New Position Paper on
Hypertension and Atrial Fibrillation

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Manolis AJ et al. J Hypertens 2012
How Prevalent is AF?
Prevalence of AF increases with age

Prevalence at baseline assessed in 6808 participants in a European population-based study

Data from Heeringa J et al. Eur Heart J 2006;27:949–53
AF is an increasingly common disorder

The overall prevalence of AF is increasing, driven by:
- Ageing of populations worldwide
- Rising prevalence of chronic heart disease
- Rising prevalence of AF risk factors, e.g. hypertension, obesity, diabetes mellitus

Hospital admissions for AF have increased by 60% over the past 20 years

Risk Factors for AF?
Risk Factors, Clinical Conditions and Markers for the Development of AF

**Risk factors**
- Age
- Hypertension
- Diabetes mellitus
- Obesity
- Metabolic syndrome
- Alcohol consumption
- Smoking

**Clinical conditions**
- Left ventricular hypertrophy
- Myocardial infarction
- Heart failure
- Obstructive sleep apnoea
- Renal dysfunction
- Valvular heart disease
- Thyroid disease

**Markers**
- Increased arterial stiffness
- Left atrial enlargement
- Increased PR interval
- P wave dispression
- Birth weight
- hs-CRP
- Inflammatory markers
- Neurohormones
- Genetic variants
- Pulse pressure
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: 80
- AVERROES: 90
- AVERROES: 86
What are the consequences of AF?
## Classification of five types of AF: ESC guidelines 2010

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>First diagnosed</td>
<td>First recognized episode of AF, irrespective of duration or the presence and severity of AF-related symptoms</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>AF that is self-terminating, usually within 48 hrs</td>
</tr>
<tr>
<td>Persistent</td>
<td>AF that persists for &gt;7 days or requires termination by cardioversion</td>
</tr>
<tr>
<td>Long-standing persistent</td>
<td>AF that has lasted for ≥1 yr when it is decided to adopt a rhythm control strategy</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>Presence of the arrhythmia is accepted by the patient (and physician)</td>
</tr>
</tbody>
</table>

EHRA = European Heart Rhythm Association

AF is a Progressive Disease

- **Paroxysmal**: Trigger dependent (Initiation)
- **Persistent**: Relative Importance
- **Permanent**: Substrate dependent (Maintenance)
Over Time AF Causes Atrial Remodelling

- **Electrical remodelling**
  - Shortening of atrial refractory periods
  - Occurs rapidly (within several days) and contributes to the increased stability of AF

- **Contractile remodelling**
  - Reduced atrial contractility
  - Sets the stage for thrombus formation
  - May lead to atrial dilation further altering electrophysiologic properties
  - Occurs rapidly

- **Structural remodelling**
  - Histologic changes
  - Left atrium and left atrial appendage enlargement
  - Decrease in cardiac output
  - Occurs after a period of weeks to months

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Van Gelder et al. Europace 2006;8:943-949
ESH/ESC Guidelines and Search for Subclinical Organ Damage

**2003 GLs**
- ↑ Scr (> 1.4-1.5 mg/dl)
- EKG †

**2007 GLs**
- ↑ Scr (> 1.4-1.5 mg/dl)
- ↓ eCrCl / GFR
- MA
- EKG †

Routine

Recommended

LVH (Echo)
CA thickening / plaques
MA

LVH (Echo)
Concentric LVH
LA enlargement
CA thickening / plaques
Ankle/Brachial ratio
Arterial stiffening (PWV)*

* Depending on availability / also shown by high SBP / low DBP
† LVH / MI-ischemia / Arrhythmias

Search for multiorgan OD
OD assessed before and during T
Transthoracic echocardiography (TTE)

- Non-invasive

- Used to identify:
  - Presence of atrial thrombi
  - Size and functioning of atria and ventricles
  - Ventricular hypertrophy
  - Pericardial disease
  - Valvular heart disease

Thrombus in left atrium

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\(^4\)

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Holter Monitoring: Asymptomatic AF
### Subclinical Atrial Fibrillation and Risk of Stroke

Asymptomatic AF and stroke evaluation in pacemaker hypertensive patients in the ASSERT trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical AF</td>
<td>5.56</td>
<td>3.78-8.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic stroke or systemic embolism</td>
<td>2.49</td>
<td>1.28-4.85</td>
<td>0.007</td>
</tr>
<tr>
<td>Ischemic stroke or systemic embolism after adjustment for stroke predictors</td>
<td>2.50</td>
<td>1.28-4.89</td>
<td>0.008</td>
</tr>
</tbody>
</table>

## CHA$_2$DS$_2$ VaSc Score and Annual Risk of Stroke

### Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Recent congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Age ≥ 75 y</td>
<td>2</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S</td>
<td>History of stroke or transient ischemic attack</td>
<td>2</td>
</tr>
<tr>
<td>V</td>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>S</td>
<td>Sex category (female sex)</td>
<td>1</td>
</tr>
</tbody>
</table>

### Relationship between CHADS$_2$ score and annual risk of stroke

- **Score:** 0 0 1 1 2 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
- **Stroke Rate %:** 1.9 2.8 4.0 5.9 8.5 12.5 18.2

- **Graph:**
  - X-axis: CHADS$_2$ Score (0 to 6)
  - Y-axis: Stroke Rate % (0 to 20)

- **Caption:** Relationship between CHADS$_2$ score and annual risk of stroke
What are the current treatment strategies for AF?
Effect of hypertension on anticoagulated Patients with atrial fibrillation

Rates of stroke/SEE rate in SPORTIF III and V by quartiles of individual patient mean SBP values (84.0-122.6, 122.7-131.3, 131.4-140.7, and 140.8-191.7mmHg)

Lip G. et al., European Heart Journal 2007
**Meta-analysis: Inhibition of renin-angiotensin system prevents new-onset atrial fibrillation**

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPPP</td>
<td>0.87</td>
<td>0.68</td>
<td>1.11</td>
<td>23.6</td>
</tr>
<tr>
<td>STOP-2</td>
<td>1.12</td>
<td>0.95</td>
<td>1.32</td>
<td>26.4</td>
</tr>
<tr>
<td>LIFE</td>
<td>0.66</td>
<td>0.54</td>
<td>0.81</td>
<td>25.2</td>
</tr>
<tr>
<td>VALUE</td>
<td>1.20</td>
<td>0.97</td>
<td>1.48</td>
<td>24.8</td>
</tr>
<tr>
<td>Pooled RR</td>
<td>0.94</td>
<td>0.72</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td><strong>Post-myocardial infarction trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSI-3</td>
<td>0.92</td>
<td>0.83</td>
<td>1.01</td>
<td>60</td>
</tr>
<tr>
<td>TRACE</td>
<td>0.52</td>
<td>0.31</td>
<td>0.87</td>
<td>40</td>
</tr>
<tr>
<td>Pooled RR</td>
<td>0.73</td>
<td>0.43</td>
<td>1.26</td>
<td></td>
</tr>
<tr>
<td><strong>Heart failure trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>0.67</td>
<td>0.54</td>
<td>0.83</td>
<td>38.7</td>
</tr>
<tr>
<td>SOLVD</td>
<td>0.22</td>
<td>0.12</td>
<td>0.43</td>
<td>21.9</td>
</tr>
<tr>
<td>CHARM</td>
<td>0.82</td>
<td>0.68</td>
<td>1.00</td>
<td>39.4</td>
</tr>
<tr>
<td>Pooled RR</td>
<td>0.57</td>
<td>0.37</td>
<td>0.89</td>
<td></td>
</tr>
</tbody>
</table>

UK-based General Practice Research Database

- 650,000 hypertensive pts
- 4,661 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

<table>
<thead>
<tr>
<th>Group Comparison</th>
<th>Odds Ratio (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCB’s vs ACE-I</td>
<td>0.75</td>
</tr>
<tr>
<td>vs ARB’s</td>
<td>0.71</td>
</tr>
<tr>
<td>vs β-blockers</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Current Treatment Strategies for AF

- Prevention of thrombo-embolism
- Rate control
- Rhythm control

ACC/AHA/ESC 2006 guidelines J Am Coll Cardiol 2006;48:854-906
## ESC AF Antithrombotic Guidelines 2010

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>CHA(_2)DS(_2)-VASc Score</th>
<th>Recommended Antithrombotic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ‘major’ risk factor or</td>
<td></td>
<td>OAC*</td>
</tr>
<tr>
<td>≥ 2 ‘clinically relevant nonmajor’ risk factors</td>
<td>≥ 2</td>
<td></td>
</tr>
<tr>
<td>1 ‘clinically relevant nonmajor’ risk factor</td>
<td>1</td>
<td>Either OAC* or aspirin 75-325 mg daily. Preferred: OAC rather than aspirin</td>
</tr>
<tr>
<td>No risk factor</td>
<td>0</td>
<td>Either aspirin 75-325 mg daily or no antithrombotic therapy. Preferred: No antithrombotic therapy rather than aspirin.</td>
</tr>
</tbody>
</table>

*OACs such as a VKA, adjusted to an intensity range of INR 2.0-3.0 (target 2.5). New OAC drugs, which may be viable alternatives to a VKA, may ultimately be considered.

Camm AJ et al. Eur Heart J. 2010;31:2369-2429
AF-related stroke is preventable

- 2/3 of strokes due to AF are preventable with appropriate anticoagulant therapy with a vitamin-K-antagonist (INR 2-3)\(^1\)

- Anticoagulation with a vitamin-K-antagonist (VKA) is recommended for patients with more than 1 moderate risk factor (age, HBP, CHF or LVD, Diabetes)

- A meta-analysis of 29 trials in 28,044 patients showed that adjusted-dose warfarin results in a reduction in ischaemic stroke and in all-cause mortality\(^1\)

Management of AF in clinical practice: prescription of VKAs in eligible patients

Treatment received:

- **No anticoagulation**
- **VKAs**

**Medicare cohort, USA**
- n = 23,657
- 64% treatment received

**EuroHeart survey**
- n = 5,333
- 67% treatment received

**ATRIA cohort (managed care system, California, USA)**
- n = 11,409
- 55% treatment received

**VKAs** = vitamin K antagonists; **ATRIA** = Anticoagulation and Risk Factors in Atrial Fibrillation

Underuse of oral anticoagulants for high-risk atrial fibrillation patients was found in most of the 54 studies (1998-2008) reporting both patient stroke risk and patients treated.

Over two thirds of studies of atrial fibrillation patients with prior stroke or transient ischemic attack reported treatment levels of under 60% of eligible patients.

Most studies based on CHADS2 score reported oral anticoagulant treatment levels of high-risk subjects below 70%.
VKAs have a narrow therapeutic window

**Graph:** Reproduced with permission: ©2010 American College of Chest Physicians


**Graphical representation:**
- **Y-axis:** Odds ratio
- **X-axis:** International normalized ratio
- **Legend:**
  - **Stroke** (green line)
  - **Intracranial bleed** (white line)

**Note:** VKAs = vitamin K antagonists

**Intended message:**
- The graph illustrates the risk of stroke and intracranial bleed as a function of the international normalized ratio, highlighting the narrow therapeutic window for vitamin K antagonists (VKAs).
Implementation of current guidelines in HTN patients with AF

200 pts
Mean age 71 ± 12yrs

Zamfir T. et al. ESH 2012 oral
## Advantages and Diasadvantages 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
Warfarin compared with Aspirin for stroke prevention in AF

Random effects model; Error bars = 95% CI; *P>0.2 for homogeneity; †Relative risk reduction (RRR) for all strokes (ischaemic and haemorrhagic)

SPAF III: adjusted-dose warfarin compared with low-intensity warfarin plus Aspirin

Ischaemic stroke or systemic embolism

<table>
<thead>
<tr>
<th>Years</th>
<th>Cumulative event rate (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5</td>
<td>2.0</td>
</tr>
<tr>
<td>1.0</td>
<td>6.0</td>
</tr>
<tr>
<td>1.5</td>
<td>10.0</td>
</tr>
<tr>
<td>2.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

**Combination therapy**
- Fixed-dose warfarin (INR 1.2–1.5)*
- + Aspirin (325 mg/d)

**Adjusted-dose warfarin**
- Warfarin (INR 2.0–3.0)

RRR 74%
(95% CI: 50–87%)
P<0.0001

*Warfarin dose adjusted between 0.5 and 3.0 mg/day to achieve international normalized ratio (INR) 1.2–1.5 when initiating therapy and then fixed for rest of study; RRR = relative risk reduction

ACTIVE W: dual antiplatelet therapy inferior to oral anticoagulation for stroke prevention in AF

**Oral anticoagulation**

VKA (target INR = 2.0–3.0)

**Dual antiplatelet therapy**

Clopidogrel (75 mg/d) + Aspirin (75–100 mg/d)

RR 1.72
(95% CI: 1.24–2.37)
P = 0.001

*InR = international normalized ratio; RR = relative risk; VKA = vitamin K antagonist*
Key features of a “new contender” in the prevention of CV events in AF

- Freedom from coagulation monitoring
- Simpler kinetic profile
- More rapid onset and offset
- Reduced or absent drug-drug and drug-food interactions
- More “user-friendly” than Warfarin
Targets for novel antithrombotic agents in the coagulation cascade

**Direct Factor Xa inhibitors:**
- Apixaban
- Rivaroxaban
- Edoxaban
- Betrixaban (Ph II ongoing)

**Indirect Factor Xa inhibitors:**
- Idraparinux (Ph III terminated)
- SSR 126517 (withdrawn 2009)

**Direct thrombin inhibitors:**
- Dabigatran etexilate (Ph III completed)
- Ximelagatran (withdrawn 2006)
- AZD0837 (Ph II completed)

**Vitamin K antagonist:**
- Tecarfarin (Ph II completed)

**AT** = antithrombin; **Ph** = Phase
Atrial Fibrillation Phase 3 Study Timelines

- **Dabigatran**: RE-LY RELYABLE
- **Rivaroxaban**: ROCKET
- **Edoxaban**: ENGAGE-AF TIMI 48
- **Apixaban**

- **2009**: Dabigatran RE-LY RELYABLE
- **2010**: Rivaroxaban ROCKET
- **2011**: Edoxaban ENGAGE-AF TIMI 48

- **Atrial Fibrillation Phase 3 Study Timelines**
  - 2009
  - 2010
  - 2011
## Trials with new oral anticoagulants

<table>
<thead>
<tr>
<th>Trial</th>
<th>RELY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug used</strong></td>
<td>Dabigatran Vs Warfarin</td>
<td>Rivaroxaban vs Warfarin</td>
<td>Apixaban vs Warfarin</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>150 or 110 mg BID vs Warfarin (INR 2-3)</td>
<td>20 or 15mg QD vs Warfarin (INR 2-3)</td>
<td>5mg BID vs Warfarin (INR 2-3)</td>
</tr>
<tr>
<td><strong>No. of Patients</strong></td>
<td>18.113</td>
<td>14.000</td>
<td>18.201</td>
</tr>
<tr>
<td><strong>Mean age (yrs)</strong></td>
<td>71.5</td>
<td>73</td>
<td>70</td>
</tr>
<tr>
<td><strong>Percentage of Hypertension</strong></td>
<td>80%</td>
<td>90%</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Mean CHADS² Score</strong></td>
<td>2.1</td>
<td>2.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>

**Conclusions:**

- **Relay:** Dabigatran 110mg non-inferior to warfarin, with 20% less major bleedings. Dabigatran 150 mg superior to warfarin with similar rate of major bleedings.
- **ROCKET-AF:** Rivaroxaban non-inferior to warfarin on intention to treat analysis but superior in on treatment analysis. Similar rate of major bleedings.
- **ARISTOTLE:** Apixaban was superior to warfarin in the risk of stroke or systemic embolism, bleeding and all cause mortality.

**Approval**

- FDA
  - Doses of 150 mg and 75mg (if Cl Cr 15-30 mL/min
- FDA approved 9/11
  - EMA: under consideration

*Manolis AJ et al. J Hypertens 2012*
# Bleeding Risk Assessment in AF: HAS-BLED Bleeding Risk Score

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical Characteristic*</th>
<th>Points Awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
</tr>
<tr>
<td>S</td>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRS</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs or alcohol</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

*Risk of bleeding >3*
Hypertension accounts for more cases of AF than any other risk factor, and has been found to affect up to 90% of the participants in AF trials. AF may occur in all stages of cardiovascular continuum, and the presence of AF at all stages increase the risk of cardiovascular morbidity and mortality.

Consequences of AF include increase in overall mortality, stroke, heart failure, hospitalization, it affects quality of life and results in impaired cognitive function.

At the very least, the co-existence of hypertension and AF will double the risk for all of the above.

More than 30% of patients have asymptomatic AF but the risk is the same as in symptomatic ones.
Box 2: AF and antihypertensive treatment

- A principal goal in patients with hypertension and AF is blood pressure reduction per se.

- Drugs blocking the renin-angiotensin-aldosterone system are reported to reduce the risk of new-onset AF. Nevertheless this effect has been mainly observed in high risk patients particularly in those with left ventricular dysfunction, left ventricular hypertrophy and post-MI patients. Most of the supportive data is from post-hoc analyses.

- Beta blockers are effective for rate control and possibly for maintaining sinus rhythm. There is not enough data regarding their use in the prevention of new-onset AF.

- There is not enough data supporting the use of the other drug classes to prevent AF in hypertension.
Box 3: AF and antithrombotic treatment

- Patients with CHADS²-VASc score >=1 should receive oral anticoagulation or aspirin treatment, although oral anticoagulation is preferred. Since most hypertensive patients are over 65 years old, of which half of them are female and most of them have subclinical or clinical organ damage, it is concluded that they should receive anticoagulation treatment.

- VKAs have been proven effective for more than 50 years and are the standard anticoagulation treatment for AF. However, they have disadvantages resulting in underutilization for different reasons.
HYPERTENSION
ATHENS 2014
JUNE 14 - 19, 2014 - ATHENS, GREECE - Megaron Concert Hall

ESH 24th Scientific Meeting of the European Society of Hypertension
ISH 22nd Scientific Meeting of the International Society of Hypertension

www.hypertension2014.com