

MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION AND/OR ATRIAL FLUTTER WHY IS IT SO HARD?

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New symbol of our profession



DISCLOSURE

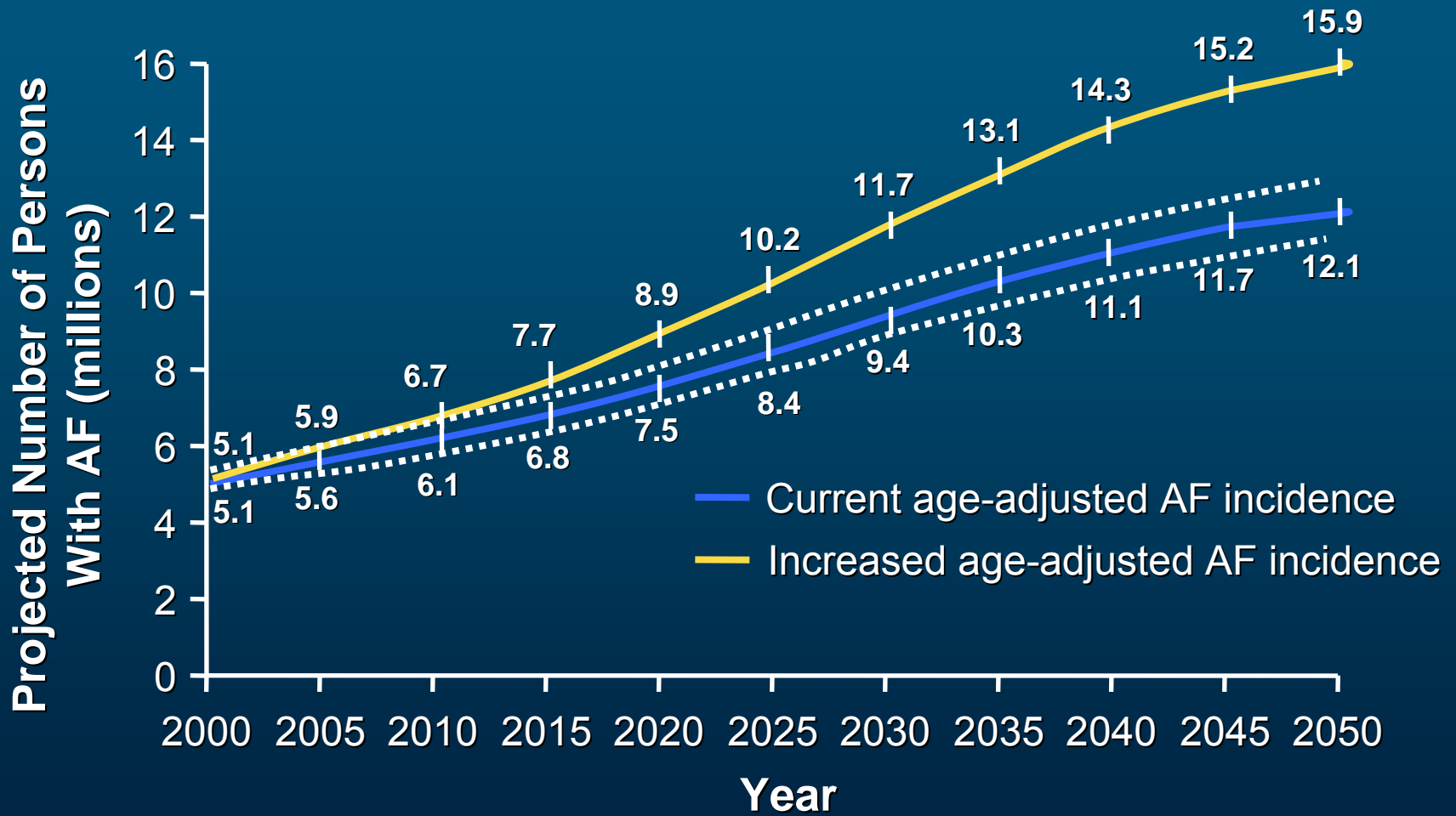
Dr. Kowey serves as a consultant, speaker and grantee for several industrial firms including but not limited to Abbott, Astellas, Astra Zeneca, Berlex, Cardiome, CVT, Eli Lilly, Glaxo-SmithKline, Guidant, Johnson & Johnson, Merck, Medtronic, Novartis, Pharmacia, Pfizer, Proctor and Gamble, Reliant, Solvay, Sanofi, Wyeth, and Cardionet. He holds equity interest in Cardionet.

Stay off the course . . . Or else!

A rectangular red sign with a white border is mounted on a dark, vertically-grained wooden surface. The sign contains white, all-caps text. The text reads: "ANY PERSONS (EXCEPT PLAYERS) CAUGHT COLLECTING GOLF BALLS ON THIS COURSE WILL BE PROSECUTED AND HAVE THEIR BALLS REMOVED". The sign is held in place by four small black screws, one in each corner.

ANY PERSONS (EXCEPT PLAYERS)
CAUGHT COLLECTING GOLF BALLS
ON THIS COURSE WILL BE
PROSECUTED AND HAVE THEIR
BALLS REMOVED

AF Prevalence Is Increasing Rapidly



The Consequences of AF

Thromboembolism

- Stroke: 4.5× increased risk
- Microemboli: reduced cognitive function
- Prothrombotic state

Hospitalizations

- Most common arrhythmia requiring hospitalization
- 2-3× increased risk for hospitalization

Reduced QoL

- Palpitations, dyspnea, fatigue, reduced exercise tolerance

Mortality

- 2× increased risk independent of comorbid CV disease
- Sudden death in HF and HCM

Impaired Hemodynamics

- Loss of atrial kick
- Irregular ventricular contractions
- HF
- Tachycardia-induced cardiomyopathy

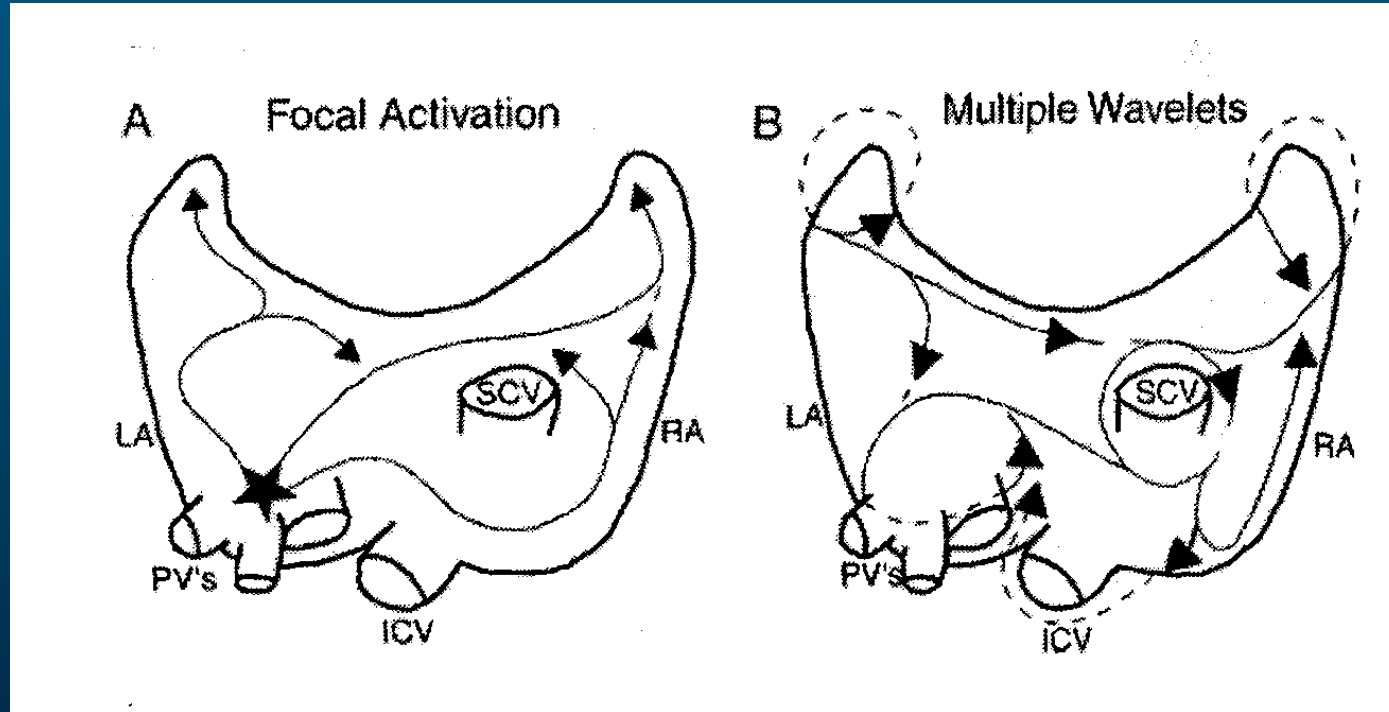
HCM=hypertrophic cardiomyopathy.

Van Gelder et al. *Europace*. 2006;8:943-949; Narayan et al. *Lancet*. 1997;350:943-950; Wattigney et al. *Circulation*. 2003;108:711-716; Wyse et al. *Circulation*. 2004;109:3089-3095; Favale et al. *PACE*. 2003;26:637-639.

ATRIAL FIBRILLATION CARDIAC CAUSES

- Hypertensive heart disease
- Ischemic heart disease
- Valvular heart disease
 - Rheumatic: mitral stenosis
 - Non-rheumatic: aortic stenosis, mitral regurgitation
- Pericarditis
- Cardiomyopathies
- Cardiac tumors: atrial myxoma
- Post-coronary surgical procedures

PRINCIPAL EP MECHANISMS OF AF



Kowey et al. Circulation 1994;89:1665

Management Decision in AF



MANAGEMENT STRATEGIES FOR ATRIAL FIBRILLATION

	Benefits	Risks
Drug Rx to Prevent AF	Symptom Relief	Ventricular Proarrhythmia Bradycardia Other A.A. Drug Toxicity
Drug Rx to Control Ventricular Rate	↓ Ventricular Proarrhythmia ↓ Other A.A. Drug Toxicity	Negative Inotropy Bradycardia Anticoagulation Persistent Symptoms

RHYTHM OR RATE CONTROL IN ATRIAL FIBRILLATION

Evidence Based

5 Prospective, Controlled, Randomized Trials Comparing
2 Different Strategies

- PIAF Pharmacological Intervention in Atrial Fibrillation
- STAF Strategies in Atrial Fibrillation (pilot)
- AFFIRM Atrial Fibrillation Follow-up Investigation of Rhythm Management
- RACE Rate Control versus Electrical Cardioversion for Atrial Fibrillation
- SAFE-T Sotalol and Amiodarone For Effectiveness Trial

AFFIRM

	Rhythm	Rate	
Deaths	356	306	.058
5 year survival	76%	79%	NS
Strokes (ischemic)*	84	79	NS
Death/Stroke/Anoxic Encephalopathy	No difference (p = 0.283)		

*(*Most with INR < 2.0)*

AF-CHF Trial: Results

- No difference in primary endpoint of CV death
 - 182 (27%) rhythm control vs 175 (25%) rate control (HR 1.06, $P=.59$)
- No difference in prespecified secondary endpoints
 - Total mortality, worsening CHF, and stroke
 - Composite of CV death, worsening CHF, and stroke
 - CV mortality
- 21% crossover from rhythm to rate control
 - Primarily due to inability to maintain SR
- 10% crossover from rate to rhythm control
 - Primarily due to worsening HF
- Higher hospitalization rate in rhythm control (46% vs 39% at 1 year; $P=.001$)
 - Mainly due to hospitalization for AF (14% vs 9%; $P=.001$) and bradyarrhythmias (6% vs 3%; $P=.02$)
- Higher rate of cardioversions in rhythm control (59% vs 9% $P<.001$)

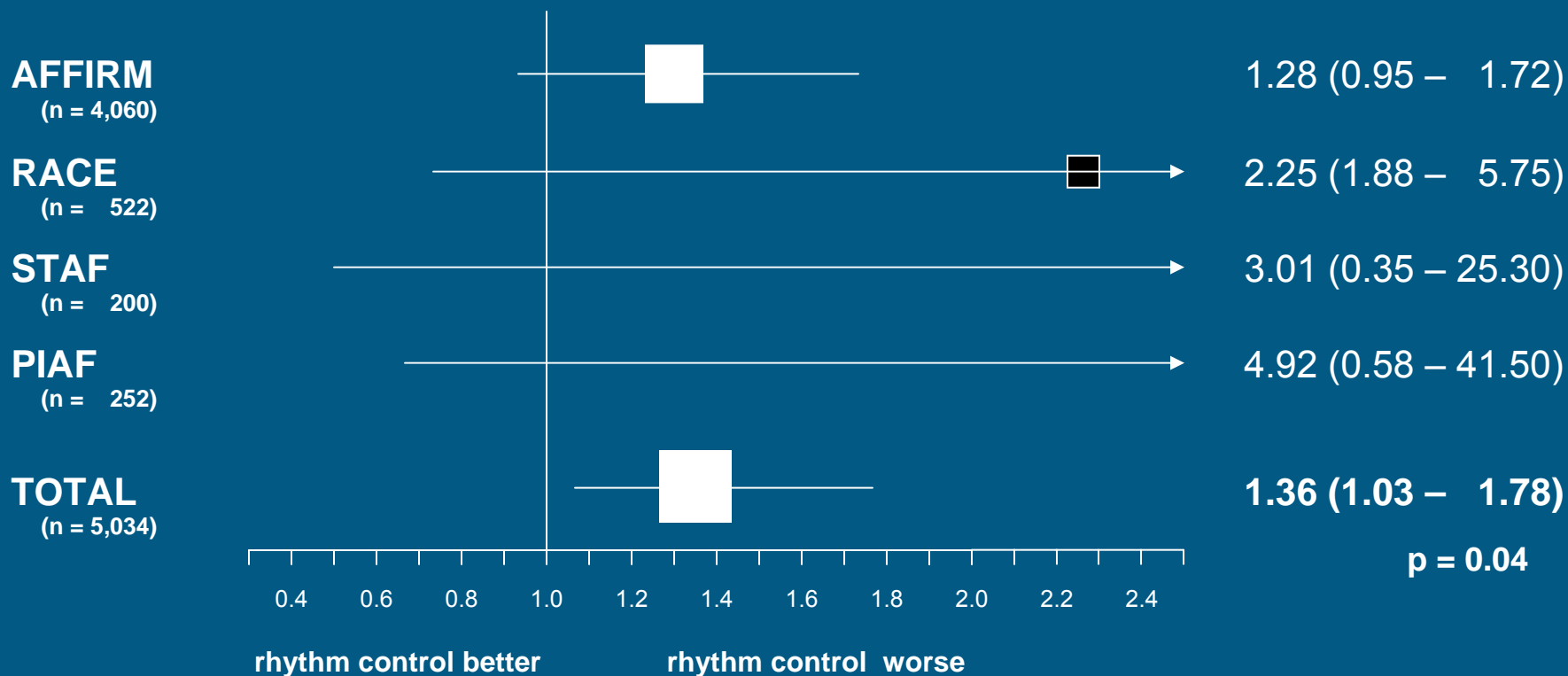
AFFIRM Results



When sinus rhythm is removed from the analysis, AADs are not associated with increased mortality. Therefore, their toxicity may be counterbalanced by improved outcome when sinus rhythm is maintained. Thus, the toxicity of AADs in part offsets the benefit of SR.

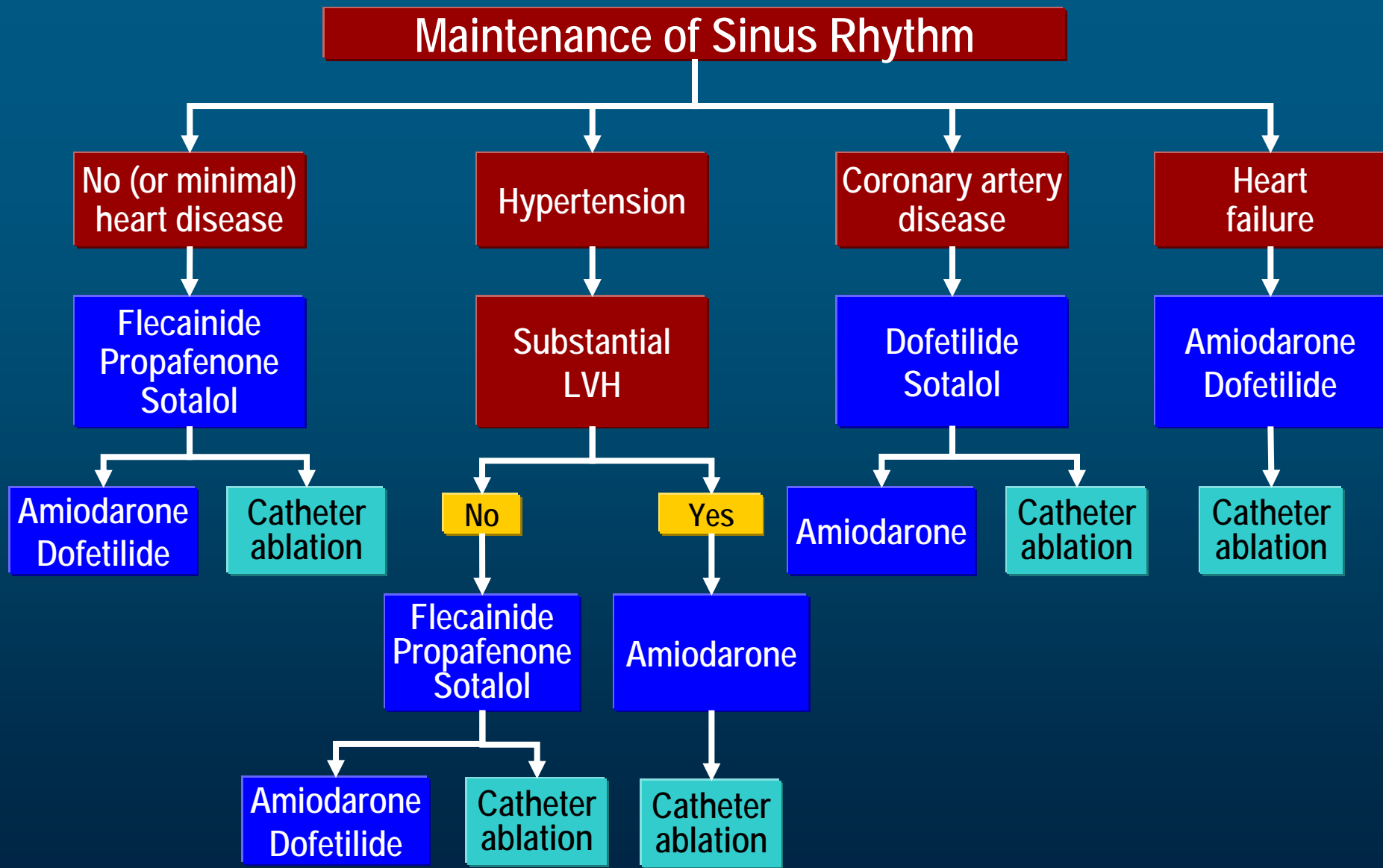
RHYTHM OR RATE CONTROL IN AF

Cerebrovascular events



AF RECURRENCE TRIALS

- Most common form of study
 - Placebo controlled
 - Inter-drug comparisons
- Randomization necessary
 - Patient selection influences outcome
 - Eliminates selection bias
- Symptomatic AF recurrence documented by ECG is highly relevant outcome



ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation.
J Am Coll Cardiol. 2006;48:854-906.

Current Issues in AF Management

- Patients with SR have better survival, but no study confirms that maintaining SR with AADs improves survival in patients with AF
- Rate-control strategy is not effective management if patients are symptomatic
- Better antiarrhythmic drugs are needed

New AAD Development: Possible Mechanisms

- β -blockers with Class I or III effects
- Amiodarone congeners
- Atrial-selective antiarrhythmic drugs
 - I_{KUR} - and I_{KACH} - blocker
 - Atrial-selective Na channel blocker
 - 5-HT₄ receptor antagonist
- Stretch activated channel blockers
- ACEI/ARB
- NCX (Na/Ca exchanger) inhibitor
- Anti-inflammatories (statins)
- Gap junction conduction facilitation

Dronedarone*

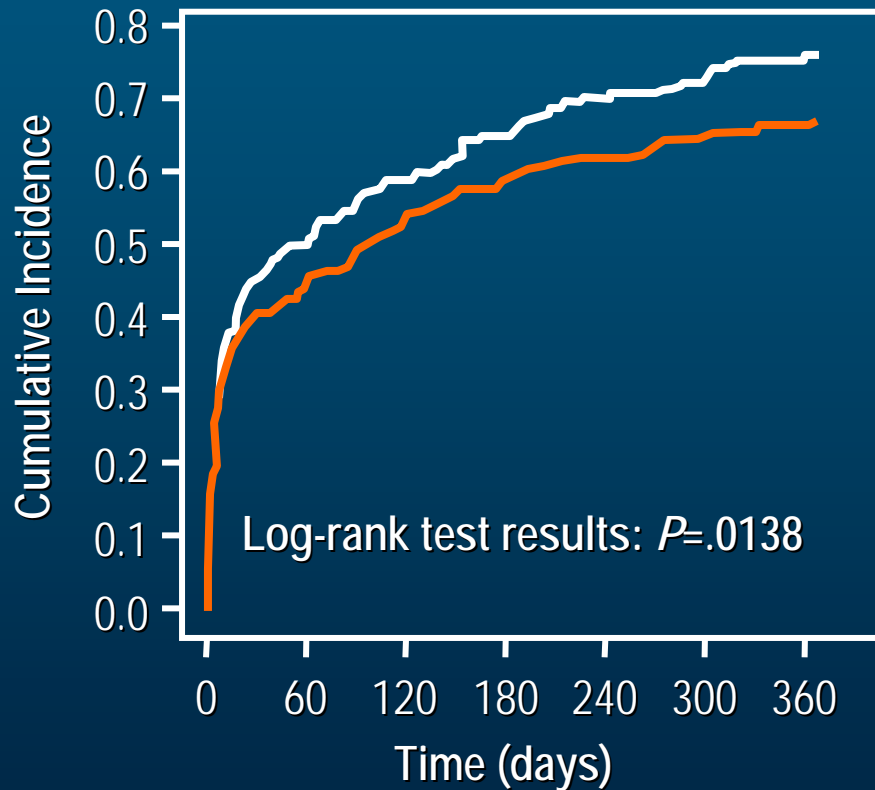
- Amiodarone-like compound lacking the iodine moiety
- Similar electrophysiologic properties
- No evidence of thyroid or pulmonary toxicity
- 24-hour half-life
- Food-fast effect
- Extensive first-pass metabolism (CYP450 3A4)

*Not FDA approved.

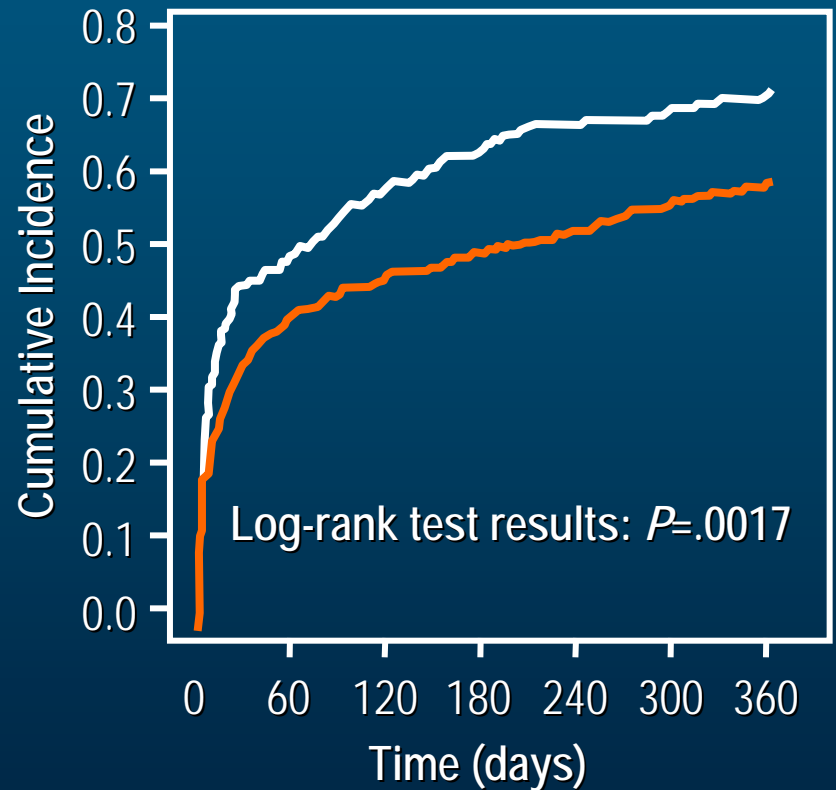
Kathofer et al. *Cardiovasc Drug Rev.* 2005;23:217-230..

Primary End Point: Patients With Adjudicated First Recurrence of AF/AFL

EURIDIS



ADONIS



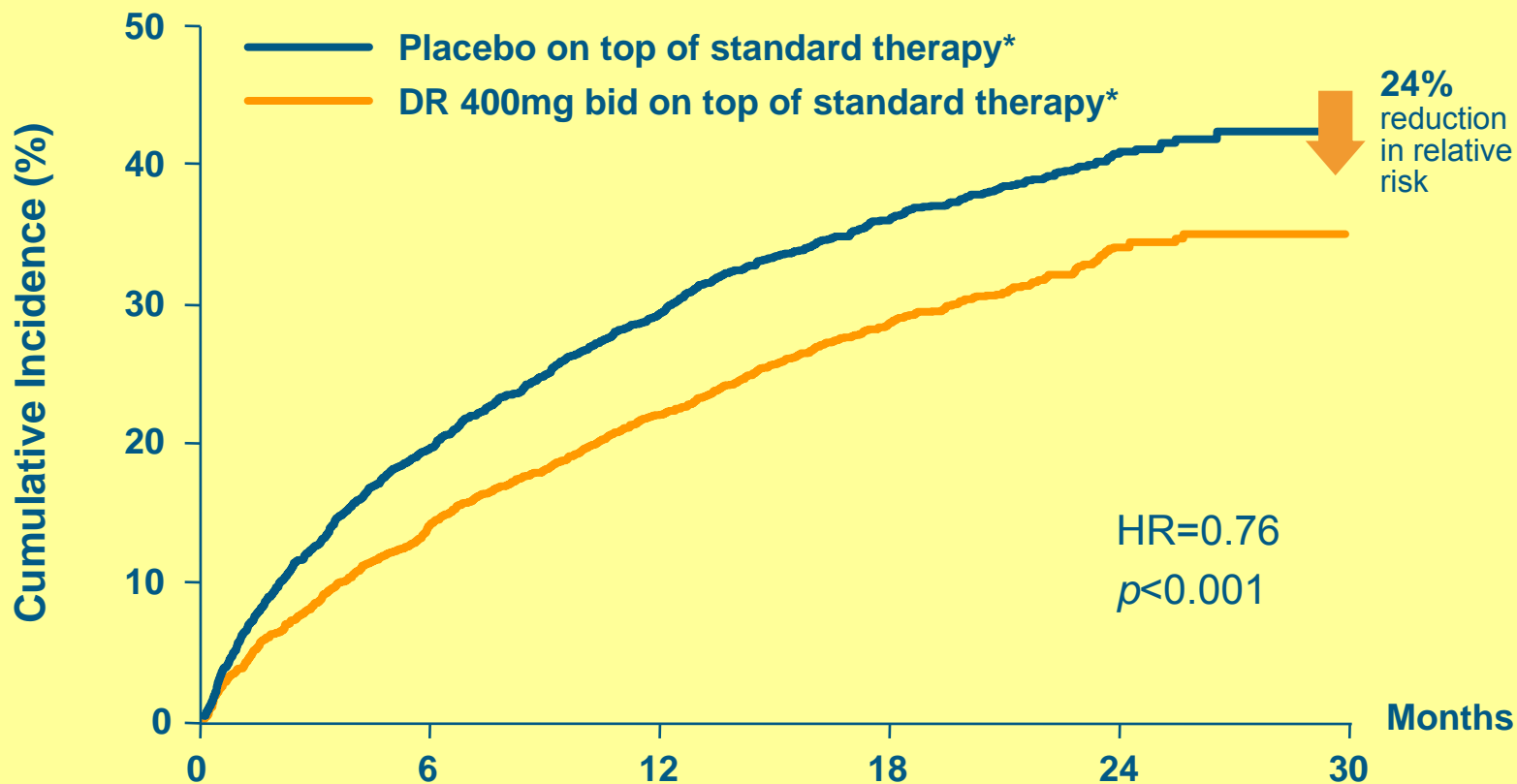
— Placebo — Dronedaronone 400 mg bid

ATHENA

A placebo-controlled, double-blind, parallel arm
Trial to assess the efficacy of dronedarone 400 mg
bid for the prevention of cardiovascular
Hospitalization or death from any cause in patiENts
with Atrial fibrillation/atrial flutter (AF/AFL)

ATHENA Primary Endpoint:

Dronedarone Significantly Decreased Risk of CV hospitalization or Death by 24%



Patients at risk:

Placebo	2327	1858	1625	1072	385	3
DR 400mg bid	2301	1963	1776	1177	403	2

*Standard therapy may have included rate control agents (beta-blockers, and/or Ca-antagonist and/or digoxin) and/or anti-thrombotic therapy (Vit. K antagonists and /or aspirin and other antiplatelets therapy) and/or other cardiovascular agents such as ACEIs/ARBs and statins.

Mean follow-up 21 ±5 months.

Hohnloser SH *et al.* *N Engl J Med* 2009;360:668-78.

Celivarone (SSR 149744 C)*

- Daughter of dronedarone
- Once-daily dosing
- Trilogy of phase 2 trials
 - MAIA (AF prevention)
 - ICARIOS (ICD)
 - CORYFEE (AF termination)

*Not FDA approved.

Gautier et al. *J Cardiovasc Pharmacol*. 2005;45:125-135; www.clinicaltrials.gov

Budiodarone

- Structural analog of amiodarone with similar EP effects
- More readily metabolized to an inactive metabolite
- More favorable PK/PD profile
- Potential for less toxicity than its congeners
- Positive results on AF burden in a Phase IIb trial

Vernakalant*

- Amino-cyclohexyl ether
- Unique ion channel-blocking profile
 - Frequency- and voltage-dependent I_{Na} block
 - Early activating K^+ channel block
 - Blocks I_{KACH}
- Rate-enhanced activity on conduction
- Atrial-selective APD/ERP prolongation
- Activity confirmed in several species
- No effect on ventricular repolarization
- No adverse hemodynamic effects

*Not FDA approved.

Batch et al. *Circulation*. 2003;108:IV-85 (B).

ACT III Results: Conversion From AF to SR or Termination of AF or AFL

AF/AFL Duration	3h–7d (<i>P</i> <.0001) [†]		3h–45d* (<i>P</i> <.0001)		8–45d* (<i>P</i> =NS) [‡]	
Treatment Group	Placebo	Vernakalant	Placebo	Vernakalant	Placebo	Vernakalant
AF	n=84 3 (3.6%)	n=86 44 (51%)	n=121 5 (4.1%)	n=118 47 (40%)	n=37 1 (2.7%)	n=32 3 (9.4%)
AF/AFL	n=92 3 (3.3%)	n=98 45 (46%)	n=131 5 (3.8%)	n=134 48 (36%)	n=39 1 (2.6%)	n=36 3 (8.3%)

*Termination of AF or AFL (defined as absence of AF or AFL).

[†]*P* value calculated using Cochran-Mantel-Haenszel test.

[‡]*P* value calculated using Fisher's exact test.

Pratt et al. Presented at the American College of Cardiology Annual Session. March 13, 2006, Atlanta, Georgia.

Oral Vernakalant: Phase 2a Efficacy Results

Dose	Patient No. (%)	P Value*
300 mg	33/54 (61%)	$P=.048$
600 mg	30/49 (61%)	$P=.060$
Placebo	24/56 (43%)	

*Drug/placebo comparison.

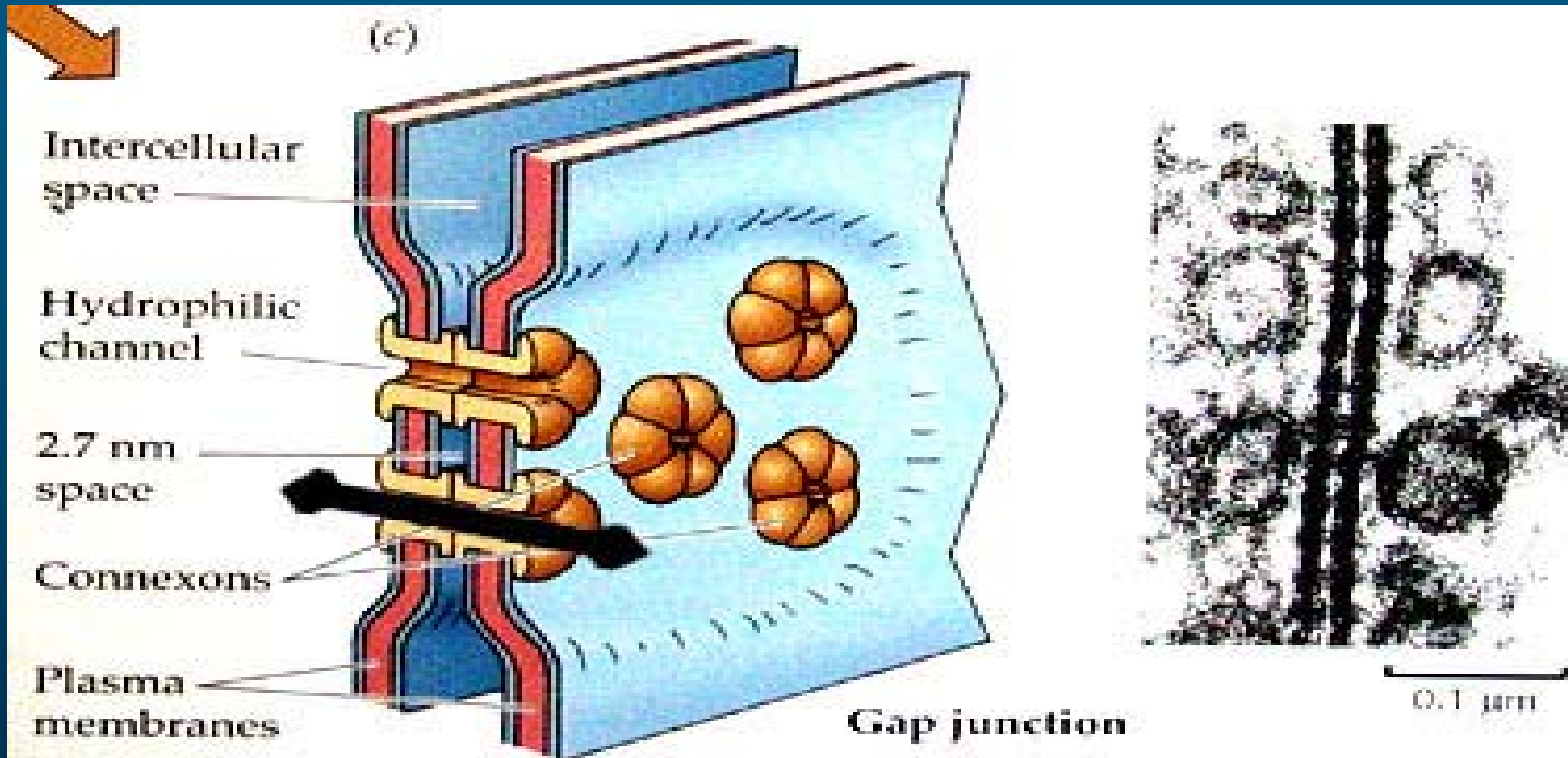
Cardiome Pharma Corp. Press release. July 24, 2006, and September 13, 2006.

Pharmacological Management of Atrial Fibrillation

Atrial-Selective Sodium Channel Blockers Ranolazine



Gap Junctions



Gap junctions are intercellular channels some 1.5–2 nm in diameter.

These permit the free passage between the cells of ions and small molecules (up to a molecular weight of about 1000 daltons).

They are constructed from 4 (sometimes 6) copies of one of a family of a transmembrane proteins called **connexins**.

Because ions can flow through them, gap junctions permit changes in membrane potential to pass from cell to cell

Upstream Therapy: Candidates

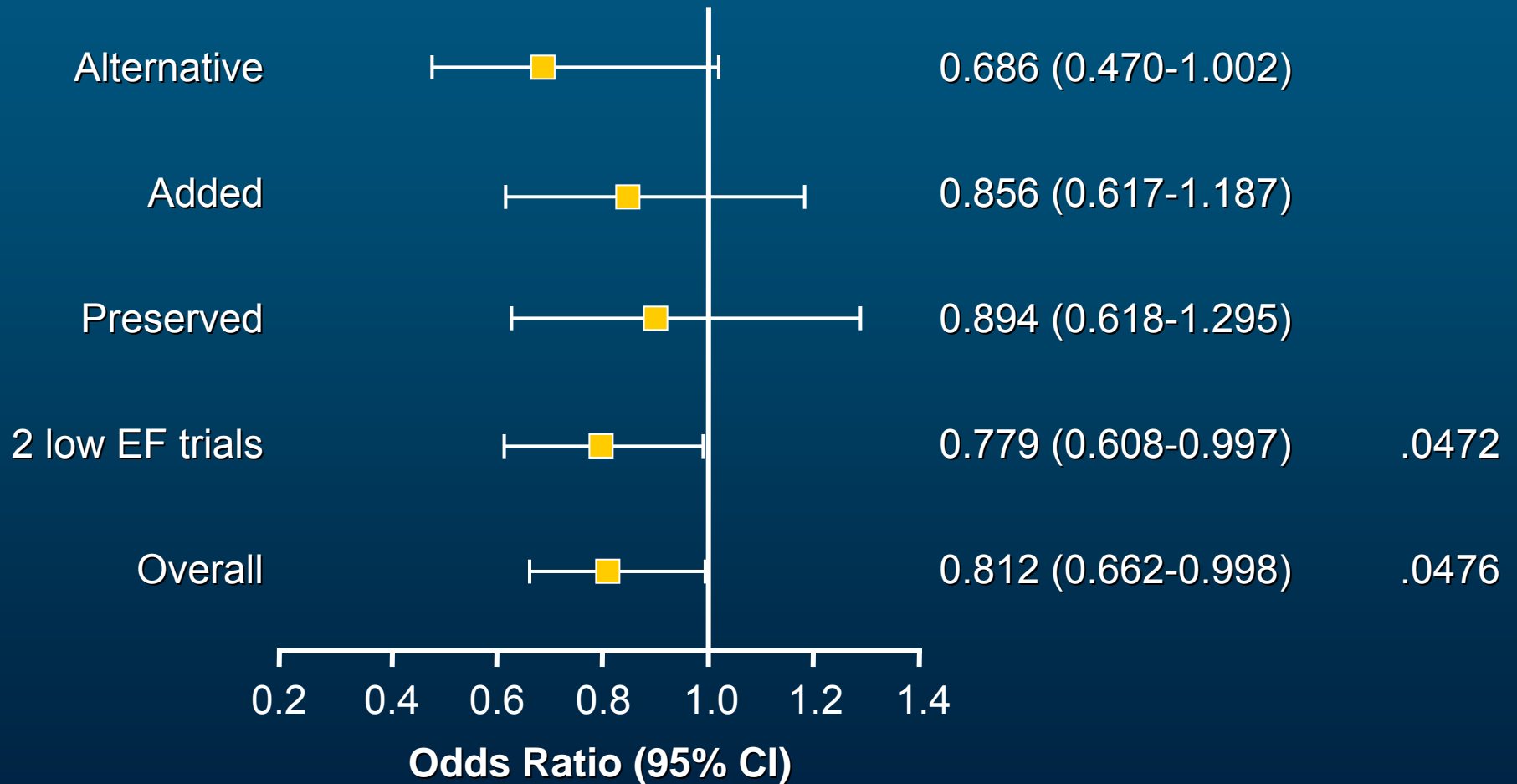
- ACEIs/ARBs
- Statins
- Fish oil
- Anti-inflammatories
- Beta blockers
- PPAR- γ modulators

Candesartan and AF in CHARM

P heterogeneity=0.57

Odds Ratio (95% CI)

P Value



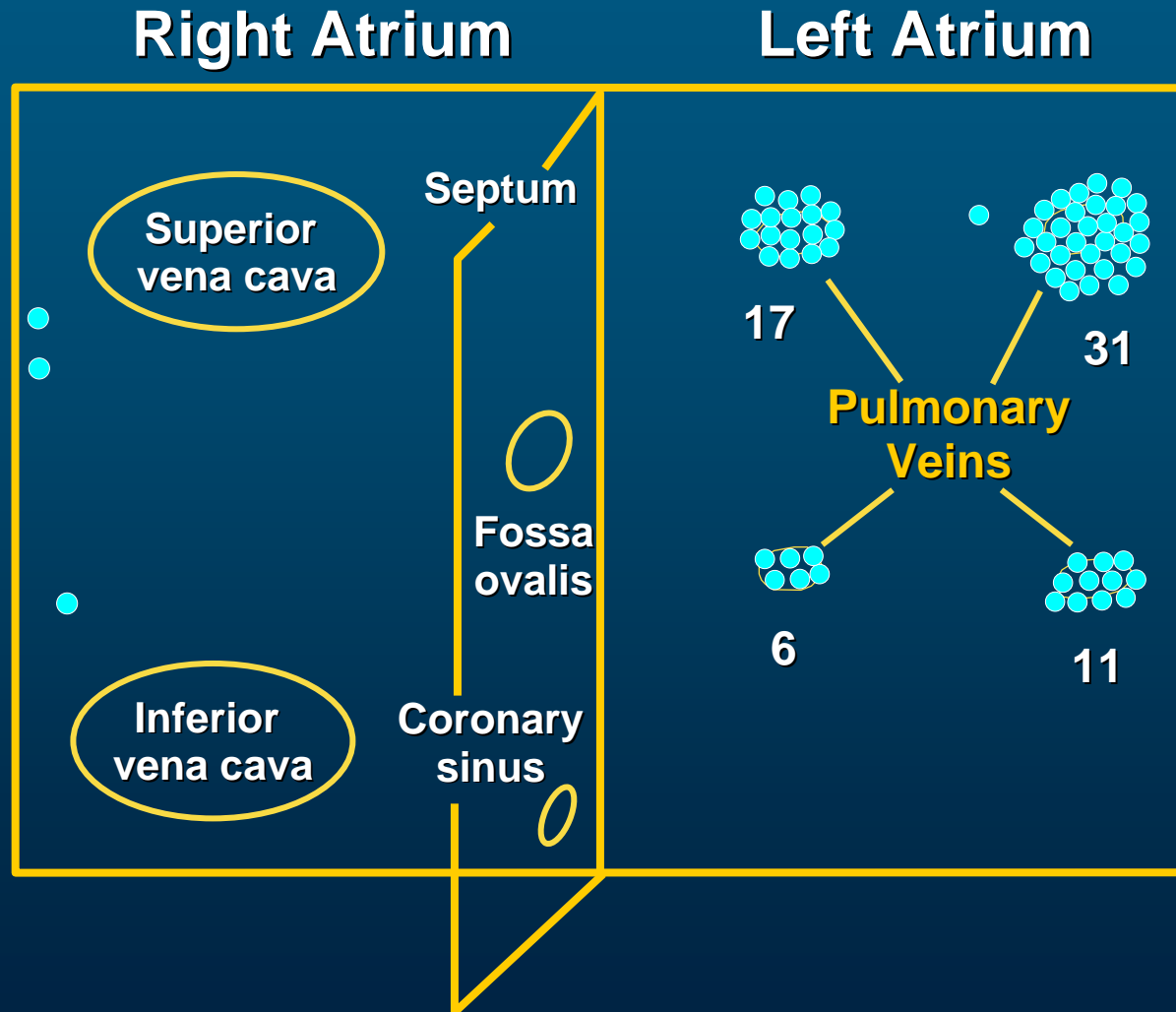
OM-8 Clinical Trial Design

- N= 660 (550 with PAF)
- 8 grams X 7 days → 4 grams daily vs placebo
- Parallel group 6 month study
- Visits week -1,0,1,4,12, 24
- TTM for documentation of events
- Anticoagulation by guidelines

NON-PHARMACOLOGIC OPTIONS

- Ablation
 - Direct
 - Surgical
 - Catheter
 - AV Node
- Pacing
- Defibrillation
 - Atrial
 - Atrial and ventricular

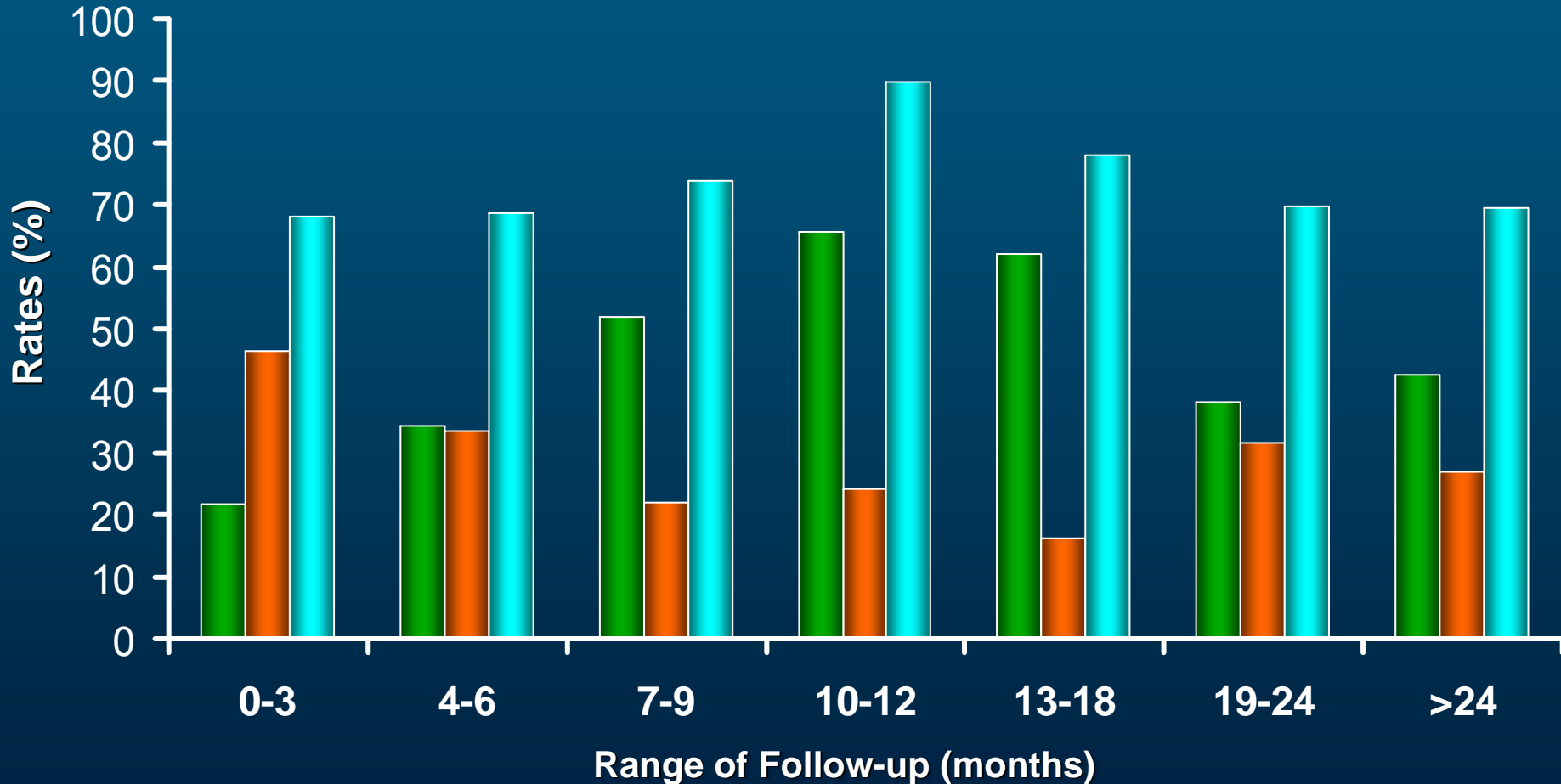
Sites of 69 Foci Triggering AF in 45 Patients



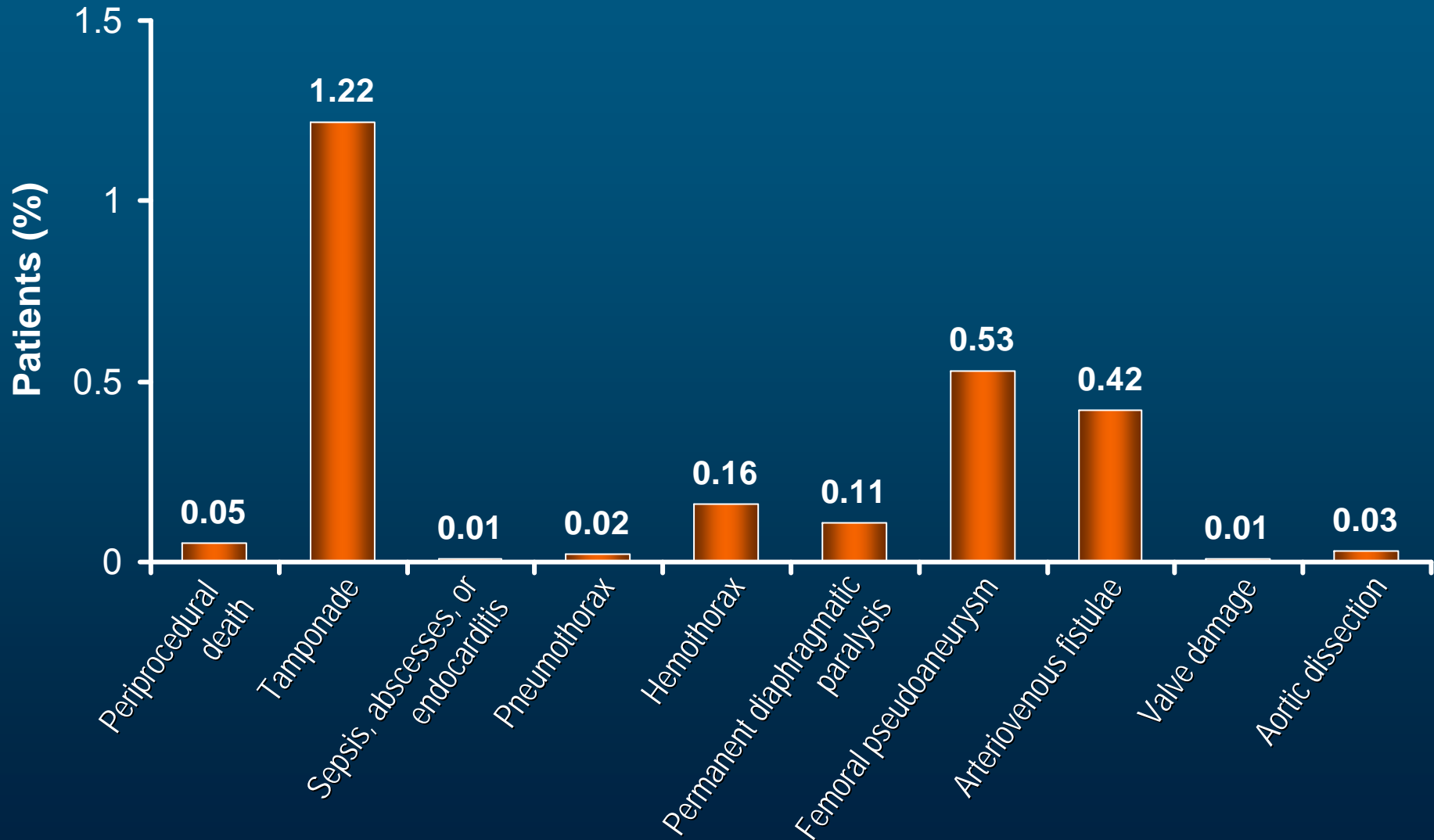
Success Rates With Ablation

Worldwide Survey

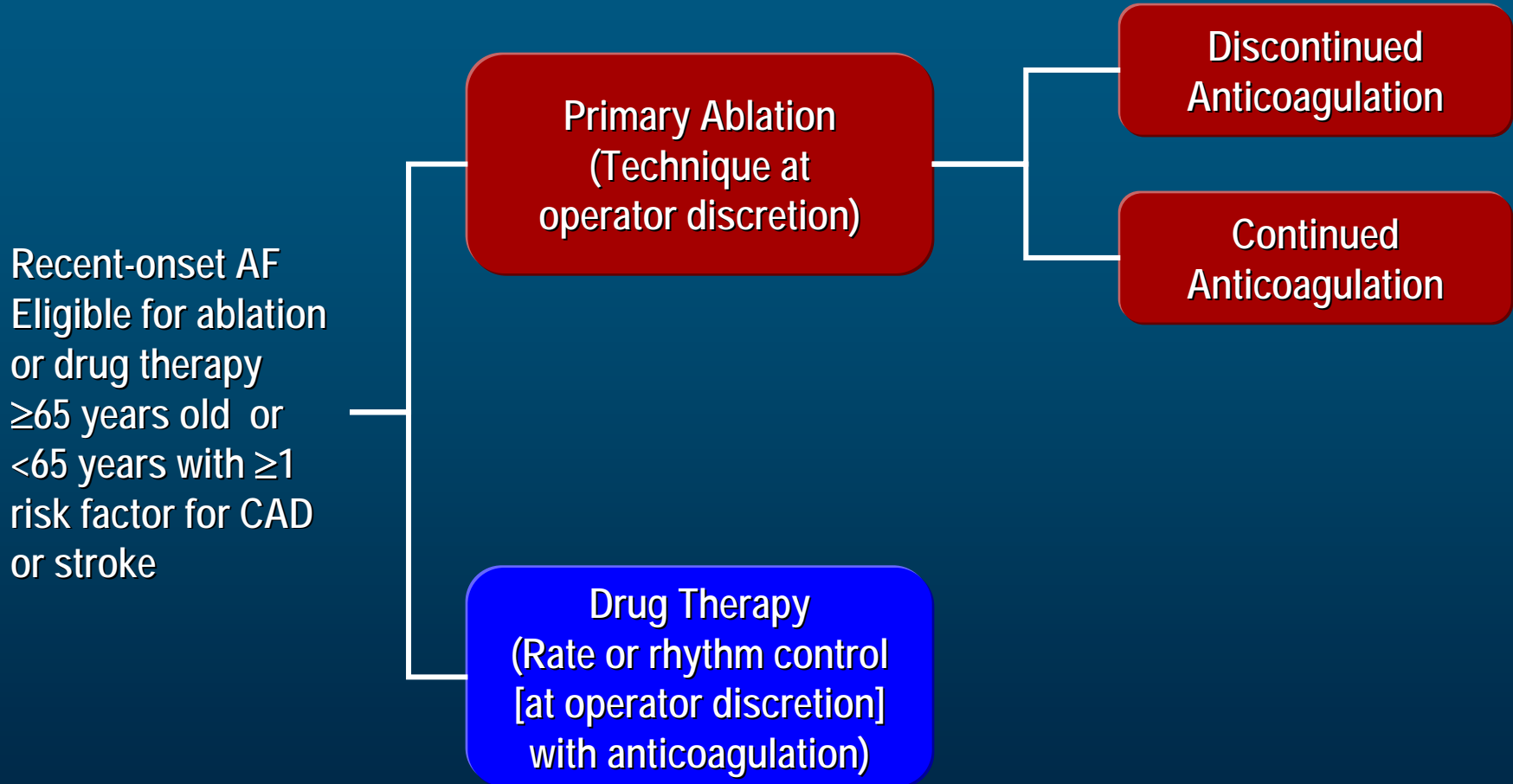
■ Success Without AADs ■ Success With AADs ■ Overall Success



Complication Rates for Catheter Ablation



CABANA Trial



Packer. Presented at 2005 Scientific Sessions of the American Heart Association.
November 13-16, Dallas, Texas.

SAFARI

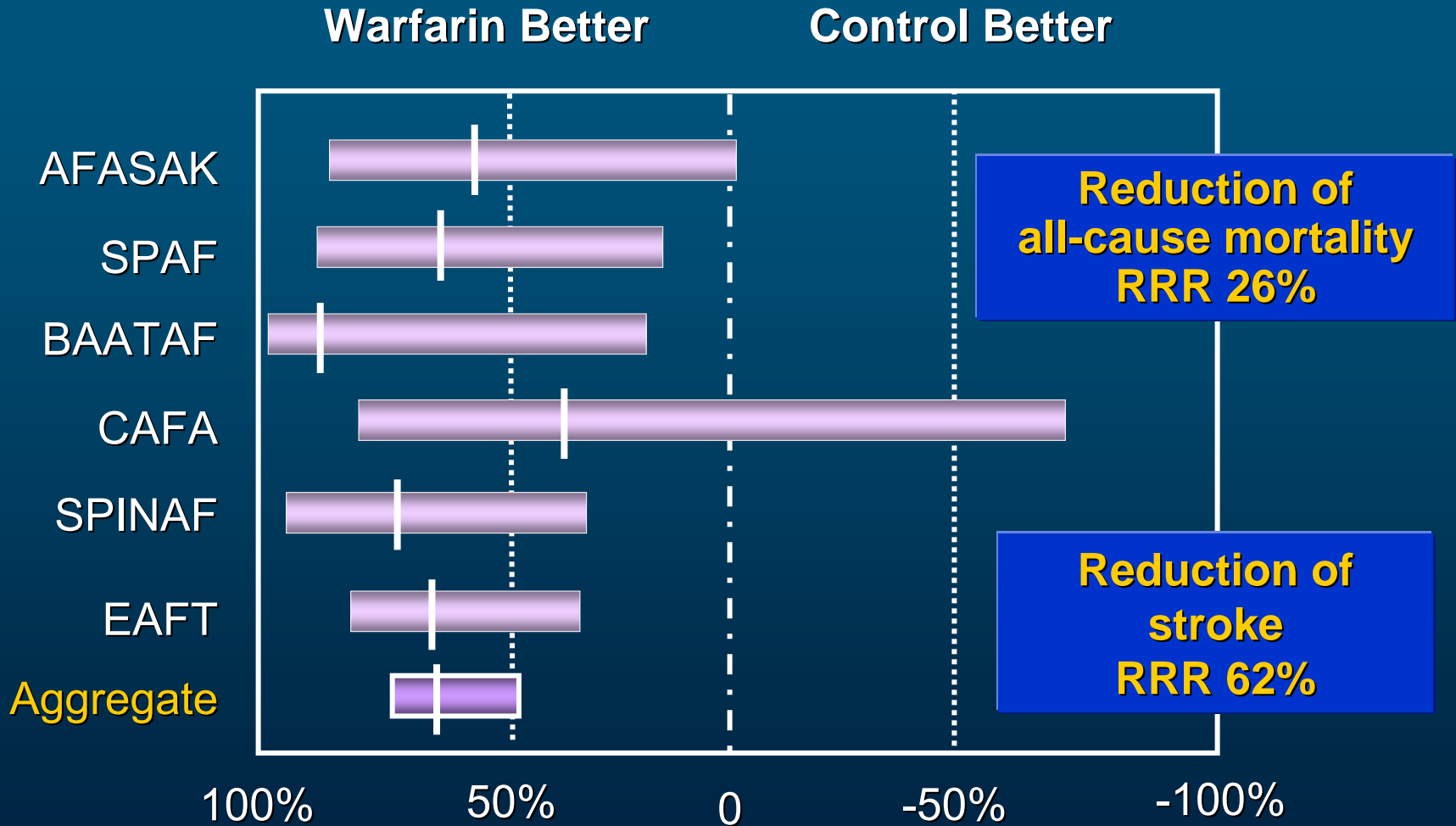
- National AF ablation registry
- Comprehensive enrollment
- Long follow-up

Management Decision in AF



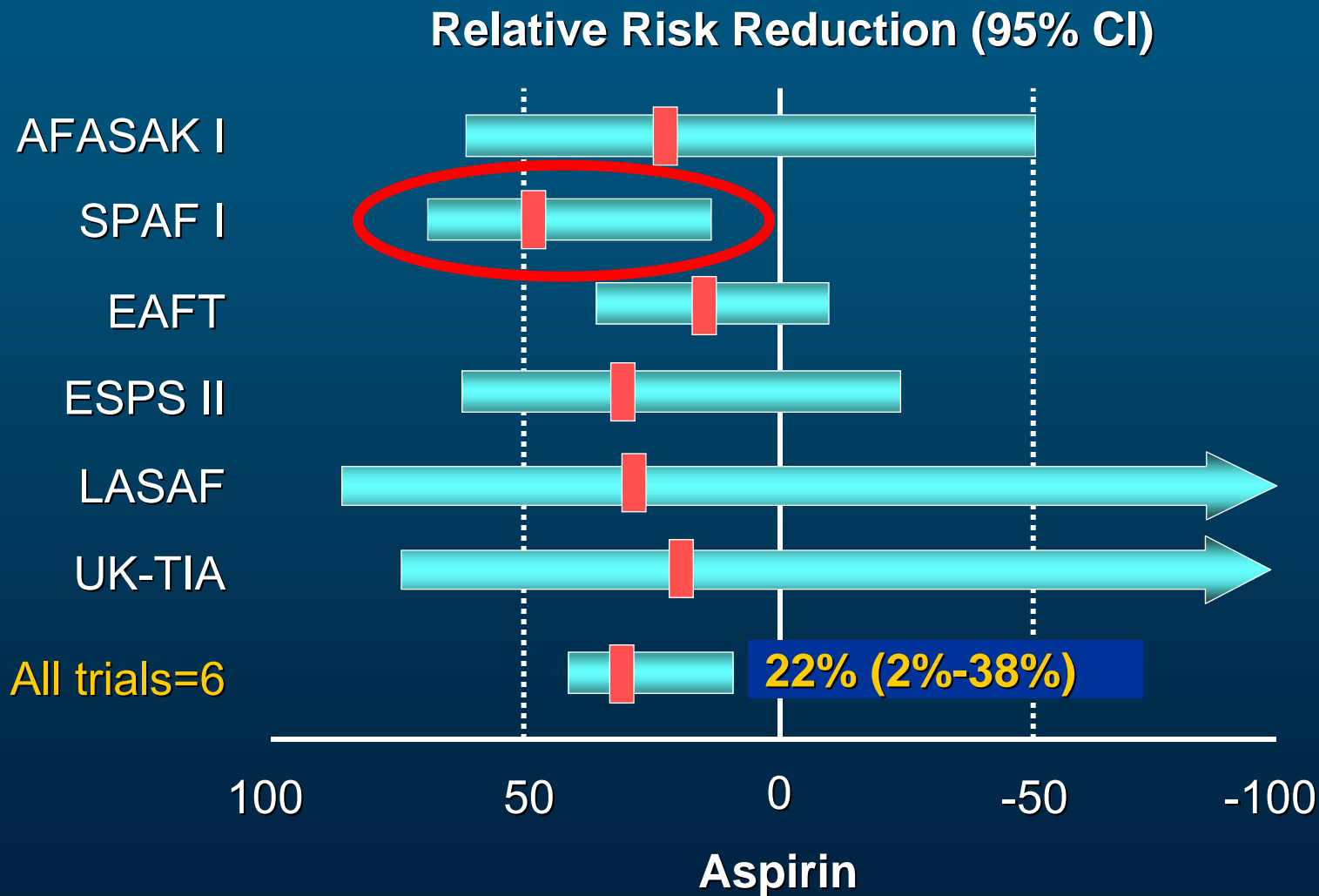
Anticoagulation in AF

Stroke Risk Reductions

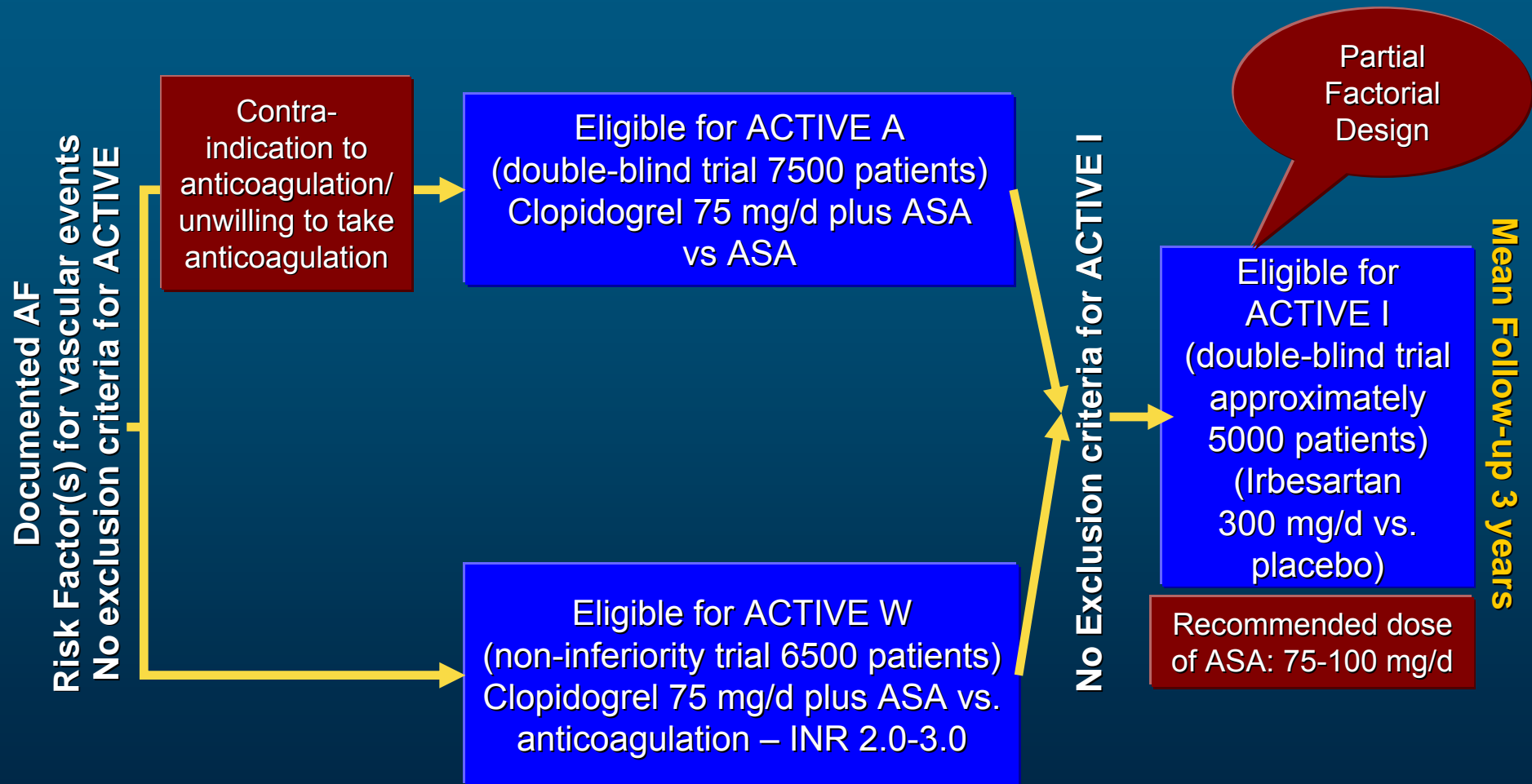


Aspirin vs Placebo

Reduction of Risk of Thromboembolism in AF

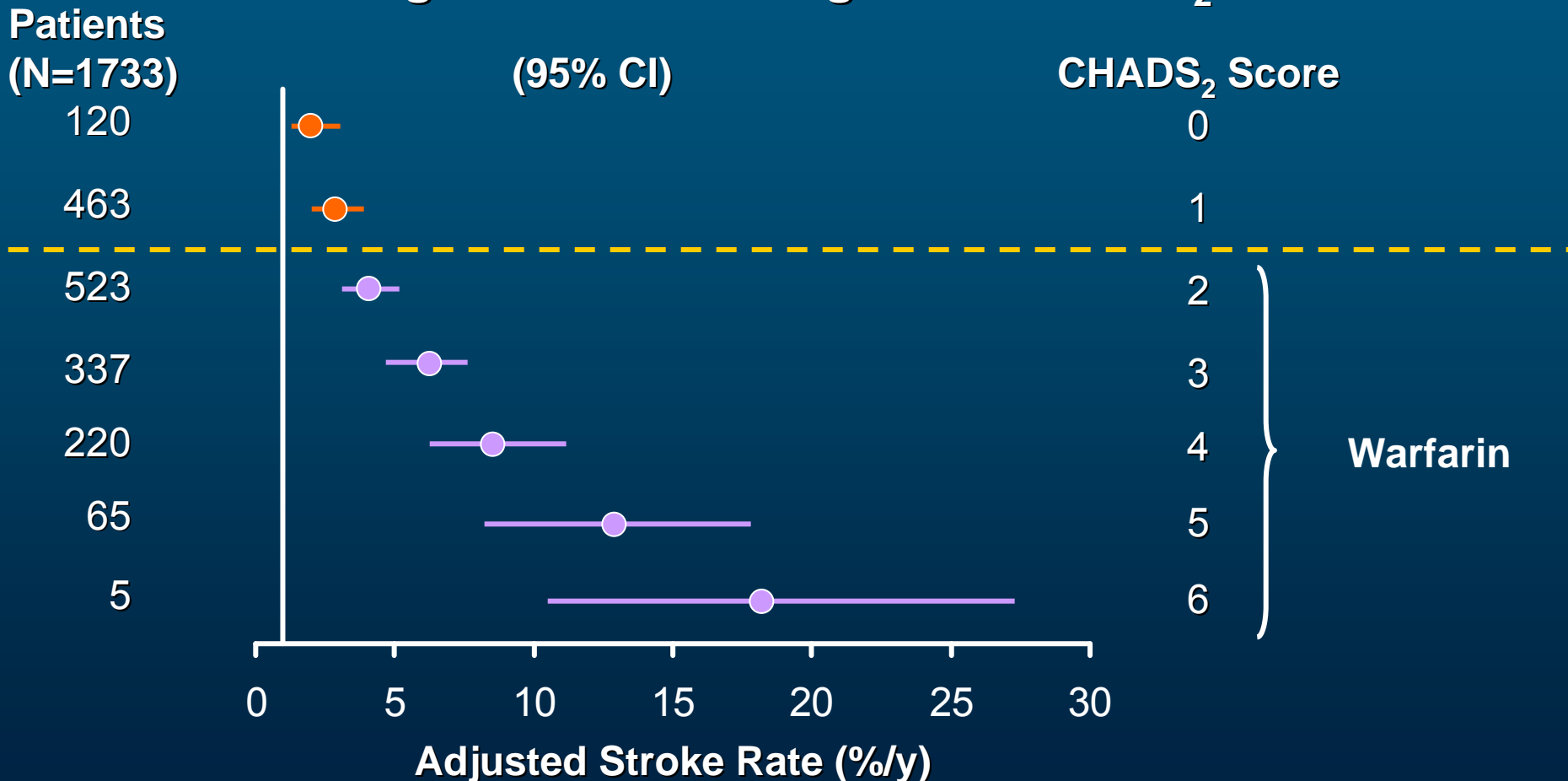


Active A, W, and I



CHADS₂ Risk Criteria for Stroke in Nonvalvular AF

Stroke Risk in Patients With Nonvalvular AF Not Treated With Anticoagulation According to the CHADS₂ Index



ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation.
J Am Coll Cardiol. 2006;48:854-906 (A).

SO WHY IS IT HARD?

- Ubiquitous disease
 - Diverse pathogenesis/etiologies
 - Potentially lethal
 - No universally effective treatment
 - Algorithms work poorly
 - Multi-component therapy
 - Some treatments are worse than disease
 - Stroke lurks
- ∴ Each new patient is a new experience