**Dipartimento di Cardiologia**
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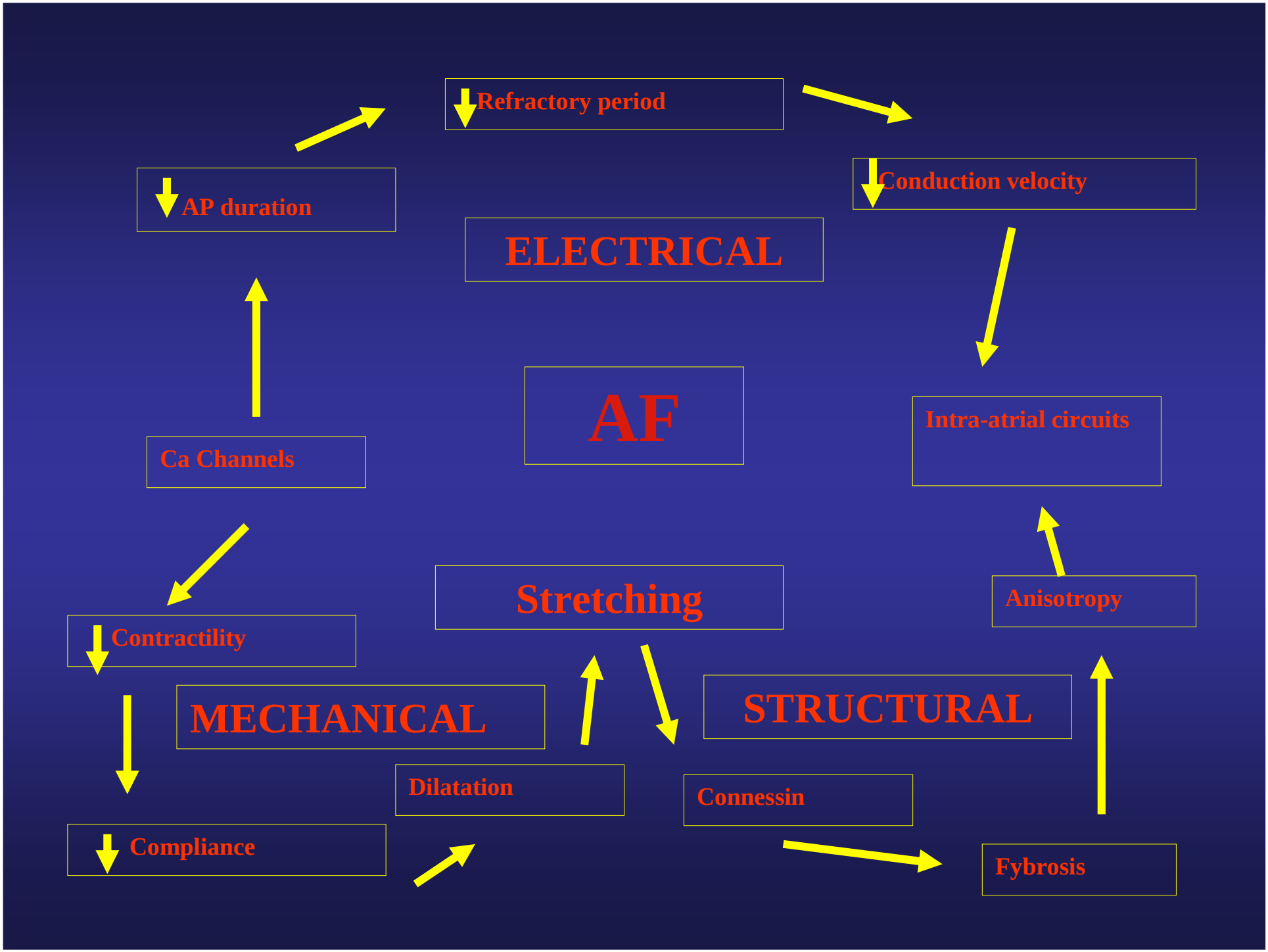
**Cona-Ferrara**

# Fibrillazione atriale persistente e Fibrillazione atriale asintomatica Rischio di stroke

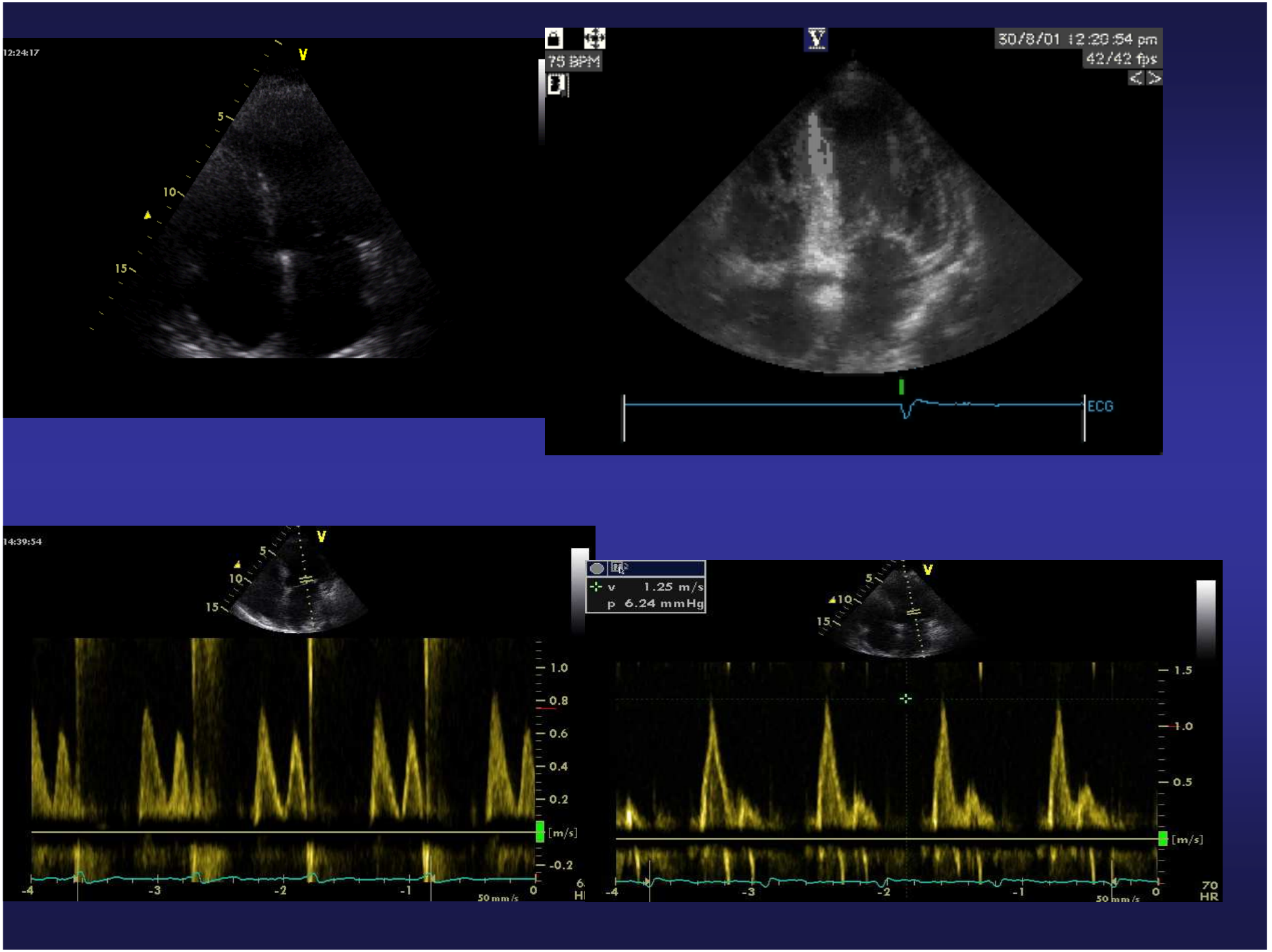
Claudio Pratola
Matteo Bertini
U.O. Cardiologia


Refractory period
AP duration
Conduction velocity
ELECTRICAL
AF
Ca Channels
Intra-atrial circuits
Stretching
Anisotropy
Contractility
MECHANICAL
STRUCTURAL
Dilatation
Connessin
Compliance
Fybrosis

# AF physiopathology

## remodeling

- Atrial refractory period shortening
- Contractility reduction
- Conduction velocity reduction
- Atrial chamber dilatation
- Fibrosis (point of no return.?.)


12:24:17
5
10
15
75 BPM
30/8/01 12:20:54 pm
42/42 fps
ECG
14:39:54
v 1.25 m/s
p 6.24 mmHg
1.0
0.8
0.6
0.4
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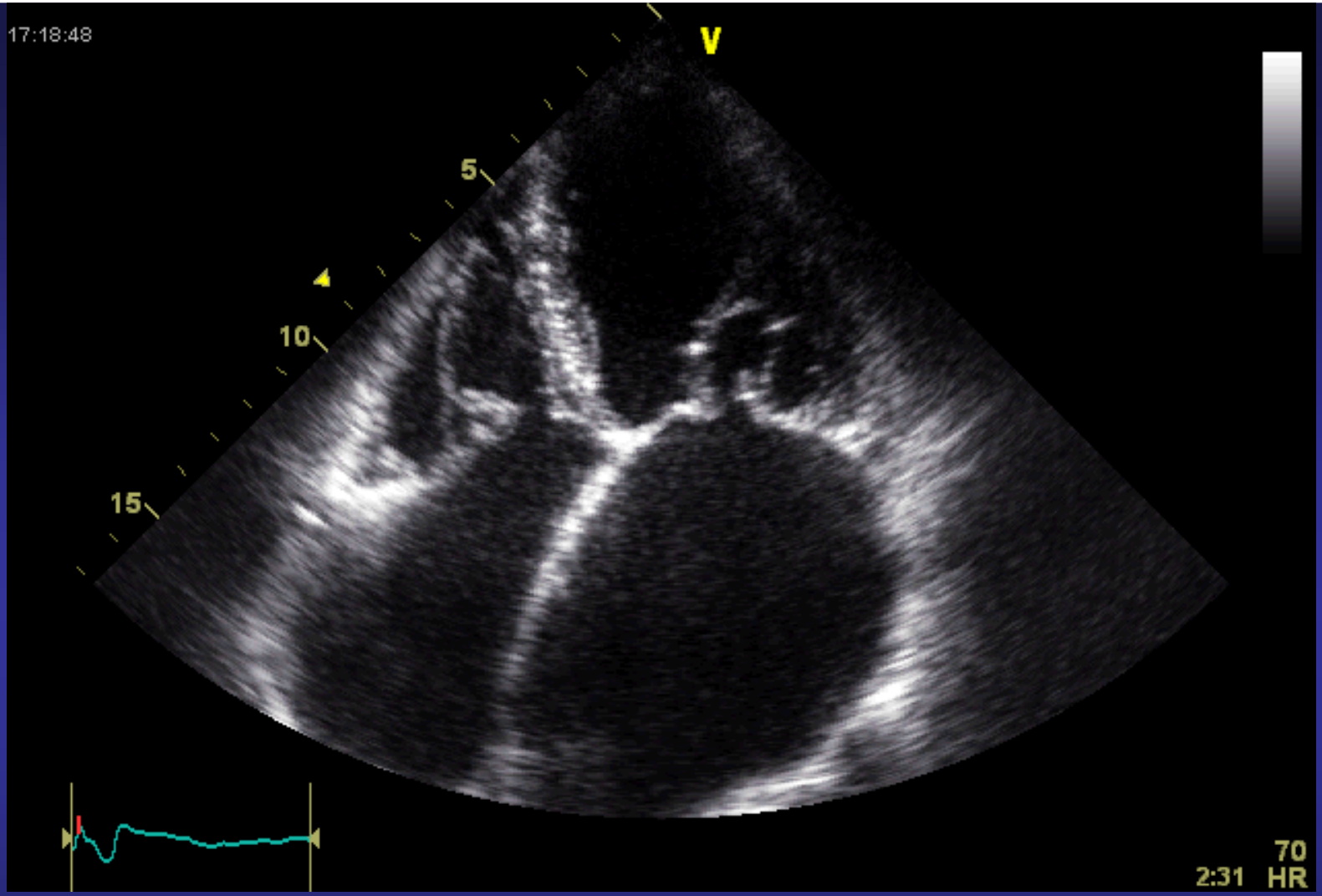
[m/s]
-0.2
-4
-3
-2
-1
0
50 mm/s
1.5
0.5
70
HR

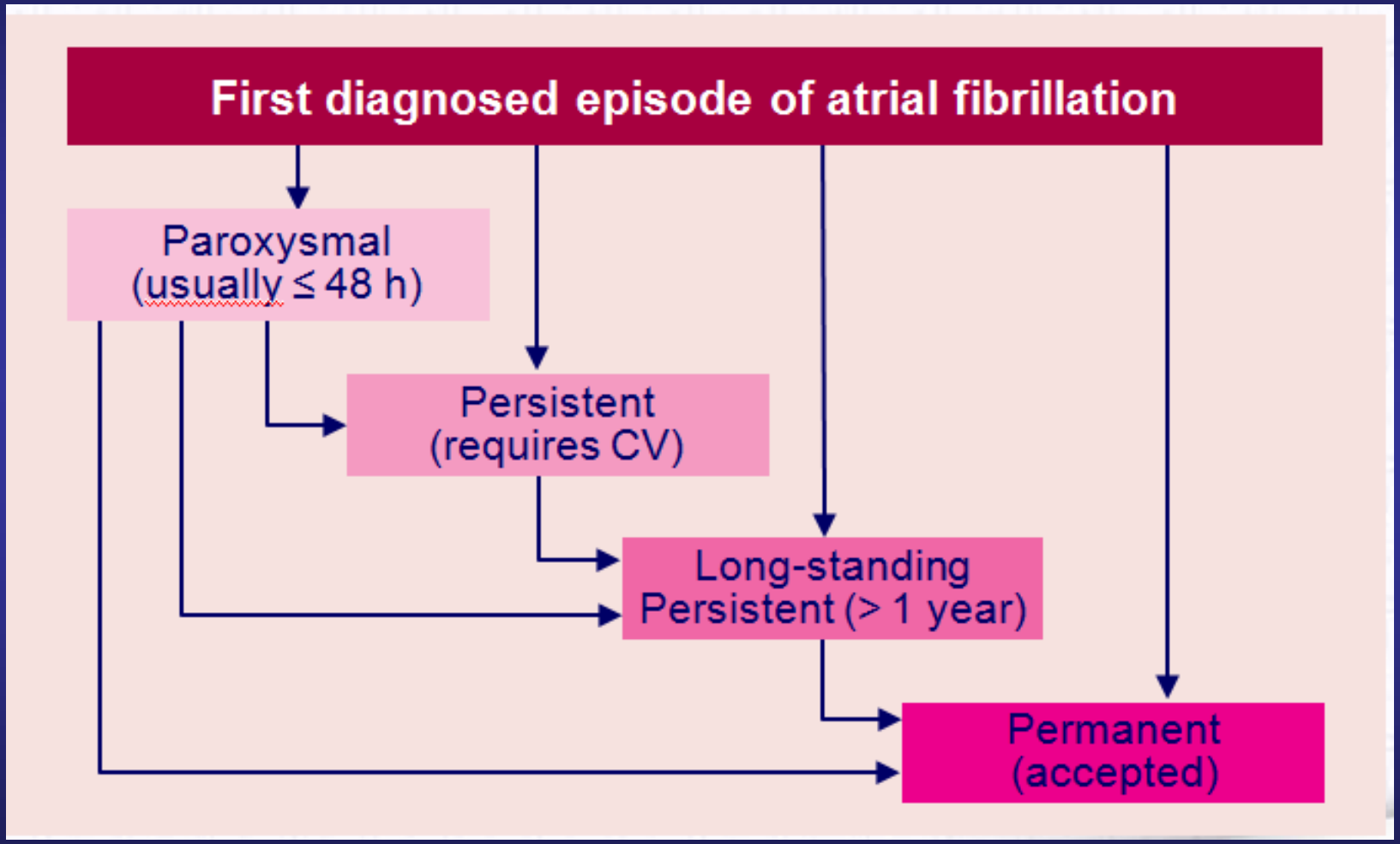



**Paroxysmal atrial fibrillation..is it always the same?**

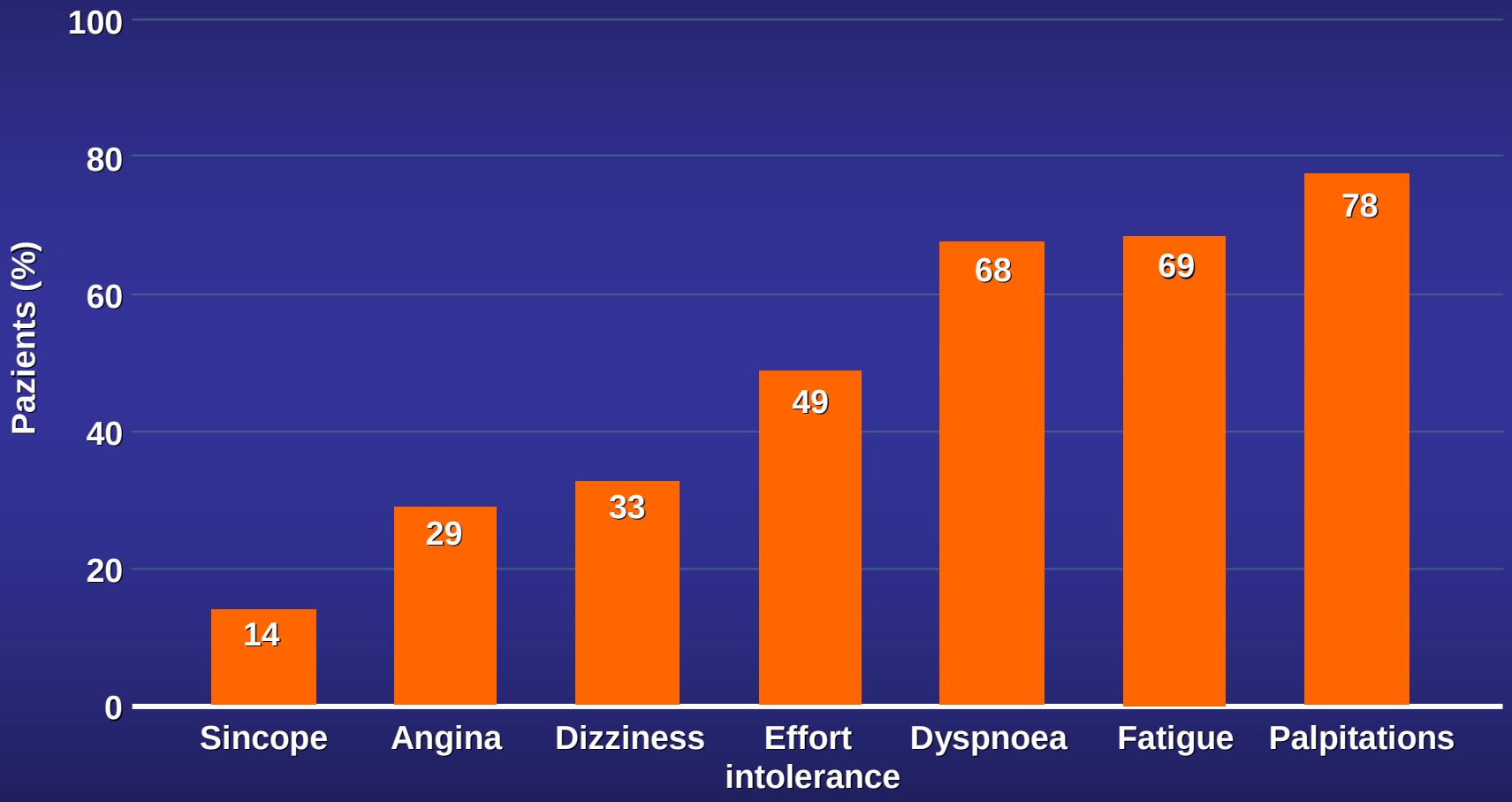
# Atrial fibrillation

- **Similar patients with different presentations (3P)**
- **Different patients with the same presentation**
- **Variable symptoms**

# Types of Atrial Fibrillation



# Symptoms




(19th Ann Scientific Sessions NASPE, 1998)

# Symptoms in AF patients

ALFA study

| Sintomi | Total population % (n=756) | Paroxysmal AF % (n=167) | Chronic AF % (n=389) | Recent onset AF % (n=200) |
|---|---|---|---|---|
| Palpitation | 54,1 | 79,0 | 44,7 | 51,5 |
| Thoracic pain | 10,1 | 13,2 | 8,2 | 11,0 |
| Dyspnoea | 44,4 | 22,8 | 46,8 | 58,0 |
| Sincope | 10,4 | 17,4 | 8,0 | 9,5 |
| Fatigue | 14,3 | 12,6 | 13,1 | 18,0 |
| Others | 0,9 | 0 | 1,8 | 0 |
| No symptoms | 11,4 | 5,4 | 16,2 | 7,0 |

(Levy S et al. Circulation 1999; 99. 3028-35)

## AF as an occasional finding

**30% - 45%**

(Furberg CD et al. Am J Cardiol 1994; Blackshear JL et al. MPC 1996)

## AF: asymptomatic/symptomatic episodes

**12:1**

(Page RL et al. Circulation 1994)

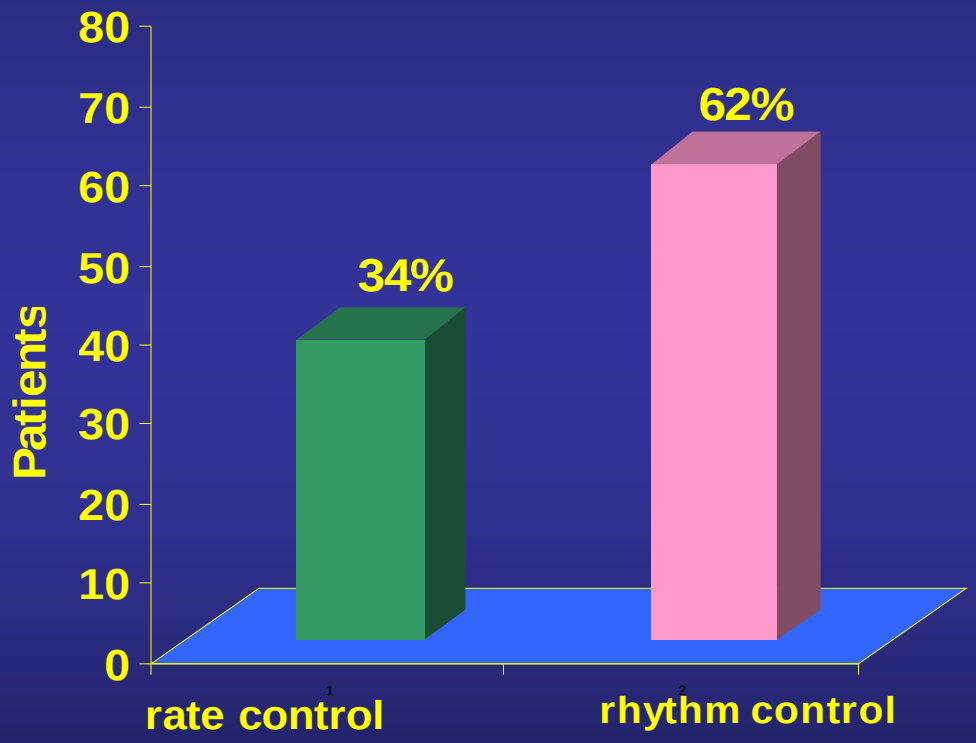
## AF: asymptomatic vs symptomatic relapses

**70% no sympotms**

(PAFAC TRIAL, Late Breaking Trial, ESC 2002)

# AFFIRM STUDY

## Sinus rhythm after five years



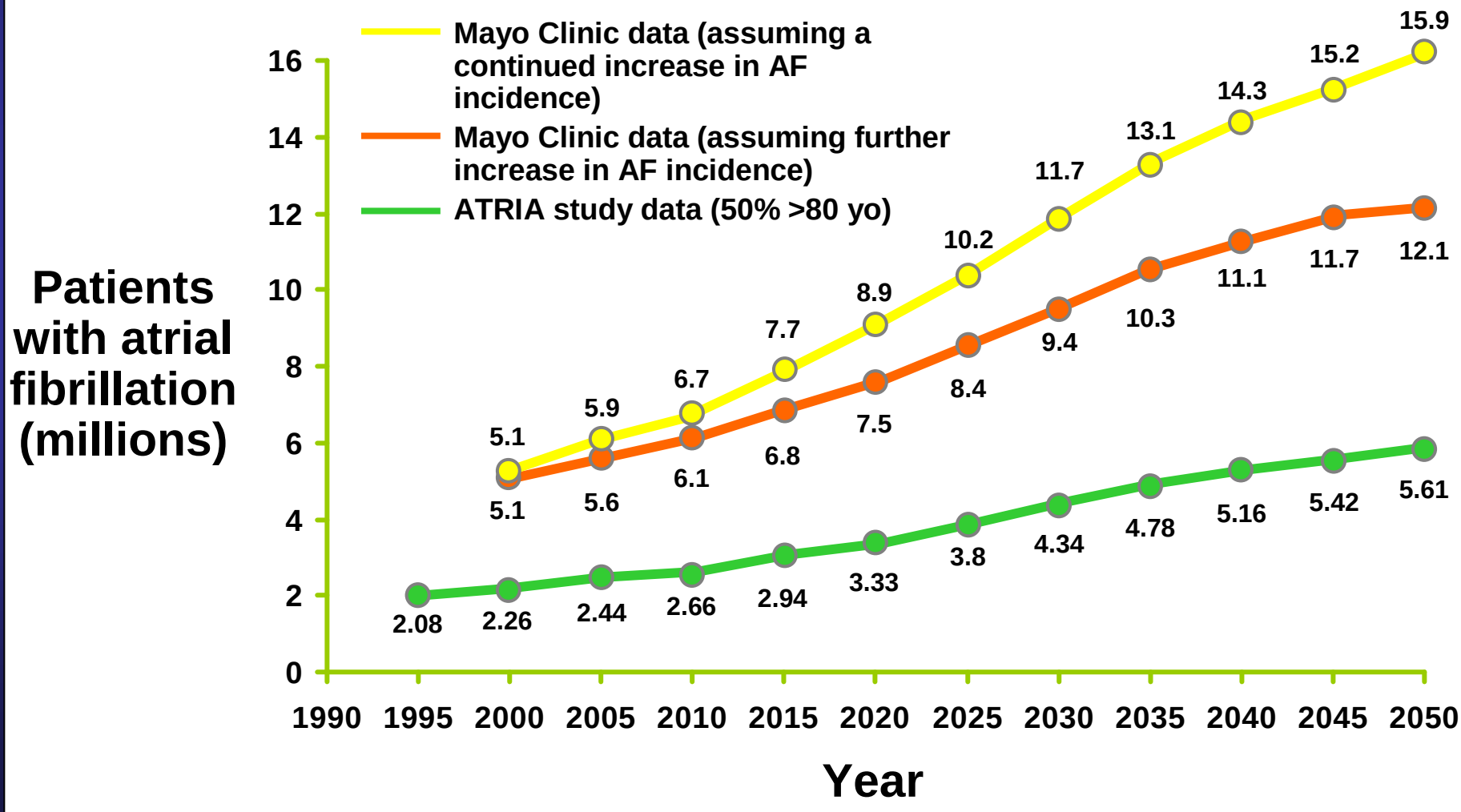
# Non-Valvular Atrial Fibrillation

- Affects 1-1.5% of population in developed world
- Lifetime risk in men & women >40 is 1 in 4
- Prevalence
    - 0.5% age 0-59
    - 9.0% age >80
- Currently 2.5 million adults in U.S.

**Savelieva: J Intern Med 250, 2001**
**Go: JAMA 285, 2001**
**Miyasaka: Circ 114, 2006**

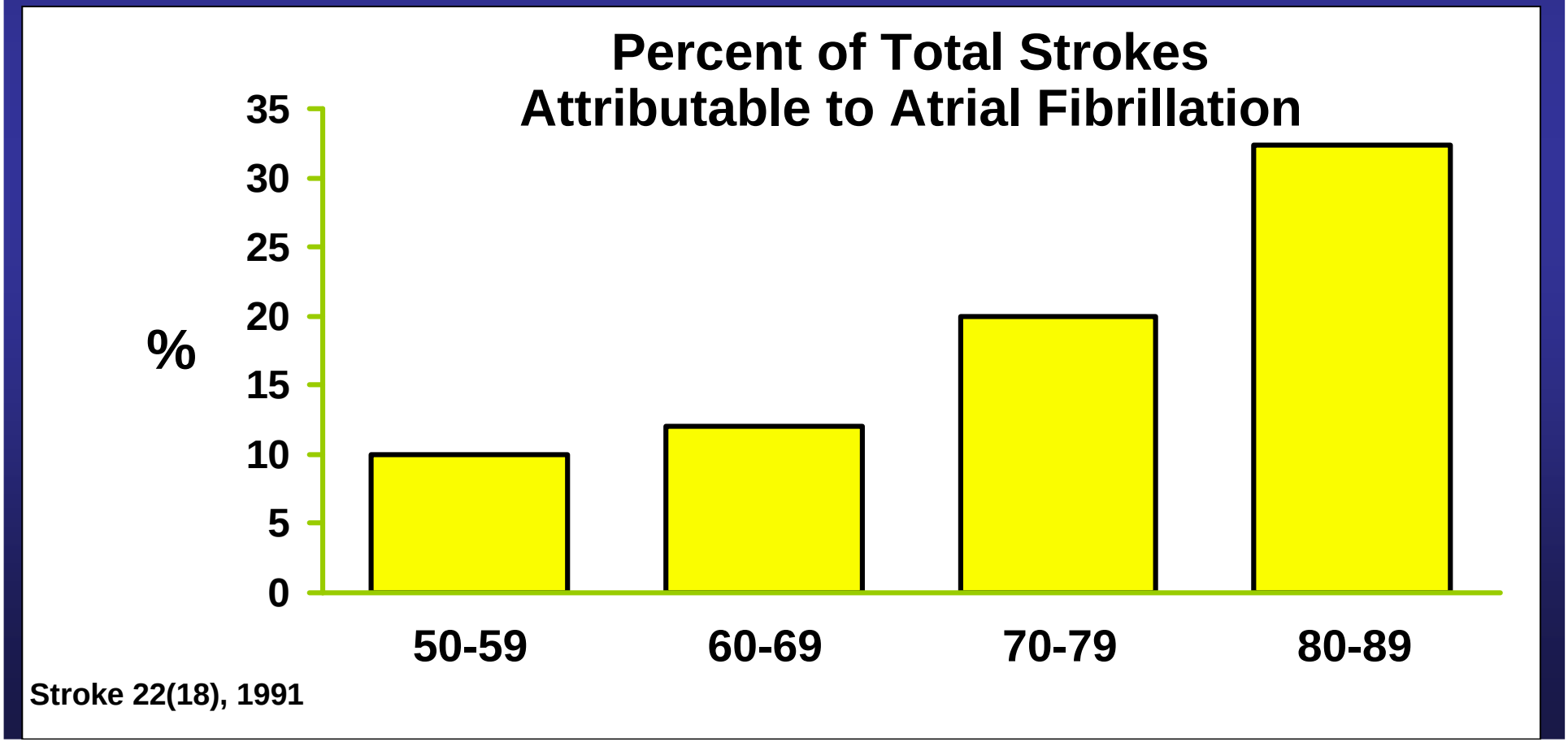
# Non-Valvular Atrial Fibrillation

## An EPIDEMIC



# Non-Valvular Atrial Fibrillation

- 500,000 strokes/year in U.S.
- Up to 20% of ischemic strokes occur in patients with atrial fibrillation




Stroke 22(18), 1991

# Conditions predisposing to, or encouraging progression of AF

- Hypertension
- Symptomatic heart failure (NYHA II - IV) including tachycardiomyopathy
- Valvular heart disease
- Cardiomyopathies including primary electrical cardiac disease
- Atrial septal defect and other congenital heart defects
- Coronary artery disease
- Thyroid dysfunction and possibly subclinical thyroid dysfunction
- Obesity
- Diabetes mellitus
- Chronic obstructive pulmonary disease (COPD) and sleep apnoea
- Chronic renal disease

# Risk factors for stroke and thrombo-embolism in non-valvular AF

| Major risk factors |
| --- |
| Previous stroke |
| TIA or systemic embolism |
| Age ≥ 75 years |

| Clinically relevant non-major risk factors |
| --- |
| CHF or moderate to severe LV systolic dysfunction [e.g. LV EF ≤ 40%] |
| Hypertension |
| Diabetes mellitus |
| Age 65-74 years |
| Female sex |
| Vascular disease |

AF= atrial fibrillation; EF = ejection fraction (as documented by echocardiography, radionuclide ventriculography, cardiac catheterization, cardiac magnetic resonance imaging, etc.); LV = left ventricular; TIA = transient ischaemic attack.

# Risk factor-based point-based scoring system - $CHA_2DS_2$-VASc

| Risk factor | Score |
|---|---|
| Congestive heart failure/LV dysfunction | 1 |
| Hypertension | 1 |
| Age ≥ 75 ans | 2 |
| Diabetes mellitus | 1 |
| Stroke/TIA/thrombo-embolism | 2 |
| Vascular disease* | 1 |
| Age 65-74 | 1 |
| Sex category [i.e. femal sex] | 1 |
| **Maximum score** | **9** |

*Prior myocardial infarction, peripheral artery disease, aortic plaque.
Actual rates of stroke in contemporary cohorts may vary from these estimates.

# Adjusted stroke rate according to $CHA_2DS_2$-VASc score

| $CHA_2DS_2$-VASc score | Patients (n = 7329) | Adjusted stroke rate (%/y) |
|---|---|---|
| 0 | 1 | 0% |
| 1 | 422 | 1.3% |
| 2 | 1230 | 2.2% |
| 3 | 1730 | 3.2% |
| 4 | 1718 | 4.0% |
| 5 | 1159 | 6.7% |
| 6 | 679 | 9.8% |
| 7 | 294 | 9.6% |
| 8 | 82 | 6.7% |
| 9 | 14 | 15.2% |

European Heart Journal (2010) **31**, 2369–2429
doi:10.1093/eurheartj/ehq278



# Guidelines for the management of atrial fibrillation

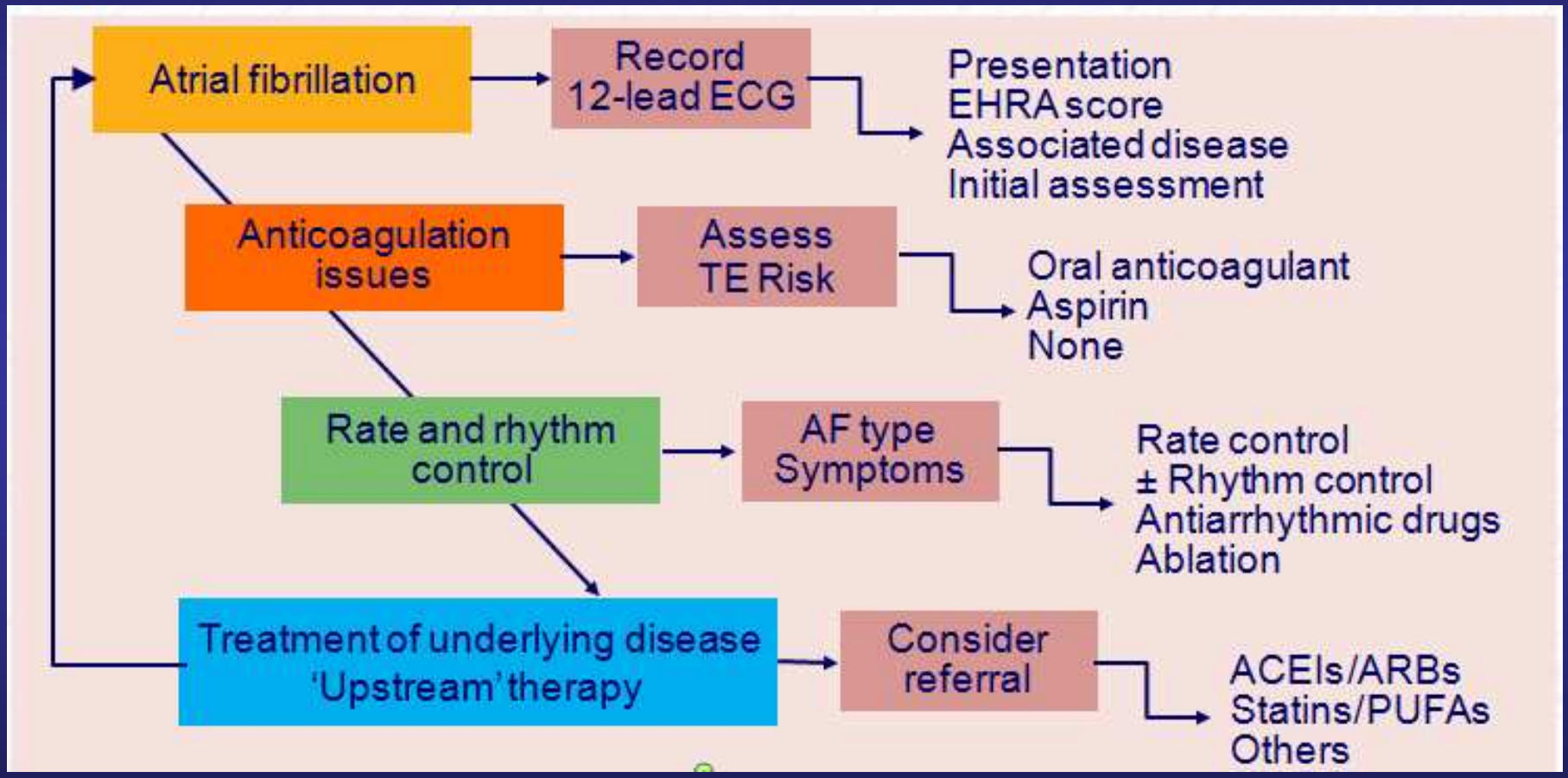
**The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC)**

**Developed with the special contribution of the European Heart Rhythm Association (EHRA)†**

**Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS)**

**Authors/Task Force Members: A. John Camm (Chairperson) (UK)*, Paulus Kirchhof (Germany), Gregory Y. H. Lip (UK), Ulrich Schotten (The Netherlands), Irene Savelieva (UK), Sabine Ernst (UK), Isabelle C. Van Gelder (The Netherlands), Nawwar Al-Attar (France), Gerhard Hindricks (Germany), Bernard Prendergast (UK), Hein Heidbuchel (Belgium), Ottavio Alfieri (Italy), Annalisa Angelini (Italy), Dan Atar (Norway), Paolo Colonna (Italy), Raffaele De Caterina (Italy), Johan De Sutter (Belgium), Andreas Goette (Germany), Bulent Gorenek (Turkey), Magnus Heldal (Norway), Stefan H. Hohloser (Germany), Philippe Kolh (Belgium), Jean-Yves Le Heuzey (France), Piotr Ponikowski (Poland), Frans H. Rutten (The Netherlands).**

# The management cascade for patients with AF




ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; PUFA = polyunsaturated fatty acid; TE = thrombo-embolism.

# Approach to thromboprophylaxis in AF

| Risk category | $CHA_2DS_2$-VASc score | Recommended antithrombotic therapy |
|---|---|---|
| One 'major' risk factor or ≥ 2 'clinically relevant non-major' risk factors | ≥ 2 | OAC |
| One 'clinically relevant non-major' risk factor | 1 | Either OAC or aspirin 75-325 mg daily.<br>Preferred: OAC rather than aspirin. |
| No risk factors | 0 | Either aspirin 75-325 mg daily or no antithrombotic therapy.<br>Preferred: no antithrombotic therapy rather than aspirin. |

AF = atrial fibrillation; $CHA_2DS_2$-VASc = cardiac failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female); INR = international normalized ratio; OAC = oral anticoagulation, such as a vitamin K antagonist (VKA) adjusted to an intensity range of INR 2.0–3.0 (target 2.5).

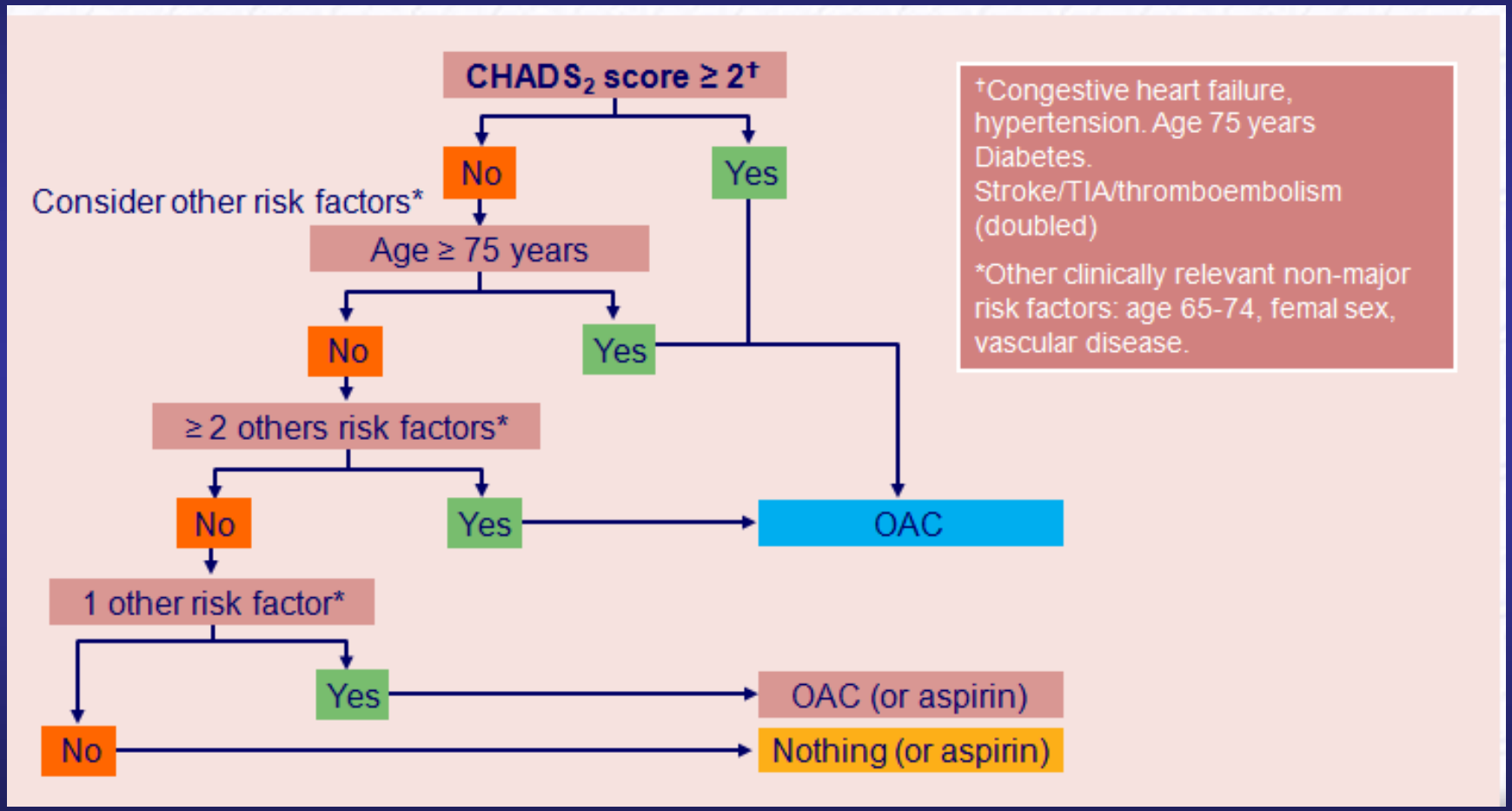
# The HAS-BLED bleeding risk score

| Letter | Clinical characteristic* | Points awarded |
|---|---|---|
| H | Hypertension | 1 |
| A | Abnormal renal and liver function (1 point each) | 1 or 2 |
| S | Stroke | 1 |
| B | Bleeding | 1 |
| L | Labile INRs | 1 |
| E | Elderly (e.g. age > 65 years) | 1 |
| D | Drugs or alcohol (1 point each) | 1 or 2 |
| | | Maximum 9 points |

*Hypertension is defined as systolic blood pressure > 160 mmHg.

INR = international normalized ratio.

# Use of oral anticoagulation for stroke prevention in AF




AF = atrial fibrillation; OAC = oral anticoagulant; TIA = transient ischaemic attack.

# Prevention of thromboembolism in AF

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those at low risk (lone AF, aged < 65 years or with contraindications). | I | A |
| It is recommended that the selection of the antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the relative risk and benefit for a given patient. | I | A |
| The $CHADS_2$ (Cardiac failure, Hypertension, Age, Diabetes, Stroke [Doubled]) score is recommended as a simple initial (easily remembered) means of assessing stroke risk in non-valvular AF. | I | A |
| For the patients with a $CHADS_2$ score of ≥ 2, chronic OAC therapy with a VKA is recommended in a dose-adjusted regimen to achieve an INR range of 2.0-3.0 (target 2.5), unless contraindicated. | I | A |
| For a more detailed or comprehensive stroke risk assessment in AF (e.g. with $CHADS_2$ score 0-1), a risk factor-based approach is recommended, considering 'major' and 'clinical relevant non-major' stroke risk factors. | I | A |
| Patients with 1 'major' or ≥ 2 'clinically relevant non-major' risk factors are high risk and OAC therapy [for example, with a VKA, dose adjusted to achieve the target intensity INR of 2.0-3.0] is recommended, unless contraindicated | I | A |
| Patient with one 'clinically relevant non-major' risk factor are at intermediate risk and antithrombotic therapy is recommended, either as: | I | A B |
| i. OAC therapy (e:g; VKA), or | I | A |
| ii. aspirin 75-325 mg daily | I | B |
| Patients with no risk factors are at low risk (essentially patients aged < 65 years with lone AF, with none of the risk factors) and the use of either aspirin 75-325 mg daily or no antithrombotic therapy is recommended. | I | B |
| For patients with AF who have mechanical heart valves, it is recommended that the target intensity of anticoagulation with a VKA should be based on the type and position of the prosthesis, maintaining an INR of at least 2.5 in the mitral position and at least 2.0 for an aortic valve. | I | B |
| Antithrombotic therapy is recommended for patients with atrial flutter as for those with AF. | I | C |

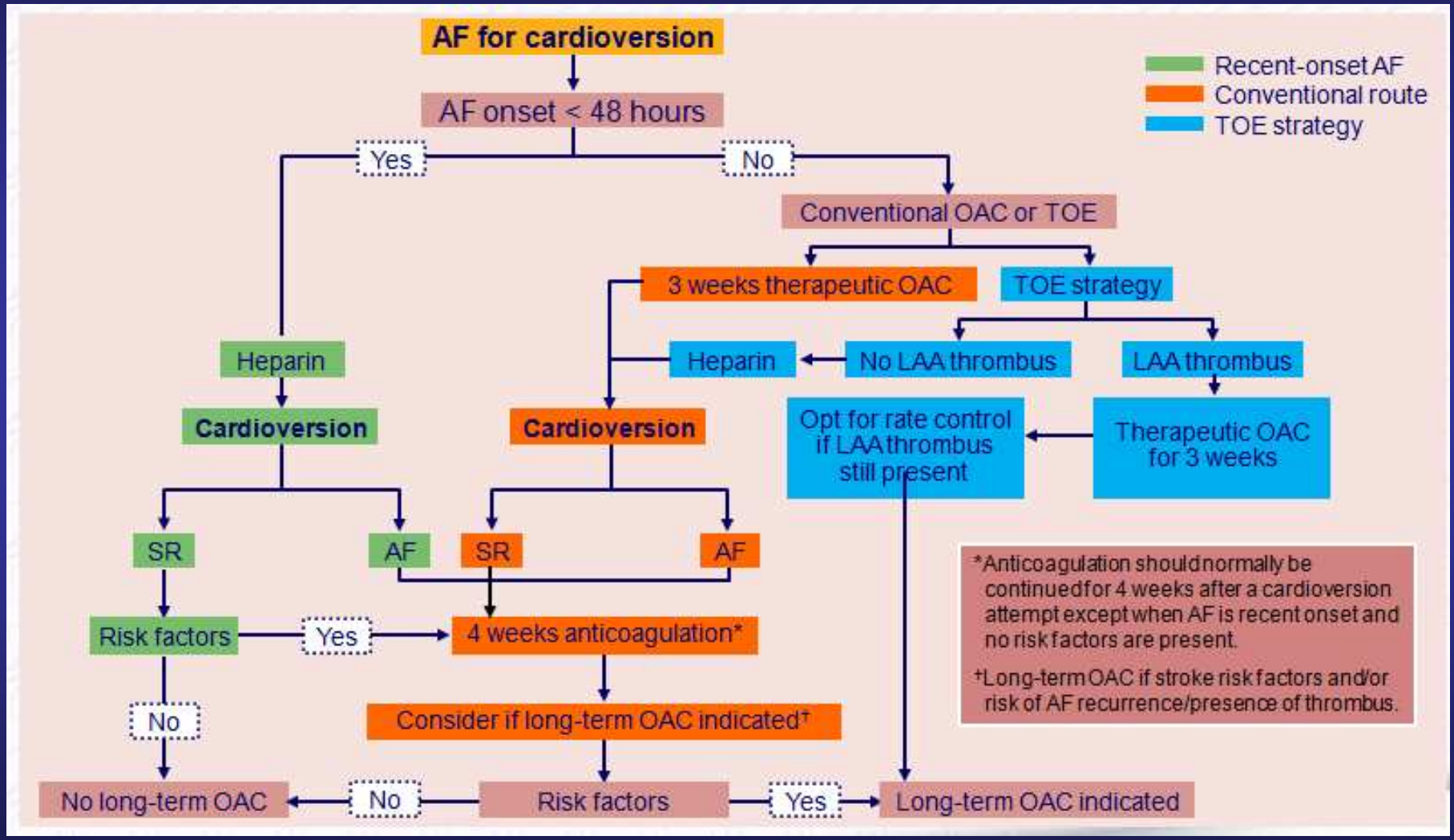
[a]Class of recommendation. [b]Level of evidence. AF = atrial fibrillation; CHADS2 = cardiac failure, hypertension, age, diabetes, stroke (doubled); INR = international normalized ratio; LMWH = low molecular weight heparin; OAC = oral anticoagulant; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

# Prevention of thromboembolism in AF

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| The selection of antithrombotic therapy should be considered using the same criteria irrespective of the pattern of AF (i.e. paroxysmal, persistent, or permanent). | IIa | A |
| Most patients with one 'clinically relevant non-major' risk factor should be considered for OAC therapy (e.g. with a VKA) rather than aspirin, based upon an assessment of the risk of bleeding complications, the ability to safely sustain adjusted chronic anticoagulation, and patient preferences. | IIa | A |
| In patients with no risk factors who are at low risk (essentially patients aged < 65 years with lone AF, with none of the risk factors), no antithrombotic therapy should be considered, rather than aspirin. | IIa | B |
| Combination therapy with aspirin 75-100 mg plus clopidogrel 75 mg daily, should be considered for stroke prevention in patients for whom there is patient refusal to take OAC therapy or a clear contraindication to OAC therapy (e.g. inability to cope or continue with anticoagulation monitoring), where there is a low risk of bleeding. | IIa | B |
| Assessment of the risk of bleeding should be considered when prescribing antithrombotic therapy (whether with VKA or aspirin), and the bleeding risk with aspirin should be considered as being similar to VKA, especially in the elderly. | IIa | A |
| The HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65), Drugs/alcohol concomitantly) should be considered as a calculation to assess bleeding risk whereby a score of ≥ 3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or aspirin. | IIa | B |
| In patients with AF who do not have mechanical prosthetic heart valves or those who are not at high risk for thromboembolism who are undergoing surgical or diagnostic procedures that carry a risk of bleeding, the interruption of OAC (with subtherapeutic anticoagulation for up to 48 h) should be considered, without substituting heparin as 'bridging' anticoagulation therapy. | IIa | C |
| In patients with a mechanical prosthetic heart valve or AF at high risk for thromboembolism who are undergoing surgical or diagnostic procedures, 'bridging' anticoagulation with therapeutic doses of either low molecular weight heparin (LMWH) or unfractionated heaparin during the temporary interruption of OAC therapy should be considered. | IIa | C |

[a]Class of recommendation. [b]Level of evidence. AF = atrial fibrillation; CHADS2 = cardiac failure, hypertension, age, diabetes, stroke (doubled); INR = international normalized ratio; LMWH = low molecular weight heparin; OAC = oral anticoagulant; TIA = transient ischaemic attack; VKA = vitamin K antagonist.

# Cardioversion, TOE and anticoagulation




AF ≡ atrial fibrillation; DCC ≡ direct current cardioversion; LA ≡ left atrium; LAA ≡ left atrial appendage; OAC ≡ oral anticoagulant; SR≡ sinus rhythm; TOE≡ transoesophageal echocardiography.

# Monitoring

ACC/AHA/ESC Guidelines

## ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text

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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**Table 6** Clinical evaluation in patients with AF

Minimum evaluation

1. *History and physical examination, to define*
   - Presence and nature of symptoms associated with AF
   - Clinical type of AF (first episode, paroxysmal, persistent, or permanent)
   - Onset of the first symptomatic attack or date of discovery of AF
   - Frequency, duration, precipitating factors, and modes of termination of AF
   - Response to any pharmacological agents that have been administered
   - Presence of any underlying heart disease or other reversible conditions (e.g., hyperthyroidism or alcohol consumption)
2. *Electrocardiogram, to identify*
   - Rhythm (verify AF)
   - LV hypertrophy
   - P-wave duration and morphology or fibrillatory waves
   - Preexcitation
   - Bundle-branch block
   - Prior MI
   - Other atrial arrhythmias
   - To measure and follow the R-R, QRS, and QT intervals in conjunction with antiarrhythmic drug therapy
3. *Transthoracic echocardiogram, to identify*
   - Valvular heart disease
   - LA and RA size
   - LV size and function
   - Peak RV pressure (pulmonary hypertension)
   - LV hypertrophy
   - LA thrombus (low sensitivity)
   - Pericardial disease
4. *Blood tests of thyroid, renal, and hepatic function*
   - For a first episode of AF, when the ventricular rate is difficult to control

Additional testing

One or several tests may be necessary.

1. *Six-minute walk test*
   - If the adequacy of rate control is in question
2. *Exercise testing*
   - If the adequacy of rate control is in question (permanent AF)
   - To reproduce exercise-induced AF
   - To exclude ischemia before treatment of selected patients with a type IC antiarrhythmic drug
3. *Holter monitoring or event recording*
   - If diagnosis of the type of arrhythmia is in question
   - As a means of evaluating rate control
4. *Transesophageal echocardiography*
   - To identify LA thrombus (in the LA appendage)
   - To guide cardioversion
5. *Electrophysiological study*
   - To clarify the mechanism of wide-QRS-complex tachycardia
   - To identify a predisposing arrhythmia such as atrial flutter or paroxysmal supraventricular tachycardia
   - To seek sites for curative ablation or AV conduction block/modification
6. *Chest radiograph, to evaluate*
   - Lung parenchyma, when clinical findings suggest an abnormality
   - Pulmonary vasculature, when clinical findings suggest an abnormality

Type IC refers to the Vaughan Williams classification of antiarrhythmic drugs (see Table 19).
AF indicates atrial fibrillation; AV, atrioventricular; LA, left atrial; LV, left ventricular; MI, myocardial infarction; RA, right atrial; RV, right ventricular.

# Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke

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ABSTRA

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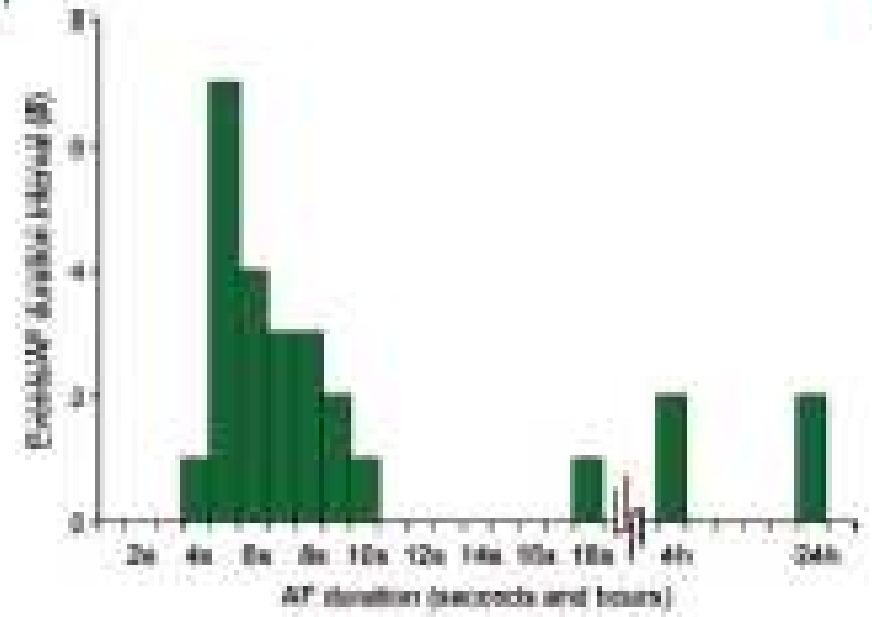
Figure Duration and distribution of 27 atrial fibrillation (AF) events detected by Mobile Cardiac Outpatient Telemetry (n = 13)




Brief and prolonged AF events were measured in seconds and hours.

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(range 2–19) days of
13 patients, of which
24 hours in duration.
multivariate analysis

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pisodes. Brief AF epi-
ically significant AF.

# Monitored Atrial Fibrillation Duration Predicts Arterial Embolic Events in Patients Suffering From Bradycardia and Atrial Fibrillation Implanted With Antitachycardia Pacemakers

Alessandro Capucci, MD,* Massimo Santini, MD,† Luigi Padeletti, MD,‡ Michele Gulizia, MD,§ GianLuca Botto, MD,‖ Giuseppe Boriani, MD,¶ Renato Ricci, MD,† Stefano Favale, MD,# Francesco Zolezzi, MD,** Natale Di Belardino, MD,†† Giulio Molon, MD,‡‡ Fabrizio Drago, MD,§§ Giovanni Q. Villani, MD,* Elena Mazzini, MS,‖‖ Marco Vimercati, MS,‖‖ Andrea Grammatico, PHD,‖‖ on behalf of the Italian AT500 Registry Investigators

*Piacenza, Rome, Florence, Catania, Como, Bologna, Bari, Vigevano, Velletri, Negrar, and Milan, Italy*

**OBJECTIVES** The aim of our study was to evaluate arterial embolism (AE) occurrence rates and predictors in patients suffering from bradycardia and wearing a pacemaker with antitachycardia pacing therapies.

**BACKGROUND** Atrial fibrillation (AF) is associated with a high incidence of AE.

**METHODS** A total of 725 patients (360 men, age 71 ± 11 years) were implanted with a DDDRP pacemaker (Medtronic AT500, Medtronic Inc., Minneapolis, Minnesota). At baseline 225 (31.0%) patients received antiplatelet therapy and 264 (36.4%) patients received anticoagulation agents.

**RESULTS** Over a median 22-month follow-up (25th to 75th interquartile range 16 to 30 months), AE occurred in 14 (1.9%) patients: 7 patients suffered a nonfatal ischemic stroke (0.6% per year), 4 patients had transient ischemic attack (0.34% per year), and 3 patients had embolic complications. Among baseline patients' characteristics, multivariate logistic analysis showed that embolic events are independently associated to ischemic heart disease (7.0 odds ratio [OR], 95% confidence interval [CI] 2.3 to 21.3, p = 0.001), prior embolic event (7.3 OR, 95% CI 1.2 to 43.9, p = 0.029), diabetes (5.0 OR, 95% CI 1.2 to 15.7, p = 0.032), and hypertension (4.1 OR, 95% CI 1.1 to 15.6, p = 0.036). The risk of embolism, adjusted for known risk factors, was 3.1 times increased (95% CI 1.1 to 10.5, p = 0.044) in patients with device-detected atrial fibrillation episodes longer than one day during follow-up.

**CONCLUSIONS** In a cohort of patients with bradycardia and AF, arterial embolism was common in patients with ischemic cardiopathy, hypertension, diabetes mellitus, and in patients with known stroke risk factors. Atrial fibrillation occurrences longer than one day were independently associated with embolic events. (J Am Coll Cardiol 2005;46:1913–20) 

Original Article | Journal of INTERNAL MEDICINE

doi: 10.1111/j.1365-2796.2007.01909.x

# Stroke event rates in anticoagulated patients with paroxysmal atrial fibrillation

G. Y. H. Lip[1], L. Frison[2] & M. Grind[2] On behalf of the SPORTIF Investigators

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**Abstract.** Lip GYH, Frison L, Grind M (Haemostasis Thrombosis and Vascular Biology Unit, City Hospital, Birmingham, England, United Kingdom; and AstraZeneca R&D Mölndal, Mölndal, Sweden). Stroke event rates in anticoagulated patients with paroxysmal atrial fibrillation. *J Intern Med* 2008; **264**: 50–61.

**Aims.** To test the hypothesis that stroke and systemic embolic events (SEE) in the stroke prevention using an oral thrombin inhibitor in atrial fibrillation (SPORTIF) III and V trials are different between paroxysmal and persistent atrial fibrillation (AF).

**Methods.** Data analysis from two cohorts of patients enroled in the prospective SPORTIF III and V clinical trials ($n$ = 7329); 836 subjects (11.4%) with paroxysmal AF [mean age 70.1 years (SD = 9.5)] were compared with 6493 subjects with persistent AF for this ancillary study.

**Results.** The annual event rates for stroke/SEE are 1.73% for persistent AF and 0.93% for paroxysmal AF. In a multivariate analysis, after adjusting for stroke risk factors, gender and aspirin usage, the differences remained statistically significant with a higher hazard ratio (HR) for stroke/SEE in persistent AF [vs. paroxysmal AF, HR 1.87, 95% confidence interval (CI) 1.04–3.36; $P$ = 0.037]. In 'high risk' patients (with ≥2 stroke risk factors) annual event rates for stroke/SEE were 2.08% for persistent AF and 1.27% for paroxysmal AF (adjusted HR = 1.68, 95% CI 0.91–3.1, $P$ = 0.098). Elderly patients had annual event rates for stroke/SEE of 2.38% for persistent AF and 1.13% for paroxysmal AF (adjusted HR = 2.27, 95% CI 0.92–5.59, $P$ = 0.075). Vitamin K antagonist (VKA)-naïve paroxysmal AF patients had a 1.89%/year stroke/SEE rate, compared with 0.61% for previous VKA takers (HR = 0.33, 95% CI 0.11–1.01, $P$ = 0.052).

**Conclusion.** In this large clinical trial cohort of anticoagulated AF patients, those with paroxysmal AF had stroke rates which were lower than for patients with persistent AF, although both groups had broadly similar stroke risk factors. Subjects with paroxysmal AF at 'high risk' had stroke/SEE rates that were not significantly different to persistent AF subjects.

**Keywords:** atrial fibrillation, paroxysmal atrial fibrillation, stroke, warfarin, ximelagatran.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
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## Arrhythmia/Electrophysiology

# Perception of Atrial Fibrillation Before and After Radiofrequency Catheter Ablation

## Relevance of Asymptomatic Arrhythmia Recurrence

Gerhard Hindricks, MD; Christopher Piorkowski, MD; Hildegard Tanner, MD; Richard Kobza, MD; Jin-Hong Gerds-Li, MD; Corrado Carbucicchio, MD; Hans Kottkamp, MD

*Background*—The objective of this study was to assess the incidence and impact of asymptomatic arrhythmia in patients with highly symptomatic atrial fibrillation (AF) who qualified for radiofrequency (RF) catheter ablation.

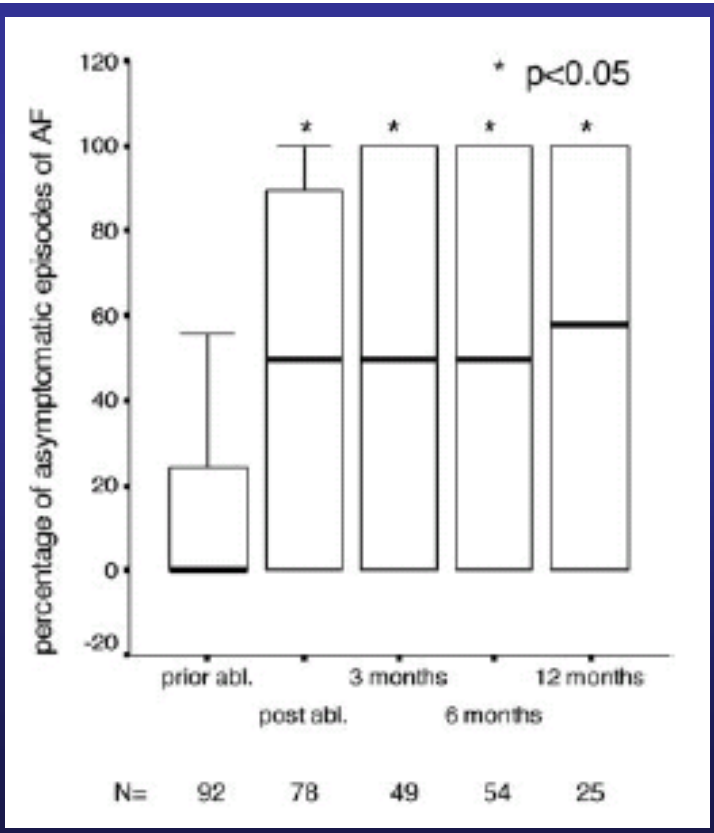
*Methods and Results*—In this prospective study, 114 patients with at least 3 documented AF episodes together with corresponding symptoms and an ineffective trial of at least 1 antiarrhythmic drug were selected for RF ablation. With the use of CARTO, circumferential lesions around the pulmonary veins and linear lesions at the roof of the left atrium and along the left atrial isthmus were placed. A continuous 7-day Holter session was recorded before ablation, right after ablation, and after 3, 6, and 12 months of follow-up. During each 7-day Holter monitoring, the patients recorded quality and duration of any complaints by using a detailed symptom log. More than 70 000 hours of ECG recording were analyzed. In the 7-day Holter records before ablation, 92 of 114 patients (81%) had documented AF episodes. All episodes were symptomatic in 35 patients (38%). In 52 patients (57%), both symptomatic and asymptomatic episodes were recorded, whereas in 5 patients (5%), all documented AF episodes were asymptomatic. After ablation, the percentage of patients with only asymptomatic AF recurrences increased to 37% ($P<0.05$) at the 6-month follow-up. An analysis of patient characteristics and arrhythmia patterns failed to identify a specific subset who were at high risk for the development of asymptomatic AF.

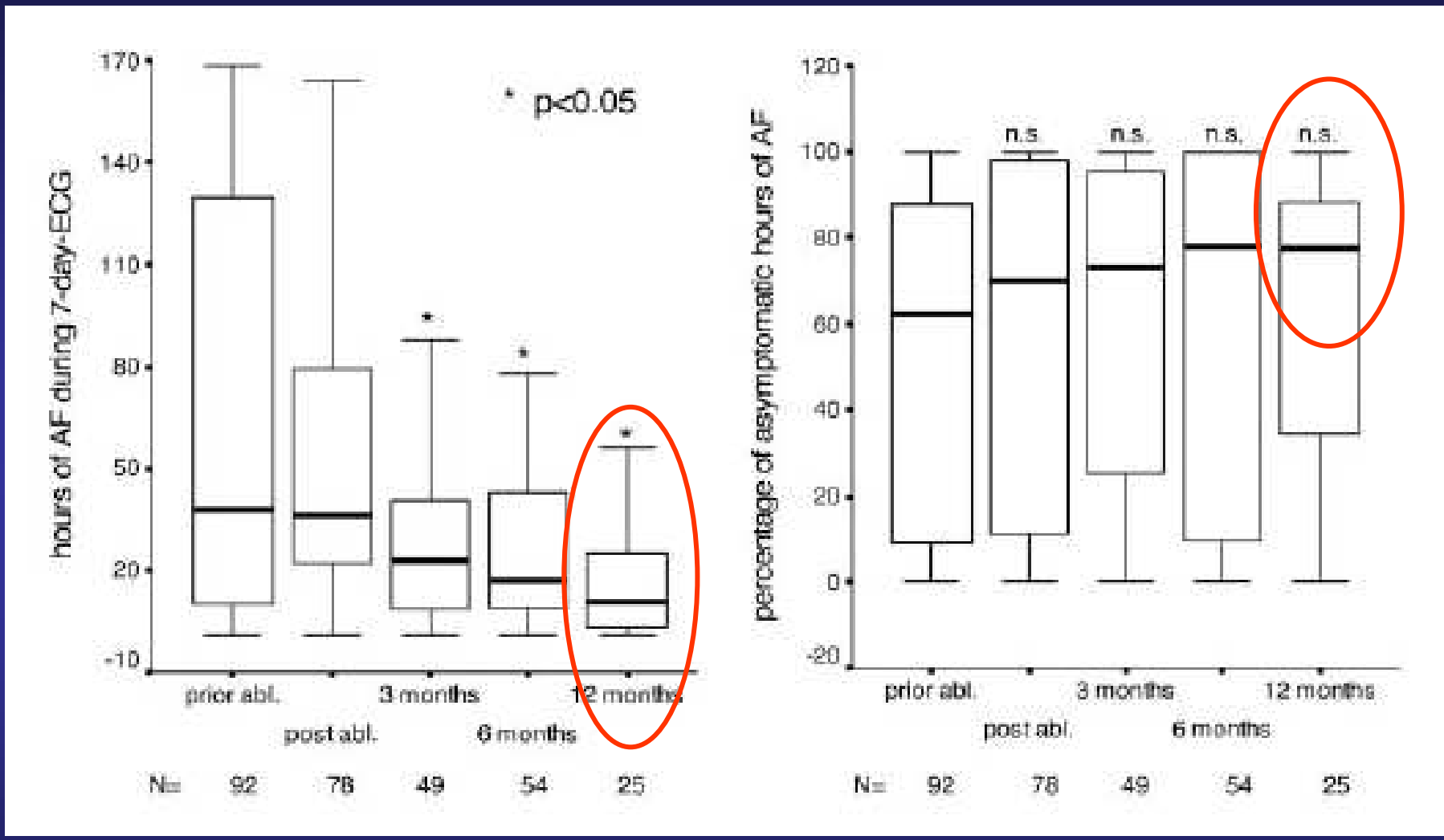
*Conclusions*—Even in patients presenting with highly symptomatic AF, asymptomatic episodes may occur and significantly increase after catheter ablation. A symptom-only–based follow-up would substantially overestimate the success rate. Objective measures such as long-term Holter monitoring are needed to identify asymptomatic AF recurrences after ablation. (*Circulation*. 2005;112:307-313.)

Key Words: atrium ■ ablation ■ arrhythmia ■ fibrillation ■ follow-up studies

**TABLE 1. Rhythm Outcome and Perception of AF Before and After RF Ablation**

| | | | Patients With AF | | | |
|---|---|---|---|---|---|---|
| | n | Patients With SR, n | n | Asymptomatic Patients Only | Symptomatic Patients Only | Symptomatic+Asymptomatic Patients |
| Before ablation | 114 | 22 (19%) | 92 | 5 (5%) | 35 (38%) | 52 (57%) |
| After ablation | | | | | | |
| Immediately | 114 | 36 (32%) $P=0.12$ | 78 | 17 (22%) $P=0.027$ | 16 (21%) $P=0.002$ | 45 (57%) $P=0.48$ |
| 3 Months | 114 | 65 (57%) $P=0.001$ | 49 | 18 (38%) $P=0.021$ | 8 (16%) $P=0.001$ | 23 (46%) $P=0.001$ |
| 6 Months | 108 | 54 (50%) $P=0.001$ | 54 | 20 (37%) $P=0.021$ | 14 (26%) $P=0.078$ | 20 (37%) $P=0.001$ |
| 12 Months | 70 | 45 (64%) $P=0.021$ | 25 | 9 (36%) $P=0.05$ | 5 (20%) $P=0.07$ | 11 (44%) $P=0.001$ |




hours of AF during 7-day-ECG
170
140
110
80
50
20
-10
* p<0.05
*
*
*
prior abl.
post abl.
3 months
6 months
12 months
N=
92
78
49
54
25
percentage of asymptomatic hours of AF
120
100
80
60
40
20
0
-20
n.s.
n.s.
n.s.
n.s.
prior abl.
post abl.
3 months
6 months
12 months
N=
92
78
49
54
25

# Role of Transtelephonic Electrocardiographic Monitoring in Detecting Short-Term Arrhythmia Recurrences After Radiofrequency Ablation in Patients With Atrial Fibrillation

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*Cirie', Maddaloni, and Mirano, Italy*

**OBJECTIVES** The aim of our study was to determine the incidence of asymptomatic recurrences of atrial fibrillation (AF) by daily transtelephonic (TT) electrocardiographic (ECG) monitoring, as compared with standard ECG and 24-h Holter recording, in patients who underwent radiofrequency catheter ablation (RCA) of AF.

**BACKGROUND** The efficacy of RCA of AF is usually evaluated by means of patients' symptoms.

**METHODS** Seventy-two patients with paroxysmal (n = 37) or persistent (n = 35) drug-refractory AF underwent circumferential RCA of the pulmonary vein (PV) ostia. Left isthmus ablation was performed in 57 patients, and cavotricuspid isthmus ablation was done in 69 patients. Patients were scheduled to obtain an ECG and Holter recordings one and four months after ablation, as well as a daily TT ECG, from 30 to 120 days after ablation or in the event of symptoms.

**RESULTS** A total of 5,585 TT ECGs were obtained (mean 77.5 per patient). In 20 patients (27.8%), AF recurrences were recorded during TT ECG, whereas ECG and Holter monitoring revealed AF recurrences in 10 patients (13.9%, p = 0.001). Ten patients had at least one asymptomatic AF recurrence, and eight were completely asymptomatic. The ECG recorded in the event of symptoms always showed AF.

**CONCLUSIONS** Transtelephonic ECG is better than standard ECG and 24-h Holter recordings in evaluating AF relapses after RCA, thus decreasing the short-term success of ablation from 86% to 72%. The absence of symptoms should not be interpreted as absence of AF, as 50% of patients were asymptomatic during at least one AF episode. (J Am Coll Cardiol 2005;45:873–6) 

# What is the real atrial fibrillation burden after catheter ablation of atrial fibrillation? A prospective rhythm analysis in pacemaker patients with continuous atrial monitoring

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*Received 11 August 2007; revised 7 January 2008; accepted 10 January 2008; online publish-ahead-of-print 9 February 2008*

**See page 964 for the editorial comment on this article (doi:10.1093/eurheartj/ehn108)**

**Aims** Rhythm follow-up after catheter ablation of atrial fibrillation (AF ablation) is mainly based on Holter electrocardiogramm (ECG), tele-ECG or on patients symptoms. However, studies using 7-day Holter or tele-ECG follow-up revealed a significant number of asymptomatic recurrences. Thus, the aim of this study was to analyse continuous atrial recordings in pacemaker patients with an incorporated Holter function before and after AF ablation in order to determine all AF recurrences and thereby the 'real' success rates.

**Methods and results** The study comprised 37 patients (64.6 $\pm$ 10 years) with prior pacemaker/implantable cardioverter defibrillator (ICD) implantation including an atrial Holter function referred for AF ablation. Holter data were obtained and correlated to patients' symptoms before and every 3-month after AF ablation. AF recurrence was defined as an atrial high frequency episode of less than 330 ms (180 b.p.m.) lasting longer than 30 s. The ablation procedure consisted of pulmonary vein isolation (PVI) in patients with paroxysmal atrial fibrillation (PAF, $n = 20$) and additional substrate modification aiming arrhythmia termination in patients with persistent or inducible AF after PVI as well as in patients with a history of long-lasting persistent AF (PersAF, $n = 17$). The mean atrial Holter monitoring period was 7.4 $\pm$ 3.3 months before and 13.5 $\pm$ 4.2 months after ablation with an overall AF burden of 33.7% prior to ablation. During follow-up, AF burden decreased from 17.3–0.65% ($P = 0.001$) in PAF patients and from 57.4 to 13.9% ($P = 0.024$) in patients with PersAF. Complete AF freedom was observed in 85% (17 patients) of PAF patients and 59% (10 patients) in patients with PersAF. The absence of symptoms correlated well with documented freedom of AF.

**Conclusion** In the present study we could show, that freedom from AF can be achieved by catheter ablation in a high percentage of patients even with PersAF. Continuous atrial monitoring reveals AF ablation success rates comparable with those assessed by clinical evaluation. Symptomatic freedom of AF correlated well with the actual freedom of AF at least in this highly symptomatic patient cohort.

**Keywords** Atrial fibrillation • Ablation • Pacemaker • Atrial Holter recording

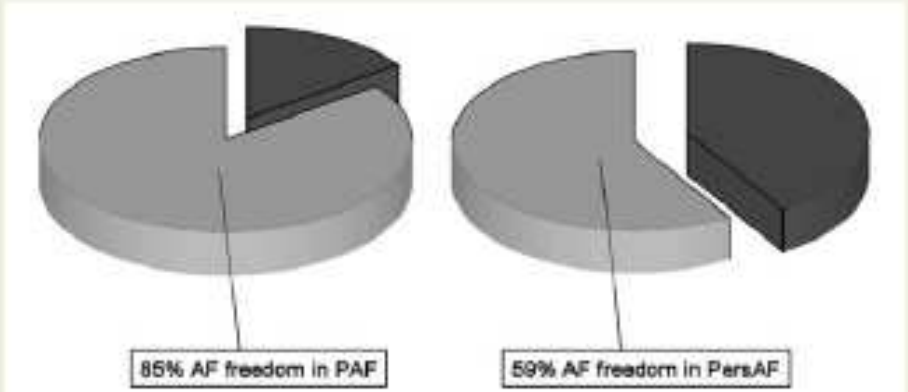



**Figure 3** Complete atrial fibrillation (AF) freedom after 12 months follow-up in the paroxysmal atrial fibrillation (PAF) and the persistent atrial fibrillation (PersAF) group, respectively. The lighter grey slices indicate proportion of patients with AF burden of 0% after 12 months follow-up.

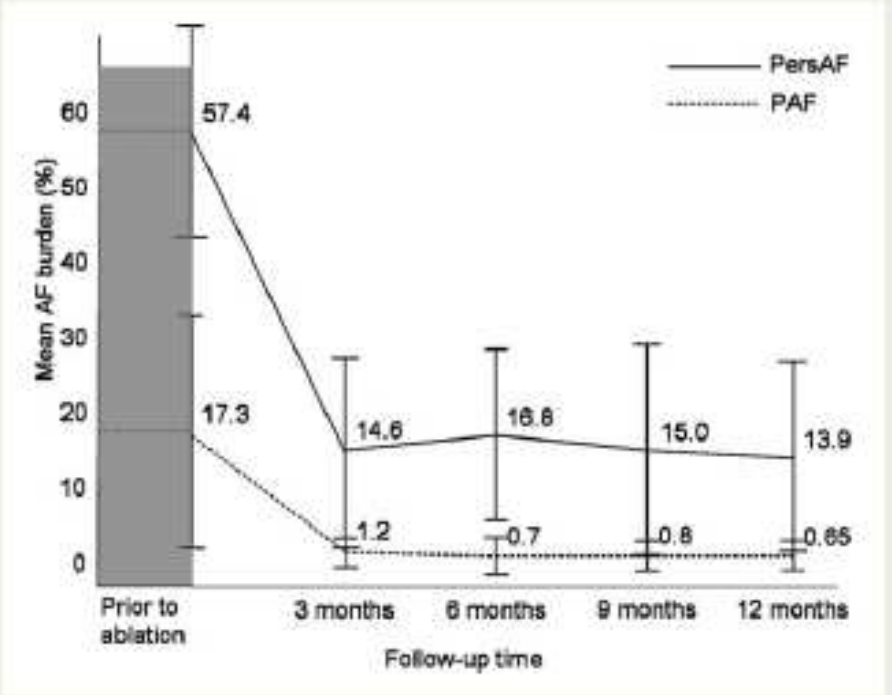



**Figure 4** Time course of atrial fibrillation (AF) recurrence during follow-up (after 3, 6, 9 and 12 months) showing the AF burden in mean percentage.


| | CONFIRM™ | REVEAL® |
|---|---|---|
| Volume | 7cc | 9cc |
| Mass | 15g | 15g |
| Length | 56.3mm | 62mm |
| Width | 18.4mm | 19mm |
| Thickness | 7.5mm | 8mm |

# Are Atrial Fibrillation Patients Receiving Warfarin in Accordance with Stroke Risk?

**Peter J. Zimetbaum, MD,[a] Amit Thosani, MD,[a] Hsing-Ting Yu, MPH,[b] Yan Xiong, MS,[b] Jay Lin, PhD,[c] Prajesh Kothawala, MD, MPH,[b] and Matthew Emons, MD, MBA[b]**

*[a]Harvard Medical School, Boston, Mass; [b]Cerner LifeSciences, Beverly Hills, Calif; [c]sanofi-aventis, Bridgewater, NJ.*

## ABSTRACT

**BACKGROUND:** Clinical guidelines for the management of atrial fibrillation and atrial flutter provide recommendations for anticoagulation based on patients' overall risk of stroke. To determine the real-world compliance of physicians with these recommendations, we conducted a retrospective cohort study examining the utilization of warfarin in atrial fibrillation/flutter patients by stroke risk level.

**METHODS:** Patients with a qualifying atrial fibrillation/flutter diagnosis during ≥18 months' continuous enrollment between January 2003 and September 2007, and with ≥6 months' eligibility after the first atrial fibrillation/flutter diagnosis, were identified from the US MarketScan database (Thomson Reuters, New York, NY). Warfarin use within 30 days of the first diagnosis was assessed according to stroke risk, estimated using the Congestive heart failure, Hypertension, Age >75 years, Diabetes, Stroke ($CHADS_2$) score.

**RESULTS:** Of 171,393 patients included in the analysis, 20.0% had a $CHADS_2$ score of 0 (low risk), 61.6% a score of 1-2 (moderate risk), and 18.4% a score of 3-6 (high risk). Warfarin, recommended for high stroke-risk patients, was given to only 42.1% of those with a $CHADS_2$ score of 3-6. A similar percentage of patients with moderate (43.5%) or low stroke risk (40.1%) received warfarin. Only 29.6% of high-risk, 33.3% of moderate-risk, and 34.1% of low-risk patients who were started on warfarin received uninterrupted therapy for 6 months following their initial prescription.

**CONCLUSIONS:** These data suggest that guideline recommendations that anticoagulation should be provided in accordance with stroke risk in atrial fibrillation patients are not routinely followed in clinical practice. The causes and clinical implications of under-utilization of anticoagulation in atrial fibrillation patients with high stroke risk warrant further study.

 • *The American Journal of Medicine (2010) 123, 446-453*

**KEYWORDS:** Anticoagulation; Atrial fibrillation; Atrial flutter; Stroke risk; Warfarin

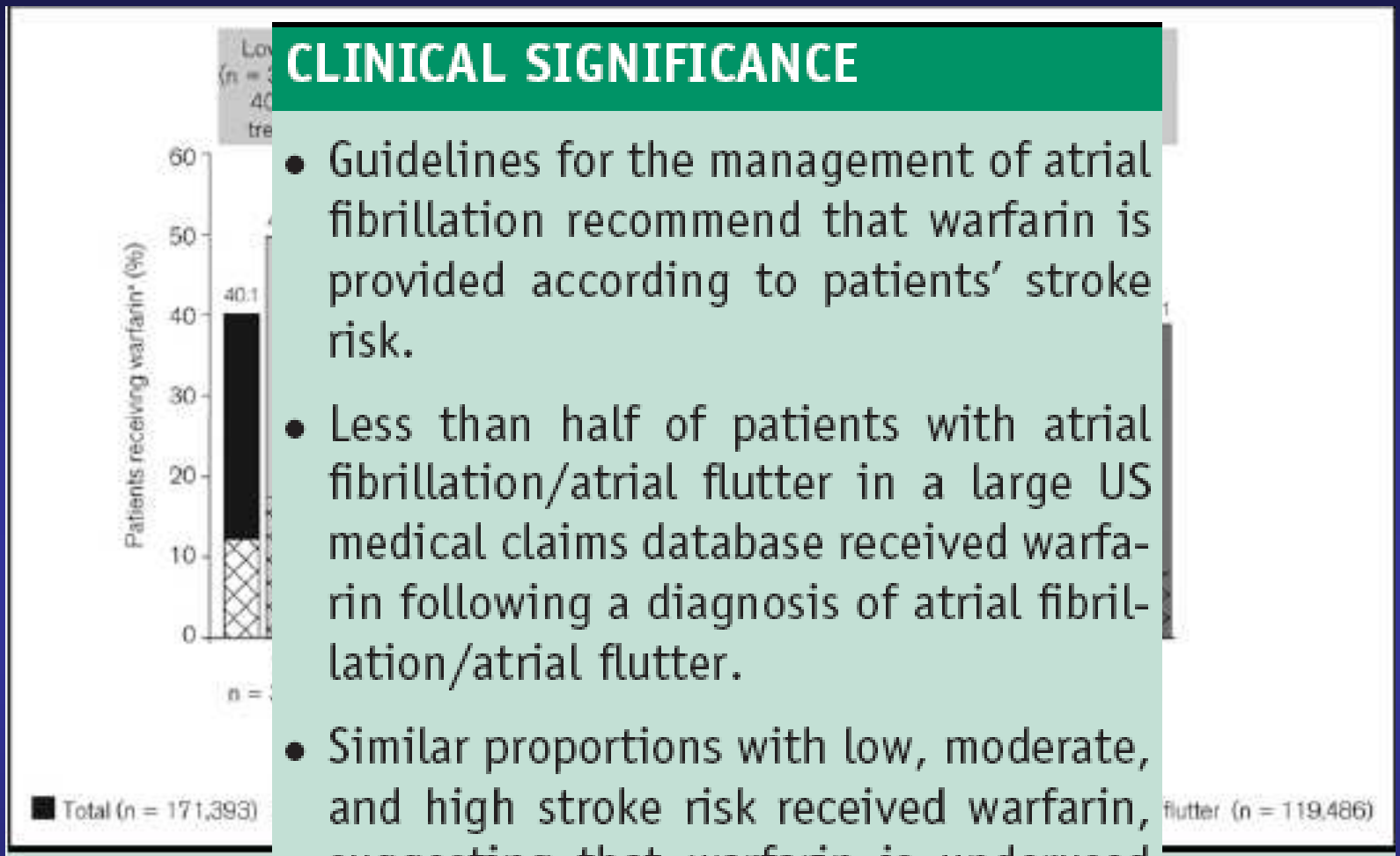



**Figure 3** War
by stroke risk le
therapy over 18(
heart failure, Hy
itter diagnosis,
uninterrupted
= Congestive

## CLINICAL SIGNIFICANCE

- Guidelines for the management of atrial fibrillation recommend that warfarin is provided according to patients' stroke risk.
- Less than half of patients with atrial fibrillation/atrial flutter in a large US medical claims database received warfarin following a diagnosis of atrial fibrillation/atrial flutter.
- Similar proportions with low, moderate, and high stroke risk received warfarin, suggesting that warfarin is underused among patients with high stroke risk, while overused in those with low stroke risk.

# Non-Valvular Atrial Fibrillation Stroke Prevention

- Warfarin cornerstone of therapy
- Assuming 51 ischemic strokes/1000 pt-yr
  - Adjusted standard dose warfarin prevents 28 strokes at expense of 11 fatal bleeds
  - Aspirin prevents 16 strokes at expense of 6 fatal bleeds
- Warfarin
  - 60-70% risk reduction vs no treatment
  - 30-40% risk reduction vs aspirin

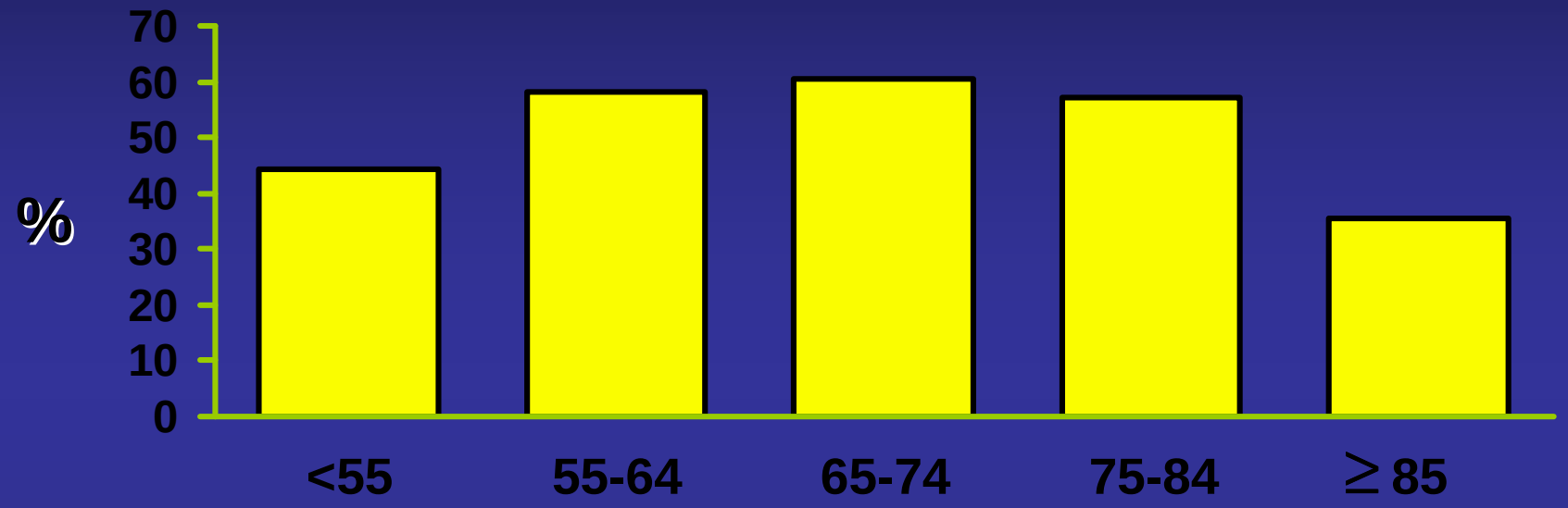
**Cooper: Arch Int Med 166, 2006**
**Lip: Thromb Res 118, 2006**

# Non-Valvular Atrial Fibrillation Stroke Prevention

Warfarin Problematic

- Narrow therapeutic window
  - Multiple drug-drug/drug-food interactions
  - Genetic variability
- Long half-life
- PCI issues – triple therapy
- Compliance
- Contraindications
- Bleeding risks

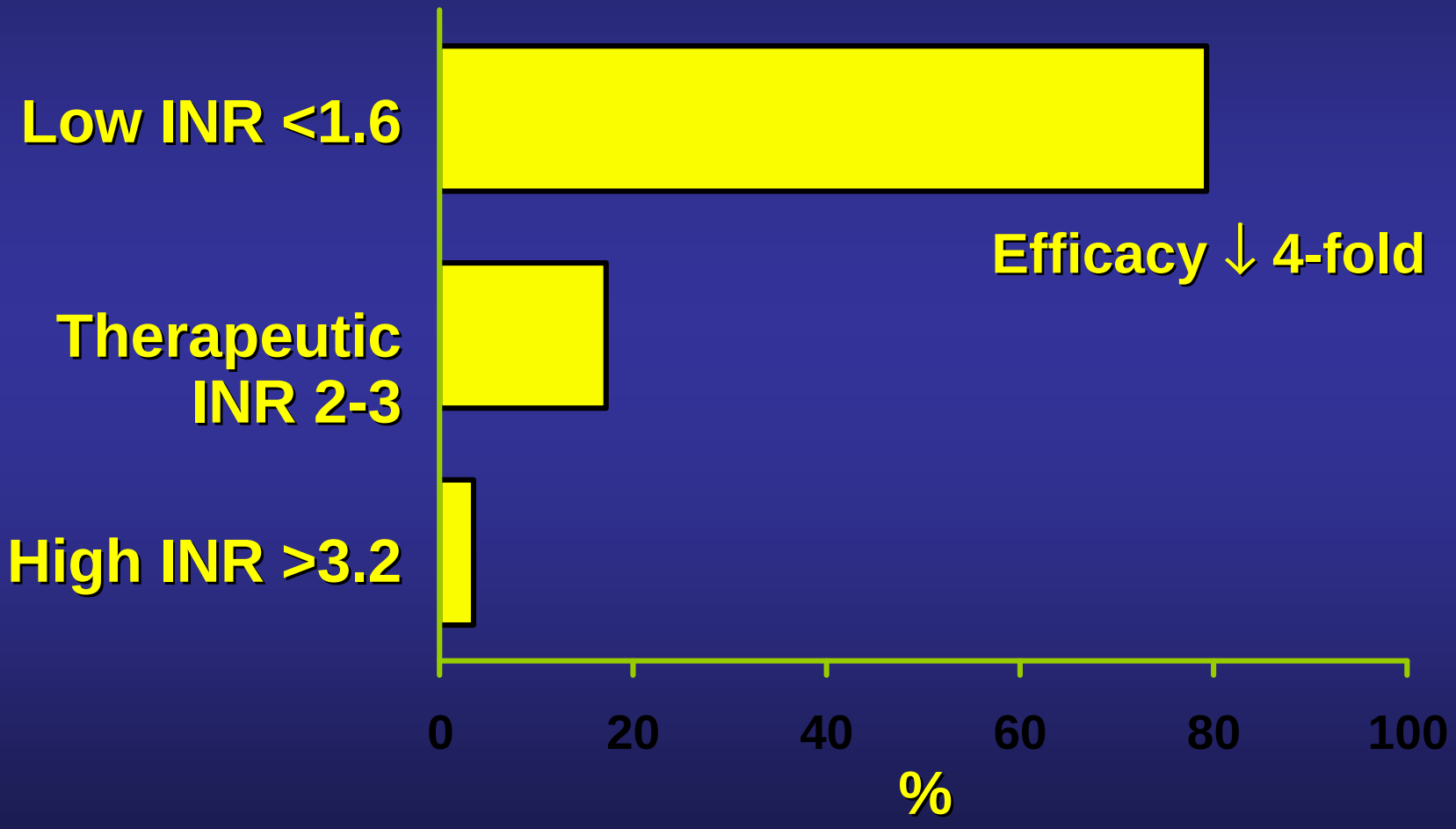
# Non-Valvular Atrial Fibrillation Warfarin Use in AF Patients by Age




- Only 55% of AF patients with no contraindications have evidence of warfarin use in previous 3 months
- Other studies cite warfarin use in AF patients from 17-50%
- Elderly patients with increased absolute risk least likely to be taking warfarin
- Contraindications 30-40%

**Ann Int Med 131(12), 1999**

# Non-Valvular Atrial Fibrillation
# Adequacy of Anticoagulation in Clinic




Bungard: Pharmacotherapy 20:1060, 2001

3000838-14

# Non-Valvular Atrial Fibrillation Stroke Pathology

- Major fatal bleed with age >75 = 3%/year (30% over 10 years)
- Intracranial hemorrhage
  - 0.3-0.5%/100 patient-years
  - 3% in INR >4.0
  - 10% if INR >4.5

**Brass. Stroke 28(12), 1997**
**VanWalraven: JAMA 288, 2002**

Journal of the American College of Cardiology
© 2010 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 55, No. 8, 2010
ISSN 0735-1097/10/$36.00
doi:10.1016/j.jacc.2009.12.008

QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

Editorial Comment

# Do Not Stop the Warfarin Until . . .*

Ivan Cakulev, MD, Albert L. Waldo, MD

*Cleveland, Ohio*

In short, although this is clearly the largest follow-up of post-atrial fibrillation ablation patients and late stroke, it is really only hypothesis generating. These data cry out for a prospective, randomized clinical trial that includes standardized methods of follow-up to assess and characterize recurrence of atrial fibrillation and to determine the incidence/prevalence of stroke.

Therefore, our conclusion: do not stop the warfarin until we have prospective, randomized clinical trials that can help guide us in providing anticoagulation therapy for our patients.

# Early and comprehensive management of atrial

*When is discontinuation of anticoagulant therapy appropriate?*

Given the fact that AF is a chronically progressing arrhythmia, anticoagulation is usually, at least conceptually, life-long.[170] Nonetheless, there is a perceived need to test whether 'apparent' sinus rhythm maintenance would allow intermittent discontinuation of anticoagulation in selected patient groups. At present, however, it appears likely that discontinuation of antithrombotic therapy in patients with AF and a risk for stroke will be confined to small, highly selected patient groups.

# 2012 focused update of the ESC Guidelines for the management of atrial fibrillation

## An update of the 2010 ESC Guidelines for the management of atrial fibrillation
## Developed with the special contribution of the European Heart Rhythm Association

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**The disclosure forms of the authors and reviewers are available on the ESC website www.escardio.org/guidelines**

# 4. Novel oral anticoagulants

The NOACs for stroke prevention in AF fall into two classes: the oral direct thrombin inhibitors (e.g. dabigatran) and oral direct factor Xa inhibitors (e.g. rivaroxaban, apixaban, etc.).[68] In contrast to VKAs, which block the formation of multiple active

## 4.1 Dabigatran etexilate

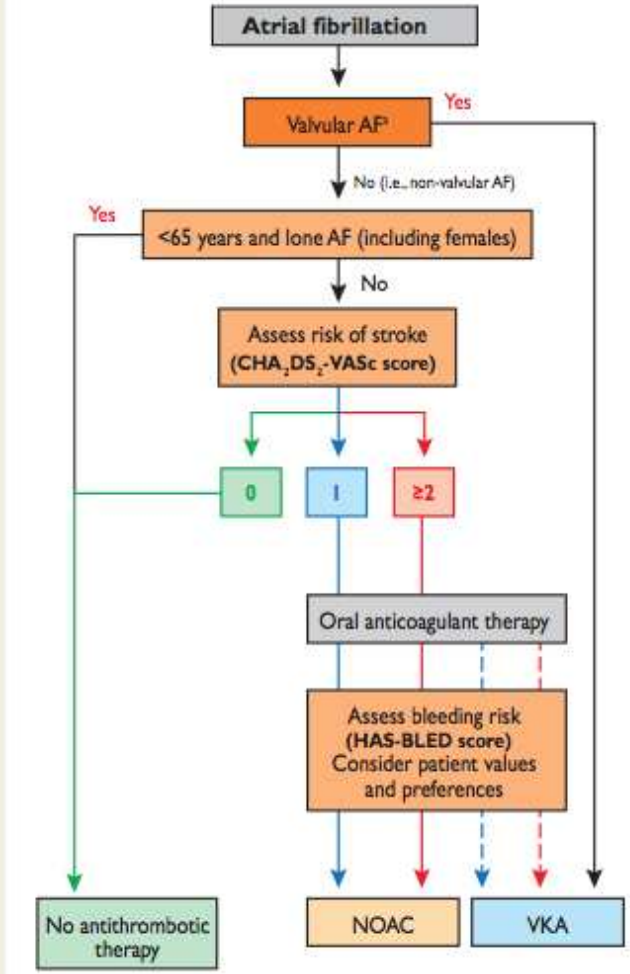
The RE-LY (Randomized Evaluation of Long-term anticoagulant therapY with dabigatran etexilate) trial was a prospective, randomized, open-label, phase III trial comparing two blinded doses of dabigatran etexilate [110 mg b.i.d. (D110) or 150 mg b.i.d. (D150)] with open-label adjusted-dose warfarin, aiming for an INR of 2.0–3.0 (*Table 4*).[70,71] For the primary efficacy endpoint

## 4.2 Rivaroxaban

The double-blind ROCKET-AF[3] trial randomized 14 264 high-risk patients with AF to either (i) treatment with rivaroxaban 20 mg o.d. [15 mg daily for those with estimated creatinine clearance (CrCl) 30–49 mL/min] or (ii) warfarin (*Table 4*). The population

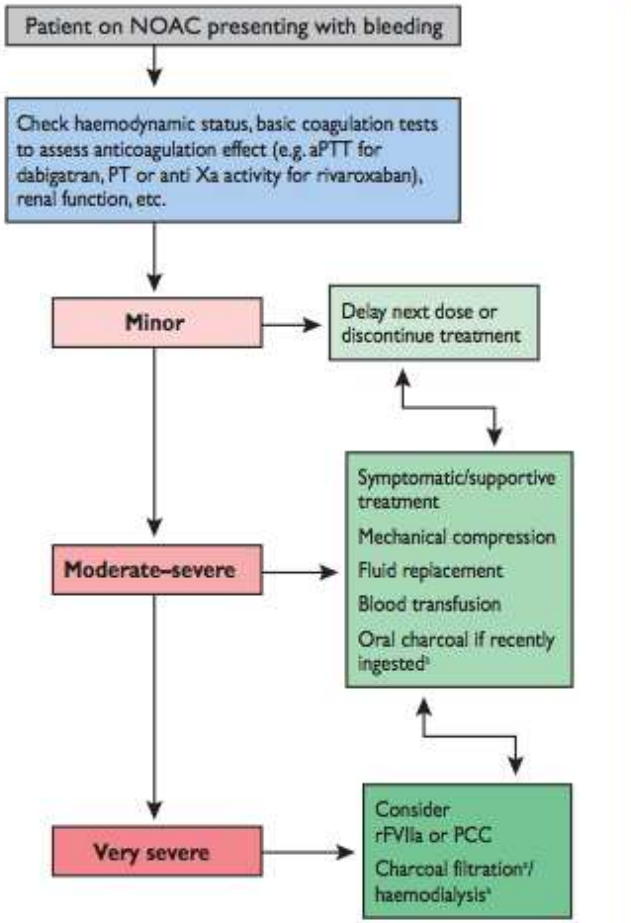
## 4.3 Apixaban

The AVERROES trial[2] randomized 5599 AF patients, who were not suitable candidates for—or were unwilling to take—VKA treatment, to double-blind, double-dummy treatment with either apixaban [5 mg b.i.d. with a dose adjustment to 2.5 mg b.i.d. in patients ≥80 years, weight ≤60kg or with a serum creatinine ≥1.5 mg/dL (133 μmol/L)] or aspirin (81–324 mg/day, with 91% taking




Antiplatelet therapy with aspirin plus clopidogrel, or—less effectively—aspirin only, should be considered in patients who refuse any OAC, or cannot tolerate anticoagulants for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered.
Colour: $CHA_2DS_2$-VASc; green = 0, blue = 1, red ≥2.
Line: solid = best option; dashed = alternative option.
AF = atrial fibrillation; $CHA_2DS_2$-VASc = see text; HAS-BLED = see text;
NOAC = novel oral anticoagulant; OAC = oral anticoagulant;
VKA = vitamin K antagonist.
[a]Includes rheumatic valvular disease and prosthetic valves.

**Figure 1** Choice of anticoagulant.




aPTT = activated partial thromboplastin time; NOAC = novel oral anticoagulant; PCC = prothrombin complex concentrate; PT = prothrombin time; rFVIIa = activated recombinant factor VII.
[b]With dabigatran.

**Figure 2** Management of bleeding in patients taking novel oral anticoagulants.

therapy or probably a NOAC. Notably, the only trial where clopidogrel use was not contraindicated was RE-LY, so the data on triple therapy with a NOAC (when given at stroke prevention doses in AF patients) are limited.

## Recommendations for prevention of thromboembolism in non-valvular AF

| Recommendations | Class[a] | Level[b] | Ref[c] |
|---|---|---|---|
| **Recommendations for prevention of thromboembolism in non-valvular AF—general** | | | |
| Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications. | I | A | 21, 63, 104, 105, 106 |
| The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient. | I | A | 21, 63, 105 |
| The $CHA_2DS_2$-VASc score is recommended as a means of assessing stroke risk in non-valvular AF. | I | A | 25, 36 ,39 |
| In patients with a $CHA_2DS_2$-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended. | I | B | 21, 36, 82 |
| In patients with a $CHA_2DS_2$-VASc score ≥2, OAC therapy with:<br>• adjusted-dose VKA (INR 2–3); or<br>• a direct thrombin inhibitor (dabigatran); or<br>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d]<br>… is recommended, unless contraindicated. | I | A | 3, 4, 70, 82 |
| In patients with a $CHA_2DS_2$-VASc score of 1, OAC therapy with<br>• adjusted-dose VKA (INR 2–3); or<br>• a direct thrombin inhibitor (dabigatran); or<br>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d]<br>…. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences. | IIa | A | 33, 44 |
| Female patients who are aged <65 and have lone AF (but still have a $CHA_2DS_2$-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered. | IIa | B | 33, 44 |
| When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively—aspirin 75–325 mg daily. | IIa | B | 21, 26, 51, 109 |
| **Recommendations for prevention of thromboembolism in non-valvular AF—NOACs** | | | |
| When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either:<br>• a direct thrombin inhibitor (dabigatran); or<br>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d]<br>… is recommended. | I | B | 2, 28, 65, 107 |
| Where OAC is recommended, one of the NOACs, either:<br>• a direct thrombin inhibitor (dabigatran); or<br>• an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d]<br>… should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit. | IIa | A | 3, 4, 70, 82 |
| Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in:<br>• elderly patients, age ≥ 80<br>• concomitant use of interacting drugs (e.g. verapamil)<br>• high bleeding risk (HAS-BLED score ≥3)<br>• moderate renal impairment (CrCl 30–49 mL/min). | IIa | B | 85, 96 |
| Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in:<br>• high bleeding risk (HAS-BLED score ≥3)<br>• moderate renal impairment (CrCl 30–49 mL/min). | IIa | C | 3, 108 |
| Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year. | IIa | B | 85 |
| NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min). | III | A | 3, 24, 70 |

## Recommendations for prevention of thromboembolism in non-valvular AF (*Continued*)

| Recommendations | Class[a] | Level[b] | Ref[c] |
|---|---|---|---|
| **Recommendations for prevention of thromboembolism in non-valvular AF—bleeding** | | | |
| Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin). | I | A | 25, 54, 59, 60 |
| The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (LoE = A).<br>Correctable risk factors for bleeding [e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.] should be addressed (LoE = B).<br>Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, but should not be used on its own to exclude patients from OAC therapy (LoE = B). | IIa | A B | 25, 54, 60 |
| The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC. | IIa | B | 18, 21, 23, 24, 26, 35 |
| **Recommendations for prevention of thromboembolism in non-valvular AF—peri-cardioversion** | | | |
| For patients with AF of ≥48 h duration, or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2-3 or dabigatran) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological). | I | B | 93 |
| In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2-3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion. | I | B | 110 |

AF = atrial fibrillation; b.i.d. = bis in die (twice daily); $CHA_2DS_2$-VASc = congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, sex category (female); CrCl = creatinine clearance; HAS-BLED = hypertension, abnormal renal/liver function (1 point each), stroke, bleeding tendency or predisposition, labile INR if on warfarin, elderly (e.g., age >65), drugs (aspirin, NSAIDs, etc.)/alcohol concomitantly (1 point each); INR = international normalized ratio; i.v. = intravenous; OAC = oral anticoagulant; NOAC = novel oral anticoagulant; NSAID = non-steroidal anti-inflammatory drug; VKA = vitamin K antagonist.

[a]Class of recommendation.

[b]Level of evidence.

[c]References.

[d]Apixaban (pending approval EMA and FDA approval): prescribing information is awaited.

**Key points**

- The efficacy of stroke prevention with aspirin is weak, with a potential for harm, since the risk of major bleeding (and ICH) with aspirin is not significantly different to that of OAC, especially in the elderly.
- The use of antiplatelet therapy (as aspirin–clopidogrel combination therapy or—less effectively—aspirin monotherapy for those who cannot tolerate aspirin–clopidogrel combination therapy) for stroke prevention in AF should be limited to the few patients who refuse any form of OAC.
- The $CHA_2DS_2$-VASc score is better at identifying 'truly low-risk' patients with AF and is as good as—and possibly better than—scores such as $CHADS_2$ in identifying patients who develop stroke and thromboembolism.

- The HAS-BLED score allows clinicians to make an informed assessment of bleeding risk and, importantly, makes them think of the correctable risk factors for bleeding. In patients with a HAS-BLED score $\geq 3$, caution and regular review are recommended, as well as efforts to correct the potentially reversible risk factors for bleeding. A high HAS-BLED score *per se* should not be used to exclude patients from OAC therapy.
- The NOACs offer better efficacy, safety, and convenience compared with OAC with VKAs. Thus, where an OAC is recommended, one of the NOACs—either a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)—should be considered instead of adjusted-dose VKA (INR 2–3) for most patients with AF.
- There is insufficient evidence to recommend one NOAC over another, although some patient characteristics, drug compliance and tolerability, and cost may be important considerations in the choice of agent.

# Indirect Comparisons of New Oral Anticoagulant Drugs for Efficacy and Safety When Used for Stroke Prevention in Atrial Fibrillation

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**Objectives** This study sought to perform an indirect comparison analysis of dabigatran etexilate (2 doses), rivaroxaban, and apixaban for their relative efficacy and safety against each other.

**Background** Data for warfarin compared against the new oral anticoagulants (OACs) in large phase III clinical trials of stroke prevention in atrial fibrillation (AF) are now available for the oral direct thrombin inhibitor, dabigatran etexilate, in 2 doses (150 mg twice daily [BID], 110 mg BID), and the oral Factor Xa inhibitors, rivaroxaban and apixaban. A "head-to-head" direct comparison of drugs is the standard method for comparing different treatments, but in the absence of such head-to-head direct comparisons, another alternative to assess the relative effect of different treatment interventions would be to perform indirect comparisons, using a common comparator. Nonetheless, any inter-trial comparison is always fraught with major difficulties, and an indirect comparison analysis has many limitations, especially with the inter-trial population differences and thus, should not be overinterpreted.

**Methods** Indirect comparison analysis was performed using data from the published trials.

**Results** There was a significantly lower risk of stroke and systemic embolism (by 26%) for dabigatran (150 mg BID) compared with rivaroxaban, as well as hemorrhagic stroke and nondisabling stroke. There were no significant differences for apixaban versus dabigatran (both doses) or rivaroxaban; or rivaroxaban versus dabigatran 110 mg BID in preventing stroke and systemic embolism. For ischemic stroke, there were no significant differences between the new OACs. Major bleeding was significantly lower with apixaban compared with dabigatran 150 mg BID (by 26%) and rivaroxaban (by 34%), but not significantly different from dabigatran 110 mg BID. There were no significant differences between apixaban and dabigatran 110 mg BID in safety endpoints. Apixaban also had lower major or clinically relevant bleeding (by 34%) compared with rivaroxaban. When compared with rivaroxaban, dabigatran 110 mg BID was associated with less major bleeding (by 23%) and intracranial bleeding (by 54%). There were no significant differences in myocardial infarction events between the dabigatran (both doses) and apixaban.

**Conclusions** Notwithstanding the limitations of an indirect comparison study, we found no profound significant differences in efficacy between apixaban and dabigatran etexilate (both doses) or rivaroxaban. Dabigatran 150 mg BID was superior to rivaroxaban for some efficacy endpoints, whereas major bleeding was significantly lower with dabigatran 110 mg BID or apixaban. Only a head-to-head direct comparison of the different new OACs would fully answer the question of efficacy/safety differences between the new drugs for stroke prevention in AF. (J Am Coll Cardiol 2012;60:738–46) 

**Table 1** Summary of the Main Clinical Trials Involving Novel Anticoagulants for Stroke Prevention in Nonvalvular AF

| | Dabigatran (RE-LY) | Rivaroxaban (ROCKET-AF) | Apixaban (ARISTOTLE) |
|---|---|---|---|
| **Drug characteristics** | | | |
| Mechanism | Oral direct thrombin inhibitor | Oral direct factor Xa inhibitor | Oral direct factor Xa inhibitor |
| Bioavailability, % | 6 | 60–80 | 50 |
| Time to peak levels, h | 3 | 3 | 3 |
| Half-life, h | 12–17 | 5–9 | 9–14 |
| Excretion | 80% renal | 2/3 liver, 1/3 renal | 25% renal, 75% fecal |
| Dose | 150 mg BID | 20 mg OD | 5 mg BID |
| Dose in renal impairment | 110 mg BID | 15 mg OD (if creatinine clearance 30–49 ml/min) | 2.5 mg BID |
| Special considerations | Intestinal absorption is pH dependent and is reduced in patients taking proton pump inhibitors. | Higher levels expected in patients with renal or hepatic failure.<br>Activity lower in fasted patients, so should be taken after food. | |
| **Study characteristics** | | | |
| Study design | Randomized open label | Multicenter, randomized, double-blind, double-dummy | Randomized control, double-blind, parallel arm |
| Number of patients | 18,113 | 14,264 | 18,201 |
| Follow-up period, months | 24 | 40 | 40 |
| Randomized groups | Dose-adjusted warfarin vs. blinded doses of dabigatran (150 mg BID, 110 mg BID) | Dose-adjusted warfarin vs. rivaroxaban 20 mg OD | Dose-adjusted warfarin vs. apixaban 5 mg BID |

ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BID = twice daily; OD = once daily; RE-LY = Randomized Evaluation of Long-Term Anticoagulant Therapy; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation.

# Cost-effectiveness of Dabigatran for Stroke Prevention in Non-valvular Atrial Fibrillation in Spain

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*Article history:*
Received 16 February 2012
Accepted 6 June 2012

*Keywords:*
Cost-effectiveness
Stroke prevention
Atrial fibrillation

ABSTRACT

*Introduction and objectives:* Assessment of the cost-effectiveness of dabigatran for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation in Spain, from the perspective of the National Health System.

*Methods:* Adaptation of a Markov chain model that simulates the natural history of the disease over the lifetime of a cohort of 10 000 patients with non-valvular atrial fibrillation. Model comparators were warfarin in a first scenario, and a real world prescribing pattern in a second scenario, in which 60% of the patients were treated with vitamin K antagonists, 30% with acetylsalicylic acid, and 10% received no treatment. Deterministic and probabilistic sensitivity analyses were performed.

*Results:* Dabigatran reduced the occurrence of clinical events in both scenarios, providing gains in quantity and quality of life. The incremental cost-effectiveness ratio for dabigatran compared to warfarin was 17 581 euros/quality-adjusted life year gained and 14 118 euros/quality-adjusted life year gained when compared to the real world prescribing pattern. Efficiency in subgroups was demonstrated. When the social costs were incorporated into the analysis, dabigatran was found to be a dominant strategy (ie, more effective and less costly). The model proved to be robust.

*Conclusions:* From the perspective of the Spanish National Health System, dabigatran is an efficient strategy for the prevention of stroke in patients with non-valvular atrial fibrillation compared to warfarin and to the real-world prescribing pattern; incremental cost-effectiveness ratios were below the 30 000 euros/quality-adjusted life year threshold in both scenarios. Dabigatran would also be a dominant strategy from the societal perspective, providing society with a more effective therapy at a lower cost compared to the other 2 alternatives.

# Costo efficacia dei nuovi anticoagulanti

- Giornate lavorative
- Spesa del Sistema Sanitario in termini di controlli
- Cardioversione
- Preparazione a procedura ablativa
- Ripresa della terapia anticoagulante e dimissione