

Anticoagulation in Atrial Fibrillation



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DISCLOSURE

Relevant Financial Relationship(s)

Speaker's Bureau – none

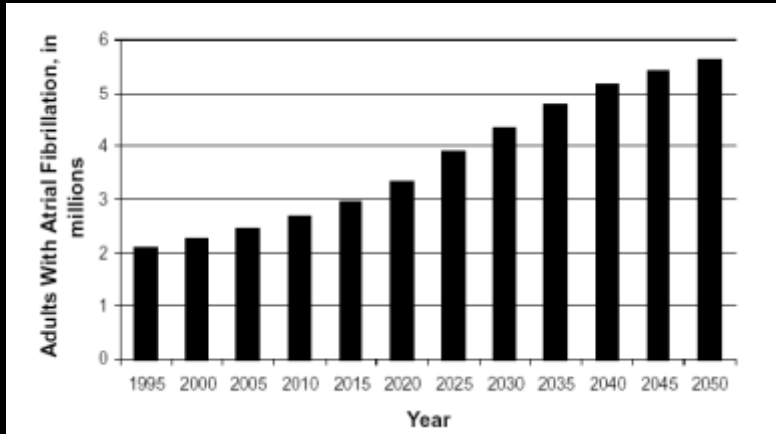
What I am Talking About

- **Benefits of Warfarin**
- **Role of new agents**
- **When to use new drugs**
- **Issues with new drugs**

The Problem

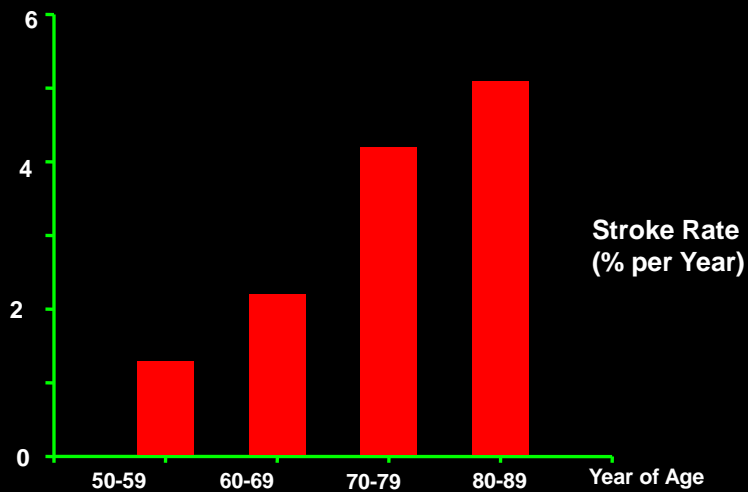
- **Stroke is a common and devastating complication of atrial fibrillation**

Increasing Incidence of Afib



JAMA, 285(18): 2370-75, May 2001.

Atrial Fibrillation and Stroke



Risk Stratification

- Can predict stroke risk by clinic factors
- Biggest risk factor is history of previous stroke/TIA!

Risk Tools

CHADS₂

Risk Factor	Score
CHF	1
Hypertension	1
Age ≥75 y	1
Diabetes	1
Stroke or TIA	2
Range	0-6

CHA₂DS₂-VASc

Risk Factor	Score
CHF	1
Hypertension	1
Age ≥75 y	2
Diabetes	1
Stroke or TIA	2
Vascular disease	1
Age 65-74 years	1
Sex - female	1
Range	0-9

Score and Stroke Risk

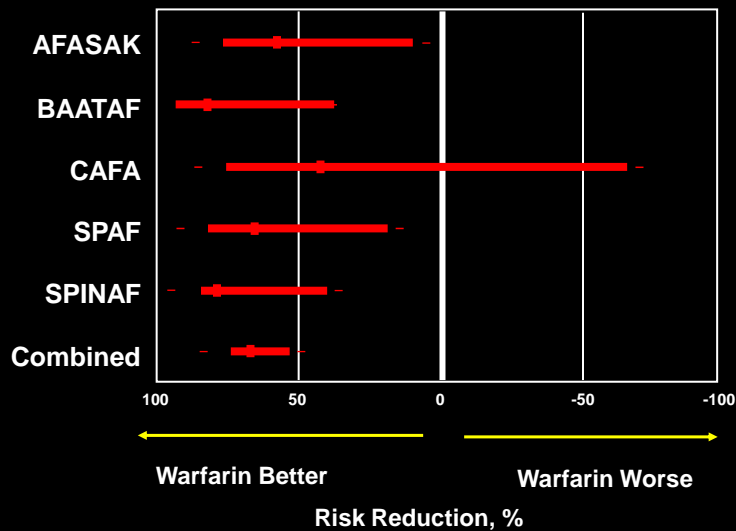
Score	CHA ₂ DS ₂ -VASc (%/y)	CHADS ₂ (%/y)
0	0ish	1.9
1	1.3	2.8
2	2.2	4
3	3.2	5.9
4	4.0	8.5
5	6.7	12.5
6	9.8	18.2
7	9.6	
8	6.7	
9	15.2	

Gage BF et al. *JAMA*. 2001;285:2864-2870.
Lip GY et al. *Chest*. 2010;137:263-272.

Is Warfarin of Benefit in Preventing Strokes in Afib?

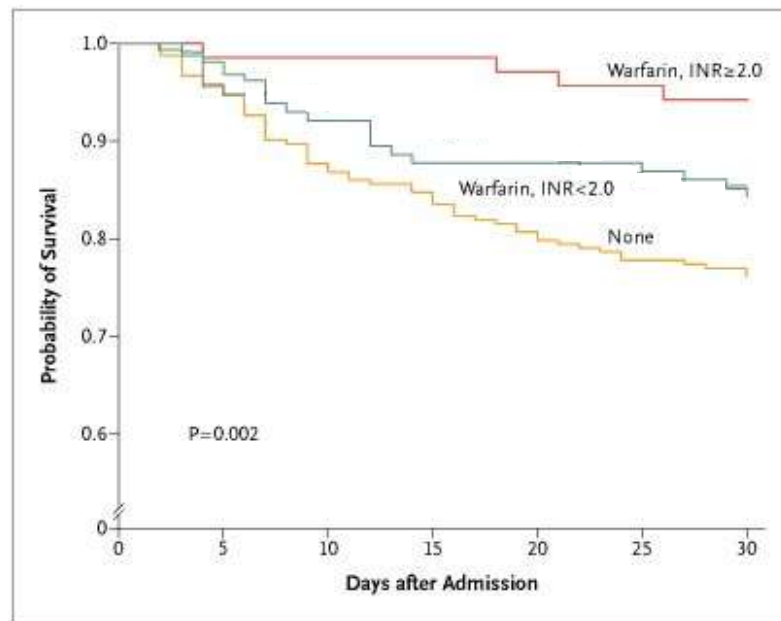
- 5 key trials demonstrated benefit of warfarin in preventing stroke
 - 4.5% to 1.5%/yr
 - Need to treat **32** patients with warfarin/yr to prevent one stroke
 - NNT **12** for secondary stroke prevention
 - Despite differences in study design findings consistent across trials

Stroke Prevention in AF: Warfarin Vs Placebo



Key of Maintaining an INR of 2-3

- Stroke rate increased with INR 1.5-2
- Bleeding **NOT** reduced
- Even if patients have strokes if there are INR 2-3:
 - Strokes are less severe
 - They are more likely to survive



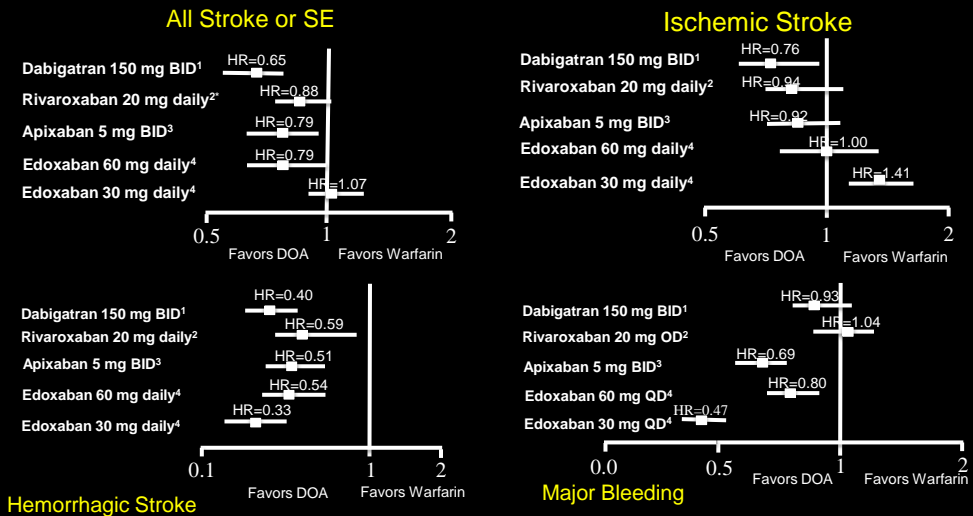
INR Goals

- Target INR of 2.5 with range of 2-3
 - Steady dietary intake of vitamin K
 - Monitor with changes in health or medications
 - Never go longer than one month between INRs
 - Home monitoring

What about the New Drugs?

- 4 new drugs with phase III trial data
 - Apixaban Xa inhibitor
 - Edoxaban Xa inhibitor
 - Dabigatran II inhibitor
 - Rivaroxaban Xa inhibitor

Direct Oral Anticoagulants



1. NEJM. 2009;363:1175-1176. 2. NEJM2011;365:883-891.
 3. NEJM. 2011;365:981-992. 4. NEJM. 2013;369:2093-2104.

Direct Oral Anticoagulants

- All are just as effective as warfarin in stroke prevention
 - Apixaban and dabigatran superior
- All same or less risk of bleeding
 - Apixaban and edoxaban less
- All have less intracranial hemorrhage

ICH – Atrial Fibrillation

	Stroke		Intracranial Hemorrhage	
	Events/ 100 years	RR	Events/ 100 years	RR
Apixaban	1.19	0.79 (0.65-0.95)	0.33	0.42 (0.30-0.58)
Dabig 110	1.53	0.91 (0.74-1.11)	0.23	0.31 (0.20-0.47)
Dabig150	1.11	0.66 (0.53-0.82)	0.30	0.40 (0.27-0.60)
Edox 60	1.69	0.88 (0.75-1.03)	0.39	0.47 (0.34-0.63)
Edox 30	1.97	1.13 (0.97-1.31)	0.26	0.30 (0.21-0.53)
Rivaroxaban	1.76	0.79 (0.66-0.96)	0.49	0.67 (0.47-0.94)

Potential for 10-12,000 less ICH in USA

Direct Oral Anticoagulants Renal Disease

- **Renal Function**
 - All renally cleared:
 - Apixaban – dose reduced to 2.5 mg bid if
 - Creatinine > 1.5 plus age over 80 or weight < 60kg
 - Dabigatran – not for CrCl < 50
 - Rivaroxaban – 15mg CrCl 49-15

Direct Oral Anticoagulants Drug Interactions

- **Apixaban and Rivaroxaban**
 - CYP3A4 + p-glycoprotein inhibitors
 - HIV drugs or azoles
- **Dabigatran - p-glycoprotein**
 - Dronedarone, azoles, rifampin, St John's wort, carbamazepine

Reversal

- **A non-issue**
 - Patients have less ICH
 - No evidence reversal helps with warfarin bleeding
 - RCT show same or better outcomes with bleeding compared to warfarin patients

Drugs with No Antidote

- Aspirin
- Clopidogrel
- Prasugrel
- Ticagrelor
- Enoxaparin
- Fondaparinux
- Vorapaxar
 - 300 hr $T_{1/2}$!

Who Should Get the Direct Agents?

- Unstable INR
- Older patients
- Patients with risk factors for stroke
- Renal insufficiency
- Patients at risk for bleeding

Who Should Stick with Warfarin?

- Stellar INR control
- Mechanical valves
- Dialysis patients
- Extreme of weight
 - < 50kg
 - > 130-150 kg

The Future

- **Monitoring**
- **Antidotes**
- **Cost issues**