Σημασία και Αντιμετώπιση της Κολπικής Μαρμαρυγής στον Υπερτασικό Ασθενή

Δρ. Δημήτρης Π. Παπαδόπουλος-FESC
Επιμελητής Α. Καρδιολογικής Κλινικής Π.Γ.Ν.Α. «ΛΑΪΚΟ»
Υπεύθυνος Τμήματος Υπέρτασης Λιπιδίων Προληπτικής Καρδιολογίας
Clinical Hypertension Specialist ESH
Disclosures

Research Grants, Honoraria, Advisory Boards

➢ SERVIER
➢ ELPEN
➢ MENARINI
➢ NOVARTIS
➢ PFIZER
➢ PHARMAMEL
➢ CHIESI
➢ ANGELINI
➢ MYLAN
EU Prevalence of Hypertension
~81 Million Adults have elevated Blood Pressure

- 81M Patients with HTN
- Diagnosed HTN
- Treated HTN
- Uncontrolled HTN
- Resistant HTN

EU Patients with HTN 81.0M
Diagnosed HTN 78%
Treated HTN 68%
Uncontrolled HTN 38%
Resistant HTN 9% - $7.2M

Lloyd-Jones D: Circulation 2010;121:e46 – e215
Persell SD: Hypertension 2011;57:1076-1080

HTN=Hypertension
The most important **modifiable** RF for CHD, stroke, HF, CKD

WHO estimates:
- 80% of CVD and t2DM, and
- 40% of cancer
could be avoided if major risk factors were eliminated.

CDC US 2014
WHO Strategy for Chronic Disease (WHO, 2008).
AF is the Most Common Cardiac Arrhythmia

Ø AF affects
  Ø 1 in 25 adults >60 years¹
  Ø 1 in 10 adults >80 years¹

Ø 6.8 million patients with AF in EU and US*¹,²

AF Prevalence is Predicted to Increase by ≥2.5-fold by 2050 in the US

Ø Upper and lower curves represent the upper and lower scenarios based on sensitivity analyses

Go AS et al. JAMA 2001;285:2370-2375
Epidemiology of AF

- Most common sustained cardiac arrhythmia\textsuperscript{1}
- Currently affects \textbf{5.1 million} Americans\textsuperscript{2}
- Prevalence expected to increase to 12.1 million by 2050 (15.9 million if increase in incidence continues)\textsuperscript{2}
- Preferentially affects men and the elderly\textsuperscript{1,2}
- Lifetime risk of developing AF: \textasciitilde{}1 in 4 for adults \texttt{\geq}40 years of age\textsuperscript{3}

\textsuperscript{1} Lloyd-Jones D, et al. December 17, 2009]. Circulation.
Classification of AF

- **Paroxysmal AF**—intermittent recurrent ≤7 days
- **Persistent AF**—sustained >7 days
- **Permanent (persistent, long-standing) AF**
- **AF due to a reversible cause**
- **Lone AF**—in the absence of structural disease

Prevalence of Hypertension in AF Trials

AF populations

Patients with hypertension, %

PIAF: 49
RACE: 55
STAF: 62.6
HOT CAFÉ: 64.4
AFFIRM predominant: 51
AFFIRM overall: 71
CHARM: 51.8
RECORD AF: 68
ACTIVE I Heart Survey: 63
ATHENA: 86.6
ROCKET: 86.3
RELY: 90
AVERROES: 86
Conditions frequently associated with AF

- **Cardiovascular conditions**
  - Hypertension
  - Ischaemic heart disease/cardiologyopathy
  - Heart failure
  - Valvular disease

- **Metabolic conditions**
  - Obesity
  - Diabetes mellitus
  - Metabolic syndrome
  - Hyperthyroidism/thyrotoxicosis

- **Other**
  - Obstructive sleep apnoea
  - Carcinoma of the bronchus
  - Pneumonia
  - Cardiopulmonary surgery

### Diagnostic workup of atrial fibrillation patients

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG documentation is required to establish the diagnosis of AF.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>A full cardiovascular evaluation, including an accurate history, careful</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>clinical examination, and assessment of concomitant conditions, is</td>
<td></td>
<td></td>
</tr>
<tr>
<td>recommended in all AF patients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transthoracic echocardiography is recommended in all AF patients to guide</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>management.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term ECG monitoring should be considered in selected patients to</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>assess the adequacy of rate control in symptomatic patients and to relate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptoms with AF episodes.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
AF Is the Leading Cause of Hospitalizations for Arrhythmia

N=517,699 (representing 10% of CV admissions).
VF, ventricular fibrillation; VT, ventricular tachycardia.
AF is an Independent Risk Factor for Stroke

- AF patients have a near 5-fold increased risk of stroke\(^1\)
- 1 in every 6 strokes occurs in a patient with AF
- Ischemic stroke associated with AF is typically more severe than stroke due to other etiologies\(^3\)
- Stroke risk persists even in asymptomatic AF\(^4\)

---

AF Is Associated With Increased Thromboembolic Risk

- Major cause of stroke in elderly
- **5-fold** ↑ in risk of stroke
- **15% of** strokes in US are attributable to AF
- Stroke severity (and mortality) is worse with AF than without AF
- Incidence of all-cause stroke in patients with AF: 5%¹
- Stroke risk persists even in asymptomatic AF

The Economics of AF

2005 mean cost per AF-related hospitalization was >$8000, with a mean length of stay of 3.5 days\(^1\)

1. Adapted from Sanoski CA. *J Manag Care Pharm.* 2009.
ΣΤΡΑΤΗΓΙΚΕΣ ΠΡΟΛΗΨΗΣ
ΣΥΜΒΑΜΑΤΩΝ
ΥΠΕΡΤΑΣΙΚΩΝ ΜΕ ΚΟΛΠΙΚΗ
ΜΑΡΜΑΡΥΓΗ
Ι. ΡΥΘΜΙΣΗ ΥΠΕΡΤΑΣΗΣ
2013 Guidelines for the Management of Arterial Hypertension

European Society of Hypertension
European Society of Cardiology

Goals of Antihypertensive Treatment

BP ↓

Favourable effects on risk factors / inflammatory markers

NOD prevention
HT prevention
AF prevention

TOD regression / prevention

CAD / MI ↓

CHF ↓

Stroke ↓

ESRF ↓

LVH
Arterial thickening / plaques
Proteinuria / microalbuminuria
Arterial stiffness
Arteriolar remodelling
Reduced GFR / ↑ SCR
Endothelial dysfunction
Arteriolar remodelling
Coronary Ca++
Cerebral lacunae / WMLs
Retinopathy
Cardiac fibrosis (collagen markers)
Cognitive dysfunction / Dementia
Blood Pressure Goals In Hypertension

- **A SBP < 140 mmHg** recommended/considered, regardless the level of risk
  - Low/moderate risk (IB)
  - Diabetes (IA)
  - Diabetic/nondiabetic CKD (IIaB)
  - Patients with CHD/previous stroke or TIA (IIaB)

- **A DBP < 90 mmHg** recommended
  
  Diabetic Patients  **A DBP < 85 mmHg** recommended
An unmasked, open-label randomized controlled multicenter trial

## Categories of BP in Adults

<table>
<thead>
<tr>
<th>BP Category</th>
<th>SBP</th>
<th>DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120 mm Hg and &lt;80 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>Elevated</td>
<td>120–129 mm Hg and &lt;80 mm Hg</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>130–139 mm Hg or 80–89 mm Hg</td>
<td>≥90 mm Hg</td>
</tr>
<tr>
<td>Stage 2</td>
<td>≥140 mm Hg or ≥90 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>

Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.

BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.)
BP Goal for Patients With Hypertension

Recommendations for BP Goal for Patients With Hypertension

For adults with confirmed hypertension and known CVD or 10-year ASCVD event risk of 10% or higher, a BP target of less than 130/80 mm Hg is recommended.

For adults with confirmed hypertension, without additional markers of increased CVD risk, a BP target of less than 130/80 mm Hg may be reasonable.
2013 Guidelines for the Management of Arterial Hypertension

European Society of Hypertension
European Society of Cardiology

Treatment strategies and choice of drugs

Diuretics (thiazides, chlorthalidone and indapamide)

- Beta-blockers
- Calcium antagonists
- ACE inhibitors, and
- Angiotensin receptor blockers

Are all suitable and **recommended for the initiation and maintenance of antihypertensive treatment**, either as monotherapy or in some combinations with each other.

**Category I – Level A**

2013 ESH Guidelines for the Management of Hypertension
# 2013 ESH/ESC Hypertension Guidelines

## Drugs To Be Preferred In Specific Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic organ damage</td>
<td>ACE inhibitor, calcium antagonist, ARB</td>
</tr>
<tr>
<td>LVH</td>
<td>ACE inhibitor, calcium antagonist, ARB</td>
</tr>
<tr>
<td>Asymptomatic atherosclerosis</td>
<td>Calcium antagonist, ACE inhibitor</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Clinical CV event</td>
<td></td>
</tr>
<tr>
<td>Previous stroke</td>
<td>Any agent effectively lowering BP</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>BB, ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>BB, calcium antagonist</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>BB</td>
</tr>
<tr>
<td>Atrial fibrillation, prevention</td>
<td>Consider ARB, ACE inhibitor, BB or mineralocorticoid receptor antagonist</td>
</tr>
<tr>
<td>Atrial fibrillation, ventricular rate control</td>
<td>BB, non-dihydropyridine calcium antagonist</td>
</tr>
<tr>
<td>ESRD/proteinuria</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>ACE inhibitor, calcium antagonist</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>ISH (elderly)</td>
<td>Diuretic, calcium antagonist</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>ACE inhibitor, ARB, calcium antagonist</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>ACE inhibitor, ARB</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Methyldopa, BB, calcium antagonist</td>
</tr>
<tr>
<td>Blacks</td>
<td>Diuretic, calcium antagonist</td>
</tr>
</tbody>
</table>
## Treatment of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic effects of non-antiarrhythmic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-Is, ARBs and beta-blockers should be considered for prevention of new-onset AF in patients with heart failure and reduced ejection fraction.</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>ACE-Is and ARBs should be considered for prevention of new-onset AF in patients with hypertension, particularly with LV hypertrophy.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Pre-treatment with ACE-Is or ARBs may be considered in patients with recurrent AF undergoing electrical cardioversion and receiving antiarrhythmic drug therapy.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>ACE-Is or ARBs are not recommended for the secondary prevention of paroxysmal AF in patients with little or no underlying heart disease.</td>
<td>III (no benefit)</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers, digoxin, diltiazem, or verapamil are recommended to control heart rate in AF patients with LVEF ≥40%.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Beta-blockers and/or digoxin are recommended to control heart rate in AF patients with LVEF &lt;40%.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>
UK-based General Practice Research Database

- 650,000 hypertensive pts
- 4661 pts with new AF

Hypertensive pts receiving long-term monotherapy with ACE-I, ARB’s, or β-blockers were less likely to develop AF than those whose received only CCB’s

CCB’s vs ACE-I OR 0.75
vs ARB’s OR 0.71
vs β-blockers OR 0.78


© American College of Cardiology Foundation and American Heart Association, Inc.
Recommendation for Treatment of Hypertension in Patients With AF

Treatment of hypertension with an ARB can be useful for prevention of recurrence of AF.
Αποτελεσματικότητα
Systematic review of the antihypertensive activity of ARBs: BP reduction over 24 hours

![Bar chart showing change in SBP and DBP for different ARBs compared to placebo.](image-url)
Ανοχή-Παρενέργειες
Cumulative Incidence of Discontinuation of Initial Antihypertensive Monotherapy over 1 Year (Lombardia Data-base; n = 445356)

- Diuretics: 1.83 (1.81-1.85)
- Beta-blockers: 1.64 (1.62-1.67)
- Alpha-blockers: 1.23 (1.20-1.27)
- Calcium channel blockers: 1.08 (1.06-1.09)
- ACE-inhibitors
- Angiotensin-receptor blockers: 0.92 (0.90-0.94)

Corrao, Zambon, Parodi, Poluzzi, Baldi, Merlino, Cesana, Mancia, J Hypert 2008; 26: 819-824
Treatment choice: Within-class discontinuation rate differences* show that side effects can affect adherence.

*Discontinuation rates showed significant heterogeneity (p<0.05) for each drug class. For ARBs, the rate was significantly greater for losartan.

Mancia et al. J Hypertens 2011;29:1012-1018
II. ΑΝΤΙΜΕΤΩΠΙΣΗ ΚΟΛΠΙΚΗΣ ΜΑΡΜΑΡΥΓΗΣ
2016 focused update of the ESC Guidelines for the management of Atrial Fib

European Heart Journal
The Five Domains of Integrated AF Management

**Treatment**
- Acute rate and rhythm control
- Manage precipitating factors
- Assess stroke risk
- Assess heart rate
- Assess symptoms

**Desired outcome**
- Haemodynamic stability
- Cardiovascular risk reduction
- Stroke prevention
- Symptom improvement, preservation of LV function

**Patient benefit**
- Improved life expectancy
- Improved quality of life, autonomy, social functioning

Additional treatments:
- *e.g.*, β-blockers, cardioversion
- Oral anticoagulation in patients at risk for stroke
- Rate control therapy
- Antiarrhythmic drugs, cardioversion, catheter ablation, AF surgery

www.escardio.org/guidelines
Current Treatment Strategies for AF

➢ Prevention of thrombo-embolism

➢ Blood pressure control

➢ Anticoagulation treatment

➢ Rate control

➢ Rhythm control
Clinical risk factors for stroke, transient ischaemic attack, and systemic embolism

<table>
<thead>
<tr>
<th>CHA₂DS₂-VASc risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Resting blood pressure &gt; 140/90 mmHg on at least two occasions or current antihypertensive treatment</td>
<td></td>
</tr>
<tr>
<td>Age 75 years or older</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Fasting glucose &gt; 125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin</td>
<td></td>
</tr>
<tr>
<td>Previous stroke, transient ischaemic attack, or thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Previous myocardial infarction, peripheral artery disease, or aortic plaque</td>
<td></td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
</tr>
</tbody>
</table>
**Stroke prevention in patients with atrial fibrillation (1)**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA$_2$DS$_2$-VASc score of 2 or more.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA$_2$DS$_2$-VASc score of 3 or more.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA$_2$DS$_2$-VASc score of 1, considering individual characteristics and patient preferences.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA$_2$DS$_2$-VASc score of 2, considering individual characteristics and patient preferences.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a Vitamin K antagonist.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>
### Previous Guidelines for primary stroke prevention in AF: AHA/ACC/ESC

<table>
<thead>
<tr>
<th>Total CHADS2 score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual risk of stroke (%)</td>
<td>1.9</td>
<td>2.8</td>
<td>4</td>
<td>5.9</td>
<td>8.5</td>
<td>12.5</td>
<td>18.2</td>
</tr>
</tbody>
</table>

- **No risk factors**
  - aspirin (81–325 mg daily)

- **One moderate-risk factor**
  - Warfarin (INR 2.0–3.0)
  - OR
  - aspirin (81–325 mg daily)

- **Any high-risk factor or > 1 moderate-risk factor**
  - Warfarin (INR 2.0–3.0)

**Antithrombotic therapy is mainstay treatment!**

INR = International normalized ratio.


Stroke prevention in atrial fibrillation

**Mechanical heart valves or moderate or severe mitral stenosis**

Yes

**Estimate stroke risk based on number of CHA₂DS₂-VASc risk factors**

No

- **0**
  - No antiplatelet or anticoagulant treatment (IIbB)

- **1**
  - OAC should be considered (IIaB)

- **≥ 2**
  - Oral anticoagulation indicated
    - Assess for contra-indications
    - Correct reversible bleeding risk factors
    - LAA occluding devices may be considered in patients with clear contra-indications for OAC (IIbC)
    - NOAC (IA)\(^b\)
    - VKA (IA)\(^c\)

\(^a\) Includes women without other stroke risk factors
\(^b\) IIaB for women with only one additional stroke risk factor
\(^c\) IIB for patients with mechanical heart valves or mitral stenosis
Anticoagulant Options for AF

- **Antiplatelet agents**
  - Aspirin
  - Clopidogrel plus aspirin

- **Antithrombotic agents**
  - Warfarin

- **New Oral Anticoagulants**
  - Apixaban
  - Dabigatran
  - Edoxaban
  - Rivaroxaban

- **Emerging devices (unapproved as yet)**
  - WATCHMAN left atrial occlusive device
  - Left atrial appendage occlusive clip

- **Surgical**
  - Left atrial appendage excision
## Advantages and Disadvantages of Current Antithrombotics

### Advantages
- Used for many years
- Well studied/experience
- Effective if INR kept in therapeutic range
- Well known drug and food interactions
- Low cost
- Antidote/easy to recover

### Disadvantages
- Erratic INR control / frequent monitoring
- Narrow therapeutic index
- Medications adjustments often required
- Drug and food interactions
- Risk of bleeding
- Patients reluctance
- Underuse in high risk patients
VKA dosing is complex

Factors influencing warfarin dosing:

- Age
- Weight
- Amiodarone interaction
- Other drug interactions
- Race
- Sex
- Plasma vitamin K level
- Co-morbid conditions (such as CHF or active malignancy)

*A large part of variation is unknown but may be at least partially attributed to drug and food interactions.

CYP2C9: Cytochrome P450 2C9; VKORC1: Vitamin K epoxide reductase complex subunit 1

Coumadin prescribing information available at [http://packageinserts.bms.com/pi/pi_coumadin.pdf](http://packageinserts.bms.com/pi/pi_coumadin.pdf);
Drug and food interactions with warfarin
INR control in routine practice is suboptimal

Retrospective, multicentre cohort study (ISAM)

Time in therapeutic range

% INRs

INR <2  INR 2–3  INR >3

US  Canada  France  Italy  Spain

Men discontinued warfarin therapy earlier than women, and patients aged 66 to 75 years more likely than olders.

Gomes T et al. Arch Intern Med 2012 on line
Targets for anticoagulants

Inactive Factor
Active Factor
Transformation
Catalysis

Initiation

Propagation

Direct Factor Xa inhibition
- Rivaroxaban
- Apixaban
- Edoxaban
- Betrixaban

Direct Factor IIa inhibition
- Dabigatran

Clot formation

VKA

TF VIIa
VI
IX
X
IXa
II
IIa

Prothrombin
Thrombin
Fibrinogen
Fibrin

## Relevant clinical characteristics and dose adjustment in the four phase III NOAC trials in patients with atrial fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (RE-LY)</th>
<th>Rivaroxaban (ROCKET-AF)</th>
<th>Apixaban (ARISTOTLE)</th>
<th>Edoxaban (ENGAGE AF-TIMI 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal clearance</strong></td>
<td>80%</td>
<td>35%</td>
<td>25%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
<td>21,105</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>150 mg or 110 mg twice daily</td>
<td>20 mg once daily</td>
<td>5 mg twice daily</td>
<td>60 mg (or 30 mg) once daily</td>
</tr>
<tr>
<td><strong>Exclusion criteria for CKD</strong></td>
<td>CrCl &lt; 30 ml/min</td>
<td>CrCl &lt; 30 ml/min</td>
<td>Serum creatinine &gt; 2.5 mg/dL or CrCl &lt; 25 ml/min</td>
<td>CrCl &lt; 30 ml/min</td>
</tr>
<tr>
<td><strong>Dose adjustment with CKD</strong></td>
<td>None</td>
<td>Rivaroxaban 15 mg once daily if CrCl 30–49 ml/min</td>
<td>Apixaban 2.5 mg twice daily if at least two of age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL (133 µmol/L)</td>
<td>Edoxaban 30 mg (or 15 mg) once daily if CrCl &lt; 50 ml/min</td>
</tr>
<tr>
<td><strong>Percentage of patients with CKD</strong></td>
<td>20% with CrCl 30–49 ml/min</td>
<td>21% with CrCl 30–49 ml/min</td>
<td>15% with CrCl 30–50 ml/dL</td>
<td>19% with CrCl &lt; 50 ml/min</td>
</tr>
<tr>
<td><strong>Reduction of stroke and systemic embolism</strong></td>
<td>No interaction with CKD status</td>
<td>No interaction with CKD status</td>
<td>No interaction with CKD status</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Reduction in major haemorrhages compared to warfarin</strong></td>
<td>Reduction in major haemorrhage with dabigatran was greater in patients with eGFR &gt; 80 ml/min with either dose</td>
<td>Major haemorrhage similar</td>
<td>Reduction in major haemorrhage with apixaban</td>
<td>NA</td>
</tr>
</tbody>
</table>
Antithrombotic therapy after an acute coronary syndrome in atrial fibrillation patients requiring anticoagulation

AF patient in need of OAC after an ACS

- **Bleeding risk low** compared to risk for ACS or stent thrombosis
  - Time from ACS:
    - 0
    - 1 month
    - 3 months
    - 6 months
    - 12 months
    - Lifelong
    - Triplet therapy (IIaB)
    - Dual therapy (IIaC)
    - OAC monotherapy (IB)

- **Bleeding risk high** compared to risk for ACS or stent thrombosis
  - Triplet therapy (IIaB)
  - Dual therapy (IIaC)
  - OAC monotherapy (IB)

Colors:
- OAC
- Aspirin 75-100 mg daily
- Clopidogrel 75 mg daily
HAS-BLED for evaluation of bleeding risk

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (systolic BP &gt;160 mm Hg)</td>
<td>1</td>
</tr>
<tr>
<td>Abnormal renal or liver function</td>
<td>1 + 1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>1</td>
</tr>
<tr>
<td>Elderly (age &gt;65 years)</td>
<td>1</td>
</tr>
<tr>
<td>Drugs or alcohol</td>
<td>1 + 1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

### Management of bleeding

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure control in anticoagulated patients with hypertension should be considered to reduce the risk of bleeding.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>When dabigatran is used, a reduced dose (110 mg twice daily) may be considered in patients &gt;75 years to reduce the risk of bleeding.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>In patients at high-risk of gastrointestinal bleeding, a VKA or another NOAC preparation should be preferred over dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, or edoxaban 60 mg once daily.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Advice and treatment to avoid alcohol excess should be considered in all AF patients considered for OAC.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Genetic testing before the initiation of VKA therapy is not recommended.</td>
<td>III (no benefit)</td>
<td>B</td>
</tr>
<tr>
<td>Reinitiation of OAC after a bleeding event should be considered in all eligible patients by a multidisciplinary AF team, considering different anticoagulants and stroke prevention interventions, improved management of factors that contributed to bleeding, and stroke risk.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>In AF patients with severe active bleeding events, it is recommended to interrupt OAC therapy until the cause of bleeding is resolved.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
HASBLED – often misunderstood

- HASBLED $\geq 3 = \text{increased bleeding risk}$
  - not mean to be a contraindication to anticoagulation per se
  - increased caution and monitoring
- Emphasizes modifiable risk factors
- Adds perspective to specific bleeding risk factors
- Highlights individualised stroke vs bleeding risk assessment

Current Treatment Strategies for AF

➢ Prevention of thrombo-embolism
➢ Rate control
➢ Rhythm control
Acute heart rate control in atrial fibrillation

Acute heart rate control of AF

LVEF <40% or signs of congestive heart failure

- Smallest dose of beta blocker to achieve rate control
  - Amiodarone is an option in patients with haemodynamic instability or severely reduced LVEF
  - Initial resting heart rate target <110 bpm

- Add digoxin
  - Initial resting heart rate target <110 bpm

Avoid bradycardia
- Perform echocardiogram to determine further management/choice of maintenance therapy
- Consider need for anticoagulation

LVEF ≥40%

- Beta blocker or diltiazem or verapamil
  - Check previous drug history to avoid concomitant administration
  - Initial resting heart rate target <110 bpm

- Add digoxin
  - Initial resting heart rate target <110 bpm
Long-term heart rate control in patients with atrial fibrillation

**Long-term heart rate control of AF**

Perform echocardiogram (IC)
Choose initial rate control therapy (IB) and combination therapy if required (IIaC)
Target initial resting heart rate <110 bpm (IIaB), avoiding bradycardia

- **LVEF <40%**
  - Beta-blocker
  - Digoxin
    - Consider early low-dose combination therapy
      - Add digoxin
      - Add beta-blocker

- **LVEF ≥40%**
  - Diltiazem/verapamil
  - Beta-blocker
    - Add therapy to achieve target heart rate or if ongoing symptoms
      - Add digoxin
      - Add digoxin
    - Digoxin
      - Add diltiazem, verapamil or beta-blocker
Current Treatment Strategies for AF

➢ Prevention of thrombo-embolism

➢ Rate control

➢ Rhythm control
Initiation of long term rhythm control therapy in symptomatic patients with atrial fibrillation

Initiation of long-term rhythm control therapy to improve symptoms in AF

- No or minimal signs for structural heart disease
  - Patient choice
    - Dronedarone (IA)
    - Flecaïnide (IA)
    - Propafenone (IA)
    - Sotalol (IA)
    - Catheter ablation (IIaB)

- Coronary artery disease, significant valvular heart disease, abnormal LVH
  - Patient choice
    - Dronedarone (IA)
    - Sotalol (IA)
    - Amiodarone (IA)

- Heart failure
  - Patient choice
    - Amiodarone (IA)
    - Catheter Ablation (IIaB)
Αξιολόγηση του Ρυθμονόρμ® SR σε ασθενείς με υποτροπιάζοντα επεισόδια κολπικής μαρμαρυγής.

Μελέτη RAFT (ΗΠΑ): Διπλά τυφλά τυχαιοποιημένη για τη...

Σύγκριση των 3 δόσεων του Ρυθμονόρμ® SR (2x 225mg, 325mg, 425mg/ημέρα) με εικονικό φάρμακο σε 523 ασθενείς.

Κριτήρια εισαγωγής:
Οι ασθενείς είχαν ιστορικό κολπικής μαρμαρυγής μέσης διάρκειας 13 μήνες και τεκμηριωμένης συμπτωματικής κολπικής μαρμαρυγής στους 12 μήνες πριν την εισαγωγή στη μελέτη.

Παρατηρήσεις:
>90% είχαν καρδιακή ανεπάρκεια σταδίου Ι κατά NYHA και 21% είχαν προηγούμενη ηλεκτρική καρδιοανάταξη.

Διάρκεια μελέτης: 39 εβδομάδες

Αποτέλεσμα: Και οι 3 δόσεις του Ρυθμονόρμ SR που χορηγήθηκαν για διάστημα μέχρι 39 εβδομάδες υπερτερούν του placebo ως προς το χρόνο μέχρι την πρώτη υποτροπή συμπτωματικής κολπικής αρρυθμίας από την ημέρα 1 της τυχαιοποίησης
Μελέτη ERAFT (Ευρώπη): Διπλά τυφλή τυχαιοποιημένη για τη...

Σύγκριση 2 δόσεων του Ρυθμονόρμ® SR (325mg x 2/ημέρα & 425mg x 2/ημέρα) και placebo σε 293 ασθενείς.

Κριτήρια εισαγωγής & αποτελέσματα:
Οι ασθενείς είχαν κολπική μαρμαρυγή μέσης διάρκειας 3,3 έτη
37% είχαν ιστορικό ελαφράς οργανικής καρδιοπάθειας και
61% χρησιμοποιούσαν φάρμακα για μείωση της καρδιακής συχνότητας
Έπρεπε 28 ημέρες πριν την εισαγωγή στη μελέτη να είχαν 1 τεκμηριωμένο επεισόδιο κολπικής μαρμαρυγής.

Σχεδιασμός:
Μετά την εισαγωγή ακολούθησε διπλά – τυφλή περίοδος η οποία αποτελούνταν από:
4 ημέρες φόρτισης και 91 ημέρες μελέτης αποτελεσματικότητας

Αποτελέσματα:
Οι συμπτωματικές αρρυθμίες είχαν τεκμηριωθεί με ECG και βρέθηκε ότι το Ρυθμονόρμ® SR
παρατείνει το χρόνο μέχρι την πρώτη επανεμφάνιση συμπτωματικής κολπικής αρρυθμίας από
tην Ημέρα 5 της τυχαιοποίησης (κύρια ανάλυση αποτελεσματικότητας) κατά τρόπο
dοσοεξαρτώμενο: 9 ημέρες στην ομάδα placebo, 35 ημέρες στην ομάδα προπαφαινόνης SR
325 mg x 2/ημέρα (p= 0,004) και 44 ημέρες στην ομάδα προπαφαινόνης SR 425 mg x 2/ημέρα
(p = 0,003). Τα αποτελέσματα συμφωνούν με τα αποτελέσματα της μελέτης RAFT.
«Στις Η.Π.Α. κάθε 45sec κάποιος υπόκειται σε ένα ΑΕΕ, κάθε 31min κάποιος πεθαίνει από ΑΕΕ»

Vladimir Hachinski Editor in Chief Stroke June 2004
ΕΠΙΛΟΓΟΣ:
«Ο καλύτερος τρόπος να μειώσεις το φορτίο των ΑΕΕ και των άλλων συμβαμάτων είναι να επενδύσεις σε αποτελεσματικές στρατηγικές πρόληψης»