

# ACC/AHA/ESC - 2006 Guidelines For the Management of Patients with Atrial Fibrillation

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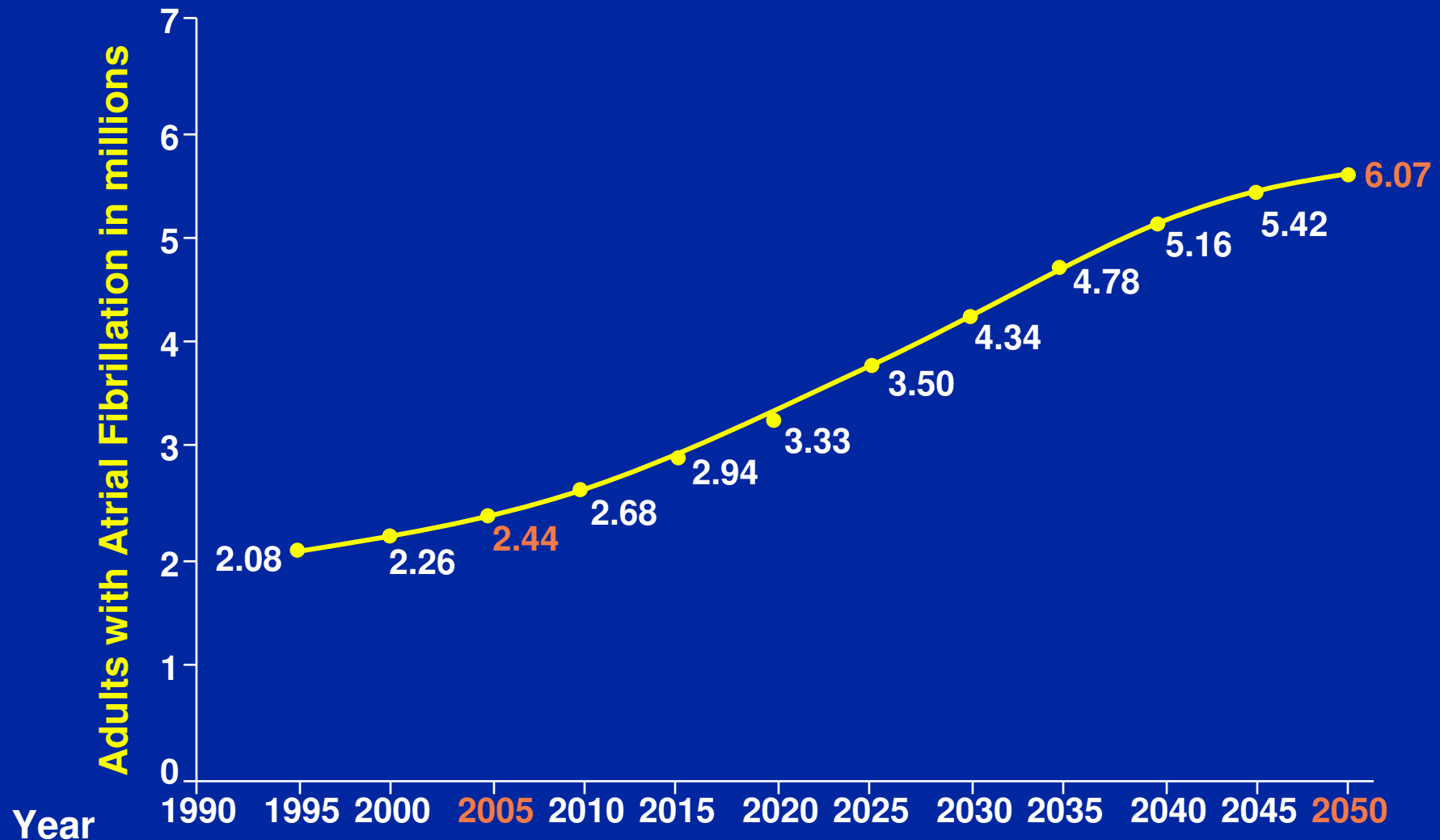
**Juan Tamargo, M.D., F.E.S.C.**

**Samuel Wann, M.D., F.A.C.C.**

# *ATRIAL FIBRILLATION CHALLENGES AND NEW OBSERVATIONS*

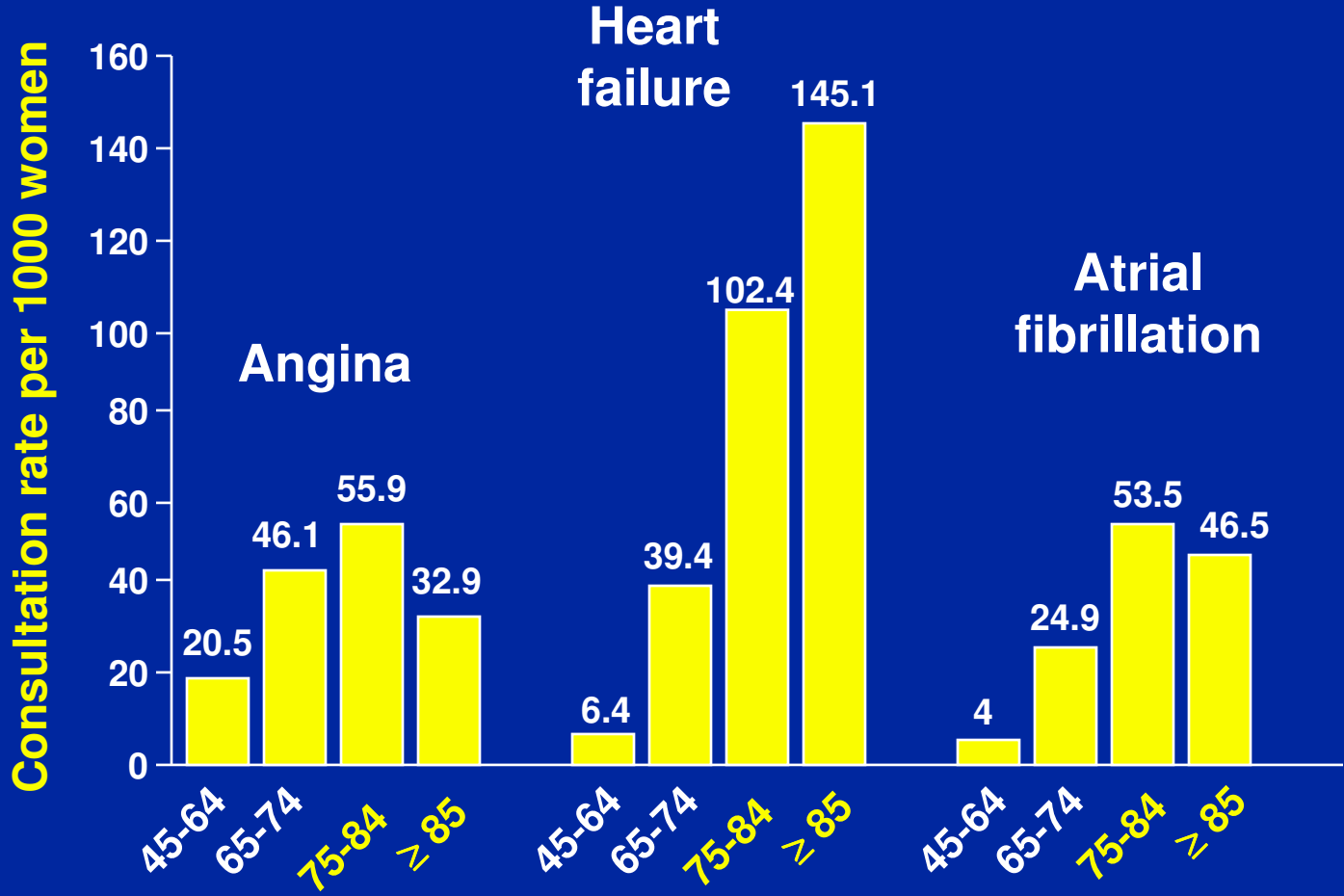
- 1. Prevalence of AF (2)**
- 2. Classification & Patterns (3)**
- 3. Pathophysiology (6)**
- 4. Approach to Management (1)**
- 5. Heart Rate Control (4)**
- 6. Antithrombotic Therapy (10)**
- 7. Rhythm Control (4)**

# 1) PREVALENCE & PROJECTED ADULTS WITH AF IN THE US 1995 AND 2050



**ATRIA** (AS Go et al.) JAMA 2001; 285: 2370 (Kaiser Permanente, North Ca)  
**Age (1% at 60 y.....+0.5% y), Cardiac Failure (1-25%) etc**

**2) AGE-STRATIFIED CONSULTATION RATES<sup>1</sup> x 1000 POPULATION FOR HEART FAILURE, ANGINA & ATRIAL FIBRILLATION IN WOMEN**

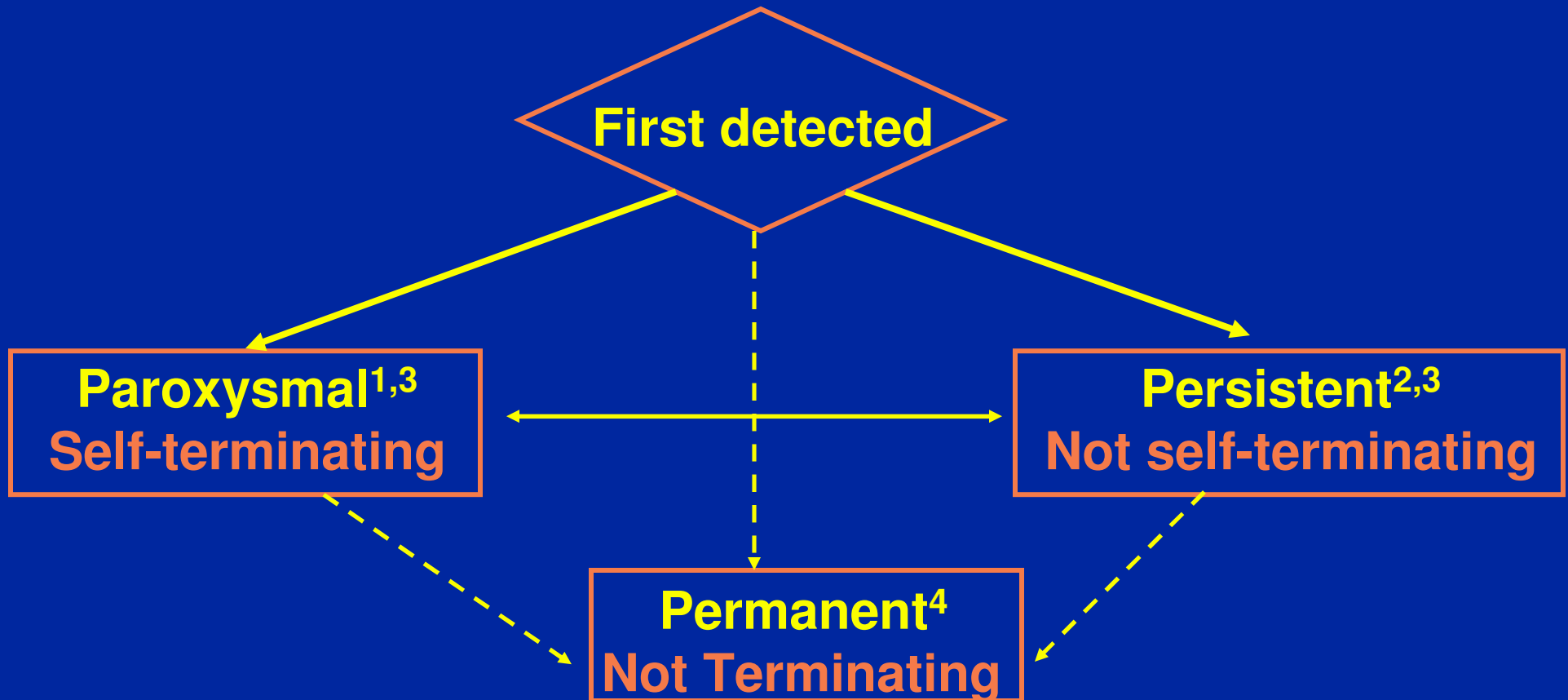


<sup>1</sup> General practitioner, Scotland (55 practices, 362155 pts, 2001-2002)  
 NF Murphy et al., Heart 2007; 93:606

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# 1) CLASSIFICATIONS & PATTERNS - ATRIAL FIBRILLATION



<sup>1</sup>Episodes generally last  $\leq 7$  days (most  $< 24$  hours)

<sup>2</sup>Usually  $> 7$  days

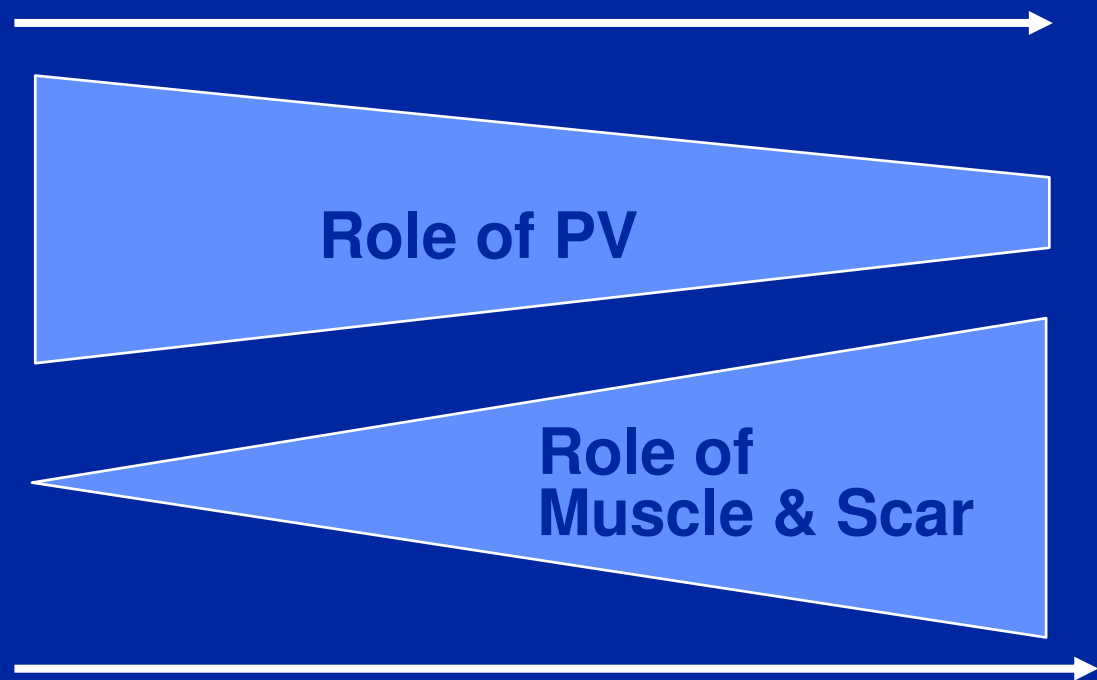
<sup>3</sup>Either paroxysmal or persistent AF may be recurrent

<sup>4</sup>Cardioversion failed or not attempted

**ACC/AHA/ESC - Circ 2006; 114:700**

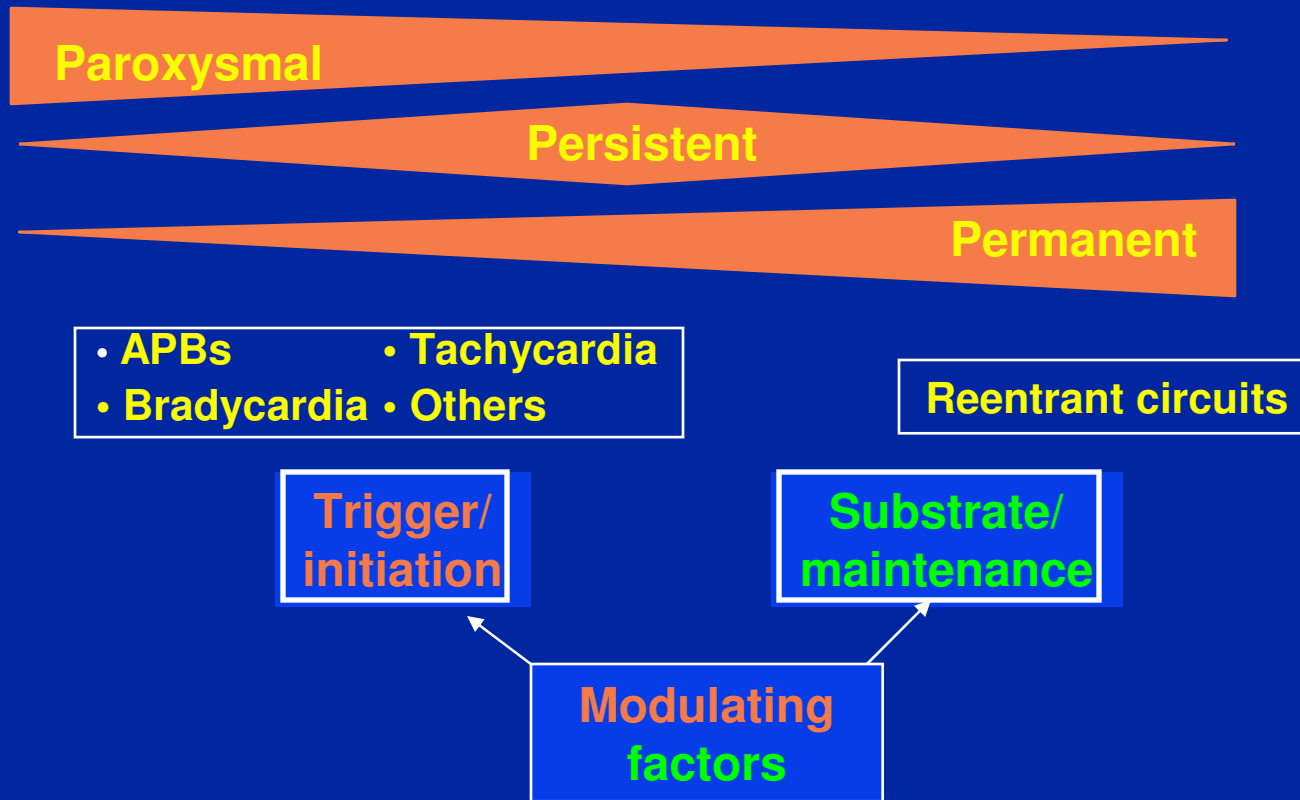
## **2) AF ABLATION: SUBSTRATE EVOLUTION LEADS TO CHANGE IN ABLATION TECHNIQUE**

**Paroxysmal, Persistent, Permanent**



**Focal Hybrid Substrate,**

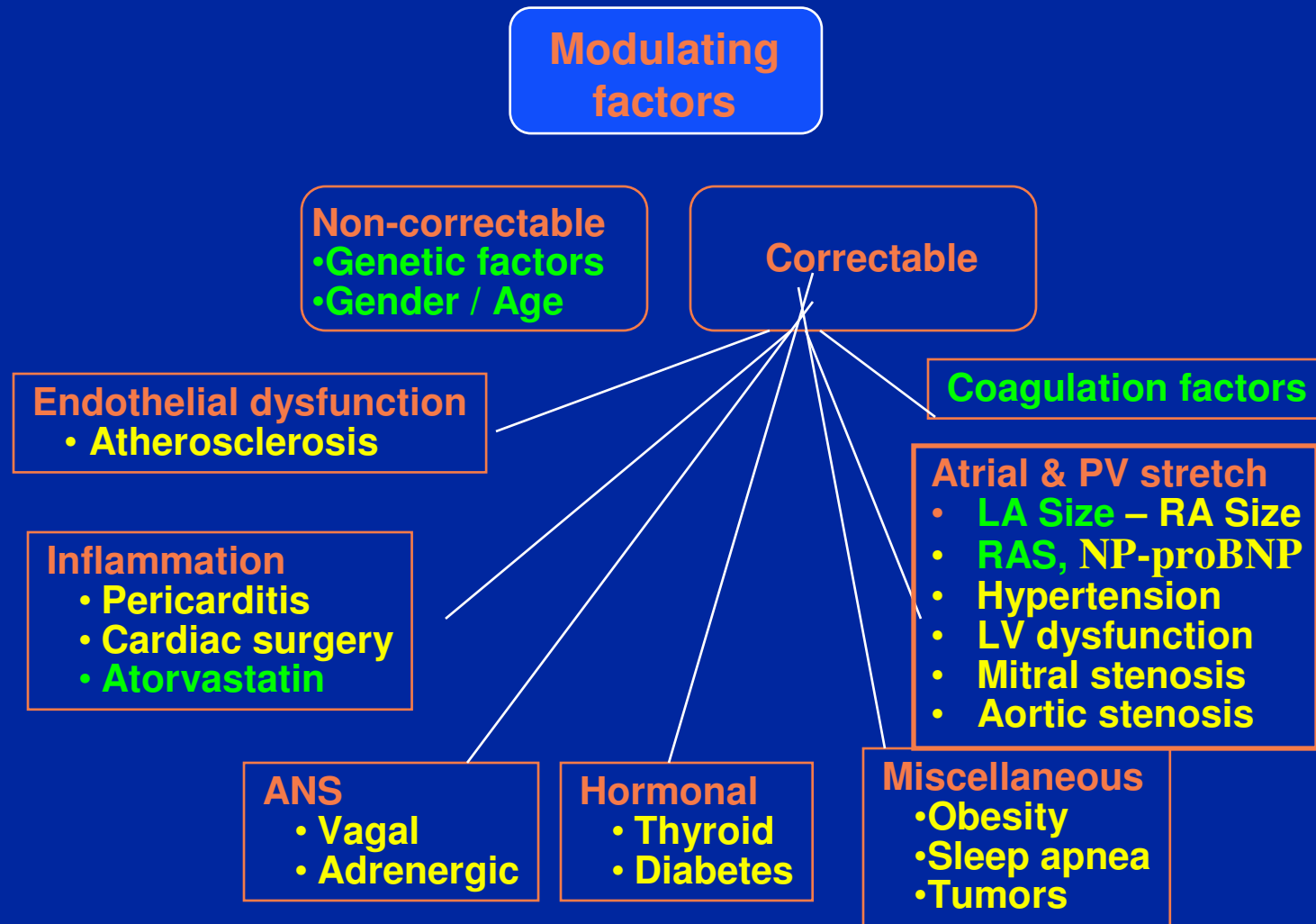
3)



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# MODULATING FACTORS FOR AF



DG Wyse, BJ Gersh. Circ **2004**; 109:308

**ALFA** (S Levy et al) Circulation **1999**;99:3028 – **Electrical** (SSS, Focal AF etc), **Intox** (alcohol etc), **Neurogenic** (stroke etc), **Idiopathic**

## 1) Do Genetics Help To Better Understand the Underlying Mechanisms of Atrial Fibrillation?

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It may be evidence that susceptibility to non-valvular AF(NVAF) may be enhanced in association with certain single nucleotide polymorphisms in the genes encoding the accessory K<sup>+</sup> channel subunit minK and the endothelial nitric oxide synthase (eNOS). The identification of susceptibility genes for **AF induction** may help to identify subjects at risk for **AF development**.

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D. Dobrev. EHJ 2006; 27:1640 –

C. Fatini et al., EHJ 2006; 27:1712

## 1) Somatic Mutations in the Connexin 40 Gene (*GJA5* in Atrial Fibrillation)

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The cardiac gap-junction protein **connexin 40** is expressed selectively in atrial myocytes and **mediates the coordinated electrical activation of the atria**. Four novel heterozygous **missense mutations were identified in 4 of 15 patients**. Mutations in *GJA5* may predispose patients to idiopathic atrial fibrillation by **impairing gap-junction assembly or electrical coupling**.

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MH Gollob et al., NEJM **2006**; 354:3677 (Ottawa)

## 2) Gender-Related Differences in Presentation, Treatment & Outcome of Patients With Atrial Fibrillation

### A Report From the Euro Heart Survey on Atrial Fibrillation

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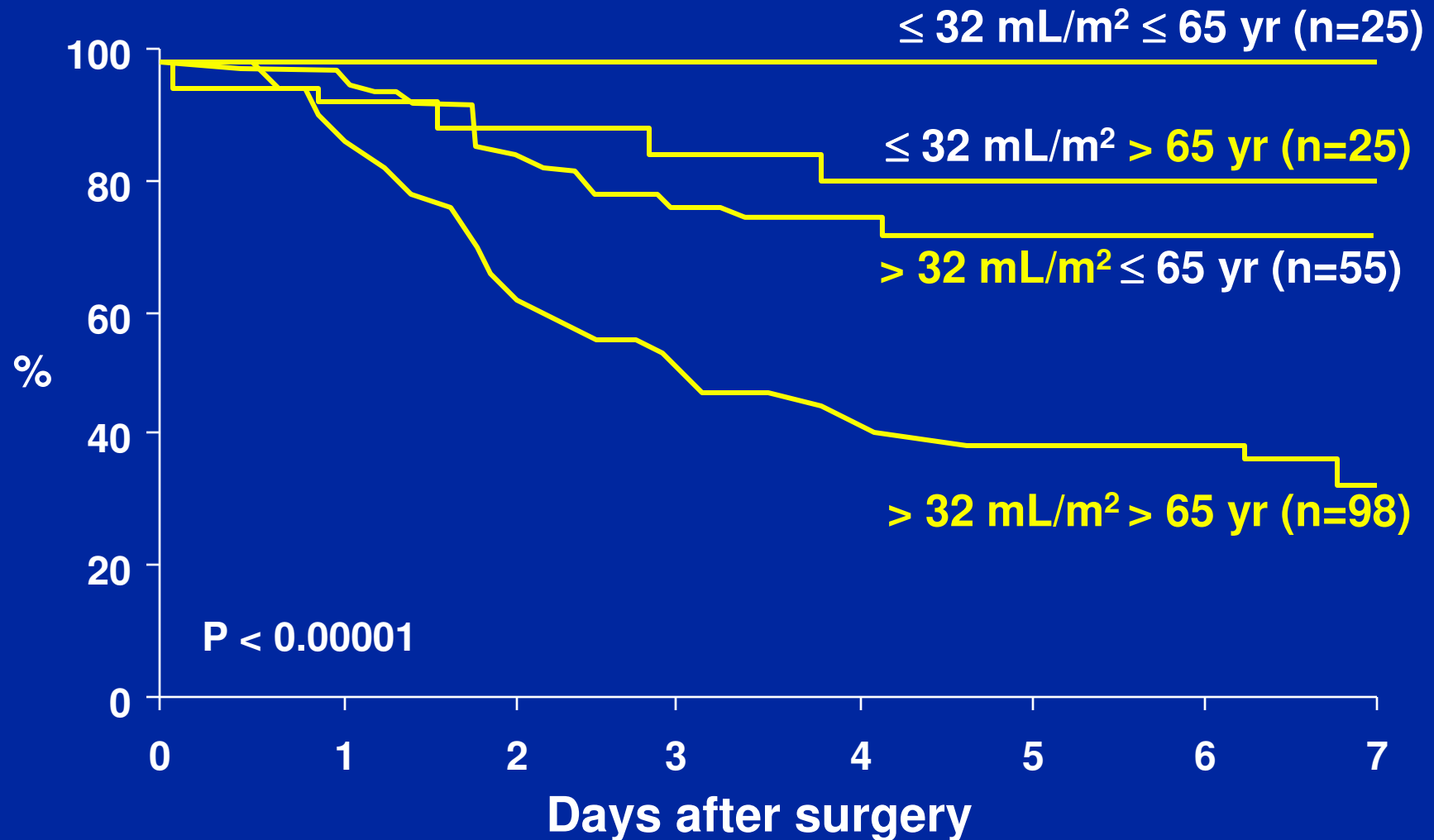
**Women with AF had more comorbidities, more HF with preserved systolic function, and a lower QoL than men.** In the large group with atypical or no symptoms, women were **treated appropriately more conservatively with less rhythm control than men.** Women had a **higher chance for stroke.** Long-term QoL changes and other morbidities and mortality were similar.

N Dagres et al., JACC 2007; 49:572

**In USA no main gender difference.**

SB Rowan et al., JACC 2007; 49:1561

### 3) LEFT ATRIAL VOLUME AND AGE INFLUENCE ON FROM POSTOPERATIVE ATRIAL FIBRILLATION



## **4) NVAF - PATHOPHYSIOLOGY OF AF & THROMBUS FORMATION** **VIRCHOW TRIAD**

**LAA - STASIS: Age-LA Size-AF<sup>1</sup>, Hypertension <sup>1,2,3</sup>, CHF <sup>3,,</sup>, Obesity <sup>4,5</sup>**

**- SEC "Smoke"<sup>6</sup>**

**- Stunning "post cardioversion"<sup>7,8</sup>**

**ENDOTHELIAL DYSFUNCTION <sup>1-5</sup>**

**- vWF, P-Selectin<sup>9,10</sup>**

**HYPERCOAGULABLE STATE**

**- C-Reactive Protein,<sup>11</sup> PAI-1**

**1. Osranek M et al JACC 2006;48:779**

**2.Zabalgoitia M et al AJC1998;31:1662 –3.Miller VT et al Neurol 1993;43:32 –**

**4.Wang TJ et al JAMA 2004;292:2471 - 5.Coromilas J JAMA 2004;292:2519**

**6.Rastegar R et al., JACC 2003; 107:3145 Fibrinogen - RBC marker**

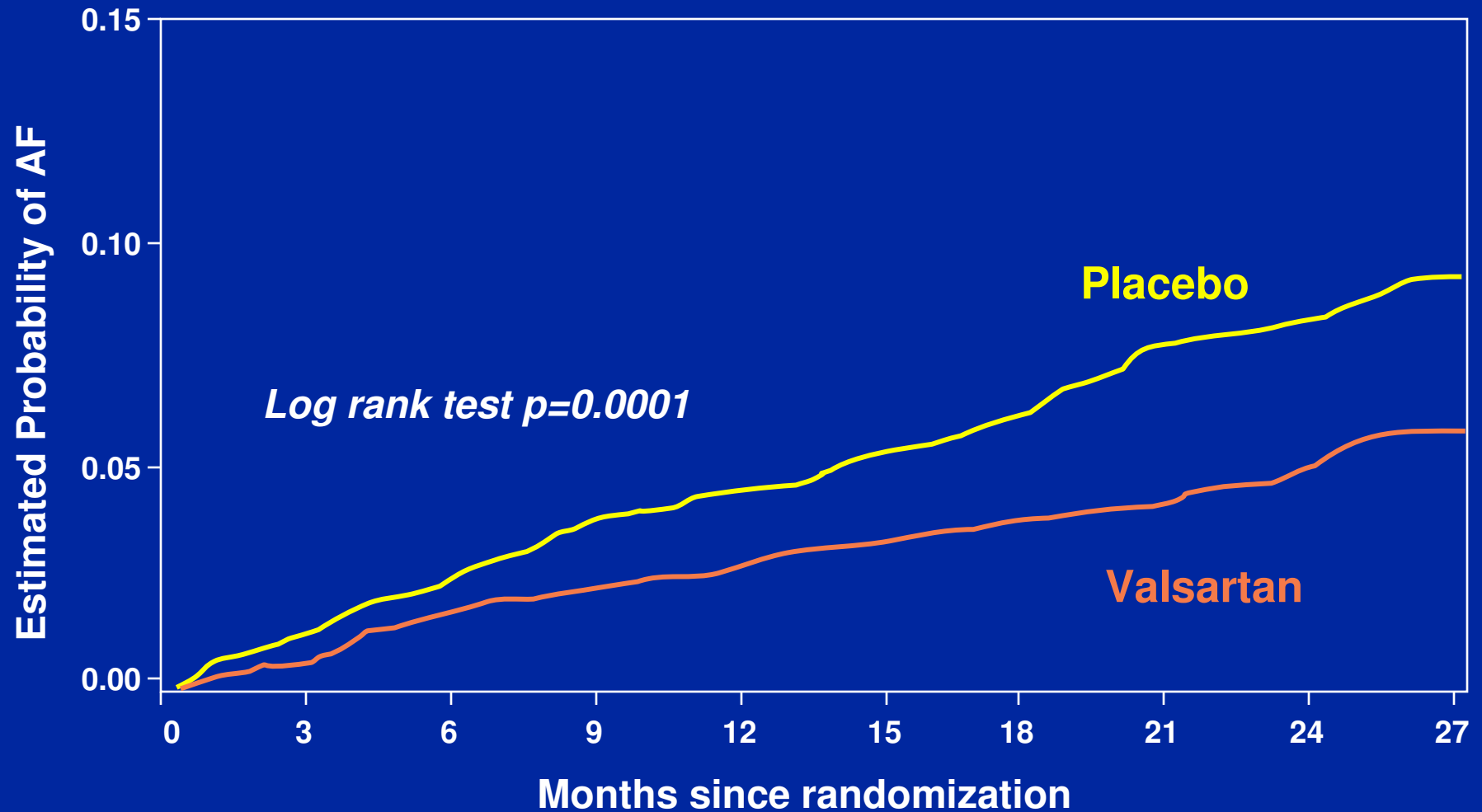
**7.Khan IA et al., AHJ 2003; 145:784 - First 10 days**

**8.Dunn MI et al., Chest 2002; 121:1 - Short (min), Long (days)**

**10.Conway DS et al., Circ 2003; 107:3141 - Endothelium → Local thrombogenicity**

**11.Anderson JL et al., AJC 2004; 94:1255 - Systemic thrombogenicity**

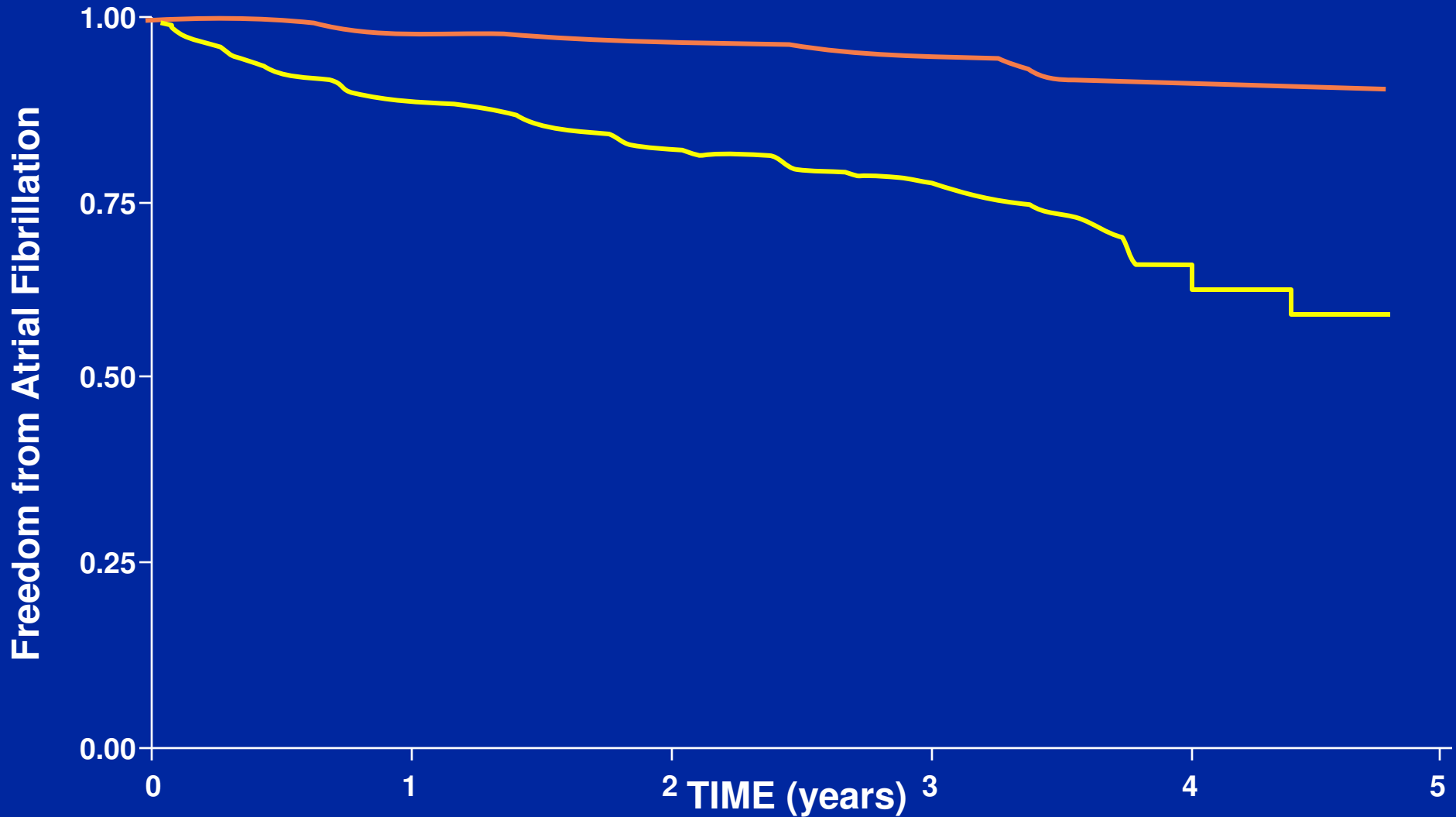
## 5) VALSARTAN REDUCES INCIDENCE OF AF (NSR AT BASELINE) IN HEART FAILURE (N=4395)



**AF Worsens outcome in heart failure.**

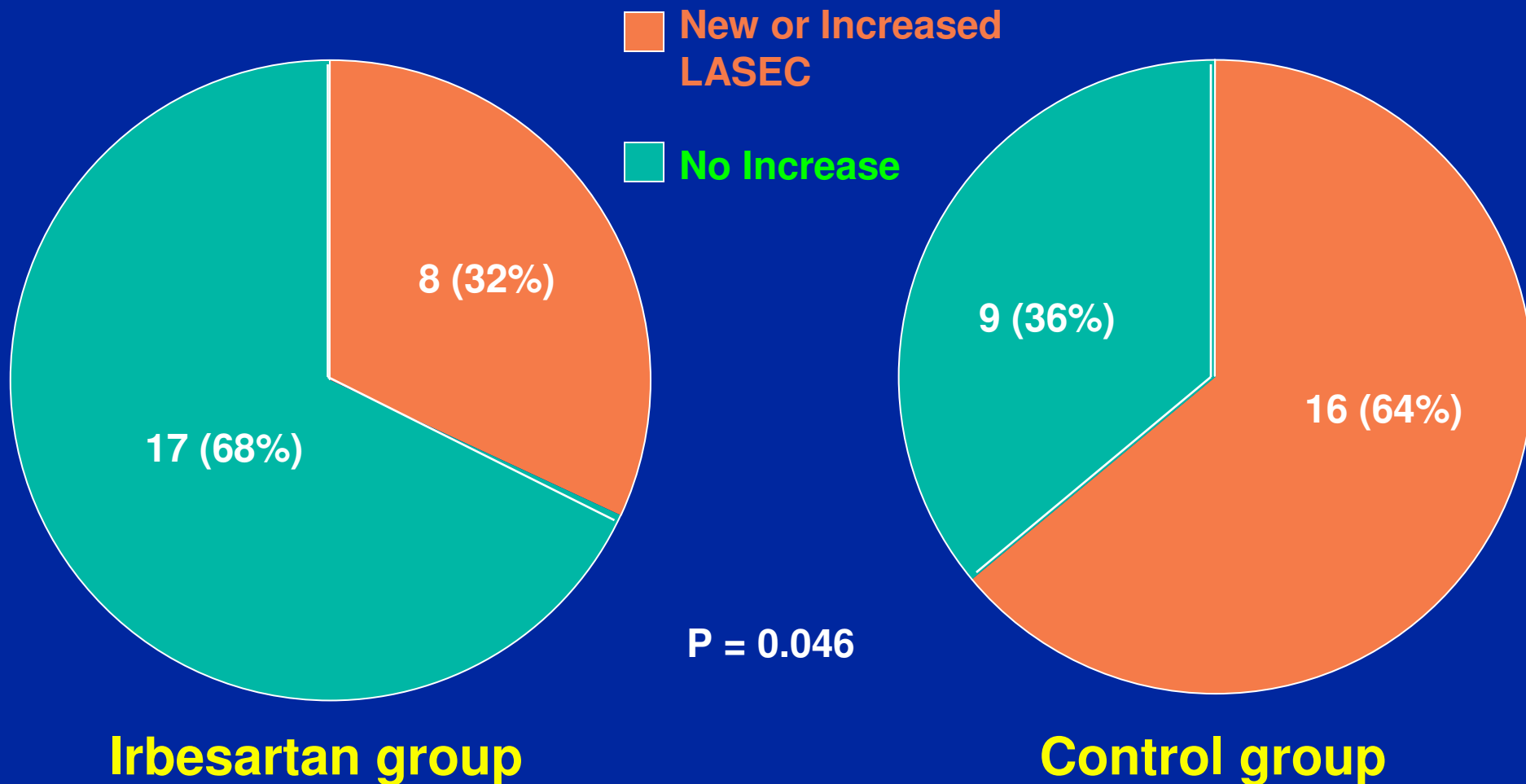
**Val-HeFT (AR Maggioni et al.) AHJ 2005; 149:548**

**5) ENALAPRIL REDUCES INCIDENCE OF AF (NSR AT BASELINE)  
IN LV DYSFUNCTION (N=374)**

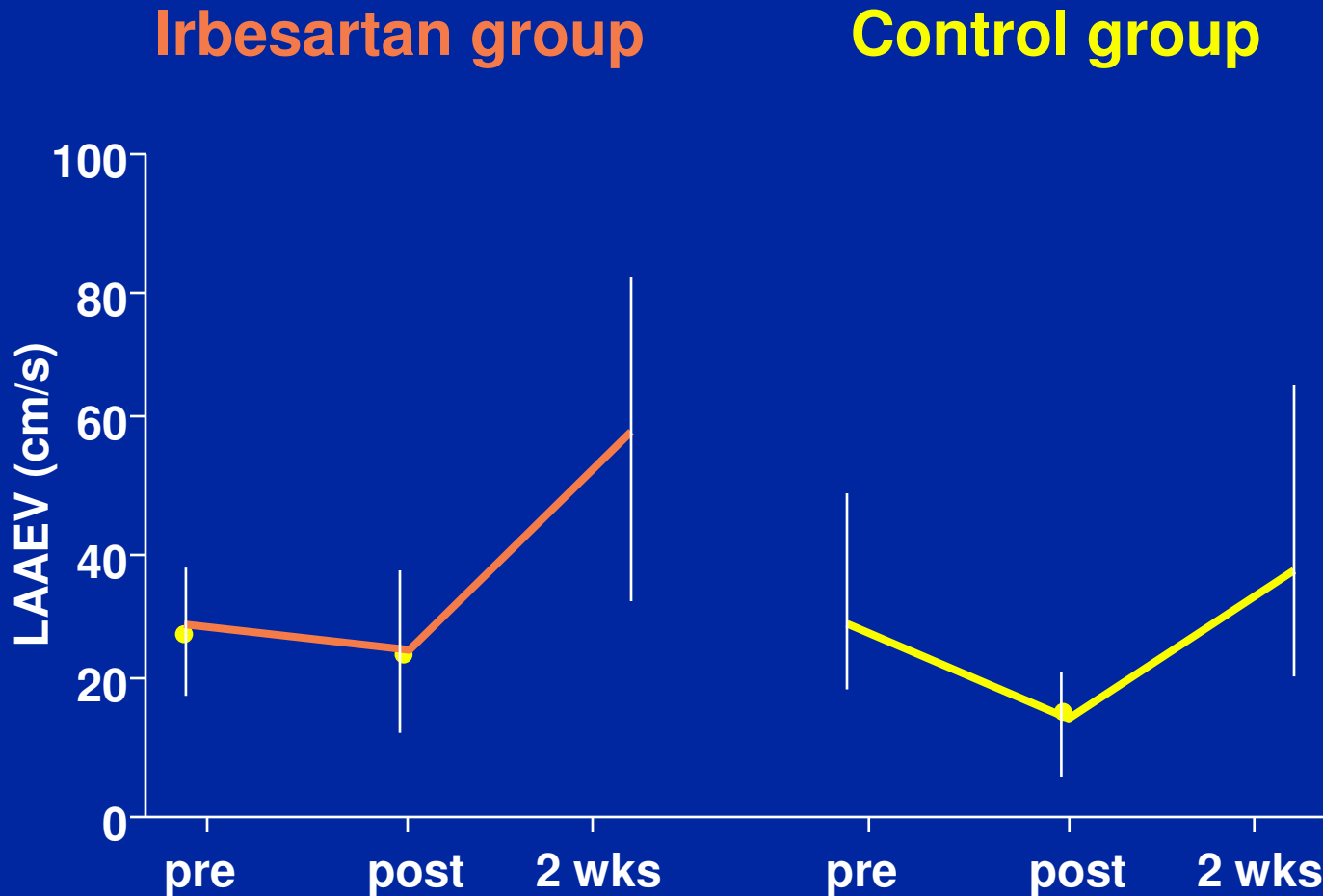


**Electrical and structural remodeling?**  
**SOLVD (F Vermer et al.) Circ 2003; 107:2426**

**5) FREQUENCY OF NEW OR INCREASED LASEC IN THE IRBESARTAN GROUP AND IN THE CONTROL GROUP IMMEDIATELY AFTER CARDIOVERSION**



**5) LAAEV IN THE IRBESARTAN AND IN THE CONTROL GROUP BEFORE (PRE), IMMEDIATELY AFTER (POST) CARDIOVERSION, AND AT 2 WEEKS**



N Dargès et al., EHJ 2006; 27:2062 (Athens, Greece)

## 6) Randomized Trial of Atorvastatin for Reduction of Postoperative AF in Patients Undergoing Cardiac Surgery

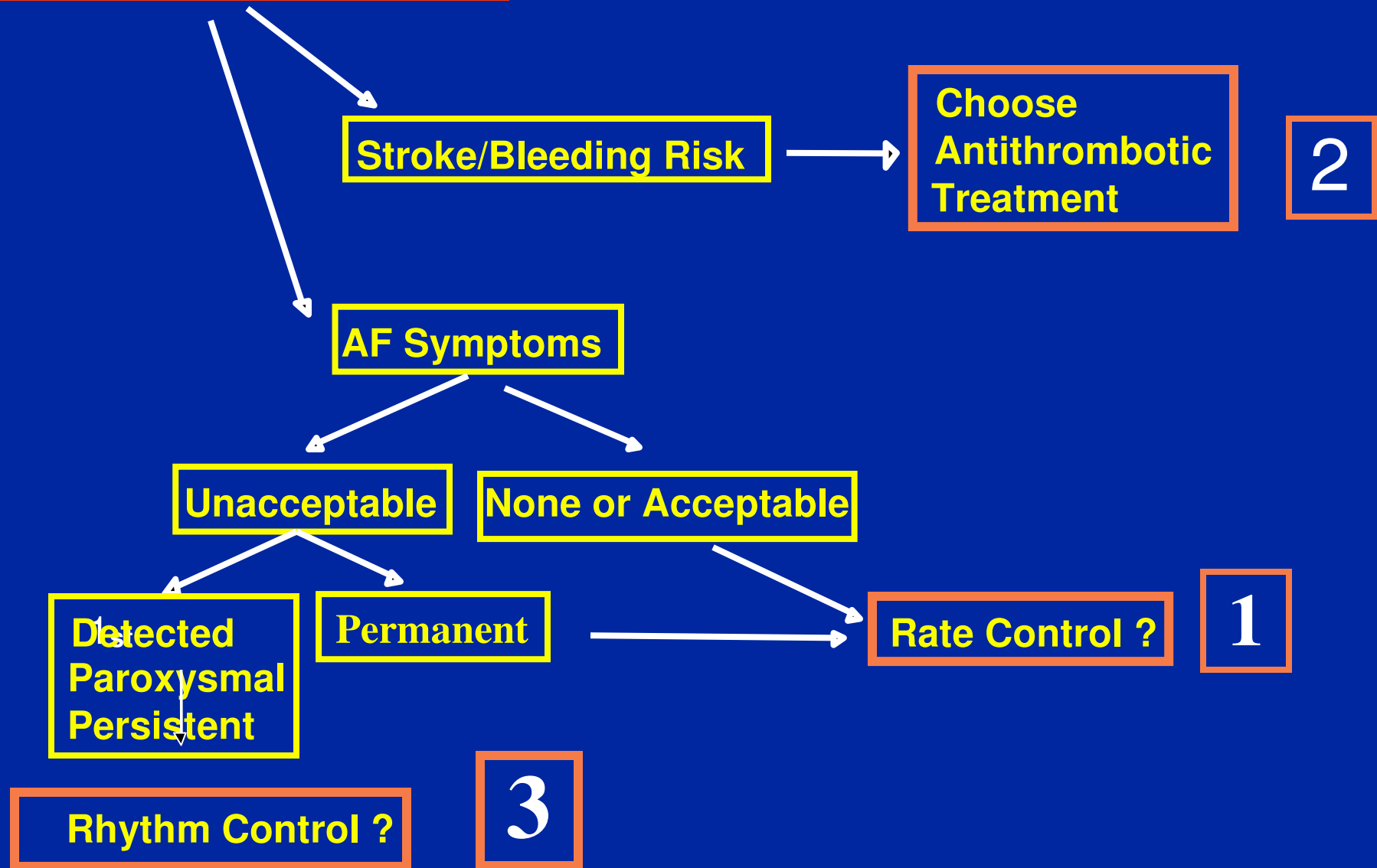
Two hundred patients undergoing elective cardiac surgery without previous statin treatment or history of AF, were enrolled. Patients were randomized to **atorvastatin (40 mg/d, n=101)** or **placebo (n=99)** at 7 days preop. Multivariable analysis showed that atorvastatin conferred **a 61% reduction in risk of AF**. High postop. **CRP levels** were associated with increased risk.

**ARMYDA-3** (G Patti et al., ) Circ **2006**; 114:1455 (Rome)

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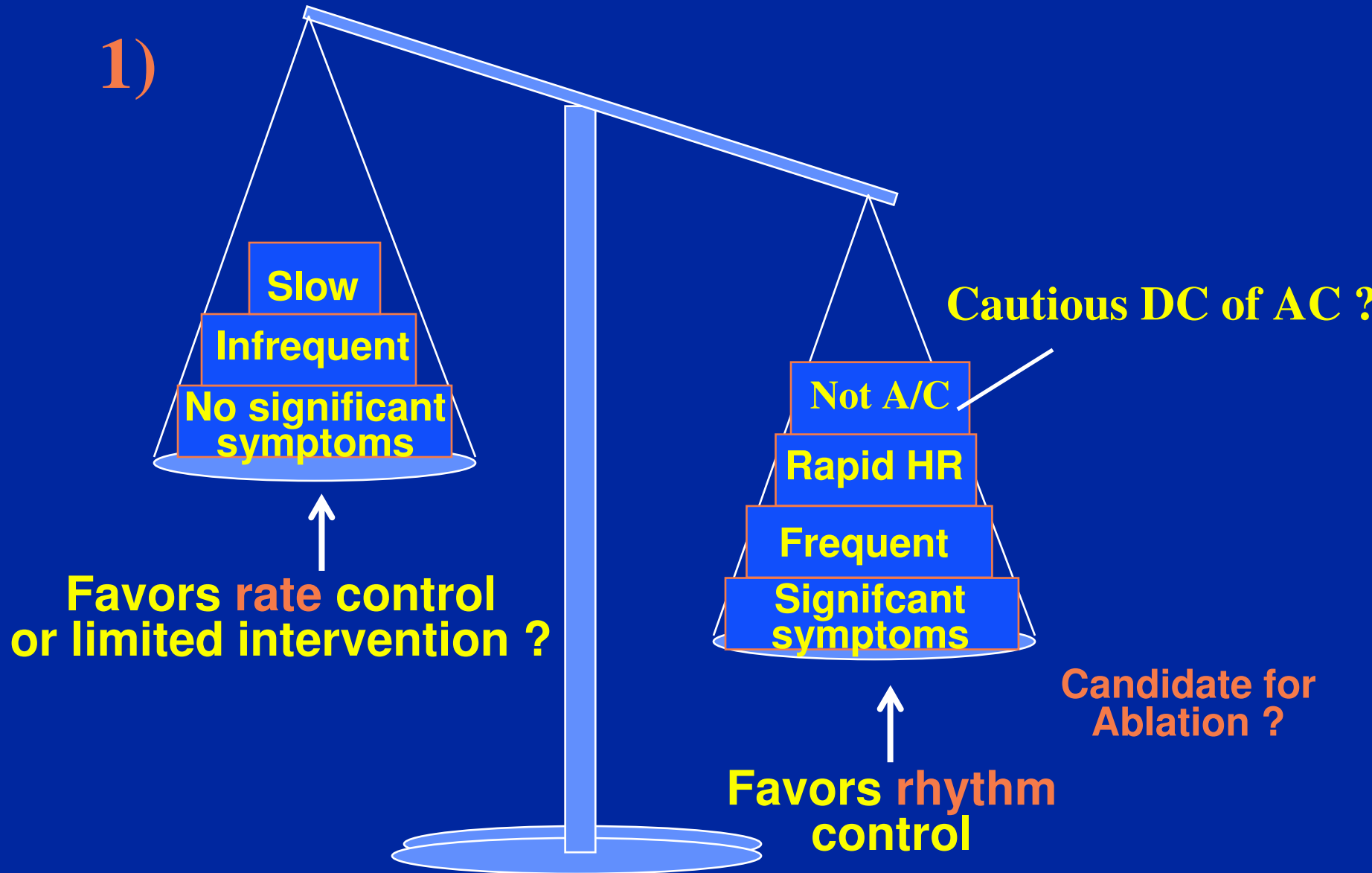
# 1) Patient with AF



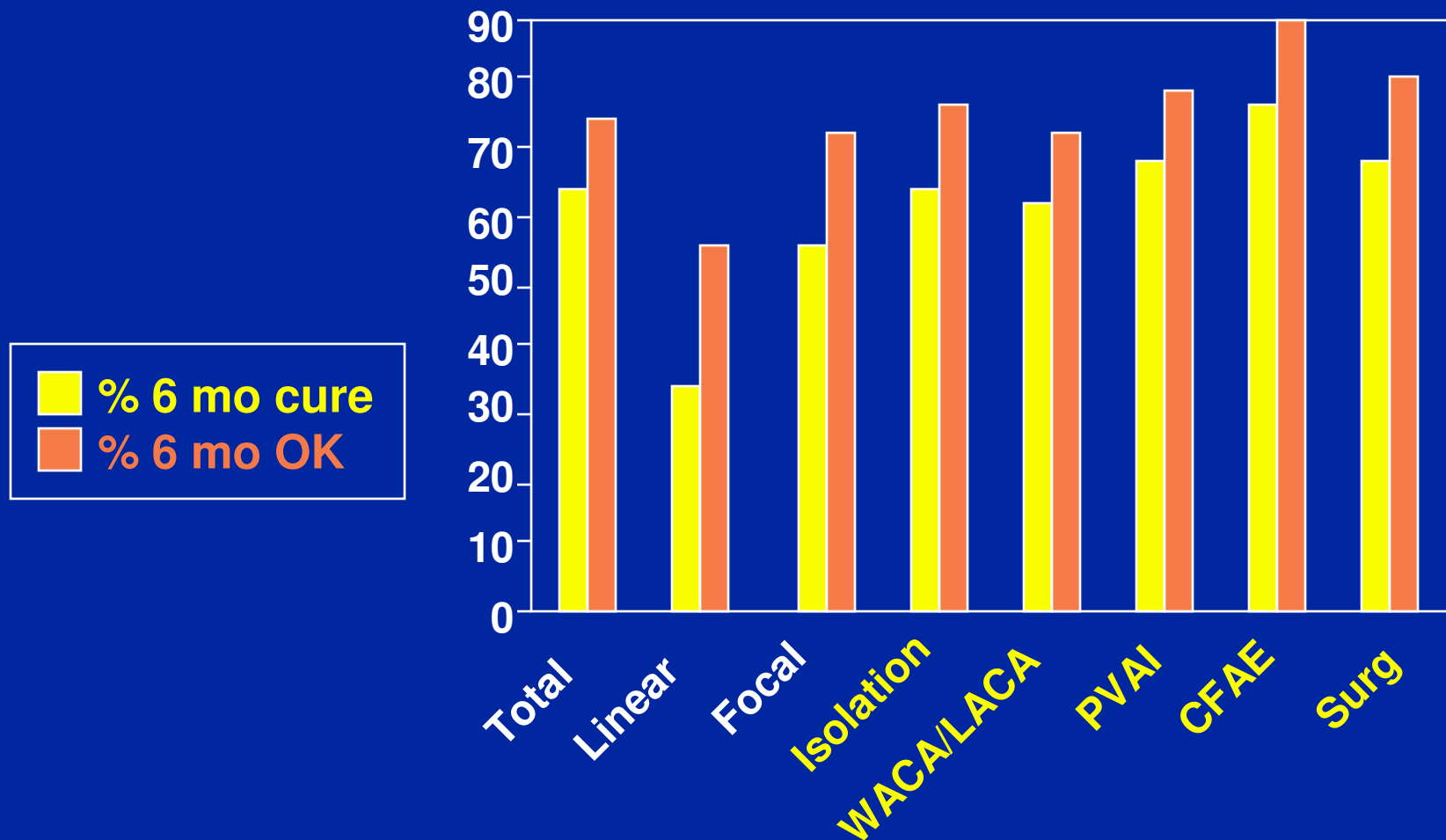
# *ATRIAL FIBRILLATION CHALLENGES AND NEW OBSERVATIONS*

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1)



## 2) AF ABLATION: METHOD vs LIKELIHOOD OF CURE OR SUBSTANTIAL IMPROVEMENT AT 6 MONTHS



### 3) A Tailored Approach to Catheter Ablation of Paroxysmal Atrial Fibrillation

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The pulmonary veins and left atrium were mapped during spontaneous or induced AF. Arrhythmogenic **pulmonary veins were isolated or encircled**. If AF was still present or **inducible, complex electrograms in the left atrium, coronary sinus, and SVC were targeted for ablation**. The end point of ablation was absence of frequent atrial ectopy and spontaneous AF during **isoproterenol infusion and noninducibility of AF**. A tailored ablation strategy that only targets triggers and drivers of AF is feasible and eliminates paroxysmal AF in **~80% of patients**.

H Oral et al., Circ **2006**; 113:1824 (Ann Arbor, Michigan)

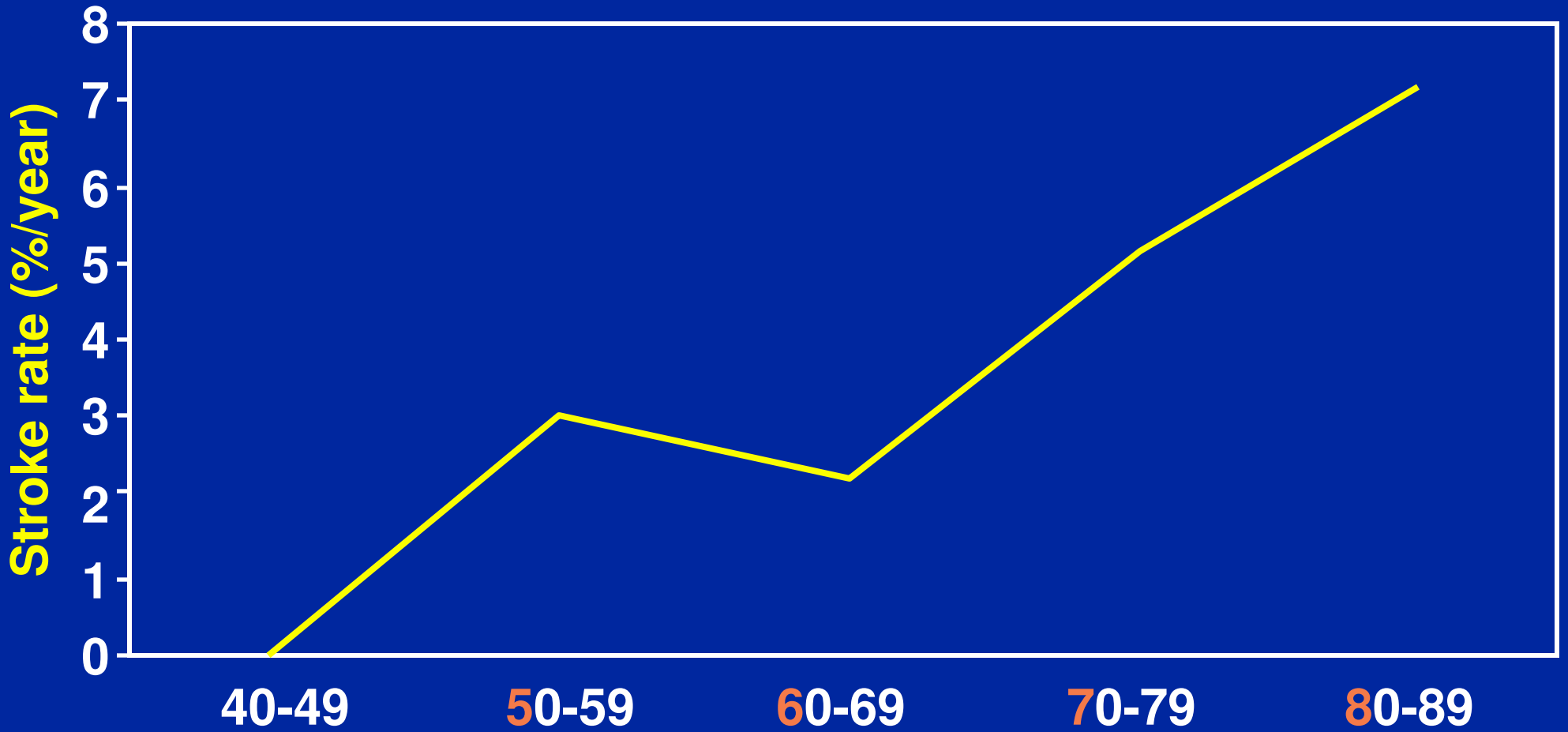
## **4) NON-PHARMACOLOGICAL MAINTENANCE OF SINUS RHYTHM**

- **Pacing to prevent AF:**  
Dual Site Atrial Pacing?
- **Internal Atrial Defibrillation: Dual chamber, Sensing, Pacing**  
Evolving Future
- **New Ablation Approach ? : AF begets AF, and ventricular compliance?**  
Drug Refractory Paroxysmal AF, Young, Normal Heart  
Evolving Technology and Future
- **Surgical Ablation of AF: If required, Surgery for Structural Disease**  
MAZE'S Evolving Technology

# *ATRIAL FIBRILLATION CHALLENGES AND NEW OBSERVATIONS*

- 1. Prevalence of AF and Rates of Stroke (2)**
- 2. Classification & Patterns (3)**
- 3. Pathophysiology (6)**
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# 1) STROKE RATES IN RELATION TO AGE AMONG PATIENTS WITH ATRIAL FIBRILLATION



**Framingham** - PA Wolf et al., Ann Int Med 1987;147:1561 – 1/2-1 Decade Unrelated to Left Atrium (CVD, other Cardiac, aorta) 25%

Bogouslavsky J et al & Miller VT et al Neurol 1990;40:1046 & 1993;43:32

## 2) Meta-analysis - Antithrombotic Therapy in Atrial Fibrillation (AF)

**Thirteen new trials are available since a 1999 meta-analysis of antithrombotic agents for stroke prevention in patients with AF.**

**This updated meta-analysis shows that adjusted-dose warfarin reduces stroke risk by 64% (6 trials) and antiplatelet agents reduce stroke risk by 22% (8 trials). Meta-analysis of 12 trials shows that adjusted-dose warfarin is more effective than antiplatelet therapy, but it doubles the risk for major extracranial and intracranial hemorrhage. But, these adverse events were only 0.2% per year.**

**Additional trials are unlikely to change current estimates of the effectiveness of vitamin K antagonists and antiplatelet agents**

**RG Hart et al., Ann Int Med 2007; 146:857 (San Antonio, Tx)**

## ***2) STROKE RATES ON ORAL ANTICOAGULATION RECENT LARGE ATRIAL FIBRILLATION TRIALS IN HIGH-RISK PTS***

<b>Trial</b>	<b>Year Published</b>	<b>INR in Therapeutic Range, %</b>	<b>Annual Event Rates in Warfarin Group</b>	
			<b>Isch. Stroke, %</b>	<b>Hemor. Stroke %</b>
<b>SPAF-III</b>	<b>1996</b>	<b>61</b>	<b>1.9</b>	<b>0.5</b>
<b>SPORTIF II</b>	<b>2003</b>	<b>66</b>	<b>1.9</b>	<b>0.4</b>
<b>SPORTIF V</b>	<b>2005</b>	<b>68</b>	<b>1.1</b>	<b>0.1</b>
<b>ACTIVE W</b>	<b>2006</b>	<b>64</b>	<b>1.0</b>	<b>0.4</b>

**SJ Connolly, S Yusuf et al., Circ 2007; 116:450**

# 3) ACTIVE Clopidogrel + Aspirin

## Atrial Fibrillation + Risk Factors

**ACTIVE - W**

**ACTIVE - A**

Anticoagulation-eligible

OAC Contraindications or Unwilling

VKA  
(INR 2-3)

Clopidogrel  
+ Aspirin

Aspirin  
+ Placebo

Clopidogrel  
+ Aspirin

Open-label  
Non-inferiority  
n=6,500

Double-blind  
Superiority  
n~7,500

Irbesartan, 300 mg/d vs. Placebo  
n ~9,000

**ACTIVE - I**

Risk Factors:

Age  $\geq 75$ , hypertension, prior stroke/TIA, LVEF $<45\%$ , PAD, age 55-74 + CAD or diabetes

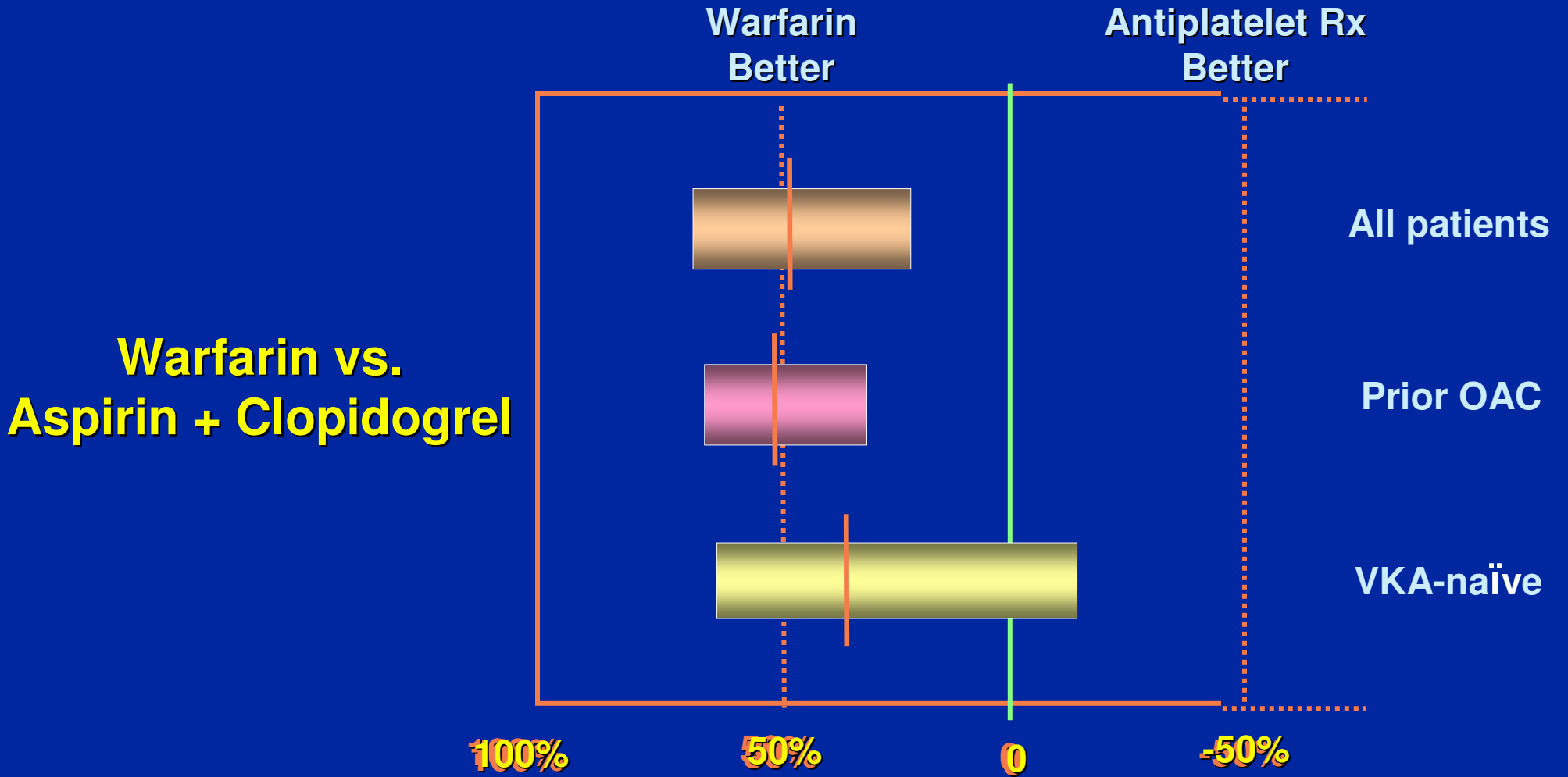
Primary outcome: Stroke, systemic embolism, MI or cardiovascular death

**Terminated**

**ACTIVE** Investigators. *Am Heart J* 2006; 151: 1187-93

### 3) ACTIVE-W Trial

## Stroke Risk Reductions

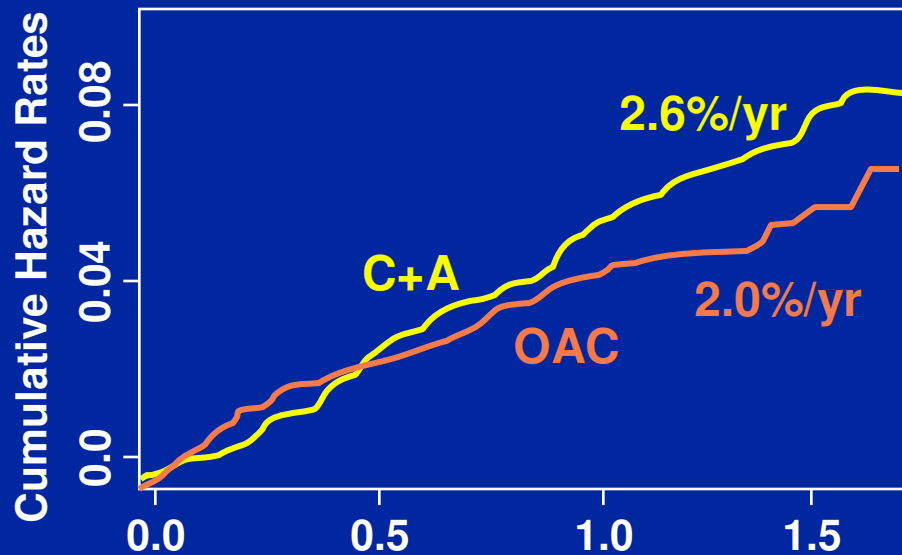


Connolly S, et al. *Lancet* 2006; 367:1903.

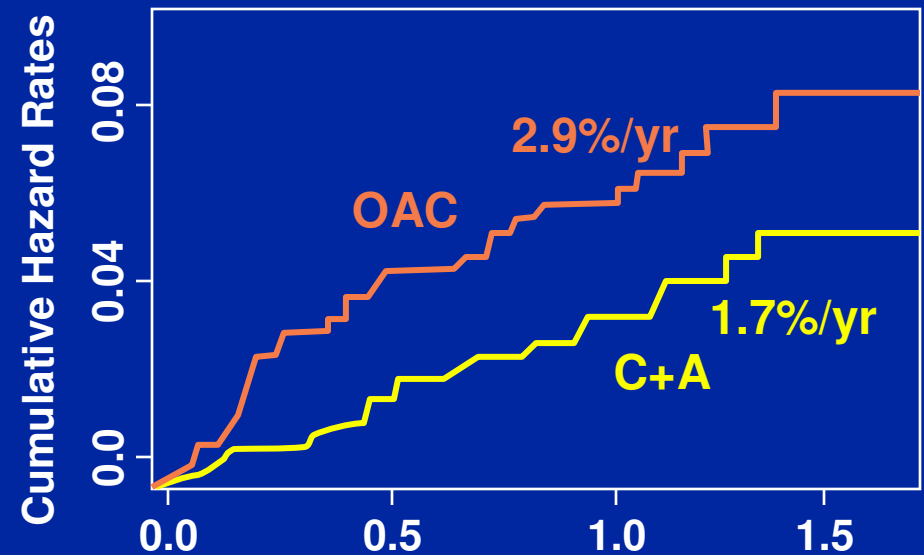
### 3) EVENT RATES IN PATIENTS ON AND NOT ON ORAL ANTICOAGULANTS (OAC)

## Major Bleeding

### Entry OAC



### No Entry OAC



**C+A:** Clopidogrel + Aspirin

**ACTIVE W** - Lancet 2006; 367; 1903

#### 4) ATRIAL FIBRILLATION - RISK OF STROKE BY CHAD\* SCORE

### CHAD Index

### Antithrombotics

**High Risk:**

TE, MS, PHV

Warfarin INR 2.0-3.5

2 RF

Warfarin INR 2-3

**Moderate Risk:**

1 RF

ASA 81-325mg

Warfarin INR 2-3 (<EF)

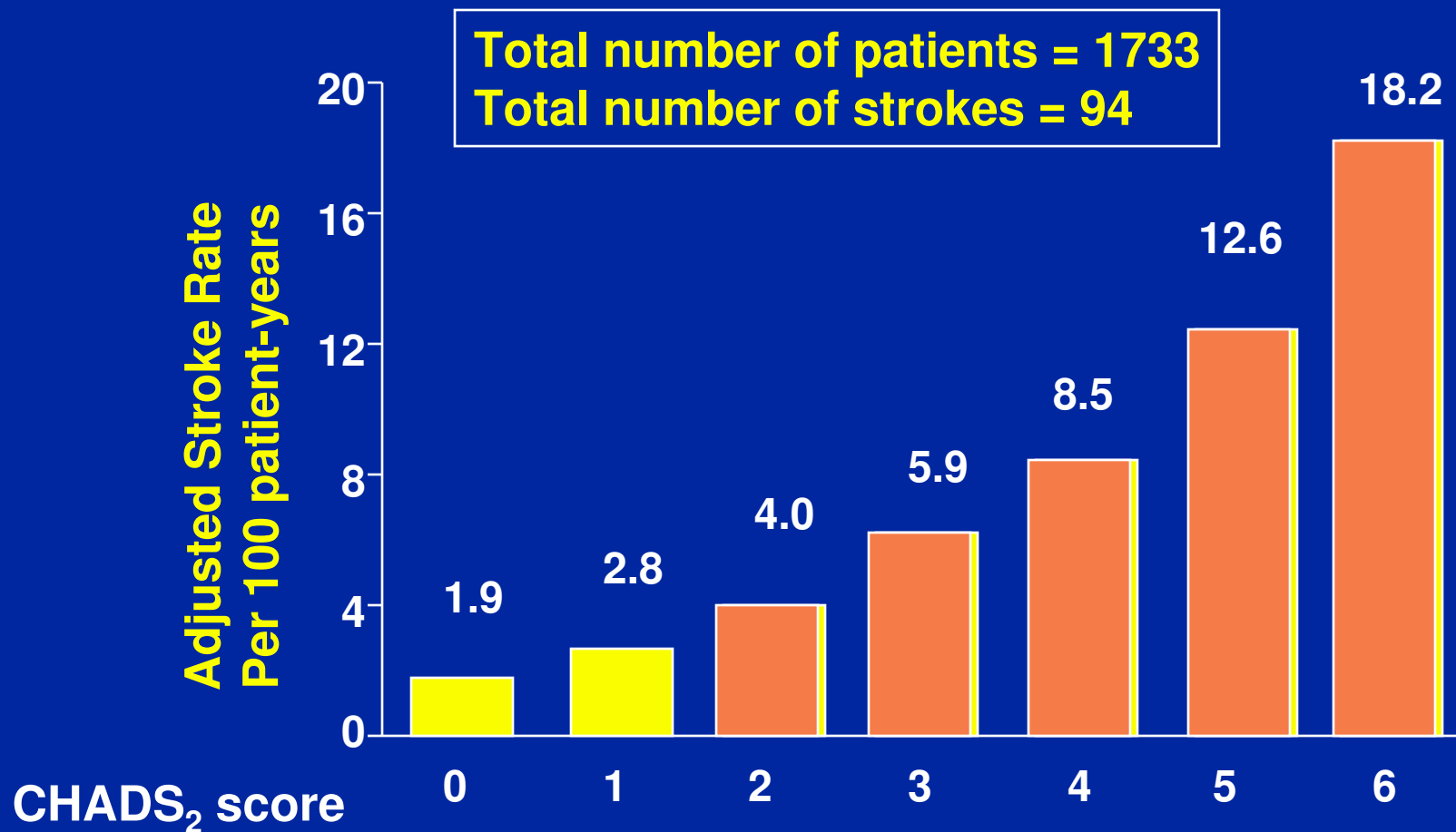
**Low Risk:**

0 RF

ASA 81-325 mg

\* RF: C.Fail./ EF <35% 1, Hypert. 1, Age >75 1, Diabetes 1,  
**ACC/AHA/ESC (Fuster V et al) Circ 2006; 114:700**

#### 4) ADJUSTED STROKE RATE STRATIFIED BY CHAD SCORE IN PATIENTS WITH NONVALVULAR AF NOT TAKING WARFARIN



Go A, et al. *JAMA* 2003; 290: 2685.

Gage BF, et al. *Circulation* 2004; 110: 2287.

## 5) USE OF ORAL ANTICOAGULANT THERAPY TO PREVENT STROKE ATRIAL FIBRILLATION - RESULTS OF RECENT SURVEYS

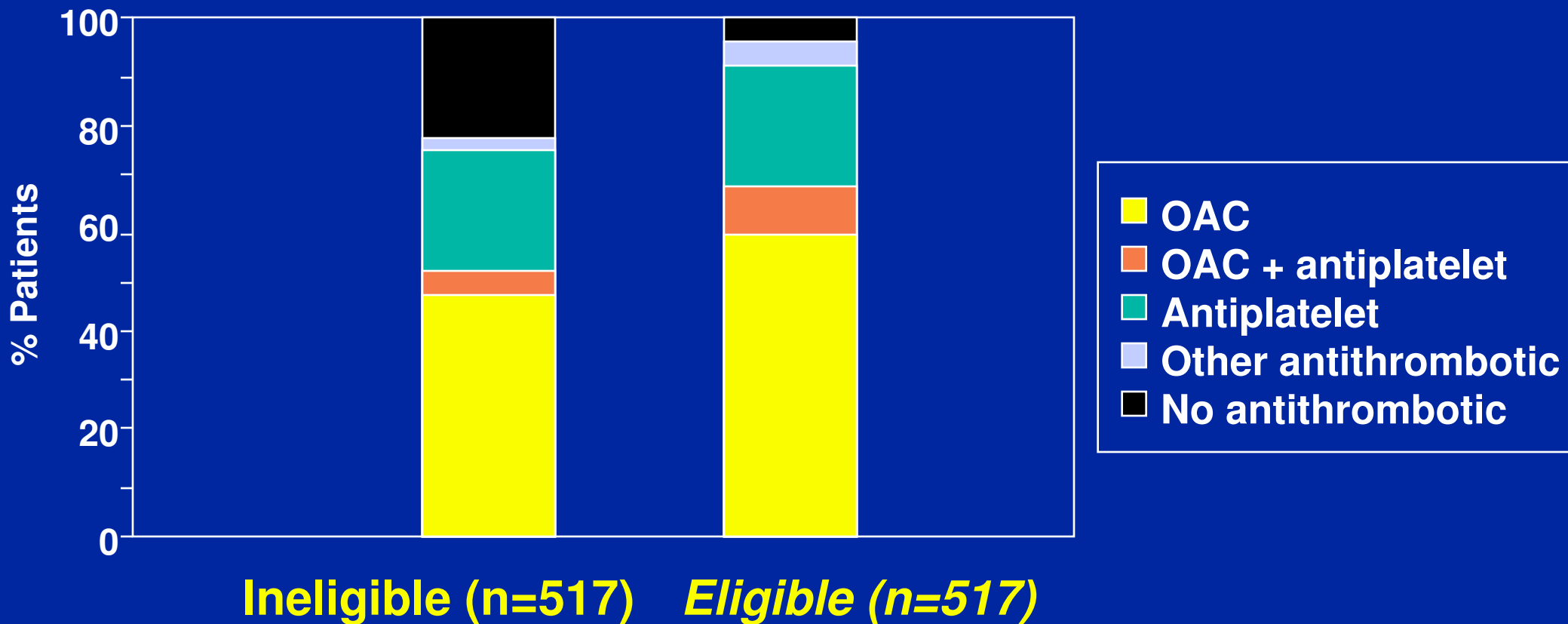
Year Published	Survey	Population	Treated w/ Warfarin, % (Patient Status)
1999	ATRIA Study	11,082 US patients large HMO - No	60
2005	NAROR Study	945 US patients from teaching, community, and VA hospital	55
2006	Euro Heart Survey	2706 outpatients in 35 European countries	64
2006	Hylek et al.	402 US patients, ≥ 55 years old, learning hospital	51
2006	Birman-Deych et al.	16,007 US Medicare patients	49

**ATRIA:** Anticoagulation and Risk Factors in Atrial Fibrillation;

**NABOR:** National Anticoagulation Benchmark and Outcomes Report.

SJ Connolly, S Yusuf et al. *Circ* 2007; 116:450

## 5) EURO HEART SURVEY ON AF ANTITHROMBOTIC Rx AT DISCHARGE<sup>1</sup> (2003-2004)



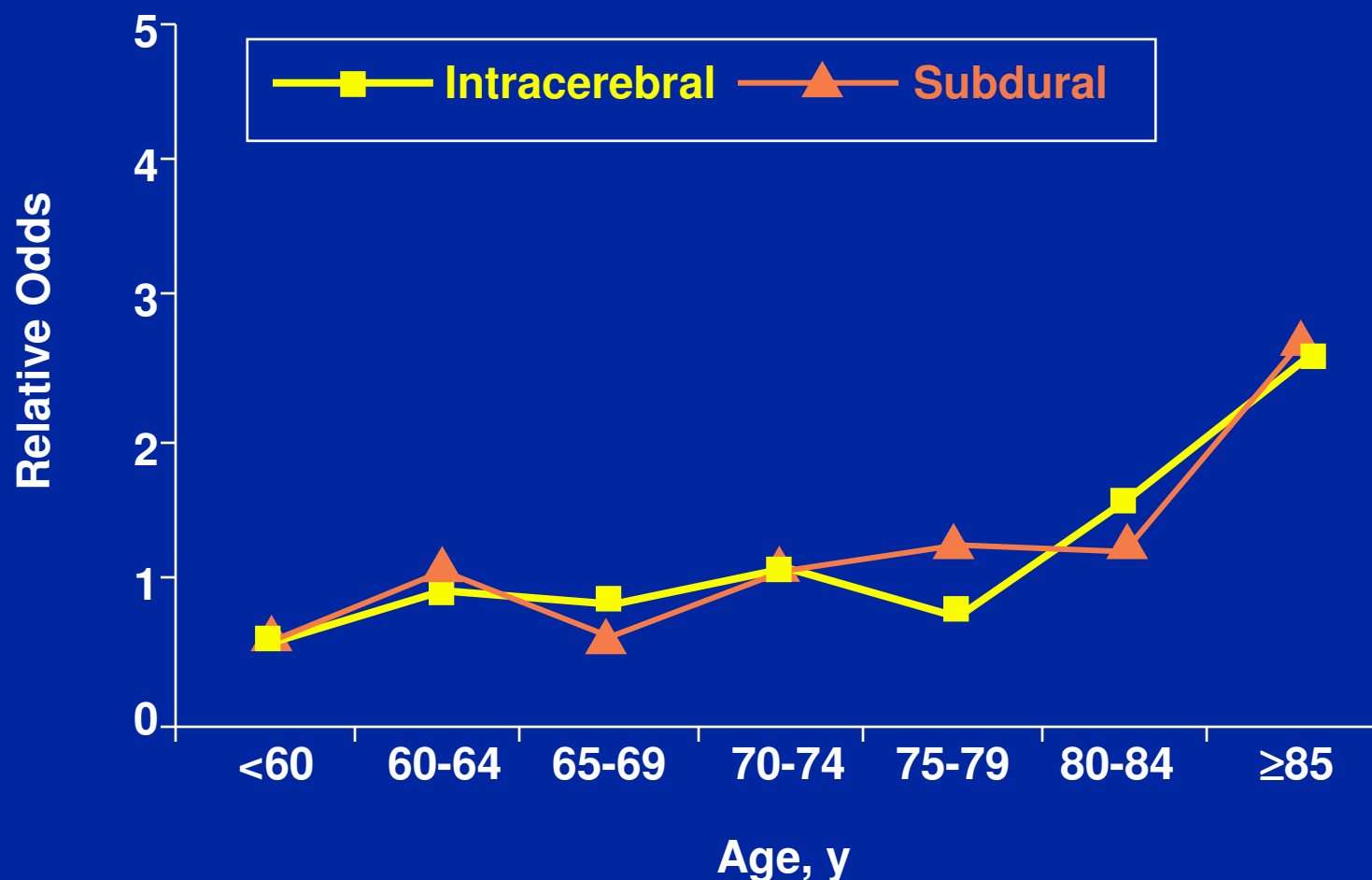
35 Countries, 182 Hosp, 5333 pts - R Nieuwlaat et al. *EHJ* 2007; 26:2422  
US - SB Rowan et al., *JACC* 2007; 49:1561

## 6) BLEEDING AND THROMBOEMBOLIC EVENTS BY INDICATION FOR TREATMENT

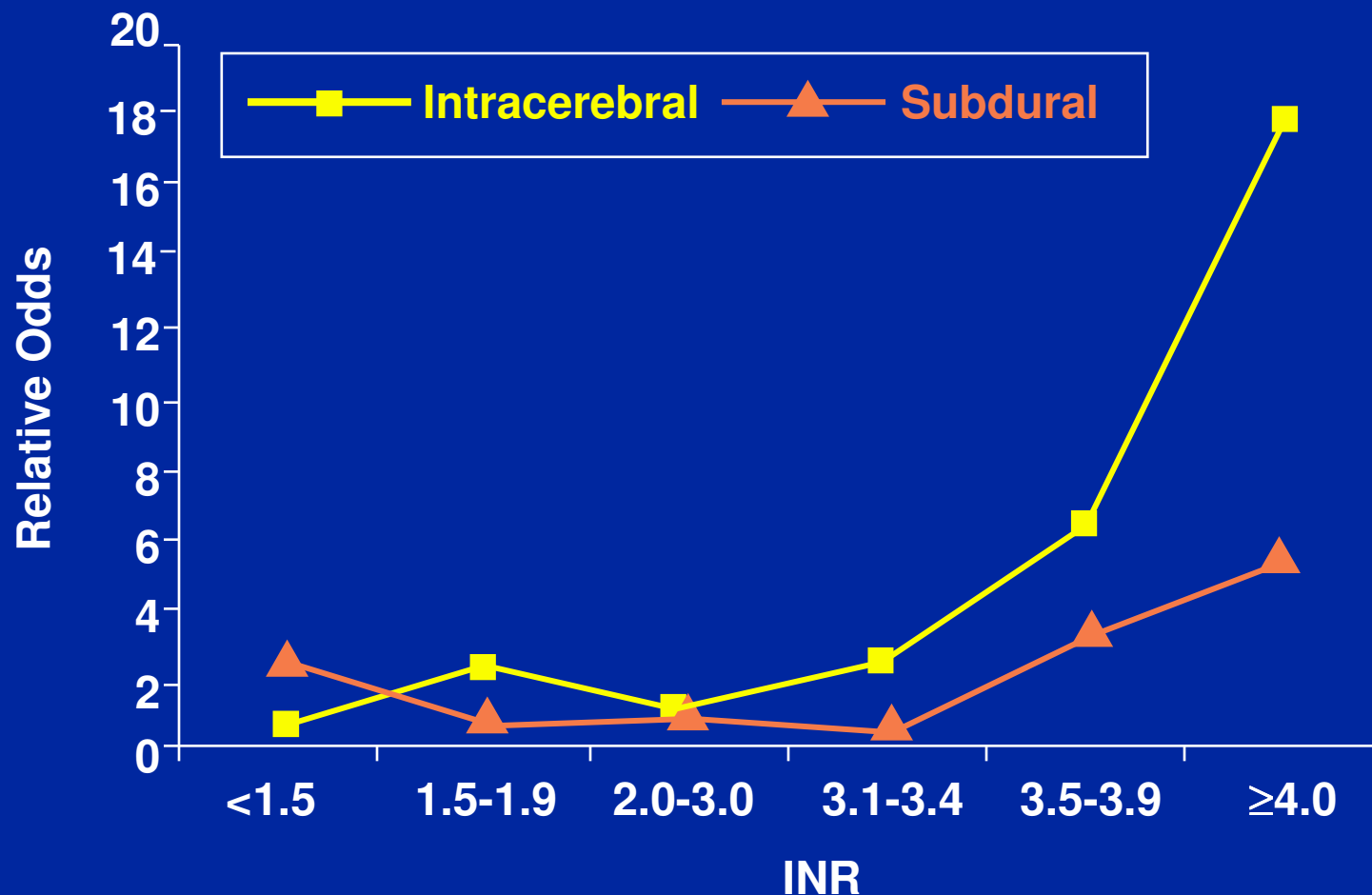
Indication/Age, y	Hemorrhage		Thromboembolism	
	No. of Events	Incidence	No. of Events	Incidence
<b>Mechanical heart valve</b>				
< 60	15	3.9	2	0.5
60-70	14	3.5	3	0.7
71-80	6	1.9	2	0.6
> 80	3	<b>4.2</b>	2	<b>2.8</b>
<b>Atrial fibrillation</b>				
< 60	2	0.5	1	0.3
60-70	17	1.9	14	1.6
71-80	44	<b>3.0</b>	20	1.4
> 80	32	<b>4.5</b>	13	<b>1.8</b>
<b>Myocardial infarction</b>				
< 60	7	0.9	13	1.6
60-70	18	1.7	15	1.4
71-80	18	1.9	21	2.2
> 80	12	<b>3.6</b>	12	<b>3.6</b>

**LEIDEN ANTIC. CLINIC** (M Torn et al.,) Ach Int Med **2005**; 165:152

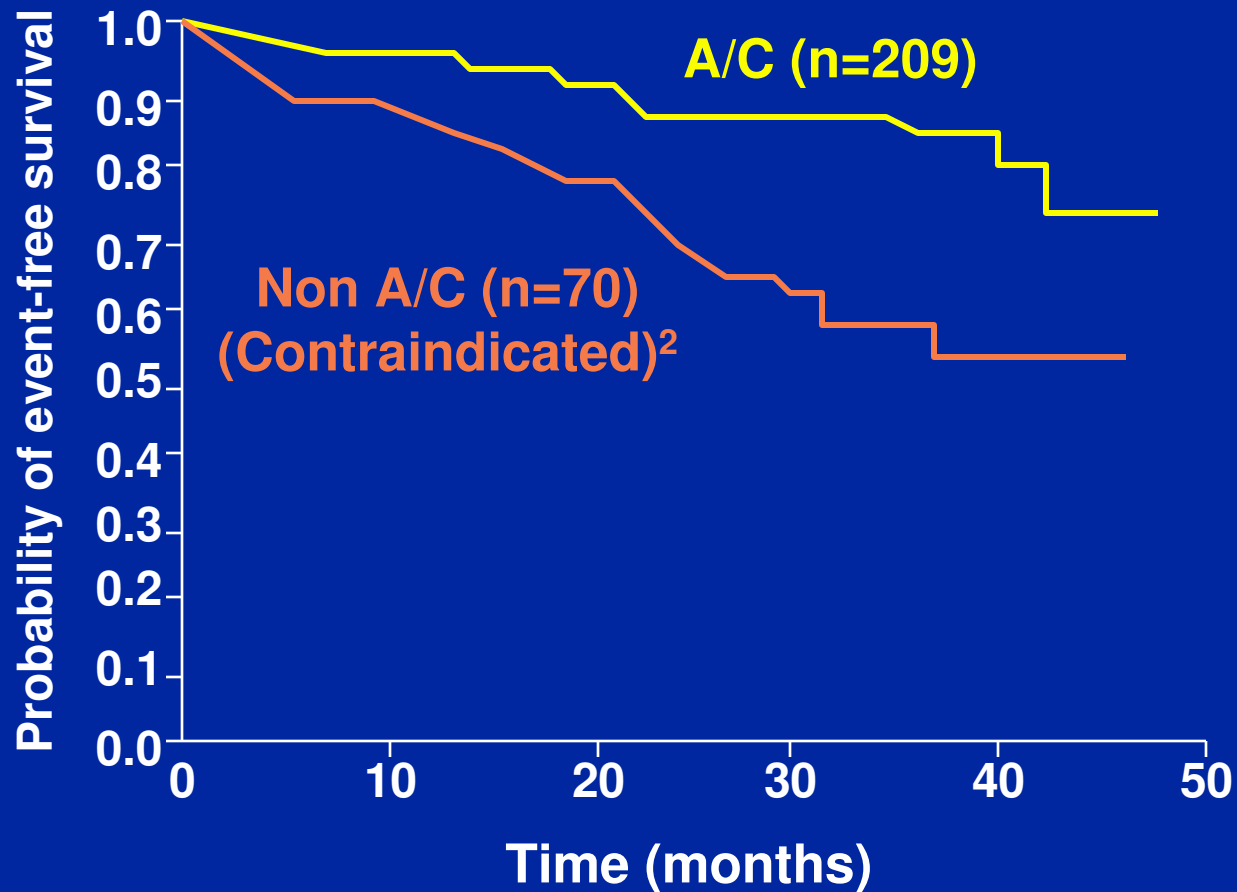
## 6) RELATIVE ODDS OF INTRACRANIAL HEMORRHAGE & AGE IN 145 CASE-PATIENTS (AF - INR 2.0-3.0) AND 870 CONTROLS



## 6) RELATIVE ODDS OF INTRACRANIAL HEMORRHAGE & INR IN 145 CASE-PATIENTS (AF - INR 2.0-3.0) AND 870 CONTROLS



## 6) *NVAF* ≥ 75 Y (n=279), PROBABILITY OF SURVIVAL FREE FROM EMBOLISM OR SEVERE BLEEDING BY TREATMENT GROUP



<sup>1</sup>Mortality Non A/C > A/C (p=0.023); Bleeding Non A/C 4.1%, A/C 2.6% (p=0.25)  
INR 1.6 – 2.5, Ideal 2.0 ?

<sup>2</sup>ASA or platelet inhibitor

M Ruiz Ortiz et al., Heart 2005; 91:1225 (Cordoba, Spain)

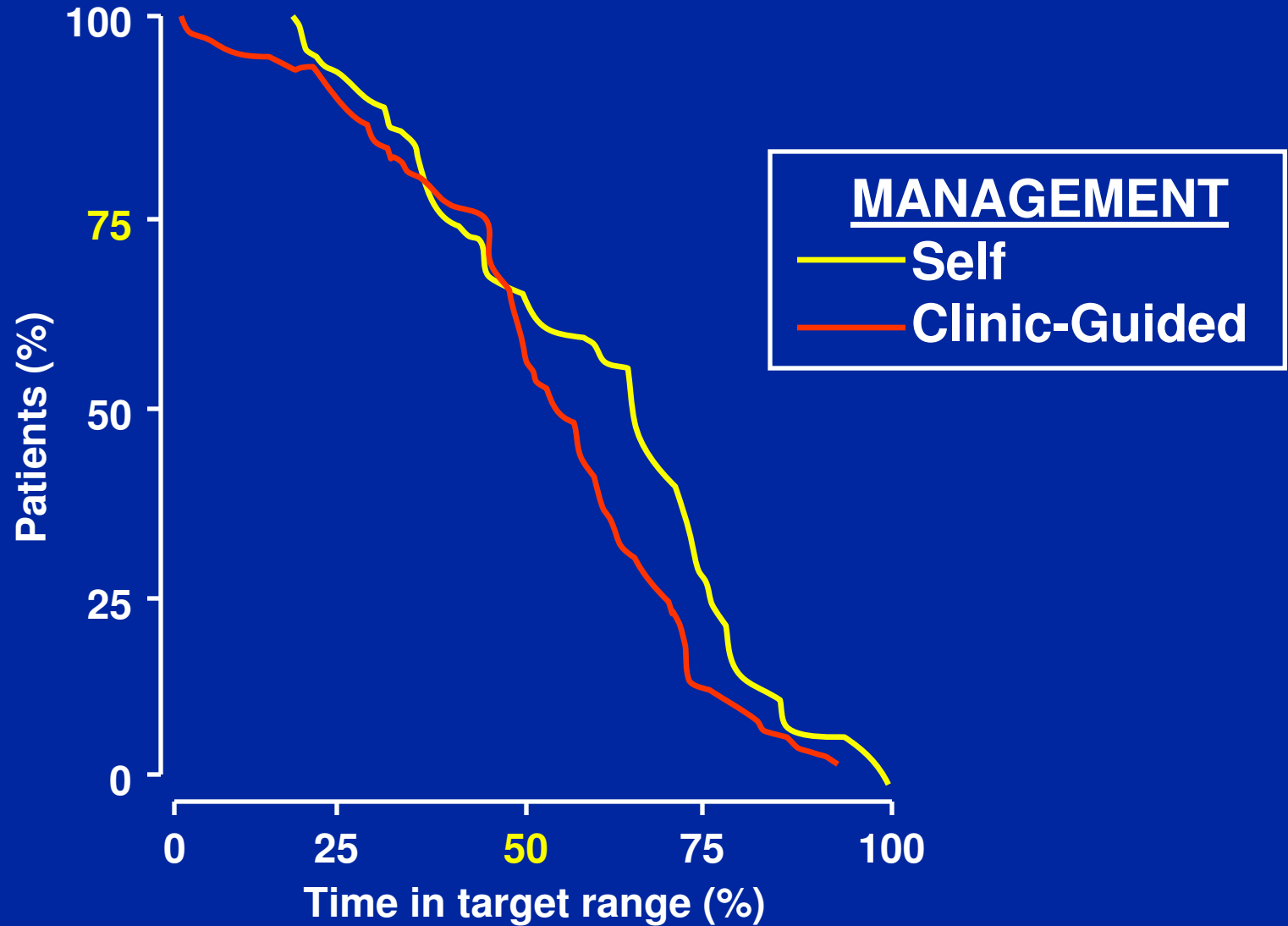
## 7) RECOMMENDATIONS FOR ANTITHROMBOTIC PRACTICE PCI REVASCULARIZATION – NEED FOR AC –

Indication	Type of antithrombotic therapy		
	Aspirin	Clopidogrel	Oral AC
Low-risk patients	Yes	Yes	No
Short-term therapy (2,3)	Yes / No	Yes	Yes
Long-term therapy (2)	Yes Only <sup>1</sup>	Yes Only <sup>2</sup>	Yes

<sup>1</sup> If No DES or if DES after 1 yr . <sup>2</sup> If DES at least 1 yr

V Fuster - Modified of G Helft et al., Nature Cardio Med 2006;3:673

## 8) COMPARISON OF CONTROL OF ANTICOAGULATION IN PATIENTS DURING SELF-MANAGEMENT AND CLINIC-GUIDED MANAGEMENT



ME Crombeecke et al., Lancet 2000; 356:97 - Netherlands

9) **Tissue Pathway**

**Blood Pathway**



TFPI  
rFVIIai

**FIBRIN  
PLATELETS**

**XIa**

**IXa**

**ATIII  
Heparins**

**VIIIa**

**VIII**

**Xa inhibitors  
Pentasaccharide**

**LMWH**

**X**

**Xa**

**V**

**Va**

**A/C**

**Prothrombin (II)**

**Thrombin (IIa)**

**Antithrombins**

**VIII**

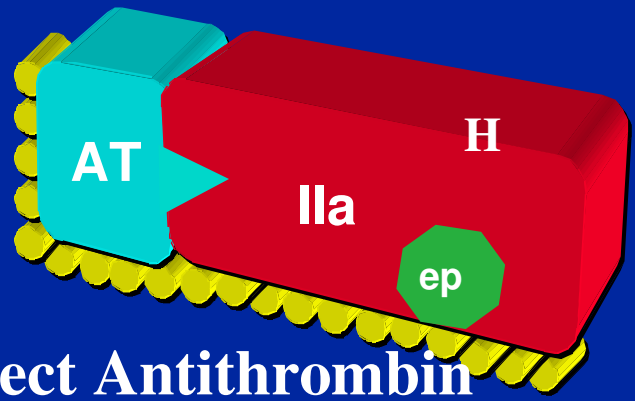
**VIIIa**

**Fibrinogen**

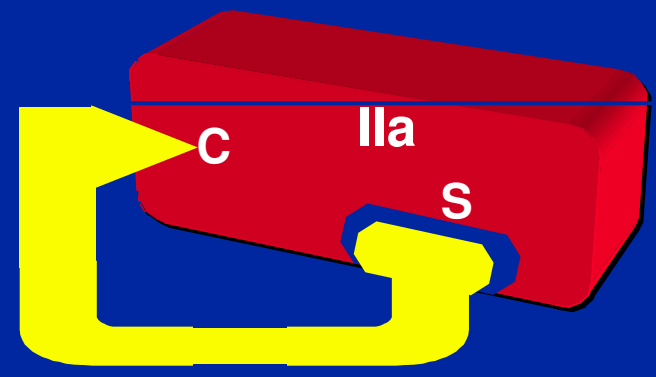
**FIBRIN**

**PLATELETS**

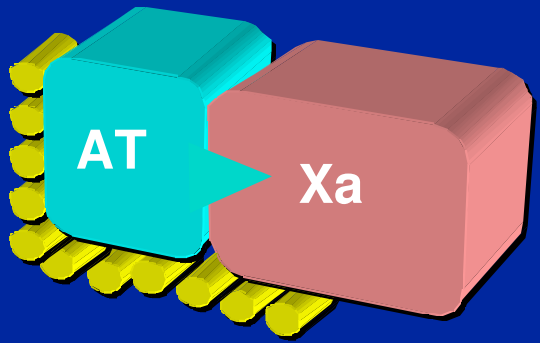
9)



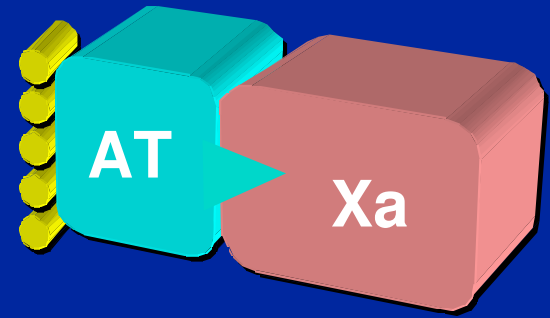
**Indirect Antithrombin**  
**UFH**



**Direct antithrombin**  
**Ximelagatera (Liver)**  
**Dabigatran**



**Indirect Anti Xa**  
**LMWH**



**Direct Anti Xa**  
**Rivaroxaban**  
**Apixaban**  
**Dupon 176b**  
**Pentasaccharide, Ind. Anti Xa**  
**Idraparinaux (sc, Bleeding)**  
**Biotinylated Idraparinaux**

# Dabigatran for Atrial Fibrillation

## *RE-LY Trial*

~15,000 patients worldwide

**Open label study vs. warfarin**

20-24 months treatment period

Patients at moderate-to-high risk of Thromb.Emb

**Efficacy: Stroke + systemic embolism**

**Safety: Bleeding events, intracranial hemorrhage**

**LFT elevations**

# ROCKET-AF

**Patients with Non-valvular AF  
at risk of thromboembolic events\***

*Double blind / Double Dummy  
(n ~ 14,000)*

**Rivaroxaban**

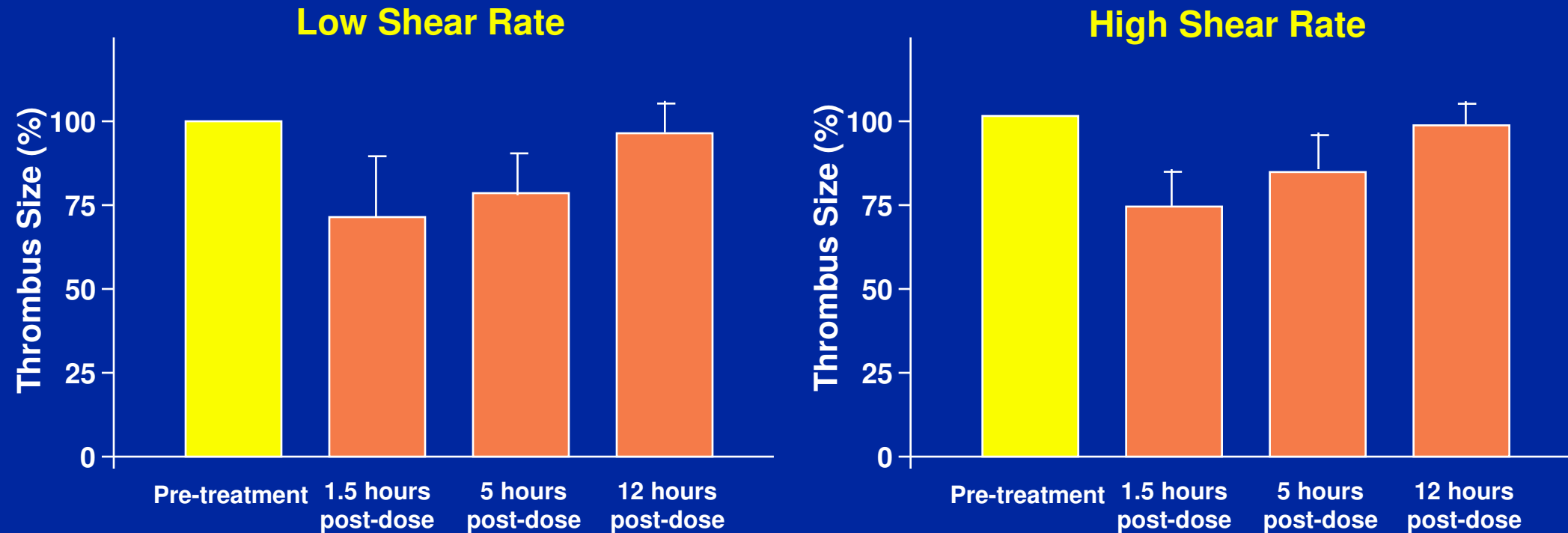
**20 mg daily  
15 mg for Cr Cl 30-49**

**Warfarin**

**INR target - 2.5  
(2.0-3.0 inclusive)**

**Primary endpoint: Stroke or non-CNS Systemic Embolism**

# EFFECT OF SINGLE ORAL 60 mg DOSE OF Fr Xa INHIBITORS<sup>1</sup> ON IN VIVO THROMBUS SIZE (N=12 HEALTHY SUBJECTS)

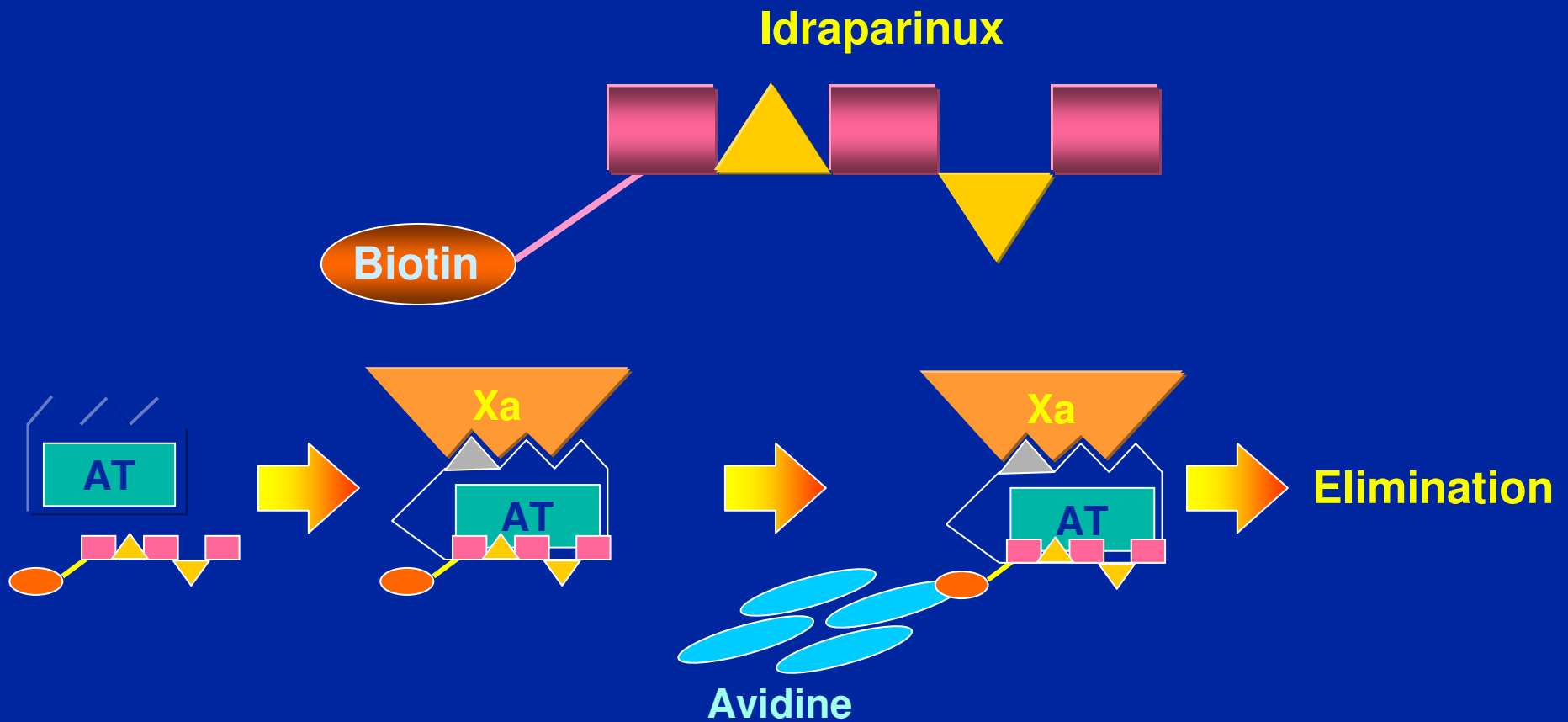


<sup>1</sup>DV-176 b - First Human Study

MU Zafar, V Fuster, JJ Badimon et al., Jnl Thromb.Haem 2007(In Press)

# Biotinylated Idraparinux

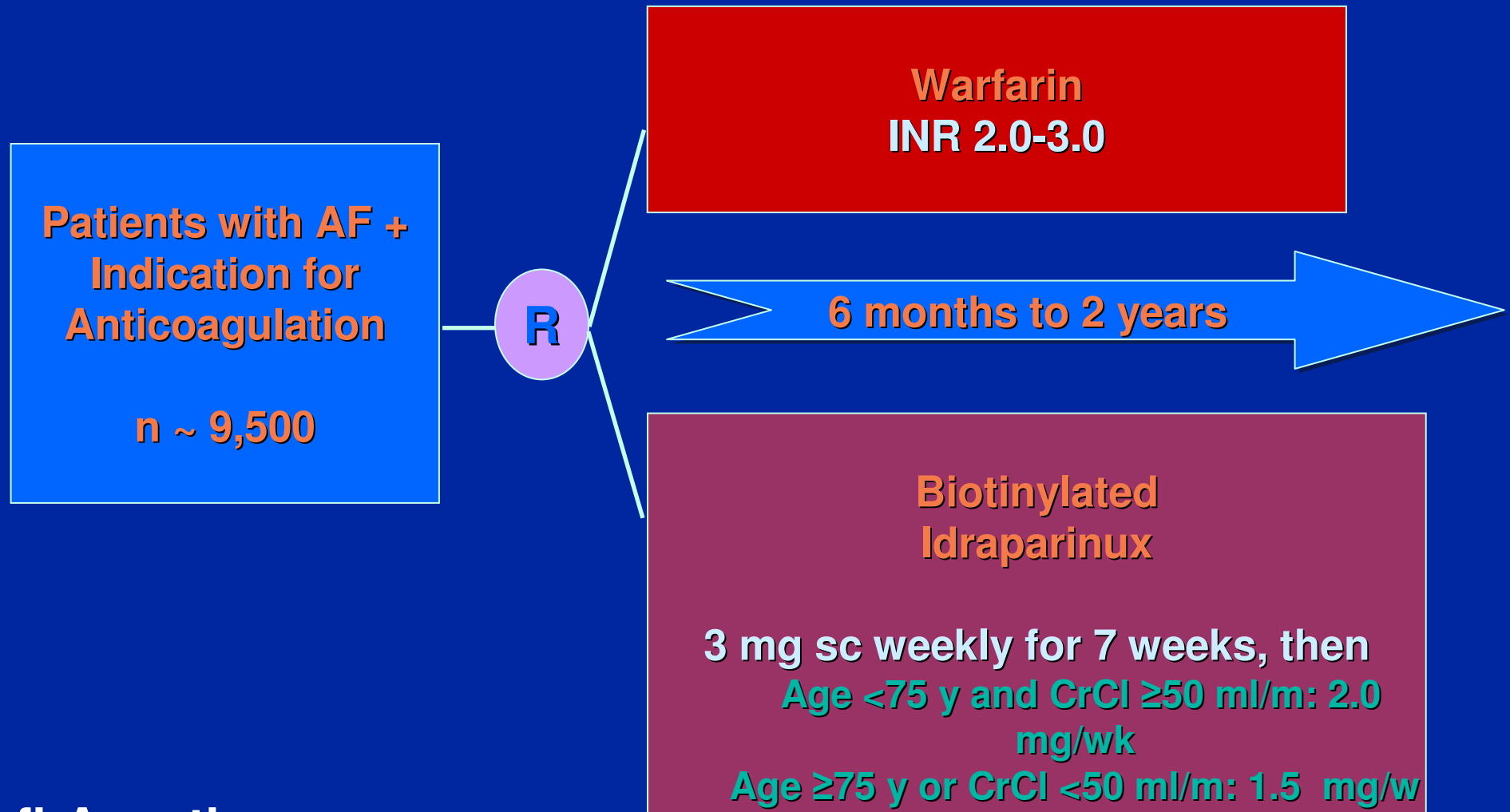
## *A Reversible Anticoagulant*



**Sanofi-Aventis**

# **BOREALIS-AF**

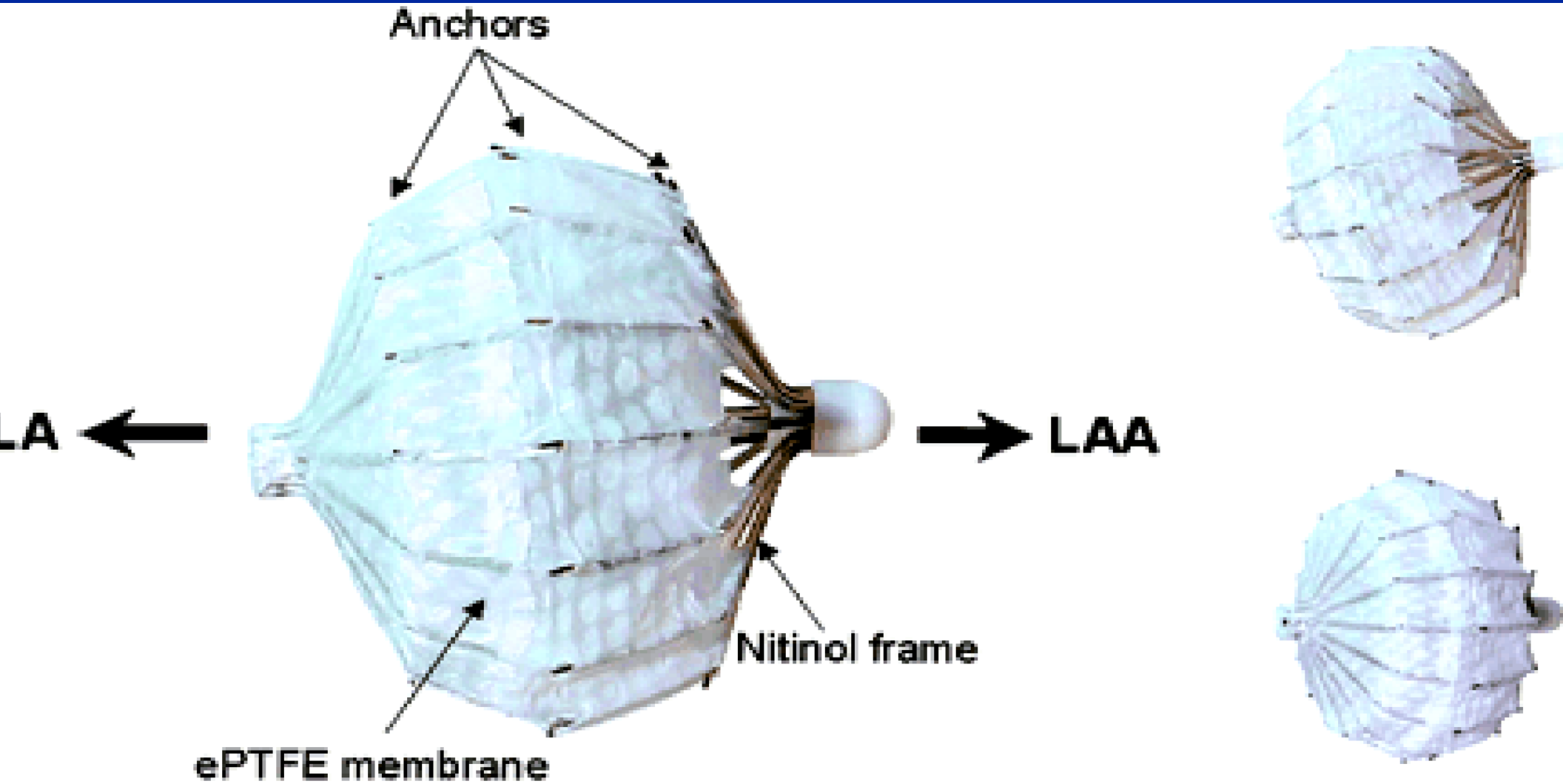
## **A Trial of Biotinylated Idraparinux**



## 10) Left Atrial Appendage Closure For Stroke Prevention in Atrial Fibrillation

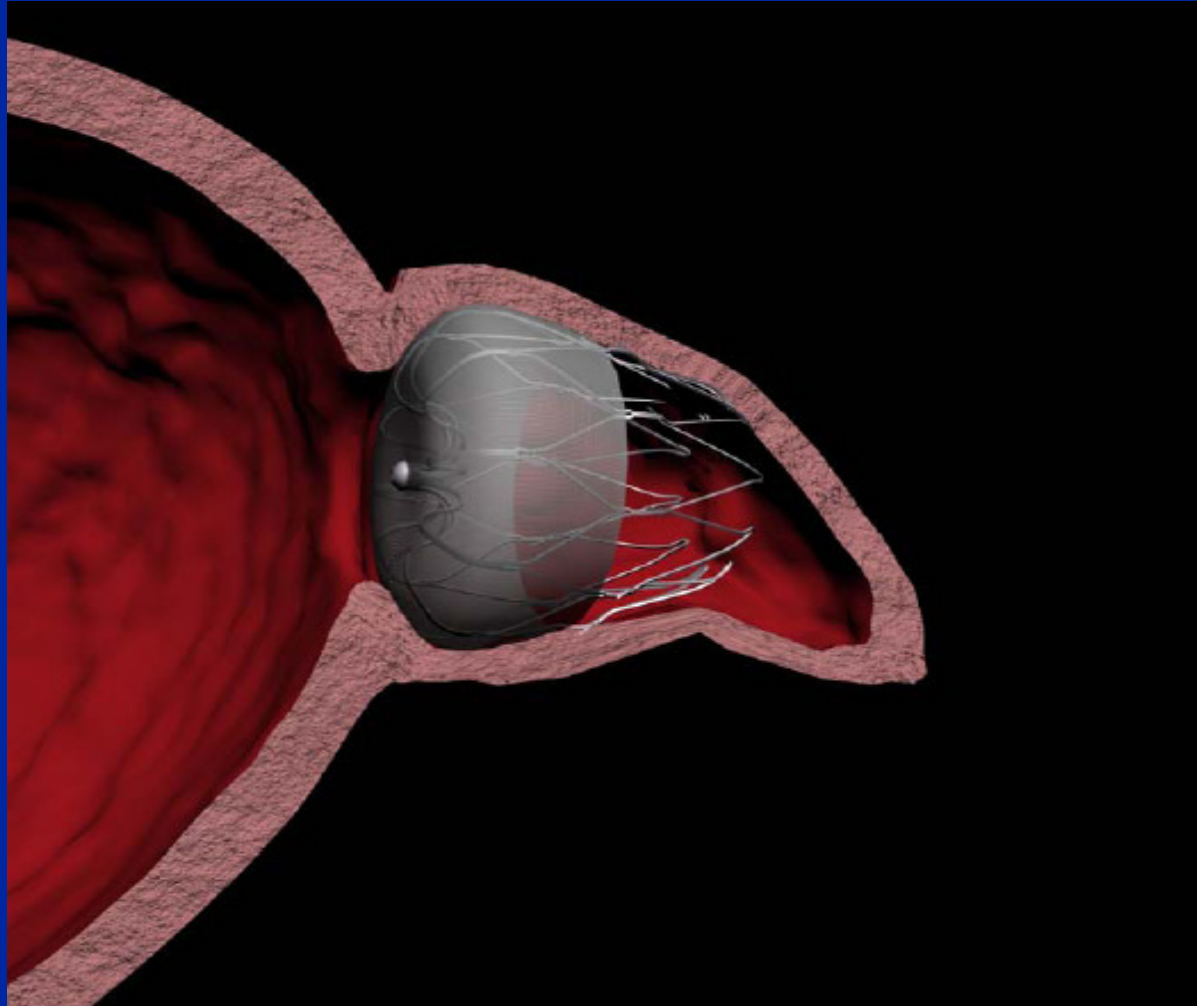
A substantial number of patients are unable to sustain chronic therapy with warfarin. Surgical exclusion of the LAA is increasingly performed in patients undergoing open-heart surgery, and **Thoracoscopic Epicardial Occlusion** of the LAA has yielded promising early results. **Percutaneous LAA occlusion devices** have shown some success initial trials, but **additional safety and efficacy** data are required before this approach can be routinely considered.

**10) PERCUTANEOUS LEFT ATRIAL APPENDAGE TRANSCATHETER OCCLUSION  
HIGH RISK PATIENTS WITH ATRIAL FIBRILLATION (N > 100)**



**PLAATO, Circ 2002;105;1887 – Promising but Recently DC**

## *10) The Watchman Device*



RB Fountain et al, AHJ 2006;151:956 –  
Trial 500 pts (AC & ASA 45 days, then ASA) –

# *ATRIAL FIBRILLATION CHALLENGES AND NEW OBSERVATIONS*

- 1. Prevalence of AF (2)**
- 2. Classification & Patterns (3)**
- 3. Pathophysiology (6)**
- 4. Approach to Management (1)**
- 5. Heart Rate Control (4)**
- 6. Antithrombotic Therapy (10)**
- 7. Rhythm Control (4)**















# ***BOREALIS-AF***

## **Key Design Features**

- **Double-blind treatment assignment**
- **Primary outcome measures**
  - **Efficacy: All stroke or systemic embolism**
  - **Safety: Clinically relevant bleeding**
- **Statistical analysis**
  - **Noninferiority criterion: Hazard ratio <1.5**
  - **Intention-to-treat**