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# Clinical Trial Designs for Cardiac Ablation Devices for Atrial Fibrillation

Food and Drug Administration  
September 20, 2007

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## ACC/AHA/ESC Practice Guidelines

### ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation—Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation)  
*Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society*

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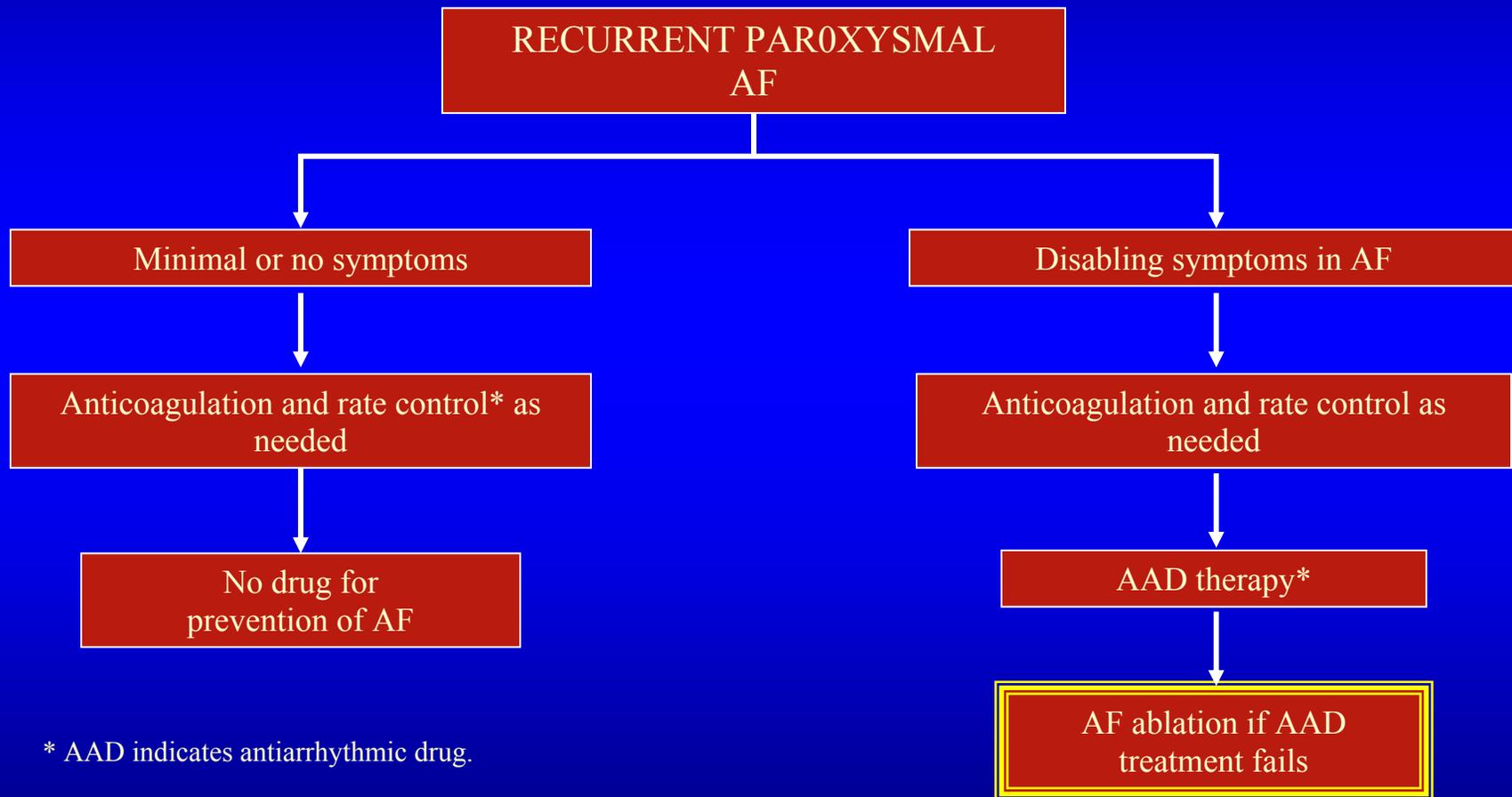


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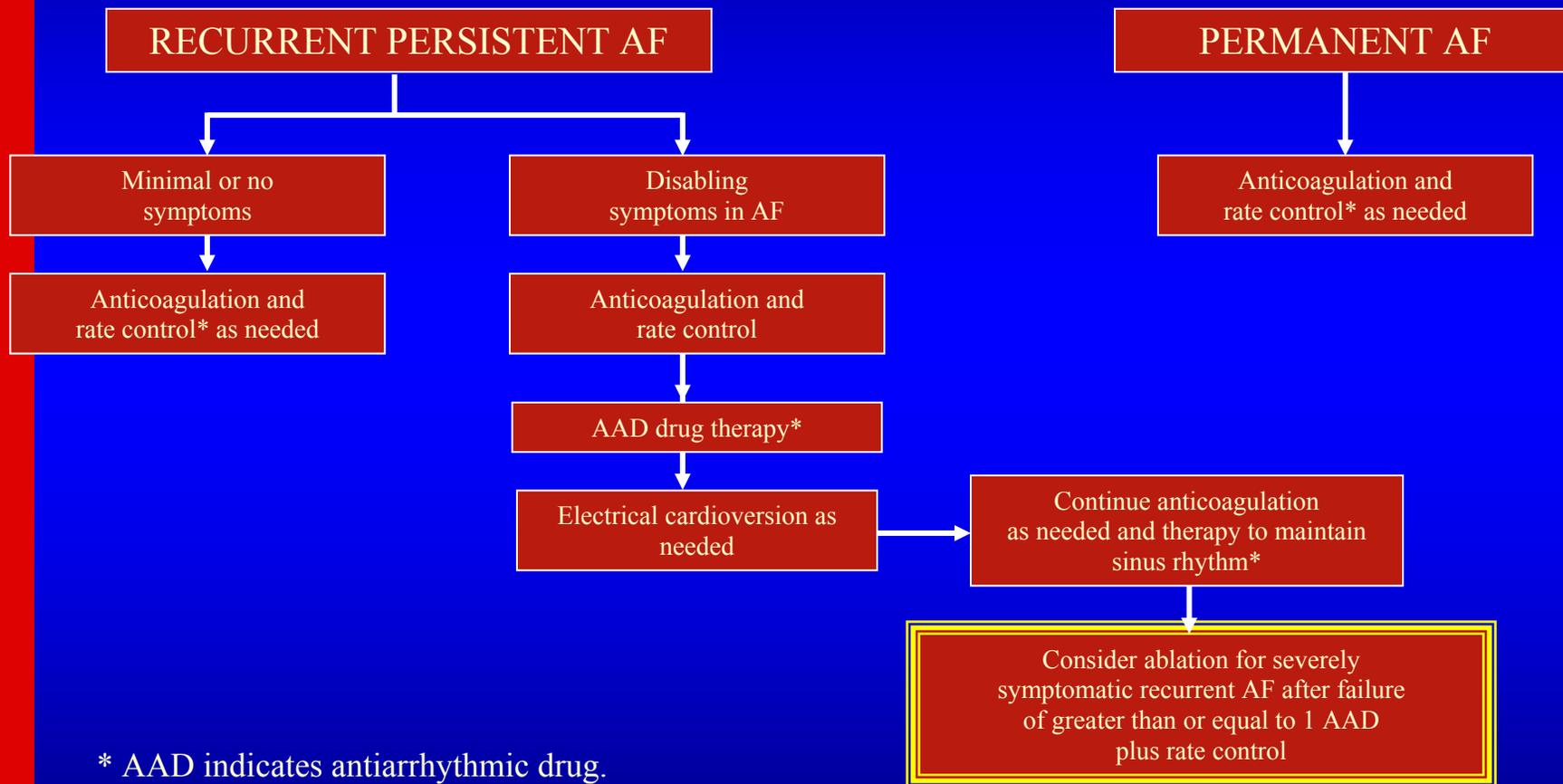
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- 1) **Method of characterizing effectiveness**
- 2) **Trial Designs**
- 3) **Appropriate Control Group**
- 4) **Performance derived goal for safety and efficacy**
- 5) **Trial Design**
- 6) **Anticoagulation**
- 7) **Significance of asymptomatic recurrences**
- 8) **Trial design for different types of AF**
- 9) **Significance of permanent or persistent AF going to paroxysmal**
- 10) **High risk patients**
- 11) **Significance of atrial transport**

# Pharmacological Management Of Patients With Recurrent Paroxysmal Atrial Fibrillation (AF)



# Pharmacological Management Of Patients With Recurrent Persistent Or Permanent Atrial Fibrillation (AF)



\* AAD indicates antiarrhythmic drug.

## **HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-Up**

**A report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation**

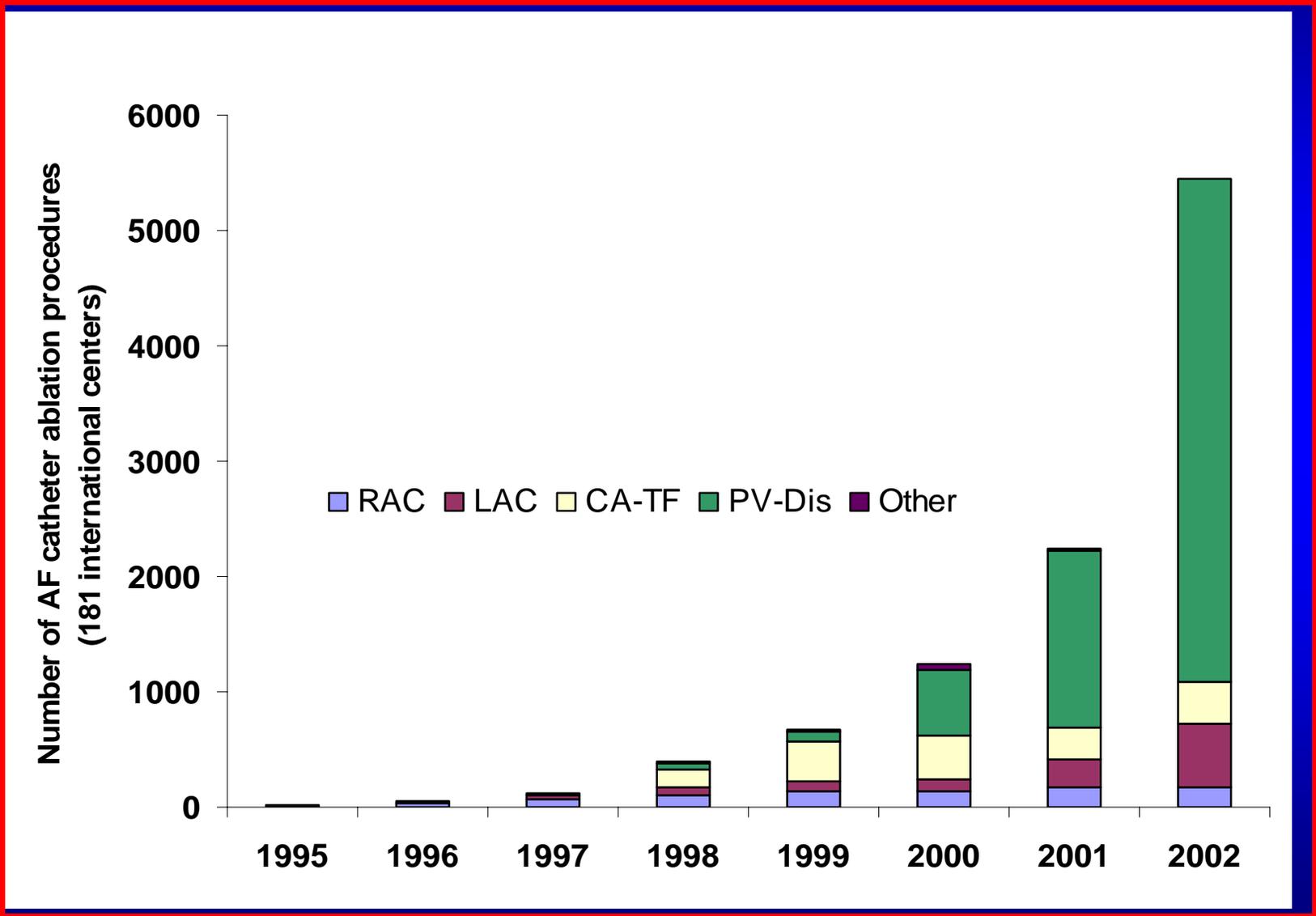
*Developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and Approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society.*

Hugh Calkins, MD, FHRS; Josep Brugada, MD, FESC; Douglas L. Packer, MD, FHRS; Riccardo Cappato, MD, FESC; Shih-Ann Chen, MD, FHRS; Harry J.G. Crijns, MD, FESC; Ralph J. Damiano Jr, MD; D. Wyn Davies, MD, FHRS; David E. Haines, MD, FHRS; Michel Haissaguerre, MD; Yoshito Iesaka, MD; Warren Jackman, MD, FHRS; Pierre Jais, MD; Hans Kottkamp, MD; Karl Heinz Kuck, MD, FESC; Bruce D. Lindsay, MD, FHRS; Francis E. Marchlinski, MD; Patrick M. McCarthy, MD; J. Lluis Mont, MD, FESC; Fred Morady, MD; Koonlawee Nademanee, MD; Andrea Natale, MD, FHRS; Carlo Pappone, MD, PhD; Eric Prystowsky, MD, FHRS; Antonio Raviele, MD, FESC; Jeremy N. Ruskin, MD; Richard J. Shemin, MD

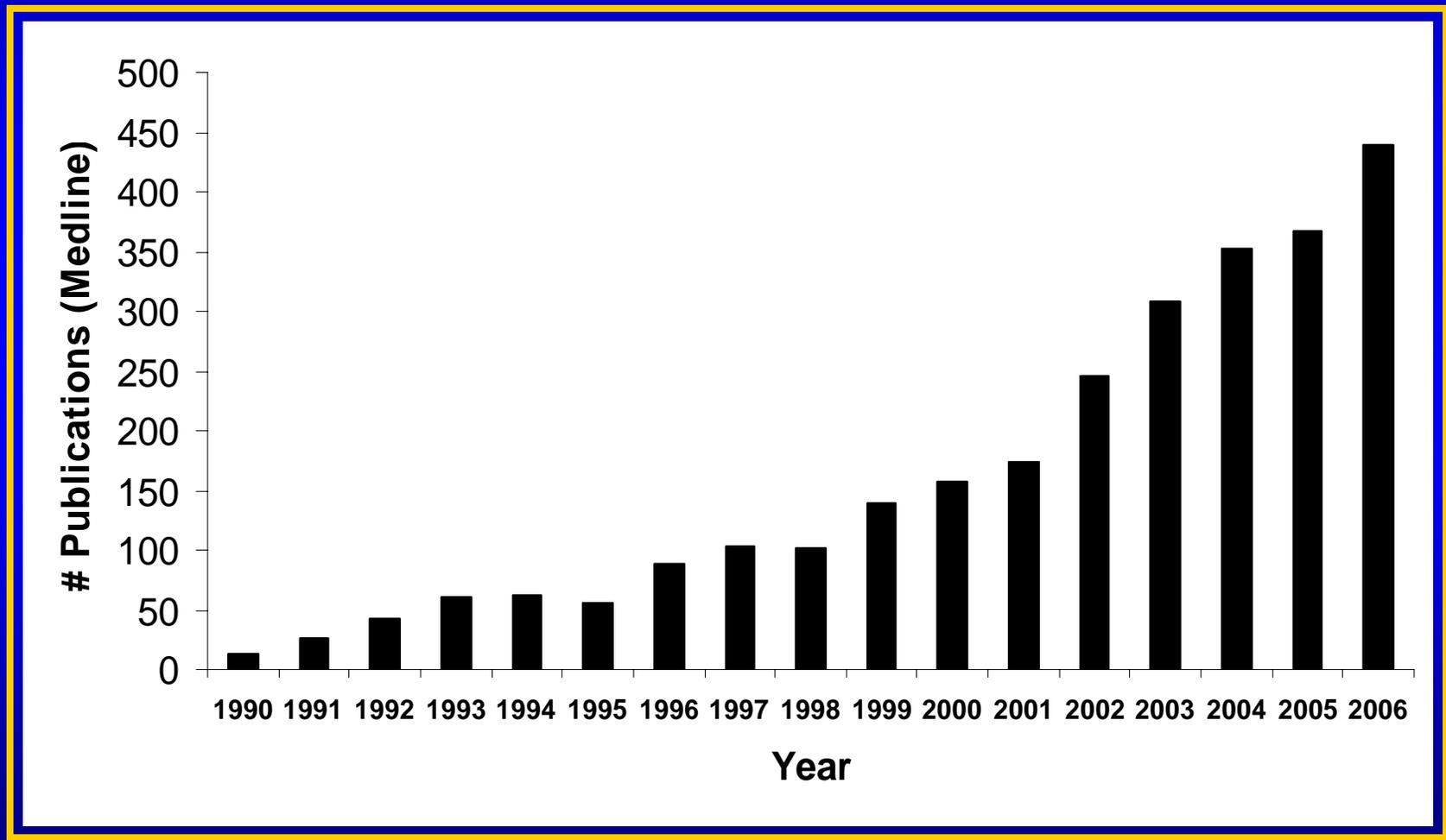
# HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-Up

**During the past decade, catheter ablation of atrial fibrillation (AF) has evolved rapidly from a highly experimental unproven procedure, to its current status as a commonly performed ablation procedure in many major hospitals throughout the world.**

MD, FESC, Shih-Ann Chen, MD, FHRS, Harry J.G. Crijns, MD, FESC, Ralph S. Damiano Jr, MD, D. Wyn Davies, MD, FHRS; David E. Haines, MD, FHRS; Michel Haissaguerre, MD; Yoshito Iesaka, MD; Warren Jackman, MD, FHRS; Pierre Jais, MD; Hans Kottkamp, MD; Karl Heinz Kuck, MD, FESC; Bruce D. Lindsay, MD, FHRS; Francis E. Marchlinski, MD; Patrick M. McCarthy, MD; J. Lluis Mont, MD, FESC; Fred Morady, MD; Koonlawee Nademanee, MD; Andrea Natale, MD, FHRS; Carlo Pappone, MD, PhD; Eric Prystowsky, MD, FHRS; Antonio Raviele, MD, FESC; Jeremy N. Ruskin, MD; Richard J. Shemin, MD



# AF Ablation Publications



# **Clinical Studies-Limitations**

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## **Limitations of Current Literature**

**Variation in endpoints**

**Substantial differences in treatment modalities**

**Definitions of acute and long-term success**

**Variability of post-ablation blanking periods, follow-up, redo  
and cross-over treatments**

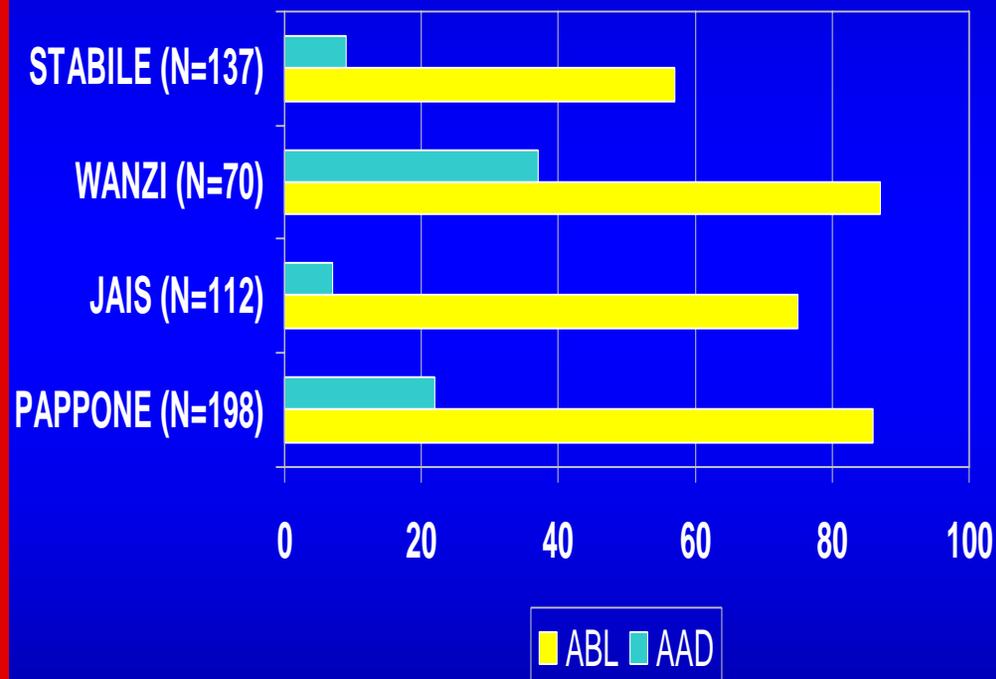
**Lack of detection of asymptomatic AF**

**Under reporting of adverse events**

**Relatively short duration of follow-up**

# RANDOMIZED TRIALS OF ABLATION FOR PAF

## ONE YEAR AF-FREE



Major complications in 1-4% of ablation groups

- **STABLE:** EHJ 2006 27:216-221; prior AAD failure; 1 episode/mo 6 mo duration; included 32% persistent AF; AAD given to ablation group; PVI+MI+CTI; blanking 1 mo; HM + 3 mo daily event monitoring; endpoint 30 sec AF
- **WANZI:** JAMA 2005: 293:2634-2640); No prior AAD; 1 episode/mo 3 mo duration; PVAI; blanking 2 mo; HM + 1,3 mo event monitoring; endpoint 15 sec AF. Pilot study for RAAFT (400 pt trial)
- **JAIS:** HRS Scientific Sessions 2006; Prior AAD failure, 2 episodes/mo 6 mo duration; PVI+CTI+lines; blanking 3 mo; HM + symptom diaries; endpoint 3 min AF or palpitations
- **PAPPONE:** JACC 2006 in press, doi 10:1016. Limited prior AAD; 2 episodes /mo 6 mo duration; CPVI+CTI+lines; blanking 6 wks, daily event monitoring; endpoint 30 sec AF

# Summary

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Trial	AF	N	Endpoint	FU	AF Free
Wazni	PAF First line	70	AF recurrence Hospitalization QoL	1 yr	85 %
Stabile	PAF or Persistent AF Failed AAD	137	AF recurrence	1 yr	56 %
Oral	Chronic AF	146	AF recurrence	1 yr	74 %
Pappone	PAF Failed AAD	198	AF recurrence	1 yr	89 %

## Definition of success

- **Freedom from AF/flutter/tachycardia off antiarrhythmic therapy is the primary endpoint of AF ablation**
- **For research purposes, time to recurrence of AF following ablation is an acceptable endpoint after AF ablation, but may under represent true benefit.**
- **Freedom from AF at various points following ablation may be a better marker of true benefit and should be considered as a secondary endpoint of ablation.**
- **Atrial flutter and other atrial tachyarrhythmias should be considered as treatment failures.**
- **An episode of AF/flutter/tachycardia detected by monitoring should be considered a recurrence if it has a duration of 30 seconds or more.**
- **Single procedure success should be reported in all trials of catheter ablation of AF.**

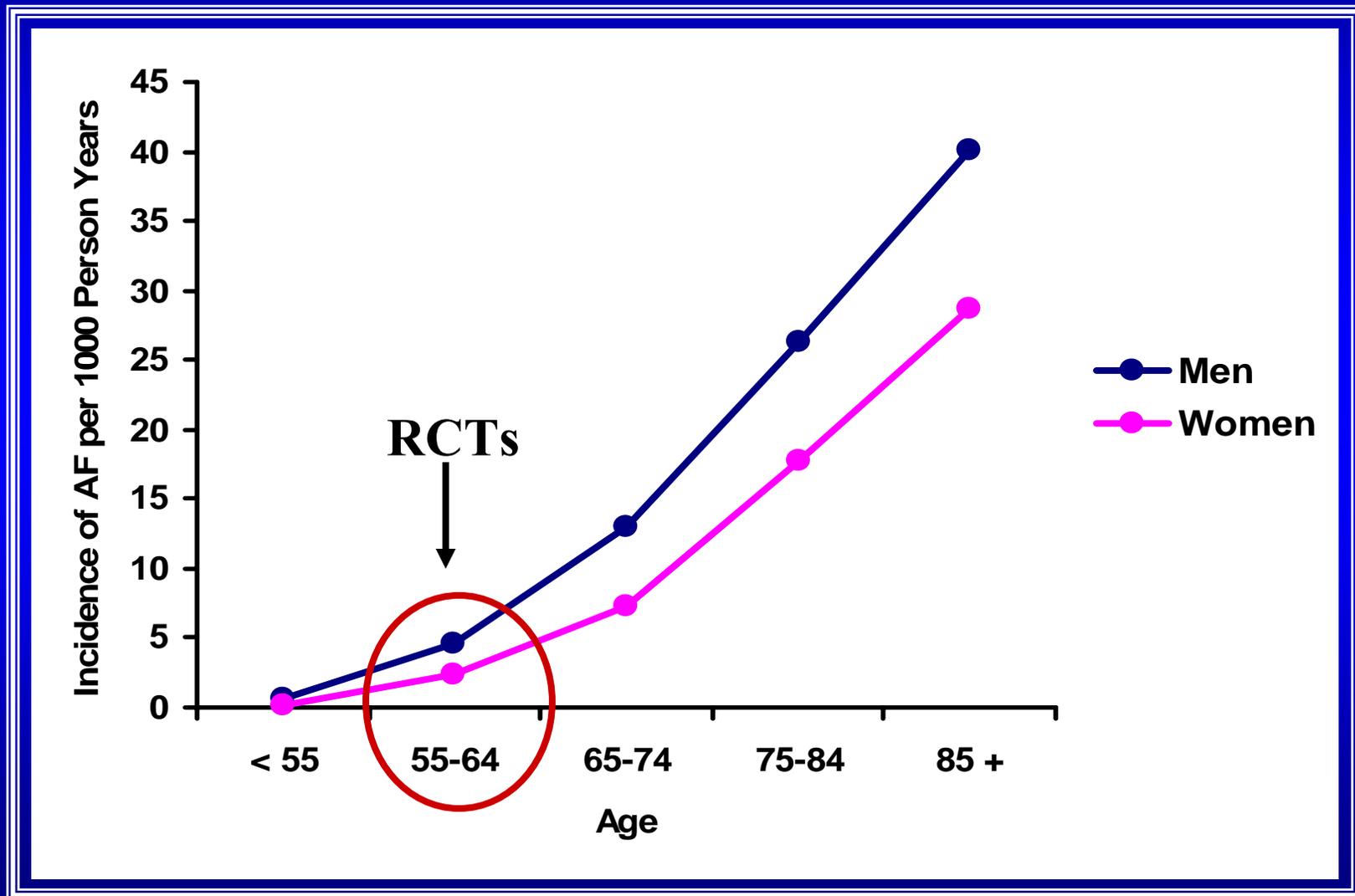
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## Monitoring

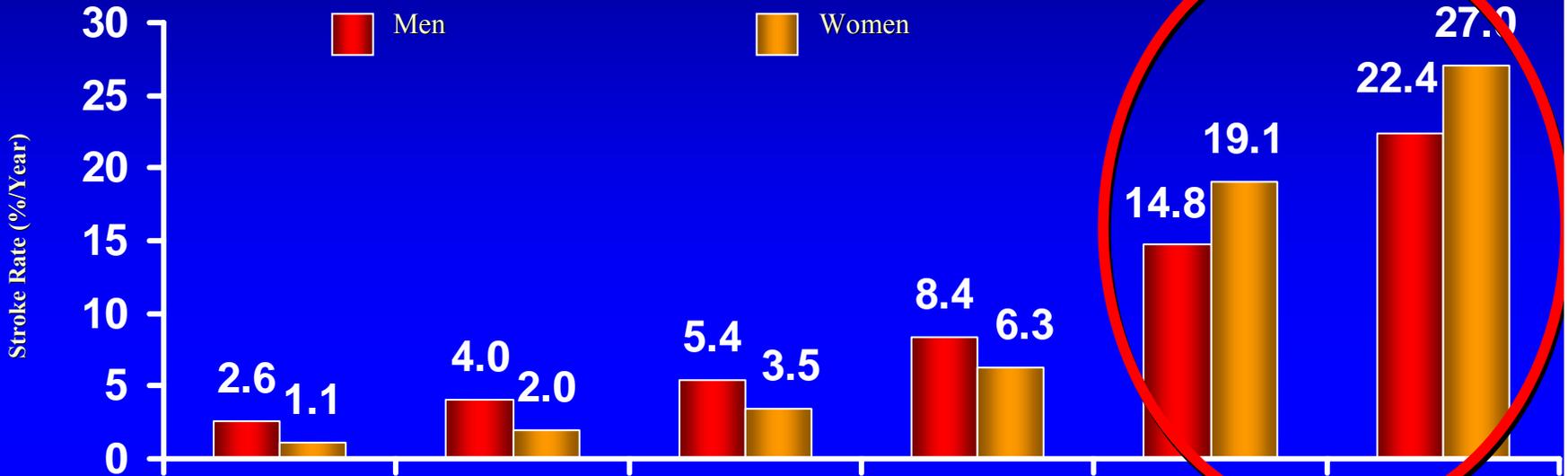
- Patients should be seen in follow-up at a minimum of three months following the ablation procedure and then every six months for at least two years.
- An event monitor should be obtained to screen for recurrent AF/flutter/tachycardia in patients who complain of palpitations during follow-up.
- An AF/flutter/tachycardia episode is present if it is document by ECG and last at least 30 seconds.
- All patients in a clinical trial should be followed for a minimum of twelve months.
- Patients being evaluated as part of a clinical trial or in whom warfarin may be discontinued should have some type of continuous ECG monitoring performed to screen for asymptomatic AF/flutter/tachycardia.
- 24-hour Holter monitoring is an acceptable minimal monitoring strategy for patients enrolled in a clinical trial and is recommended at three to six months intervals for one to two years following ablation.

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# PATIENTS



# Estimated 10-Year Stroke Risk in 55-Year-Old Adults According to Levels of Various Risk Factors



	A	B	C	D	E	F
Systolic BP*	95-105	130-148	130-148	130-148	130-148	130-148
Diabetes	No	No	Yes	Yes	Yes	Yes
Cigarettes	No	No	No	Yes	Yes	Yes
Prior AF	No	No	No	No	Yes	Yes
Prior CVD	No	No	No	No	No	Yes

\*Blood pressures are in millimeters of mercury (mm Hg).  
Source: Wolf et al. *Stroke*. 1991;22:312-318.

- 
- Decisions regarding the use of warfarin more than two months following ablation should be based on the patient's risk factors for stroke and not on the presence or type of AF.
  - Discontinuation of warfarin therapy post ablation is generally not recommended in patients who have a CHADs score  $\geq 2$ .

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- It remains uncertain whether apparent cures represent elimination of AF or transformation into an asymptomatic form of paroxysmal AF.
  - The distinction has important implications for the duration of anticoagulation therapy in patients with risk factors for stroke associated with AF.
  - Little information is available about the late success of ablation in patients with HF and other advanced structural heart disease, who may be less likely to enjoy freedom from AF recurrence and in whom the risk of thromboembolic events is higher.

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- Double-blind studies are almost impossible to perform, yet there is a need for randomized trials in which evaluation of outcomes is blinded as to treatment modality.
  - A comprehensive evaluation of the favorable and adverse effects of various ablation techniques should include measures of quality of life, cost, and recurrence rates compared with pharmacological strategies.
  - Generation of these comparative data over relatively long periods of observation would address the array of invasive and conservative management approaches available for management of patients with AF and provide a valuable foundation for future practice guidelines.

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# Maintenance of Sinus Rhythm

