

Overview of Anticoagulation to prevent Stroke in patients with Atrial Fibrillation

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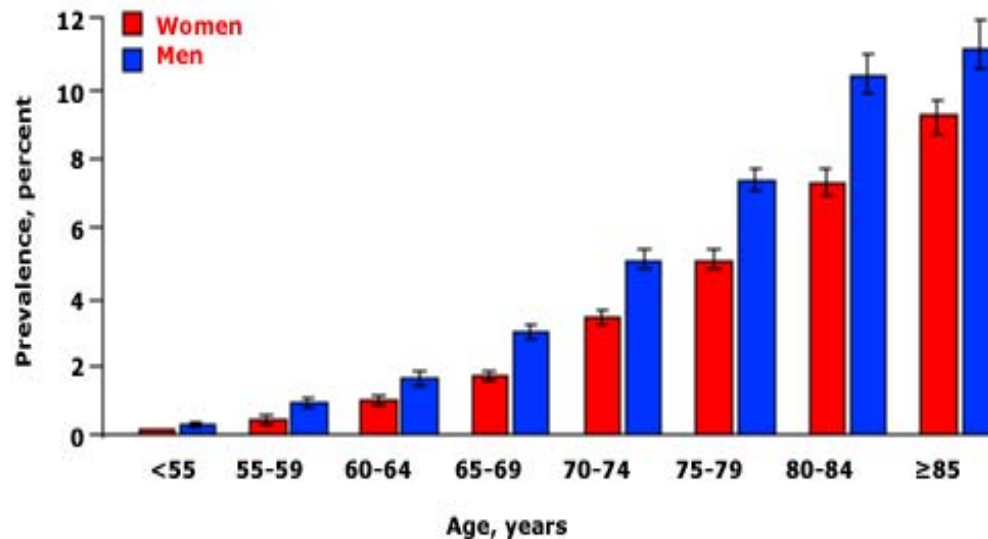


Risk Factors for Atrial Fibrillation

- Age
- Hypertension
- Valvular heart disease
- Coronary artery disease
- Hyperthyroidism
- Family History

Risk Factors

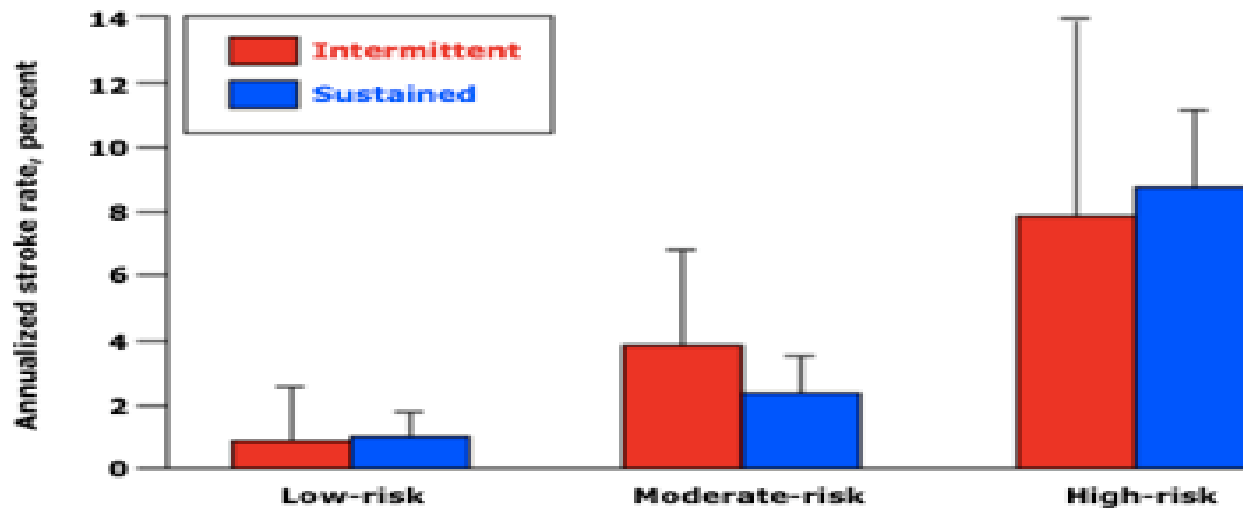
Prevalence of atrial fibrillation with age



In a cross-sectional study of almost 1.9 million men and women, the prevalence of atrial fibrillation increases with age, ranging from 0.1 for those less than 55 years of age to over 9 percent in those ≥85 years of age. At all ages, the prevalence is higher in men than women.

Data from Go, AS, Hylek, EM, Phillips, K, et al, JAMA 2001; 285:2370.

Rate of ischemic stroke is related to risk category

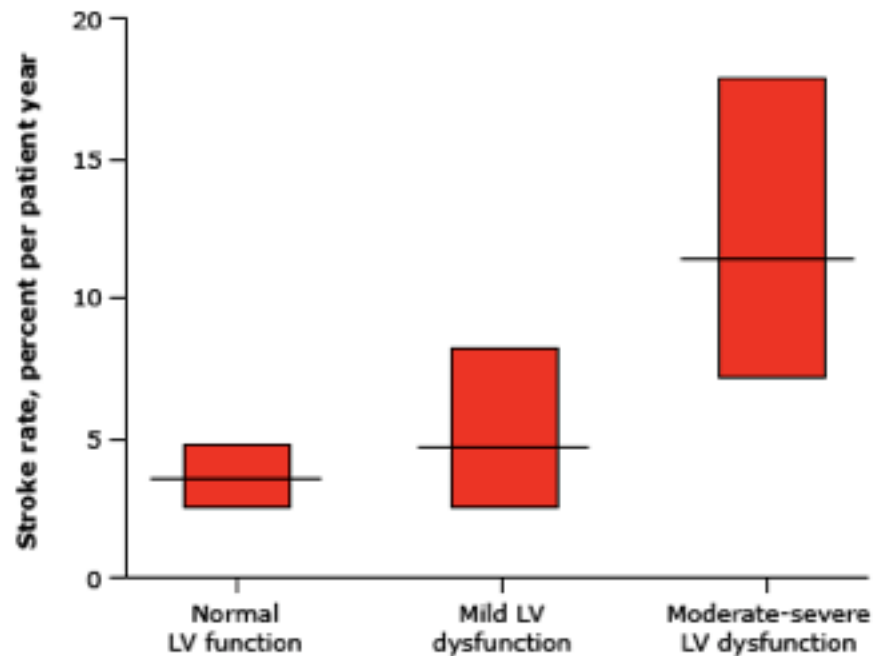


The incidence of a stroke in patients with either intermittent or sustained atrial fibrillation (AF) is related to risk category; the patients were treated with aspirin and followed for a mean of two years. Among those with intermittent AF, 24 percent were high risk, 32 percent are moderate risk and 43 percent are low risk; among those with sustained AF, the respective values were 30, 34, and 36 percent. The stroke risk was similar in patients with intermittent and sustained AF.

High risk: any of the following - age >75 and hypertension, age >75 and female, systolic BP >160 mmHg, prior stroke or transient ischemic attack; Moderate risk: either of - hypertension and age ≤75 or diabetes and no high risk features; Low risk: no moderate or high risk features.

Data from Hart, RG, Pearce, LA, Rothbart, RM, et al, *J Am Coll Cardiol* 2000; 35:183.

Significant left ventricular dysfunction predicts stroke in AF



In a prospective study of 1066 patients entered into three clinical trials evaluating the role of anticoagulation in nonvalvular AF (BAATAF, SPINAF, and SPAF) the incidence of a stroke was 9.3 percent per year in patients with moderate to severe left ventricular dysfunction compared to 4.4 percent per year in those with normal or mildly abnormal left ventricular function.

Data from: Atrial Fibrillation Investigators, Arch Intern Med 1998; 158:1316.

Congestive heart Failure

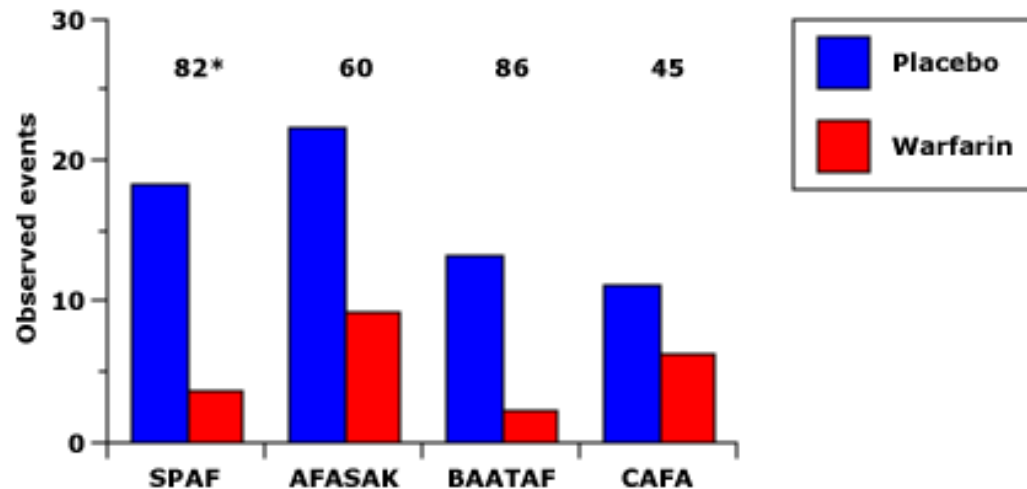
Hypertension

Age (greater than 75)

Diabetes mellitus

Secondary prevention(2pts)

Benefit of warfarin in chronic atrial fibrillation



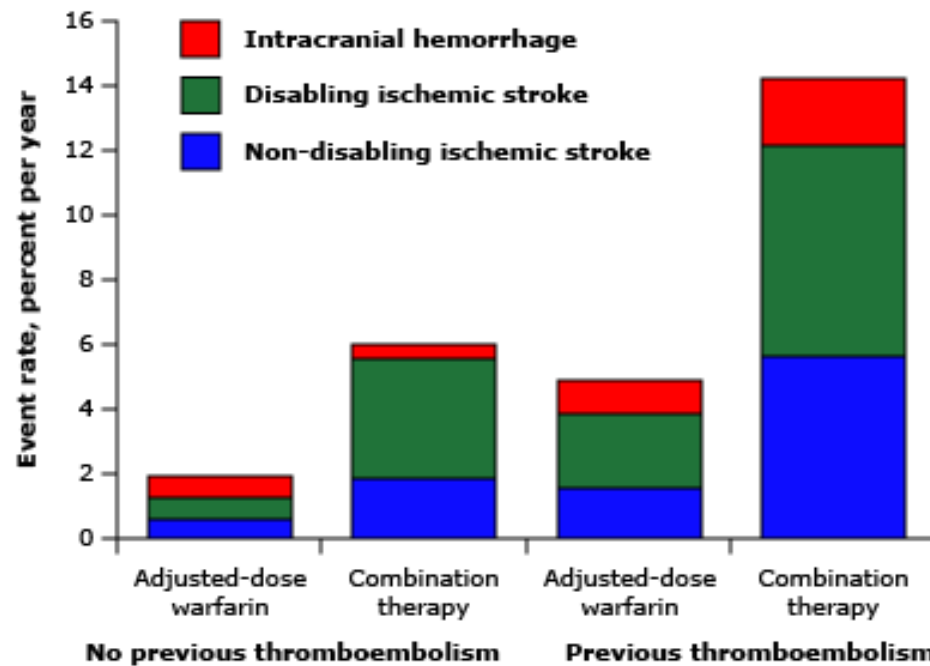
Efficacy of anticoagulation with warfarin to prevent ischemic stroke and other thromboemboli in four major studies. An intention to treat approach was used and transient ischemic attack and hemorrhage were excluded. The numbers at the top represent the risk reduction with warfarin therapy which ranged from 45 to 82 percent.

SPAF: Stroke Prevention in Atrial Fibrillation; AFASAK: Copenhagen AFASAK Study; BAATAF: Boston Area Anticoagulation Trial for Atrial Fibrillation; and CAFA: Canadian Atrial Fibrillation Anticoagulation Study.

* The data in the warfarin group in the SPAK assumes that half of the events were attributable to warfarin toxicity.

Data from Connolly, SJ, Laupacis, AN, Gent, M, et al, *J Am Coll Cardiol* 1991; 18:349.

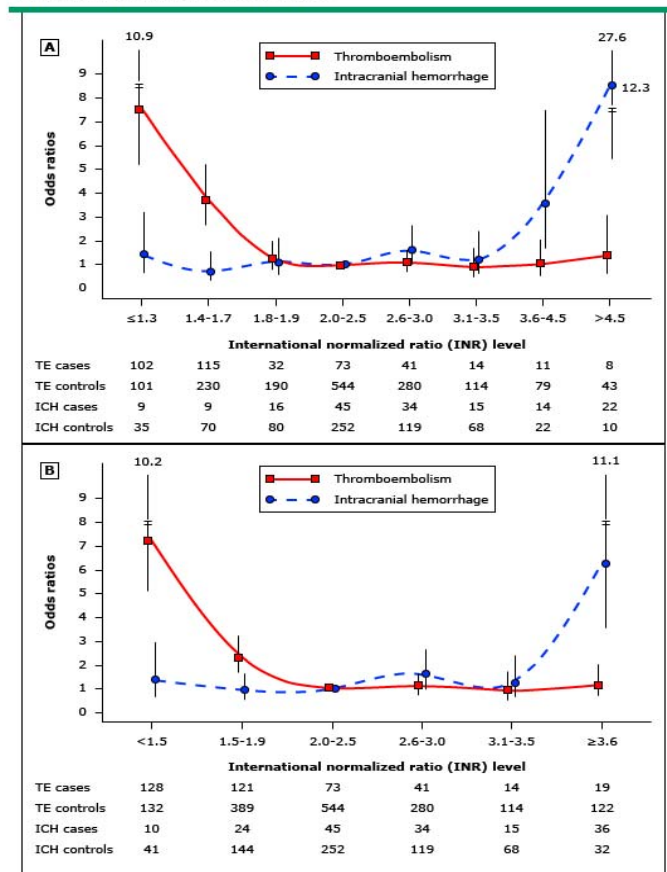
Increased stroke risk with low dose warfarin plus aspirin in AF



Results from the SPAF III trial of high-risk patients showing significantly higher event rates for intracranial hemorrhage and ischemic stroke in patients treated with fixed low dose warfarin plus aspirin compared with standard adjusted-dose warfarin. The risk was greater in those with a previous thromboembolic event.

Data from Stroke Prevention in Atrial Fibrillation Investigators. Lancet 1996; 348:633.

Optimal INR in atrial fibrillation

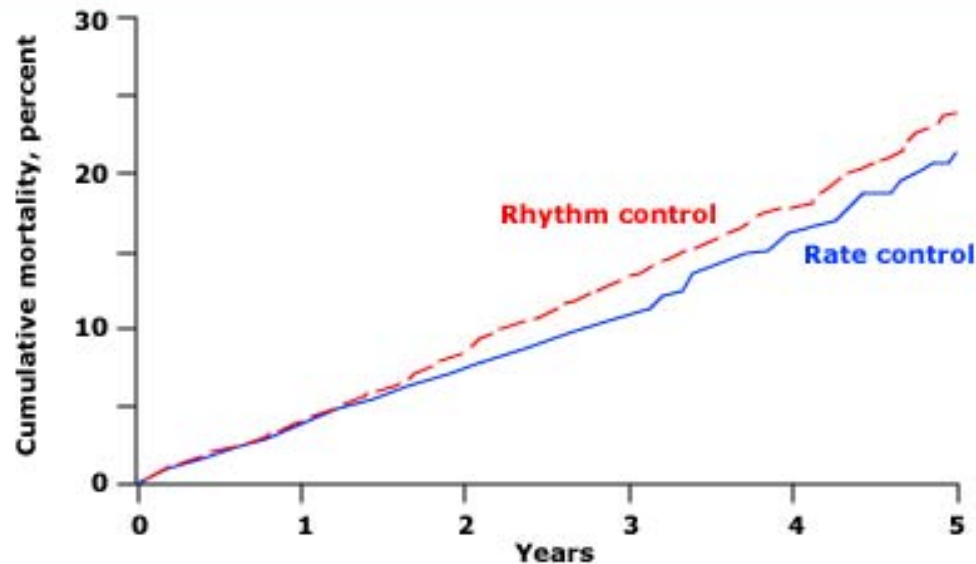


(A) ORs for TE (396 cases, 1581 controls) and ICH (164 cases, 656 controls) by INR level in adults with nonvalvular AF, with 8 INR categories using INR 2.0 to 2.5 as the referent. Vertical bars indicate 95 percent CIs. The numbers of cases and controls for each INR category are given below the figure.

(B) ORs for TE (396 cases, 1581 controls) and ICH (164 cases, 656 controls) by INR level in adults with nonvalvular AF, with 6 INR categories using INR 2.0 to 2.5 as the referent. Vertical bars indicate 95 percent CIs. The numbers of cases and controls for each INR category are given below the figure.

Reproduced with permission from: Singer, DE, Chang, Y, Fang, MC, et al. Should patient characteristics influence target anticoagulation intensity for stroke prevention in nonvalvular atrial fibrillation? The ATRIA study. *Circ Cardiovasc Qual Outcomes* 2009; 2:297. Copyright © 2009 Lippincott Williams & Wilkins.

Rate control versus rhythm control in AFFIRM

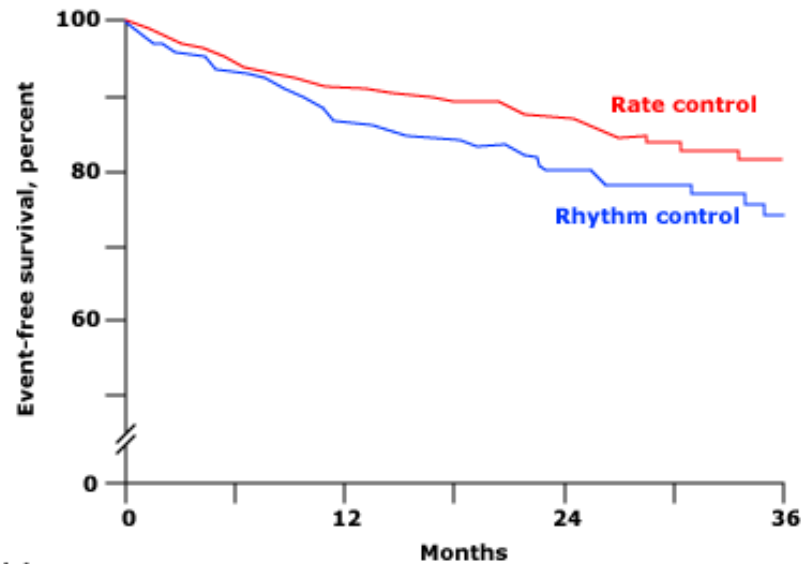


	No. of deaths					
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

Results of the AFFIRM trial in which 4060 patients with atrial fibrillation (AF) that was likely to be recurrent were randomly assigned to rhythm or rate control. The primary end point was overall mortality. There was an almost significant trend toward lower mortality with rate control (21.3 versus 23.8 percent, hazard ratio 0.87, 95 percent CI 0.75 to 1.01).

Data from Wyse, DG, Waldo, AL, DiMarco, JP, et al. *N Engl J Med* 2002; 347:1825.

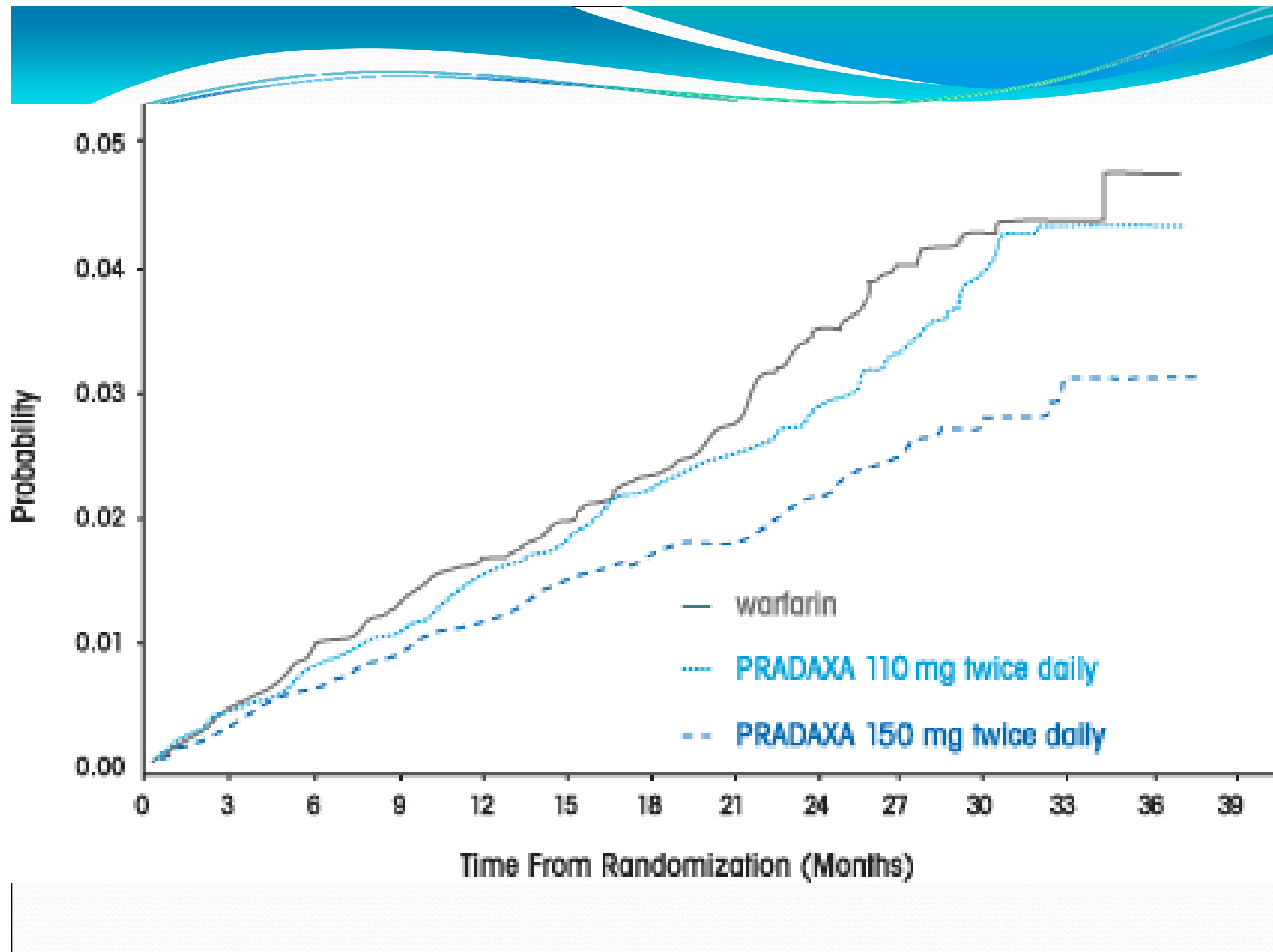
Rate control versus rhythm control in RACE



No. at risk	0	12	24	36
Rate control	256	239	232	222
Rhythm control	266	243	224	218

Results of the RACE trial in which 522 patients with recurrent persistent atrial fibrillation (AF) were randomly assigned to rhythm or rate control. The primary end point was a composite of cardiovascular death, heart failure, thromboembolism, bleeding, pacemaker placement, and antiarrhythmic drug side effects. There was an almost significant trend toward a lower incidence of the primary end point with rate control (17.2 versus 22.6 percent with rhythm control, hazard ratio 0.73, 90 percent CI 0.53 to 1.01).

Data from Van Gelder, IC, Hagens, VE, Bosker, HA, et al. *N Engl J Med* 2002; 347:1834.



	PRADAXA 150 mg twice daily	PRADAXA 110 mg twice daily	warfarin
Patients randomized	6076	6015	6022
Patients (%) with events	134 (2.2%)	183 (3%)	202 (3.4%)
Hazard ratio vs warfarin (95% CI)	0.65 (0.52, 0.81)	0.90 (0.74, 1.10)	
<i>P</i> -value for superiority	0.0001	0.3	
Hazard ratio vs PRADAXA 110 mg (95% CI)	0.72 (0.58, 0.90)		
<i>P</i> -value for superiority	0.004		

CI= confidence interval.

	PRADAXA 150 mg twice daily N (%)	warfarin N (%)	Hazard ratio (95% CI^{**})
Randomized patients	6076	6022	
Patient-years	12,033	11,794	
Intracranial hemorrhage^{†‡}	38 (0.3)	90 (0.8)	0.41 (0.28, 0.60)
Life-threatening bleed[§]	179 (1.5)	218 (1.9)	0.80 (0.66, 0.98)
Major bleeds[¶]	399 (3.3)	421 (3.6)	0.93 (0.81, 1.07)
Any bleed	1993 (16.6)	2166 (18.4)	0.91 (0.85, 0.96)

*Patients contributed multiple events and events were counted in multiple categories.

**Confidence interval.

The risk of major bleeds was similar with PRADAXA 150 mg and warfarin across major subgroups defined by baseline characteristics, with the exception of age, where there was a trend towards a higher incidence of major bleeding on PRADAXA (HR 1.2, 95% CI: 1.0 to 1.4) for patients ≥75 years of age.

Anticoagulation, recommendations for nonvalvular atrial fibrillation:

- **All patients who have had a prior embolic event.**
- **CHADS₂ score above 1.**
- **CHADS₂ score of 1 has the option of full anticoagulation vs. Aspirin therapy.**
- **No anticoagulation for patients with a CHADS₂ score of 0.**

Conclusions:

- **Incidence of atrial fibrillation increasing as the population ages.**
- **Majority of the morbidity associated with atrial fibrillation is due to stroke.**
- **Risk factors for stroke summarized in CHADS**
- **Anticoagulation reduces the risk of stroke in most patients with atrial fibrillation.**

Conclusions, cont:

- **The decision to anticoagulate is independent of the frequency of the atrial fibrillation.**
- **CHADS₂**
- **Warfarin has been the standard of care for stroke risk reduction in patients with atrial fibrillation.**
- **Direct thrombin inhibitors are a new class of agents proven to be equivalent to warfarin in stroke reduction with lower bleeding risk.**

Conclusions, cont.

- **Pradaxa (dabigatran) was approved for use by the FDA in 2010 after the results of the RE-LY trial.**
- **Onset of action is within 2-hours of the first dose.**
- **Short half-life requires twice daily dosing.**
- **No known antidote for patients presenting with bleeding side-effects.**
- **Renally excreted: dose must be adjusted for patients with renal insufficiency.**

Conclusions, cont.

- **No need for PT/INR monitoring with direct thrombin inhibitors.**
- **Lower bleeding risk at cost of lack of blood test to monitor anticoagulation and no antidote for patients presenting with bleeding.**
- **More investigational agents likely to be available soon.**