

Atrial Fibrillation in Chinese

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Atrial Fibrillation

- Recognition and prevalence
 - Risk of Stroke and Prevention
 - Conversion from AF to normal sinus rhythm (NSR)
 - Maintenance of NSR
 - Control of ventricular rate
 - Curative procedures
- Theme: Comparison to Chinese patients**

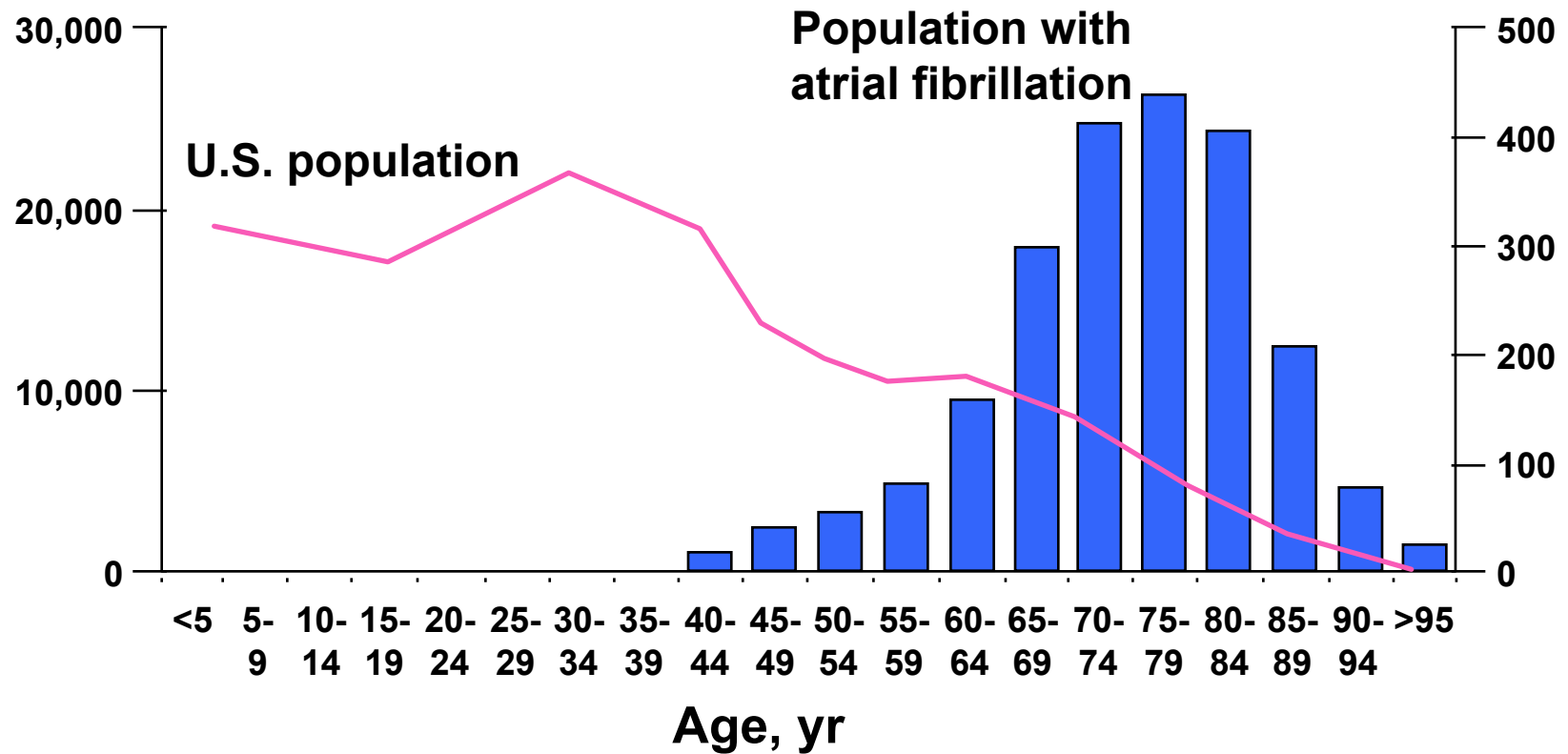
Atrial Fibrillation

- Recognition and Prevalence

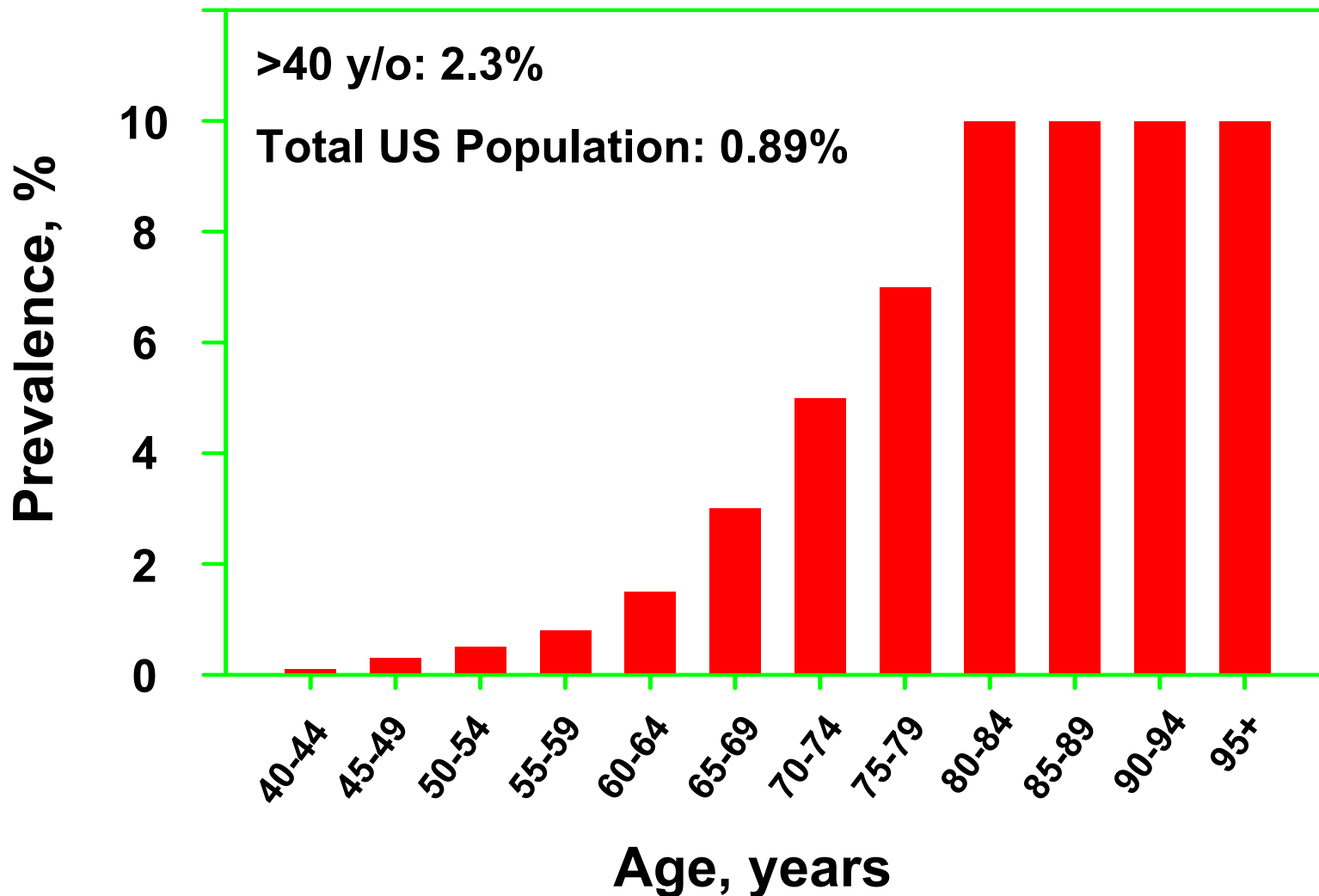
Atrial Fibrillation Demographics by Age

U.S. population
x 1000

Population with AF
x 1000



Age and Incidence of AF



Atrial Fibrillation

- Common and age-dependent
2 - 5% over age 65
- Significant risk of stroke
4% per year (Framingham Study)
- High risk of embolism with cardioversion

Atrial Fibrillation in Chinese

Prevalence of atrial fibrillation has not been examined in large studies

- Chinese Acute Stroke Trial (CAST)¹:
 - 7% of 20,655 Chinese patients (68% ≥ Age 60) with ischemic stroke had AF

¹ CAST, *Stroke* 2000;31:1240

Atrial Fibrillation and Stroke in Chinese

Prevalence of stroke in atrial fibrillation has not been examined in large studies

- ◆ Woo, Lau (*Neuroepidemiology* 1990;9:131):

- In 427 Chinese aged 60 years

- Subjects who initially had a history of transient ischemic attacks (TIA) and non-rheumatic atrial fibrillation had a greater than 10-fold increased risk of stroke in the subsequent 30 months

- Cao, et al (*Chinese Med J* 2000;113:320)

- Autopsy series. Cerebral embolism observed in 27 of 93 (29%) patients with AF

- Average age = 73 years

- AF > 3 years, heart failure, or diabetes had higher incidence

Atrial Fibrillation and Stroke in Chinese

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Atrial Fibrillation: Causes

- Cardiac
- Non-cardiac
- “Lone” atrial fibrillation

Atrial Fibrillation: Cardiac Causes

- Hypertensive heart disease
- Ischemic heart disease
- Valvular heart disease
 - Rheumatic: mitral stenosis
 - Non-rheumatic: aortic stenosis, mitral regurgitation
- Pericarditis
- Cardiac tumors: atrial myxoma
- Sick sinus syndrome
- Cardiomyopathy
 - Hypertrophic
 - Idiopathic dilated (? cause vs. effect)
- Post-coronary bypass surgery

Atrial Fibrillation: Non-Cardiac Causes

- Pulmonary
 - COPD
 - Pneumonia
 - Pulmonary embolism
- Metabolic
 - Thyroid disease: hyperthyroidism
 - Electrolyte disorder
- Toxic: alcohol ('holiday heart' syndrome)

“Lone” Atrial Fibrillation

- Absence of identifiable cardiovascular, pulmonary, or associated systemic disease
- Approximately 0.8 - 2.0% of patients with atrial fibrillation (Framingham Study)¹
- In one series of patients undergoing electrical cardioversion, 10% had lone AF²

¹ *JAMA* 1985;254:3449

² *Am J Cardiol* 1991;68:41

Atrial Fibrillation: Clinical Problems

- Embolism and stroke (presumably due to LA clot)
- Acute hospitalization with onset of symptoms
- Anticoagulation, especially in older patients (> 75 yr.)
- Congestive heart failure
 - Loss of AV synchrony
 - Loss of atrial “kick”
 - Rate-related cardiomyopathy due to rapid ventricular response
- Rate-related atrial myopathy and dilatation
- Chronic symptoms and reduced sense of well-being

Atrial Fibrillation

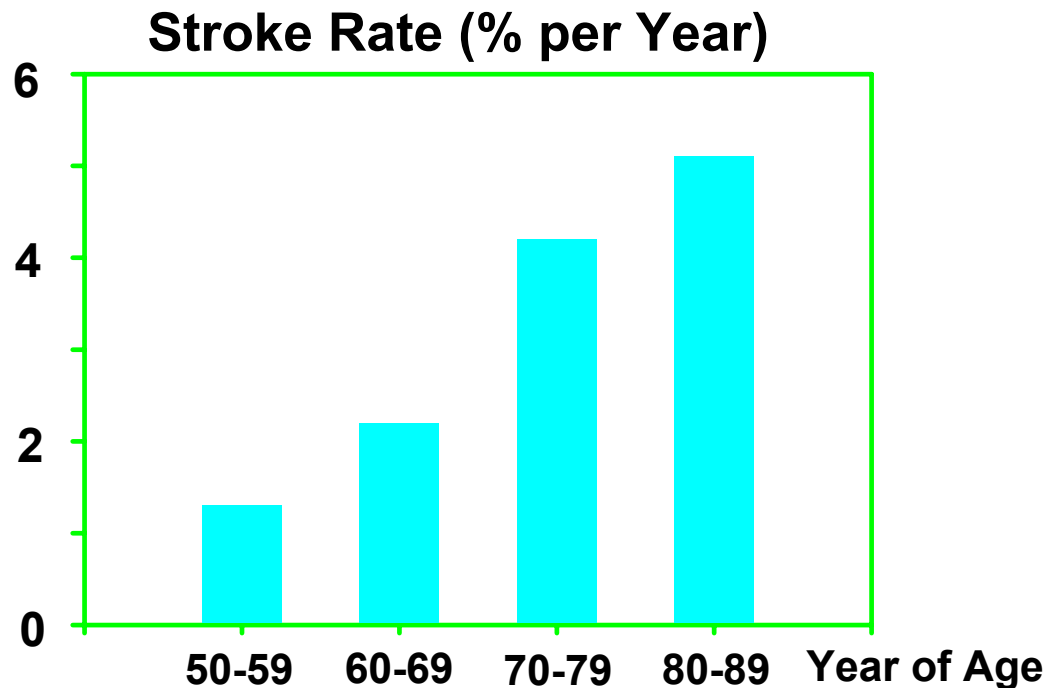
- Risk of Stroke and Prevention with Anticoagulation or Aspirin

Atrial Fibrillation and Stroke

- Anticoagulant therapy is clearly indicated and beneficial in rheumatic atrial fibrillation

Atrial Fibrillation and Stroke

- Risk: 5 - 8% per year in high-risk patients
- Stroke rate increases with age¹ (50% of AF related strokes occur in patients > 75 years old)



¹ *Am J Med* 2000;108:36

Atrial Fibrillation and Stroke

- Associated with silent cerebral infarctions
 - 1.3% per year¹
- Worse outcome (high mortality, more disability) in patients with AF who suffer a stroke² . 3 times the risk of death in CAST (Chinese Acute Stroke Trial)
 - Reasons unknown (older, larger infarct , impaired consciousness or clotting cascade)
- Similar stroke risk in patients with chronic and paroxysmal AF³

¹ *SPINAF, Circ 1995;92:2178*

² *Framingham Study, Stroke 1966;27:1760; European Community Stroke Project, Stroke 2001;32:392; CAST, Stroke 2000;31:1240*

³ *Boston Trial, N Engl J Med 1990;323:1505*
SPINAF, Circ 1991;84:527

Atrial Fibrillation and Stroke

- Embolic events can occur with acute AF for as little as 72 hours
- Up to 90% of paroxysmal AF are not detected by the patient
- Episodes of AF lasting more than 48 hours may be asymptomatic in 40% of the patients

Risk Factors for Thromboembolism in Non- Rheumatic Atrial Fibrillation

- History of hypertension: (systolic BP > 160 mm Hg)
- Prior stroke or TIA
- Diabetes
- Recent heart failure or reduced LV function
- Thyrotoxicosis
- Age > 65 - 75 years

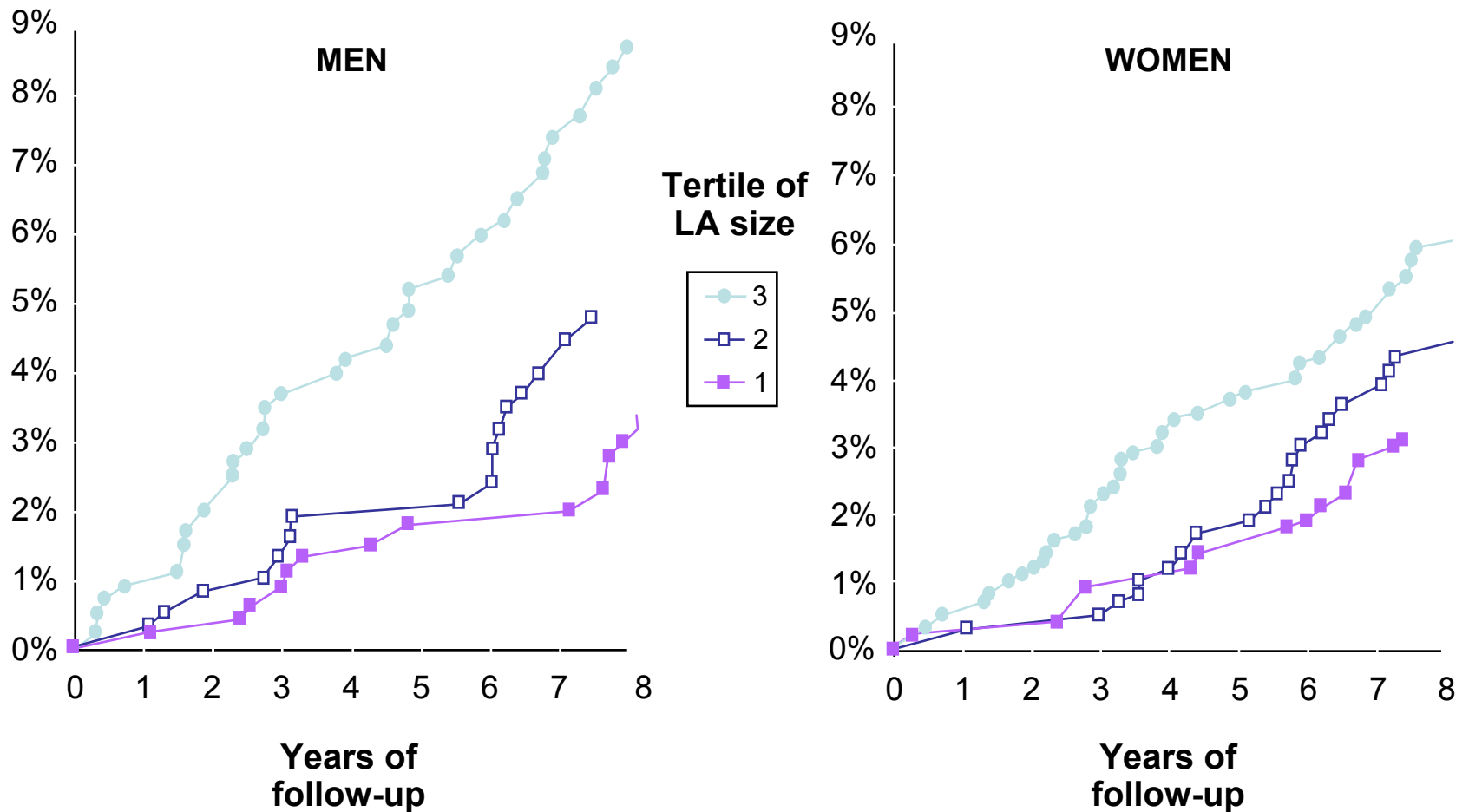
Risk Factors for Thromboembolism in Non-Rheumatic Atrial Fibrillation

Risk Factors	Relative Risk
Prior stroke or TIA	2.5
History of hypertension	1.6
Congestive heart failure	1.4
Advanced age	1.4
Diabetes mellitus	1.7
Coronary artery disease	1.5

Echocardiographic Risk Factors for Stroke Factors in Patients with AF

- LV systolic dysfunction (RR=2.5)
- Stasis in the left atrial appendage (LAA)
 - Peak flow velocity < 20 cm/sec
- Spontaneous echo contrast (“smoke”) in LA
 - Not resolved with anticoagulation
 - Present in 1/2 to 2/3 of patients
- Increased LA size

Incidence of Stroke by Left Atrial Size (Framingham Study)



Role of Transesophageal echo (TEE) in Atrial Fibrillation

- Detection of left atrial abnormality (7.8% per year)
 - Thrombus, LAA stasis, stroke
 - More sensitive (92%) and specific (98%) for detecting left atrial clot than TTE
 - Thromboembolic event is presumably due to left atrial clot
 - Most clots are in left atrial appendage but poorly visualized by transthoracic surface echo
- Documentation of complex aortic plaque (12% per year)
- Both LAA and aortic plaque (20.5% per year)

Rationale for Precardioversion TEE

- Absence of clot on TEE may obviate need for anticoagulation.
- Avoiding delay necessary for prolonged anticoagulation prior to cardioversion increases likelihood of successful cardioversion and maintenance of normal sinus rhythm.

Major Clinical Trials in Primary Prevention of Stroke in Non-Rheumatic Atrial Fibrillation

- SPAF¹ Stroke Prevention in Atrial Fibrillation
- BAATAF² Boston Area Anticoagulation Trial for Atrial Fibrillation
- CAFA³ Canadian Atrial Fibrillation Anticoagulation
- AFASAK⁴ Copenhagen Investigators
- SPINAF⁵ Stroke Prevention in Nonrheumatic Atrial Fibrillation
- EAFT⁶ European Atrial Fibrillation Trial

¹ *Circulation* 1991;84:527

² *N Engl J Med* 1990;323:1505

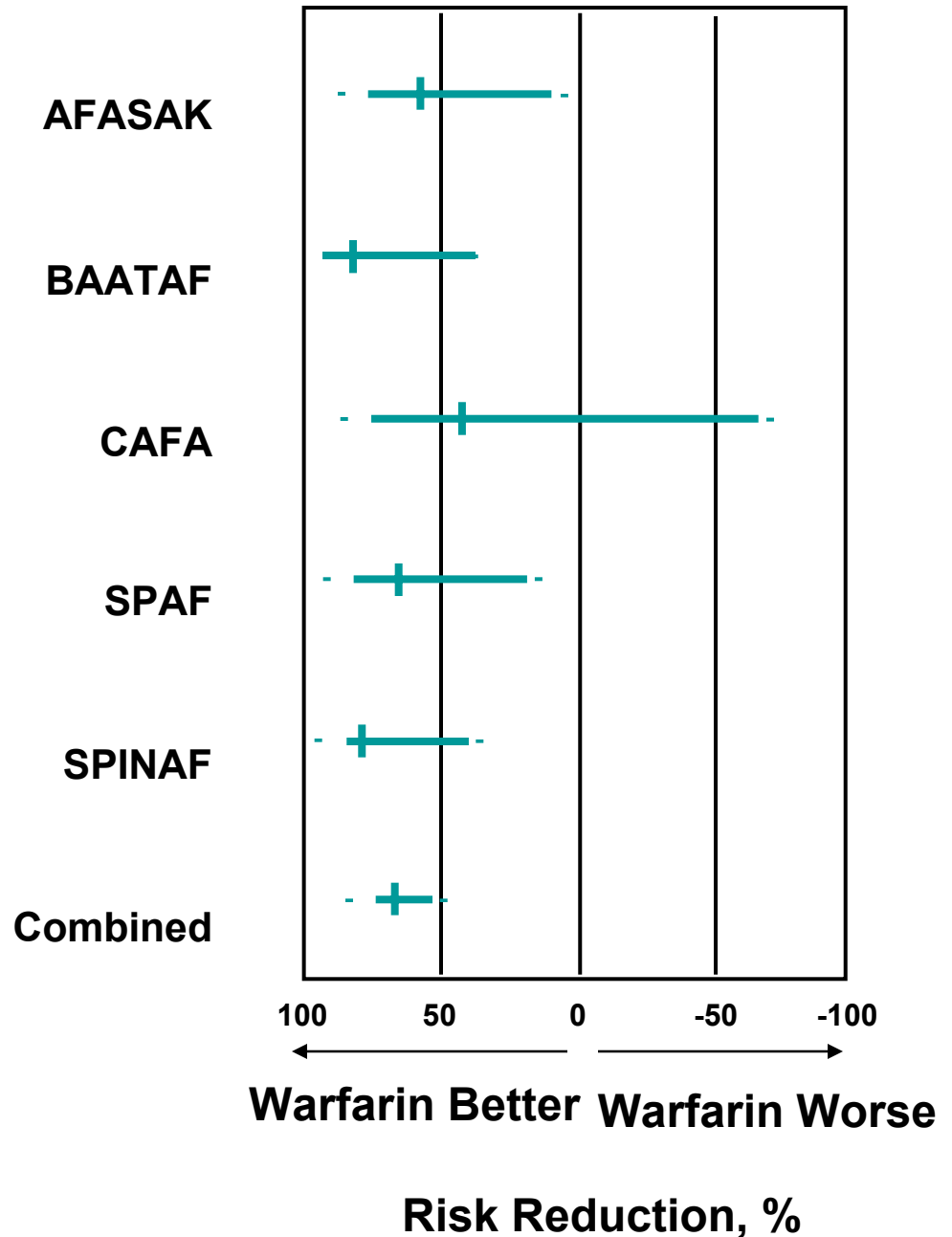
³ *J Am Coll Cardiol* 1991;18:349

⁴ *Lancet* 1989;1:175

⁵ *N Eng J Med* 1992;327:1406

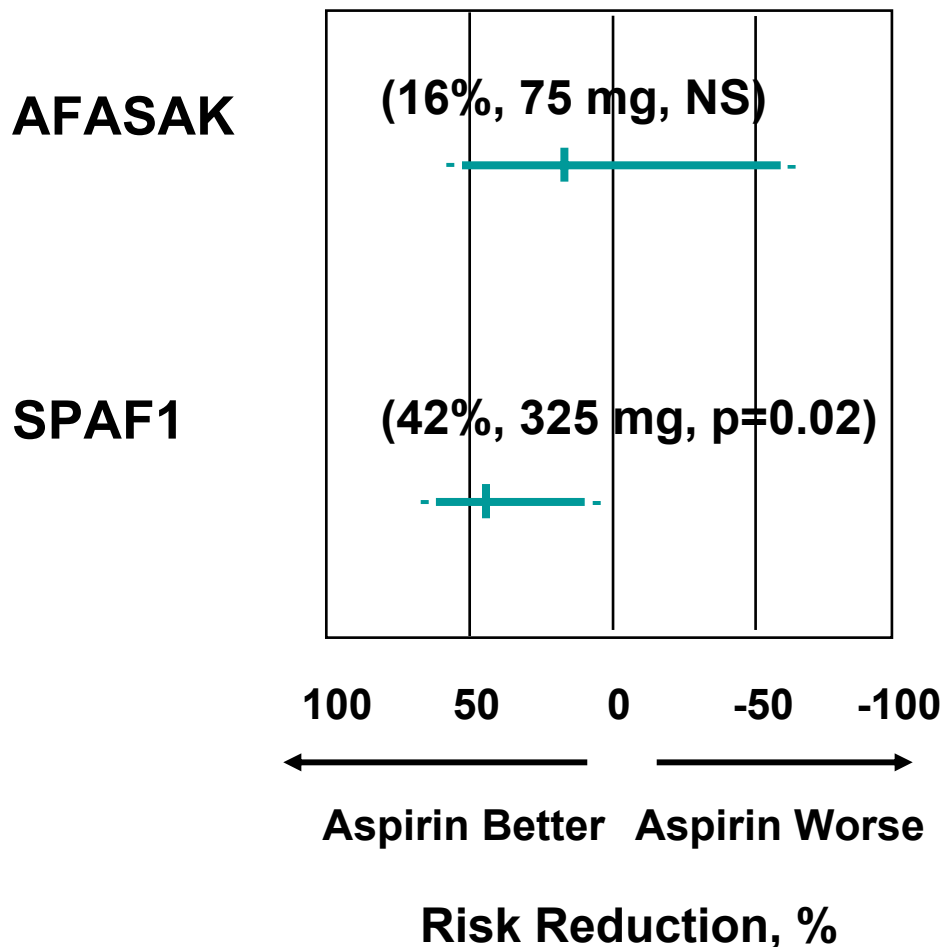
⁶ *Lancet* 1993;342:1255

Stroke Prevention in Atrial Fibrillation: Warfarin vs placebo

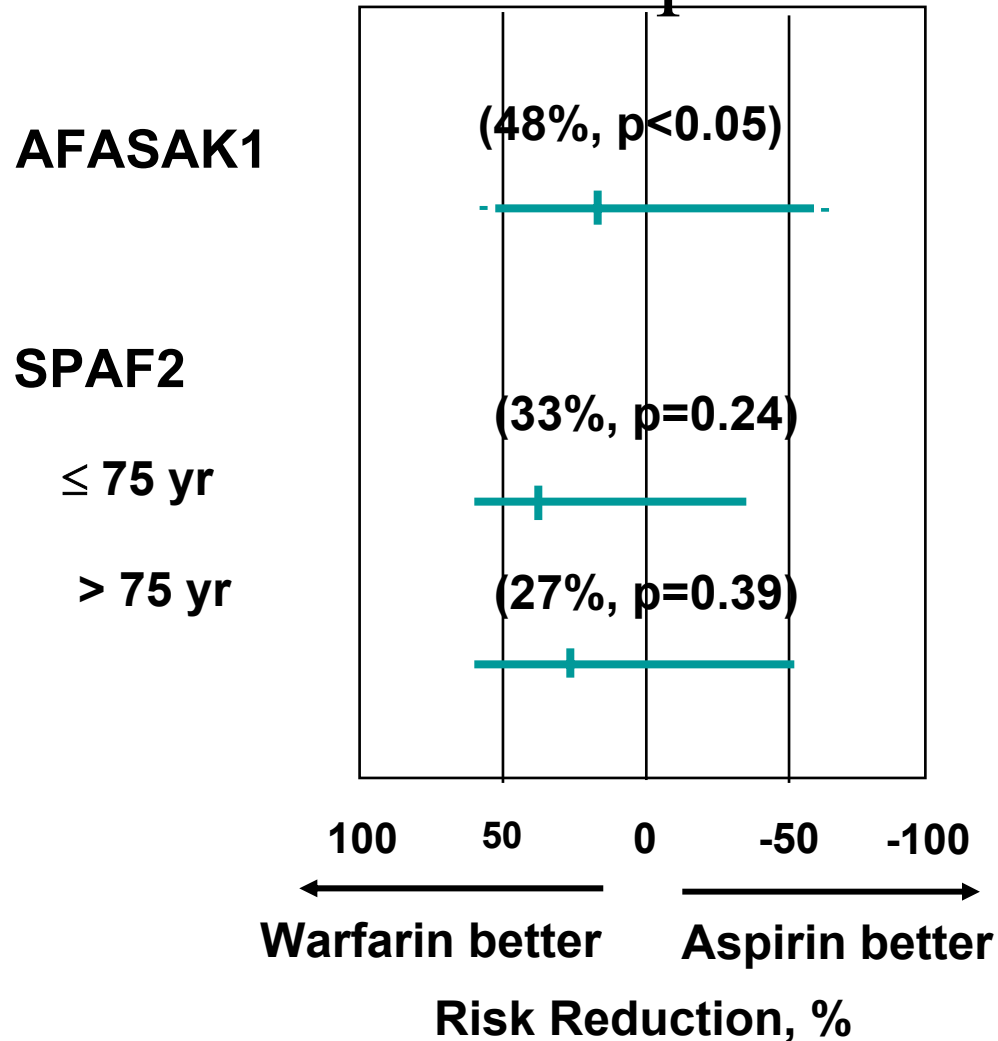


*Atrial Fibrillation Investigators.
Arch Intern Med. 1994;154:1449*

Stroke Prevention in Atrial Fibrillation: ASA vs Placebo



Stroke Prevention in Atrial Fibrillation: Warfarin vs Aspirin



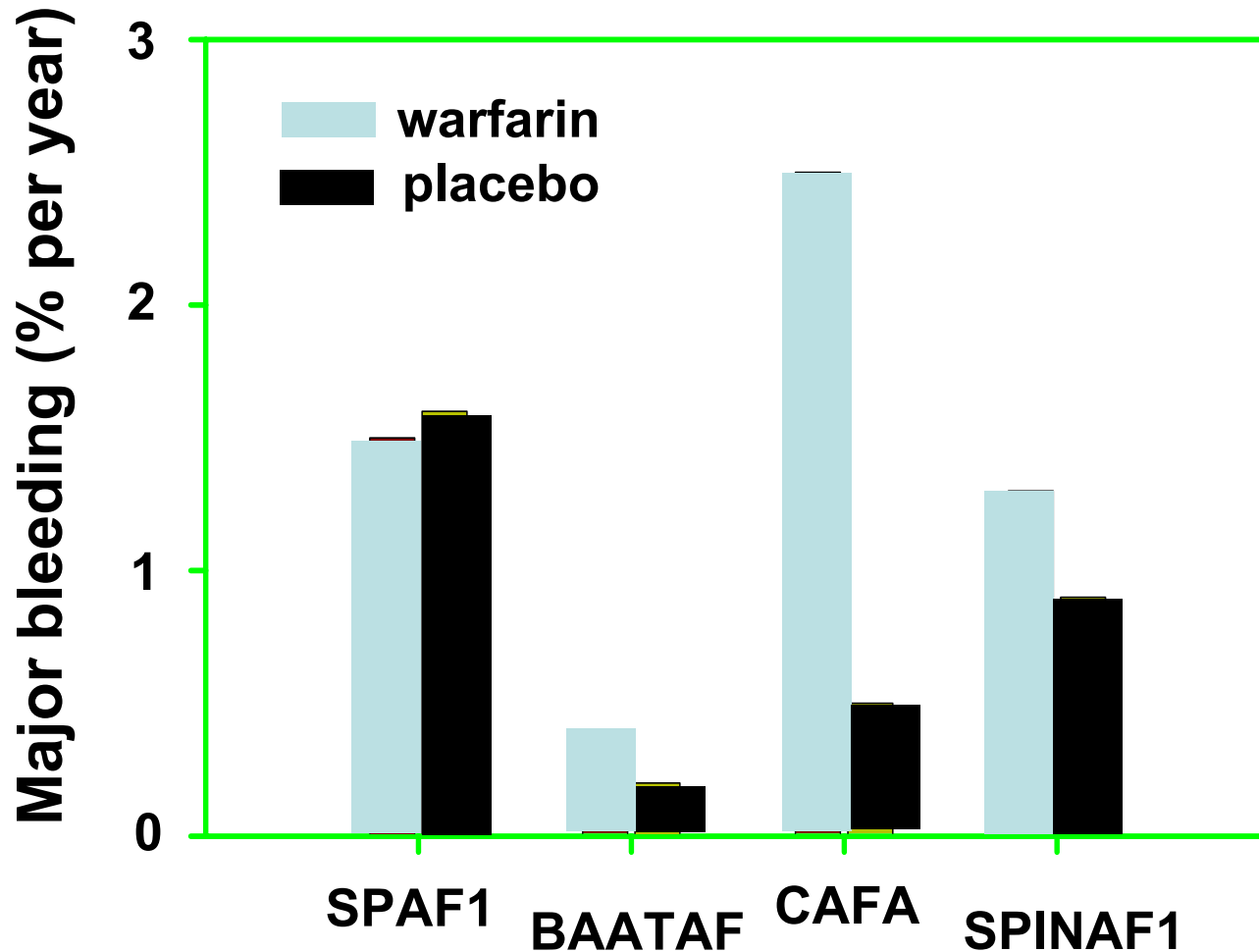
Efficacy of ASA for Stroke Prevention

(summary)

- Unlike warfarin, efficacy is not clear and remains controversial
- Has some degree of efficacy for preventing stroke in AF
 - minor strokes
 - Age 65 – 75 years without risk factors
- Probably less effective than warfarin

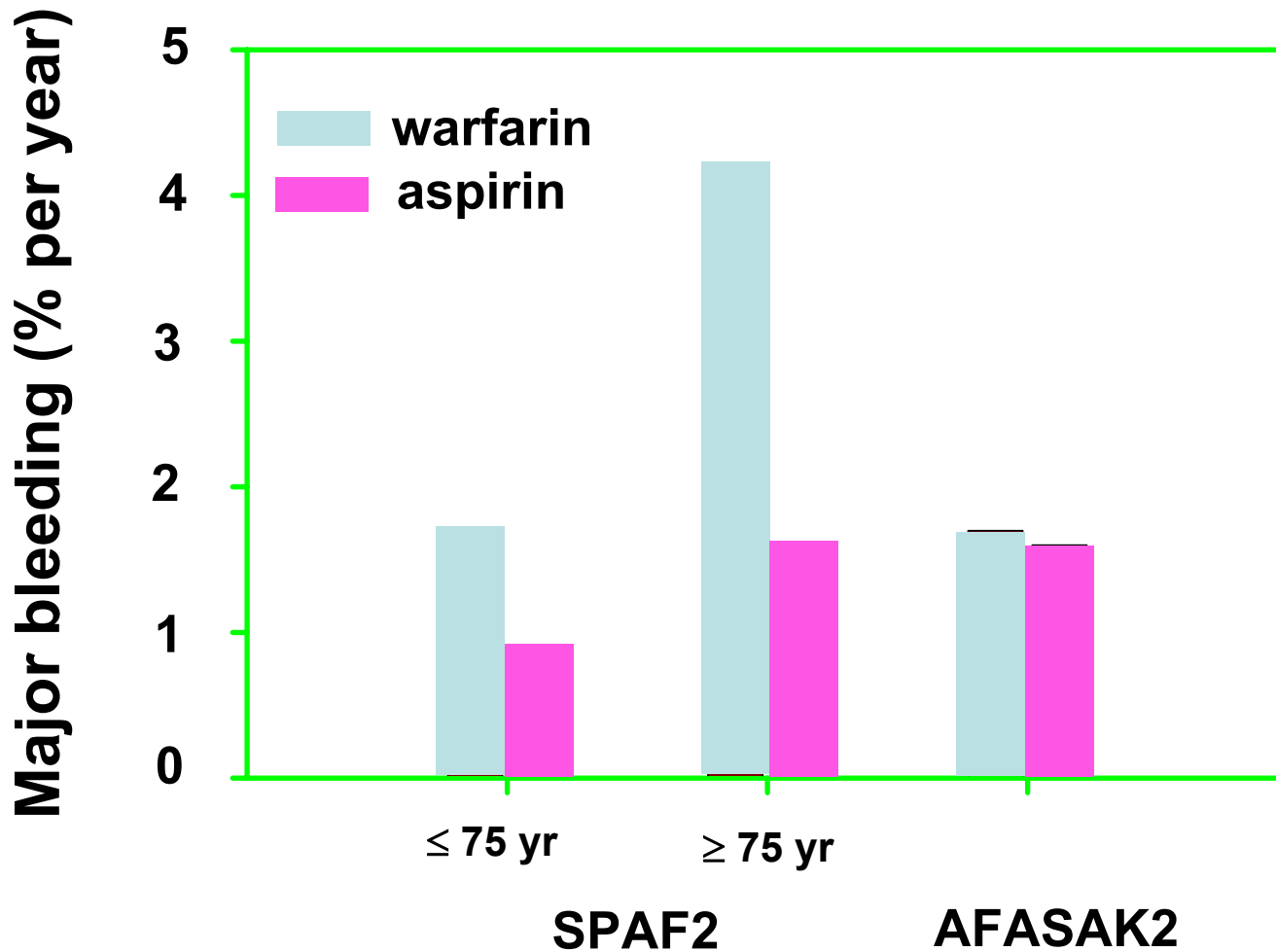
Major Bleeding in AF Trials

Warfarin vs Placebo



Major Bleeding in AF Trials

Warfarin vs Aspirin



Bleeding Risk Index

- Age ≥ 65
- History of Stroke
- History of GI bleed
- Recent MI
- One or more of the following:
 - Hematocrit $< 30\%$
 - Serum creatinine > 1.5 mg/dl (> 133 μM)
 - Diabetes mellitus

Recommendations for Anticoagulation for Non-rheumatic AF

American College of Chest Physicians

Risk Group/Status	Annual Risk	Recommendation
Low	1%	Aspirin (325 mg/day)
One moderate risk factor	1- 4%	Aspirin or warfarin (INR = 2.5; 2.0-3.0)
High or > 1 moderate risk factor	8-12%	Warfarin (INR = 2.5; 2.0-3.0)

High Risk: History of TIA, systemic embolism or stroke, hypertension, valve diseases, heart failure or reduced LV function, thyroid disease or age ≥ 75

Moderate Risk: Age 65-75 years, diabetes, coronary heart disease with preserved left ventricular function

Low Risk: Age < 65 years without any of the above clinical diagnosis

Warfarin Usage in Chinese Patients

General perceptions by physicians:

- -Warfarin is less commonly used for Chinese patients
- -Risks and benefits of anticoagulation demonstrated in Western trials may not apply to Chinese patients
- -Chinese patients treated with warfarin have higher bleeding risks than Caucasian patients
- -It is more difficult to maintain a therapeutic INR range in Chinese patients
- -Chinese patients require less warfarin dosage
- -Optimal INR for Chinese patients may be lower

Warfarin is less commonly used for Chinese patients?

- Western studies: 21 to 67% patients with indications for warfarin received this treatment
- Limited data for Chinese patients are available:
 - One small study from Hong Kong: 44% of 91 patients with non-rheumatic AF were appropriately treated with warfarin (Hong Kong Med J 2003;9:179)

Bleeding Risk with Warfarin Treatment in Chinese Patients

Study	Location	n	Age	AF	INR	Major	Minor
Chan, Tiu ¹	HK	131	68	60% [§]	NA [†]	1.8%	18.5%
Sun, Hu ²	CN	435	~65	100%	NA	1.2%	6%
Leung, Tam ³	HK	91/207	>65	100%	1.96	2.14%	8.56%
Chenhsu ⁴	Tapei	226	NA	NA	1.9	14% [‡]	

Western AF Trials:

Major *: 0.5 to 2.6% per year (SPAF II: 4.2% in age >75 years)

¹ *J Chin Med Assoc* 2004;67:55

² *Zhonghua Nei Ke Za Zhi* 2004;43:258

³ *Hong Kong Med J* 2003;9:179

⁴ *Ann Pharmacother* 2000;34:1395

* Bleeding requiring transfusion or resulting in permanent disability or death

§ Non-rheumatic AF

† 50% time within targeted INR range

‡ 38.4% in 34 months

Warfarin Requirement in Chinese Patients

- ◆ Yu, Chan, Critchley, Woo. (*QJM* 1996;89:127)
 - 151 Chinese out-patients on stable maintenance dose of warfarin with international normalized ratio of 2 to 2.5
 - Mean daily warfarin requirement was 3.3 ± 1.4 mg
 - Progressively lower warfarin requirement with increasing age
- ◆ Sun, Hu (*Zhonghua Nei Ke Za Zhi* 2004;43:258)
 - Mean dose of warfarin for 435 AF patients was 2.8 ± 0.8 mg (achieved INR value not reported)
- ◆ Chenhsu, Chiang, Chou, Lin (*Ann Pharmacother* 2000 34:1395)
 - Mean dose of warfarin for 226 patients was 3.1 ± 1.2 mg (INR=1.9)

Chinese patients may have a lower warfarin requirement to achieve a therapeutic INR range than Caucasian patients (4- 6 mg)

Possible Interactions in Chinese Patients

Results of PubMed search using “Chinese AND amiodarone”, “Chinese AND amiodarone”, “Chinese AND sotalol”, “Chinese AND procainamide”, “Chinese AND flecainide” and “Chinese herbs AND arrhythmias:

- 4 days of drinking a concentrated Chinese herbal tea made from **Lycium barbarum L. fruits** (3-4 glasses daily) elevated previous stable INR of 2-3 to 4.1 (*Ann Pharmacother* 2001;35:1199)
- **Dong quai** (Phytochemical analyses found it to consist of natural coumarin derivatives) potentiated effect of warfarin (*Pharmacotherapy* 1999;19:870)
- Rootstocks of **aconitum plants** (chuanwu and caowu) may be arrhythmogenic (*Pacing Clin Electrophysiol* 1992;15:831, *Drug Saf* 2002;25:823)

Possible pharmacokinetics alterations of commonly used drugs in AF in Chinese patients

Results of PubMed search using “Chinese AND amiodarone”, “Chinese AND propafenone”, “Chinese AND sotalol”, “Chinese AND procainamide”, and “Chinese AND flecainide” :

No clinically relevant data were found

Challenges faced by Chinese Physicians

- Large-scale, critically-designed multi-center epidemiology studies to evaluate the incidence of atrial fibrillation and thrombo-embolism, risks and benefits of treatment among Chinese patients
- China is a developing country. Anticoagulation requiring a vigorous follow-up program (anti-coagulation clinic) involving frequent monitoring of INR

Challenges faced by Chinese Physicians

- Education of healthcare providers on the risks of thromboembolic risks and the importance of the use and monitoring of anticoagulation therapy
- Prevalent use of alternative medicine in Chinese patients with unknown interactions with traditional western drugs

The following slides have been included for references only. They will not be presented during the lecture

Rate versus Rhythm Control in Management of AF

- -Maintaining sinus rhythm
 - Cardioversion and treatment with antiarrhythmic drugs
 - Loss of AV synchrony
 - Loss of atrial “kick”
- -Rate control
 - Controlling ventricular response rate with drugs

AFFIRM

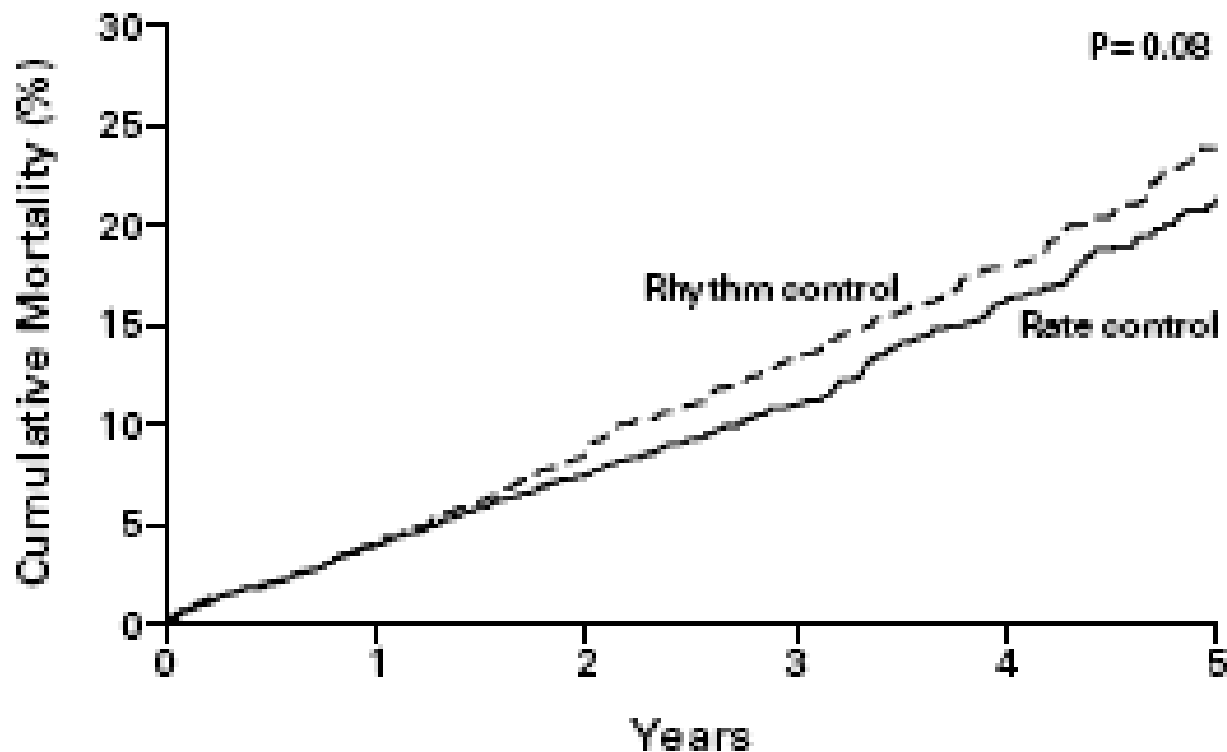
- Atrial Fibrillation Follow-up Investigation of Rhythm Management
- Hypothesis: Effect on mortality of antiarrhythmic therapy to maintain sinus rhythm vs. ventricular rate control alone, in the presence of anticoagulation
- Primary endpoint: Total mortality
- Secondary endpoint: Disabling CVA
Cost of therapy
Quality of life

AFFIRM: Patient Characteristics

- Patients enrolled 4,060
- Age 69.7 ± 9.0 years
- Hypertension 70.8%
- Coronary artery disease 38.2%
- Left ventricular EF 0.55 ± 0.14
- LVEF < 0.50 26%

AFFIRM: Cumulative All Cause Mortality

No difference in mortality



NO. OF DEATHS

Rhythm control
Rate control

number (percent)

0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

AFFIRM

- More patients in rhythm-control group than in the rate-control group were hospitalized
- More adverse events in the rhythm-control group
- No difference in embolization frequency
- The majority of strokes occurred after warfarin was stopped or INR subtherapeutic
- Patients with rhythm control (in sinus rhythm) remain at risk for embolization
 - Anticoagulation should be continued

Atrial Fibrillation

- Conversion from AF to Normal Sinus Rhythm (NSR)
 - cardioversion with
 - anti-arrhythmic drugs
 - direct current shock

Timing of Cardioversion for Atrial Fibrillation

- Chronic
 - 1 month warfarin → cardioversion (CV)
- Uncertain duration
 - Stable → 1 month warfarin → CV
 - Unstable → TEE → CV
- Continue 1 month warfarin after cardioversion
- Maintain INR at 2.0 to 3.0 with warfarin

Pharmacologic Cardioversion

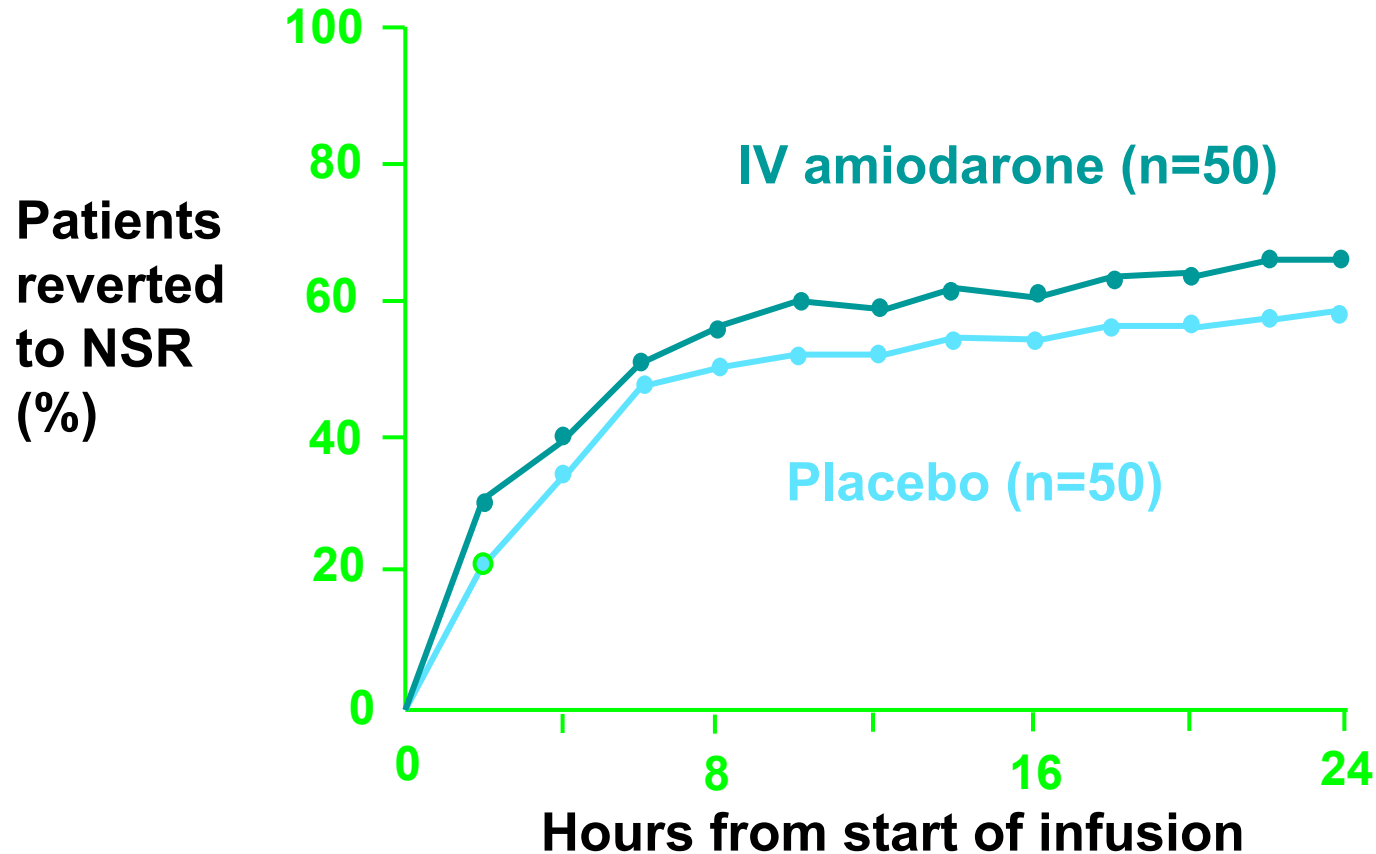
- Class 1A: quinidine, procainamide, disopyramide
- Class 1C: Flecainide, propafenone
- Class III: amiodarone, sotalol, ibutilide

Pharmacologic Cardioversion

- There are minimal data from randomized clinical trials to show one drug is better than others in converting atrial fibrillation to NSR

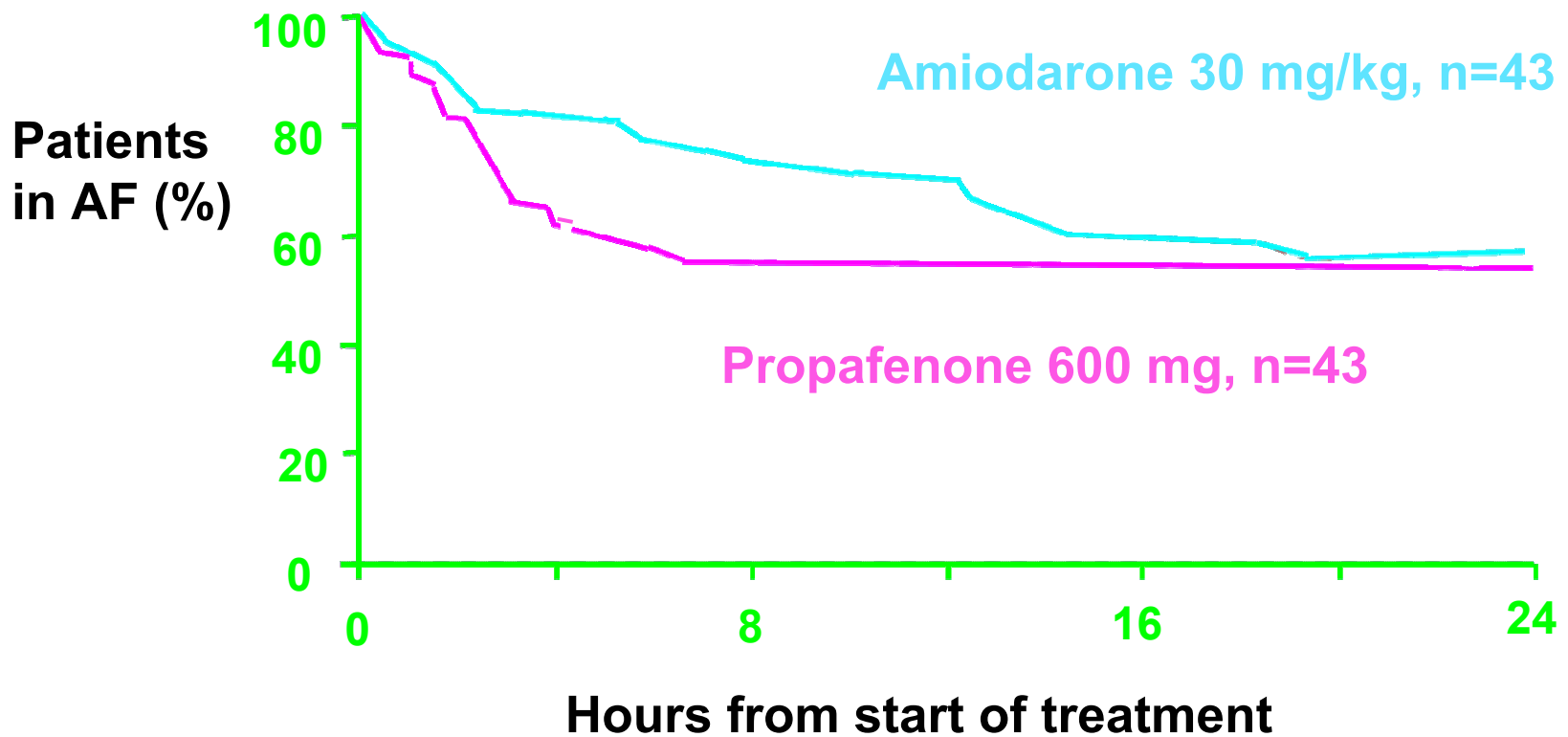
Pharmacological Cardioversion

Amiodarone is not effective in the acute conversion of AF (< 1 week) to NSR



Pharmacological Cardioversion

Single oral dose of amiodarone is as effective as propafenone in the acute conversion of AF (< 2 week) to NSR



Use of Amiodarone in Cardioversion

- Data on amiodarone are confusing because the drug may be given intravenously, orally, or by both routes concurrently.
- The drug is modestly effective for pharmacological cardioversion of recent-onset AF (Recommendation: IIa)
- Acts less rapidly and probably less effectively than other agents.
- Restoration of sinus rhythm may not occur for days or weeks.

From ACC/AHA Clinical Practice Guidelines, 2001

Use of Amiodarone in Cardioversion

In-patient:

- Oral
 - 1.2-1.8 g per day until 10 g total, then 200-400 mg per day maintenance
- IV/Oral:
 - 5-7 mg/kg over 30-60 min, then 1.2-1.8 g per day IV or in divided oral doses until 10 g total, then 200-400 mg per day maintenance
- **Out-patient:**
- 600-800 mg per day until 10 g total, then 200-400 mg per day maintenance

A Few Words of Cautions in Amiodarone Usage

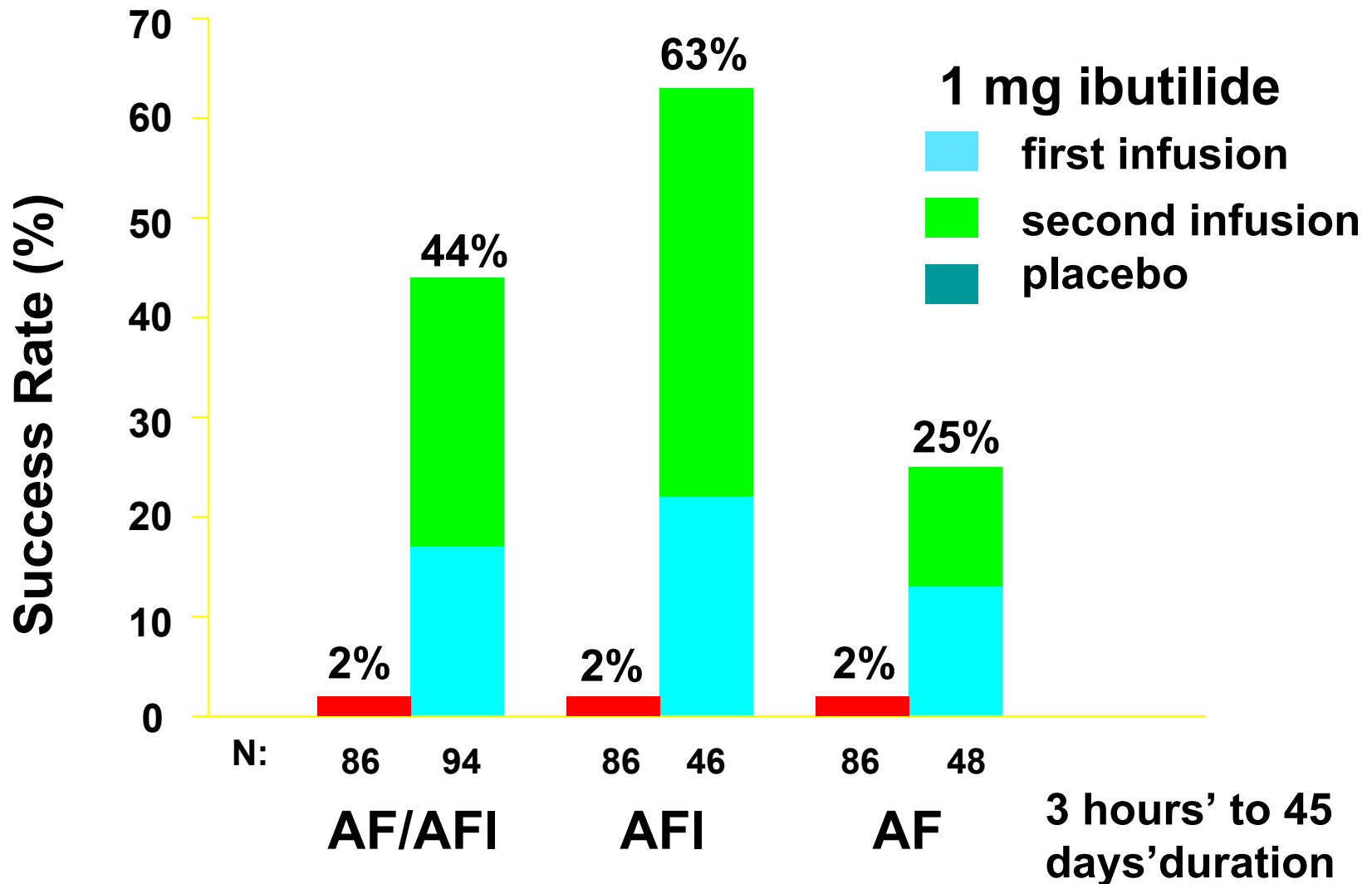
- Rapid and large dosing of amiodarone (oral or IV) may result in heart failure and hypotension because of the beta-blocking properties of amiodarone
- Administration of amiodarone to patients who are already receiving β -blockers may result in marked bradycardia, heart block or even ventricular asystole
- Pro-rhythmia (torsade de pointes)
- Amiodarone increases warfarin action
- Amiodarone increases digoxin serum level

Ibutilide

- Rapidly acting class III antiarrhythmic agent (intravenous administration)
- Prolongs atrial and ventricular action potential duration and QT interval
 - enhances a slow inward sodium current
or
 - blocks a potassium current I_{KR}

Cardioversion

Ibutilide Success Rate After 2 Infusions



Ibutilide: Pro-rhythmic Effect

Continuous ECG monitoring during and for at least 4 hours after infusion

In 586 patients:

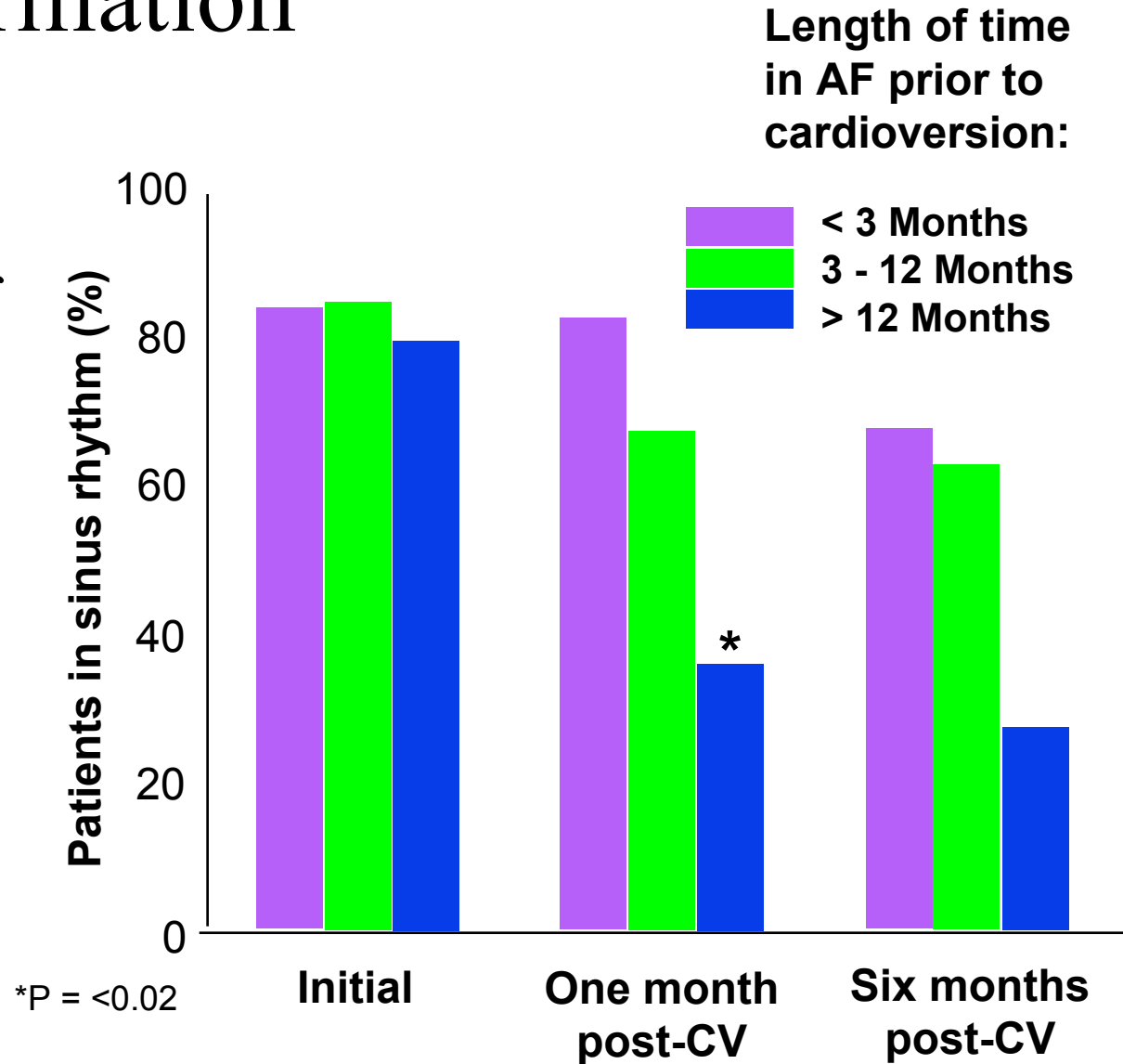
- Polymorphic ventricular tachycardia
 - Sustained 1.7%
 - Nonsustained 2.7%
- Monomorphic ventricular tachycardia
 - Nonsustained 4.9%

Atrial Fibrillation

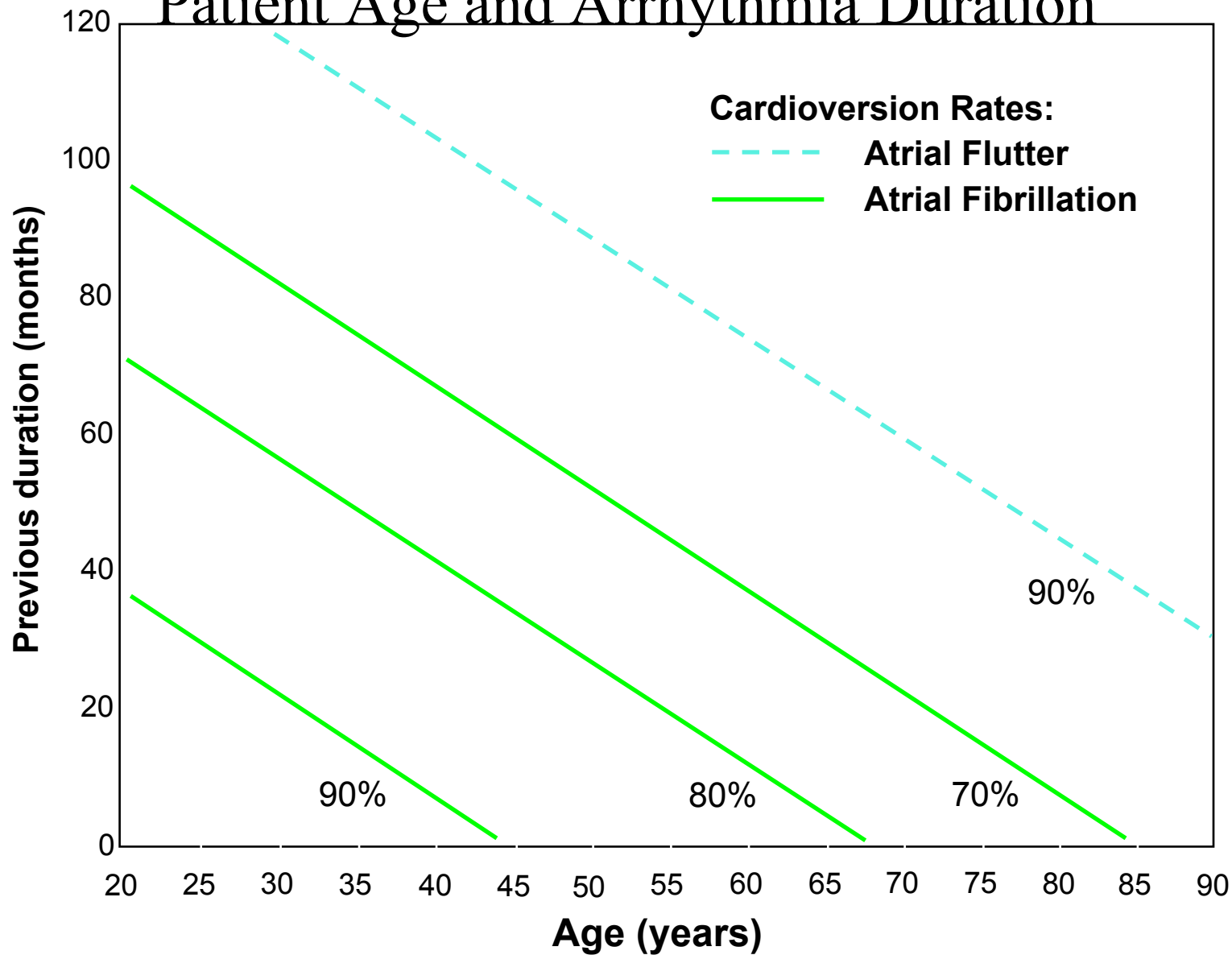
- Maintenance of NSR with Drugs after Cardioversion

Atrial Fibrillation

Duration of atrial fibrillation may predict likelihood of remaining in normal sinus rhythm after cardioversion



Dependence of Cardioversion Rate on Patient Age and Arrhythmia Duration



Antiarrhythmic Drugs to Suppress Atrial Fibrillation

- Class I agents
 - IA: quinidine, procainamide, disopyramide
 - IC: flecainide, propafenone
- Class III agents
 - amiodarone, sotalol

Maintenance of Sinus Rhythm after Cardioversion

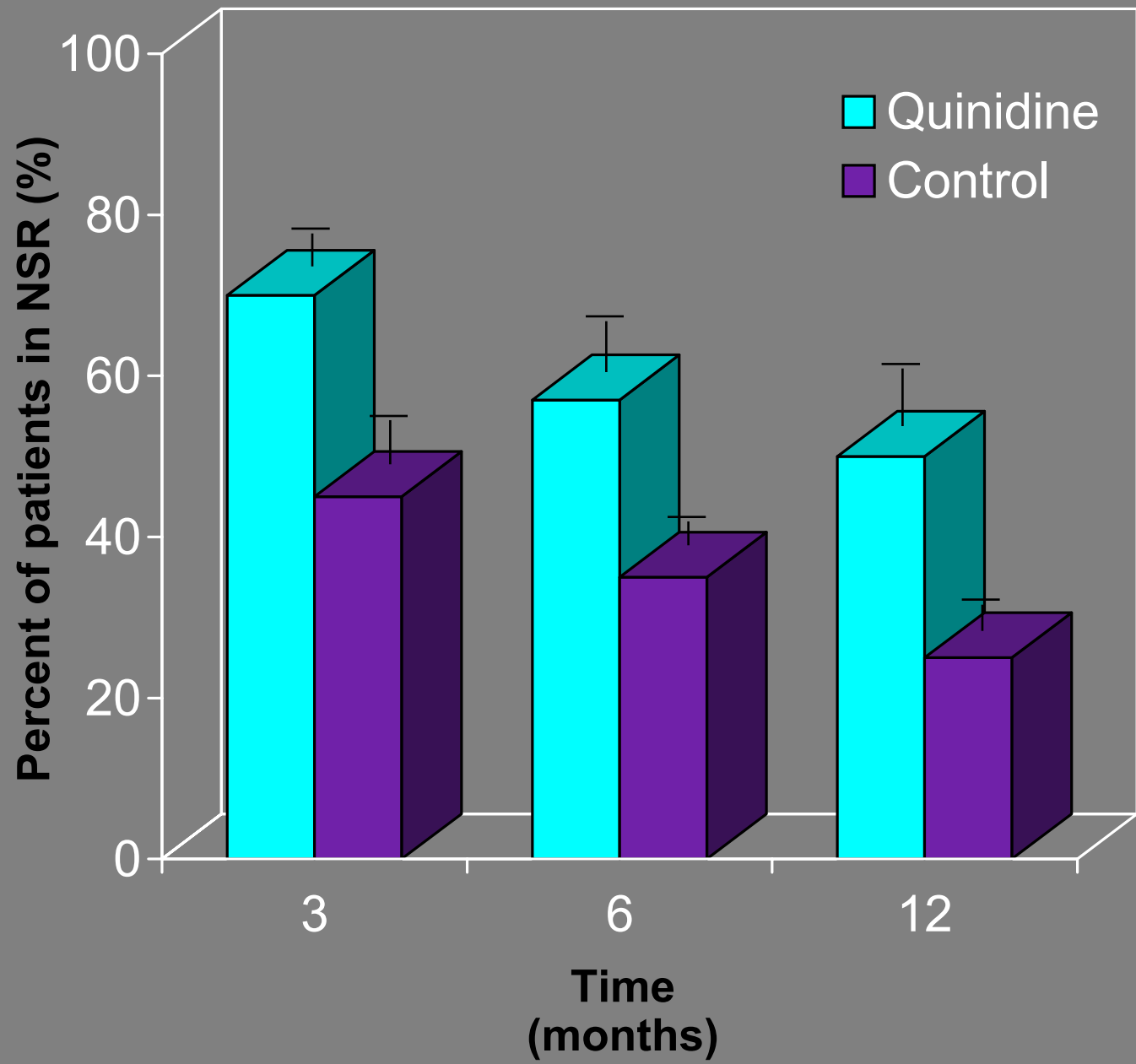
- Without anti-arrhythmic drugs. Only 20 to 40% of patients remain in sinus rhythm in 12 months
- With anti-arrhythmic agents, about 40 to 50% remains in sinus rhythm in 12 months.

Prevention of AF recurrence with Anti-arrhythmic Drugs

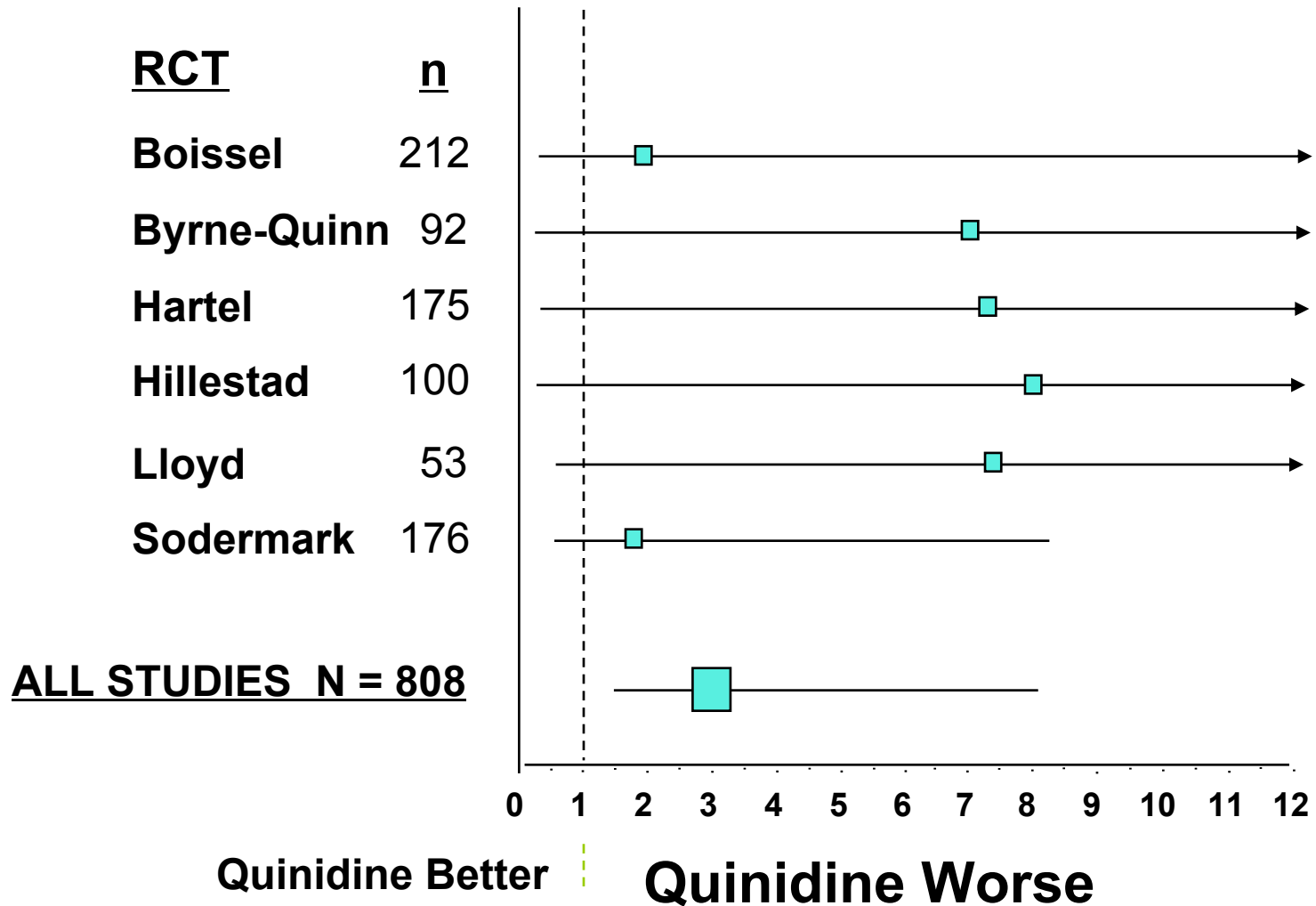
- Drugs that are effective in maintaining normal sinus rhythm may **increase** cardiac events or death because of their pro-arrhythmic effect
- Class I agents
 - IA: quinidine, procainamide, disopyramide
 - IC: flecainide, propafenone
- Class III agents
 - Sotalol, amiodarone (rare)

Atrial Fibrillation: Prevention of Recurrence

Quinidine-treated group remained in NSR better than control group ($p < 0.001$).



Odds Ratio for Total Mortality for Patients Treated with Quinidine Compared to Control



Canadian Trial of Atrial Fibrillation

Hypothesis

Low doses of amiodarone is more effective in preventing recurrence of atrial fibrillation than therapy with sotalol and propafenone

Method

- At least 1 episode of AF > 10 min in the preceding 6 mos. AF confirmed by ECG
- AF < 6 months
- **Amiodarone**: 201 patients (327 to 186 mg daily)
- **Propafenone**: 101 patients (547 to 471 mg daily)
- **Sotalol**: 101 patients (230 to 224 mg daily)
- Primary endpoint : time to first recurrence of AF (>10 min)

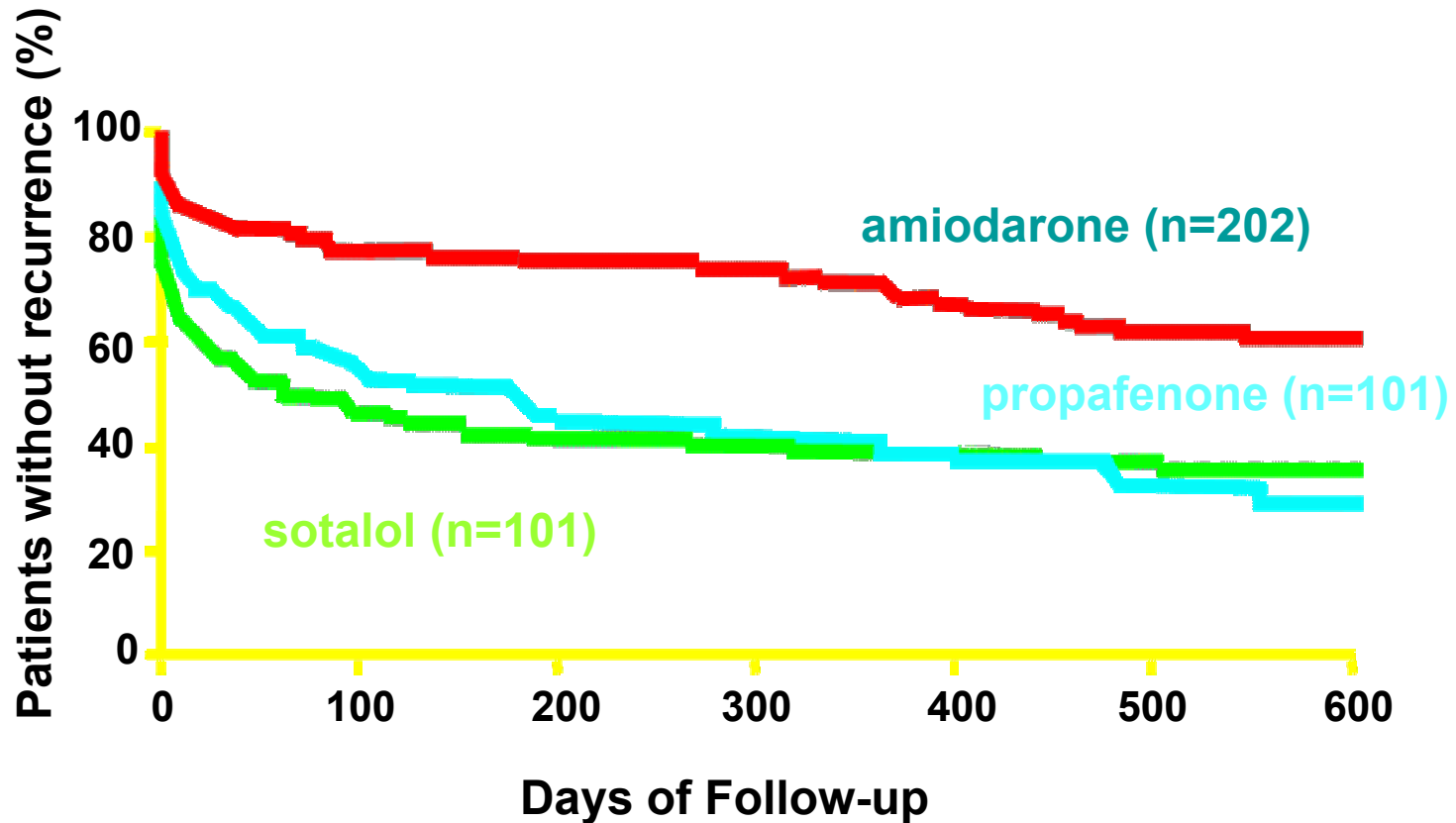
Results

Primary End Point: AF recurrence

Mean follow-up period of 468 ± 150 days

- First recurrence of AF:
 - Amiodarone: 71 patients (35%)
 - Propafenone or sotalol: 127 patients (63%)
($p < 0.001$)
- Probability of remaining in sinus rhythm for one year without recurrence of AF:
 - Amiodarone: 69%
 - Propafenone or sotalol: 39% ($p < 0.001$)

Percentage of Patients Remaining Free of Recurrence of Atrial Fibrillation



Conclusion

Amiodarone is more effective than either propafenone or sotalol in preventing recurrences of atrial fibrillation

Recommendations for Prevention of AF Recurrence

- With normal left ventricular ejection fraction and no history of myocardial infarction:
 - propafenone, sotalol or amiodarone
- With reduced left ventricular ejection fraction and prior myocardial infarction:
 - amiodarone
- Amiodarone potentiates the anticoagulation effect of warfarin. Warfarin dose must be reduced and INR monitored when starting amiodarone

Atrial Fibrillation

- Control of Ventricular Rate
 - Pharmacological: antiarrhythmic drugs
 - RF catheter modification of AV node
 - RF catheter ablation of AV node with implantation of a permanent pacemaker
- Validated by AFFIRM and RACE trials

Control of Ventricular Rate in Atrial Fibrillation

- Digoxin
 - minimally effective in ambulatory patients
- Calcium channel blockers
 - verapamil, diltiazem
 - may prevent atrial remodeling
- Beta blockers

Calcium Channel Blockers and Electrical Remodeling

- AF causes electrical remodeling of the atria
 - atrial refractory period is decreased
 - atrial refractory period does not decrease with faster pacing rate
- Calcium channel blockers prevent such remodeling and may be effective in preventing recurrence of AF

Atrial Fibrillation

- Curative Procedures
 - Surgery (The Maze Procedure)
 - Catheter ablation
 - linear lesions
 - focal atrial fibrillation ablation
 - Pulmonary vein isolation

Recommendations for Management of Atrial Fibrillation < 48 Hours

Atrial Fibrillation < 48 hours

Control ventricular rate
Consider antithrombotic therapy
Observe for spontaneous conversion

Prompt electrical or pharmacologic conversion

Antiarrhythmic therapy
if

Unstable hemodynamics
or frequent recurrences

No antiarrhythmic therapy
if

Stable hemodynamics,
infrequent
recurrences, or first
episode

Recommendations for Management of Atrial Fibrillation > 48 Hours

