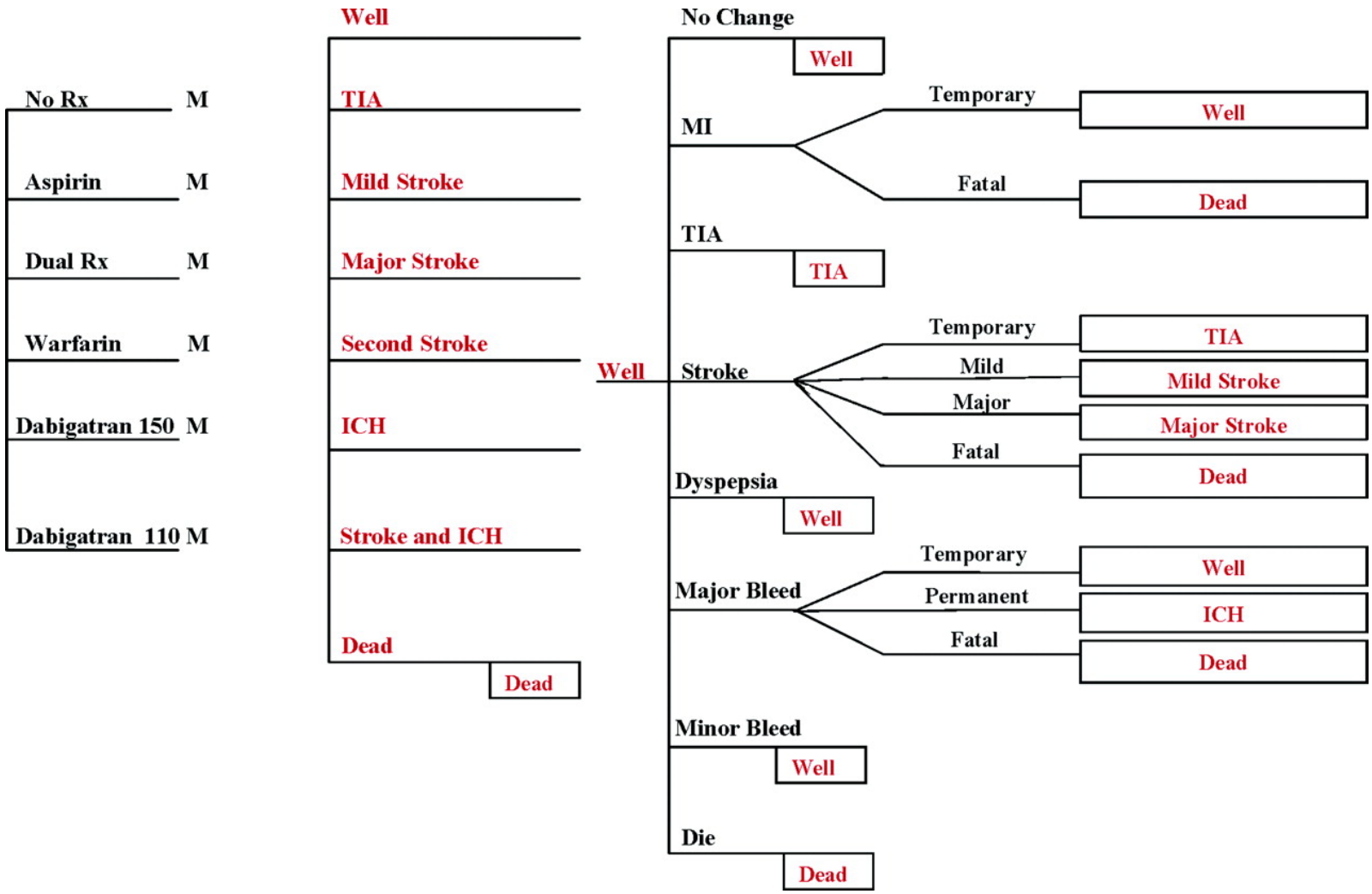
Cost-Effectiveness for AF Population

Considering

- the added cost of serum coagulation testing

- any saved costs and productivity
  - from loss of work
  - avoided strokes
  - avoided bleeds
  - hospitalizations saved

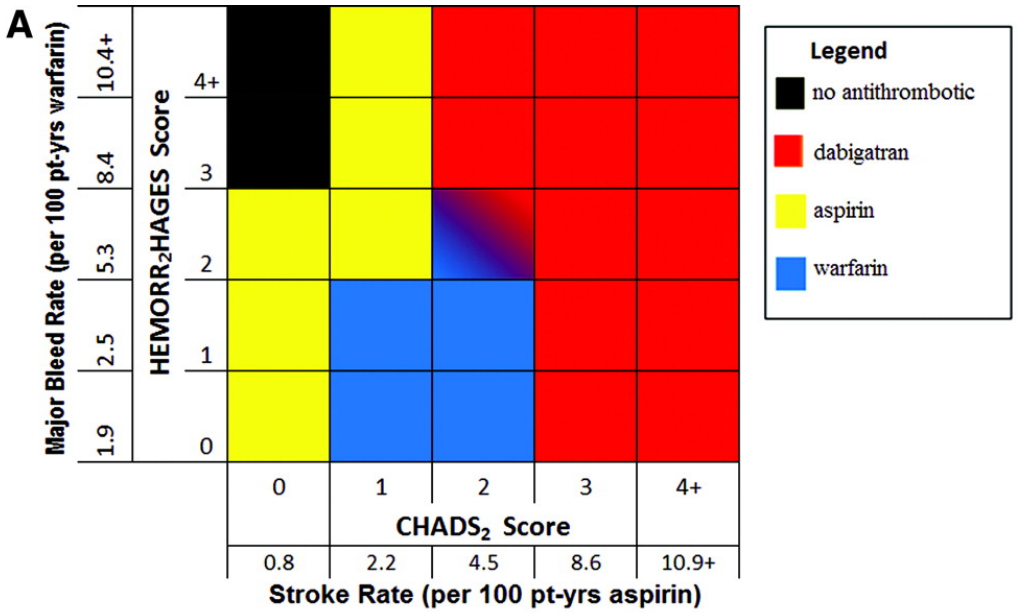
Representation of the Decision Model (Markov Model)



Shah S V , Gage B F Circulation 2011;123:2562-2570

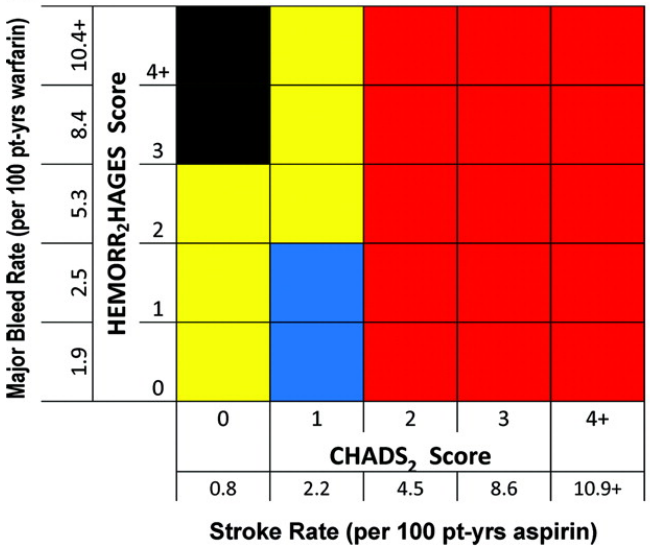
Two-way Sensitivity Analysis of Stroke and Hemorrhage Risk With Cost Effectiveness

Base-case scenario

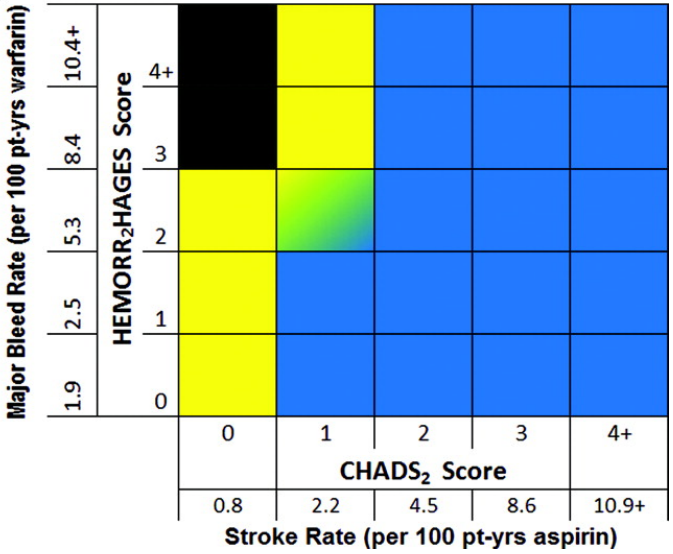


TTR: Time in therapeutic range of INR

TTR < 57.1%



TTR > 72.6%



Shah S V , Gage B F Circulation 2011;123:2562-2570

Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in AF

- For patients already taking warfarin who have excellent INR control, dabigatran 150 mg (twice daily) was not cost-effective

- The benefits of dabigatran outweigh costs in AF patients at moderate to high risk of stroke and/or hemorrhage unless their INR control with warfarin therapy would be excellent

Elective Cardioversions of AF

- Pretreatment with warfarin for at least 3 weeks at target range INR followed by cardioversion or early cardioversion guided by transesophageal echocardiogram to exclude left atrial thrombus

- Anticoagulation is then continued for at least 4 weeks following the cardioversion

N Engl J Med. 2001;344(19):1411-1420.

Elective Cardioversions of AF

RE-LY substudy in which close to **2000 cardioversions** in 1270 patients : D110, D150, and warfarin

- The rates of stroke and systemic thromboembolism (SSE) at 30 days were similar (0.8%, 0.3%, and 0.6%, respectively), as were the rates of major bleeding events (1.7%, 0.6%, and 0.6%, respectively).

- However, retrospective study, no randomized data

Circulation. 2011;123(2):131-136.

Peri-AF Ablation Anticoagulation to Prevent Thromboembolic Events

- In patients undergoing AF ablation, periprocedural dabigatran use significantly increases the risk of bleeding or thromboembolic complications compared with uninterrupted warfarin therapy.

Lakkireddy D et al. J Am Coll Cardiol 2012;59:):1168-74

- Dabigatran did not cause bleeding complications and there were no thromboembolic events. Dabigatran appears to be an alternative to warfarin after AF ablation

Winkle RA, et al. J Cardiovasc Electrophysiol 2011 Sep 28

Questions?

- Are new OACs as effective as warfarin, when administered as long-term therapy beyond the initial 6 to 12 months?
- How will the risk-to-benefit profile change when new OACs are administered in a more heterogeneous patient population (eg, renal insufficiency, obesity, pediatric patients)?
- What are the roles of new OACs in patients with AF and concomitant malignancy of using long-term dabigatran or rivaroxaban?
- When these newer agents are more widely used, will they have rare but severe side effects?

RE-LY Trial Exclusion Criteria

- Severe valvular disorder
- Stroke in last 14 days, or severe stroke in last 6 months
- Conditions that increase risk of hemorrhage
- Active liver disease
- Pregnancy
- Creatinine clearance less than 30 mL per minute

Conclusions

- Warfarin is still considered a first line agent for the prevention of stroke and systemic thromboembolism in AF

- In the case of variable control on warfarin, the New OACs can be considered especially with patient preference, high stroke and hemorrhage risk

New OACs

Warfarin